Cover Page

Universiteit Leiden

The handle http://hdl.handle.net/1887/29980 holds various files of this Leiden University dissertation

Author: Kruis, Annemarije
Title: The effectiveness of integrated disease management in COPD patients
Issue Date: 2014-12-09

The **Effectiveness** of **Integrated Disease Management** in **COPD Patients**

Annemarije Kruis

The **Effectiveness** of **Integrated Disease Management** in **COPD Patients**

Annemarije Kruis

The effectiveness of integrated disease management in COPD patients

Department of Public Health and Primary Care of the Leiden University Medical Center
A.L. Kruis, Leiden, the Netherlands, 2014

ISBN: 978-90-9028584-9

Cover design: Marc Kruis, Annemarije Kruis
Layout & Printing: Optima Grafische Communicatie, Rotterdam, The Netherlands

The **Effectiveness** of **Integrated Disease Management** in **COPD Patients**

Proefschrift

ter verkrijging van
de graad van Doctor aan de Universiteit Leiden,

op gezag van Rector Magnificus prof.mr. C.J.J.M. Stolker,

volgens besluit van het College voor Promoties
te verdedigen op dinsdag 9 december 2014
klokke 15.00 uur

door

Annemarije Louise Kruis

geboren te Stolwijk
in 1985

PROMOTIECOMMISSIE

Promotores:	Prof. dr. W.J.J. Assendelft
	Prof. dr. M.P.M.H. Rutten-van Mölken (Erasmus Universiteit Rotterdam)
	Prof. dr. J. Gussekloo
Co-promotor:	Dr. N.H. Chavannes
Overige leden:	Prof. Dr. M.E. Numans
	Prof. Dr. G.J. Wesseling (Universiteit Maastricht)
	Dr. G. ter Riet (Universiteit van Amsterdam)

The studies presented in this thesis were funded by ZonMW (The Netherlands Organizaton for Health Research and Development) and Stichting Achmea, a Dutch Healthcare insurance company. The supplementary funding for providing a COPD specific exercise training for the RECODE study was provided by two local Dutch healthcare insurers: "Centraal Ziekenfonds (CZ) Zorgverzekeringen" and "Zorg en Zekerheid." Financial support for printing of this thesis was kindly provided by the SBOH (employer of GP trainees in the Netherlands).

CONTENTS

Chapter 1	General introduction	9
	Part 1 Primary care and COPD management	21
Chapter 2	Primary care COPD patients compared to large COPD study populations: an UNLOCK validation study *PLoS One 2014;9(3):e90145*	23
Chapter 3	Potential benefits of integrated disease management in COPD patients *Monaldi Arch Chest Dis 2010;73(3):130-4*	45
	Part 2 The effectiveness of integrated disease management in COPD patients	59
Chapter 4	Cochrane Review: Integrated disease management interventions in patients with chronic obstructive pulmonary disease *Cochrane Database Syst Rev 2013;10:CD009437* *Thorax 2014. doi: 10.1136/thoraxjnl-2013-20497*	61
Chapter 5	COPD multidisciplinary team meetings in the UK: health care professionals perceptions of aims and structure *COPD: in press*	131
Chapter 6	Self-management in COPD does not equal solitary confinement but requires pro-active guidance. *Lancet Respir Med 2013;1(9):670-2*	141
Chapter 7	Sustained effects of integrated COPD management on health status and exercise capacity in primary care patients *Int J Chron Obstruct Pulmon Dis 2010;5:407-13.*	149
Chapter 8	RECODE: Design and baseline results of a cluster randomized trial on cost-effectiveness of integrated COPD management in primary care. *BMC Pulm Med. 2013;13:17*	163
Chapter 9	Effectiveness of integrated disease management for primary care COPD patients. *BMJ 2014;349:g5392*	189
Chapter 10	General discussion	209
Chapter 11	Summary	223
Chapter 12	Nederlandse samenvatting	231
	Dankwoord	239
	Curriculum vitae and bibliography	241

Chapter 1

General introduction

BACKGROUND

Chronic obstructive pulmonary disease (COPD) is a common reason for seeking medical care; it is a disabling chronic disease which affects 210 million people worldwide.[1] According to the Global Burden of Disease Study, COPD was the third leading cause of death in 2010.[2] Prevalence estimates show considerable variability across populations, suggesting that risk factors can affect populations differently.[3] In 2011, there were 360.000 patients with a diagnosis of COPD in the Netherlands.[4] Unfortunately, COPD is largely underdiagnosed worldwide independent of overall prevalence, with a proportion of underdiagnosis ranging from 72% in Spain to 93% in Montevideo (Uruguay) in population-based studies.[5-9] In the Netherlands, the prevalence of undetected COPD was estimated as 29% in patients older than 50 years with persistent cough.[10]

COPD is a preventable disease: there are primary (smoking cessation, adequate treatment of asthma), secondary (early detection of disease and modification of risk factor exposure) and tertiary (prevention of complications) prevention strategies available.[3] Although COPD is not fully reversible, it is a treatable disorder. However, individuals with similar smoking and exposure histories vary greatly in severity of symptoms and their response to treatment.[3;11;12] Frequent comorbidities add to this: depression, osteopenia and cardiovascular disease are often seen, making optimal treatment even more complicated.[3] In all patients, smoking cessation could prevent further progression of the disease.[13] Nonetheless, it is discouraging that a substantial percentage of patients with moderate to severe COPD continue to smoke, ranging from 36% to 52% in recent large clinical trials of patients with moderate to severe COPD.[14-19]

People with early or undiagnosed COPD are most likely to encounter the health care system in the primary care setting.[20] Consequently, accurate knowledge of diagnosis and the prevalence of COPD in this setting are critical to planning and implementing strategies for the management of the disease.[20] A recent study in Canada concluded one of every five adults over 40 years who visited a general practitioner for any reason in combination with a smoking history of at least 20 pack-years, met the spirometric criteria of COPD.[20] Although more than three-quarters of the patients with COPD reported at least one respiratory symptom, two-thirds were unaware of their diagnosis.[20] Furthermore, once diagnosed, patients greatly underestimate the severity of their disease, as they often regard their disease as mild to moderate while suffering from relatively severe dyspnoea and disability.

As a consequence of underreported symptoms, disappointing effects of medical treatment and a lack of knowledge about the (heterogeneity of the) disease, doctors found themselves in a somewhat frustrating position.[21] They have to recognize COPD treatment is not about *cure* rather than optimal *care* for patients, which mainly consists

of improving one's quality of life, daily functioning and provide patients with essential tools to learn to live with the disease.
So, from these perspectives, what is optimal management for COPD patients? The studies presented in this thesis explore optimal COPD care, as well as the potential role of integrated disease management for COPD patients, specifically in primary care.

OPTIMAL MEDICAL TREATMENT

Firstly, when it comes to medical treatment for COPD patients, the evidence published in guidelines is a reflection of large pharmaceutically sponsored trial results, aimed at evaluating the effect of inhalation medication therapies.[22;23] These trials, usually designed (often by the industry) to maximize significant effects, applied strict inclusion criteria for patients. Often, only those patients were eligible who fulfilled the criterion of severe lung function loss, a high exacerbation rate and possessed both time and motivation to participate in a trial. Patients with comorbidities are excluded from these studies. Pharmaceutical companies sometimes generalize the results of their studies to all COPD patients, but do the results hold true for less severe patients in primary care? Which part of our primary care population would actually be eligible for inclusion in such a trial? In **Chapter 2,** we investigate the external validity of the company sponsored COPD trials published in the last decade, by using a large combined international primary care dataset, comparing patient characteristics of primary care patients to patients included in trials.

PULMONARY REHABILITATION

Besides smoking cessation, the most effective treatment for COPD patients is pulmonary rehabilitation (PR), which is a comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies including exercise training, education, and behaviour change, designed to improve the physical and psychological condition and to promote the long-term adherence to health-enhancing behaviours.[24] PR has been proven to be effective in all patients in whom respiratory symptoms cause diminished quality of life and a reduced exercise tolerance.[25;26] Unfortunately, the use of PR is limited worldwide, due to low accessibility and availability[27-30], high costs[31], and lack of motivation of patients to integrate learned skills into daily life after the program has been finished.[32]

INTEGRATED DISEASE MANAGEMENT

In recent years, attention has shifted from questions regarding the effectiveness of PR for those who successfully attend and complete a programme, to meeting challenges for the delivery of PR to the wider population with COPD, including patients in primary care. As a result, there is considerable interest in developing and testing alternative models of delivery of PR to improve general health, knowledge of the disease and self-care.[33] Following this interest, the concept of integrated disease management (IDM) was introduced in the last decade. For example, if PR programs could be tailored to fit into general practice in an integrated disease management model, would it then be possible to extend the benefits to a larger part of the population? Would it then be possible to let milder, primary care COPD patients benefit of these adapted PR programs? In **Chapter 3,** we further elaborate on this hypothesis and focus on key aspects of PR programs tailored for primary care, providing a framework for further research on the effectiveness of such primary care integrated disease management programmes.[34]

Currently, there is no consensus on a definition of IDM, although it is usually described as a group of coherent, multidisciplinary interventions for chronic diseases.[35] The World Health Organization defines integrated care as "a concept bringing together inputs, delivery, management and organization of services related to diagnosis, treatment, care, rehabilitation and health promotion". There is great overlap in literature on the use of terminology of pulmonary rehabilitation, self-management and IDM.[36;37] For example, some of the extended 'self-management' programmes exceed the level of support that many comprehensive PR programmes offer.[38;39] A model (Figure 1) presented by Wagg might offer clarification of the used terms and the underlying relationships between self-management, pulmonary rehabilitation and IDM.[37] In this model, IDM can be seen as the extension of ongoing support after a program has been finished, including different elements of care, such as education, action plans, self-management and PR. Moreover, although not apparent in this figure, IDM consists usually of other components of care, such as dietary interventions, optimal medication, psychosocial support or smoking cessation.

The aim of optimal IDM is to improve quality of life and exercise tolerance, and to prevent exacerbation related hospital admissions. Several systematic reviews have been published that evaluated the effectiveness of IDM; however, these were either out-of-date, assessed not all important clinical outcomes, or were unable to perform meta-analyses.[40-43] Therefore, we systematically and comprehensively evaluate all randomized clinical trials between 1990 and 2012 that published the effects of IDM in COPD patients on these outcomes, using the rigid systematic approach of the Cochrane collaboration. This Cochrane systematic review is described in **Chapter 4.**

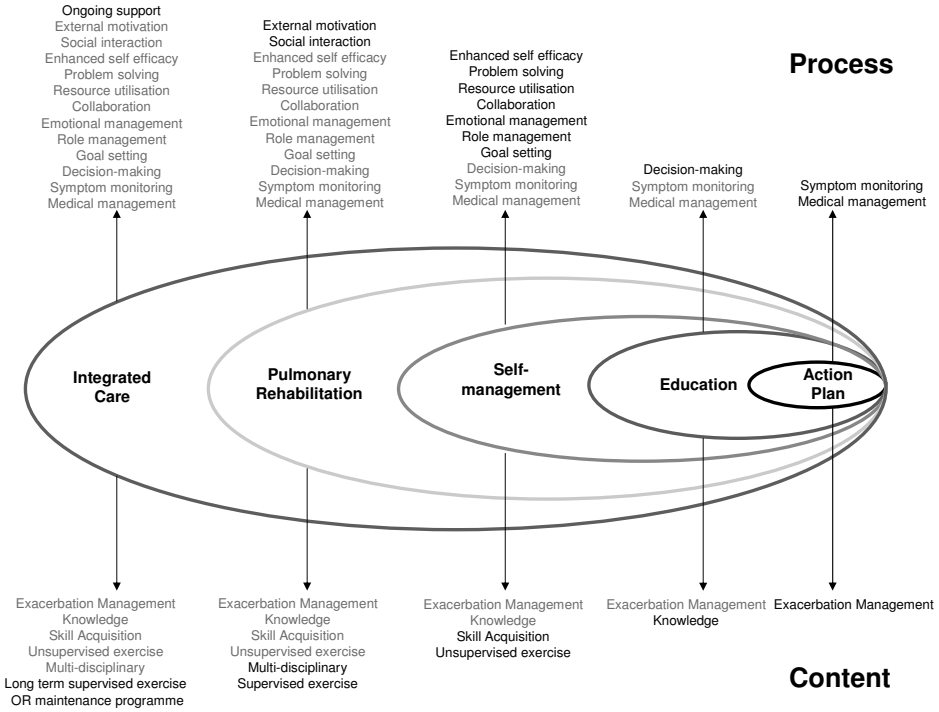


Figure 1. The spectrum of self-management, pulmonary rehabilitation and integrated disease management programmes for COPD (adapted from Wagg[44])

IDM is delivered in a team setting, in which doctors, nurses, physiotherapists, occupational therapists, pharmacists, dieticians, social workers and mental health specialists can be involved and contribute within their field of expertise. Since ten years, several of such community and hospital-based multidisciplinary teams (MDTs) have evolved within the UK, mostly on healthcare members' own initiatives. Currently, there is no research published on the perception and satisfaction of these healthcare providers working in a team setting for COPD patients. Do they think it is useful, and which patients are usually discussed during their meetings? What do they think is the purpose of the meetings, and do they have suggestions for improvement? How do they feel outcomes of a successful team can be measured? Insight in the perceptions of these experienced and well-developed teams is presented in **Chapter 5,** and can be used to inform other healthcare providers working or willing to work in integrated teams.

EXACERBATION SELF-MANAGEMENT AND ACTION PLANS

An important aspect of IDM COPD programmes is implementing self-management strategies. Self-management is intended to help patients acquire and practice the skills they need to carry out medical regimens, to change their health behaviour and to provide emotional support, resulting in adjustment of their roles for optimal function and control of their disease.[45] Self-management suits the concept of integrated and collaborative care very well, in which well-informed patients actively participate in the decision making processes regarding their chronic disease.[46] While doctors are experts about diseases, patients are experts about their own lives. Once physicians recognize patients as individual self-experts, they can add their medical knowledge to what patients feel about their own lives to create a tailor-made plan that will help patients to achieve personal goals[47], for instance recognizing exacerbations at an early stage. Nonetheless, the term self-management in the literature is widely used for a whole range of different interventions. In general, collaborative care is defined by a patient-physician relationship in which physicians and patients make health care decisions together. The term self-management refers to the realm of patient education and includes a plan that provides patients with problem-solving skills to enhance their lives.[46] Bourbeau and colleagues were the first to demonstrate beneficial effects of a COPD self-management programme in a widely cited Canadian trial.[48] This led to numerous attempts to replicate these findings worldwide; however, this led to a contradictory body of literature: some trials demonstrated reductions in hospital admissions and improvements in quality of life[49;50], while other trials revealed absence of these effects[51-53], or even showed increased mortality rates in the self-management group.[54] The contrast in findings is further discussed in **Chapter 6**, where we focus on the characteristics of both the positive as the negative trials. Which factors are associated with success and which with failure? For what group of patients is self-management actually successful?

INTEGRATED DISEASE MANAGEMENT PROGRAMS IN PRIMARY CARE

After addressing these theoretical concepts and the potential of primary care IDM programmes, followed by the evidence of IDM and self-management programmes in general, the effectiveness of IDM programmes in primary care is further explored in the last part of this thesis.

Firstly, we describe the long term results of a controlled clinical trial and implementation study conducted in the Netherlands, which is presented in **Chapter 7:** Sustained effects of integrated COPD management on health status and exercise capacity in primary care patients.

There is a lack of well-conducted randomized clinical trials evaluating an IDM approach delivered in primary care, with a long-term follow-up. Therefore, we conducted a pragmatic cluster randomized trial (the RECODE trial) to evaluate the clinical and cost-effectiveness of IDM for COPD patients in primary care. This trial was specifically designed to allow for subgroup analysis, and therefore we included a large and broad range of heterogeneous COPD patients, ranging from mild to very severe patients. We aimed to answer the question whether it was possible to define subgroups in the population that determine clinical outcomes, such as disease specific quality of life or exacerbations. The design and baseline results of this study are described in **Chapter 8,** and the clinical results are described in **Chapter 9.**

In **Chapter 10:** General discussion, the components of optimal COPD management are further explored and the current state-of-the-art of IDM is summarised, based on the thesis chapters and current literature. The implications for practice, based on the results presented in this thesis and the recommendations for further research, are proposed in this Chapter as well.

REFERENCES

(1) Rennard S, Decramer M, Calverley PM et al. Impact of COPD in North America and Europe in 2000: subjects' perspective of Confronting COPD International Survey. *Eur Respir J* 2002;20:799-805.

(2) Barr RG, Celli BR, Martinez FJ et al. Physician and patient perceptions in COPD: the COPD Resource Network Needs Assessment Survey. *Am J Med* 2005;118:1415.

(3) World Health Organization. World Health Statistics 2008. Geneva Switzerland, World Health Organization 2008.

(4) Nici L, Donner C, Wouters E et al. American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation. *Am J Respir Crit Care Med* 2006;173:1390-1413.

(5) Rabe KF, Hurd S, Anzueto A et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 2007;176:532-555.

(6) Lacasse Y, Martin S, Lasserson TJ, Goldstein RS. Meta-analysis of respiratory rehabilitation in chronic obstructive pulmonary disease. A Cochrane systematic review. *Eura Medicophys* 2007;43:475-485.

(7) Maltais F, Bourbeau J, Shapiro S et al. Effects of home-based pulmonary rehabilitation in patients with chronic obstructive pulmonary disease: a randomized trial. *Ann Intern Med* 2008;149:869-878.

(8) Wijkstra PJ, Strijbos JH, Koeter GH. Home-based rehabilitation for patients with COPD: organization, effects and financial implications. *Monaldi Arch Chest Dis* 2000;55:130-134.

(9) Strijbos JH, Postma DS, van Altena R., Gimeno F, Koeter GH. A comparison between an outpatient hospital-based pulmonary rehabilitation program and a home-care pulmonary rehabilitation program in patients with COPD. A follow-up of 18 months. *Chest* 1996;109:366-372.

(10) Man WD, Polkey MI, Donaldson N, Gray BJ, Moxham J. Community pulmonary rehabilitation after hospitalisation for acute exacerbations of chronic obstructive pulmonary disease: randomised controlled study. *BMJ* 2004;329:1209.

(11) Lacasse Y, Goldstein R, Lasserson TJ, Martin S. Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2009;CD003793.

(12) Nici L, Raskin J, Rochester CL et al. Pulmonary rehabilitation: WHAT WE KNOW AND WHAT WE NEED TO KNOW. *J Cardiopulm Rehabil Prev* 2009;29:141-151.

(13) Landry MD, Hamdan E, Al MS, Brooks D. The precarious balance between 'supply' and 'demand' for health care: the increasing global demand for rehabilitation service for individuals living with chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis* 2008;3:393-396.

(14) Yohannes AM, Connolly MJ. Pulmonary rehabilitation programmes in the UK: a national representative survey. *Clin Rehabil* 2004;18:444-449.

(15) Brooks D, Sottana R, Bell B et al. Characterization of pulmonary rehabilitation programs in Canada in 2005. *Can Respir J* 2007;14:87-92.

(16) Kida K, Jinno S, Nomura K, Yamada K, Katsura H, Kudoh S. Pulmonary rehabilitation program survey in North America, Europe, and Tokyo. *J Cardiopulm Rehabil* 1998;18:301-308.

(17) Griffiths TL, Phillips CJ, Davies S, Burr ML, Campbell IA. Cost effectiveness of an outpatient multidisciplinary pulmonary rehabilitation programme. *Thorax* 2001;56:779-784.

(18) Zuwallack R, Hedges H. Primary care of the patient with chronic obstructive pulmonary disease-part 3: pulmonary rehabilitation and comprehensive care for the patient with chronic obstructive pulmonary disease. *Am J Med* 2008;121:S25-S32.

(19) Rabe KF, Hurd S, Anzueto A et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 2007;176:532-555.
(20) Berry MJ, Rejeski WJ, Adair NE, Zaccaro D. Exercise rehabilitation and chronic obstructive pulmonary disease stage. *Am J Respir Crit Care Med* 1999;160:1248-1253.
(21) Takigawa N, Tada A, Soda R et al. Comprehensive pulmonary rehabilitation according to severity of COPD. *Respir Med* 2007;101:326-332.
(22) Chavannes N, Vollenberg JJ, van Schayck CP, Wouters EF. Effects of physical activity in mild to moderate COPD: a systematic review. *Br J Gen Pract* 2002;52:574-578.
(23) Tiep BL. Disease management of COPD with pulmonary rehabilitation. *Chest* 1997;112:1630-1656.
(24) Tiep B, Barnett MC. Disease Management for Chronic Obstructive Pulmonary Disease. A Clinical Strategy. *Dis Manage Health Outcomes* 2008;16:305-313.
(25) Vieira DS, Maltais F, Bourbeau J. Home-based pulmonary rehabilitation in chronic obstructive pulmonary disease patients. *Curr Opin Pulm Med* 2010;16:134-143.
(26) Maurer J, Rebbapragada V, Borson S et al. Anxiety and depression in COPD: current understanding, unanswered questions, and research needs. *Chest* 2008;134:43S-56S.
(27) Scharloo M, Kaptein AA, Schlosser M et al. Illness perceptions and quality of life in patients with chronic obstructive pulmonary disease. *J Asthma* 2007;44:575-581.
(28) Dowson CA, Town GI, Frampton C, Mulder RT. Psychopathology and illness beliefs influence COPD self-management. *J Psychosom Res* 2004;56:333-340.
(29) Seemungal TA, Donaldson GC, Bhowmik A, Jeffries DJ, Wedzicha JA. Time course and recovery of exacerbations in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000;161:1608-1613.
(30) Chavannes N. Integrated Chronic Obstructive Pulmonary Disease Management in Primary Care. *Dis Manage Health Outcomes* 2008;16:315-318.
(31) Holman H, Lorig K. Patient self-management: a key to effectiveness and efficiency in care of chronic disease. *Public Health Rep* 2004;119:239-243.
(32) Bourbeau J, van der Palen J. Promoting effective self-management programmes to improve COPD. *Eur Respir J* 2009;33:461-463.
(33) Bourbeau J, Bartlett SJ. Patient adherence in COPD. *Thorax* 2008;63:831-838.
(34) Gibson PG, Powell H, Coughlan J et al. Self-management education and regular practitioner review for adults with asthma. *Cochrane Database Syst Rev* 2009;CD001117.
(35) Walters JA, Turnock AC, Walters EH, Wood-Baker R. Action plans with limited patient education only for exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2010;5:CD005074.
(36) Robinson A, Courtney-Pratt H, Lea E et al. Transforming clinical practice amongst community nurses: mentoring for COPD patient self-management. *J Clin Nurs* 2008.
(37) Effing T, Monninkhof EM, van der Valk PD et al. Self-management education for patients with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2007;CD002990.
(38) Bourbeau J, Julien M, Maltais F et al. Reduction of hospital utilization in patients with chronic obstructive pulmonary disease: a disease-specific self-management intervention. *Arch Intern Med* 2003;163:585-591.
(39) World Health Organization. 2008-2013 Action Plan for the Global Strategy for the Prevention and Control of Noncommunicable Diseases. 2008. Geneva, Switzerland, WHO Document Production Services.

(40) Schermer T, van WC, Barten F et al. Prevention and management of chronic obstructive pulmonary disease (COPD) in primary care: position paper of the European Forum for Primary Care. *Qual Prim Care* 2008;16:363-377.

(41) Chavannes NH, Grijsen M, van den Akker M et al. Integrated disease management improves one-year quality of life in primary care COPD patients: a controlled clinical trial. *Prim Care Respir J* 2009;18:171-176.

(42) van Wetering CR, Hoogendoorn M, Mol SJ, Rutten-van Molken MP, Schols AM. Short- and long-term efficacy of a community-based COPD management programme in less advanced COPD: a randomised controlled trial. *Thorax* 2010;65:7-13.

(43) van Wetering CR, van Nooten FE, Mol SJ, Hoogendoorn M, Rutten-van Molken MP, Schols AM. Systemic impairment in relation to disease burden in patients with moderate COPD eligible for a lifestyle program. Findings from the INTERCOM trial. *Int J Chron Obstruct Pulmon Dis* 2008;3:443-451.

Part 1

Primary care and COPD management

CHAPTER 2

Primary care COPD patients compared with large pharmaceutically-sponsored COPD studies: an UNLOCK validation study

Annemarije L. Kruis, Björn Ställberg, Rupert C.M. Jones, Ioanna G. Tsiligianni, Karin Lisspers, Thys van der Molen, Jan Willem H. Kocks, Niels H. Chavannes

PLoS One 2014;9(3):e90145

ABSTRACT

Background

Guideline recommendations for chronic obstructive pulmonary disease (COPD) are based on the results of large pharmaceutically-sponsored COPD studies (LPCS). There is a paucity of data on disease characteristics at the primary care level, while the majority of COPD patients are treated in primary care.

Objective

We aimed to evaluate the external validity of six LPCS (ISOLDE, TRISTAN, TORCH, UPLIFT, ECLIPSE, POET-COPD) on which current guidelines are based, in relation to primary care COPD patients, in order to inform future clinical practice guidelines and trials.

Methods

Baseline data of seven primary care databases (n=3508) from Europe were compared to baseline data of the LPCS. In addition, we examined the proportion of primary care patients eligible to participate in the LPCS, based on inclusion criteria.

Results

Overall, patients included in the LPCS were younger (mean difference (MD)-2.4; p=0.03), predominantly male (MD 12.4; p=0.1) with worse lung function (FEV1% MD -16.4; p<0.01) and worse quality of life scores (SGRQ MD 15.8; p=0.01). There were large differences in GOLD stage distribution compared to primary care patients. Mean exacerbation rates were higher in LPCS, with an overrepresentation of patients with ≥1 and ≥2 exacerbations, although results were not statistically significant. Our findings add to the literature, as we revealed hitherto unknown GOLD I exacerbation characteristics, showing 34% of mild patients had ≥1 exacerbations per year and 12% had ≥2 exacerbations per year. The proportion of primary care patients eligible for inclusion in LPCS ranged from 17% (TRISTAN) to 42% (ECLIPSE, UPLIFT).

Conclusion

Primary care COPD patients stand out from patients enrolled in LPCS in terms of gender, lung function, quality of life and exacerbations. More research is needed to determine the effect of pharmacological treatment in mild to moderate patients. We encourage future guideline makers to involve primary care populations in their recommendations.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is one of the most complex diseases seen by respiratory physicians and general practitioners (GPs). Patients suffer from fluctuating episodes of exacerbations and airway symptoms which are difficult to control and may not sufficiently respond to inhalation therapy.

In the last 30 years, more than 50 (inter)national guidelines on the management of COPD have been published worldwide.[1] However, despite international dissemination and intensive promotion, guidelines are not widely adopted in daily practice.[2] Recently, two surveys revealed that COPD management by GPs was well below guideline-recommended levels, with many GPs having very limited knowledge of COPD and its management.[3;4] Furthermore, about 25% of the GPs reported to be unfamiliar with GOLD and one-third with ATS/ERS guidelines.[4] Overall, non-guideline-informed management was a consequence of no availability, no confidence in gauging pharmacologic response, or because the GPs considered the guidelines too long, not relevant, or expressed no agreement with guidelines.[3;4]

Recommendations in guidelines are usually based on the strongest category of evidence: (meta-analyses of) randomized clinical trials (RCTs). These RCTs, particularly in medication studies, included large and selected COPD populations to ensure that the effect of the studied treatment is not concealed by confounding factors.[5] Furthermore, mild COPD patients are often neglected in these trials, as inclusion criteria are restricted to values of predicted forced-expiratory volume in 1 second (FEV_1% predicted) below 70%. Moreover, selected patients are generally those with sufficient motivation and time to participate in a trial, and most likely to comply with medication and regular appointments. It is questionable whether the results of such RCTs can be extrapolated to all patients with COPD.[5;6] However, reliable judgments about the external validity of RCTs are essential if treatments are to be used correctly in as many patients as possible in routine clinical practice.[7] Recent GOLD guidelines acknowledge this limited generalizability in COPD studies and state some considerations related to the results of these trials.[8]

However, there still remains a paucity of data in the literature regarding COPD patient characteristics at the primary care level, and therefore it still remains unknown if there is overlap in disease characteristics of populations included in large RCT's compared to the population seen in primary care. For example, exacerbation prevalence data in mild COPD patients remains still unknown, and exacerbation prevalence data in the other GOLD stages are solely based on the results of large trials.[8]

To this end, the aim of this study was to evaluate the external validity of six large pharmaceutically sponsored COPD studies.[9-14] We aimed to provide insight into disease characteristics of COPD patients in primary care, in order to inform future guidelines and

trialists. A secondary aim was to describe the proportion of primary care COPD patients eligible for inclusion in these studies.

MATERIAL AND METHODS

Study subjects

UNLOCK patients

Seven primary care databases from the UK, the Netherlands, Sweden and Greece were combined to create an extensive dataset of primary care COPD patients in the UNLOCK study.[15] All individual datasets included baseline data collected as part of on-going real-life cohort studies or pragmatic clinical trials in primary care. Inclusion criteria consisted of spirometrically validated COPD patients according to GOLD guidelines[8]; all studies applied few/limited or no exclusion criteria. Additional information on the methodology of the relevant studies is reported in the references. The UK dataset was a cohort study including 375 COPD diagnosed patients gathered to derive and validate a multicomponent assessment tool of COPD severity (the DOSE index); exclusion criteria consisted of serious co-morbidity affecting the patient's ability to take part or to perform spirometry.[16] The Netherlands had four primary care datasets: two studies (one controlled clinical trial, Bocholtz study; n=154[17] and one cluster RCT, RECODE trial (Netherlands Trial Register (NTR) number 2268); n=1086[18]] aimed to evaluate the long-term effects of a multidisciplinary disease management program on quality of life. Both these studies included COPD patients and had limited exclusion criteria (terminal disease, immobility, substance abuse and inability to fill in questionnaires). The third dataset included 51 COPD diagnosed patients with a smoking history of > 10 years enrolled in a pilot for a RCT (The MARCH study; NTR number 2643) assessing the effect of health status guided care compared to GOLD guideline guided care in the primary care setting.[19] Exclusion criteria were patients with a myocardial infarction < 3 months ago, history of asthma/allergic rhinitis before age 40 years, oxygen use, dementia, or unstable or life-threatening comorbid condition. The fourth dataset comprised 1736 patients who were diagnosed and followed-up by the Asthma/COPD service in the Netherlands. This consultation service (including medical history, health status, lung function test and inhalation technique evaluation) is used by GPs for patients with (a suspicion of) asthma or COPD. For this latter study, only COPD patients were included and no exclusion criteria were applied. The Greek cohort study was designed to explore issues on quality of life, physical activity and dyspnea and included 109 primary care COPD patients with a smoking history of > 10 years; exclusion criteria were history of asthma, unstable cardiovascular disease, or any other respiratory disease other than COPD.[20] The dataset from Sweden

included a cohort study (PRAXIS-study) of 775 primary care COPD patients aged 45-75 years, randomly selected from the medical records of 56 primary healthcare centres; there were no exclusion criteria.[21;22]

Ethical approval

The UK dataset was obtained with the aim to collect anonymised data on COPD patients. The South West Multicentre Research Ethics Committee confirmed that as a service evaluation, formal research ethics approval was not required for the audit. Patients were informed about the study and confidentiality issues. Patient consent was obtained to collect and analyse the data using an electronic consent form approved by the NHS information security and registration authority.[16] In the Dutch Bocholtz clinical trial, the regional Medical Ethics Committee of the Atrium Medical Centre, Heerlen, approved the study protocol. All patients gave written informed consent.[17] The Medical Ethics Committee of the Leiden University Medical Centre approved the Dutch RECODE trial, and all patients gave written informed consent.[18] Data from the Bocholtz and RECODE study is hosted at the department of Public Health and Primary Care at the Leiden University Medical Centre. The MARCH study was approved by the Medical Ethical Committee of the University Medical Centre Groningen, and data is hosted at the University Medical Centre Groningen. All patients gave written informed consent.[19] The fourth Dutch study consisted of observational, anonymised data from the large Asthma/COPD service in the Netherlands. The privacy regulation of the study was registered at the Dutch Data Protection Authority. According to current Dutch legislation, neither informed consent nor approval is required from a medical ethics committee for observational studies using anonymised data records.[23] The Greek study was approved by the local medical ethics committee of the University Hospital of Heraklion, Crete, Greece and all patients gave written informed consent. The data is hosted at the department of Thoracic Medicine in the University Hospital of Heraklion, Crete, Greece.[20] The Swedish study was approved by the Regional Ethical Review Board of Uppsala University, Uppsala, Sweden (Dnr 2004:M-445, Dnr 2010/090 and Dnr 2012/252). Written consent to use the information for future analysis was obtained for all participating patients in 2005. The data is hosted in the University of Uppsala, Sweden, at the department of Medical Sciences: Respiratory Medicine & Allergology.[21;22] The first and last author received all anonymised study datasets and combined these in one dataset.

Large pharmaceutically sponsored COPD studies (LPCS)

We compared the patient characteristics of the UNLOCK datasets with baseline data (if available) from six large pharmaceutically sponsored COPD studies (hereafter called the LPCS). These studies were published in the year 2000 or later: the ISOLDE[9;24;25], TRISTAN[10], TORCH[11;26-29], UPLIFT[12;30], ECLIPSE[13;31;32] and POET-COPD[14] studies. In addition

to five large trials, we decided to include the ECLIPSE cohort study as well, because this is an important observational study often cited in guidelines, especially with regard to exacerbation frequency patterns.

Outcomes

Measurements

Measurements included age, gender, smoking status, pack years, body mass index (BMI), lung function, dyspnea, health-related quality of life, and exacerbations. For smoking status, participants were categorized as never, ex- and current smokers and, if available, the number of pack years was calculated. BMI was calculated using (weight (kg)/(height (m))^2. In all patients, spirometry was performed according to international guidelines.[8] We grouped patients into GOLD stage categories based on their post-bronchodilator FEV_1% predicted as follows: stage I corresponds to post-bronchodilator $FEV_1 \geq 80\%$ predicted, stage II to post-bronchodilator FEV_1 50% to < 80% predicted, stage III corresponds to 30% to <50% predicted, and stage IV corresponds to ≤ 30% predicted.[8]

Definition of exacerbations

The definition of exacerbation used in the UNLOCK, ISOLDE[9], TRISTAN[10], TORCH[29] and ECLIPSE[32] studies was based on worsening of symptoms and the decision by a patient's clinician (or by study personnel) to prescribe antibiotics or systemic corticosteroids, alone or in combination. In the UPLIFT[30] and POET-COPD[14] studies, an exacerbation was defined as an increase in or the onset of more than one respiratory symptom (cough, sputum, sputum purulence, wheezing, or dyspnea) lasting 3 days or more and requiring treatment with an antibiotic or a systemic corticosteroid. The mean exacerbation rate per person per year was calculated and subsequently distributed per GOLD stage. We also calculated the proportion of patients with at least one or two exacerbations per year and compared these to baseline values of the LPCS. If baseline data were missing, we contacted the authors of the studies to request more information. When we received no response or baseline data was not available, we used placebo-limb data of the LPCS. Additionally, we used recent data of the GOLD 2013 guidelines[8], in which reference values of exacerbation rates distributed per GOLD stage are stated.

Dyspnea and health-related quality of life questionnaires

Dyspnea was measured with the Medical Research Council (MRC) dyspnea score.[33] We used the St Georges Respiratory Questionnaire (SGRQ) which is designed to measure health- related quality of life in patients with asthma and COPD.[34] The Clinical COPD Questionnaire (CCQ) was also used: this is a disease-specific 10-item questionnaire that calculates an overall score and three domain scores: symptoms, functional state and

emotional state; patients are required to respond to each item on a 7-point scale with 0 representing the best possible score and 6 representing the worst possible score.[35]

Data acquisition

Data on age, gender, lung function and GOLD stage were available for all patients. The UNLOCK datasets had additional data on the following subsets: current smoke status (98%), CCQ (98%), number of exacerbations (79%), BMI (61%), MRC dyspnea score (41%), SGRQ (32%) and pack years (25%). Mean exacerbation rates in the UNLOCK study were calculated using the number of exacerbations per patient in the year prior to inclusion in the study, divided by the total number of patients in the dataset, which provided data on the number of exacerbations.

Data analysis

All analyses were performed with SPSS software, version 21. There were seven UNLOCK datasets. We calculated proportions for frequencies, and means for continuous variables, for every individual UNLOCK dataset. We used the means of the LPCS reported in the original publications as a comparison. Using independent sample t-tests, we tested the means of the seven (or less, in case of subsets of data) UNLOCK studies to the means of the six LPCS and reported mean differences, 95% confidence intervals (CI) and p-values. We performed a sensitivity analysis on primary care patients with GOLD stage II or above, in order to compare whether patients enrolled in trials were similar to the more severe patients in the primary care setting.

Furthermore, step-by-step we applied the inclusion criteria of the trials[9;10;14;29;30;32] to the UNLOCK population and calculated the proportion of patients eligible for inclusion.

RESULTS

Baseline comparisons

Individual datasets

The UNLOCK datasets included a total of 4286 patients diagnosed with COPD by a GP or respiratory physician. After exclusion of patients with missing lung function data (N=524; 12%) and a ratio of FEV_1/FVC of ≥ 0.7 (N=254; 7%), baseline characteristics of the remaining 3508 primary care COPD patients were compared with those of the LPCS. Results of baseline characteristics of the individual UNLOCK datasets and the LPCS are reported in Table 1.

Table 1. Descriptive baseline data of the seven primary care UNLOCK datasets, compared with baseline data of six large pharmaceutically sponsored COPD studies.

Characteristic	UNLOCK 1 NL	UNLOCK 2 UK	UNLOCK 3 NL	UNLOCK 4 NL	UNLOCK 5 GR	UNLOCK 6 SW	UNLOCK 7 NL	ISOLDE 2000	TRISTAN 2003	TORCH 2007	UPLIFT 2008	ECLIPSE 2010	POET-COPD 2011
Patients (N)	86	375	1665	51	96	333	902	751	1465	6112	5992	2164	7376
Age, years	65.1 (9.9)	69.2 (8.6)	66.8 (10.7)	63.6 (10.5)	66.3 (8.7)	63.3 (8)	68.5 (10.9)	63.7 (7.1)	62.7 (8.7)	65.0 (8.3)	64.5 (8.4)	63.4 (7.1)	62.9 (9.0)
Male, % (n/N)	70 (60/86)	60 (223/375)	59 (976/1665)	61 (31/51)	92 (88/96)	41 (137/333)	45 (407/902)	75	75	76	75	65	74
Current smokers, % (n/N)	42 (36/86)	32 (120/375)	50 (826/1665)	57 (29/51)	50 (48/96)	35 (117/333)	37 (313/855)	36	52	43	29	36	48
Pack years	35.1 (22)	45.1 (27)	-	39.5 (17.9)	66 (33.2)	-	32 (26.5)	44 (30)	42.0 (22.4)	47.0 (26.5)	49.0 (28.0)	48.6 (27.1)	38.8 (20.0)
BMI, kg/m2	25.8 (5.4)	26.7 (5.6)	26.4 (4.6)	-	-	-	-	24.5 (4.8)	-	25.4 (5.2)	26.0 (5.1)	26.5 (5.7)	-
Postbronchodilator FEV1 (% predicted)	62.9 (19)	49.9 (14.4)	68 (17.9)	75.8 (16)	55.3 (18.7)	68.9 (23.9)	65.9 (19.9)	50.3 (14.9)	44.8 (14.7)*	44.3 (12.3)	47.7 (12.7)	48.3 (15.8)	49.2 (13.3)
FEV1:FVC (%)	59.4 (10.2)	-	55 (10.8)	-	56.1 (10.4)	-	55.2 (11.7)	43 (12)	-	48.7 (10.8)*	43.6 (10.8)	44.8 (11.6)	52.5 (10.8)
GOLD distribution													
Mild GOLD I, %	20 (17/86)	-	26 (440/1665)	35 (18/51)	6 (6/96)	33 (111/333)	25 (232/902)	0	-	0	0	0	0
Moderate GOLD II, %	50 (43/86)	52 (196/375)	57 (943/1665)	59 (30/51)	60 (58/96)	42 (139/333)	53 (477/902)	52	-	35	46	44	48
Severe GOLD III, %	27 (23/86)	39 (145/375)	16 (263/1665)	6 (3/51)	19 (18/96)	21 (71/333)	19 (168/902)	III & IV: 48	-	49	44	42	43
Very severe GOLD IV, %	3 (3/86)	9 (34/375)	1 (19/1665)	-	15 (14/96)	4 (12/333)	3 (25/902)		-	15	8	14	9
Patient-reported outcomes													
SGRQ score	33.4 (20.5)	-	-	23.6 (14.8)	37.5 (20)	-	35.8 (20.3)	49.9 (17.4)	47.1 (15.7)	49.3 (17.1)	45.7 (17.0)	50.1 (20.3)	-
CCQ score	1.5 (1.0)	2.0 (1.1)	1.5 (1.0)	1.1 (0.8)	1.6 (0.9)	1.9 (1.2)	1.5 (1.0)	-	-	-	-	-	-
MRC score	2.3 (1.1)	2.7 (1.0)	-	0.7 (0.8)	2.0 (1.0)	2.8 (1.4)	2 (1.3)	-	-	-	-	2.7 (1.1)	-
MRC score > 2, % (n/N)	35 (30/86)	49 (164/337)	-	2 (1/49)	27 (26/96)	47 (152/324)	34 (303/898)	-	-	50	-	53	-

Results are means, unless otherwise noted. "-" indicates data not available. *indicates Pre-bronchodilator values.

Note: In TORCH, UPLIFT, POET-COPD, TRISTAN mean data for total group were not published, we used the following baseline data: POET-COPD: Tiotropium group; UPLIFT: Tiotropium group; ECLIPSE: total group; TORCH: combination therapy group; TRISTAN: Salmeterol/Fluticasone group; ISOLDE: Fluticasone group.

Abbreviations: NL: Netherlands; UK: United Kingdom; GR: Greece; SW: Sweden; BMI: body mass index; FEV1: forced expiratory volume in 1 second; GOLD: Global initiative for chronic Obstructive Lung Disease; SGRQ: St Georges Respiratory Questionnaire; CCQ: Clinical COPD Questionnaire; MRC: Medical Research Counsil

Overall means of the UNLOCK and LPCS studies

The overall means of the UNLOCK studies and the LPCS, including the results of the independent sample t-tests, are reported in Table 2. Compared with the UNLOCK studies, the LPCS included a statistically significant (mean difference (MD) -2.4; p=0.03) younger population with a higher proportion of males (MD 12.4; p=0.1) and significant lower FEV_1% predicted values (MD -16.4; p<0.01) and lower FEV1/FVC values (MD -9.2; p<0.01). There were large differences in GOLD distribution between the UNLOCK studies and the LPCS. There was total absence of GOLD I in the LPCS, whilst in the UNLOCK studies, mild and moderate patients (GOLD I and II) comprised 74% of the total COPD population. In the LPCS, the proportion of GOLD III patients were more than doubled compared to the UNLOCK population (44.5% versus 21%, MD 23.5; p<0.01). In addition, primary care patients in the UNLOCK studies had significantly better health-related quality of life (measured with the SGRQ) compared with LPCS (MD 15.8; p=0.01). In the TORCH and ECLIPSE studies, the proportion of patients with an MRC score >2 was measured, and in ECLIPSE the mean MRC

Table 2. Baseline comparison of the UNLOCK studies versus large COPD studies, including independent sample t-tests.

Characteristic	UNLOCK studies	Large COPD studies (LPCS)	Mean difference between UNLOCK – LPCS (95% CI)	p-value
Patients (N)	3508	23860		
Age, years	66.1 (2.3)	63.7 (0.9)	-2.4 (-4.6 — -0.3)	0.03*
Male, %	60.9 (16.7)	73.3 (4.1)	12.4 (-3.1—27.9)	0.1
Current smokers, %	42.9 (9.5)	40.7 (8.6)	-2.2 (-13.2—8.8)	0.67
Pack years	43.6 (13.5)	44.9 (4.03)	1.3 (-15.2—17.8)	0.84
BMI, kg/m2	26.3 (0.5)	25.6 (0.9)	-0.7 (-2 —0.6)	0.23
Postbronchodilator FEV1, % predicted	63.8 (8.7)	47.4 (2.4)	-16.4 (-24—-8.2)	<0.01*
FEV1:FVC, %	55.7 (0.7)	46.5 (4.0)	-9.2 (-14.1 —-4.2)	<0.01*
GOLD distribution				
Mild GOLD I	20.7 (13.2)	-	-	-
Moderate GOLD II	53.3 (6.2)	45 (6.3)	-8.3 (-16.6—0.1)	0.05
Severe GOLD III	21 (10.1)	44.5 (3.1)	23.5 (13.9—33.1)	<0.01*
Very severe GOLD IV	5.8 (5.2)	11.5 (3.5)	5.7 (-0.71—12)	0.08
Patient-reported outcomes				
SGRQ	32.6 (6.2)	48.4 (1.9)	15.8 (6.3—25.4)	0.01*
CCQ (mean)	1.6 (0.3)	-	-	-
MRC (mean)	2.1 (0.8)	2.7 (1.1)	0.6 (-1.5—2.7)	0.5
MRC score > 2 (%)	32.3 (17)	51.5 (2.1)	19.2 (1.3—37)	0.04*

Data are overall mean values (SD), in which every dataset or study contributed equally to the overall means. "-" indicates data not available. 95% CI: 95% confidence interval. Abbreviations: BMI: body mass index; FEV1: forced expiratory volume in 1 second; GOLD: Global initiative for chronic Obstructive Lung Disease; SGRQ: St Georges Respiratory Questionnaire; CCQ: Clinical COPD Questionnaire; MRC: Medical Research Counsil

scores were reported as well. Overall mean MRC scores were similar in the UNLOCK studies compared to ECLIPSE: 2.1 (0.8) and 2.7 (1.1), respectively. However, overall 51.5% of the patients in the ECLIPSE and TORCH studies had an MRC score >2, meaning walking slower than most people on the level, whereas in the UNLOCK studies this overall proportion was 32.3%, this mean difference was statistically significant (p=0.04).

Exacerbation data

Individual datasets

UNLOCK studies reporting exacerbation data were compared with baseline data of the ISOLDE, TRISTAN, TORCH, UPLIFT and ECLIPSE studies (Table 3). There was heterogeneity between UNLOCK studies, with studies from the Netherlands reporting lower exacerbation rates compared to the UK study.

Table 3. Exacerbation data of the UNLOCK studies, compared with exacerbation data of the large pharmaceutically sponsored COPD studies.

Characteristic	UNLOCK 1 NL	UNLOCK 2 UK	UNLOCK 3 NL	UNLOCK 7 NL	ISOLDE 2000	TRISTAN 2003	TORCH 2007	UPLIFT 2008	ECLIPSE 2010
Patients (N)	86	375	1665	902	370 *	361 *	6112	5992	2138
Mean exacerbation rate p/year	1.05 (1.3)	1.32 (1.6)	0.72 (1.1)	0.54 (1.19)	1.90 (2.63)*	1.30 *	1.0 (1.3)	0.85 (0.02)*	0.9 (1.2)
≥1 in preceding year, % (n/N)	55 (47/85)	59 (222/374)	43 (713/1661)	27 (174/636)	63*	-	57	68*	47
≥2 in preceding year, % (n/N)	29 (25/85)	33 (124/374)	19 (312/1661)	11 (72/636)	-	-	32	-	29

Data are baseline data and mean values (SD), unless stated otherwise. *indicates data from placebo group; "-" indicates data not available.

Overall means of the UNLOCK and LPCS studies

The UNLOCK studies reported a lower mean exacerbation rate per year compared to the LPCS (MD 0.3; p=0.31), as well as a lower proportion of patients with ≥ 1 (MD 15; p=0.21) or ≥ 2 exacerbations (MD 8; p=0.24); Table 4.

Table 4. Mean exacerbation data of the UNLOCK studies, compared with mean exacerbation data of the large pharmaceutically sponsored COPD studies, including independent sample t-tests

Characteristic	UNLOCK studies	Large COPD studies (LPCS)	Mean difference between UNLOCK-LPCS (95% CI)	p-value
Patients (N)	3028	14973		
Mean exacerbation rate p/year	0.9 (3.5)	1.2 (0.4)	0.3 (-0.3—0.9)	0.31
Mean % of patients with ≥1 exacerbation in preceding year	44 (14.4)	59 (9)	15 (-12—42)	0.21
Mean % of patients with ≥2 in preceding year	22 (10)	30 (2.1)	8 (-9—25)	0.24

Data are overall mean values (SD), in which every dataset or study contributed equally to the overall means. 95% CI: 95% confidence interval

Table 5. Exacerbation characteristics distributed per GOLD stages: large COPD studies, compared to UNLOCK primary care datasets.

Characteristic	UNLOCK 1 NL	UNLOCK 2 UK	UNLOCK 3 NL	UNLOCK 7 NL	ISOLDE 2000	TRISTAN 2003	TORCH 2007	UPLIFT 2008	ECLIPSE 2010	GOLD GUIDELINE 2013
Patients (N)	86	375	1665	902	370 *	361 *	6112	5992	2138	
≥1 exacerbations p/year distributed per GOLD stage										
GOLD I, % (n/N)	47 (8/17)	-	32 (140/438)	24 (38/160)	-	-	-	-	-	-
GOLD II, % (n/N)	44 (19/43)	58 (114/196)	46 (435/941)	24 (83/346)	71*	-	-	65*	29	-
GOLD III, % (n/N)	82 (18/22)	60 (86/143)	49 (128/263)	42 (47/113)	GOLD III&IV: 84*	-	-	71*	52	-
GOLD IV, % (n/N)	67 (2/3)	62 (21/34)	53 (10/19)	35 (6/17)		-	-	69*	62	-
≥2 exacerbations p/y distributed per GOLD stage										
GOLD I, % (n/N)	12 (2/17)	-	14 (60/438)	10 (16/160)	-	-	-	-	-	-
GOLD II, % (n/N)	26 (11/43)	30 (59/196)	21 (194/941)	8 (28/346)	-	-	-	-	22	-
GOLD III, % (n/N)	50 (11/22)	36 (51/143)	21 (55/263)	21 (24/113)	-	-	-	-	33	-
GOLD IV, % (n/N)	33 (1/3)	38 (13/34)	16 (3/19)	24 (4/17)	-	-	-	-	47	-
Exacerbation rate distributed per GOLD stage										
GOLD I	0.65	-	0.53	0.46	-	-	-	-	-	-
GOLD II	0.81	1.23	0.78	0.41	0.92*	-	0.9	0.70*	0.85	0.7-0.9
GOLD III	1.82	1.3	0.86	1	III&IV: 1.75*	-	1.0	0.97*	1.34	1.1-1.3
GOLD IV	1	1.79	0.74	1		-	1.3	1.15*	2.00	1.2-2.0

Data are proportions and mean values (SD). "-" indicates data not available. * indicates data from placebo group.
GOLD guideline data was reported in the GOLD guidelines of 20138 and was based on the placebo-limbed data of the TORCH, UPLIFT and ECLIPSE studies.
Abbreviations: GOLD: Global initiative for chronic Obstructive Lung Disease

Exacerbation data distributed per GOLD stage

Exacerbation characteristics distributed per GOLD stage are shown in Table 5 (individual datasets) and Table 6 (overall means). When the severity of COPD increased (as measured with GOLD), the proportion of COPD patients with at least one or two exacerbations also increased, the exception being patients in GOLD stage IV in UNLOCK patients, which had a lower proportion compared to GOLD III on all these variables. Furthermore, differences between GOLD stages in patients with ≥ 1 or ≥ 2 exacerbation in the UNLOCK studies were not as high as reported in the LPCS (Table 6).

Table 6. Exacerbation characteristics distributed per GOLD stages: means of the large COPD studies, compared to mean of the UNLOCK studies

Characteristic	UNLOCK studies	Large COPD studies (LPCS)	Mean difference between UNLOCK-LPCS (95% CI)	p-value
Patients (N)	3028	14973		
≥1 exacerbations p/year distributed per GOLD stage				
GOLD I, % (n/N)	34.3 (11.7)	-	-	
GOLD II, % (n/N)	43 (14.1)	58.3 (17)	15.3 (-18.6—49.2)	0.28
GOLD III, % (n/N)	58.3 (17.5)	69 (16.1)	10.7 (-22.8—44.3)	0.33
GOLD IV, % (n/N)	54.3 (14.1)	71.7 (11.2)	17.4 (-7.3—42.1)	0.13
≥2 exacerbations p/y distributed per GOLD stage				
GOLD I, % (n/N)	12 (2.0)	-	-	
GOLD II, % (n/N)	21.3 (9.6)	22	15.3 (-18.6—49.2)	0.28
GOLD III, % (n/N)	32 (13.9)	33	10.7 (-22.8—44.3)	0.33
GOLD IV, % (n/N)	27.8 (9.7)	47	17.4 (-7.3—42.1)	0.13
Exacerbation rate distributed per GOLD stage				
GOLD I	0.55 (1)	-	-	
GOLD II	0.81 (0.3)	0.84 (1)	0.03 (-0.5—0.5)	0.85
GOLD III	1.25 (0.4)	1.27 (0.4)	0.02 (-0.7—0.7)	0.95
GOLD IV	1.13 (0.5)	1.55 (0.4)	0.42 (-0.32—1.16)	0.22

Data are overall mean values (SD), in which every dataset or study contributed equally to the overall means. "-" indicates data not available. 95%CI : 95% confidence interval. Abbreviations: GOLD: Global initiative for chronic Obstructive Lung Disease

Sensitivity analysis

We performed a sensitivity analysis on the UNLOCK datasets including only patients with GOLD stage II or above, in order to compare whether patients enrolled in the trials are similar to the more severe patients in primary care. There was no difference between the sensitivity analysis (Supporting Information Table 1) and Tables 2 and 4.

Selection for large COPD studies

The proportion of patients from primary care that would be eligible to be included in the LPCS ranged from 17% (TRISTAN trial) to 42% (ECLIPSE and UPLIFT study) (Table 7). The LPCS inclusion criteria of at least one exacerbation in the preceding year and an FEV_1 of < 60% predicted, excluded the largest proportion of primary care patients, as only 44% (≥ 1 exacerbation in previous year) and 39.3% (FEV_1≤ 60% predicted) of the patients, respectively, fulfilled these criteria.

Table 7. Percentage of patients remaining after introduction of different selection criteria used in six large COPD studies

Inclusion criteria	ISOLDE 2000	TRISTAN 2003	TORCH 2007	UPLIFT 2008	ECLIPSE 2010	POET-COPD 2011
Age	40-75 years	-	40-80 years	≥ 40 years	40-75 years	≥ 40 years
% of patients in primary care	77.2		89.9	99.7	77.2	99.7
FER	≤ 70%	≤ 70%	≤ 70%	≤ 70%	≤ 70%	≤ 70%
% of patients in primary care	93.2	93.2	93.2	93.2	93.2	93.2
FEV1	< 85%	25-70%	< 60%	≤ 70%	< 80%	≤ 70%
% of patients in primary care	83.4	57.9	39.3	59.3	76.5	59.3
Reversibility	≤ 10%	≤ 10%	≤ 10%	-	-	-
% of patients in primary care	78.4	78.4	78.4			
Smoking status	Current/ex-smoker	-	Current/ex-smoker	Current/ex-smoker	Current/ex-smoker	-
% of patients in primary care	82.3		82.3	82.3	82.3	
Pack years	-	≥ 10 pack years	≥ 10 pack years	≥ 10 pack years	≥ 10 pack years	≥ 10 pack years
% of patients in primary care		93	93	93	93	93
Exacerbation	-	≥ 1 exacerbation in previous year	-	-	-	≥ 1 exacerbation in previous year
% of patients in primary care		44				44
Total % of patients in primary care	**39**	**17**	**20**	**42**	**42**	**23**

DISCUSSION

This is the first study using a large international COPD primary care dataset from Europe to compare disease characteristics of primary care COPD patients with disease characteristics of COPD populations included in large pharmaceutically-sponsored COPD studies (the LPCS). We demonstrated there were clear differences in gender, age, distribution of GOLD stages, quality of life scores and exacerbation characteristics between COPD patients seen in primary care and included in the LPCS. As a result, the majority (58-83%) of COPD patients in primary care would not serve as a candidate for inclusion in these LPCS.

The present study provides insight into the disease characteristics of COPD in primary care, including the milder affected patients. According to GOLD guidelines[8], prevalence data on exacerbation rates in GOLD I were currently lacking in literature, whereas data on GOLD II-IV stages were based on selected COPD populations of the LPCS and were not validated in primary care. In the ECLIPSE study, Hurst et al. showed that the best predictor of exacerbations (across all GOLD stages) was an exacerbation history.[13] Interestingly, we determined that 12% of GOLD I patients in primary care were frequent exacerbators (≥ 2 exacerbations per year). Furthermore, we demonstrated 34% of GOLD I patients exacerbated at least once yearly. Since moderate COPD is more prevalent than very severe COPD, the overall burden of exacerbations in terms of FEV_1 decline, and the costs may be greater with milder disease.[13] On the other hand, physicians should be aware that the majority of mild COPD patients are often symptom free and often remain undiagnosed, as earlier demonstrated in the international BOLD and PLATINO studies.[36;37] It could be important to intervene at an early stage of the disease[38], but pharmacological intervention should in general be reserved for symptomatic patients or frequent exacerbators, whilst asymptomatic GOLD I patients can be offered non-pharmacological strategies, such as smoking cessation, aimed at preventing further worsening of the disease.

Interestingly, we demonstrated the majority of COPD patients in primary care would not serve as a candidate for inclusion in large pharmaceutically sponsored studies. As a result, primary care physicians are left to treat patients based on results derived from trials that their patients would not have been eligible to join. The economic impact of this low external validity potentially leads to considerable avoidable costs. Over-prescribing of inhaled steroids in primary care is described in various countries.[16;39-42] One recent UK primary care study concluded 38% of patients were over-treated regarding their GOLD stage, with considerable potential for harm and a mean extra per patient cost of £553.56/year.[41] This is in line with results of a Spanish primary care study, in which 18.2% of patients received inhalation therapy not meeting criteria for its use as recommended in guidelines, which was associated with lower physical health status and higher annual costs.[42] The revised GOLD 2013 guidelines acknowledge the lack of evidence concern-

ing anti-inflammatory and bronchodilator medications in patients with GOLD stage I and II.[8] Subsequent post-hoc analysis of the TORCH trial concluded that a combination of salmeterol and fluticasone propionate reduced exacerbations and FEV_1 decline in patients with a FEV_1 of 50-60% predicted.[28] However, that study was not specifically powered to show differences between GOLD stages and, as inclusion was restricted to FEV_1 of 60%, many GOLD II patients were not included. Subgroup analysis of UPLIFT showed promising results of tiotropium in GOLD II patients on FEV_1 decline[12], but inclusion was limited to patients with FEV1<70%, leading to incomplete representation of GOLD II. More research is needed to determine the effect of inhalation therapies in mild to moderate COPD patients, and we strongly encourage guideline makers to base their recommendations on primary care studies as well.

Our population based data reflect the recent tendency towards an increasing prevalence of COPD in women, drawing a different picture of the current COPD patient than the one represented in the LPCS. In fact, underrepresentation of women in large medical trials is not uncommon, resulting in a call in Nature for other journals, funding agencies and researchers to give women parity with men.[43] As the prevalence of COPD in women is rising, we advise future trialists to include not only milder COPD patients, but also more female participants, in order to study whether biological differences affect the way women respond to medications and therapeutic strategies.

Two studies published in 2005 and 2007 evaluated the external validity in COPD patients using smaller datasets.[5;6] Although their results are in line with our conclusions, there are some important differences. Herland et al. used a population of mixed obstructive lung disease and concluded that only 17% of these patients were eligible for inclusion in a typical COPD RCT; included COPD patients (n=366) were not classified according to GOLD criteria, but were graded using a 10-cm free-graded visual analogue scale which had to differentiate between asthma, COPD and mixed obstructive lung disease.[5] In the study of Travers et al., only 0-9% of COPD patients were eligible for inclusion based on the very strict criteria of trials conducted between 1994 and 2003.[6] It is likely that in more recent years less strict inclusion criteria were used for participation in a trial.

This study has several limitations that should be addressed. First, the current analysis of primary care COPD patients was restricted to seven datasets from four different countries in Europe; as a consequence, our data will probably not be representative for all primary care populations worldwide. Second, as there are differences in COPD patients between countries, there was considerable heterogeneity between populations in the different databases, with for example patients from the UK having more exacerbations per year and worse quality of life scores compared to Dutch patients. Although it would be interesting to further evaluate these differences between countries, the present study does not allow drawing firm conclusions about these differences. Perhaps this study will provide an useful starting point for further validation in a larger, more diverse

population of COPD patients across a multitude of different countries. Third, all individual datasets included baseline data collected in different designs of studies ranging from pragmatic clinical trials to real-life cohort studies. Irrespective of these varying designs, all studies had few or no exclusion criteria, making the dataset a reasonably representative sample of primary care populations in these countries. Fourth, as data were accessed retrospectively from different types of studies, some data were available on subsets of outcomes. As a result of heterogeneity and a low number of studies used for independent sample t-tests, on some outcomes mean differences were large and represented important findings, whilst showing no statistically significance. Therefore, the statistical tests performed in this study should be interpreted with caution. However, our aim was to provide illustrative findings rather than to be conclusive, and we assumed that our findings are based on a representative sample of primary care patients. In addition, we feel we provided an overall dataset large enough to make reliable comparisons with the LPCS, as we evaluated a similar number of included patients. Finally, another limitation is that, for comparison purposes, the present study compared primary care data to six LPCS. Although many other large COPD studies have been published over the years, we chose to evaluate the studies most frequently referred to in the guidelines, and published in the last decade.

CONCLUSION

This study provides an informative insight into COPD patient characteristics in primary care. Overall, compared to primary care patients, patients in large pharmaceutically sponsored trials were younger, predominantly male with worse lung function and worse quality of life scores. Our findings add to the literature, as we revealed hitherto unknown GOLD I exacerbation characteristics, showing 34% of mild patients had ≥1 exacerbations per year and 12% had ≥ 2 exacerbations per year. Additionally, the majority of patients seen in primary care would not be eligible to be included a large pharmaceutically sponsored trial. Therefore, more research is needed to determine the effect of pharmacological treatment in mild to moderate patients. Furthermore, we encourage future guideline makers to involve primary care populations in their recommendations as well.

REFERENCES

(1) Pierson DJ. Clinical practice guidelines for chronic obstructive pulmonary disease: a review and comparison of current resources. *Respiratory Care* 2006;51:277-288.

(2) Glaab T, Banik N, Rutschmann OT, Wencker M. National survey of guideline-compliant COPD management among pneumologists and primary care physicians. *COPD* 2006;3:141-148.

(3) Aisanov Z, Bai C, Bauerle O et al. Primary care physician perceptions on the diagnosis and management of chronic obstructive pulmonary disease in diverse regions of the world. *Int J Chron Obstruct Pulmon Dis* 2012;7:271-282.

(4) Salinas GD, Williamson JC, Kalhan R et al. Barriers to adherence to chronic obstructive pulmonary disease guidelines by primary care physicians. *Int J Chron Obstruct Pulmon Dis* 2011;6:171-179.

(5) Herland K, Akselsen JP, Skjonsberg OH, Bjermer L. How representative are clinical study patients with asthma or COPD for a larger "real life" population of patients with obstructive lung disease? *Respir Med* 2005;99:11-19.

(6) Travers J, Marsh S, Caldwell B et al. External validity of randomized controlled trials in COPD. *Respir Med* 2007;101:1313-1320.

(7) Rothwell PM. Factors that can affect the external validity of randomised controlled trials. *PLoS Clin Trials* 2006;1:e9.

(8) Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Available from: http://www.goldcopd.org. Accessed 2012 Dec 31

(9) Burge PS, Calverley PM, Jones PW, Spencer S, Anderson JA, Maslen TK. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. *BMJ* 2000;320:1297-1303.

(10) Calverley P, Pauwels R, Vestbo J et al. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 2003;361:449-456.

(11) Calverley PM, Anderson JA, Celli B et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007;356:775-789.

(12) Decramer M, Celli B, Kesten S, Lystig T, Mehra S, Tashkin DP. Effect of tiotropium on outcomes in patients with moderate chronic obstructive pulmonary disease (UPLIFT): a prespecified subgroup analysis of a randomised controlled trial. *Lancet* 2009;374:1171-1178.

(13) Hurst JR, Vestbo J, Anzueto A et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N Engl J Med* 2010;363:1128-1138.

(14) Vogelmeier C, Hederer B, Glaab T et al. Tiotropium versus salmeterol for the prevention of exacerbations of COPD. *N Engl J Med* 2011;364:1093-1103.

(15) Chavannes N, Stallberg B, Lisspers K et al. UNLOCK: Uncovering and Noting Long-term Outcomes in COPD to enhance knowledge. *Prim Care Respir J* 2010;19:408.

(16) Jones RC, Dickson-Spillmann M, Mather MJ, Marks D, Shackell BS. Accuracy of diagnostic registers and management of chronic obstructive pulmonary disease: the Devon primary care audit. *Respir Res* 2008;9:62.

(17) Chavannes NH, Grijsen M, van den Akker M et al. Integrated disease management improves one-year quality of life in primary care COPD patients: a controlled clinical trial. *Prim Care Respir J* 2009;18:171-176.

(18) Kruis AL, Boland MR, Schoonvelde CH et al. RECODE: Design and baseline results of a cluster randomized trial on cost-effectiveness of integrated COPD management in primary care. *BMC Pulm Med* 2013;13:17.

(19) Kocks J, de JC, Berger MY, Kerstjens HA, van der Molen T. Putting health status guided COPD management to the test: protocol of the MARCH study. *BMC Pulm Med* 2013;13:41.

(20) Tsiligianni IG, van der Molen T, Moraitaki D et al. Assessing health status in COPD. A head-to-head comparison between the COPD assessment test (CAT) and the clinical COPD questionnaire (CCQ). *BMC Pulm Med* 2012;12:20.

(21) Sundh J, Janson C, Lisspers K, Montgomery S, Stallberg B. Clinical COPD Questionnaire score (CCQ) and mortality. *Int J Chron Obstruct Pulmon Dis* 2012;7:833-842.

(22) Sundh J, Janson C, Lisspers K, Stallberg B, Montgomery S. The Dyspnoea, Obstruction, Smoking, Exacerbation (DOSE) index is predictive of mortality in COPD. *Prim Care Respir* J 2012;21:295-301.

(23) Dutch CCMO guidelines.(2013) Available from: http://www.ccmo-online.nl/main.asp?pid = 1&taal = 1. Accessed Jan 31 2014.

(24) Spencer S, Calverley PM, Burge PS, Jones PW. Impact of preventing exacerbations on deterioration of health status in COPD. *Eur Respir J* 2004;23:698-702.

(25) Jones PW, Willits LR, Burge PS, Calverley PM. Disease severity and the effect of fluticasone propionate on chronic obstructive pulmonary disease exacerbations. *Eur Respir J* 2003;21:68-73.

(26) Celli B, Vestbo J, Jenkins CR et al. Sex differences in mortality and clinical expressions of patients with chronic obstructive pulmonary disease. The TORCH experience. *Am J Respir Crit Care Med* 2011;183:317-322.

(27) Celli BR, Thomas NE, Anderson JA et al. Effect of pharmacotherapy on rate of decline of lung function in chronic obstructive pulmonary disease: results from the TORCH study. *Am J Respir Crit Care Med* 2008;178:332-338.

(28) Jenkins CR, Jones PW, Calverley PM et al. Efficacy of salmeterol/fluticasone propionate by GOLD stage of chronic obstructive pulmonary disease: analysis from the randomised, placebo-controlled TORCH study. *Respir Res* 2009;10:59.

(29) Vestbo J. The TORCH (towards a revolution in COPD health) survival study protocol. *Eur Respir J* 2004;24:206-210.

(30) Tashkin DP, Celli B, Senn S et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med* 2008;359:1543-1554.

(31) Agusti A, Calverley PM, Celli B et al. Characterisation of COPD heterogeneity in the ECLIPSE cohort. *Respir Res* 2010;11:122.

(32) Vestbo J, Anderson W, Coxson HO et al. Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE). *Eur Respir J* 2008;31:869-873.

(33) Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. *Thorax* 1999;54:581-586.

(34) Jones PW, Quirk FH, Baveystock CM. The St George's Respiratory Questionnaire. *Respir Med* 1991;85 Suppl B:25-31.

(35) van der Molen T, Willemse BW, Schokker S, ten Hacken NH, Postma DS, Juniper EF. Development, validity and responsiveness of the Clinical COPD Questionnaire. *Health Qual Life Outcomes* 2003;1:13.

(36) Menezes AM, Perez-Padilla R, Jardim JR et al. Chronic obstructive pulmonary disease in five Latin American cities (the PLATINO study): a prevalence study. *Lancet* 2005;366:1875-1881.

(37) Buist AS, McBurnie MA, Vollmer WM et al. International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. *Lancet* 2007;370:741-750.

(38) Rabe KF, Wedzicha JA. Controversies in treatment of chronic obstructive pulmonary disease. *Lancet* 2011;378:1038-1047.

(39) Miravitlles M, de la Roza C, Naberan K, Lamban M, Gobartt E, Martin A. Use of spirometry and patterns of prescribing in COPD in primary care. *Respir Med* 2007;101:1753-1760.

(40) Bourbeau J, Sebaldt RJ, Day A et al. Practice patterns in the management of chronic obstructive pulmonary disease in primary practice: the CAGE study. *Can Respir J* 2008;15:13-19.

(41) White P, Thornton H, Pinnock H, Georgopoulou S, Booth HP. Overtreatment of COPD with inhaled corticosteroids--implications for safety and costs: cross-sectional observational study. *PLoS One* 2013;8:e75221.

(42) de Miguel-Diez J, Carrasco-Garrido P, Rejas-Gutierrez J et al. Inappropriate overuse of inhaled corticosteroids for COPD patients: impact on health costs and health status. *Lung* 2011;189:199-206.

(43) Kim AM, Tingen CM, Woodruff TK. Sex bias in trials and treatment must end. *Nature* 2010;465:688-689.

Table S1. Sensitivity analysis on UNLOCK patients with GOLD stage II or above; comparison with large COPD studies, including independent sample t-tests.

Characteristic	UNLOCK studies	Large COPD studies (LPCS)	Mean difference between UNLOCK – LPCS (95% CI)	p-value
Patients (N)	3508	23860		
Age, years	66.3 (2.3)	63.7 (0.9)	-2.6 (-4.8—-0.4)	0.03*
Male, %	59.6 (16.2)	73.3 (4.1)	13.7 (-1.3—28.8)	0.07
Current smokers, %	42.4 (9.1)	40.7 (8.6)	-1.7 (4.9—-12.5)	0.73
Pack years	43.6 (13.5)	44.9 (4)	1.3 (-15.2—17.8)	0.84
BMI, kg/m2	26.2 (0.5)	25.6 (0.9)	-0.6 (-2—0.7)	0.28
Postbronchodilator FEV1, % predicted	57 (5.4)	47.4 (2.4)	-9.6 (-14.8— -4.4)	<0.01*
FEV1:FVC, %	53.5 (1.6)	46.5 (4)	-7 (-11.9—-2.1)	0.01*
GOLD distribution				
Moderate GOLD II	68.7 (12.5)	45 (6.3)	-23.7 (-36—11.3)	<0.01*
Severe GOLD III	25.6 (44.5)	44.5 (3.1)	18.9 (9.5—28.2)	<0.01*
Very severe GOLD IV	6.6 (5)	11.5 (3.5)	4.9 (-1.4—11.1)	0.11
Patient-reported outcomes				
SGRQ	35.1 (5.8)	48.4 (1.9)	13.3 (4.5—22.2)	0.02*
CCQ (mean)	1.7 (0.3)	-		
MRC (mean)	2.1 (0.8)	2.7	0.6 (-1.8—3)	0.54
MRC score > 2 (%)	32.3 (18.9)	51.5 (2.1)	19.2 (-4.11—42.4)	0.09
Exacerbation-related outcomes				
Mean exacerbation rate p/yr	1.0 (0.3)	1.2 (0.4)	0.2 (-0.4—0.8)	0.39
≥1 exacerbation in preceding yr	48 (14)	58.8 (9)	10.7 (-10.6—32)	0.25
≥2 exacerbation in preceding yr	24.8 (10.6)	30.5 (2.1)	5.7 (-10.6—22)	0.37

CHAPTER 3

Potential benefits of integrated COPD management in primary care

Annemarije L. Kruis and Niels H. Chavannes

Monaldi Arch Chest Dis 2010;73(3):130-134

ABSTRACT

Chronic obstructive pulmonary disease (COPD) represents a major and progressive cause of morbidity and mortality worldwide, resulting in an important financial and health burden in coming decades. Pulmonary rehabilitation (PR) has been proven to be the most effective treatment in all patients in whom respiratory symptoms are associated with diminished functional capacity or reduced quality of life. Nevertheless, despite wide recommendation and proven efficacy, the use of PR is limited in daily practice. Reasons for these include low accessibility and availability, high costs, and lack of motivation to continue a healthy life style after treatment. By contrast, it has been demonstrated that primary care patients can be reactivated by formulating personal targets and designing individualized treatment plans in collaboration with their general practitioner or practice nurse. Based on these personal plans and targets, specific education must be provided and development of self management skills should be actively encouraged. Ideally, elements of pulmonary rehabilitation are tailored into a comprehensive primary care integrated disease management program. In that way, the benefits of PR can be extended to a substantially larger part of the COPD population, to reach even those with milder stages of disease. Favorable long-term effects on exercise tolerance and quality of life in a number of studies have been demonstrated in recent years, but broad introduction in the primary care setting still needs further justification in the form of a proper (cost) effectiveness analysis.

BACKGROUND

COPD is a smoke-related disease, characterized by largely irreversible airflow obstruction. Patients suffer from variable grades of impaired quality of life and the disease is often complicated by co-morbidities, making it one of the more complex chronic diseases seen by general practitioners.

Because of the complexity of the disease, diagnostic problems are common: symptoms are not always recognised by patients and health care workers, and patients greatly underestimate the severity of their disease.[1] Moreover, when diagnosed, patients frequently receive insufficient treatment.[2]

COPD forms a major cause of chronic morbidity and mortality worldwide and, according to the WHO, will be the third leading cause of death in 2030.[3] Given the rise in incidence, COPD constitutes an important financial and health burden in coming decades.

The most effective non-pharmacological and pharmacological treatment, besides smoking cessation, is pulmonary rehabilitation (PR), which has been widely recommended.[4;5] PR refers to an integrated, multidisciplinary treatment of COPD, aiming at reducing dyspnoea and symptoms. Integrated into the treatment of the patient, PR is designed to optimize functional status, increase participation and reduce healthcare costs. Ideally, PR programs are individually tailored and designed to promote education and self-management skills in combination with personal exercise training.[4] Beneficial effects are well established in severe to very severe patients[6], and significant improvements in exercise capacity, dyspnoea and health-related quality of life have been reported.[7-10] Nevertheless, despite proven efficacy and wide recommendation[4;5;11;12], PR is still not available in the vast majority of cases.

CAPACITY PROBLEMS

Even though the benefits of PR are widely established, daily use is limited. There are several reasons for this.

First, access is poor and services are frequently unavailable for patients who would benefit from PR programs.[13] Overall, admission to a program is only considered for a small proportion of the COPD population, usually the most severely affected patients.

A disequilibrium between demand and supply of PR services is the result, and consequently, health care workers are confronted with capacity problems.[13] As a striking example, it was concluded in a UK survey that only 1% of the COPD population had access to a PR program.[14] These results are confirmed in a more recent Canadian study, where it was found that only 1.2% of the COPD population was able to follow a PR program.[15] Availability of PR programs at hospital settings differs considerably among countries.

A survey across North America, Europe and Japan in 1999 indicated that PR programs were available at 56% of hospitals in North America and 74% in Europe, but at only 20% of hospitals in Tokyo.[16]

Second, due to its highly specialized setting, PR programs are costly (but cost-effective) interventions: each rehabilitation program (maximum of 20 patients) has been calculated to cost £12.120, equalling approximately €14.280 per patient.[17] As a result of these high costs, services have often been available for those patients in whom quality of life has already deteriorated to a large extent only, and prognosis is dire.

Generally speaking, it is considered a "last-ditch" effort for patients with only the most severe forms of COPD.[18] This is in contrast with the American Thoracic Society/European Respiratory Society (ATS/ERS) Statement on Pulmonary Rehabilitation and recent GOLD Guidelines, that actually recommend PR for all patients in whom respiratory symptoms are associated with diminished functional capacity or reduced quality of life.[4;19] This recommendation is backed up by results of earlier studies, where PR has been proven to be effective, regardless of disease severity.[20;21] In fact, especially improvements in milder stages of disease could slow down disease progression considerably. In addition, exercise training on its own, which forms one of the major component of PR, has shown improvements in fitness of mild to moderate COPD patients.[22]

A third problem with PR is the fact that it usually consists of a separate program running parallel to standard care. Furthermore, it is only administered during a limited period of time. Patients are frequently not motivated to continue a more active and healthy life style after returning home, and benefits usually dissolve over time. Ideally, when the general practitioner and/or practice nurse would be involved in the PR program, they could partake in counteracting this imminent lack of motivation, and could support the patient in maintaining physical exercise training on a daily basis. In reality, primary physicians are rarely involved in rehabilitative efforts, and as a result, largely unable to support program methods or integrate the program into their plans of continuous care.[23] What is needed for a successful long term effective intervention, accessible for all eligible patients in primary care, is to integrate the tools of PR into standard care, as was also suggested before by other authors[18;23;24], which will likely lead to substantial cost reduction. Our case would gain strength when it would no longer be doubted that home-based or outreaching PR programs can in fact be as efficacious as more traditional inpatient programs, and would be considered an equivalent alternative in less severe patients.[7;25]

REACTIVATION

In chronic disease conditions, patients not uncommonly express feelings of helplessness, negatively colored thoughts and a diminished belief in a useful and worthwhile future. Anxiety and depression appear frequently, and can even occur in mildly affected patients.[26] Illness perceptions in COPD patients have been proven to influence their quality of life: increased attention to symptoms, less positive beliefs about the effects and outcomes of illness and strong emotional reactions to the illness have found to be associated with lower quality of life scores.[27] In the same way, patients with a current depression, previous history of alcohol dependency and those who perceive that their actions have a low influence over their disease course may have difficulty with learning and applying self-management plans.[28]

In COPD, there is a saddening lack of communication between healthcare providers and patients. As a striking example, up to 50% of COPD exacerbations are not reported to healthcare providers.[29] This troublesome lack of communication could be the result of the negative spiral of dyspnoea, deconditioning and social deprivation that COPD patients find themselves in.[30] Through their daily decisions about taking medication, applying self-measurements and performing exercise, people with chronic diseases play a central role in determining the course of their disease.[31;32] Because suboptimal adherence is associated with a significant health and economic burden in patients with COPD[33], efforts must be aimed at changing an attitude of perceived helplessness into an active approach, in order to break through this negative spiral. In other words, acquiring and applying self-management skills for an individual patient should be a crucial part of our treatment plan.

Ideally, patients and health care providers constitute partners in disease management, in order to take better control over daily symptoms and management. In these continuous decision-making processes, a clearly formulated written action plan in combination with approachable and committed health care providers can be a helpful and reliable instrument. The concept of written action plans is based on their successful application in asthma patients, where programs that enable people to adjust their medication dosage using a written action plan appear to be more effective than other forms of asthma self-management.[34] In COPD however, pharmacological treatment is considerably less effective than in asthma patients. Nevertheless, it has been demonstrated that action plans can be helpful in guiding COPD patients to recognize and react appropriately to an exacerbation, even in cases where limited COPD education is provided.[35] In practice, patients must be trained in adequate symptom recognition and encouraged to state individual goals for the coming six months, which should then be put on record. Information provided by general practitioners or practice nurses through different stages of disease must be directed to these goals and can result in an individualized treatment

plan, designed realistically in collaboration with the patient. When written and signed by the patient, patients will gain a greater feeling of self-efficacy and increase involvement to achieve these targets. For example, when the personal goal is formulated as 'to go biking for 30 minutes every other day' or 'play in the park with my grandchildren during weekends, without acute hindrance by feelings of breathlessness', efforts must be made to maximize exercise tolerance. If the target is 'to quit smoking within two weeks', different smoking cessation therapies and behavioral guidance strategies must be explored. When goals are chosen that are close to one's beliefs, needs and personal situation, the impact will be greater.

General practitioners and nurse practitioners have a unique position: they are often familiar with the patients' habitat, are easily involved in one's family situation and patients usually report a great trust in their general practitioner. It is essential for partners and relatives to be involved as they can offer support in achieving desired prospects in future. In keeping goals simple, realistic, relevant for daily life and patient-driven, patients' self-efficacy will be supported and, as a result, intrinsic motivation will increase. In formulating these relevant and realistic goals, modern techniques such as *motivational interviewing* can be very useful, but require additional training of practice nurses and/or other health personnel.[36]

Self-management is a 'hot topic' in current COPD management, and an increasing number of healthcare professionals agree that patients suffering of a chronic disease should receive support to help them self-manage their disease as effectively as possible.[32] A well informed patient will be better enabled to make his or her own decisions and can assist in maintaining healthy behaviours during different stages and complications when disease progresses.[32] Self-management education has proven to be effective as it increases knowledge and enhances self-confidence.[37] Furthermore, proper self-management is associated with a reduction in COPD-related hospital admissions.[38]

INTEGRATED DISEASE MANAGEMENT PROGRAMMES IN PRIMARY CARE

At present, the majority of COPD patients present themselves in a primary care setting, of which an estimated 80% are suffering from mild to moderate disease (see Table 1).

The World Health Organisation promotes primary care as the most viable cost-effective setting to combat non-communicable diseases on a global scale[39], anticipating a substantial need for chronic disease-management in coming decades. Due to the resulting large-scale shift of COPD patients from secondary and tertiary care to primary care, general practitioners and practice nurses find themselves at a focal point in the organisation of care for COPD patients.

Table 1 Current and expected rise in prevalence according to GOLD stage in the Dutch COPD population.

Gold stage	Characteristics	Current prevalence and expected rise in coming decade		
I Mild	FEV1/FVC < 0.7 FEV1 > 80%	28%	®	+ 120%
II Moderate	FEV1/FVC < 0.7 50% ≤ FEV1 < 80%	54%	®	+ 27%
III Severe	FEV1/FVC < 0.7 30% ≤ FEV1 < 50%	15%	®	+ 30%
IV Very severe	FEV1/FVC < 0.7 FEV1 < 30%	3%	®	+ 120%

FEV1: Forced Expiratory Volume in 1 second. FVC: Forced Vital Capacity.
Modified from: Smeele IJ, van Weel C, van Schayck CP, van der Molen T, Thoonen B, Schermer T et al. Dutch College of General Practitioners Guideline for COPD Diagnosis. Huisarts Wet 2007;50(8):362-79.

COPD remains a complex disease to treat. Multidisciplinary collaboration can improve diagnosis and management of COPD in primary care.[40] To establish a program of interventions based on individual needs and strengths, sufficient cooperation within several disciplines in primary care and collaboration with secondary and tertiary care is necessary. As a result, a multidisciplinary team should be formed, in which different health care workers participate and contribute to the required care in their field of expertise, e.g. physiotherapists, general practitioners, pulmonary physicians, dieticians and practice nurses. Patients are at a central position and their role in achieving success is decisive. An integrated disease management (IDM) program, where the elements of PR are integrated into a tailor-made program consisting of self-management, regular exercise and individualized targets, can effectively introduce certain elements of pulmonary rehabilitation into the large population that can be reached by primary care (see Figure 1). Patients are managed in their own home-setting, making the benefits accessible for all COPD patients eligible. It is likely that costs will be lower while patients are helped at an earlier stage, possibly reducing decline and disease progression in the long term.[41]
In past few years, we have demonstrated favourable results in applying primary care integrated disease management (IDM) programs. In the Picasso Bocholtz study, 150 primary care patients were followed up for two years during which the intervention group received an IDM program and the control group received usual care. The program consisted of exacerbation management, physical reactivation, and optimal medication. After one year, the results revealed a significant and clinically relevant improvement of quality of life in favour of the IDM group, being strongest in patients with MRC-dyspnoea score >2.[41] The long-term results of this study are expected soon.
Based on the experiences of this study, the Kroonluchter disease management program was initiated in Rotterdam, the Netherlands. In this implementation programme, over 200 primary care COPD patients have been treated since 2005, aimed at tailored COPD

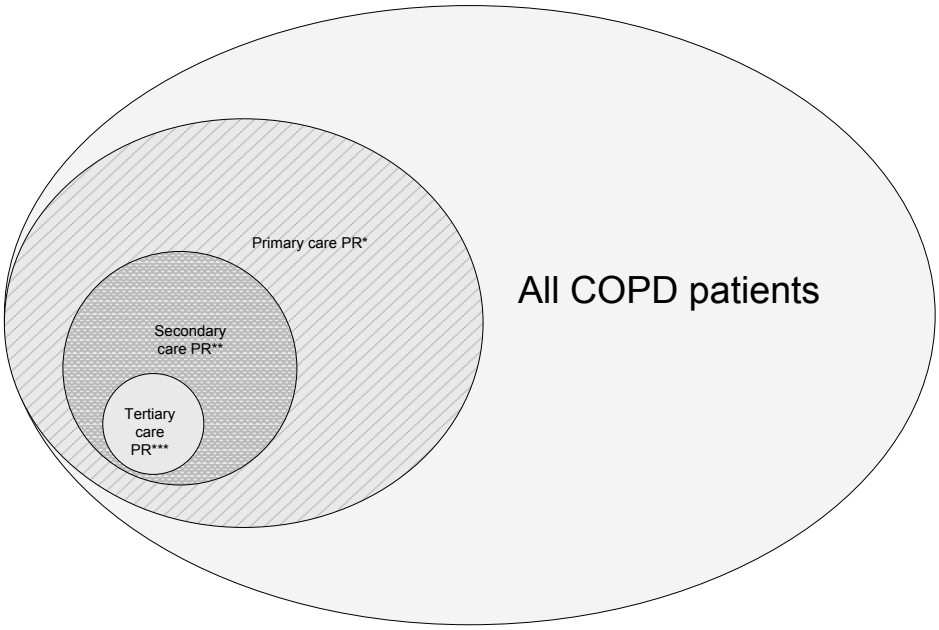


Figure 1. Estimated yield of patients with potential benefits of pulmonary rehabilitation
PR = pulmonary rehabilitation
* Proportion of potential COPD patients that could benefit from PR in primary care
** Proportion of COPD patients referred to secondary care PR for workup and guidance
*** Proportion of COPD patients referred to intensive tertiary care PR programs.

rehabilitation in primary care. Depending on their individual disease burden, patients may receive optimization of their medication by their primary care physician, a tailored 6-month specific training program with a physiotherapist, or medication compliance monitoring and repeated inhalation instruction by a pharmacist. Drop out rates are very low (12%) and the majority of participants report perceptible and measurable improvements in exercise tolerance after two years follow-up. Furthermore, a strong collaboration has developed between primary care providers, patients and secondary care.[30] These results are consistent with another two-year randomized controlled trial, the INTERCOM study, in which patients were included with less advanced airflow obstruction but impaired exercise capacity. In this study, the intervention group received exercise training, education, nutritional therapy and smoking cessation counselling in a community-based, multidisciplinary setting. Quality of life, functional exercise capacity, and breathlessness remained significantly favourable in the intervention group versus usual care over the entire two-year intervention.[42]

Despite encouraging results in earlier studies as described above, more research is needed. We recommend large pragmatic randomized controlled trials, addressing the costs and long-term clinical effectiveness of an IDM program in primary care.

CONCLUSION

PR has proven to be the most effective treatment for COPD patients[4;5;11;12], but its use in daily practice is limited due to low availability and accessibility, high costs and short duration of administration.[13-17] When a program is provided where the elements of PR are integrated into a tailor-made program consisting of proper self-management, regular exercise and based on individualized targets, people can be managed in their home environment, while primary care providers are more involved and in the position to coach this process directly.[41] Training in motivational interviewing techniques is a prerequisite to actively include personal goals and stimulate the patients' intrinsic motivation. Our aim should be to make the benefits of PR available to the large population of eligible COPD patients, and possibly diminish disease progression in less severe patients at an earlier stage. Encouraging results have been published[30;41;43], but more research is needed in the form of a proper cost-effectiveness analysis.

REFERENCES

(1) Rennard S, Decramer M, Calverley PM et al. Impact of COPD in North America and Europe in 2000: subjects' perspective of Confronting COPD International Survey. *Eur Respir J* 2002;20:799-805.

(2) Barr RG, Celli BR, Martinez FJ et al. Physician and patient perceptions in COPD: the COPD Resource Network Needs Assessment Survey. *Am J Med* 2005;118:1415.

(3) World Health Organization. World Health Statistics 2008. Geneva Switzerland, World Health Organization 2008.

(4) Nici L, Donner C, Wouters E et al. American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation. *Am J Respir Crit Care Med* 2006;173:1390-1413.

(5) Rabe KF, Hurd S, Anzueto A et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 2007;176:532-555.

(6) Lacasse Y, Martin S, Lasserson TJ, Goldstein RS. Meta-analysis of respiratory rehabilitation in chronic obstructive pulmonary disease. A Cochrane systematic review. *Eura Medicophys* 2007;43:475-485.

(7) Maltais F, Bourbeau J, Shapiro S et al. Effects of home-based pulmonary rehabilitation in patients with chronic obstructive pulmonary disease: a randomized trial. *Ann Intern Med* 2008;149:869-878.

(8) Wijkstra PJ, Strijbos JH, Koeter GH. Home-based rehabilitation for patients with COPD: organization, effects and financial implications. *Monaldi Arch Chest Dis* 2000;55:130-134.

(9) Strijbos JH, Postma DS, van Altena R., Gimeno F, Koeter GH. A comparison between an outpatient hospital-based pulmonary rehabilitation program and a home-care pulmonary rehabilitation program in patients with COPD. A follow-up of 18 months. *Chest* 1996;109:366-372.

(10) Man WD, Polkey MI, Donaldson N, Gray BJ, Moxham J. Community pulmonary rehabilitation after hospitalisation for acute exacerbations of chronic obstructive pulmonary disease: randomised controlled study. *BMJ* 2004;329:1209.

(11) Lacasse Y, Goldstein R, Lasserson TJ, Martin S. Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2009;CD003793.

(12) Nici L, Raskin J, Rochester CL et al. Pulmonary rehabilitation: WHAT WE KNOW AND WHAT WE NEED TO KNOW. *J Cardiopulm Rehabil Prev* 2009;29:141-151.

(13) Landry MD, Hamdan E, Al MS, Brooks D. The precarious balance between 'supply' and 'demand' for health care: the increasing global demand for rehabilitation service for individuals living with chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis* 2008;3:393-396.

(14) Yohannes AM, Connolly MJ. Pulmonary rehabilitation programmes in the UK: a national representative survey. *Clin Rehabil* 2004;18:444-449.

(15) Brooks D, Sottana R, Bell B et al. Characterization of pulmonary rehabilitation programs in Canada in 2005. *Can Respir J* 2007;14:87-92.

(16) Kida K, Jinno S, Nomura K, Yamada K, Katsura H, Kudoh S. Pulmonary rehabilitation program survey in North America, Europe, and Tokyo. *J Cardiopulm Rehabil* 1998;18:301-308.

(17) Griffiths TL, Phillips CJ, Davies S, Burr ML, Campbell IA. Cost effectiveness of an outpatient multidisciplinary pulmonary rehabilitation programme. *Thorax* 2001;56:779-784.

(18) Zuwallack R, Hedges H. Primary care of the patient with chronic obstructive pulmonary disease-part 3: pulmonary rehabilitation and comprehensive care for the patient with chronic obstructive pulmonary disease. *Am J Med* 2008;121:S25-S32.

(19) Rabe KF, Hurd S, Anzueto A et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 2007;176:532-555.
(20) Berry MJ, Rejeski WJ, Adair NE, Zaccaro D. Exercise rehabilitation and chronic obstructive pulmonary disease stage. *Am J Respir Crit Care Med* 1999;160:1248-1253.
(21) Takigawa N, Tada A, Soda R et al. Comprehensive pulmonary rehabilitation according to severity of COPD. *Respir Med* 2007;101:326-332.
(22) Chavannes N, Vollenberg JJ, van Schayck CP, Wouters EF. Effects of physical activity in mild to moderate COPD: a systematic review. *Br J Gen Pract* 2002;52:574-578.
(23) Tiep BL. Disease management of COPD with pulmonary rehabilitation. *Chest* 1997;112:1630-1656.
(24) Tiep B, Barnett MC. Disease Management for Chronic Obstructive Pulmonary Disease. A Clinical Strategy. *Dis Manage Health Outcomes* 2008;16:305-313.
(25) Vieira DS, Maltais F, Bourbeau J. Home-based pulmonary rehabilitation in chronic obstructive pulmonary disease patients. *Curr Opin Pulm Med* 2010;16:134-143.
(26) Maurer J, Rebbapragada V, Borson S et al. Anxiety and depression in COPD: current understanding, unanswered questions, and research needs. *Chest* 2008;134:43S-56S.
(27) Scharloo M, Kaptein AA, Schlosser M et al. Illness perceptions and quality of life in patients with chronic obstructive pulmonary disease. *J Asthma* 2007;44:575-581.
(28) Dowson CA, Town GI, Frampton C, Mulder RT. Psychopathology and illness beliefs influence COPD self-management. *J Psychosom Res* 2004;56:333-340.
(29) Seemungal TA, Donaldson GC, Bhowmik A, Jeffries DJ, Wedzicha JA. Time course and recovery of exacerbations in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000;161:1608-1613.
(30) Chavannes N. Integrated Chronic Obstructive Pulmonary Disease Management in Primary Care. *Dis Manage Health Outcomes* 2008;16:315-318.
(31) Holman H, Lorig K. Patient self-management: a key to effectiveness and efficiency in care of chronic disease. *Public Health Rep* 2004;119:239-243.
(32) Bourbeau J, van der Palen J. Promoting effective self-management programmes to improve COPD. *Eur Respir J* 2009;33:461-463.
(33) Bourbeau J, Bartlett SJ. Patient adherence in COPD. *Thorax* 2008;63:831-838.
(34) Gibson PG, Powell H, Coughlan J et al. Self-management education and regular practitioner review for adults with asthma. *Cochrane Database Syst Rev* 2009;CD001117.
(35) Walters JA, Turnock AC, Walters EH, Wood-Baker R. Action plans with limited patient education only for exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2010;5:CD005074.
(36) Robinson A, Courtney-Pratt H, Lea E et al. Transforming clinical practice amongst community nurses: mentoring for COPD patient self-management. *J Clin Nurs* 2008.
(37) Effing T, Monninkhof EM, van der Valk PD et al. Self-management education for patients with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2007;CD002990.
(38) Bourbeau J, Julien M, Maltais F et al. Reduction of hospital utilization in patients with chronic obstructive pulmonary disease: a disease-specific self-management intervention. *Arch Intern Med* 2003;163:585-591.
(39) World Health Organization. 2008-2013 Action Plan for the Global Strategy for the Prevention and Control of Noncommunicable Diseases. 2008. Geneva, Switzerland, WHO Document Production Services.

(40) Schermer T, van WC, Barten F et al. Prevention and management of chronic obstructive pulmonary disease (COPD) in primary care: position paper of the European Forum for Primary Care. *Qual Prim Care* 2008;16:363-377.

(41) Chavannes NH, Grijsen M, van den Akker M et al. Integrated disease management improves one-year quality of life in primary care COPD patients: a controlled clinical trial. *Prim Care Respir J* 2009;18:171-176.

(42) van Wetering CR, Hoogendoorn M, Mol SJ, Rutten-van Molken MP, Schols AM. Short- and long-term efficacy of a community-based COPD management programme in less advanced COPD: a randomised controlled trial. *Thorax* 2010;65:7-13.

(43) van Wetering CR, van Nooten FE, Mol SJ, Hoogendoorn M, Rutten-van Molken MP, Schols AM. Systemic impairment in relation to disease burden in patients with moderate COPD eligible for a lifestyle program. Findings from the INTERCOM trial. *Int J Chron Obstruct Pulmon Dis* 2008;3:443-451.

PART 2

The effectiveness of integrated disease management in COPD patients

CHAPTER 4

Integrated disease management interventions for chronic obstructive pulmonary disease

Annemarije L. Kruis, Nynke Smidt, Willem J.J. Assendelft, Jacobijn Gussekloo, Melinde R.S. Boland, Maureen P.H.M. Rutten-van Mölken, Niels H. Chavannes

Cochrane Database Syst Rev 2013;10:CD009437
Thorax 2014. doi: 10.1136/thoraxjnl-2013-20497

ABSTRACT

Background

In people with chronic obstructive pulmonary disease (COPD) there is considerable variation in symptoms, limitations and well-being, which often complicates medical care. To improve quality of life (QoL) and exercise tolerance, while reducing the number of exacerbations, a multidisciplinary program including different elements of care is needed.

Objectives

To evaluate the effects of integrated disease management (IDM) programs or interventions in people with COPD on health-related QoL, exercise tolerance and number of exacerbations.

Search methods

We searched the Cochrane Airways Group Register of trials, CENTRAL, MEDLINE, EMBASE and CINAHL for potentially eligible studies (last searched 12 April 2012).

Selection criteria

Randomized controlled trials evaluating IDM programs for COPD compared with controls were included. Included interventions consisted of multidisciplinary (two or more health care providers) and multi-treatment (two or more components) IDM programs with a duration of at least three months.

Data collection and analysis

Two review authors independently assessed trial quality and extracted data; if required, we contacted authors for additional data. We performed meta-analyses using random-effects modeling. We carried out sensitivity analysis for allocation concealment, blinding of outcome assessment, study design and intention-to-treat analysis.

Main results

A total of 26 trials involving 2997 people were included, with a follow-up ranging from 3 to 24 months. Studies were conducted in 11 different countries. The mean age of the included participants was 68 years, 68% were male and the mean forced expiratory volume in one second (FEV1)% predicted value was 44.3% (range 28% to 66%). Participants were treated in all types of healthcare settings: primary (n = 8), secondary (n = 12), tertiary care (n = 1), and in both primary and secondary care (n = 5). Overall, the studies were of high to moderate methodological quality.

Compared with controls, IDM showed a statistically and clinically significant improvement in disease-specific QoL on all domains of the Chronic Respiratory Questionnaire after 12 months: dyspnea (mean difference (MD) 1.02; 95% confidence interval (CI) 0.67 to 1.36); fatigue (MD 0.82; 95% CI 0.46 to 1.17); emotional (MD 0.61; 95% CI 0.26 to 0.95) and mastery (MD 0.75; 95% CI 0.38 to 1.12). The St. George's Respiratory Questionnaire (SGRQ) for QoL reached the clinically relevant difference of four units only for the impact domain (MD -4.04; 95% CI -5.96 to -2.11, P < 0.0001). IDM showed a significantly improved disease-specific QoL on the activity domain of the SGRQ: MD -2.70 (95% CI -4.84 to -0.55, P = 0.01). There was no significant difference on the symptom domain of the SGRQ: MD -2.39 (95% CI -5.31 to 0.53, P = 0.11). According to the GRADE approach, quality of evidence on the SGRQ was scored as high quality, and on the CRQ as moderate quality evidence. Participants treated with an IDM program had a clinically relevant improvement in six-minute walking distance of 43.86 meters compared with controls after 12 months (95% CI 21.83 to 65.89; P < 0.001, moderate quality). There was a reduction in the number of participants with one or more hospital admissions over three to 12 months from 27 per 100 participants in the control group to 20 (95% CI 15 to 27) per 100 participants in the IDM group (OR 0.68; 95% CI 0.47 to 0.99, P = 0.04; number needed to treat = 15). Hospitalization days were significantly lower in the IDM group compared with controls after 12 months (MD -3.78 days; 95% CI -5.90 to -1.67, P < 0.001). Admissions and hospital days were graded as high quality evidence. No adverse effects were reported in the intervention group. No difference between groups was found on mortality (OR 0.96; 95%CI 0.52 to 1.74). There was insufficient evidence to refute or confirm the long term effectiveness of IDM.

Authors' conclusions

In these COPD participants, IDM not only improved disease-specific QoL and exercise capacity, but also reduced hospital admissions and hospital days per person.

BACKGROUND

Description of the condition

Chronic obstructive pulmonary disease (COPD) is a heterogeneous, systemic condition characterized by restricted airflow which is not fully reversible. It is a major cause of morbidity, due to the ageing of the world's population and the continued use of tobacco and exposure to indoor biomass pollution. The prevalence of COPD is expected to increase substantially in the coming decades (Lopez 2006; GOLD 2009). According to the World Health Organization (WHO), COPD will be the third leading cause of death in 2020 (Lopez 2006; WHO 2008). Given the rise in prevalence, COPD has important financial consequences, with high reported direct costs (healthcare resources, medication prescriptions) and indirect costs (absence from paid work, consequences of disability) (Britton 2003).

Optimal management of COPD is complex, as it is a multi-component disease. Clinical, functional and radiological presentation varies greatly from patient to patient, despite having a similar degree of airflow limitation (Wedzicha 2000; GOLD 2009; Agusti 2010). Evidence suggests that the previous 2007 Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification of disease severity, solely based upon the degree of airflow limitation, is a poor predictor of other important negative features of COPD (Agusti 2010; Burgel 2010).

Health-related quality of life (HRQoL) and exercise tolerance may be more important to people with COPD than the more traditional measure of lung function. This is because COPD has a profound impact on HRQoL and exercise tolerance, even in those with modest airflow limitation (Engstrom 1996). Furthermore, impaired HRQoL (Domingo-Salvany 2002; Fan 2002; Martinez 2006) and exercise tolerance (Gerardi 1996; Pinto-Plata 2004) have been associated with an increased risk of mortality (Cote 2009).

In addition, some people are more prone than others to episodes of acute exacerbations, which are an important cause of morbidity, mortality, hospital admission and impaired health status (Seemungal 1998; Wedzicha 2000; Calverley 2003). Although exacerbations become more severe and occur more frequently with increased severity of COPD, this is not always the case. There is some evidence for a 'frequent-exacerbation' phenotype (or group of people) that exacerbate more often than would be expected given their 'severity' as predicted by lung function testing (Hurst 2010).

Episodes of exacerbations are often not reported by patients to health care providers (Seemungal 2000). An important reason for patients' delay in reporting an increase in symptoms to their doctor is the fear of being sent to hospital. This passive behavior can eventually lead to a respiratory crisis, indeed necessitating urgent referral. In order to break through the self reinforcing negative spiral of dyspnoea, deconditioning and social deprivation doctors need to collaborate with their patients, with a focus on self

management skills: "if symptoms increase, you need to let us know rapidly to prevent further worsening" (Chavannes 2008). In viewing COPD as a disease process with a clinical, heterogeneous picture of progressive deterioration, an integrated system of care could be built on a disease management model. Ideally, it is based on active self management to slow down progression of the disease, including daily self care, patient-physician collaboration and exacerbation management. Information should be tailored to the person's needs, knowledge level and clinical profile and be accessible by the patient when they need it most (Tiep 1997; Bourbeau 2013).

Description of the intervention

In the last decade, the concept of integrated disease management (IDM) was introduced as a mean of improving quality and efficiency of care. IDM interventions are aimed at reducing symptoms and avoiding fragmentation of care, while containing costs. Therefore, IDM programs are generally believed to be cost-effective, but the available evidence is inconclusive. Several systematic reviews have shown positive results, at least for some outcomes of chronic IDM, in people with chronic heart failure (Gonseth 2004; Roccaforte 2005), diabetes (Norris 2002; Knight 2005; Pimouguet 2010) and depression (Badamgarav 2003; Neumeyer-Gromen 2004).

However, there is no consensus in the literature about the definition of IDM. Several definitions have been proposed since the introduction of the concept 'disease management'. In order to facilitate the communication between researchers, policy makers and IDM program leaders, Schrijvers proposed a definition, based on earlier reported definitions (Care Continuum Alliance; Dellby 1996; Epstein 1996; Ellrodt 1997; Zitter 1997; Weingarten 2002; Faxon 2004): *"Disease management consists of a group of coherent interventions designed to prevent or manage one or more chronic conditions using a systematic, multidisciplinary approach and potentially employing multiple treatment modalities. The goal of chronic disease management is to identify persons at risk for one or more chronic conditions, to promote self-management by patients and to address the illness or conditions with maximum clinical outcome, effectiveness and efficiency regardless of treatment setting(s) or typical reimbursement patterns"* (Schrijvers 2009). In addition, Peytremann-Bridevaux and Burnand added more elements, adapting the definition as follows: *"Chronic disease prevention and management consists of a group of coherent interventions, designed to prevent or manage one or more chronic conditions using a community wide, systematic and structured multidisciplinary approach potentially employing multiple treatment modalities. The goal of chronic disease prevention and management is to identify persons with one or more chronic conditions, to promote self-management by patients and to address the illness or conditions according to disease severity and patient needs and based on the best available evidence, maximizing clinical effectiveness and efficiency regardless of treatment setting(s) or typical reimbursement patterns. Routine process*

and outcome measurements should allow feedback to all those involved, as well as to adapt the programme" (Peytremann-Bridevaux 2009).

How the intervention might work

There is great variation in the symptoms, functional limitations and degrees of psychological well-being of COPD patients, as well as the speed of the progression of COPD towards more severe stages (Agusti 2010). This calls for a multi-faceted response, including different elements (e.g. smoking cessation, physiotherapeutic reactivation, self management, optimal medication adherence) targeted at the patient, professional or organizational level. Therefore, IDM programs have been developed to improve effectiveness and economic efficiency of chronic care delivery (Norris 2003) by combining patient-related, professional-directed and organizational interventions (Wagner 2001; Lemmens 2009).

Why it is important to do this review

As health-related quality of life, exercise tolerance and number of exacerbations are the most important patient-related outcomes in COPD, the focus in this review will be on these primary outcomes.

Several systematic reviews have been published that evaluated the effect of IDM in COPD patients (Adams 2007; Niesink 2007; Peytremann-Bridevaux 2008; Lemmens 2009; Steuten 2009). These reviews differ from our review in various ways. Adams' review focused solely on interventions which could be arranged according to the chronic care model of Wagner (Wagner 1996; Adams 2007). Furthermore, Adams included studies between 1966 and 2005. Since then, several studies focusing on IDM in COPD patients have been published. Niesink and colleagues evaluated the quality of life in COPD patients, but did not report outcomes of exacerbations or exercise tolerance. Furthermore, the authors decided not to perform a meta-analysis; reasons for this were not clearly described (Niesink 2007). Peytremann-Bridevaux performed a meta-analysis and focused on quality of life, exacerbations and exercise tolerance. However, they did not take into account the differences in study design (randomised controlled trials (RCT) versus before/after uncontrolled studies) in their conclusions (Peytremann-Bridevaux 2008). Lemmens' review examined the effectiveness of IDM in a mix of patients with COPD, asthma or both (Lemmens 2009). No subgroup analysis was performed for patients with COPD. Furthermore, conclusions were drawn irrespective of the study designs (i.e. RCTs, controlled clinical trials, quasi-experimental, controlled before and after time studies and time series designs; Lemmens 2009). Steuten et al aimed to determine the cost-effectiveness of COPD programs and the authors did not perform a meta-analysis of clinical effects (Steuten 2009).

Overall, all reviews suggested some beneficial effects on health status. However, firm conclusions could not be made regarding the effectiveness of IDM, due to the large heterogeneity in the interventions, study populations, outcome measurements and methodological quality. The literature searches of the aforementioned reviews for relevant RCTs investigating the effectiveness of IDM for patients with COPD were carried out between December 2006 and May 2008. Since then, several studies have been published. Furthermore, none of the former published systematic reviews were carried out according to the latest methods for conducting a systematic review (Higgins 2011). Within the framework of The Cochrane Collaboration, we have systematically and comprehensively evaluated the effectiveness of IDM in people with COPD.

OBJECTIVES

To evaluate the effectiveness of IDM programs or interventions in people with COPD on health-related quality of life, exercise tolerance and the number of exacerbations.

METHODS

Criteria for considering studies for this review

Types of studies
We included only randomised controlled trials (RCTs) in which IDM programs or interventions were compared to controls in people with COPD. Cluster-randomized trials were also eligible. There were no restrictions regarding the language of the paper.

Types of participants
People with a clinical diagnosis of COPD according to the GOLD criteria were included: people having chronic respiratory symptoms (i.e. coughing, sputum or dyspnoea) and a limited post-bronchodilator forced expiratory volume in one second (FEV1) to forced vital capacity (FVC) ratio of < 0.7. Severity of airflow obstruction was classified using the GOLD stages of 2009 (GOLD 2009). All GOLD stages were accepted. Studies including participants with other diagnoses than COPD were only eligible if the results of participants with COPD were available separately.

Types of interventions
We included studies where the IDM intervention consisted of strategies to improve the care for participants with COPD, including organizational, professional, patient-directed

and financial interventions. We classified these according to the Cochrane Effective Practice and Organization of Care Group (EPOC) taxonomy of interventions (EPOC 2008), complemented with patient-directed interventions (i.e. self management and education). Our definitive checklist consisted of the following components of the IDM intervention that could be scored:

1. Education/self management: i.e. education, self-management, personal goals and/or action plan, exacerbation management
2. Exercise: i.e. (home) exercise training and/or strength and/or endurance training
3. Psychosocial: cognitive behavioral therapy, stress management, other psychological assessment and/or treatment
4. Smoking cessation
5. Medication: optimal medication/prescription of medication adherence
6. Nutrition: dietary intervention
7. Follow-up and/or communication: structural follow-up and/or communication, case management by nurses, optimal diagnosis
8. Multidisciplinary team: active participation and formation of teams of professional caregivers from different disciplines, revision of professional roles, integration of services, local team meetings
9. Financial intervention: fees/payment/grants for providing IDM.

As IDM includes different components mentioned above, delivered by different healthcare disciplines, the RCT studies had to include:

1. at least two components of interventions as mentioned above;
2. active involvement of at least two different categories of healthcare providers; and
3. a minimum duration of the IDM intervention of three months.

In all studies, we determined the dominant component of the program.

We compared IDM versus controls (varying from usual care or no treatment to single interventions, mono-disciplinary interventions).

Types of outcome measures

Primary outcomes

1. Health-related quality of life (HRQoL), as reported by one of the following questionnaires: a validated disease-specific questionnaire, e.g. Clinical COPD Questionnaire (CCQ; van der Molen 2003; Kocks 2006), Chronic Respiratory Questionnaire (CRQ; Guyatt 1987), St. George's Respiratory Questionnaire (SGRQ; Jones 1991; Jones 2005), COPD Assessment Test (CAT; Jones 2009) or a generic questionnaire, e.g. Short Form-36 (SF-36; Ware 1992), Euro Qol-5D (EQ-5D; EuroQol Group 1990)).
2. Maximal or functional exercise capacity, as reported by one of the following outcomes: the peak capacity measured in the exercise laboratory using an incremental

exercise test defined according to the results of timed walk tests e.g. 6- or 12-minute walk test (Redelmeier 1997) or shuttle run test (Singh 1992)).
3. Exacerbation-related outcomes, as reported by one of the following: time to first exacerbation, number of exacerbations, duration and/or severity, and measured by reporting of symptoms, antibiotics or prednisolone prescriptions and/or hospital admissions or hospital days related to exacerbations.

Secondary outcomes

Clinical outcomes

1. Dyspnea, as measured by the Medical Research Council (MRC) Dyspnea Scale (Bestall 1999) or Borg score (Borg 1970).
2. Survival (mortality).
3. Lung function (FEV1, FVC).
4. Depression, as measured by the Hospital Anxiety and Depression Scale (HADS) (Zigmond 1983) or the Beck Depression Inventory (BDI) score (Beck 1961).

Process-related outcomes

1. Co-ordination of care, e.g. accessibility of care, participation rate in the disease management program, satisfaction of health care providers and participants with regard to the program, or the extent to which disease management was implemented, from the perspective of the patient (PACIC; Glasgow 2005) and the caregiver (Bonomi 2002).

We evaluated outcomes at the following endpoints: a) short-term (12 months or less); b) long-term (longer than 12 months) follow-up, if possible.

Search methods for identification of studies

Electronic searches

We identified trials using the Cochrane Airways Group Register of trials, the Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library, MEDLINE, EMBASE and CINAHL. The search was performed without language restrictions, using the highly sensitive Cochrane Collaboration search strategy, which aims to identify all randomised controlled trials (Lefebvre 2009). We used specific MeSH headings and additional keywords to identify all RCTs on IDM in COPD patients. As IDM programs were first described in 1990, our search was restricted to publications from 1990 onwards. The complete search strategies for the database searches are provided in the appendices (MEDLINE Appendix 1; EMBASE Appendix 2; CINAHL Appendix 3; CENTRAL Appendix 4; Airways Register Appendix 5). The search has been conducted up to April 2012. We

ran an update search on 12 April 2013, but the results have not been fully incorporated: nine studies have been added as 'ongoing studies' and three studies have been added as 'studies awaiting classification'.

Searching other resources

In order to identify all possible studies, we carried out an additional search for systematic reviews in the Cochrane Database of Systematic Reviews. We screened reference lists of included RCTs and systematic reviews for potential studies for this review. To identify ongoing or new studies, we searched databases of ongoing studies, including ClinicalTrials.gov and other relevant registers.

Data collection and analysis

Selection of studies

Two review authors (AK and NS) independently assessed the title and abstract of all identified citations. We excluded all trials that were not randomised controlled trials or in which participants had no diagnosis of COPD. All studies excluded by the first two review authors because of the nature of the intervention were double-checked by a third review author (NC). Furthermore, if there was any doubt, we retrieved the full-text article and examined it for inclusion eligibility. Disagreements were discussed in a consensus meeting.

Data extraction and management

We collected the following information from included studies in our review: 1) the study design (i.e. randomisation method, sample size, blinding); 2) participant characteristics (i.e. diagnosis COPD according to GOLD criteria, age, sex); 3) interventions (i.e. setting, number of professionals involved, elements of IDM program/intervention, frequency and duration of intervention); 4) outcome measures and timing of outcome assessment; 5) results (i.e. loss to follow-up, outcomes). The outcome data were extracted by one author (AK) and checked by another (NC) using a standardized data extraction form. In case of missing data, we contacted the authors of these studies for additional information or clarification.

Assessment of risk of bias in included studies

Two of us (AK and NC) independently assessed risk of bias for each study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011), according to the following items:

1. Allocation sequence generation
2. Concealment of allocation

3. Blinding of participants and health care providers, in relation to the intervention
4. Blinding of outcome assessment
5. Incomplete outcome data
6. Selective outcome reporting

As cluster-randomized trials were also considered for inclusion, we added the following design-related criteria for these types of studies:

1. Recruitment bias (i.e. individuals are recruited after the clusters have been randomised)
2. Baseline imbalance between groups (i.e. the risk of baseline differences can be reduced by using stratified or pair-matched randomisation of clusters)
3. Loss of follow-up of clusters (i.e. missing clusters and missing outcomes for individuals within clusters may lead to a risk of bias in cluster-randomized trials)
4. Methods of analysis adequate for cluster-randomized controlled trials (i.e. taking clustering into account in the analysis) (Higgins 2011)

We judged all items as high, low or unclear risk of bias. We resolved disagreements in a consensus meeting.

Measures of treatment effect

We analyzed the results of the studies using RevMan 5, using random-effects modeling. We used forest plots to compare results across trials. The results were related to the minimal clinically important difference (MCID).

We expressed the results of each RCT as risk ratios (RR) with corresponding 95% confidence intervals (95% CI) for dichotomous data, and mean difference (MD) or standardized mean difference (SMD) for continuous data, depending on the similarity of outcome measurement scale (i.e. MDs are used when all studies use the same outcome measurement scale and SMDs when studies use different outcome measurement scales). We summarized data in a meta-analysis only if the data are clinically and statistically sufficiently homogenous. If the meta-analysis led to statistically significant overall estimates, we transformed these results (pooled estimate of RR, MD or SMD) back into measures which are clinically useful in daily practice. We planned to use the number needed to treat for an additional beneficial outcome (NNTB) and the absolute and/or relative improvement on the original units in order to report these as the final results of the review.

Unit of analysis issues

In case of a unit of analysis error occurrence in cluster-randomized controlled trials, we adjusted for the design effect by reducing the size of the trial to its "effective sample size" (Rao 1992). The effective sample size of a single intervention group in a cluster-randomized trial is its original sample size divided by a quantity called the 'design effect'.

The design effect is 1+ (M-1)* ICC, where M is the average cluster size and ICC is the intra-cluster correlation coefficient. For dichotomous data, both the number of participants and the number experiencing the event were divided by the design effect. For continuous data, only the sample sizes were reduced; means and standard deviations remained unchanged (Higgins 2011).

Dealing with missing data

In case of missing data, we planned to contact the authors for additional information about the missing data for individuals. We sent a reminder if we did not receive a response. Secondly, we planned to assume the missing values to have a poor outcome. For continuous outcomes (i.e. health-related quality of life, exercise capacity) and dichotomous outcomes (i.e. mortality), we planned to calculate the effect size (SMD, MD, RR) based on the number of participants analyzed at the time point. If the number of participants analyzed is not reported for each time point, we planned to use the number of randomised participants in each group at baseline. We planned to perform sensitivity analysis to investigate whether our assumptions have been reasonable (i.e. comparing results using number of participants analyzed with number of participants randomised).

Assessment of heterogeneity

We measured clinical and statistical heterogeneity using the I^2 statistic (Higgins 2011). A P value of less than 0.10 or an I2 value greater than 50% indicates substantial heterogeneity. In case of heterogeneity, we assessed studies, if possible, with respect to:

1. control group: a) no treatment; b) treatment with one health care provider; c) treatment with one component; d) other disease management programs (short duration of therapies);
2. intervention group, with regard to a) type of health care providers (i.e. general practitioner, lung specialist, physiotherapist, practice nurse); b) different components as listed by the EPOC classification (EPOC 2008); c) frequency and duration of intervention.

In case of substantial heterogeneity, we explored the data further, including subgroup analyses (see *Subgroup analysis and investigation of heterogeneity)* in an attempt to explain the heterogeneity.

Assessment of reporting biases

In order to determine whether reporting bias was present, we evaluated whether the protocol for the RCT was published before recruitment of patients of the study was started. For studies published after 1 July 2005, we screened the Clinical Trial Register at the International Clinical Trials Registry Platform of the World Health Organization (http://apps.who.int/trialsearch) (De Angelis 2004). For each study, we evaluated wheth-

er selective reporting of outcomes was present (outcome reporting bias). Furthermore, we made a funnel plot to assess the possibility of reporting bias.

Data synthesis

We pooled results of the studies using the random-effects model. For continuous data, we recorded the mean change from baseline to endpoint and standard deviation (SD) for each group. For dichotomous data we recorded the number of participants with each outcome event and calculated the odds ratio (OR). We used results reported at three months, as our predetermined inclusion criteria postulated a program of at least three months duration (to ensure sufficient impact). If data at three months were unavailable, we analyzed the data measured most closely to this time point. We evaluated outcomes at short- (3 to 12 months) and long-term (> 12 months) follow-up.

We presented the main results of the review in a 'Summary of findings' table, which includes an overall grading of the evidence using the GRADE approach in accordance with the recommendations laid out in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). This involves making separate ratings for quality of evidence for each patient-important outcome and identifies five factors that can lower the quality of evidence, including: study limitations; indirectness of evidence (also called clinical heterogeneity with regard to study population, intervention, control group and outcomes); unexplained heterogeneity or inconsistency of results (i.e. statistical heterogeneity); imprecision of results (i.e. due to small sample sizes and few events); and high probability of publication bias. However, other factors can increase the quality of evidence, such as large magnitude of effect; plausible confounding, which could reduce the demonstrated effect; and dose-response gradient (GRADE Working Group 2004). We presented the short- and long-term outcomes for our primary outcomes in the 'Summary of findings' table if possible.

Subgroup analysis and investigation of heterogeneity

In order to explain heterogeneity between the results of the included studies, we planned the following subgroup analyses a priori (where data were available) to determine if outcomes differed among:

1. patients with different severity of disease, according to GOLD stage (GOLD 2009) or MRC Dyspnea Scale (Bestall 1999) (e.g. patients with GOLD 1/2 versus GOLD 3/4, and/or patients with a MRC score 0 to 2 versus MRC 3 to 5);
2. the setting of the IDM intervention (e.g. primary, secondary or tertiary care);
3. design of the studies (individually randomised patients versus cluster-randomized patients (with and without adjusting for design effect));

4. control group: a) no treatment; b) treatment with one health care provider; c) treatment with one component; d) other disease management interventions (short duration of therapies);
5. intervention group, with regard to a) type of health care provider (i.e. general practitioner, lung specialist, physiotherapist, practice nurse); b) different components as listed by the EPOC classification (EPOC 2008); c) frequency and duration of intervention.

Sensitivity analysis

We carried out sensitivity analyses for the primary outcome measurements, in order to explore effect size differences and the robustness of conclusions. We planned sensitivity analysis determined a priori based on:

1. studies without study limitations with regard to a) allocation concealment; b) blinding of participants and investigators; c) recruitment bias; d) baseline imbalance between groups; e) loss of follow-up of clusters; f) adequate analysis;
2. method of analysis: a) results of studies using number of patients analyzed; b) studies using number of patients randomised.

We presented the main results of the review in a 'Summary of findings' table, which includes an overall grading of the evidence using the GRADE approach (GRADEpro; GRADE Working Group 2004) and a summary of the available data on the main outcomes, as described in Chapter 11 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011).

RESULTS

Description of studies

See *Characteristics of included studies*.

Results of the search

Our literature search identified 6700 titles and abstracts, resulting in 4776 references after de-duplication. Two review authors (AK, NS) screened the title/abstracts of these studies based on the predetermined inclusion criteria. Studies that were excluded because of the IDM intervention were double-checked by a third review author (NC). We retrieved the full-text articles of these studies and they were discussed in a consensus meeting. Finally, we identified 49 potentially relevant articles about IDM in COPD patients. We obtained full-text versions of these papers and data were extracted by one review author (AK) and double-checked by a second review author (NC). Finally, a total

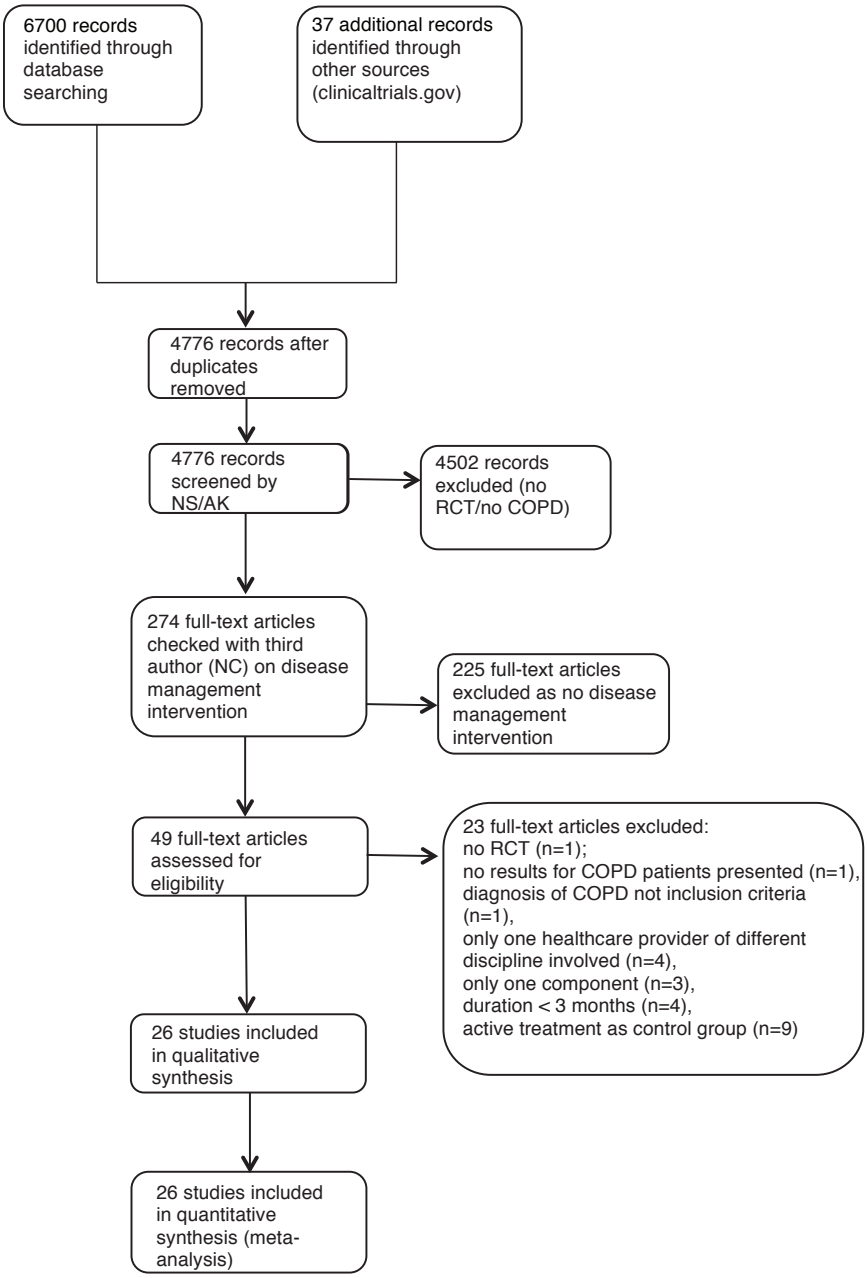


Figure 1. Study flow diagram

of 26 (cluster) randomised controlled trials were included in the review. The PRISMA flow diagram is presented in Figure 1.

Included studies

Characteristics of the included studies are described in Table 1, Table 2 and *Characteristics of included studies.*

Twenty-six RCTs met the eligibility criteria for the review, of which two were cluster-randomized trials (Rea 2004; Wood-Baker 2006). One trial was a cross-over trial (Cambach 1997). The studies were published between 1994 and 2011. Five studies originated from the Netherlands (Wijkstra 1994; Strijbos 1996; Cambach 1997; van Wetering 2010; Trappenburg 2011), four studies from Spain (Güell 2000; Farrero 2001; Güell 2006; Fernandez 2009), three studies from Australia (Smith 1999; Boxall 2005; Wood-Baker 2006), three from the United Kingdom (Littlejohns 1991; Dheda 2004; Sridhar 2008) and three from the United States (Aiken 2006; Koff 2009; Rice 2010). Two studies were conducted in Denmark (Bendstrup 1997; Gottlieb 2011), two originated from Sweden (Engstrom 1999; Theander 2009) and one each from Brazil (Mendes 2010), Canada (Bourbeau 2003), Japan (Wakabayashi 2011) and New Zealand (Rea 2004).

Participants

A total of 2997 COPD patients were randomised in the 26 studies, with a range of 30 to 713 patients per study. Of these, 2523 (84%) patients completed the studies (range 18 to 725). The mean age of the study population was 68 years (SD 3.7), with 68% being male. Patients had a mean FEV1 % predicted of 44.3% (range 28 to 66).

Interventions

Patients were treated in all types of healthcare settings: primary care (eight studies), secondary care (12 studies), tertiary care (one study) and a combination of primary and secondary health care (five studies). The number of health care providers involved in the IDM program ranged from two to seven, with a mean number of three. Furthermore, we calculated the number of components per program, which ranged from two to eight, with a mean number of four.

A priori, we planned to arrange the interventions in order to perform subgroup analysis based on type of intervention, according to type of health care providers, different components, and frequency and duration of intervention. However, it was not possible to determine the mean intensity, frequency or duration of all programs, due to lack of data. Furthermore, as the studies were too heterogeneous, it was not possible to arrange programs according to different combinations of components or combinations of health care providers. Therefore, we determined the dominant component of the IDM program in all studies. The main component of the intervention could directly be determined in

nine studies (Littlejohns 1991; Smith 1999; Farrero 2001; Bourbeau 2003; Dheda 2004; Aiken 2006; Wood-Baker 2006; Koff 2009; Trappenburg 2011) from the objective or title of the study. For example, in Aiken 2006: "*The objective is to document outcomes of a randomised trial of the PhoenixCare demonstration program of palliative care and coordinated care/case management for seriously chronically ill individuals who simultaneously received active treatment from managed care organizations. Intensive home-based case management provided by registered nurse case managers, in coordination with patients' existing source of medical care, comprised the intervention".*

In the remaining 17 studies, the main component was not directly clear from the objective. In 15 studies (Wijkstra 1994; Strijbos 1996; Bendstrup 1997; Cambach 1997; Engstrom 1999; Güell 2000; Boxall 2005; Güell 2006; Fernandez 2009; Theander 2009; Mendes 2010; Rice 2010; van Wetering 2010; Gottlieb 2011; Wakabayashi 2011), we chose the main component of the intervention as the component on which most of the time of the intervention was spent. For example: Bendstrup 1997: *"The intervention programme lasted 12 weeks. The programme consisted of the following components. Exercise training: the patients trained together at the hospital for 1h, three times a week for 12 weeks. Occupational therapy: two lessons each group. Education: 12 sessions. Smoking cessation: only for patients wishing to stop smoking."*

In one study (Sridhar 2008) there were two components on which most of the time of the intervention was spent (exercise and self management action plan). In another study (Rea 2004) there were two main components: self management action plan and structured follow-up. Therefore we arranged these two studies as separate categories.

We made the following categories:

1. IDM dominant component exercise (13 studies: Wijkstra 1994; Strijbos 1996; Bendstrup 1997; Cambach 1997; Engstrom 1999; Güell 2000; Boxall 2005; Güell 2006; Fernandez 2009; Theander 2009; Mendes 2010; van Wetering 2010; Gottlieb 2011).
2. IDM dominant component self management with an exacerbation action plan (five studies: Bourbeau 2003; Wood-Baker 2006; Koff 2009; Rice 2010; Trappenburg 2011).
3. IDM structured follow-up with nurses/GP (five studies: Littlejohns 1991; Smith 1999; Farrero 2001; Dheda 2004; Aiken 2006).
4. IDM exercise and self management action plan (one study: Sridhar 2008).
5. IDM self management action plan and structured follow-up (one study: Rea 2004)
6. IDM program of educational sessions, follow by a phase of individually tailored education according to scores on the Lung Information Needs Questionnaire score (one study: Wakabayashi 2011).

In two studies, IDM was compared to another IDM intervention and a control group (Strijbos 1996; Mendes 2010). Both studies involved two intervention groups including an IDM program with a focus on exercise training and one control group. In both studies, we combined and pooled data from the two intervention arms as one group. One

study had a cross-over design with drug treatment after three months (Cambach 1997). Therefore, we used solely the data for the intervention and control group at baseline and at three months.

Control groups consisted of usual care in 20 studies, in two studies control patients received a mono-disciplinary treatment including optimization of drug treatment (Cambach 1997; Güell 2006) and in four studies control patients received a treatment solely with education (Wood-Baker 2006; Fernandez 2009; Rice 2010; Wakabayashi 2011). Usual care consisted in all studies of regular follow-up visits to health care providers, which depended on the type of setting. There was access to health care providers on a 'need to' basis, without additional treatment or management programs. In all studies, no attempts were made to influence this usual care.

Outcomes

We recorded the number of studies reporting a specific outcome as follows:

- Quality of life (22 studies)
- Exercise capacity (18 studies)
- Exacerbation-related outcomes: measured by number of exacerbations; hospital admissions; hospitalisation days; emergency department (ED) visits; number of prednisolone or antibiotics courses (15 studies)
- Lung function (14 studies)
- Survival, mortality (five studies)
- Depression (four studies)
- Dyspnea, measured by MRC Dyspnea score (three studies) or Borg score (three studies)
- Co-ordination of care (three studies)

Details of the included studies are provided in *Characteristics of included studies.*

We requested additional data from the authors of 14 studies. Of these, 11 authors responded (79%) and six (43%) could provide us with additional data. Therefore, it was not necessary to impute missing data as described in our research protocol (see *Dealing with missing data).*

Excluded studies

After the first selection based on abstract and title, 49 potentially eligible studies were identified. Finally, after reading the full-text papers, we excluded 23 studies for one of the following reasons:

1. not a RCT (n = 1);
2. no diagnosis of COPD or no obtainable results reported for COPD as a subgroup (n = 2);
3. intervention includes one component of care (n = 3);

4. intervention includes one health care provider of different disciplines (n = 4);
5. duration of intervention is less than three months (n = 4);
6. active treatment as a control group (n = 9).

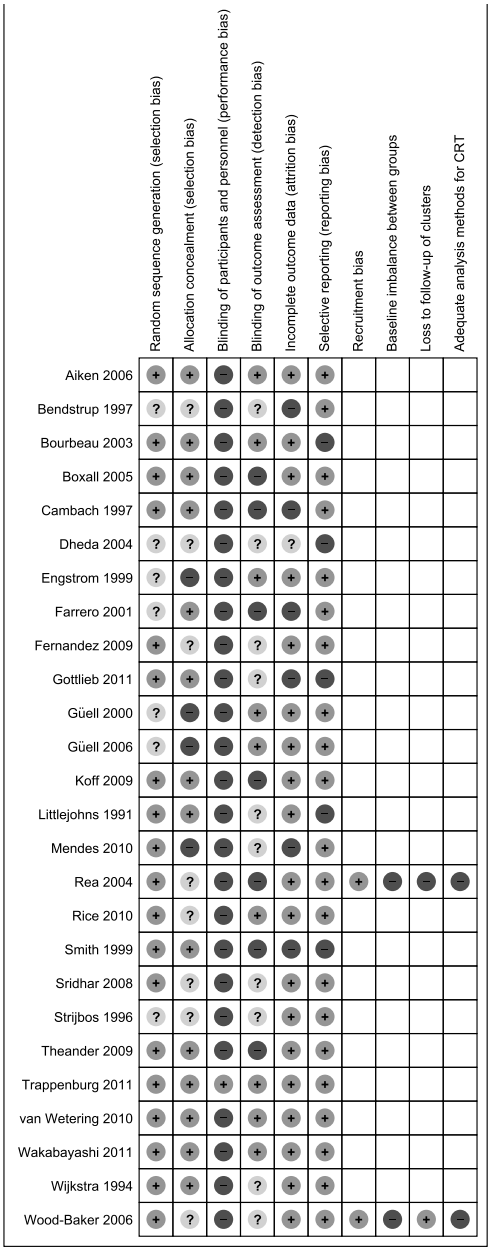


Figure 2. 'Risk of bias' summary: review authors' judgments about each risk of bias item for each included study.

The reasons for exclusion are further specified in *Characteristics of excluded studies.* For ongoing studies, refer to *Characteristics of ongoing studies.*

Risk of bias in included studies

For full details of 'Risk of bias' judgments see *Characteristics of included studies* and for an overview see Figure 2.

Allocation

Nineteen studies reported full details of adequate sequence generation and we judged them to be of low risk of bias. We judged the remaining seven studies as having unclear risk of bias as they were reported as randomised, but gave no description of the methods used to conceal the sequence. Fourteen studies reported adequate allocation concealment, while we judged four studies as high risk of bias. There were insufficient details for the remaining six studies for us to reach a firm conclusion so we judged them to be at unclear risk of bias. There were 13 studies in which both the sequence generation and concealment of allocation were adequately described, thus selection bias was minimized in these studies.

Blinding

The nature of the intervention precludes the possibility of blinding patients or health care providers. Therefore, we judged all the studies, except Trappenburg 2011, to be at high risk of performance bias. Trappenburg 2011 made a good attempt in using a modified informed consent procedure (postponed information), which meant that patients were unaware of the major aim of the study (education and an action plan), thereby enabling a single-blind study design (Trappenburg 2011). Therefore, we scored this study as low risk of bias. While blinding of health care providers and patients is impossible with this type of intervention, outcome assessors could be blinded to participants' allocation. This was reported in nine trials indicating a low risk of bias. Outcome assessors were unblinded in seven studies (high risk) and 10 studies provided insufficient information (unclear risk).

Incomplete outcome data

We judged 19 out of the 26 studies as low risk of bias, as they had low drop-out rates, drop-out rates were balanced across groups or trial authors performed an intention-to-treat analysis. We rated seven studies as high risk of bias and they were likely to be subject to attrition bias. Three out of these seven studies (Dheda 2004; Mendes 2010; Gottlieb 2011) had unbalanced drop-out rates, with higher rates in the intervention group compared to the control group. One study had a high drop-out rate balanced in both groups (31%) and the authors performed no intention-to treat-analysis (Bendstrup

1997). Cambach 1997 excluded all patients who did not return for one or more of the assessments from the final analyses. In Farrero 2001, quality of life was only investigated in the first 40 consecutive patients, therefore inducing risk of bias. In Smith 1999, all control participants refused to fill in the quality of life questionnaire and expressed that the burden of participating in a study, including questionnaires, was greater than expected.

Selective reporting

We rated 21 studies as low risk of bias and five studies as high risk of bias. Three studies (Rice 2010; van Wetering 2010; Trappenburg 2011) published a study protocol, with which we could compare the results sections. In the other studies, we checked whether the outcomes reported in the methods section of the article were reported in the results section. Five studies (Littlejohns 1991; Smith 1999; Bourbeau 2003; Dheda 2004; Gottlieb 2011) selectively reported outcomes. In two studies (Bourbeau 2003; Dheda 2004) the authors reported no statistically significant difference in the outcome and therefore did not present data, indicating selection bias. In the other three studies (Littlejohns 1991; Smith 1999; Gottlieb 2011), it remained unclear why it was planned to measure an outcome but it was not ultimately published.

Other potential sources of bias

We included two cluster-randomized trials (Rea 2004; Wood-Baker 2006). Unfortunately, both studies introduced noteworthy biases related to cluster-randomization in different ways. In one study (Wood-Baker 2006) recruitment bias remained unclear, as the authors provided insufficient information regarding the cluster-randomization process. In contrast, we judged Rea 2004 to have low risk of bias, as clusters were randomised before patients were recruited. Furthermore, we rated both studies as high risk of bias for baseline imbalance between groups, which could have been reduced when stratified or if pair-matched randomisation of the clusters had been used instead (Higgins 2011). In the Rea 2004 study, there was loss to follow-up of five clusters (four control and one intervention cluster), therefore this study was subject to bias. There was no follow-up of clusters in Wood-Baker 2006 (low risk of bias). Finally, both studies introduced bias as they analyzed data by incorrect statistical methods, not taking the clustering into account. This may account for the over-precise results and can result in much more weight in a meta-analysis (Higgins 2011). Therefore, in our meta-analyses we adjusted for the design effect by reducing the size of the trial to its "effective sample size" (Rao 1992). Based on similar primary care cluster-randomized trials, we used an intra-class correlation coefficient (ICC) of 0.01 (Kerry 1998; Campbell 2001). For dichotomous data, we divided both the number of participants and the number experiencing the event by the design effect. For continuous data, we reduced the sample sizes; means and standard deviations remained unchanged (Higgins 2011).

Effects of interventions

See: *Summary of findings for the main comparison: Integrated disease management compared to control for patients with chronic obstructive pulmonary disease*

In the majority of the outcomes, heterogeneity was not encountered. However, there was substantial heterogeneity present in SGRQ total score, six-minute walk distance (6MWD), CRQ dyspnoea (long-term), hospital admissions for all causes, hospital days and ED visits. If possible, we performed sensitivity and subgroup analysis on these outcomes to see if the heterogeneity could be explained. Our a priori determined subgroup analysis based on type of health care provider and the frequency and duration of intervention was impossible, as there was large heterogeneity among combinations of health care providers and the exact composition in terms of duration, frequency and intensity of programs was often not clearly reported. In addition, we were not able to perform subgroup analysis on GOLD stage or MRC Dyspnea score, as most studies did not report GOLD stages or MRC Dyspnea score. Furthermore, the definitions and classifications of GOLD stages have been changed over the years, resulting in large variation in severity within subgroups.

Instead, we performed subgroup analysis based on type of setting of the intervention (primary, secondary, tertiary care) and type of control group. Furthermore, we performed subgroup analysis with regard to the dominant component of the IDM program.

We used unadjusted data for meta-analyses, as only unadjusted data were reported, with the exception of two studies (van Wetering 2010; Trappenburg 2011).

Primary outcomes

1. Quality of life

Of the 26 included studies, 23 measured HRQoL using six different instruments (see Characteristics of included studies):

1. St. George's Respiratory Questionnaire (SGRQ) (13 studies);
2. Chronic Respiratory Questionnaire (CRQ) (eight studies);
3. Short Form-36 (SF-36) (three studies);
4. Sickness Impact Profile (SIP) (two studies);
5. Dartmouth Primary Care Co-operative Quality of Life questionnaire (COOP) (one study).

The SGRQ and CRQ are both disease-specific quality of life questionnaires. However, a meta-analysis combining CRQ and SGRQ score should not be used as Puhan 2006 has shown that the CRQ is more responsive than the SGRQ. Furthermore, the included generic quality of life questionnaires (SF-36, SIP and COOP) measure other dimensions of generic health quality of life, and therefore combining data in a meta-analysis across tools was not possible.

1.1 Respiratory-specific QoL

1.1.1.1 SGRQ total score - short-term

The SGRQ is a disease-specific, validated questionnaire with a scale from 0 (good health) to 100 (worse health status). A negative sign on this questionnaire indicates improvement, and the minimal clinically important difference (MCID) is -4 points (Jones 1991). Thirteen studies with a total population of 1425 patients provided data on the SGRQ total score with a follow-up of 3 to 12 months (Engstrom 1999; Bourbeau 2003; Dheda 2004; Boxall 2005; Wood-Baker 2006; Koff 2009; Fernandez 2009; Theander 2009; Rice 2010; van Wetering 2010; Gottlieb 2011; Trappenburg 2011; Wakabayashi 2011). The pooled mean difference (MD) on the SGRQ total score was -3.71 in favor of IDM (95% confidence interval (CI) of -5.83 to -1.59; Analysis 1.1; Figure 3; Summary of findings for the main comparison) which reached statistical significance ($P < 0.001$) and was close to, but did not reach, the MCID of -4 points. In other words, those treated with IDM had 3.71 out of 100 points better quality of life on this questionnaire. Pooling indicated a high degree of heterogeneity ($I^2 = 56\%$, $P = 0.01$). Heterogeneity was due to differences in the quality of studies. We were able to reduce heterogeneity if we performed multiple sensitivity analyses based on studies with adequate allocation concealment, adequate blinding of outcome assessment, cluster-randomization bias, or studies analyzing outcomes by intention-to-treat. Sensitivity analysis on studies with adequate allocation concealment (Bourbeau 2003; Boxall 2005; Koff 2009; Theander 2009; van Wetering 2010; Gottlieb 2011; Trappenburg 2011; Wakabayashi 2011) demonstrated that there was still a statistically significant effect in favor of the intervention group (MD -3.16; 95% CI -4.75 to -1.57, $P < 0.001$). In the same way, in trials (Engstrom 1999; Bourbeau 2003; van Wetering 2010; Rice 2010; Trappenburg 2011; Wakabayashi 2011) with adequate blinding of outcome assessment the effect did not change (MD -3.16; 95% CI -4.81 to -1.51, $P < 0.001$). A sensitivity analysis excluding the cluster-randomized study of Wood-Baker 2006, in which there was an unclear risk of recruitment bias and a high risk of bias on baseline imbalance, the effect changed to a clinically and statistically significant MD in favor of IDM (-4.22; 95% CI -6.14 to -2.30, $P < 0.001$). Lastly, a sensitivity analysis on the studies that analyzed the data using the intention-to-treat principle (Bourbeau 2003; Rice 2010) showed a statistically significant and clinically relevant difference in favor of IDM (MD -4.65; 95% CI -6.69 to -2.62, $P < 0.0001$) compared to controls.

Subgroup analysis based on type of setting

There were six studies conducted in primary care on 456 participants (Boxall 2005; Wood-Baker 2006; Koff 2009; Fernandez 2009; van Wetering 2010; Gottlieb 2011) and seven studies in secondary care on 969 participants (Engstrom 1999; Bourbeau 2003; Dheda 2004; Theander 2009; Rice 2010; Trappenburg 2011; Wakabayashi 2011). No stud-

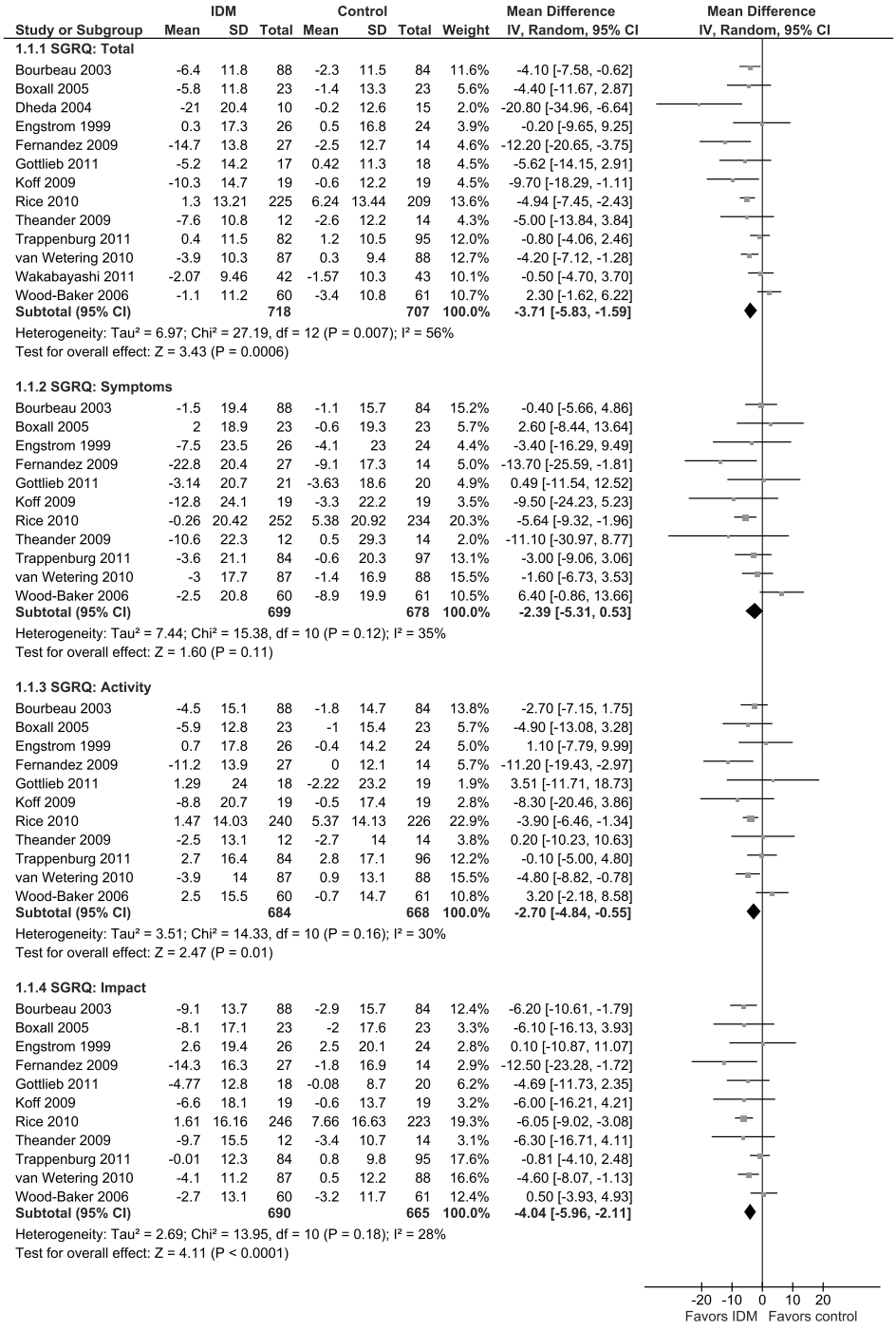


Figure 3. Forest plot of comparison: 1 Integrated disease management versus control, outcome: 1.1 SGRQ: short-term (3 to 12 months).

ies were performed in tertiary care. Subgroup analysis based on primary care studies showed a clinically relevant mean difference of -4.68 (95% CI -8.80 to -0.56) in favor of IDM. This result was statistically significant and clinically relevant. Subgroup analysis on secondary care studies showed a statistically significant difference of -3.41 (95% CI -5.97 to -0.85)(Analysis 1.3). This difference was not clinically relevant. The test for subgroup difference did not show a statistically significant difference in treatment effects in patients treated in different types of health care setting ($Chi^2 = 0.27$, df = 1 (P = 0.61)).

Subgroup analysis based on study design

We performed subgroup analysis based on study design and compared RCTs (n = 1304) versus cluster-RCTs (n = 121). There was no difference in SGRQ total score between intervention and control in the cluster-RCT of Wood-Baker 2006 (MD 2.30; 95% CI -1.62 to 6.22; Analysis 1.4). Pooled meta-analysis of RCTs showed a clinically relevant effect in favor of the IDM group of -4.22 (95% CI -6.14 to -2.30, P < 0.0001). The test for subgroup differences showed a statistically significant difference between the pooled analysis of the RCTs and the effect in the cluster-RCT ($Chi^2 = 8.57$, df = 1 (P = 0.003)).

Subgroup analysis based on type of control group

In nine studies including 744 participants, control patients received usual care, and in four studies (n = 681) the control group received a mono-disciplinary treatment of education. Meta-analysis of the usual care studies showed a significant difference between groups of -4.09 (95% CI -6.35 to -1.84, P < 0.001) (Analysis 1.5). Subgroup analysis of studies in which the control group received education showed no significant difference in effect between groups (MD -2.98; 95% CI -7.69 to 1.74, P = 0.022), which was neither statistically nor clinically relevant. There was no statistically significant difference in the test for subgroup difference ($Chi^2 = 0.17$, df = 1 (P = 0.68)).

Subgroup analysis based on dominant component of the program

There were four studies including 942 patients (Bourbeau 2003; Wood-Baker 2006; Koff 2009; Rice 2010) in which self management was the dominant component, and six studies including 373 patients in which exercise training was the dominant component (Engstrom 1999; Boxall 2005; Theander 2009; Fernandez 2009; van Wetering 2010; Gottlieb 2011). One study (Wakabayashi 2011) evaluated an individual tailored education program and one study (Dheda 2004) focused mainly on structured follow-up with nurses and GPs. Subgroup analysis of the self management studies revealed neither a statistically nor a clinically relevant mean difference: MD -2.76 (95% CI -5.88 to 0.36, P = 0.08). Subgroup analysis of exercise studies showed a statistically and clinically relevant difference of -4.74 in favor of IDM (95% CI -7.05 to -2.43, P < 0.0001). There was

no statistically significant difference between subgroups (Chi^2 = 1.00, df = 1 (P = 0.32)) (Analysis 1.6).

1.1.1.2. SGRQ - long-term

Two studies including 189 participants measured the long-term effect on the SGRQ total score: at 18 (Gottlieb 2011) and 24 (van Wetering 2010) months follow-up. There was no statistically significant difference between groups (MD -0.22; 95% CI -7.43 to 6.99, P = 0.95; I^2 = 54%, P = 0.14)(Analysis 1.2).

1.1.2.1 SGRQ domain scores - short-term

Eleven studies with a total population of 1377 patients reported scores on the SGRQ domains of symptoms, activity and impact. For all domains, there was no significant heterogeneity (I^2 between 35% and 28%) (Analysis 1.1). We found the following results:
Symptom domain: MD -2.39 (95% CI -5.31 to 0.53, P = 0.11)
Activity domain: MD -2.70 (95% CI -4.84 to -0.55, P = 0.01)
Impact domain: MD -4.04 (95% CI -5.96 to -2.11, P < 0.0001)

1.1.2.2. SGRQ domain scores - long-term

Two studies measured the long-term effect on the SGRQ at 18 months (van Wetering 2010; Gottlieb 2011). Mean differences on all domains had wide confidence intervals and included zero (Analysis 1.2).

1.1.3.1. CRQ domain scores - short-term

The Chronic Respiratory Disease Questionnaire (CRQ), with a scale from 0 to 7 and a MCID of 0.5, was reported in eight trials (Wijkstra 1994; Bendstrup 1997; Cambach 1997; Güell 2000; Farrero 2001; Rea 2004; Güell 2006; Sridhar 2008). Three of these (Bendstrup 1997; Farrero 2001; Rea 2004) could not be used in a meta-analysis. Bendstrup 1997 and Rea 2004 reported insufficient data and the authors could not provide us with additional data. In addition, Farrero 2001 administered the CRQ in the first 40 consecutive patients and therefore outcomes were not published.
The pooled results of four studies including 160 participants (Wijkstra 1994; Cambach 1997; Güell 2000; Güell 2006) measuring the CRQ until 12 months follow-up are shown in Figure 4 and Analysis 1.7. For each of the CRQ domains, the MD was well above the MCID of 0.5 units and differences in scores were statistically significant: dyspnoea (MD 1.02; 95% CI 0.67 to 1.36, P < 0.0001), fatigue (MD 0.82; 95% CI 0.46 to 1.17, P < 0.0001), emotion (MD 0.61; 95% CI 0.26 to 0.95, P < 0.0005) and mastery (MD 0.75; 95% CI 0.38 to 1.12, P < 0.0001). The results showed homogeneity across studies.

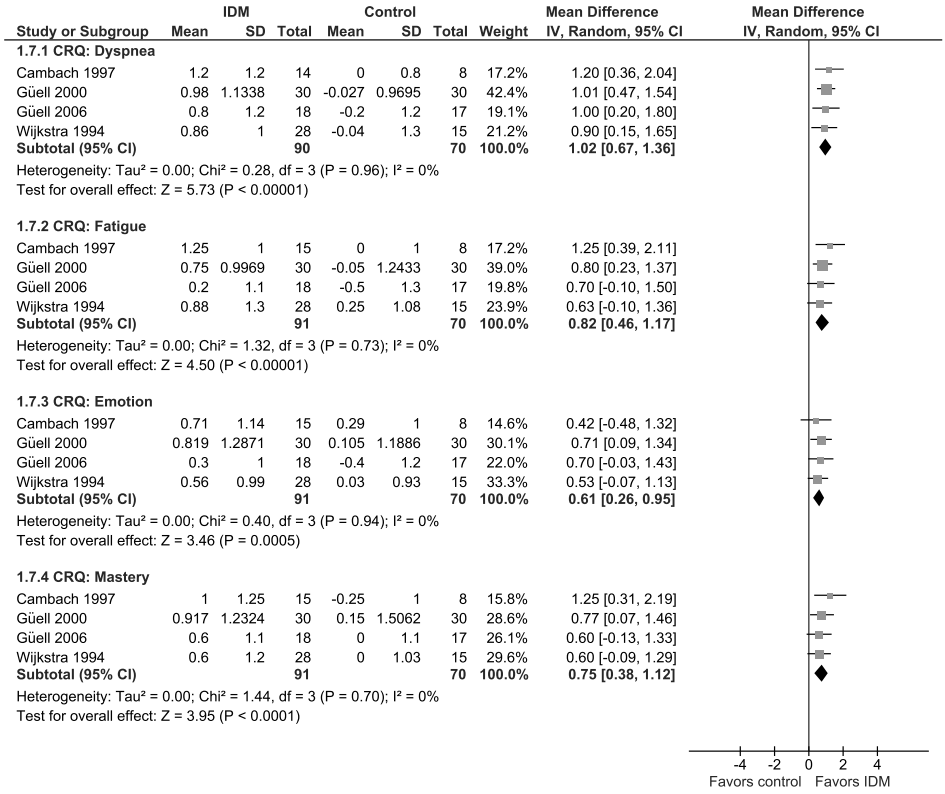


Figure 4. Forest plot of comparison: 1 Integrated disease management versus control, outcome: 1.7 CRQ: short-term (3 to 12 months).

1.1.3.2. CRQ domain scores - long-term

Two studies (n = 151) (Güell 2000; Sridhar 2008) measured the long-term effectiveness on CRQ domain scores at 24 months follow-up(Analysis 1.8). There was no difference between groups on the CRQ dyspnoea domain: MD 0.47 (95% CI -0.31 to 1.25, P = 0.24). Pooled data showed substantial heterogeneity (I^2 = 70%, P = 0.07), which was related to differences in the type of intervention (exercise in the Güell 2000 study versus structured follow-up with a respiratory nurse and exacerbation plan in Sridhar 2008). Güell 2000 demonstrated a significant difference in favor of IDM (MD 0.92; 95% CI 0.19 to 1.65, P = 0.01). In contrast, there was no statistically significant difference between groups on the CRQ dyspnoea domain in Sridhar 2008 (MD 0.12; 95% CI -0.32 to 0.58, P = 0.61).

Pooled mean differences on the domains fatigue, emotion and mastery showed homogeneity across studies. On the CRQ fatigue domain, there was a statistically significant but not clinically relevant difference of 0.45 in favor of IDM (95% CI 0.05 to 0.85, P = 0.03). On the CRQ emotion and mastery domain, the statistically and clinically relevant effect

was in favor of IDM: emotion MD 0.53 (95% CI 0.10 to 0.95, P = 0.02) and mastery MD 0.80 (95% CI 0.37 to 1.23, P < 0.01).

1.2 General health-related QoL

General HRQoL was measured with the SF-36 in three studies (Dheda 2004; Rea 2004; Aiken 2006). The authors of these studies could not provide us with sufficient data for pooling in a meta-analysis. Neither study found a significant effect between groups. Two of these studies (Dheda 2004; Aiken 2006) suffer from small sample sizes varying from 15 to 10 patients per group per study, which makes it difficult to detect an effect (underpowered studies).

We pooled the data from two studies (Littlejohns 1991; Engstrom 1999) reporting data on the SIP (Analysis 1.9). No between-group differences in any domain of the SIP were found. One other study used the York Quality of Life Questionnaire (Bendstrup 1997) and reported no significant difference. Smith 1999 used a modified version of the Dartmouth Primary COOP. In this study, the authors analyzed only the data from the intervention group (n = 30) due to lack of data in the control group. The authors concluded that the total COOP scores in the intervention group significantly improved HRQoL at 12 months.

2. Exercise capacity

Seventeen studies measured exercise capacity using either the 6MWD or the cycle ergometer test. The MCID on the 6MWD is estimated at 35 meters (Puhan 2008). There is no MCID reported in the current literature for the cycle ergometer test. Results are shown in Figure 5.

2.1.1 Functional exercise capacity - short-term

We pooled data from 14 studies using the 6MWD including 871 participants. One study could not be pooled, as the authors reported no data because there was no significant difference between groups at 12 months follow-up (Bourbeau 2003).

Patients treated with IDM improved their 6MWD by a statistically and clinically relevant 43.86 meters (95% CI 21.83 to 65.89)(Figure 5; Analysis 1.10). There was heterogeneity between the results of the studies (I^2 = 83%). This heterogeneity is explained by differences in the quality of studies. We performed sensitivity analysis on studies with adequate allocation concealment, which reduced heterogeneity (I^2 = 0%) and reduced the effect to a MD of 15.15 meters, which was still statistically significant (95% CI 6.37 to 23.93, P < 0.001), however no longer clinically relevant. Furthermore, we performed subgroup analysis based on type of setting, type of control group and dominant component of the intervention.

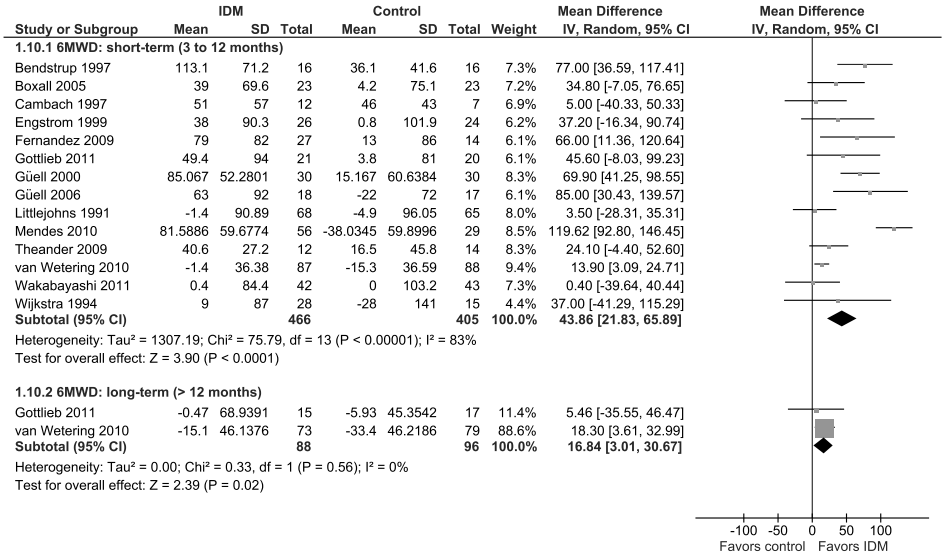


Figure 5. Forest plot of comparison: 1 Integrated disease management versus control, outcome: 1.10 Functional exercise capacity: 6MWD mean difference.

Subgroup analysis based on type of setting

There were seven studies with 427 participants (Wijkstra 1994; Cambach 1997; Boxall 2005; Fernandez 2009; van Wetering 2010; Mendes 2010; Gottlieb 2011) conducted in primary care, seven studies with 438 participants (Littlejohns 1991; Bendstrup 1997; Engstrom 1999; Güell 2000; Theander 2009; Mendes 2010; Wakabayashi 2011) in secondary care and one study in tertiary care with 35 participants (Güell 2006). Both subgroup analyses showed similar statistically and clinically relevant improvements: exercise training in primary care revealed a MD of 45.16 meters (95% CI 8.65 to 81.67, P = 0.02), whereas in the secondary care setting the MD was 49.18 meters (95% CI 14.28 to 84.08, P = 0.006). The tertiary care study showed a significant effect in favor of IDM of 85 meters (95% CI 30.43 to 139.57). Results are shown in Analysis 1.11 and Figure 6.

Subgroup analysis based on control group

We pooled four studies with 180 participants in which control patients received a treatment with optimal medication (Cambach 1997; Güell 2006) or an education session (Fernandez 2009; Wakabayashi 2011) in a subgroup analysis. In the same way, we pooled 10 studies (Littlejohns 1991; Wijkstra 1994; Bendstrup 1997; Engstrom 1999; Güell 2000; Boxall 2005; Theander 2009; Mendes 2010; van Wetering 2010; Gottlieb 2011) including 691 participants in which the control group consisted of usual care.

Subgroup analysis in which one component of treatment was used showed no difference between groups (MD 35.99; 95% CI -5.34 to 77.31, P = 0.09)(Analysis 1.12). In studies in

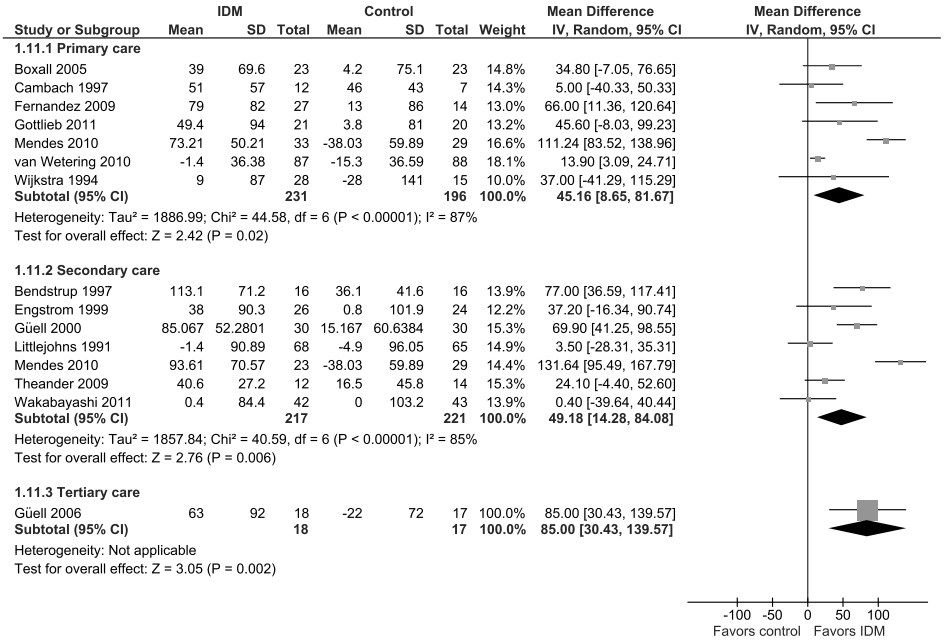


Figure 6. Forest plot of comparison: 1 Integrated disease management versus control, outcome: 1.11 Subgroup analysis 6MWD based on type of setting.

which the control group consisted of usual care, the 6MWD improved clinically and statistically significantly by 46.59 meters in favor of IDM (95% CI 19.68 to 73.51, P = 0.0007). However, the test for subgroup differences did not show any difference between control groups (Chi^2 = 0.18, df = 1 (P = 0.67)).

Subgroup analysis based on dominant component of intervention

Twelve out of the 14 studies (n = 653) measuring exercise capacity incorporated some kind of exercise training in their IDM programs. We performed subgroup analysis, which showed that the 6MWD improved by 51.47 meters (95% CI 26.53 to 76.40). This effect was statistically and clinically relevant. In the remaining two studies (n = 218), exercise was not part of the IDM programs. In one study (Wakabayashi 2011), which consisted of individually tailored education sessions, there was no difference between groups (MD 0.40; 95% CI -39.64 to 40.44, P = 0.98). The other study (Littlejohns 1991), in which there was a focus on structured follow-up with GP and nurses, revealed no effect (MD 3.50; 95% CI -28.31 to 35.31, P = 0.83). In conclusion, studies incorporating exercise training in their IDM programs demonstrated larger effect sizes; this was statistically significant using the test for subgroup difference (Chi^2 = 7.49, df = 2 (P = 0.02))(Analysis 1.13).

2.1.2 Functional exercise capacity - long-term

Two studies on 184 participants published long-term results on the 6MWD (van Wetering 2010; Gottlieb 2011). Both studies showed that IDM statistically significantly improved exercise capacity measured on the 6MWD by 16.8 meters (MD 16.84; 95% CI 3.01 to 30.67) compared to the control group. However, this effect did not exceed the MCID. There was no heterogeneity present. Results are shown in Figure 5 and Analysis 1.10.

2.2. Maximal exercise capacity

Four studies on 298 participants assessed the maximal exercise capacity (in Watts) using the cycle ergometer test. Both studies showed that IDM statistically significantly improved the maximal exercise capacity by 7 Watts (MD 6.99; 95% CI 2.96 to 11.02, P < 0.0001)(Analysis 1.14).

3. Exacerbations

3.1.1 Number of patients experiencing at least one exacerbation - short-term

Two studies (Bourbeau 2003; Trappenburg 2011) including 407 patients reported on the number of patients experiencing at least one exacerbation during 12 months of follow-up. Both studies used the same definition and defined an exacerbation as an increase in symptoms, with deterioration of dyspnoea or purulent sputum. Pooled meta-analysis showed homogeneity and a pooled OR of 1.21 (95% CI 0.77 to 1.91) (Analysis 1.15), which showed no statistically or clinically relevant difference between groups. The trial authors of the Bourbeau 2003 study reported that although there were more patients experiencing at least one exacerbation in the intervention group (85 versus 81), the total number of exacerbations was higher in the control group (362) compared to the intervention group (299). This was of borderline significance (P = 0.06). Similarly, the number of patients experiencing three or more exacerbations during 12-month follow-up was higher in the control group (67.9%), compared to the action plan group (62.3%). Exacerbations in the intervention group were treated successfully at an early stage, which probably resulted in fewer patients with a hospital admission (17.2% versus 36.3%, P < 0.01). Trappenburg 2011 reported similar findings: although exacerbation rates did not differ between groups, exacerbations in the action plan group were perceived as substantially milder by patients, and they reported on average three days faster than those in the control group.

3.1.2. Number of patients experiencing at least one exacerbation - long-term

Two studies (Sridhar 2008; van Wetering 2010) including 301 patients assessed the number of patients experiencing at least one exacerbation at 24 months follow-up. Both studies related the definition of an exacerbation to health care. Sridhar 2008 stated they

defined an exacerbation as the "unscheduled need for healthcare, or need for steroid tablets, or antibiotics for worsening of their COPD". Similarly, van Wetering 2010 defined a moderate exacerbation as "a visit to the general practitioner or respiratory physician in combination with a prescription of antibiotics and/or prednisolone or a visit to the emergency department or day care of a hospital, which according to the patient, was related to a COPD exacerbation. A severe exacerbation was defined as a hospitalisation for a COPD exacerbation". Pooled meta-analysis demonstrated no difference between groups (OR 1.53; 95% CI 0.90 to 2.60, P = 0.12) (Analysis 1.16). There was homogeneity between studies. Sridhar 2008 stated that patients in the intervention group were more likely to have exacerbations treated with oral steroids alone or oral steroids and antibiotics than the control group. The initiator of treatment was statistically more likely to be the patient themselves compared to the GP in the control group.

3.1.3 Mean exacerbation rate - long-term

Two studies (Güell 2000; van Wetering 2010) including 226 participants reported on the exacerbation rate in both groups at 24 months follow-up. Data on exacerbations were skewed in the van Wetering study, therefore we decided not to pool both studies in a meta-analysis. In Güell 2006, control group patients (n = 23) experienced 207 exacerbations, with an average of 6.9 (3.9) exacerbations per patients, ranging from 0 to 16 exacerbations during the 24 months. The IDM group experienced 111 exacerbations, with an average of 3.7 (2.2) exacerbations per patients, ranging from 0 to 9 exacerbations during the 24 months. This difference was statistically significant (P < 0.0001) favoring IDM. In van Wetering 2010, the exacerbation rate was 2.78 in the IDM group and 2.16 in the control group, resulting in a rate ratio of 1.29 (95% CI 0.89 to 1.87), which was not statistically significant (P = 0.113).

3.2.1 Hospital admissions, all causes - short-term

Two studies on 266 participants (Littlejohns 1991; Rea 2004) reported data on the number of patients who were admitted for all causes until 12 months follow-up. There was no heterogeneity and there was no difference between groups (OR 0.62; 95% CI 0.36 to 1.07, P = 0.49) (Analysis 1.17).

3.2.2. Hospital admissions, all causes - long-term

Two studies including a total of 283 patients (Sridhar 2008; van Wetering 2010) assessed the number of patients admitted until 24 months follow-up. Pooled results showed heterogeneity (I^2 = 53%), which could be explained as van Wetering 2010 showed a positive effect in favor of IDM and Sridhar 2008 showed no significant difference in effect between groups. Therefore, a pooled meta-analysis showed no difference between groups (OR 0.78; 95% CI 0.38 to 1.57)(Analysis 1.18).

3.3.1. Respiratory-related admissions - short-term

We pooled data from seven studies (Smith 1999; Bourbeau 2003; Rea 2004; Boxall 2005; Koff 2009; Rice 2010; Trappenburg 2011) measuring respiratory-related admissions until 12 months follow-up in a meta-analysis. Studies were homogeneous. Pooled estimates

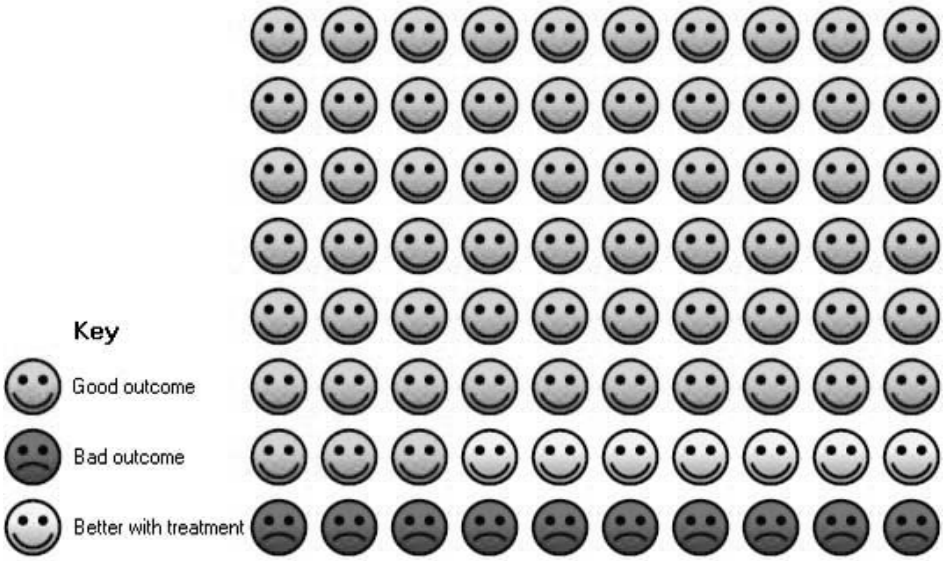


Figure 7. Number needed to treat
In the control group 27 people out of 100 had a respiratory-related hospital admission over 3 to 12 months, compared to 20 (95% CI 15 to 27) out of 100 for integrated disease management group.

showed a statistically significant difference in favor of IDM (OR 0.68; 95% CI 0.47 to 0.99, P = 0.04)(Analysis 1.19). In the control group 27 people out of 100 had a respiratory-related hospital admission over 3 to 12 months, compared to 20 (95% CI 15 to 27) out of 100 in the integrated disease management group, as presented in Figure 7. Over the course of a year, the number needed to treat with IDM to prevent one hospital admission was NNT(B) 15 (95% CI 9 to 506).

3.3.2. Respiratory-related admissions - long-term

Data from one trial (van Wetering 2010) presented data on the number of patients admitted until 24 months follow-up. There was no difference between the control and IDM group on the number of respiratory-related admissions (OR 0.59; 95% CI 0.28 to 1.22, P = 0.16)(Analysis 1.20).

3.4.1 Hospital days per patient - short-term

Six studies on 741 patients (Engstrom 1999; Farrero 2001; Bourbeau 2003; Rea 2004; Boxall 2005; Trappenburg 2011) reported the difference in mean hospitalisation days per patient per group (intervention versus control). Patients treated with IDM were on average discharged from the hospital nearly four days earlier compared to control patients, with a confidence interval from six to two days (MD -3.78; 95% CI -5.90 to -1.67, $P < 0.001$) (Analysis 1.21). There was heterogeneity in the results ($I^2 = 55\%$). Inspection of the forest plot shows that this was the result of one outlying study (Engstrom 1999), which reported more days for intervention patients. The authors stated that the data on admission days in his study were skewed, as one patient accounted for 50% of the increase in the IDM group. Reanalysis with exclusion of this trial did not change the significance, direction or effect of the mean difference.

3.4.2. Hospital days per patient - long-term

One trial with 175 patients (van Wetering 2010) reported the difference in mean number of total hospital days per patient per group at 24 months follow-up. There was no difference between groups (MD 0.60; 95% CI -3.01 to 4.21, $P = 0.74$) (Analysis 1.22).

3.5 Emergency Department (ED) visits

Six trials (Smith 1999; Farrero 2001; Bourbeau 2003; Rea 2004; Rice 2010; Wakabayashi 2011) assessed in various ways the number of ED visits. We were able to pool the data from four studies with 1161 patients (Smith 1999; Bourbeau 2003; Rea 2004; Rice 2010), which revealed no difference between groups with high heterogeneity (OR 0.64; 95% CI 0.33 to 1.25; $I^2 = 71\%$)(Analysis 1.23). Sensitivity analysis on two studies which analyzed by intention-to-treat and which blinded outcome assessors revealed a mean difference of 0.49 in favor of the control group (MD 0.49; 95% CI 0.36 to 0.67, $P < 0.0001$, $I^2 = 0\%$). Three studies could not be pooled, due to lack of required data. Of these excluded studies, Trappenburg 2011 and Wakabayashi 2011 reported the mean ED visits per patient at baseline and follow-up. Both studies concluded no statistically significant difference between groups compared to baseline. On the other hand, Farrero 2001 reported a significant decrease in ED visits per patient in favor of the IDM group (0.45 ± 0.83 for intervention group, 1.58 ± 1.96 for control group; $P = 0.0001$). There were no data presented on the number of ED visits at long-term follow-up.

3.6 Patients using at least one course of oral steroids

We pooled data from three studies including 348 patients (Littlejohns 1991; Farrero 2001; Rea 2004) on the number of patients using at least one course of oral steroids until 12 months follow-up. Results were homogeneous and there was no difference between groups (OR 1.13; 95% CI 0.64 to 2.01, $P = 0.66$) (Analysis 1.24).

3.7. Patients using at least one course of antibiotics

There were two studies with 236 participants (Littlejohns 1991; Rea 2004) reporting on the number of patients using at least one course of antibiotics. The studies presented conflicting results and heterogeneity was large, as Rea 2004 was a primary care, cluster-randomized trial and Littlejohns 1991 was a RCT in the secondary care setting. The number of patients using at least one course of antibiotics was not different between groups, and the OR had a wide confidence interval (OR 1.43; 95% CI 0.24 to 8.48, P = 0.69) (Analysis 1.25).

SECONDARY OUTCOMES

4. Dyspnea

Four studies reported the MRC Dyspnea Scale as an outcome (Mendes 2010; van Wetering 2010; Gottlieb 2011; Wakabayashi 2011), however Gottlieb failed to publish any results. We pooled data from the remaining three studies, including 345 patients. Dyspnea was improved in the IDM group by -0.30 points (MD -0.30; 95% CI -0.48 to -0.11, I^2 = 0%, P < 0.001)(Analysis 1.26).

Furthermore, three studies on 145 patients used the Borg score to detect changes in perceived dyspnoea (Güell 2000; Boxall 2005; Gottlieb 2011). These data were pooled and revealed no change in dyspnoea (MD 0.14; 95% CI -0.70 to 0.98, P = 0.74, I^2 = 39%) (Analysis 1.27).

5. Mortality

Five trials assessing 1207 patients explicitly recorded mortality as an outcome. Of these, four trials assessed mortality at 12 months (Littlejohns 1991; Smith 1999; Farrero 2001; Rice 2010) and one study at 24 months (Sridhar 2008). There was no statistically significant difference between groups at short- (OR 0.96; 95% CI 0.52 to 1.74, P = 0.33; I^2 = 59%) and long-term follow-up (OR 0.45; 95% CI 0.16 to 1.28, P = 0.13) (Analysis 1.28). Heterogeneity in the short-term studies is due to different dominant components of the interventions.

6. Lung function

Lung function was measured in three different ways in 10 trials (Littlejohns 1991; Wijkstra 1994; Güell 2000; Farrero 2001;Bourbeau 2003; Wood-Baker 2006; Sridhar 2008; Fernandez 2009; van Wetering 2010; Wakabayashi 2011). Therefore, we created three different subgroups, which we pooled in two different meta-analyses: forced expiratory volume in one second (FEV1) in liters and FEV1 as per cent predicted for age, gender and height (FEV1% predicted), as well as the mean difference in FEV1% predicted from base-

line. All pooled data on short- as well as on long-term outcome revealed no significant difference in lung function between groups(Analysis 1.29; Analysis 1.30).

7. Anxiety and depression

Four studies assessed depression as an outcome (Engstrom 1999; Littlejohns 1991; Güell 2006; Trappenburg 2011). Two studies (Littlejohns 1991; Trappenburg 2011) used the HADS, one study (Engstrom 1999) used the Mood Adjective Check List (MACL) and one study (Güell 2006) used a Revised Symptom Checklist. We pooled results on the HADS in a meta-analysis including 316 patients, which revealed no statistically significant difference between groups for anxiety (MD 0.22; 95% CI -0.41 to 0.85, $I^2 = 0\%$) or depression (MD 0.21, 95% CI -0.39 to 0.81, $I^2 = 0\%$)(Analysis 1.31). Engstrom 1999 used the MACL, a shortened 38-item version covering three basic dimensions of mood: pleasantness/unpleasantness, activation/deactivation and calmness/tension. No significant differences were found between groups. The aim of Güell 2006 was specifically to evaluate the effect of a pulmonary rehabilitation program on psychosocial morbidity (without including any specific psychological intervention), as well as effort capacity and HRQoL. Therefore, the authors used a Revised Symptom Checklist, containing 90 items, which included depression and anxiety. Following a per protocol analysis, the intervention group showed a significant improvement in depression ($P \leq 0.01$) and anxiety ($P \leq 0.05$).

8. Co-ordination of care

Three studies (Littlejohns 1991; Bendstrup 1997; Koff 2009) reported in some way on the co-ordination of care. However, these studies had different intervention programs and reported on co-ordination of care in different ways. Therefore, interpretation of outcomes is difficult. Bendstrup 1997 reported an attendance rate of 78% of patients following a 12-week IDM program (consisting of education, exercise training, smoking cessation and occupational therapy).

Patient satisfaction with regard to the provided health care was measured in two studies. In Koff 2009, satisfaction with a self management/action plan program was assessed on a scale from 1 to 10 in the intervention group, with 1 being strongly dissatisfied and 10 completely satisfied. Patients expressed high satisfaction with all of the equipment used, except for the pedometer. Littlejohns 1991 designed a satisfaction questionnaire for his study, which included questions on satisfaction with level of care, the information given to patients and their knowledge of medication. The questionnaire was used in both study groups. At 12 months follow-up, there was little difference in the level of satisfaction with the service provided between groups.

DISCUSSION

Summary of main results

We reviewed the results of 26 randomised controlled trials evaluating the effect of an integrated disease management (IDM) program in patients with COPD. All included studies contained a program provided by caregivers from at least two different disciplines, with two different components (for example exercise, education, self management etc) and with a duration of at least three months. Firstly, pooled data showed statistically and clinically relevant improvements in disease-specific quality of life on the CRQ in the IDM group: dyspnoea (MD 1.02; 95% CI 0.67 to 1.36); fatigue (0.82; 95% CI 0.46 to 1.17); emotional (0.61; 95% CI 0.26 to 0.95) and mastery (0.75; 95% CI 0.38 to 1.12). All domains (dyspnoea, fatigue, emotional and mastery) exceeded the minimum clinically relevant difference until 12 months follow-up. Only two studies measured long-term results on the CRQ, which showed that the positive effect was maintained for the fatigue, emotion and mastery domains at 24 months follow-up. Furthermore, disease-specific quality of life was also measured with the SGRQ. There was considerable heterogeneity in the score on the SGRQ. After multiple sensitivity analyses, we concluded that there was a difference in the SGRQ total score in favor of patients treated with IDM, which lies around the minimal clinically relevant difference of four units. The effect was greatest for the impact domain. We could not find a difference in the SGRQ total score at long-term follow-up. Remarkably, only two studies could provide data.

Second, the pooled data showed statistically significant improvements in maximal and functional exercise capacity, with an improvement of 7 Watts and 44 meters in favor of the IDM group, respectively. Sensitivity analysis of the 6MWD lowered the effect to 15 meters, indicating the likelihood of an overestimated effect in the lower quality studies. Thirdly, the total number of patients with at least one respiratory-related hospital admission decreased from 27 per 100 to 20 per 100 patients in favor of the intervention group, with a number needed to treat of 15 patients to prevent one being admitted to hospital over three to 12 months. Mean hospitalisation days decreased on average by three days in the IDM group. The effects on the aforementioned primary outcomes are summarized in the Summary of findings for the main comparison. There was no evidence of an effect on generic quality of life, the number of patients with at least one exacerbation, the number of hospital admissions for all causes, emergency department visits, courses of antibiotics/prednisolone, dyspnoea, lung function parameters or depression scores.

Overall completeness and applicability of evidence

We found sufficient studies to address the objective of this review. All studies reported at least one primary outcome, and all studies were included in at least one pooled analysis. The COPD population in the included studies ranged from mild to very severe COPD

and trials were conducted across all types of healthcare settings in a range of different countries. Although the results of this review appear therefore to be applicable to all COPD patients worldwide, one should bear in mind that applicability may depend on the context of available healthcare resources. The IDM programs included in this review differed in the type of health care providers involved, type of components and duration of intervention, reflecting the diversity of daily practice. Overall, programs containing at least two health care providers and two different elements, showed improvements in quality of life and exercise capacity, and reduced the number of hospital admissions and days spent in the hospital. We found no differences in quality of life and exercise tolerance between patients treated in primary or secondary care. Although the mean differences between groups were lower in studies using a mono-disciplinary treatment as a control group compared to usual care, the subgroup difference did not reach statistical significance. Furthermore, subgroup analysis on studies focusing mainly on exercise programs showed a statistically significant greater improvement in exercise capacity. Further research is required to define the optimal combination, intensity and duration of components in IDM programs.

Quality of the evidence

We included RCTs only and found 26 trials assessing almost 3000 participants. A priori, we intended to perform meta-analyses on some outcomes when feasible. However, with this amount of data we were able to perform pooled data analysis for all outcomes. As a result of the complex intervention, there was a certain amount of clinical and statistical heterogeneity among studies. We have incorporated heterogeneity into the estimated effects by using random-effects analyses, where possible. Using the GRADE approach, we specified the levels of quality of the evidence (high, moderate, low and very low) in our 'Summary of findings' table. According to this approach, we checked if the included trials had limitations in terms of design, indirectness of the evidence, unexplained heterogeneity or inconsistency of the results, imprecision of the results or high probability of publication bias. If one of these factors was present, we downgraded the evidence. On the SGRQ, there was considerable variation in risk of bias between studies. Risk of bias tended to be lower in the more recently published trials compared to older trials. Sensitivity analyses based on studies with low quality did not change the direction, significance or magnitude of the effect. Therefore we concluded that the quality of the evidence was 'high'. For the CRQ, there were four studies which were all of moderate quality and presented with some form of bias, therefore we did downgrade the evidence to 'moderate' quality. We downgraded the evidence on functional exercise capacity for inconsistency, as substantial heterogeneity (I^2 = 84%) was present. After performing sensitivity analysis, the mean difference substantially decreased to 15 meters. We did not downgrade for respiratory-related admissions or hospitalisation days, as we feel the

studies presented consistent, homogeneous results. We expect that additional trials with proper description of their methods and data collection could upgrade the quality of evidence and further our findings.

Potential biases in the review process

Several methodological strengths minimized the risk of bias in this review. As definitions of IDM are still under debate, we a priori strictly determined the inclusion criteria for an IDM program, which was published in our protocol. Our definition was derived from the definitions published in the literature (Peytremann-Bridevaux 2009; Schrijvers 2009). Overall, they reported on "multiple interventions, designed to manage chronic conditions, with a focus on a multidisciplinary approach". Furthermore, these definitions suggest that IDM interventions should "focus on maximum clinical outcome, regardless of treatment setting(s) or typical reimbursement patterns". As a result, we chose to include all interventions, independent of treatment setting, and to keep our definition as simple as possible, in order to be easily understandable for readers and easy to use for us as authors when checking on all relevant literature. Therefore, we restricted the inclusion of trials to multi-component, multidisciplinary programs of at least three months duration. Furthermore, we performed comprehensive searches to identify possible studies, leading to almost 4800 potentially relevant abstracts being identified. Subsequently, three different assessors assessed the abstracts. All studies that were excluded by two authors because of the type of intervention were triple-checked by a third review author to make sure all studies describing an IDM program were included. We reached consensus on all included studies. Although we followed the inclusion criteria for IDM as stated in our protocol, final decisions on the inclusion of studies are open to interpretation or criticism.

Limitations of this review include possible bias from inconsistent reporting of data from included studies. We requested additional data from 14 authors and received an answer from 11. Six of them could provide us with additional data, which could potentially have biased the results. Furthermore, only three out of 26 studies published a study protocol with which we could compare the results sections. In the other studies, we examined whether the outcomes reported in the methods section of the paper were reported in the results section. It is possible that this could have introduced bias if the authors blanked out outcomes from their methods section.

Lastly, there was heterogeneity present in the control group as we used a broad a priori definition of controls, varying from no treatment to treatment including one component of COPD care. We acknowledge the fact that controls and usual care differ between countries and between healthcare settings. Therefore, we performed subgroup analysis to investigate to what extent a difference between the control groups possibly influenced the results. From these analyses we concluded that the effect between intervention and

control groups is less strong if patients in control groups receive one component of IDM compared to patients receiving no treatment or usual care.

Agreements and disagreements with other studies or reviews

This review adds to the results of four earlier systematic reviews analyzing IDM for COPD patients (Adams 2007; Niesink 2007; Peytremann-Bridevaux 2008; Lemmens 2009). The current review brings together new trials that were not included in any of these reviews. Some of these earlier reviews analyzed some of our primary outcomes. Adams 2007 examined the effectiveness of programs for COPD patients including chronic care model components and pooled six trials including at least two components. Pooled results did not demonstrate statistically significant differences on the SGRQ. Patients with COPD who received interventions with two or more chronic care model components had lower rates of hospitalisation and a shorter length of stay compared with control groups, comparable to our results. Lemmens 2009 examined the effectiveness of multiple interventions in asthma and COPD patients. The authors pooled data on the SGRQ from three studies in which two components of IDM were compared to usual care and three studies in which three components of IDM were compared to usual care. The effect on the SGRQ was larger if three components of IDM were used (MD -4.69; 95% CI -8.34 to -0.83 versus MD -0.95; 95% CI -4.23 to 2.34). Pooled data from five studies showed a decrease in the number of respiratory-related hospitalizations, with a pooled OR of 0.58, which is comparable to the OR of 0.67 found in this review. Niesink 2007 evaluated quality of life in COPD patients, but did not perform a meta-analysis; reasons for this were not clearly described. Five out of 10 studies showed a clinically relevant improvement in quality of life. Peytremann-Bridevaux 2008 examined the effectiveness of IDM in COPD patients on exercise tolerance, quality of life, hospital admissions and mortality. Only data on hospital admissions and exercise tolerance were pooled. Positive effects on exercise capacity are in line with this review. The authors demonstrated a mean improvement of 32 meters on the 6MWD in five studies, which is comparable to our results. Furthermore, a pooled odds ratio of 0.85 (95% CI 0.54 to 1.36) for mortality is comparable to our review. Differences between this review and these other reviews are related to differences in the inclusion criteria for patients and the focus of programs. All reviews used different definitions of IDM; however there was some overlap with this review. Lemmens 2009 et al also based their definition on the EPOC list (EPOC 2008), whereas Adams 2007 and Steuten 2009 based their definition of IDM on the chronic care model as reported by Wagner 1996. The definition used by Peytremann-Bridevaux 2008 was similar to our definition, with the only difference being a duration of the intervention of at least 12 months instead of three months. Finally, all the aforementioned systematic reviews included study designs other than RCTs.

Our findings from the St. George's Respiratory Questionnaire (SGRQ) showed improvements of a similar magnitude to those reported in two recent Cochrane reviews evaluating two other supposedly important pharmaceutical cornerstones of COPD treatment, tiotropium (Karner 2012a) and inhaled corticosteroids (Yang 2012). IDM resulted in a higher MD on the SGRQ of -3.71 compared to the MD of tiotropium (-2.89); however, the confidence interval for IDM is wider (95% CI -5.83 to -1.59) compared to the confidence interval (95% CI -3.35 to -2.44) for tiotropium.

Eight studies in this review are also evaluated in a Cochrane review assessing the effectiveness of pulmonary rehabilitation (Lacasse 2006) and four studies included in this review are also evaluated in a Cochrane review assessing the effect of self management programs (Effing 2007). In line with the review of Effing 2007 (OR 0.64; 95% CI 0.47 to 0.89) we found a decrease in respiratory-related hospital admissions (OR 0.64; 95% CI 0.47 to 0.89). Furthermore, both reviews demonstrated improvements in disease-specific quality of life, although the effects tended to be higher and clinically relevant in the pulmonary rehabilitation review (Lacasse 2006), whereas in the self management review the improvement was too small to be of clinical relevance (Effing 2007). A priori we determined subgroup analyses on the type of dominant intervention in the program. Subgroup analysis of studies containing some form of exercise training showed greater improvement in quality of life, which exceeded the clinically relevant threshold on almost all domains. These results are in line with the Lacasse review. However, a subgroup analysis performed on studies that mainly focused on self management did not exceed the minimum clinically important difference, in line with the Effing review.

Furthermore, Effing 2007 and Lacasse 2006 reported pooled estimates for functional exercise capacity. Not surprisingly, as the focus in most included pulmonary rehabilitation studies lies on exercise training, the 6MWD improved significantly by 48 meters in the Lacasse review. This effect size is comparable to our overall estimate of 44 meters and our subgroup analyses on studies including an exercise program in which we found a mean difference of 50 meters. In contrast to these results, Effing did not find any significant differences in exercise capacity at all (weighted mean difference -6.25; 95% CI -24.05 to 11.05).

We did not find a difference between groups in the number of patients with at least one exacerbation. However, we concluded that there was a reduction in the number of patients admitted and the mean number of hospital days related to exacerbations. Self management education including the use of action plans might lead to more and better self treatment of exacerbations. As a result, hospital admissions will decrease (Effing 2007). In our included studies, a self management program caused patients to respond three days sooner on complaints (Trappenburg 2011). Furthermore, patients more often initiated treatment by themselves, which could then be successfully treated with oral steroids at an early stage (Sridhar 2008). As a result, perceived exacerbations were rated

as substantially milder (Trappenburg 2011) and were less likely to result in an admission (Bourbeau 2003).

In the past few years, several systematic reviews evaluating IDM for various other chronic conditions have been published (Norris 2002; Badamgarav 2003; Gonseth 2004; Neumeyer-Gromen 2004; Knight 2005; Roccaforte 2005; Pimouguet 2010). Overall, quality of care improved with these programs, however some of the differences were in fact clinically modest (Peytremann-Bridevaux 2008). We found that the results of this review were most comparable to a systematic review evaluating patients with heart failure, which demonstrated that all-cause and heart failure-related hospitalisation rates were significantly reduced: OR 0.76 (CI 0.69 to 0.94, P < 0.0001) and OR 0.58 (CI 0.50 to 0.67, P < 0.0001), respectively (Roccaforte 2005). In studies evaluating depression and diabetes, differences in health care use and quality of care were less clear (Neumeyer-Gromen 2004; Knight 2005).

AUTHORS' CONCLUSIONS

Implications for practice

This meta-analysis provides evidence for the efficacy of integrated disease management (IDM) programs of at least three months duration for chronic obstructive pulmonary disease (COPD) patients, for up to 12 months follow-up. We found positive effects on disease-specific quality of life and exercise capacity in studies containing an exercise program, suggesting that exercise training is an important element in an IDM program. Long-term effects are still unclear, as only a few studies evaluated these. The magnitude of improvement in disease-specific quality of life was clinically relevant, especially using the Chronic Respiratory Questionnaire (CRQ).

We calculated that seven hospital admissions related to respiratory problems can be prevented for every 100 patients treated with IDM for three to 12 months, giving to a number needed to treat of 15 patients to prevent one being admitted. Furthermore, hospitalisation decreased by three days in patients treated with IDM compared to controls. This is of utmost importance, as hospitalizations contribute to the highest burden and costs in patients with COPD. The effects of IDM on the total number of patients suffering at least one exacerbation still remain unclear. It is possible that patients who have learned from education and have an action plan may recognize exacerbations at an early stage and can start medical treatment directly. It is therefore likely that further worsening of health status and hospital admissions can be prevented in these patients.

Implications for research

The following issues could be assessed if authors are planning future trials regarding the effectiveness of IDM:

1. Study quality: Overall, studies included in this systematic review were of moderate quality, as not all aspects of risk of bias were appropriately addressed. Therefore, there is a need for future trials to report a proper description of the processes of randomisation and data collection. Preferentially, a study protocol including measured outcomes should be published in advance to minimize selection and reporting bias.
2. More detailed description of intervention: A detailed description of the precise nature of the intervention is important, in order to be able to determine in the future which components, duration and intensity of a program are most effective. Ideally, we wish to determine which combination of health care providers and which components are most effective in IDM programs.
3. Consensus on reporting common outcomes: Given the huge variation in outcome measures and follow-up time points, we strongly recommend consensus on the reporting of common outcomes, such as change from baseline in health-related quality of life, in order to be able to combine more results in future meta-analyses. We advise future trial authors to measure at least one of the following outcomes: quality of life, exercise tolerance or exacerbation-related outcomes.
4. Adequate power calculation and methods of analysis: two cluster-randomized controlled trials introduced noteworthy bias due to inadequate methods of analysis, not taking the clustering into account (Rea 2004; Wood-Baker 2006) and loss to follow-up of clusters (Rea 2004). Therefore, we recommend performing a proper power calculation beforehand and, if needed, adjusting this calculation for intra-cluster effects (Guyatt 2011; Higgins 2011).

Finally, given the heterogeneity of interventions, there is a need to reach consensus on which interventions are likely to yield the best results when applying integrated care programs for COPD.

REFERENCES TO STUDIES

Included studies

Aiken 2006

Aiken LS, Butner J, Lockhart CA, Volk-Craft BE, Hamilton G, Williams FG. Outcome evaluation of a randomized trial of the PhoenixCare intervention: program of case management and coordinated care for the seriously chronically ill. Journal of Palliative Medicine 2006;9(1):111-26.

Bendstrup 1997

Bendstrup KE, Ingemann Jensen J, Holm S, Bengtsson B. Out-patient rehabilitation improves activities of daily living, quality of life and exercise tolerance in chronic obstructive pulmonary disease. European Journal of Respiratory Diseases 1997;10(12):2801-6.

Bourbeau 2003

Bourbeau J, Collet JP, Schwartzman K, Ducruet T, Nault D, Bradley C. Economic benefits of self-management education in COPD. Chest 2006;130(6):1704-11.

* Bourbeau J, Julien M, Maltais F, Rouleau M, Beaupre A, Begin R, et al. Reduction of hospital utilization in patients with chronic obstructive pulmonary disease: a disease-specific self-management intervention. Archives of Internal Medicine 2003;163(5):585-91.

Sedeno MF, Nault D, Hamd DH, Bourbeau J. A self-management education program including an action plan for acute COPD exacerbations. COPD 2009;6(5):352-8.

Boxall 2005

Boxall AM, Barclay L, Sayers A, Caplan GA. Managing chronic obstructive pulmonary disease in the community. A randomized controlled trial of home-based pulmonary rehabilitation for elderly housebound patients. Journal of Cardiopulmonary Rehabilitation 2005;25(6):378-85.

Cambach 1997

Cambach W, Chadwick-Straver RV, Wagenaar RC, van Keimpema AR, Kemper HC. The effects of a community-based pulmonary rehabilitation programme on exercise tolerance and quality of life: a randomized controlled trial. European Respiratory Journal 1997;10(1):104-13.

Dheda 2004

Dheda K, Crawford A, Hagan G, Roberts CM. Implementation of British Thoracic Society guidelines for acute exacerbation of chronic obstructive pulmonary disease: impact on quality of life. Postgraduate Medical Journal 2004;80(941):169-71.

Engstrom 1999

Engstrom CP, Persson LO, Larsson S, Sullivan M. Long-term effects of a pulmonary rehabilitation programme in outpatients with chronic obstructive pulmonary disease: a randomized controlled study. Scandinavian Journal of Rehabilitation Medicine 1999;31(4):207-13.

Farrero 2001

Farrero E, Escarrabill J, Prats E, Maderal M, Manresa F. Impact of a hospital-based home-care program on the management of COPD patients receiving long-term oxygen therapy. Chest 2001;119(2):364-9.

Fernandez 2009

Fernandez AM, Pascual J, Ferrando C, Arnal A, Vergara I, Sevila V. Home-based pulmonary rehabilitation in very severe COPD: is it safe and useful? Journal of Cardiopulmonary Rehabilitation and Prevention 2009;29(5):325-31.

Gottlieb 2011

Gottlieb V, Lyngso AM, Nybo B, Frolich A, Backer V. Pulmonary rehabilitation for moderate COPD (GOLD 2)--does it have an effect? COPD 2011;8(5):380-6.

Güell 2000

Güell R, Casan P, Belda J, Sangenis M, Morante F, Guyatt GH, et al. Long-term effects of outpatient rehabilitation of COPD: A randomized trial. Chest 2000;117(4):976-83.

Güell 2006

Güell R, Resqueti V, Sangenis M, Morante F, Martorell B, Casan P, et al. Impact of pulmonary rehabilitation on psychosocial morbidity in patients with severe COPD. Chest 2006;129(4):899-904.

Koff 2009

Koff PB, Jones RH, Cashman JM, Voelkel NF, Vandivier RW. Proactive integrated care improves quality of life in patients with COPD. European Respiratory Journal 2009;33(5):1031-8.

Littlejohns 1991

Littlejohns P, Baveystock CM, Parnell H, Jones PW. Randomised controlled trial of the effectiveness of a respiratory health worker in reducing impairment, disability, and handicap due to chronic airflow limitation. Thorax 1991;46(8):559-64.

Mendes 2010

Mendes de Oliveira JC, Studart Leitao Filho FS, Malosa Sampaio LM, Negrinho de Oliveira AC, Hirata RP, Costa D, et al. Outpatient vs. home-based pulmonary rehabilitation in COPD: a randomized controlled trial. Multidisciplinary Respiratory Medicine 2010;5(6):401-8.

Rea 2004

Rea H, McAuley S, Stewart A, Lamont C, Roseman P, Didsbury P. A chronic disease management programme can reduce days in hospital for patients with chronic obstructive pulmonary disease. Internal Medicine Journal 2004;34(11):608-14.

Rice 2010

Rice KL, Dewan N, Bloomfield HE, Grill J, Schult TM, Nelson DB, et al. Disease management program for chronic obstructive pulmonary disease: a randomized controlled trial. American Journal of Respiratory and Critical Care Medicine 2010;182(7):890-6.

Smith 1999

Smith BJ, Appleton SL, Bennett PW, Roberts GC, Del Fante P, Adams R, et al. The effect of a respiratory home nurse intervention in patients with chronic obstructive pulmonary disease (COPD). Australian and New Zealand Journal of Medicine 1999;29(5):718-25.

Sridhar 2008

Sridhar M, Taylor R, Dawson S, Roberts NJ, Partridge MR. A nurse led intermediate care package in patients who have been hospitalised with an acute exacerbation of chronic obstructive pulmonary disease. Thorax 2008;63(3):194-200.

Strijbos 1996

Strijbos JH, Postma DS, van Altena R, Gimeno F, Koeter GH. A comparison between an outpatient hospital-based pulmonary rehabilitation program and a home-care pulmonary rehabilitation program in patients with COPD. A follow-up of 18 months. Chest 1996;109(2):366-72.

Theander 2009

Theander K, Jakobsson P, Jorgensen N, Unosson M. Effects of pulmonary rehabilitation on fatigue, functional status and health perceptions in patients with chronic obstructive pulmonary disease: a randomized controlled trial. Clinical Rehabilitation 2009;23(2):125-36.

Trappenburg 2011

Trappenburg JC, Koevoets L, de Weert-van Oene GH, Monninkhof EM, Bourbeau J, Troosters T, et al. Action Plan to enhance self-management and early detection of exacerbations in COPD patients; a multicenter RCT. BMC Pulmonary Medicine 2009;9:52.

* Trappenburg JC, Monninkhof EM, Bourbeau J, Troosters T, Schrijvers AJ, Verheij TJ, et al. Effect of an action plan with ongoing support by a case manager on exacerbation-related outcome in patients with COPD: a multicentre randomised controlled trial. Thorax 2011;66(11):977-84.

van Wetering 2010

Hoogendoorn M, van Wetering CR, Schols AM, Rutten-van Molken MP. Is INTERdisciplinary COMmunity-based COPD management (INTERCOM) cost-effective? European Respiratory Journal 2010;35(1):79-87.

* van Wetering CR, Hoogendoorn M, Mol SJ, Rutten-van Molken MP, Schols AM. Short- and long-term efficacy of a community-based COPD management programme in less advanced COPD: a randomised controlled trial. Thorax 2010;65(1):7-13.

Wakabayashi 2011

Wakabayashi R, Motegi T, Yamada K, Ishii T, Jones RC, Hyland ME, et al. Efficient integrated education for older patients with chronic obstructive pulmonary disease using the Lung Information Needs Questionnaire. Geriatrics & Gerontology International 2011;11(4):422-30.

Wijkstra 1994

Wijkstra PJ, Ten Vergert EM, van Altena R, Otten V, Kraan J, Postma DS, et al. Long term benefits of rehabilitation at home on quality of life and exercise tolerance in patients with chronic obstructive pulmonary disease. Thorax 1995;50(8):824-8.

Wijkstra PJ, Van Altena R, Kraan J, Otten V, Postma DS, Koeter GH. Quality of life in patients with chronic obstructive pulmonary disease improves after rehabilitation at home. European Respiratory Journal 1994;7(2):269-73.

Wijkstra PJ, van der Mark TW, Kraan J, van Altena R, Koeter GH, Postma DS. Effects of home rehabilitation on physical performance in patients with chronic obstructive pulmonary disease (COPD). European Respiratory Journal 1996;9(1):104-10.

Wijkstra PJ, van der Mark TW, Kraan J, van Altena R, Koeter GH, Postma DS. Long-term effects of home rehabilitation on physical performance in chronic obstructive pulmonary disease. American Journal of Respiratory and Critical Care Medicine 1996;153(4 Pt 1):1234-41.

Wood-Baker 2006

Wood-Baker R, McGlone S, Venn A, Walters EH. Written action plans in chronic obstructive pulmonary disease increase appropriate treatment for acute exacerbations. Respirology (Carlton, Vic.) 2006;11(5):619-26.

Additional references

Adams 2007

Adams SG, Smith PK, Allan PF, Anzueto A, Pugh JA, Cornell JE. Systematic review of the chronic care model in chronic obstructive pulmonary disease prevention and management. Archives of Internal Medicine 2007;167(6):551-61.

Agusti 2010

Agusti A, Calverley PM, Celli B, Coxson HO, Edwards LD, Lomas DA, et al. Characterisation of COPD heterogeneity in the ECLIPSE cohort. Respiratory Research 2010;11:122.

Badamgarav 2003

Badamgarav E, Weingarten SR, Henning JM, Knight K, Hasselblad V, Gano A Jr, et al. Effectiveness of disease management programs in depression: a systematic review. American Journal of Psychiatry 2003;160(12):2080-90.

Beck 1961

Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Archives of General Psychiatry 1961;4:561-71.

Bestall 1999

Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. Thorax 1999;54(7):581-6.

Bonomi 2002

Bonomi AE, Wagner EH, Glasgow RE, VonKorff M. Assessment of chronic illness care (ACIC): a practical tool to measure quality improvement. Health Services Research 2002;37(3):791-820.

Borg 1970

Borg G. Perceived exertion as an indicator of somatic stress. Scandinavian Journal of Rehabilitation Medicine 1970;2(2):92-8.

Bourbeau 2013

Bourbeau J, Saad N. Integrated care model with self-management in chronic obstructive pulmonary disease: From family physicians to specialists. Chronic Respiratory Disease 2013;10:93-4.

Britton 2003

Britton M. The burden of COPD in the U.K.: results from the Confronting COPD survey. Respiratory Medicine 2003;97(Suppl C):S71-9.

Burgel 2010

Burgel PR, Paillasseur JL, Caillaud D, Tillie-Leblond I, Chanez P, Escamilla R, et al. Clinical COPD phenotypes: a novel approach using principal component and cluster analyses. European Respiratory Journal 2010;36(3):531-9.

Calverley 2003

Calverley PM, Walker P. Chronic obstructive pulmonary disease. Lancet 2003;362(9389):1053-61.

Campbell 2001

Campbell MK, Mollison J, Grimshaw JM. Cluster trials in implementation research: estimation of intracluster correlation coefficients and sample size. Statistics in Medicine 2001;20(3):391-9.

Care Continuum Alliance

Care Continuum Alliance (CCA) Definition of Disease Management. www.carecontinuum.org/ (accessed 19 May 2011).

Chavannes 2008

Chavannes NH. Integrated chronic obstructive pulmonary disease management in primary care. Disease Management & Health Outcomes 2008;16(5):1.

Cote 2009

Cote CG, Celli BR. BODE index: a new tool to stage and monitor progression of chronic obstructive pulmonary disease. Pneumonologia i Alergologia Polska: organ Polskiego Towarzystwa Ftyzjopneumonologicznego, Polskiego Towarzystwa Alergologicznego, i Instytutu Gruzlicy i Chorob Pluc 2009;77(3):305-13.

De Angelis 2004

De Angelis C, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R, et al. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. Annals of Internal Medicine 2004;141(6):477-8.

Dellby 1996

Dellby U. Drastically improving health care with focus on managing the patient with a disease: the macro and micro perspective. International Journal of Health Care Quality Assurance 1996;9(2):4-8.

Domingo-Salvany 2002

Domingo-Salvany A, Lamarca R, Ferrer M, Garcia-Aymerich J, Alonso J, Felez M, et al. Health-related quality of life and mortality in male patients with chronic obstructive pulmonary disease. American Journal of Respiratory and Critical Care Medicine 2002;166(5):680-5.

Effing 2007

Effing T, Monninkhof EEM, van der Valk PP, Zielhuis GGA, Walters EH, van der Palen JJ, et al. Self-management education for patients with chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews 2007, Issue 4. Art. No.: CD002990. DOI: 10.1002/14651858.CD002990.pub2.

Ellrodt 1997

Ellrodt G, Cook DJ, Lee J, Cho M, Hunt D, Weingarten S. Evidence-based disease management. JAMA 1997;278(20):1687-92.

Engstrom 1996

Engstrom CP, Persson LO, Larsson S, Ryden A, Sullivan M. Functional status and well being in chronic obstructive pulmonary disease with regard to clinical parameters and smoking: a descriptive and comparative study. Thorax 1996;51(8):825-30.

EPOC 2008

Cochrane Effective Practice and Organization of Care Review Group. Data collection checklist.

Epstein 1996

Epstein RS, Sherwood LM. From outcomes research to disease management: a guide for the perplexed. Annals of Internal Medicine 1996;124(9):832-7.

EuroQol Group 1990

The EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy 1990;16(3):199-208.

Fan 2002

Fan VS, Curtis JR, Tu SP, McDonell MB, Fihn SD. Using quality of life to predict hospitalization and mortality in patients with obstructive lung diseases. Chest 2002;122(2):429-36.

Faxon 2004

Faxon DP, Schwamm LH, Pasternak RC, Peterson ED, McNeil BJ, Bufalino V, et al. Improving quality of care through disease management: principles and recommendations from the American Heart Association's Expert Panel on Disease Management. Circulation 2004;109(21):2651-4.

Gerardi 1996

Gerardi DA, Lovett L, Benoit-Connors ML, Reardon JZ, ZuWallack RL. Variables related to increased mortality following out-patient pulmonary rehabilitation. European Respiratory Journal 1996;9(3):431-5.

Glasgow 2005

Glasgow RE, Wagner EH, Schaefer J, Mahoney LD, Reid RJ, Greene SM. Development and validation of the Patient Assessment of Chronic Illness Care (PACIC). Medical Care 2005;43(5):436-44.

GOLD 2009

GOLD. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease 2009. http://www.goldcopd.com/ (accessed 4/10/13).

Gonseth 2004

Gonseth J, Guallar-Castillon P, Banegas JR, Rodriguez-Artalejo F. The effectiveness of disease management programmes in reducing hospital re-admission in older patients with heart failure: a systematic review and meta-analysis of published reports. European Heart Journal 2004;25(18):1570-95.

GRADE Working Group 2004

GRADE Working Group. Grading quality of evidence and strength of recommendations. BMJ 2004;328:1490-4.

Guyatt 1987

Guyatt GH, Berman LB, Townsend M, Pugsley SO, Chambers LW. A measure of quality of life for clinical trials in chronic lung disease. Thorax 1987;42(10):773-8.

Guyatt 2011

Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coello P, et al. GRADE guidelines: 4. Rating the quality of evidence--study limitations (risk of bias). Journal of Clinical Epidemiology 2011;64(4):407-15.

Higgins 2011

Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1 (updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Hurst 2010

Hurst JR, Vestbo J, Anzueto A, Locantore N, Mullerova H, Tal-Singer R, et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. New England Journal of Medicine 2010;363(12):1128-38.

Jones 1991

Jones PW, Quirk FH, Baveystock CM. The St George's Respiratory Questionnaire. Respiratory Medicine 1991;85 Suppl B:25-31; discussion 33-7.

Jones 2005

Jones PW. St. George's Respiratory Questionnaire: MCID. COPD 2005;2(1):75-9.

Jones 2009

Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD Assessment Test. European Respiratory Journal 2009;34(3):648-54.

Karner 2012a

Karner C, Chong J, Poole P. Tiotropium versus placebo for chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews 2012, Issue 7. Art. No.: CD009285. DOI: 10.1002/14651858.CD009285.pub2.

Kerry 1998

Kerry SM, Bland JM. The intracluster correlation coefficient in cluster randomisation. BMJ (Clinical research ed.) 1998;316(7142):1455.

Knight 2005

Knight K, Badamgarav E, Henning JM, Hasselblad V, Gano AD Jr, Ofman JJ, et al. A systematic review of diabetes disease management programs. American Journal of Managed Care 2005;11(4):242-50.

Kocks 2006

Kocks JW, Tuinenga MG, Uil SM, van den Berg JW, Stahl E, van der Molen T. Health status measurement in COPD: the minimal clinically important difference of the clinical COPD questionnaire. Respiratory Research 2006;7:62.

Lacasse 2006

Lacasse Y, Goldstein R, Lasserson TJ, Martin S. Pulmonary rehabilitation for chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews 2006, Issue 4. Art. No.: CD003793. DOI: 10.1002/14651858.CD003793.pub2.

Lefebvre 2009

Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions 5.1 (updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Lemmens 2009

Lemmens KM, Nieboer AP, Huijsman R. A systematic review of integrated use of disease-management interventions in asthma and COPD. Respiratory Medicine 2009;103(5):670-91.

Lopez 2006

Lopez AD, Shibuya K, Rao C, Mathers CD, Hansell AL, Held LS, et al. Chronic obstructive pulmonary disease: current burden and future projections. European Respiratory Journal 2006;27(2):397-412.

Martinez 2006

Martinez FJ, Foster G, Curtis JL, Criner G, Weinmann G, Fishman A, et al. Predictors of mortality in patients with emphysema and severe airflow obstruction. American Journal of Respiratory and Critical Care Medicine 2006;173(12):1326-34.

Neumeyer-Gromen 2004

Neumeyer-Gromen A, Lampert T, Stark K, Kallischnigg G. Disease management programs for depression: a systematic review and meta-analysis of randomized controlled trials. Medical Care 2004;42(12):1211-21.

Niesink 2007

Niesink A, Trappenburg JC, de Weert-van Oene GH, Lammers JW, Verheij TJ, Schrijvers AJ. Systematic review of the effects of chronic disease management on quality-of-life in people with chronic obstructive pulmonary disease. Respiratory Medicine 2007;101(11):2233-9.

Norris 2002

Norris SL, Nichols PJ, Caspersen CJ, Glasgow RE, Engelgau MM, Jack L, et al. The effectiveness of disease and case management for people with diabetes. A systematic review. American Journal of Preventive Medicine 2002;22(Suppl 4):15-38.

Norris 2003

Norris SL, Glasgow RE, Engelgau MM, O'Connor PJ, McCulloch D. Chronic disease management: a definition and systematic approach to component interventions. Disease Management and Health Outcomes 2003;11(8):477-88.

Peytremann-Bridevaux 2008

Peytremann-Bridevaux I, Staeger P, Bridevaux PO, Ghali WA, Burnand B. Effectiveness of chronic obstructive pulmonary disease-management programs: systematic review and meta-analysis. American Journal of Medicine 2008;121(5):433-43.e4.

Peytremann-Bridevaux 2009

Peytremann-Bridevaux I, Burnand B. Letter to the editor. Disease management: a proposal for a new definition. International Journal of Integrated Care 2009;9:1.

Pimouguet 2010

Pimouguet C, Le Goff M, Thiebaut R, Dartigues JF, Helmer C. Effectiveness of disease-management programs for improving diabetes care: a meta-analysis. Canadian Medical Association Journal 2010;183(2):E115-27.

Pinto-Plata 2004

Pinto-Plata VM, Cote C, Cabral H, Taylor J, Celli BR. The 6-min walk distance: change over time and value as a predictor of survival in severe COPD. European Respiratory Journal 2004;23(1):28-33.

Puhan 2006

Puhan MA, Soesilo I, Guyatt GH, Schunemann HJ. Combining scores from different patient reported outcome measures in meta-analyses: when is it justified? Health and Quality of Life Outcomes 2006;4:94.

Puhan 2008

Puhan MA, Mador MJ, Held U, Goldstein R, Guyatt GH, Schunemann HJ. Interpretation of treatment changes in 6-minute walk distance in patients with COPD. European Respiratory Journal 2008;32(3):637-43.

Rao 1992

Rao JNK, Scott AJ. A simple method for the analysis of clustered binary data. Biometrics 1992;48:577-85.

Redelmeier 1997

Redelmeier DA, Bayoumi AM, Goldstein RS, Guyatt GH. Interpreting small differences in functional status: the Six Minute Walk test in chronic lung disease patients. American Journal of Respiratory and Critical Care Medicine 1997;155(4):1278-82.

RevMan 5

Review Manager (RevMan) (Computer program]. Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008.

Roccaforte 2005

Roccaforte R, Demers C, Baldassarre F, Teo KK, Yusuf S. Effectiveness of comprehensive disease management programmes in improving clinical outcomes in heart failure patients. A meta-analysis. European Journal of Heart Failure 2005;7(7):1133-44.

Schrijvers 2009

Schrijvers G. Disease management: a proposal for a new definition. International Journal of Integrated Care 2009;9:e06.

Seemungal 1998

Seemungal TA, Donaldson GC, Paul EA, Bestall JC, Jeffries DJ, Wedzicha JA. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. American Journal of Respiratory and Critical Care Medicine 1998;157(5 Pt 1):1418-22.

Seemungal 2000

Seemungal TA, Donaldson GC, Bhowmik A, Jeffries DJ, Wedzicha JA. Time course and recovery of exacerbations in patients with chronic obstructive pulmonary disease. American Journal of Respiratory and Critical Care Medicine 2000;161(5):1608-13.

Singh 1992

Singh S. The use of field walking tests for assessment of functional capacity in patients with chronic airways obstruction. Physiotherapy 1992;78:102-4.

Steuten 2009

Steuten LM, Lemmens KM, Nieboer AP, Vrijhoef HJ. Identifying potentially cost effective chronic care programs for people with COPD. International Journal of Chronic Obstructive Pulmonary Disease 2009;4:87-100.

Tiep 1997

Tiep BL. Disease management of COPD with pulmonary rehabilitation. Chest 1997;112(6):1630-56.

van der Molen 2003

van der Molen T, Willemse BW, Schokker S, ten Hacken NH, Postma DS, Juniper EF. Development, validity and responsiveness of the Clinical COPD Questionnaire. Health and Quality of Life Outcomes 2003;1:13.

Wagner 1996

Wagner EH, Austin BT, Von Korff M. Improving outcomes in chronic illness. Managed Care Quarterly 1996;4(2):12-25.

Wagner 2001

Wagner EH, Austin BT, Davis C, Hindmarsh M, Schaefer J, Bonomi A. Improving chronic illness care: translating evidence into action. Health Affairs (Project Hope) 2001;20(6):64-78.

Ware 1992

Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Medical Care 1992;30(6):473-83.

Wedzicha 2000

Wedzicha JA. The heterogeneity of chronic obstructive pulmonary disease. Thorax 2000;55(8):631-2.

Weingarten 2002

Weingarten SR, Henning JM, Badamgarav E, Knight K, Hasselblad V, Gano A Jr, et al. Interventions used in disease management programmes for patients with chronic illness - which ones work? Meta-analysis of published reports. BMJ (Clinical Research Ed.) 2002;325(7370):925.

WHO 2008

World Health Organization. World Health Statistics 2008. Available from: http://www.who.int/whosis/whostat/2008/en/index.html.

Yang 2012

Yang IA, Clarke MS, Sim EHA, Fong KM. Inhaled corticosteroids for stable chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews 2012, Issue 7. Art. No.: CD002991. DOI: 10.1002/14651858.CD002991.pub3.

Zigmond 1983

Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatrica Scandinavica 1983;67(6):361-70.

Zitter 1997

Zitter M. A new paradigm in health care delivery: disease management. In: Todd WE, Nash D, editor(s). Disease Management: a Systems Approach to Improving Patient Outcomes. Chicago: American Hospital Association, 1997:1-25.

Characteristics of included studies

Aiken 2006	
Methods	RCT; follow-up: unknown; control group: usual care, which means patients receiving care from managed care organizations (MCO)
Participants	Eligible: 192 (COPD and congestive heart failure); Randomized COPD: 61 Mean age/sex: not reported for COPD patients Inclusion criteria: COPD or congestive heart failure patients, palliative treatment residing at home, receiving care by MCO, mean life expectancy of 2 years, saturation < 88%, oxygen usage, marked limitation of physical functioning, recent exacerbation
Interventions	Phoenix Care palliative intervention services were added to treatment services of local MCOs. Registered nurse case managers (serving 30 to 35 patients) provided the intervention service. These nurses worked with protocols and held contact with the attending physicians. Furthermore, they developed care plans, provided education to patients and tailored self management of the disease. They supported services including assessing psychological and spiritual needs. During exacerbation episodes, the nurses assessed medical status, implemented a symptom control intervention and contacted the physician Included health care providers (HCP): GP, nurse case manager
Outcomes	SF-36, medical utilization
Notes	Main component of program: structured follow-up with nurses/GP

Bendstrup 1997	
Methods	RCT; follow-up: 24 weeks; control group: no treatment
Participants	Eligible: 47 Completed: 32 Mean age I: 64 yrs, C: 65 yrs Sex (% male) both groups: 56% Inclusion criteria: diagnosis of COPD according to GOLD, FEV1 of 25% to 55% of predicted value, Tiffeneau index less than 70%, stable condition for 4 weeks (no change in exercise status, sputum color/quantity, no change in medication) Major exclusions: heart disease, musculoskeletal disease limiting exercise, intermittent claudication limiting exercise
Interventions	12 week program including: - Exercise training (strength training, backwards/sideways walking, endurance training): 3 times per week for 1 hour during 12 weeks. Patients were encouraged to train at home - Occupational therapy: 2 group sessions - Education: 12 sessions, including proper administration, inhalation techniques, psychological education, socioeconomic problems and nutrition - Smoking cessation: free nicotine patches, education Included HCP: practice nurse, physiotherapist, dietician, psychologist, occupational therapist, social worker, physician
Outcomes	Chronic Respiratory Disease Questionnaire (CRDQ), York Quality of Life Questionnaire (YQLQ), 6MWD, lung function, patient attendance, staff working hours
Notes	Main component of program: exercise

Bourbeau 2003	
Methods	RCT; follow-up: 12 months; control group: usual care
Participants	Eligible: 469 Randomized: 191 Completed: 165 Mean age: I: 69 yrs; C: 70 yrs; Sex (% male): I: 52%; C: 59%; Inclusion criteria: stable COPD with at least one hospitalisation for an exacerbation in preceding year, age ≥ 50 yrs, pack yrs ≥ 10 yrs, FEV1% predicted (post-bronchodilator): 25% to 70%, FEV1/VC < 70%; Major exclusions: no previous diagnosis of asthma or left congestive heart failure, terminal disease, dementia, uncontrolled psychiatric disease, no pulmonary rehab < 1 yrs ago, no long-term facility stays
Interventions	A disease-specific self management program (Living Well with COPD) of 7 to 8 weeks of follow-up including: - Individual sessions of education by an experienced health professional at the patient's home - Content of education: COPD knowledge, breathing and coughing techniques, energy conservation during day-by-day activities, relaxation exercises; preventing and controlling symptoms through inhalation techniques, understanding and using a plan of action for acute exacerbation, adopting a healthy lifestyle, leisure activities and travelling, a simple home exercise program and long-term home oxygen therapy - An action plan for acute exacerbations was customized for each patient Intensity: education 1 hour per week during 7 to 8 weeks, follow-up first 2 months weekly telephone calls, then once a month a telephone call. Exercise evaluation (not mandatory): 3 times per week, 30 to 45-min/session + exercise teaching Included HCP: nurse, physiotherapist, physician, pulmonologist
Outcomes	SGRQ, exacerbations, spirometry, FEV1 (L), forced vital capacity, hospital admissions, symptoms, emergency room visits, outpatients visits, 6MWT, walking distance
Notes	Main component of program: self management (including action plan)

Boxall 2005	
Methods	RCT; follow-up 12 weeks; control group: usual care
Participants	Eligible: not clear; Randomized: 60; Completed: 46; Mean age I: 78 yrs; C: 76 yrs; Sex (% male): I: 48%; C: 65%; Inclusion criteria: diagnosis of COPD by a respiratory specialist, age > 60 yrs, dyspnoea on exertion, live locally, motivated to exercise daily unsupervised, stable for 2 weeks, functionally housebound; Major exclusions: attending outpatient based PR, restricted shoulder movement, living in nursing home, previous lung volume surgery, pain limiting mobility
Interventions	12 week program including: - Exercise consisting of walking (level 1 to 10) and arm exercises (1 to 18) + education sessions. Patients were required to carry out exercise daily. Weekly physiotherapy visits were scheduled for the first 6 weeks, and then visits were made until week 12 of the program. Visits were used to monitor exercise performance, progress exercises, retest 6MWT at regular intervals (weeks 1, 4, 6, 8 and 12 of the program) and provide encouragement to patients - Educational sessions for patients and carers were conducted by physiotherapists, nurses and occupational therapy staff in their homes. Those sessions covered: anatomy and physiology of the lungs, use of respiratory devices, medications, breathing techniques, secretion removal techniques, energy conservation, use of adaptive aids and stress management. Patients received on average 11 home visits during the program Included HCP: physiotherapists, nurses, occupational therapist
Outcomes	Health status: SGRQ, 6MWD, hospital admissions, average length of stay, dyspnoea Borg Scale
Notes	Main component of program: exercise

Cambach 1997	
Methods	RCT with cross-over design; follow-up 6 months; control group: drug treatment only
Participants	Eligible: 89 (asthma and COPD) Analyzed: 23 (COPD); Mean age I : 62 yrs, C: 62 yrs; Sex (% male): I: 47%, C: 75%; Diagnosis of asthma or COPD according to guidelines, evidence of dyspnoea and decreased exercise tolerance as a result of obstructive lung disease, 18 to 75 yrs, ability to travel independently to the physiotherapy practice, medication prescribed by a pulmonary physician, motivation to improve self care, informed consent. Major exclusions: 1) manifest cardiac complaints, 2) hypercapnia and/or hypoxia
Interventions	12 weeks intervention including: Exercise group sessions of 3 to 4 participants including techniques of breathing retraining and evacuation of mucus, exercise training, patient education, relaxation techniques and recreational activities. Training was 3 days a week for 90 minutes. Exercise training was performed twice a week on a cycle ergometer and by stair-walking. Recreational activities were once a week for 45 min. Education sessions were every week for 45 min Included HCP: nurse, physiotherapist
Outcomes	6MWT, incremental cycle ergometer test, CRQ
Notes	Main component of program: exercise

Dheda 2004	
Methods	RCT; follow-up 6 months; control group: primary care follow-up
Participants	Eligible: 33; Completed: 25; Mean age I: 68 yrs, C: 71 yrs; Sex (% male) both groups: unknown. Diagnosis COPD according to British Thoracic Society guidelines, patients with a first admission to hospital, with progressive symptoms, a smoking history of > 20 pack-years. Major exclusions: another dominant medical condition, a mandatory reason for hospital follow-up
Interventions	Intervention program of 6 months A respiratory nurse and/or chest physician reviewed the intervention group at least 4 times in the 6 month period (at 6, 8, 12 or 16 weeks). The following interventions were made at some or all of these visits: spirometry with reversibility, review of inhaler technique and peak flow diary, ambulatory oxygen assessment, smoking cessation advice, steroid trial, nebuliser assessments, review of medication, advice about nutrition and exercise, and introduction to a patient support group Included HCP: nurse, chest physician
Outcomes	SGRQ, SF-36
Notes	Main component of program: structured follow-up with nurse/GP

Engstrom 1999	
Methods	RCT; follow-up 12 months; control group: usual outpatient care
Participants	Eligible: 58; Randomized: 55; Completed: 50; Mean age I: 66 yrs, C: 67 yrs; Sex (% male) I: 54%, C: 50%. Clinical diagnosis of COPD, developing after at least 10 yrs of smoking, FEV1 < 50%, debut of symptoms after 40 yrs of age, dyspnoea mainly elicited by exercise or infections, no allergy. Major exclusions: disabling or severe diseases, co-existence of other causes of impaired pulmonary function
Interventions	12 months rehabilitation program including: - Exercise training sessions (bicycle, arm and breathing techniques), 2/week for 6 weeks, once weekly for 6 weeks, once every second week for 6 weeks and then once a month for remaining period. Every session: 45 min. Furthermore, instructions for daily walks and an individualized daily 30-min home-training program - Individualized educational program with outpatient team (nurse and physician) on visit every 3 months - Occupational therapist gave 2 group sessions about energy saving techniques and 2 global education sessions - Dietician gave information about nutrition in COPD patients and intervened in malnutrition Included HCP: physiotherapist, nurse, physician, dietician, occupational therapist
Outcomes	SGRQ, 6-MWD, W-max, days in hospital, SIP, Mood Adjective Check List (MACL)
Notes	Main component of program: exercise

Farrero 2001	
Methods	RCT; follow-up 12 months; control group: usual care
Participants	Randomized: 122; Completed: 94; Mean age I: 69 yrs, C: 69 yrs Clinical diagnosis of COPD, requiring oxygen for at least 6 months, with willingness to participate in a hospital based home-care program, and with residence within easy reach of the hospital
Interventions	Hospital based home-care program of 12 months with the aim of combining home-care management and easy access to hospital resources. Program included: - Monthly telephone calls and 3-monthly home visits from a nurse, working closely with a physician. Patients could also request with an immediate response, which varied according to a home visit, a hospital visit, telephone advice or a control visit. Included HCP: nurse and physician
Outcomes	CRQ, spirometry, mortality, hospital admissions, hospital days, ED visits
Notes	Main component of program: structured follow-up with nurses

Fernandez 2009	
Methods	RCT; follow-up 12 months; control group: education (mono-disciplinary intervention)
Participants	Eligible: 50; Randomized: 50 (I: 30; C: 20); Mean age: 66 yrs, C: 70 yrs; Sex: 100% male (both groups) Inclusion criteria: GOLD 4 patients, younger than 80 yrs of age, stable COPD, defined as a period of 2 months without any exacerbations, defined as signs of acute dyspnoea requiring medical attention, changes in the quantity and characteristics of sputum, an increase in pulmonary noise or an increase in the necessity for medication, the correct administration of pharmacological treatment according to GOLD, home treatment with oxygen for at least 6 months prior to the commencement of the study Major exclusions: severe cardiovascular pathology, unstable angina, acute myocardial infarction, cerebral vascular accident, or physical or psychological disorder that impede the practice of physical exercise
Interventions	Rehab program of 11 months At the start: 2 one-hour sessions of respiratory re-education in the hospital, where exercises at home were taught. Home-rehab program : - 1 hour of exercise per day (respiratory reeducation, muscular inspiratory training, muscular training of upper and lower limbs) - First 2 months: attendance of physiotherapist at home (who visited twice monthly for 1 hour) - Month 2 to 9: single monthly visits physiotherapist, included resistance training, respiratory reeducation, isotonic training, training of respiratory muscles - 3 respiratory education sessions by nursing staff (handling of inhalers, knowledge of the illness, what to do in the event of attack) Included HCP: nurse, physiotherapist
Outcomes	Pulmonary function, SGRQ, 6MWD
Notes	Main component of program: exercise

Gottlieb 2011	
Methods	RCT; follow-up: 18 months; control group: usual care
Participants	Eligible: 133; Randomized: 61; Completed: 26; Mean age I: 74 yrs, C: 73 yrs; Sex (% male): I: 32%, C: 35%. Inclusion criteria: a diagnosis of moderate COPD, FEV1/FVC < 0.7 and 50% ≤ FEV1 < 80% with motivation for pulmonary rehabilitation. Exclusion criteria:1. Co-morbidity contraindicating rehabilitation, 2. Participation in PR within the last year, 3. Cognitive disorders limiting the ability to participate in physical training and educational sessions
Interventions	Program of intensive training for 7 weeks, with maintenance program for 6 months, including: - Intensive 7-week physical training and educational phase led by a multidisciplinary team. Furthermore, smoking cessation counseling given on an individual basis and a dietary intervention consisted of group cookery classes and individual sessions - Final interview following completion of the program, in which participants' achievements were compared to the original goals - Maintenance program for 6 months, including a 90-min monthly session focusing on ways of incorporating exercise in daily life, and 2 sessions on exercise activities in the local community, and another 2 sessions on exercise as well as on repetition of relevant topics Included HCP: multidisciplinary team, not further specified. Authors were unreachable for further information.
Outcomes	SGRQ, 6MWD, MRC, Borg dyspnoea scale, Sit-to-Stand test
Notes	Main component of program: exercise

Güell 2000	
Methods	RCT; follow-up: 24 months; control group: usual care
Participants	Eligible: 65; Randomized: 60; I: 30, C: 30; Completed (24 months): 47 (I: 23; C: 24); Mean age I: 66 yrs, C: 64 yrs; Sex (% male) both groups: 100% Inclusion criteria: age ≤ 75 years, FEV1 < 70%, FEV1/FVC < 65%, PaO2 > 55 mm Hg at rest with no indication for prescribing home oxygen therapy. Major exclusion criteria: clinically apparent heart disease, bone or joint disease. Exacerbation or hospitalisation in previous month
Interventions	6 months intensive rehabilitation program, followed by a 6-month maintenance program - First 3 months: 2 30-min sessions each week: breathing retraining, combined with a low-level home exercise program. If indicated, patients also received chest physiotherapy, which involved teaching effective cough and postural drainage. Patients attended educational sessions on the anatomy and basic physiology of the respiratory system as well as on the nature of their disease and of PR - Month 3 to 6: exercise training program of 5 30-min sessions weekly on a stationary cycle ergometer. During this period, patients also began a program of home exercise with either 30 min of pedaling on a stationary cycle or 1 h of walking - Month 6 to 12: single weekly session in groups during which they performed exercises for breathing and leg-arm co-ordination - Month 12 to 24: instructed to do home exercises without supervision Included HCP: nurse, physiotherapist, pulmonologist
Outcomes	Lung function, 6MWD, cycle ergometer, VAS, MRC, CRQ, exacerbations, hospital admissions
Notes	Main component of program: exercise

Güell 2006	
Methods	RCT; follow-up: 4 months; control group: usual care
Participants	Randomized: 40; I: 20; C: 29; Completed: 35; I: 18, C: 17; Mean age: I: 68 yrs, C: 66 yrs; Male: I: 88%, C: 100%. Inclusion criteria: age ≤ 75 years, FEV1 < 70%, FEV1/FVC < 65%, PaO2 > 55 mm Hg at rest with no indication for prescribing home oxygen therapy. Exclusion criteria: psychiatric disturbances, no heart, bone or joint disease. Exacerbation or hospitalisation in previous 2 months
Interventions	PR program of 4 months, including: - First 2 months: 2 30-min sessions each week, including relaxation techniques, breathing retraining, and chest wall and abdominal muscle wall work. Patients attended 4 45 to 60-min educational sessions - Month 2 to 4: 5 30-min sessions weekly exercise training on cycle ergometer Included HCP: nurse, physiotherapist, pulmonologist
Outcomes	Millon Behavior Health Inventory (MBHI), Revised Symptom Checklist (SCL-90-R), 6MWD, CRQ
Notes	Main component of program: exercise

Koff 2009	
Methods	RCT; follow-up 3 months; control group: usual care
Participants	Eligible: 40; randomised: 40; completed 38; Mean age I: 67 yrs, C: 65 yrs; Sex (% male): I: 45%, C: 50% Inclusion criteria: clinical diagnosis of COPD, GOLD 3+4, with a telephone land line Exclusion criteria: active treatment for lung cancer, illiteracy, non-English speaking, inability to complete a 6MWD
Interventions	3-month intervention program, including: - Disease-specific education, by respiratory therapist at enrolment and daily by Health Buddy System (tele healthcare) Education included disease description, medications and their use, nutrition, breathing techniques - Teaching of self management skills (use of an oximeter and increased awareness of clinical changes/problems). Patients could contact the co-ordinator in case of deterioration - Patients were remotely monitored 5 days per week with the Health Buddy system for change in symptoms, saturation, 6MWD and lung function. The study co-ordinator reviewed these results and patients were contacted if they were at high risk for exacerbation. They started exacerbation management or had contact with respiratory physician/GP Included HCP: physician, pulmonologist
Outcomes	SGRQ, 6MWD, exacerbations, hospitalizations, ED visits, equipment satisfaction, number of calls
Notes	Main component of program: self management

Littlejohns 1991	
Methods	RCT; follow-up 12 months; control group: usual care
Participants	Eligible: 166; Randomized: 152; I:73, C: 79; Completed (12 months): 133; I: 68, C: 65; Mean age I: 63 yrs, C: 63 yrs; Sex (% male): I: 67, C: 63. Inclusion criteria: COPD diagnosed by spirometry, according to guidelines. Inclusion criteria: age 30 to 75 yrs, prebronchial FEV1 % < 60%, stable state, no change in medication for at least 6 weeks before recruitment, no other major disease
Interventions	Intervention group received the care of the respiratory health worker while continuing with their routine outpatient appointments during 12 months. The health worker provided: - Health education directed at the patient and the primary care team - Monitoring of treatment compliance and optimizing treatment by ensuring correct inhalation techniques and supervision of domiciliary oxygen - Monitoring of the results of spirometry and the patients's symptoms to enable acute exacerbations and worsening heart failure to be detected and treated early - Liaison between GP and hospital-based services (including domiciliary physiotherapy services and social services) Included HCP: GP, respiratory health worker
Outcomes	Mortality, spirometry, 6MWD, step test, MRC chronic bronchitis questionnaire, HADS, SIP, hospital admissions, drug prescriptions, visits to GP or clinic, satisfaction
Notes	Main component of program: structured follow-up with respiratory health worker

Mendes 2010	
Methods	RCT; follow-up 12 weeks; 2 intervention groups (at home PR versus outpatient PR), 1 control group: usual care
Participants	Eligible: 117; Randomized: 117 (Intervention I: 42; Intervention II: 46; Control: 29); Analyzed: 85 (Intervention group I: 33; Intervention II: 23; Control: 29) Mean age: Intervention I: 66 yrs, Intervention II: 71, Control: 71; Sex (% male): Intervention I: 82%, Intervention II: 83, Control: 66%; Inclusion criteria: diagnosis of COPD according to GOLD, stable at inclusion. Major exclusions: hospitalisation or COPD instability, presence of neuromuscular disease, associated respiratory disease, orthopedic or neurological disease that affected gait, recent impairment due to co-morbidities, such as myocardial infarction, heart failure, stroke or neoplasm; prior pneumonectomy or other thoracic surgery
Interventions	Intervention program of 3 months performed either at home or at the outpatient clinic: - Both intervention groups received 1 session of education about COPD, treatment and relevance of PR - Both intervention groups trained 3 mornings a week for 3 months, with aerobic and strengthening exercises. Patients in the outpatient clinic trained under supervision; patients who trained at home were instructed in the clinic and received support by telephone calls. Included HCP: physiotherapist, pulmonologist
Outcomes	6-MWD, MRC, FEV1, BMI, all included in BODE index (body mass, obstruction, dyspnoea, exercise tolerance- index)
Notes	Main component of program: exercise

Rea 2004	
Methods	Cluster RCT; follow-up: 12 months; control: conventional care
Participants	Eligible: 158; Randomized: 135; I: 83, C: 52; Completed: 117; Mean age of both groups: 68 yrs; Sex (% male) of both groups: 41.5%. Inclusion criteria: COPD diagnosed by ICD-9-CM codes and GP records for a clinical diagnosis of moderate to severe COPD. Major exclusion criteria for patients: chronic asthma, bronchiectasis, comorbidity more significant than COPD, unable to give informed consent, prognosis < 12 months, long-term oxygen therapy or too unwell, deceased. Major exclusion criteria GP: no longer enrolled with participating GP practice or moved out of area, unable to contact patient, insufficient practice nurse resource
Interventions	A chronic disease management program was implemented including: - An action plan, which was implemented by patient's own GP and practice nurse, with advice from the respiratory nurse and specialist physician. The plan comprised a timetable for regular maintenance checks and set achievable goals for lifestyle changes - Patients visited the nurse monthly, the GP 3 monthly and at other times if worsening symptoms demanded more visits - Patients received education about smoking cessation, medication. Annual influenza vaccination and pulmonary rehabilitation were recommended Included HCP: GP, nurse, pulmonologist
Outcomes	Health status, SF-36, CRQ, shuttle walk test, spirometry, hospital admissions, medication, courses of oral steroids, courses of antibiotics, smoking cessation Randomization at cluster level, analysis at patient level
Notes	Main component of program: self management/action plan and structured follow-up by GP/ nurse

Rice 2010	
Methods	RCT; follow-up 12 months; control: single intervention (one page of information and telephone number)
Participants	Eligible: 743; Randomized: 743; I: 372, C: 371; Completed: 743. Mean age I: 69 yrs, C: 71 yrs; Sex (% male) I: 98%, C: 98%. Inclusion criteria: COPD diagnosed by spirometry. Inclusion criteria: at high risk for hospitalisation as predicted by one or more of the following during the previous year: hospital admission or ED visit for COPD, chronic home oxygen use, or a course of systemic corticosteroids for COPD. Major exclusion criteria: any condition that might preclude effective participation in the study or that would reduce life expectancy to less than a year, or no access to a telephone
Interventions	Chronic disease management program of 12 months, including: - Group session (1-1, 5-hour): general information about COPD, medication, smoking cessation, vaccinations and exercise - All patients received an individualized written action plan including prescriptions for prednisone and antibiotics with contact information with a case manager. Participants were in possession of action plan medications at all times and were to refill prescriptions immediately upon initiating the action plan - The case manager made monthly telephone calls Included HCP: case manager, pharmacist
Outcomes	ED and hospital admissions related to COPD, SGRQ, mortality, number of telephone contacts
Notes	Main component of program: self management/action plan

Smith 1999	
Methods	RCT; follow-up 12 months; control: usual care
Participants	Eligible: 105; Randomized: 96; I: 48, I: 48; Completed: 36 (data only completed in Intervention group); Mean age I: 70 yrs, C: 70 yrs. Major inclusion criteria: COPD diagnosis according to guidelines, age > 40 years, FEV1/FVC less than 60%, in a stable state, have a carer involved in their management, be able to speak and read English and give written consent. Major exclusion criteria: no other active illness
Interventions	An intervention of 12 months including: - Follow-up planning of in- and outpatients with a nurse in shared care approach with GP and medical staff. Goals for discharge and nurses discussed with the GP the needs and facilitated involvement of domiciliary service. Goals were inserted into patients' notes - During 12 months every 2 to 4 weeks there was a home visit including education, spirometry, optimal medication, exacerbation management, smoking cessation and fitness advice Included HCP: nurse, GP, social worker, hospital medical officer
Outcomes	COOP (HRQoL), mortality, hospital admissions, lung function
Notes	Main component of program: structured follow-up with nurses/GP

Sridhar 2008	
Methods	RCT; 104 weeks; control group: usual care
Participants	Eligible: 297; Randomized: 122 (I: 61; C: 61); Mean age both groups: 70 yrs; Sex (% male): both groups: 49%; Inclusion criteria: diagnosis of COPD and admitted between 2000 and 2004 with an acute exacerbation of COPD. Exclusion criteria: significant comorbidity (severe heart disease or cancer, or any condition that would preclude participation in the physical therapy component of a PR program)
Interventions	Intervention program of 24 months: - Patients started with a PR program for 4 weeks, including general education about disease and treatment, and physical training program - After 4 weeks, patients received a home visit, including a written COPD action plan for exacerbations. The GPs provided medication - Patients received monthly telephone calls and a home visit every 3 months until 24 months follow-up. They reinforced advice regarding treatments, smoking cessation, the need to continue their exercise therapy and reinforced the self management education Included HCP: GP, nurse, physiotherapist
Outcomes	CRQ, mortality, exacerbations, hospital admissions, lung function
Notes	Main component of program: exercise + action plan

Strijbos 1996	
Methods	RCT; 18 months; intervention group 1: hospital based PR, intervention group 2: home based PR, control group: usual care
Participants	Eligible: 50; Randomized: 50; I group 1: 18, I group 2: 17, C: 15; Completed: 41; Mean age I 1: 61 yrs, I 2: 60 yrs, C: 63. Sex (% male): I 1: 93%, I2: 80%, C: 80%. Inclusion criteria: diagnosis COPD as evidenced by history, physical examination, chest radiograph and pulmonary function test results, PaCO2 at rest of less than 6.5 kPa, and PaO2 at rest of more than 7.5 kPa; FEV1 < 65% predicted. Major exclusion: ischaemic heart disease, musculoskeletal disorders or other disabling diseases that could restrict the rehab therapy
Interventions	12-week rehabilitation program: - Both groups: exercise twice a week during 12 weeks, 1 hour each session - In the hospital group exercise was administered by a physiotherapist (1 hour twice a week) and patients were instructed to practice daily exercise for at least 15 min. Patient education 3 times/1 hour by a respiratory nurse - In the home-care group, exercise was carried out at home by the local physiotherapist and home-care nurse, under supervision of the GP. Patients received an individualized exercise program from physiotherapist of 30 minutes (24 sessions), and were instructed to exercise at least 15 to 30 min. They received 3 times education by a nurse and 3 times a visit by the physician or GP - Both groups were intended to continue exercise daily at home, after completion of the program Included HCP: nurse, physiotherapist and GP or pulmonologist
Outcomes	4minute walking test (4MWT), cycle test (measured as maximum watts, W-max) and interviews
Notes	Main component of program: exercise

Theander 2009	
Methods	RCT; 3 months; control group: usual care
Participants	Eligible: 30; Randomized: 30; I:15, C:15; Completed: 26. Mean age I: 66; C: 64 yrs; Sex (% male): I: 25%; C: 71%. Inclusion criteria: diagnosis of COPD: according to British guidelines, with FEV1 between 60% to 25% post bronchodilation, and age ≤ 75 yrs. Major exclusions: disabling or severe disease other than COPD, impaired pulmonary function due to other disease, long-term oxygen therapy, alpha1-antitrypsine deficiency, cancer disease, untreated obstructive sleep apnea syndrome and no COPD-related symptoms affecting their activities of daily life
Interventions	Multidisciplinary program: - Physiotherapy 2 days per week (1 hour) for 12 weeks, with additional home training after q month - Dietician support (3 sessions of 1 hour): education and, if needed, additional nutritional supplementation - Occupational therapist: education and teaching - Nurse (two sessions of 1 hour): education and self care advice Included HCP: physiotherapist, dietician, occupational therapist, nurse
Outcomes	BMI, FEV1, fatigue impact scale, 6MWD, grip strength, SGRQ, SF-36
Notes	Main component of program: exercise

Trappenburg 2011	
Methods	RCT; follow-up 6 months; control group: usual care
Participants	Eligible: 391; Randomized: 233, I: 111, C: 122; Completed (6 months): 193; I: 91, C: 102. Mean age: I 66 years, C: 65 years. Sex (% male): I: 65% C: 69% Inclusion criteria: COPD diagnosed by spirometry, age > 40 years, smoking history of > 20 years or 15 pack-years, diagnosis of COPD as a major functionally limiting disease, current use of bronchodilator therapy. Major exclusions: primary diagnosis of asthma, primary diagnosis of cardiac disease, presence of disease that could either affect mortality or participation in the study
Interventions	6-month self management/action plan program: - Individualized action plan with treatment prescriptions related to a color-coded symptom status to enhance an adequate response to periods of symptom deterioration - The action plan included ongoing support of a case manager, in concordance with a GP/ respiratory physician. There were 2 reinforcement sessions by telephone at 1 and 4 months Included HCP: GP, nurse, pulmonologist
Outcomes	Exacerbation rates and recovery time, SGRQ, HADS, courses of antibiotics, corticosteroids, ED visits for exacerbation, CCQ score during exacerbation
Notes	Main component of program: self management/action plan

van Wetering 2010	
Methods	RCT; follow-up: 24 months, control group: usual care (pharmacotherapy according to guidelines, short smoking cessation advice by chest physician and recommendation to eat more in case of nutritional depletion)
Participants	Eligible: 199; Randomized: 199; I: 102, C: 97; Completed 4 months: I: 87; C: 88; Completed 24 months: I: 77; C: 81. Mean age I: 66 yrs, C: 67 yrs. Sex: I: 71%; C: 71% Inclusion criteria: diagnosis of COPD according to guidelines, other inclusion criteria: impaired exercise capacity, W-max < 70%, GOLD 2+3 and clinical stable at inclusion. Major exclusion criteria: prior rehabilitation and patients with serious co-morbidity that precluded exercise therapy were excluded
Interventions	24-month program including: - Intensive 4-month standardized, supervised physiotherapy 2/week (30 min), with home-based exercises - Patients participated in an individualized education program - All smokers were offered smoking cessation counselling - Nutritionally depleted patients received counseling from a dietician - During the 20-month active maintenance phase, patients were instructed to train at home and visited the physiotherapist once a month. Dietician support was continued Included HCP: nurse, physiotherapist, dietician
Outcomes	SGRQ, total score and number of exacerbations, MRC dyspnoea scale, exercise performance (measured as maximum Watts: W-max), 6MWD, muscle strength, isometric quadriceps peak torque, maximal inspiratory mouth pressure, fat-free mass and lung function
Notes	Main component of program: exercise

Wakabayashi 2011	
Methods	RCT; follow-up 12 months; control group: single intervention (education)
Participants	Eligible: 102; Randomized: 102; I: 52, C: 50; Completed: 85; I: 42, C: 43. Clinical diagnosis of COPD, > 65 years, exclusively visit the clinic with monthly scheduled appointments, have a history of cigarette smoking. Exclusion criteria: history of atopy or any apparent asthmatic features, were illiterate or had cognitive impairment score of less than 26 on MMSE, lived in a residential care facility or a nursing home, had exacerbations during preceding 3 months, or had other respiratory diseases such as bronchiectasis, any type of pulmonary fibrosis or congestive heart failure
Interventions	Patients underwent a program of educational sessions for 6 months, individually tailored according to their domain scores on the LINQ questionnaire, which was designed to assess the need for information from a patients' perspective. The program was given by respiratory nurses and pulmonary physicians. There were six domains: 1) understanding of COPD, 2) pharmacological treatments, 3) exercise, 4) avoidance of exacerbations, including action plan with instructions in the event of exacerbations, 5) smoking cessation, 6) nutrition. All patients were provided with a booklet that was used during each session. After the intensive education period, each patient was followed up for 6 months in the same way as the patients in the usual care group Included HCP: nurse, pulmonologist
Outcomes	FEV1, MRC, SGRQ, 6MWD, Lung Information Needs Questionnaire (LINQ), BMI, BODE index (body mass index, dyspnoea, airflow obstruction, exercise capacity), Activities of Daily Living (ADL), co-morbidities, hospitalizations
Notes	Main component of program: self management/action plan

Wijkstra 1994	
Methods	RCT; follow-up 12 weeks; control group: no treatment
Participants	Randomized: 45; Completed: 43 (I: 28; C: 15); Mean age I: 64 yrs, C: 62 yrs; Sex (% male): I: 82%, C: 93%. Inclusion criteria: diagnosis of COPD with FEV1 % < 60%, FEV1/IVC < 50%. Exclusion criteria: evidence of ischaemic heart disease, intermittent claudication, musculoskeletal disorders or other disabling diseases that could restrict the rehab program
Interventions	Intervention program of 12 weeks: - Patients were supervised by a multidisciplinary team: pulmonologist, physiotherapist, nurse, GP - Patients visited physiotherapist twice a week for 12 weeks and the program consisted of conventional physiotherapy, upper limb training, inspiratory muscle training, exercise training. They had to practice twice a day for half an hour at home - Furthermore, they received education at home from a nurse (once a month) - They visited the GP once a month and he supervised clinical status and maintenance treatment Included HCP: GP, physiotherapist, nurse
Outcomes	Lung function, CRQ, cycle ergometer test
Notes	Main component of program: exercise

Wood-Baker 2006	
Methods	Cluster-RCT; follow-up 12 months, control group: education + usual care
Participants	Eligible: 218; Randomized: 138; I: 67, C: 72; Completed (12 months): 112; I: 54, C: 58; Mean age I: 69 yrs, C: 71 yrs. Sex (% male): I: 49%, C: 71% Inclusion criteria: COPD diagnosed by spirometry, age > 50 yrs, tobacco smoking history of greater than 10 pack-years and FEV1 < 65% predicted. Exclusion criteria: nursing home residents
Interventions	Control + intervention group: COPD information booklet, individual education session with nurse. Intervention group: written self management plan, which was developed in consultation with their treating GP. Patients were encouraged to make early contact with their GP during an exacerbation Included HCP: GP, nurse
Outcomes	SGRQ, exacerbations (courses of antibiotics/prednisone), ED and hospital admissions, GP consultations, spirometry, mortality, physical exercise (pedometer)
Notes	Prior to commencement of the randomisation process, only 50% of the included GPs attended one of a series of educational workshops on the management of COPD. Main component of program: self management/action plan

SUMMARY OF FINDINGS TABLE

Disease management compared to control for patients with chronic obstructive pulmonary disease (COPD)

Patient or population: patients with chronic obstructive pulmonary disease (COPD)
Settings: 8 studies in primary care, 12 studies in secondary care, 1 study in tertiary care, 5 studies in both primary and secondary care
Intervention: Integrated disease management
Comparison: control (usual care)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Control	Corresponding risk Disease management				
Disease specific quality of life on the SGRQ, total score. Follow up: 3-12 months	The mean change in the SGRQ (total score) ranged from 3.4 lower to 6.24 higher	The mean SGRQ in the intervention groups was 3.71 lower (5.83 to 1.59 lower).	MD -3.71 (-5.83 to -1.59)	1425 (13 studies)	⊕⊕⊕⊕ high2	Minimal clinically important difference (MCID) = -4 points, lower score means improvement
Disease specific quality of life on the CRQ Dyspnea domain. Follow up: 3-12 months	The mean change in the CRQ (dyspnea domain) ranged from 0 to 0.2 lower	The mean CRQ dyspnoea domain in the intervention groups was 1.02 higher (0.67 to 1.36 higher)	MD 1.02 (0.68 to 1.36)	160 (4 studies)	⊕⊕⊕⊖ moderate1	MCID = 0.5 points. Results on the other domains of the CRQ (fatigue, emotion, mastery) were also all statistically and clinically relevant
Functional exercise capacity Follow-up: 3-12 months	The mean change in the 6MWD ranged from 38 lower to 36 higher	The mean functional exercise capacity in the intervention groups was 43.86 higher (21.83 to 65.89 higher).	MD 43.86 (21.83 – 65.89)	838 (14 studies)	⊕⊕⊕⊖ moderate3	MCID = 35 meters. Sensitivity analysis did show there was inconsistency in the effect. After removing the low quality studies, the MD was 15.15 meters (95% CI 6.37 to 23.93, $p < 0.001$)
Respiratory related hospital admissions Follow-up: 3-12 months	27 per 100 patients	20 per 100 patients (15 to 27)	OR 0.68 (0.47 to 0.99)	1470 (7 studies)	⊕⊕⊕⊕ high	
Number of hospital days per patient (all causes) Follow-up: 3-12 months	The mean change in hospital days ranged from 1.6 to 11.9 higher	The mean number of hospital days per patient in the intervention groups was 3.78 lower (5.9 to 1.67 lower)	MD -3.78 (-5.9 to -1.67)	741 (6 studies)	⊕⊕⊕⊕ high	

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: confidence interval; IDM: integrated disease management; MCID: minimal clinically important difference; MD: mean difference; OR: odds ratio. 1We downgraded one as there was considerable risk of bias in two studies on allocation concealment and two studies did not blind the outcome assessor. 2We did not downgrade due to risk of bias, as studies contributing more than 2.7% to the meta-analysis had a low risk of bias. Sensitivity analysis on high-risk studies did not change the effect or significance of the effect.
3We downgraded one as all included studies were of moderate to low quality. If we removed studies which had high or unclear risk of bias on allocation concealment, the effect decreased to 15 meters.
GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.

Components of IDM in each included study

Author	Education	Self-management	Exacerbation/ action plan	Exercise	Psychosocial/ occupational	Smoking	Optimal medication	Nutrition	Follow-up	Case management	Multi-disciplinary
Aiken 2006	x	x	x				x			x	
Bendstrup 1997	x			x	x	x					
Bourbeau 2003	x		x	x					x		
Boxall 2005	x			x							
Cambach 1997	x			x							
Dheda 2004	x				x		x		x		
Engstrom 1999	x			x	x			x			
Farrero 2001									x	x	
Fernandez	x			x							
Gottlieb 2011	x			x		x		x			
Güell 2000	x			x					x		
Güell 2006	x			x							
Koff 2009	x	x	x						x		
Littlejohns 1991	x						x		x	x	
Mendes 2010	x			x							
Rea 2004	x		x	x					x		x
Rice 2010	x	x	x								
Smith 1999	x	x	x	x		x	x			x	x
Sridhar 2008	x		x	x					x		
Strijbos 1996	x			x					x		
Theander 2009	x			x	x			x			
Trappenburg 2011	x	x	x								
Wakabayashi 2011	x	x	x			x					
Wetering 2010	x			x		x		x			
Wijkstra 1995	x			x							
Wood-Baker 2006	x	x	x								

Characteristics of included studies

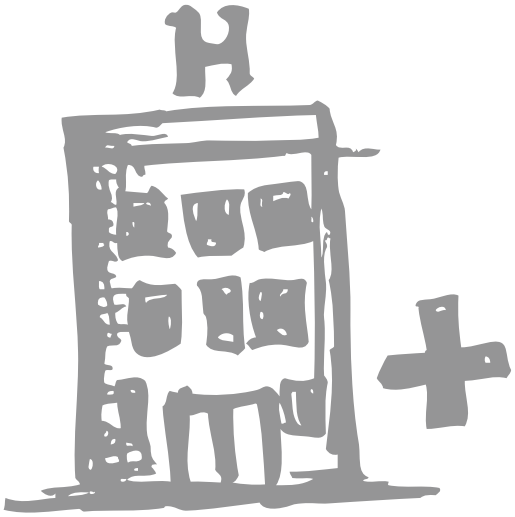
Study	Country	N (randomised)	N (completed)	Number of components intervention	Number of health care providers	Main component intervention	Setting	Control group
Aiken 2006	US	41	18	5	2	SF	PRIM	U
Bendstrup 1997	Denmark	42	32	4	7	E	SEC	U
Bourbeau 2003	Canada	191	165	4	4	SM	SEC	U
Boxall 2005	Australia	60	46	2	3	E	PRIM	U
Cambach 1997	Netherlands	43	23	2	2	E	PRIM	DRUG
Dheda 2004	UK	33	25	4	2	SF	SEC	U
Engstrom 1999	Sweden	55	50	4	5	E	SEC	U
Farrero 2001	Spain	122	94	2	2	SF	SEC	U
Fernandez 2009	Spain	50	41	2	2	E	PRIM	EDU
Gottlieb 2011	Denmark	61	26	4	Multidisciplinary team, not specified	E	PRIM	U
Güell 2000	Spain	60	47	3	3	E	SEC	U
Güell 2006	Spain	40	25	2	4	E	TERT	DRUG
Koff 2009	US	40	38	4	2	SM	PRIM	U
Littlejohns 1991	UK	152	133	4	3	SF	SEC	U
Mendes 2010	Brazil	117	85	2	2	E	PRIM/SEC	U
Rea 2004	New Zealand	135	117	5	4	SM/SF	PRIM/SEC	U
Rice 2010	US	743	743	3	2	SM	SEC	EDU
Smith 1999	Australia	96	36	8	3	SF	PRIM/SEC	U
Sridhar 2008	UK	122	104	4	3	E/SM	PRIM/SEC	U
Strijbos 1996	Netherlands	50	41	3	3	E	PRIM/SEC	U
Theander 2009	Sweden	30	26	4	4	E	SEC	U
Trappenburg	Netherlands	233	193	3	3	SM	SEC	U
Wakabayashi 2011	Japan	102	85	4	2	IT EDU	SEC	EDU
Wetering 2010	Netherlands	199	175	4	3	E	SEC	U
Wijkstra 1995	Netherlands	45	43	2	3	E	PRIM	U
Wood-Baker 2006	Australia	135	112	3	2	SM	PRIM	EDU

CHAPTER 5

COPD multidisciplinary team meetings in the UK: health care professionals perceptions of aims and structure

Annemarije L. Kruis, Michael Soljak, Niels H. Chavannes, Sarah L. Elkin

COPD: in press



ABSTRACT

Over the last ten years, community and hospital-based multidisciplinary teams (MDTs) have been set up for the management of patients with chronic obstructive pulmonary disease (COPD) in the UK. Meetings of the MDTs have become a regular occurrence, mostly on healthcare professionals' own initiatives. There are no standardized methods to conduct an MDT meeting and although cancer MDT meetings are widely implemented, the value and purpose of COPD MDT meetings are less clear. Therefore, the aim of this study was to conduct a cross-sectional descriptive online survey to explore COPD MDT members' perceptions of the purpose and usefulness of MDT meetings, and to identify suggestions or requirements to improve the meetings.

In total, we received 68 responses from 10 MDTs; six teams (n=36 members) were located in London and four (n=32 members) outside. Analysis of the replies by two independent researchers found that MDT meetings aim to optimise management and improve pathways for respiratory patients by improving communication between providers across settings and disciplines. Education of the MDT members also occurs with the aim of safer practice. Discussed patients are characterised by (multiple) comorbidities, frequent exacerbations and admissions, social and mental health problems, unclear diagnosis and suboptimal responses to interventions. Members reported participating in a COPD MDT as very useful (74%) or useful (20%). Meetings could be improved by ensuring attendance through requirement in job plans, by clear documentation and sharing of derived plans with a wider audience including general practitioners and patients.

INTRODUCTION

There is increasing interest in implementing integrated multidisciplinary teams (MDTs) in the care of patients with chronic diseases including chronic obstructive pulmonary disease (COPD).[1] In chronic disease care, MDTs have the potential to improve coordination, communication, and decision making between healthcare professionals and patients[2], and lead to fewer hospital admissions whilst improving quality of life.[3] Over the last ten years, community and hospital-based COPD MDT meetings have evolved within the UK, mostly on the initiative of healthcare professionals. Doctors, nurses, physiotherapists, occupational therapists, pharmacists, dieticians, social workers and mental health specialists can be involved and contribute within their field of expertise.[1]
While the quality of cancer MDT meetings is well studied[4], little is known about COPD MDT members' attitudes, perceptions and satisfaction. The aim of this study was to explore COPD MDT members' perceptions of the purpose and usefulness of MDT meetings, and to identify suggestions or requirements to improve the meetings. Through this process we wished to explore which patients should be discussed, how value and outcomes can be measured, and if other healthcare providers or patients themselves should be included in the meetings.

METHODS

We conducted a cross-sectional descriptive online survey to assess the attitudes, perceptions and experiences of UK healthcare professionals participating in a COPD MDT meeting. The survey was developed by the first and last author and comprised 15 questions: six closed and nine open-ended. Questions were intended to determine members' perceptions on the purpose of the meeting, its usefulness, examples of discussed patients, suggestions for improvement, the need to involve patients and other healthcare providers in the meeting and ideas on how to measure the success of the meeting. The survey was developed and distributed using Qualtrics survey tool (www.qualtrics.com). The first author visited six COPD MDTs in London and collected 48 team members' email-addresses. Four chairpersons of known MDTs outside London were requested to disseminate the survey to all their team members on our behalf. All MDT members participated voluntarily and remained anonymous, so that they are not individually identifiable in the results. To optimise response rates, non-respondents were followed up with three additional mailings over a four-week period. Surveys and reminders were sent out between 23rd of January and the 21st of February 2014. The first and last author individually performed thematic analysis of the survey through an inductive process.[5]

Chi squared tests were used to compare findings between different healthcare providers and between MDT members in and outside London.

RESULTS

In total, 68 MDT members participated in the survey, of which 36 (53%) were nurses, 14 (21%) physiotherapists, 10 (15%) respiratory physicians, three general practitioners (GPs) and five other healthcare providers. Fifty-three percent (n=36) were working in London and 47% (n=32) outside London.

Purpose of the MDT

The first question was about the purpose of the MDT.
The main themes that emerged were:

1. Communication: around 49% reported the MDT meetings improved communication and team working, and established more consistent and efficient care across settings.
2. Education and improvement of knowledge: 40% of the respondents considered the MDT as a platform for information exchange and believed participation in an MDT improved their knowledge about the disease.
3. Devising management plans: 81% percent of respondents reported the aim of the meeting was to obtain a proper diagnosis and assessment, to create a management plan or to obtain quick and efficient referral to other disciplines. Other aims mentioned were to reduce hospital admissions or to discuss end of life issues.
4. Co-ordination of care: 44% felt the meetings helped align pathways and processes between professions and organisations so that care became more coordinated for patients.

The perceived purpose appeared to be 'to optimise management and improve pathways for respiratory patients by improving communication between providers across settings and disciplines.' There were no differences in answers between disciplines and between professionals working in or outside London.

Examples of patients that should be discussed

When asked about which patients were usually discussed in the MDT, the themes that emerged were:

1. Complex needs: the majority of the respondents stated that those with complex needs, including anxiety and depression, social care, and comorbidities should be discussed.

2. Palliative care: there appears to be a need for support in the management of patients nearing the end of life. Both researchers rated this as the second most cited group of patients requiring discussion.
3. Admission to, and discharge from hospital: as part of coordinated care pathways.
4. Managing severe disease; including those on oxygen and non-invasive ventilation.
5. Exacerbation management and disease optimisation.

Patients that the MDT members felt should be discussed were sub-optimally managed patients with complex needs and comorbidities, an unclear diagnosis, psychological/social problems, frequent exacerbations or hospital admissions, or those requiring oxygen or palliative care. There were no differences in answers between disciplines or between members working in or outside London.

Usefulness of the MDT meetings and suggestions for improvement

Ninety four percent of the members rated their MDT meetings as either very useful (74%) or useful (20%). The professionals outside London rated the MDT meetings more often as very useful compared to the professionals working in London ($p=0.03$). Six percent gave no answer; nobody rated the MDT meetings as not useful. Nurses and physiotherapists reported the meetings were an opportunity to discuss management plans and to receive support and advice on their decisions from the consultants and senior colleagues. Furthermore, they mentioned the meetings were an opportunity to learn more about the disease and share knowledge. Finally, the meetings improved communication between healthcare providers and were a unique way to further improve integrated working. Thirty-one percent of the members suggested meetings could be improved by formalising the structure to include clear objectives, adequate preparation of cases and accountability of outcomes. Other suggestions included a (rotating) chairperson (7%) and to end every meeting with a proper documentation of the derived agreements (17%) in the form of a care plan to be shared with the patient. They also suggested reporting outcomes to primary care (5%).

Involving the GP

In our sample, there were only three GPs included from two MDTs, one in London and one outside London. Almost all (99%) members reported they wanted the GP to somehow be included in the meeting. They mentioned GPs to be an essential part of the team as they have knowledge of their patients including comorbidities and social background and are responsible for the care in the community. Others felt involving the GP could assure better care delivery and could make the treatment more successful. Finally, they mentioned GPs could increase their own disease-specific knowledge when participating in the MDT. Concerns for feasibility included GPs' time and cost.

Involving other healthcare professionals

Eighty-three percent of the members reported it would be useful to extend the membership of the MDT. There was a need for social service expertise (33%), community matrons or district nurses (28%), palliative care (15%), mental health workers (15%), nutritionists (13%) and oxygen specialist therapists (13%). Sixteen percent indicated that they had no need to include other healthcare professionals.

Involving patients

Although 43% of the respondents reported they would like to invite the discussed patients to the meeting, most of them expressed practical reasons not to do so. There were, however, differences between healthcare providers: 75% of the respiratory physicians wished to include the patient, while in nurses it was 50% and in physiotherapists 21%. Lack of time during the meetings and logistical problems were the main reasons given (84%) for not inviting patients. Others expressed problems with confidentially or healthcare providers including too much medical details in professional discussions, which might not necessarily benefit the patient. However, members appeared to agree that sharing the care plan with the patient was important, especially to gain more insight into the patients or family's perspective of the plan, and to assure patients would comply with the plans ('no decision about me, without me'). However, they suggested this could be discussed and fed back in a separate consultation with the patient and carers.

Outcomes for success

When asked how the success of a meeting could be measured the following outcomes were suggested:

1) Number of management plans devised per meeting;
2) Number of interventions/care plans implemented;
3) Team satisfaction or team surveys;
4) Patient satisfaction or related outcomes, such as health-related quality of life;
5) Decrease in emergency hospital admissions or attendances.

DISCUSSION

This cross-sectional survey of members of COPD multidisciplinary teams (MDT) in the UK shows that the majority rate participation in MDT meeting as (very) useful. The meetings aim to optimise management and improve pathways for COPD patients by improving communication between providers across settings and disciplines. Education of the MDT members is an important aim to ensure safer practice and maintain up to date knowledge. Discussed patients are often characterized by (multiple) comorbidities, frequent

exacerbations or admission to hospital, social or mental health problems, an unclear diagnosis or suboptimal responses to interventions. Meetings could be improved by ensuring attendance through requirement in job plans, by clear documentation, sharing of derived plans and by inclusion of the GP and patient in the meeting outcomes.

Our findings are subject to certain limitations. The sample size was relatively small, and with the sampling method outside London we were not able to estimate the representativeness of respondents. However, the sample adequately represented types of respondents across core hospital and community based MDTs in and outside London, in which a variety of patients are discussed. Furthermore, our survey was not developed using an iterative process of consultations with experts, but was developed by clinicians with expertise in MDTs, in order to provide illustrative findings rather than to be conclusive. As a result of the high response rate and extensive responses, this is the first study to date which gained insight into members' perceptions on the value of COPD MDT meetings.

Despite recommendations in the recent NICE guidelines[1], there is currently no standardized method of conducting a COPD MDT meeting. Our survey indicated a need for a more structured approach, with an agenda and chairperson, more pre-planned discussions linked to specific questions and evidence based learning and outcomes. There should be clear documentation of the derived plan and actions that are shared with the extended MDT including GPs and possibly patients. In addition, the measurement of the effectiveness of COPD MDT meetings remains debatable. It may not be possible to attribute changes in usage of healthcare to the success of MDTs only, as there are more recent developments influencing these outcomes.[5] In our survey, patient and team satisfaction were also suggested as a way to measure success of team working. In cancer MDTs, there is evidence that the ability of an MDT to reach a decision on first-case presentation and ability of decisions to be implemented appear to be a useful marker of the performance of the MDT meetings.[3] This study demonstrates a need for further evaluation of MDT meetings to define how the effectiveness can be measured, and if standardisation of team meetings can lead to better outcomes for the patient and higher satisfaction within the whole team.

REFERENCES

(1) National Clinical Guideline Centre. Chronic obstructive pulmonary disease: management of chronic obstructive pulmonary disease in adults in primary and secondary care. 2010. London, National Clinical Guideline Centre.

(2) Lamb BW, Sevdalis N, Taylor C, Vincent C, Green JS. Multidisciplinary team working across different tumour types: analysis of a national survey. *Ann Oncol* 2012;23(5):1293-300.

(3) Kruis AL, Smidt N, Assendelft WJ, Gussekloo J, Boland MR, Rutten-van MM, et al. Integrated disease management interventions for patients with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2013;10:CD009437.

(4) Lamb BW, Brown KF, Nagpal K, Vincent C, Green JS, Sevdalis N. Quality of care management decisions by multidisciplinary cancer teams: a systematic review. *Ann Surg Oncol* 2011;18(8):2116-25.

(5) Guest GS, MacQueen KM, Namey E.E. Introduction to Applied thematic analysis. In: Applied thematic analysis. *In: SAGE Publications INC*.United States: 2012.

(6) Cramm JM, Rutten-Van Molken MP, Nieboer AP. The potential for integrated care programmes to improve quality of care as assessed by patients with COPD: early results from a real-world implementation study in The Netherlands. *Int J Integr Care* 2012;12:e191.

(7) Szecsenyi J, Rosemann T, Joos S, Peters-Klimm F, Miksch A. German diabetes disease management programs are appropriate for restructuring care according to the chronic care model: an evaluation with the patient assessment of chronic illness care instrument. *Diabetes Care* 2008 ;31(6):1150-4.

(8) Curry N, Holder H, Smith J, et al. North West London Integrated Care Pilot Evaluation. Imperial College London 2012.

(9) Curry N, Harris M, Gunn LH, Pappas Y, Blunt I, Soljak M, et al. Integrated care pilot in north-west London: a mixed methods evaluation. *Int J Integr Care* 2013;13:e027.

(10) Cioffi J, Wilkes L, Cummings J, Warne B, Harrison K. Multidisciplinary teams caring for clients with chronic conditions: experiences of community nurses and allied health professionals. *Contemp Nurse* 2010;36(1-2):61-70.

(11) Fleissig A, Jenkins V, Catt S, Fallowfield L. Multidisciplinary teams in cancer care: are they effective in the UK? *Lancet Oncol* 2006;7(11):935-43.

CHAPTER 6

Successful patient self-management of COPD requires hands-on guidance

Annemarije L. Kruis, Onno C.P. van Schayck, Johannes C.C.M. in 't Veen, Thys van der Molen, Niels H. Chavannes

Lancet Respir Med 2013;1(9):670-2

In the past decade, self-management of chronic obstructive pulmonary disease (COPD) has often been regarded as the way forward to reduce the sharply increasing costs of treatment and limit future demands on health-care capacity. In 2003, Bourbeau and colleagues[1] were the first to show substantial reductions of up to 40% in exacerbation-related hospital admissions and emergency department visits from a self-management programme in Canada. Numerous attempts were made to replicate these promising results, of which two trials[2;3] showed similar beneficial effects on hospital admissions and emergency department visits. By contrast, an increasing number of trials with mixed or negative results have also been reported, revealing a striking absence of these positive effects in Scotland and the Netherlands[4-7], or even showing unsettling excess mortality in the self-management group in a well-designed trial in the USA.[8] So what can we learn from this growing, but rather contradictory, evidence? Should we now be cautious with the rolling out of self-management, or even refrain from it? Or might we be able to identify factors that affect the effectiveness of self-management for COPD, and thus identify patients for whom it does actually work?

An important characteristic of the positive trials[1-3] is the presence of substantial room for improvement all patients had advanced, symptomatic COPD, and were at high risk for hospital admission. Furthermore, patients were in regular, sometimes intensive contact with a case manager, a key individual who worked closely with the treating physician. In other words, these patients were not being left alone with their self-management materials, but acted to some extent under proactive guidance.

When looking closely at the trials with mixed or negative results, several observations can be made. In two of these studies, no effect was seen in COPD-related hospital admissions[5;7] or deaths[7] in the intervention groups overall. However, both studies reported relevant effects in a subgroup of apparently successful self-managers, representing about 40% of patients with COPD. This subgroup was characterised by being of relatively younger age[5;7], living with others[7], having severe airflow obstruction[5], and having cardiac comorbidity.[5] Another study[6] into the effects of an individualised action plan showed a clinically relevant effect on health status and suggested some positive effects on exacerbation length, but this finding was not significant, suggesting that the study was probably underpowered. However, exacerbations in the intervention group were perceived by the patients as having become substantially milder, and patients also showed enhanced recovery of health status and reduced average length of exacerbations. Therefore, inclusion of an action plan with sufficient education and support can be a key component of self-management programmes in patients with COPD.

Despite assessing a population with disease severity comparable to the two trials with positive results[1;2], the study by Fan and colleagues[8] was stopped early because of an increase in mortality in the intervention group. One crucial difference in this negative study might have been the number of telephone calls from case managers; these calls

were scheduled every month for 1 year in the two positive studies[1;2], whereas in the negative study[8] they were made on a monthly basis for the first 3 months, and only every 3 months thereafter. Patients might have underreported symptoms and delayed referral by misplaced overconfidence in the self-management system, possibly leading to a self-management delay that has now been shown to be potentially lethal. These findings suggest that we should probably not try to apply self-management in patients with severe COPD without proper case management in place.

Self-management is not a goal in itself, but a means of treatment and one element of integrated care. It does not replace the proactive involvement of health-care workers. In a Dutch study[9]into adherence to an online self-management application for patients with COPD or asthma, patients tended to use the online application on a regular basis when the health-care provider was involved, whereas patients on their own used the application only sporadically. No other parameter (sex, age, lung function, or clinical severity) seemed to be correlated with adherence to the programme. This finding is in line with the results of a study in Scotland[7], which showed that a dedicated health-care provider, spouse, or family member makes all the difference in the successful management of complex diseases such as COPD. The importance of this point is further emphasised by Koff and colleagues[3] and Vandivier and colleagues[10], who report that a staggering 47~78% of self-managed patients did not make the crucial telephone call to the case manager despite being warned by an online application that they had symptoms of an exacerbation. In another study by Koff and colleagues[11], as a result of proactive coordinators who contacted patients nonetheless, the investigators noted a non-significant decrease in mortality, which contrasts with the increased mortality seen in Fan and colleagues' study.[8]

Health-care providers should be aware that reducing the total number of exacerbations might be difficult to achieve when a programme is targeted at early recognition of exacerbations. It might be the case that well-implemented self-management strategies actually detect increased numbers of exacerbations overall, but of lesser severity and with fewer days spent in hospital, as a result of vigilant early treatment. Additionally, improvement in symptom awareness does not necessarily result in adequate detection of exacerbations, since non-pulmonary symptoms are often misinterpreted as pulmonary alarm symptoms, and vice versa.[12]

In summary, interventions to enhance self-management in patients with COPD are very diverse and lead to conflicting outcomes. Self-management seems not to be suitable for everyone, but when hands-on guidance is provided (by a case manager, or a dedicated spouse, friend, or family member), it can be successful in a subgroup of up to 40% of patients. This finding should be further investigated in large, carefully designed studies. Furthermore, reports of future studies should describe precisely the nature of the intervention, including the intensity and frequency of contact with a case manager, to

allow valid comparisons across different programmes. In this way, guidelines could be formulated for health-care providers on the best way to deliver self-management to patients with COPD.

REFERENCES

(1) Bourbeau J, Julien M, Maltais F, Rouleau M, Beaupre A, Begin R, et al. Reduction of hospital utilization in patients with chronic obstructive pulmonary disease: a disease-specific self-management intervention. *Arch Intern Med* 2003;163(5):585-91.

(2) Rice KL, Dewan N, Bloomfield HE, Grill J, Schult TM, Nelson DB, et al. Disease management program for chronic obstructive pulmonary disease: a randomized controlled trial. *Am J Respir Crit Care Med* 2010;182(7):890-6.

(3) Koff PB, Jones RH, Cashman JM, Voelkel NF, Vandivier RW. Proactive integrated care improves quality of life in patients with COPD. *Eur Respir J* 2009;33(5):1031-8.

(4) Bischoff EW, Akkermans R, Bourbeau J, van WC, Vercoulen JH, Schermer TR. Comprehensive self management and routine monitoring in chronic obstructive pulmonary disease patients in general practice: randomised controlled trial. *BMJ* 2012;345:e7642.

(5) Bischoff EW, Hamd DH, Sedeno M, Benedetti A, Schermer TR, Bernard S, et al. Effects of written action plan adherence on COPD exacerbation recovery. *Thorax* 2011;66(1):26-31.

(6) Trappenburg JC, Monninkhof EM, Bourbeau J, Troosters T, Schrijvers AJ, Verheij TJ, et al. Effect of an action plan with ongoing support by a case manager on exacerbation-related outcome in patients with COPD: a multicentre randomised controlled trial. *Thorax* 2011;66(11):977-84.

(7) Bucknall CE, Miller G, Lloyd SM, Cleland J, McCluskey S, Cotton M, et al. Glasgow supported self-management trial (GSuST) for patients with moderate to severe COPD: randomised controlled trial. *BMJ* 2012;344:e1060.

(8) Fan VS, Gaziano JM, Lew R, Bourbeau J, Adams SG, Leatherman S, et al. A comprehensive care management program to prevent chronic obstructive pulmonary disease hospitalizations: a randomized, controlled trial. *Ann Intern Med* 2012;156(10):673-83.

(9) In 't Veen JCCM, Mennema B, van Noort E. Online self-management in COPD or asthma: with or without the healthcare provider ? *Eur Respir J* 2012; 40 (suppl 56): 237s.

(10) Vandivier RW, Linderman DJ, Koff PB. A comprehensive care management program to prevent chronic obstructive pulmonary disease hospitalizations. *Ann Intern Med* 2012;157(7):530-1.

(11) Koff PB, Min S, Freitag TJ et al. Proactive integrated care reduces critical care & improves quality-of-life in COPD. *American Thoracic Society* 2009 International Conference; San Diego, USA 2009; A3100.

(12) Main J, Moss-Morris R, Booth R, Kaptein AA, Kolbe J. The use of reliever medication in asthma: the role of negative mood and symptom reports. *J Asthma* 2003;40(4):357-65.

CHAPTER 7

Sustained effects of integrated COPD management on health status and exercise capacity in primary care patients

Annemarije L. Kruis, Joan van Adrichem, Magda R. Erkelens, Huub Scheepers, Johannes C.C.M. in 't Veen, Jean W.M. Muris, Niels H. Chavannes

Int J Chron Obstruct Pulmon Dis 2010;5:407-13.

ABSTRACT

Background

COPD constitutes a worldwide growing health care problem. Integrated Disease Management (IDM) of mild to moderate COPD-patients has been demonstrated to improve exercise capacity and health status after one year, but long-term results are currently lacking in primary care.

Methods

Long-term data from the Bocholtz Study, a controlled clinical trial comparing the effects of IDM versus usual care on health status in 106 primary care COPD patients during 24 months follow-up, were analyzed using the Clinical COPD Questionnaire (CCQ). In addition, the Kroonluchter IDM-implementation program has treated 216 primary care patients with mild to moderate COPD since 2006. Longitudinal six-minute walking distance (6MWD) results of patients reaching 24 months of follow-up were analyzed using paired-samples T-tests. In pre-specified subgroup analyses, the differential effects of baseline CCQ score, MRC Dyspnoea scale and 6MWD were investigated.

Results

In the Bocholtz Study, subjects were aged 64 years, with an average post-bronchodilator FEV_1 of 63% predicted and FEV_1/FVC ratio of 0.56. No significant differences existed between groups at baseline. CCQ improved significantly and clinically relevant with 0.4 points during 24 months; effect sizes were doubled in patients with CCQ>1 at baseline and tripled in patients with MRC>2. In the Kroonluchter Cohort, 56 subjects had completed follow-up, were aged 69 with an FEV_1/FVC ratio of 0.59, while their post-bronchodilator FEV_1 of 65% predicted was somewhat lower than the total group. 6MWD improved significantly and clinically relevant up to 93m at 12 months and was sustained at 83m during 24 months; the effect occurred faster in patients with MRC>2. In patients with baseline 6-MWD<400m the improvement remained >100 meters at 24 months.

Conclusion

In this study, integrated disease management (IDM) improves and sustains health status and exercise capacity in primary care COPD-patients during two years follow-up. Improvements in health status are consistently higher in patients with CCQ >1 at baseline, being strongest in patients with baseline MRC Dyspnoea score >2. Improvements in exercise capacity remain highest in patients with 6MWD < 400m at baseline and seem to occur earlier in patients with MRC Dyspnoea score >2.

BACKGROUND

COPD constitutes a major and progressive health care problem worldwide and is expected to be the third cause of global death over the next twenty years.[1] Besides smoking cessation, pulmonary rehabilitation (PR) is the recommended treatment and has been proven to be effective across the whole spectrum of COPD patients.[2-5] A recent meta-analysis shows that PR relieves dyspnoea and fatigue, improves mental status and enhances patients' control over their disease.[6] However, despite proven efficacy, PR is still only available for a small proportion of the worst patients, due to capacity problems and high costs.[7] It is expected that the rise in prevalence of COPD will progressively cause an even higher burden on rehabilitation programmes in the future.

At present, the majority of COPD patients are treated in primary care, of which approximately 80% suffer from mild to moderate disease.[8] As a result, general practitioners often find themselves at a crossroads in the organisation of care for COPD patients. Nevertheless, interdisciplinary cooperation between primary health care providers as well as primary and secondary care is often needed. In earlier reports[9;10], we hypothesized that when components of PR would be tailored into an integrated disease management program available for primary care and carried out by a multidisciplinary, integrated care team, the benefits of PR could be extended to a larger population of COPD patients in need. This would explicitly include those with milder stages of disease, given that they have sufficient symptom burden to justify an integrated intervention. Elements that often can be integrated are: smoking cessation, exacerbation management, optimal medication, self-management, patient education, dietary intervention and physiotherapeutic reactivation.

In an earlier paper, we demonstrated that our IDM program in primary care improved health status clinically relevant in mild to moderate COPD patients at 12 months follow-up. Greatest room for improvement was shown in COPD patients with a Medical Research Council Dyspnoea score >2.[9] As we had thus demonstrated 12 months' efficacy of the IDM program in a controlled setting, a real-life implementation cohort was set up in the city of Rotterdam. In this pragmatic IDM program, we focused on improving exercise capacity, as we believed this would be an important driver to sustain effectiveness. Currently, long-term results of PR programs are mixed and some authors report that most benefits of PR dissolve over time.[11-13] Similarly, the longer-term effect of IDM in primary care is still unclear. The aim of the present study is thus to determine the long-term effects of IDM on health status and exercise capacity in primary care COPD patients.

METHODS

In this study we analyzed 24 months follow up data of both the controlled clinical *Bocholtz* trial and the *Kroonluchter* implementation cohort of primary care IDM programs. In both studies, the study population consisted of primary care patients with chronic respiratory symptoms and a post-bronchodilator $FEV_1/FVC<0.7$, in accordance with national and international guidelines.[3,8] Exclusion criteria consisted of terminal or immobile patients, substance abuse or inability to fill in questionnaires. In the Bocholtz clinical trial, the regional Medical Ethics Committee of the Atrium Medical Centre Heerlen approved of the study protocol. All participating patients gave their written informed consent. In the Kroonluchter cohort, all patients gave their written informed consent for participating in the implementation program.

Below follows a short description of both study settings and design. We refer to our previous publications for an extensive description of the clinical one-year results and methods of the Bocholtz study[9], as well as background and design of the Kroonluchter IDM program.[10]

Picasso Bocholtz study

The Picasso Bocholtz study is a pragmatic controlled clinical trial, comparing the effects of integrated disease management (IDM) on health status. COPD patients of two comparable primary health care centres in the south of the Netherlands were followed up for two years, during which the intervention group received an IDM program and the control group received usual care. Patients were included based on chronic respiratory complaints, post-bronchodilator lung function testing and adequate work-up in case of more complex disease by the local pulmonologist, on indication by the patients' primary care physician. In the intervention setting, an integrated COPD management team was formed including two physiotherapists, a respiratory nurse, a physician assistant, a dietician, a pharmacist, a supervising primary care physician and a logistical manager. All team members contributed in their area of expertise to a written standardised treatment protocol, which included different elements of IDM, based on the joint ATS/ERS COPD Standards.[14] Examples included personalised physical activity training programmes, optimal medication prescribing and adherence monitoring, rapid action plans for exacerbations, and continuous self-management education.[9]

Kroonluchter cohort

Based on the favourable experiences of the Bocholtz study, the Kroonluchter integrated disease management program was implemented in a low-SES borough in Rotterdam, the Netherlands. Since 2006, a total of 216 primary care patients with chronic respiratory complaints have been included, after clinical assessment including post-bronchodilator lung

function testing confirmed eligibility according to GOLD-criteria. A multidisciplinary, dedicated team of primary care physicians, nurse specialists and physiotherapists was formed and trained to establish a locally agreed collaborative protocol. Diagnostic work-up in case of complex disease was provided by collaborating pulmonologists, after referral by the primary care physician. In cooperation with the patient, an individualized, tailor-made plan of action was designed, based on an explicitly formulated personal target, varying from "quitting smoking with guidance within 6 months" to "climbing a short flight of stairs without hindrance by feelings of dyspnoea within 6 months". Based on disease burden and patient needs, an individual program was assembled, that could include self-management training and exacerbation management, an exercise training program, smoking cessation strategies, better medication use and personalized disease education.

In case of obesity or muscular depletion, referral to a dietician for a dietary intervention was possible. Because of good local collaboration and arrangements for additional workup, patients could be referred to pulmonary physicians on a short notice. In addition, extra attention was given to follow up of patients after an exacerbation. Patients with a Medical Research Council (MRC) Dyspnoea score>2 or notoriously inactive patients (according to their primary care physician) were assigned to a 6-month COPD-specific training program by specialized physiotherapists. Physical exercise training consisted of one month of individual training, followed by five months of group training. Training was focused on strength as well as endurance exercises, and was tailored to individual abilities and deficiencies of the patient. Patients trained 2 times for one hour per week under supervision and were instructed to train 1 hour per week at home. After 6 months, there was a follow-up of 1 hour per week in order to sustain any effects over time.[10]

Outcomes and measurements

Baseline measurements in both studies included age, gender, smoking habits, body mass index (BMI), lung function and score on the MRC Dyspnoea scale: a short and valid questionnaire to quantify dyspnoea.[15]

In the Bocholtz study, the Clinical COPD Questionnaire (CCQ) was used to assess health status, since it is well validated and easy to administer in primary care.[15] Primary outcome at 24 months in the Bocholtz study was the difference in CCQ at 24 months compared to baseline CCQ score in both the intervention and control groups.

In the Kroonluchter cohort, the 6 minute walking distance (6MWD), a measure of functional capacity, was conducted according to international recommendations.[16] The 6MWD is a practical, self-paced test, measuring the maximum distance subjects can walk in 6 minutes. Primary outcome of this program was the difference in 6MWD at 24 months compared to baseline 6MWD score.

Power calculation

In the Bocholtz study, we calculated that a sample size of 2x45 patients was needed (with a power of 80% with $\alpha = 0.05$) to detect a minimum clinically important difference (MCID) of -0,4 unit change in quality of life on the CCQ.[15]

As the Kroonluchter project was designed as an ongoing implementation program, no formal group comparison and hence no power calculation was conducted. On the basis of earlier studies and an MCID of 54m which represents the threshold value for a clinically significant change on the 6MWD[16], a minimum group size of 50 patients was deemed necessary to analyze 24 month results. In this study the first batch of consecutive COPD patients completing 6MWD measurements at baseline, 3, 6, 12 and 24 months were analyzed.

Statistical analysis

Data were analyzed with SPSS version 13, using independent T-tests and chi-square tests for baseline characteristics comparison. Baseline and annual differences in CCQ (Bocholtz) and 6-MWD (Kroonluchter) were compared using paired sample T-tests. In pre-specified subgroup analyses, the differential effects of baseline CCQ score, MRC scale and 6MWD were investigated.

RESULTS

Patients

In the Bocholtz study, 106 COPD patients according to GOLD classification were analyzed for baseline measurements, 59 patients in the intervention and 47 patients in the control group. In table 1, this initial COPD population is described. Subjects were aged 64 years, with an average post-bronchodilator FEV_1 of 63% predicted (SD 19) and FEV_1/FVC ratio of 0.56. There were no significant differences in demographic variables, smoking habits or lung function between intervention and control groups at baseline. Of the initial population of 106 patients, 86 patients (81%) completed follow up of two years (44 in the intervention group and 42 in the control group) and could be further analyzed.

Of the original group of 216 patients in the Kroonluchter cohort, 18% (39 persons) dropped out due to relocation, severe co-morbidity or unwillingness to fill out questionnaires repeatedly. Of the initial 216 patients, 104 (48%) were referred to a physiotherapy training program, based on MRC>2 or inactivity that necessitated an integrated approach. So far, 56 patients (54%) completed the 24 months 6MWD, and their data could be used for analysis. Table 2 shows the baseline characteristics of the initial cohort and the group that has finished 24 months follow-up. The mean age of the latter group was

69 years, with an FEV_1/FVC ratio of 0.59, while their post-bronchodilator FEV_1 of 65% was somewhat lower than in the total group (71%).

Table 1 Baseline characteristics of intervention versus control group in primary care COPD-patients of the Bocholtz Study

	Intervention (n=59)	Control (n=47)	p-value#
Age (yrs)	64.7 (10)	62.3 (9)	0.99
Gender (% male)	66.4	64.3	0.12
Current smoking (%)	33.9	46.8	0.08
Body Mass Index	25.8 (5)	26.0 (5)	0.75
FEV1 post-BD (%)	63.9 (21)	61.7 (17)	0.06
FEV1/FVC post-BD	0.55 (.10)	0.57 (.10)	0.72
MRC>2 (%)	38.6	33.3	0.32
CCQ	1.4 (1)	1.6 (1)	0.75

*all values are means (SD) except when stated otherwise; #no significant difference between groups at baseline.
Abbreviations: MRC, Medical Research Council Dyspnoea Score; CCQ, Clinical COPD Questionnaire

Table 2 Baseline characteristics of total versus 6MWD group in primary care COPD-patients of the Kroonluchter Cohort

	Total (n=216)	6MWD (n= 56)	p-value
Age (yrs)	67.1 (14)	69.2 (10)	0.11
Gender (% male)	42.1	37.3	0.38
Current smoking (%)	41.2	33.3	0.78
Body Mass Index	27.3 (6)	27.8 (5)	0.45
FEV1 post-BD (%)	70.5 (18)	64.5 (17)	0.002#
FEV1/FVC post-BD	0.61 (.12)	0.59 (.14)	0.098
MRC>2 (%)	45.8	51.9	0.24
6MWD (m)	364.0 (128)	354.6 (126)	0.44

*all values are means (SD) except when stated otherwise; #significant difference between groups at baseline
Abbreviations: MRC, Medical Research Council Dyspnoea Score; 6-MWD, 6- Minute Walking Distance

Primary outcome Bocholtz study

Table 3 shows the long-term changes in CCQ scores in COPD patients in the intervention and control groups of the Bocholtz study. Compared to baseline, a statistically significant change of -0.4 is sustained in the intervention group during 24 months, while the control group shows non-significant changes during 24 months. The pre-specified subgroup analysis of patients with baseline CCQ >1 shows a statistically significant and clinically relevant difference of -0.9, while the control group shows no significant improvement. In patients with MRC scores >2, the effect on CCQ score is tripled and shows a statistically significant and clinically relevant difference of -1.2, compared to a non-significant change of -0.02 in the control group.

Table 3 Longterm effects of Integrated Disease Management on Health Status in primary care COPD patients of the Bocholtz Study

		Intervention Group CCQ difference*/ 95% CI		p-value	Control Group CCQ difference**/ 95% CI		p-value
All patients							
	12 mo	-0.4	[-0.6, -0.2]	0.001	+0.01	[-0.2, 0.2]	0.9
	24 mo	-0.4	[-0.7, -0.1]	0.004	+0.02	[-0.4, 0.5]	0.9
Subgroup baseline CCQ>1							
	12 mo	-0.8	[-1.1, -0.4]	0.001	-0.1	[-0.3, 0.08]	0.2
	24 mo	-0.9	[-1.2, -0.5]	0.001	-0.03	[-0.5, 0.5]	0.9
Subgroup baseline MRC>2							
	12 mo	-0.9	[-1.4, -0.4]	0.002	+0.01	[-0.3, 0.3]	1.0
	24 mo	-1.2	[-1.8, -0.5]	0.004	-0.02	[-0.8, 0.8]	1.0

*paired samples T-test; p is considered significant at values<0.05; **MCID CCQ = -0.4 [15]
Abbreviations: CCQ, Clinical COPD Questionnaire; MRC, Medical Research Council Dyspnoea Score

Primary outcome Kroonluchter cohort

Table 4 shows the long-term changes in 6MWD in the Kroonluchter cohort at 3, 6, 12 and 24 months. The 6MWD improves significantly and clinically relevant up to 93m at 12 months and remains at 83m during 24 months. In patients with MRC-scores >2,

Table 4 Longterm effects of Integrated Disease Management on Exercise Tolerance in primary care COPD patients of the Kroonluchter Cohort

	6-MWD difference *** compared to baseline		95% CI	p-value
All patients				
	3 mo	38.3	[27.2, 49.4]	<0.0001
	6 mo	62.5	[47.4, 77.7]	<0.0001
	12 mo	93.5	[71.4, 115.6]	<0.0001
	24 mo	83.3	[60.0, 106.6]	<0.0001
Subgroup baseline MRC>2				
	3 mo	52.1	[37.1, 67.2]	<0.0001
	6 mo	59.2	[40.8, 77.7]	<0.0001
	9 mo	93.0	[62.9, 123.1]	<0.0001
	12 mo	80.0	[44.7, 115.3]	<0.0001
Subgroup baseline 6MWD<400m				
	3 mo	52.7	[38.9, 66.5]	<0.0001
	6 mo	78.2	[52.5, 103.9]	<0.0001
	9 mo	112.3	[77.9, 146.7]	<0.0001
	12 mo	101.4	[64.3, 138.6]	<0.0001

*paired samples T-test; *p* is considered significant at values<0.05; **MCID 6MWD = 54m [17]
Abbreviations: 6-MWD, 6- Minute Walking Distance; MRC, Medical Research Council Dyspnoea Score

6MWD differences are comparable in significance and clinical relevance, but seem to occur somewhat earlier, at 3 months. In patients with baseline 6MWD <400m, the 6MWD difference is 112 meters at 12 months and remains statistically significant and clinically relevant at 24 months with effect sizes over 100 meters.

DISCUSSION

Our studies demonstrate that IDM programmes can be successfully implemented in real-life populations in primary care. Even after two years, considerable proportions of the patients involved in the programs still show significant and clinically relevant improvements in health status and exercise tolerance. In patients with a baseline CCQ >1 and in patients with an MRC >2, the long-term effect on CCQ score seems to be doubled and even tripled, respectively. In patients with baseline 6MWD <400m, the 6MWD difference remains substantially large during two years, with effect sizes exceeding 100 meters.

The typical structured program of PR in the secondary and tertiary care setting is usually of relatively short duration, ranging from 6 to 12 weeks.[17] Positive results during up to 3 months have been widely published[6;17-19], but several clinical trials report that initial benefits of the intervention usually recede over time. Often, the effects above clinical relevance thresholds are lost again between 6 to 18 months follow-up.[11;12;13;20;21]

As a result, recommendations regarding prolonged duration of PR have been issued, and several studies have evaluated longer-term programs in more severe patients, with inconclusive results. Guell randomized 60 GOLD III COPD patients to 12 months of intervention or standard care and followed up for 2 years. Benefits on exercise tolerance, dyspnoea and quality of life were present, but diminished in the second year of follow-up.[22] In an RCT in moderate to very severe COPD patients, Berry concluded that an 18 month exercise program resulted in greater improvements in self-reported disability and physical functioning when compared with a 3-month exercise program.[4] Wijkstra and colleagues reported improvements in quality of life over 18 months in GOLD III patients following rehabilitation at home for three months, followed by once monthly physiotherapy sessions. The authors concluded however that change in quality of life was not associated with a change in exercise tolerance.[23] Positive findings in selected patient groups from secondary and tertiary care, following a prolonged PR programme, were further confirmed by Troosters, Engstrom and Bendstrup, suggesting that structured, supervised exercise participation should be continued for extended periods in patients undergoing PR.[24-26]

To the best of our knowledge, this is the first publication describing long-term follow up results of IDM in primary care. Our positive results can be explained by two important differences, as compared to the mixed results summarized above. First, we studied the

effect of integrated disease management programs especially developed for primary care, which consisted of an interdisciplinary approach with different primary health care team members, aided by secondary care where needed. Furthermore, other PR studies included usually more severe COPD patients, while our programs were especially directed at the whole range of COPD patients, including those with milder stages of disease, but with sufficient symptom burden to justify intervention.

Our results are probably more in line with the recent INTERCOM study, that included secondary care COPD-patients with less advanced airflow obstruction, but impaired exercise capacity. In this RCT, the intervention group received exercise training, education, nutritional therapy and smoking cessation counselling in a community-based, multidisciplinary setting. Quality of life, functional exercise capacity and breathlessness remained significantly favourable in the intervention group versus usual care over the entire two-year intervention.[27]

It is well-known that COPD patients have a less active lifestyle compared to healthy elderly persons.[28] One study by Pitta showed that significant improvements in time spent walking in daily life was only obtained after 6 months of rehabilitation, but were not yet present at 3 months.[29] These findings are mirrored in our Kroonluchter cohort results on the 6MWD, stressing the importance of implementing programmes at least 6 months to optimize the potential room to improve. It is likely that benefits achieved after following an exercise program tend to dissolve after the initial intervention and when the accompanying supervision terminates. Therefore, we successfully developed a training program which included an extra follow-up training of 1 hour per week after the initial 6 months, intended to enhance social support in training groups and sustain results on the long term. It is likely that our clinically relevant and statistically significant results on the 6MWD at 24 months of follow up are the result of more prolonged supervision of physiotherapists and the offered peer-support in training groups.

Our studies had several methodological limitations. The Bocholtz study was designed as a clinical controlled trial, but was not randomized, as it was primarily developed to measure a maximally achievable effect of an IDM program on a primary care practice level. Indeed, the study setting was thus chosen to include demographically comparable villages that hardly interact in daily life, leading to a virtual absence of contamination between groups.[12] The Kroonluchter cohort was based on lessons learned in the Bocholtz study, and was primarily developed as an implementation program in real-life setting. As a result, a power calculation was not conducted beforehand. Nevertheless, our significant 6MWD results at 24 months reached far beyond the MCID of 54 meters, demonstrating an adequate sample size. The first adequate batch of consecutive COPD patients completing 6MWD measurements at 24 months analyzed in this study may represent a selection of more motivated patients, although baseline characteristics differ little from the total group (see table 2). Indeed, we have observed that higher levels of

intrinsic motivation usually comes along with a higher burden of symptoms at baseline. This may be part of the reason that indicators of disease burden (CCQ>1, MRC>2, 6MWD<400m) do seem to increase chances of reaching clinically relevant effects on health status in mild to moderate COPD patients. These results suggest potential usefulness for phenotypic profiling in a primary care COPD population, which we intend and recommend to study further.

Regaining control over one's own disease state is probably a crucial factor in the success of both of our programs. During the IDM-program, improved feelings of self-efficacy and independency became notable in participating patients. Overall, greatest improvements were found in patients with baseline MRC >2, and to a lesser extent in patients with CCQ>1. At this stage, lung function is still relatively well-maintained and thus patients perceive tangible change in symptom burden. When asked, they felt more capable of actually breaking through the vicious circle of inactivity, anxiety and increasing dyspnoea. This was prominently reflected in the patient group with a baseline 6MWD below 400 meter, achieving the most dramatic improvements in exercise capacity. This cut-off was in fact more sensitive than the 350 meters cut-off point applied in the BODE-index, probably reflecting larger room for improvement in primary care COPD patients.[30] When COPD patients are treated with IDM at an earlier stage, it is likely that costs per patient will be lower, while larger groups of eligible patients can benefit. Further disease progression in terms of health status and exercise capacity will be positively influenced and, if sustained, even long-term deterioration of lung-function may be reduced. We have demonstrated that teams of general practitioners, physiotherapists and nurse practitioners, backed up by pulmonary physicians, can provide adequate IDM designed for primary care, as patients' health status and exercise capacity improved substantially, even after two years of follow-up. In the future, we therefore recommend large pragmatic RCTs, addressing the costs and long-term effectiveness of large-scale IDM programs in primary care.

CONCLUSION

In this study, integrated disease management (IDM) improves and sustains health status and exercise capacity in primary care COPD-patients during two years follow-up. Improvements in health status are consistently higher in patients with CCQ >1 at baseline, being strongest in patients with MRC Dyspnoea score >2. Improvements in exercise capacity remain highest in patients with 6MWD < 400m at baseline and seem to occur earlier in patients with MRC Dyspnoea score >2.

REFERENCES

(1) World Health Organization. World Health Statistics 2008. Geneva: World Health Organization; 2008.

(2) Nici L, Donner C, Wouters E et al. American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation. *Am J Respir Crit Care Med* 2006;173:1390-1413.

(3) Rabe KF, Hurd S, Anzueto A et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 2007;176:532-555.

(4) Berry MJ, Rejeski WJ, Adair NE, Ettinger WH, Jr., Zaccaro DJ, Sevick MA. A randomized, controlled trial comparing long-term and short-term exercise in patients with chronic obstructive pulmonary disease. *J Cardiopulm Rehabil* 2003;23:60-68.

(5) Takigawa N, Tada A, Soda R et al. Comprehensive pulmonary rehabilitation according to severity of COPD. *Respir Med* 2007;101:326-332.

(6) Lacasse Y, Martin S, Lasserson TJ, Goldstein RS. Meta-analysis of respiratory rehabilitation in chronic obstructive pulmonary disease. A Cochrane systematic review. *Eura Medicophys* 2007;43:475-485.

(7) Landry MD, Hamdan E, Al MS, Brooks D. The precarious balance between 'supply' and 'demand' for health care: the increasing global demand for rehabilitation service for individuals living with chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis* 2008;3:393-396.

(8) Smeele IJM, van Weel C, van Schayck CP et al. Dutch College of General Practitioners Guideline for COPD Diagnosis. *Huisarts Wet* 2007;50:362-379.

(9) Chavannes NH, Grijsen M, van den Akker M et al. Integrated disease management improves one-year quality of life in primary care COPD patients: a controlled clinical trial. *Prim Care Respir J* 2009;18:171-176.

(10) Chavannes N. Integrated Chronic Obstructive Pulmonary Disease Management in Primary Care. *Dis Manage Health Outcomes* 2008;16:315-318.

(11) Ries AL, Kaplan RM, Limberg TM, Prewitt LM. Effects of pulmonary rehabilitation on physiologic and psychosocial outcomes in patients with chronic obstructive pulmonary disease. *Ann Intern Med* 1995;122:823-832.

(12) Griffiths TL, Burr ML, Campbell IA et al. Results at 1 year of outpatient multidisciplinary pulmonary rehabilitation: a randomised controlled trial. *Lancet* 2000;355:362-368.

(13) Vale F, Reardon JZ, ZuWallack RL. The long-term benefits of outpatient pulmonary rehabilitation on exercise endurance and quality of life. *Chest* 1993;103:42-45.

(14) Celli BR, MacNee W. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J* 2004;23:932-946.

(15) Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. *Thorax* 1999;54:581-586.

(16) Redelmeier DA, Bayoumi AM, Goldstein RS, Guyatt GH. Interpreting small differences in functional status: the Six Minute Walk test in chronic lung disease patients. *Am J Respir Crit Care Med* 1997;155:1278-1282.

(17) Nici L, Raskin J, Rochester CL et al. Pulmonary rehabilitation: WHAT WE KNOW AND WHAT WE NEED TO KNOW. *J Cardiopulm Rehabil Prev* 2009;29:141-151.

(18) Maltais F, Bourbeau J, Shapiro S et al. Effects of home-based pulmonary rehabilitation in patients with chronic obstructive pulmonary disease: a randomized trial. *Ann Intern Med* 2008;149:869-878.

(19) American Thoracic Society. Pulmonary Rehabilitation. *Am J Respir Crit Care Med* 1999;159:1666-1682.

(20) Guyatt GH, Berman LB, Townsend M. Long-term outcome after respiratory rehabilitation. *CMAJ* 1987;137:1089-1095.

(21) Strijbos JH, Postma DS, van Altena R., Gimeno F, Koeter GH. A comparison between an outpatient hospital-based pulmonary rehabilitation program and a home-care pulmonary rehabilitation program in patients with COPD. A follow-up of 18 months. *Chest* 1996;109:366-372.

(22) Guell R, Casan P, Belda J et al. Long-term effects of outpatient rehabilitation of COPD: A randomized trial. *Chest* 2000;117:976-983.

(23) Wijkstra PJ, Ten Vergert EM, van Altena R. et al. Long term benefits of rehabilitation at home on quality of life and exercise tolerance in patients with chronic obstructive pulmonary disease. *Thorax* 1995;50:824-828.

(24) Troosters T, Gosselink R, Decramer M. Short- and long-term effects of outpatient rehabilitation in patients with chronic obstructive pulmonary disease: a randomized trial. *Am J Med* 2000;109:207-212.

(25) Engstrom CP, Persson LO, Larsson S, Sullivan M. Long-term effects of a pulmonary rehabilitation programme in outpatients with chronic obstructive pulmonary disease: a randomized controlled study. *Scand J Rehabil Med* 1999;31:207-213.

(26) Bendstrup KE, Ingemann JJ, Holm S, Bengtsson B. Out-patient rehabilitation improves activities of daily living, quality of life and exercise tolerance in chronic obstructive pulmonary disease. *Eur Respir J* 1997;10:2801-2806.

(27) van Wetering CR, van Nooten FE, Mol SJ, Hoogendoorn M, Rutten-van Molken MP, Schols AM. Systemic impairment in relation to disease burden in patients with moderate COPD eligible for a lifestyle program. Findings from the INTERCOM trial. *Int J Chron Obstruct Pulmon Dis* 2008;3:443-451.

(28) Pitta F, Troosters T, Spruit MA, Probst VS, Decramer M, Gosselink R. Characteristics of physical activities in daily life in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005;171:972-977.

(29) Pitta F, Troosters T, Probst VS, Langer D, Decramer M, Gosselink R. Are patients with COPD more active after pulmonary rehabilitation? *Chest* 2008;134:273-280.

(30) Celli BR, Cote CG, Marin JM et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med* 2004;350:1005-1012.

CHAPTER 8

RECODE: Design and baseline results of a cluster randomized trial on cost-effectiveness of integrated COPD management in primary care

Annemarije L. Kruis, Melinde R.S. Boland, Catharina H. Schoonvelde, Willem J.J. Assendelft, Maureen P.M.H. Rutten-van Mölken, Jacobijn Gussekloo, Apostolos Tsiachristas, Niels H. Chavannes

BMC Pulm Med 2013;13:17.

ABSTRACT

Background

Favorable effects of formal pulmonary rehabilitation in selected moderate to severe COPD patients are well established. Few data are available on the effects and costs of integrated disease management (IDM) programs on quality of care and health status of COPD patients in primary care, representing a much larger group of COPD patients. Therefore, the RECODE trial assesses the long-term clinical and cost-effectiveness of IDM in primary care.

Methods/design

RECODE is a cluster randomized trial with two years of follow-up, during which 40 clusters of primary care teams (including 1086 COPD patients) are randomized to IDM or usual care. The intervention started with a 2-day multidisciplinary course in which healthcare providers are trained as a team in essential components of effective COPD IDM in primary care. During the course, the team redesigns the care process and defines responsibilities of different caregivers. They are trained in how to use feedback on process and outcome data to guide implement guideline-driven integrated healthcare. Practice-tailored feedback reports are provided at baseline, and at 6 and 12 months. The team learns the details of an ICT program that supports recording of process and outcome measures. Afterwards, the team designs a time-contingent individual practice plan, agreeing on steps to be taken in order to integrate a COPD IDM program into daily practice. After 6 and 12 months, there is a refresher course for all teams simultaneously to enable them to learn from each other's experience. Health status of patients at 12 months is the primary outcome, measured by the Clinical COPD Questionnaire (CCQ). Secondary outcomes include effects on quality of care, disease-specific and generic health-related quality of life, COPD exacerbations, dyspnea, costs of healthcare utilization, and productivity loss.

Discussion

This article presents the protocol and baseline results of the RECODE trial. This study will allow to evaluate whether IDM implemented in primary care can positively influence quality of life and quality of care in mild to moderate COPD patients, thereby making the benefits of multidisciplinary rehabilitation applicable to a substantial part of the COPD population.

Trial registration: Netherlands Trial Register (NTR): NTR2268

BACKGROUND

Chronic obstructive pulmonary disease (COPD) is a smoking-related pulmonary disorder, characterized by largely irreversible airflow obstruction, multisystemic manifestations and frequent co-morbidities.[1] According to current guidelines, stable COPD is managed with a combination of different treatment components (e.g. smoking cessation, physiotherapeutic reactivation, self-management, optimization of medication adherence)[1], involving different healthcare providers. Currently, treatment is mostly guided by the severity of airflow limitation.[2] However, COPD is a complex disease, with great variation in symptoms, functional limitations and co-morbidities as well as in progression towards more severe stages.[3] Therefore, the existence of several clinically relevant phenotypes calls for a more personalized approach.[4] Ideally, optimal care of COPD patients requires an individualized, patient-centered approach that recognizes and treats all aspects of the disease, addresses the systemic effects and co-morbidities, and integrates medical care among healthcare professionals and across healthcare sectors.[5] Since professional treatment, hospital admissions and loss of work contribute to the economic burden of disease worldwide, there is much interest in systematically improving the quality of care, while reducing total costs for patients with COPD and other chronic illness. Integrated Disease Management (IDM) programs have proliferated as a means of improving the quality and efficiency of care. The most frequently applied IDM programs in COPD patients are pulmonary rehabilitation (PR) programs. According to a Cochrane systematic review, the effectiveness of PR on exercise tolerance and quality of life is well established.[7] In international reports and guidelines, it is acknowledged that PR is indicated for all individuals with COPD who have decreased exercise tolerance, exertional dyspnea or fatigue, and/or impairment of activities of daily living.[1;8;9] However, widespread access is restricted, due to limited availability of resources and high costs.[10-12] Furthermore, PR programs usually include only the more severe patients and last only for a limited period of time[13], while initial benefits seem to decline over time.[14-18] After returning home, patients are frequently insufficiently motivated to continue a more physically active and healthy lifestyle. Unfortunately, general practitioners (GPs) are rarely involved in PR programs and, as a consequence, are often unable to support program methods after a rehabilitation phase has formally been concluded.[13]

We previously argued that when components of PR are integrated into a primary care IDM program, patients can be treated in their home environment. Primary care providers can then be (more) involved as direct coaches of this process.[19-21] To establish such a program of combined interventions, the set-up of a multidisciplinary team is vital, in which different healthcare professionals participate and provide their share in the spectrum of the required care (Figure 1). Ideally, patients and healthcare providers are close partners in IDM, in order to better control daily symptoms and promote self-man-

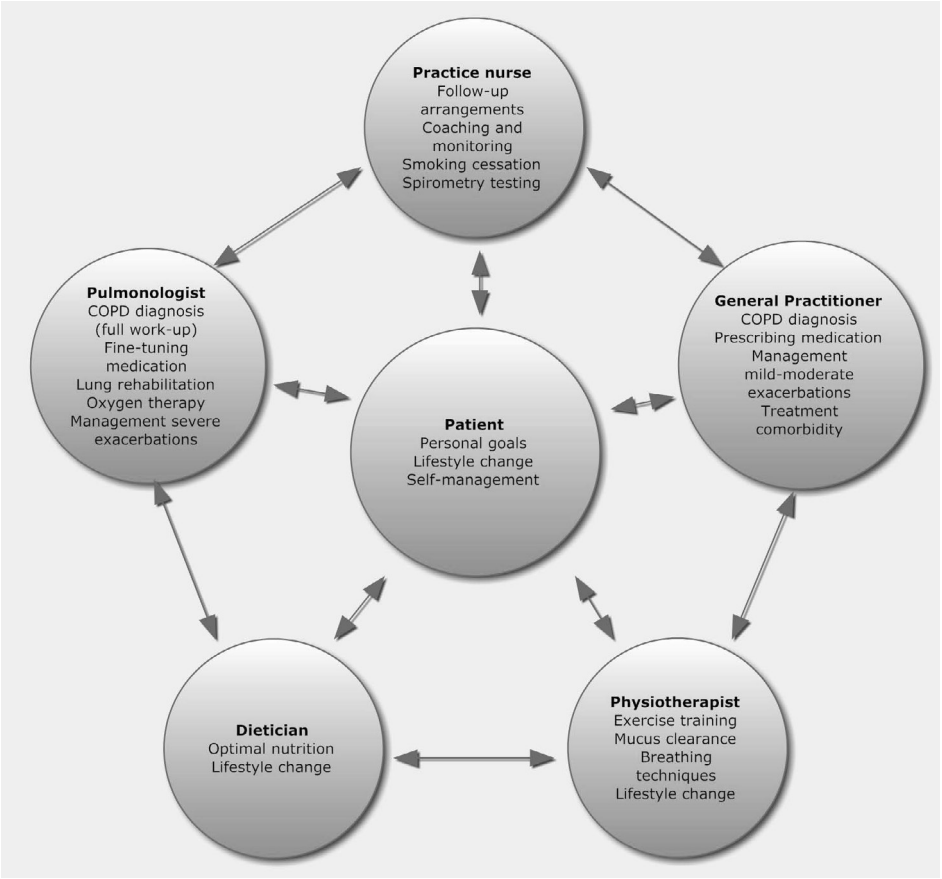


Figure 1 Components of an Integrated Disease Management program for COPD patients in primary care

agement. Furthermore, strong cooperation between several disciplines in primary care and mutually agreeable collaboration with secondary and tertiary care are prerequisites for integrated chronic care.[19]

Systematic reviews of disease management for COPD patients emphasise the need for well-designed, practical multicenter trials[22;23], including broad representative patient samples[24], with a wide range of physicians and settings to improve external validity.[23] Furthermore, authors of systematic reviews advocate studies designed to evaluate the long-term effectiveness of IDM[23], and advise more health economic studies across different care settings.[24] When considering the large number of eligible patients for IDM in the community, the potential impact is high. However, no trials have been published that are specifically targeted to measure the cost-effectiveness of IDM in patients recruited in primary care.

Therefore, the aim of the current RECODE (acronym for Randomized Clinical Trial on Effectiveness of integrated COPD management in primary care) cluster randomized clinical trial (NTR 2268) is to assess the cost-effectiveness of an IDM program for COPD patients in primary care in the Netherlands. Based on an earlier controlled clinical trial evaluating the effect of an IDM program in mild to moderate COPD, we found the greatest improvements on quality of life in patients with a MRC dyspnea score >2.[25] As a result, we based our sample size estimates on the a priori planned subgroup of patients with MRC dyspnea score >2. This article describes the design, rationale and baseline results of this trial.

METHODS

Study objective and design

The RECODE trial is a two-group parallel cluster-randomized clinical trial with a two-year follow-up, conducted in the primary care setting. Our objective is to evaluate the clinical and cost-effectiveness of IDM for COPD patients in primary care. The intervention is delivered by the primary care team, including a GP, practice nurse, physiotherapist and dietician, with a consulting pulmonary physician at hand. To avoid contamination between treatment groups within practices, primary care practices are randomized rather than patients. The Medical Ethics Committee of the Leiden University Medical Centre approved the trial.

Participants

GPs

Inclusion of GPs and patients started in September 2010 and was finished in September 2011. Practices were considered as candidates if they were willing to create an integrated COPD management team, in which each member has responsibility for their respective areas of expertise. The practices had to include at least one GP, one practice or extramural respiratory nurse, and one physiotherapist specialized in COPD care. If multiple practices were collaborating (for example with one practice nurse), they formed one cluster which was used for randomization. Our recruitment goal was to enrol representative groups of primary healthcare providers from a broad spectrum of practices in order to enhance external validity. This study was embedded in the Leiden Primary Care Research Network (LEON), which is managed by the department of Public Health and Primary Care of the Leiden University Medical Center. This multi-center research network consists of some 100 general practices in the western region of the Netherlands, in which these practices signed an agreement to collaborate in scientific research.

Patients

We included all patients who were diagnosed with COPD by their treating physician. We selected patients from electronic medical records (EMRs) of general practices. For all included patients, we attempted to verify the diagnosis by lung function according to the GOLD criteria[1]. If spirometry data were not available, patients were invited to participate for a formal lung function assessment, according to the ATS/ERS guidelines for spirometry[26]. Exclusion criteria consisted of terminally ill patients, dementia or cognitive impairment, inability to fill in Dutch questionnaires, and hard drug or alcohol abusers. We did not exclude patients if a pulmonary physician was considered the main healthcare provider. The GPs checked the selected patients against the formal inclusion and exclusion criteria before the recruitment procedure started. All patients provided written informed consent before participation in the study.

Intervention

The intervention consists of an IDM program, which is implemented by a multidisciplinary team in general practice. The team consists of at least three members: the GP, the practice nurse, and a cooperating physiotherapist with specific certified training in COPD care. Depending on the team needs, a collaborating pulmonary physician and dietician were added to the intervention team.

We trained the multidisciplinary teams of intervention practices in a two-day course during 2010-2011. During this course, essential components of IDM for effective integrated COPD care in primary care were explained, trained and rehearsed and supervised. Elements of this course are further outlined in Table 1 and included a review of the advice from international guidelines, performing/interpreting spirometry and assessment of disease burden, and motivational interviewing to stimulate a healthier lifestyle including more physical activity and smoking cessation. Furthermore, the healthcare providers were trained in adopting self-management action plans, including early recognition and treatment of exacerbations, encouragement of regular exercise and guideline-based physical reactivation, cooperation and collaboration with secondary care, and instructions in dietician support for nutritionally depleted patients. In addition, they were trained in how to use feedback on process and outcome data to guide and implement guideline-driven integrated healthcare. This CME course was developed according to recent national and international guidelines[1;27] and was provided by teachers with hands-on experience with the program. At the end of the course, the team designed a time-contingent individual practice plan, agreeing on steps to be taken in order to integrate a COPD IDM program into daily practice. Intervention practices were free in the fulfilment of their individual plans, as long as they were feasible and relevant for the practice. After 6 and 12 months, there was a refresher course for the intervention practices.

Table 1. Components of IDM included in the RECODE course for multidisciplinary teams in primary care

DM interventions	Example
Optimal medication adherence	Tailoring of advices from international guidelines, e.g. frequent exacerbations necessitate inhaled corticosteroids; daily respiratory complaints necessitate long-acting bronchodilators
Proper diagnosis	Performing and interpreting spirometry, assessment of disease burden using MRC and CCQ
Motivational interviewing	Understanding and making use of patients' personal goal in physical reactivation and lifestyle changes
Smoking cessation counselling	Review of the recent literature, discussion of bottlenecks, applying behavioural techniques and drug therapy for smoking cessation
Applying self-management plans	Teaching self-management techniques, including early recognition and treatment of exacerbations
Guideline based physiotherapeutic reactivation	Using a patients' personal goal, referral for physiotherapeutic reactivation in patients with MRC score >2.
Dietary interventions	Early recognition and treatment of nutritionally depleted patients

Web-based disease management application

During the course, the team learned the details of an ICT program that supports recording of process and outcome measures by access to a flexible web-based IDM application, named Zorgdraad (in English 'Care Ties'). This application combined a patient and a healthcare provider portal. The patient portal provided patients with disease-specific easy written education, and allows personal goals and personal notes. The healthcare portal left space for a protocol for COPD follow-up guidance, quality of life scores, physiotherapy follow-up and examination, smoking cessation, medication records, and facilitates tailored benchmark reports at 6 and 12 months. These reports were generated by the researchers and sent to the practices to support prioritizing the healthcare needs. An experienced instructor provided the practices during the course with all information about Zorgdraad. An account manager supported the practice nurse and GP on individual use of the program in daily practice. It was intended that practice nurses give the COPD patients directions for use on the patient-portal of Zorgdraad.

All practices were in essence free in the usage of Zorgdraad, and in the fulfilment of their plans. Therefore, not all patients received all components of the program, but individual patient-specific care plans are negotiated by the team, in collaboration with the patient. The intensity of the IDM program depended upon the health status and needs of the patient, resulting in some patients receiving all interventions (e.g. smoking cessation, physiotherapy, nutritional support), while stable patients only had regular 6-monthly or

12-monthly follow-up by nurses. Implementation of the intervention was assessed at 24 months (see "Outcomes").

Financial coverage of the intervention

We arranged with the local healthcare insurer that all RECODE patients with dyspnea on moderate or worse exertion (indicated by a Medical Research Council (MRC) score of >2) would be totally reimbursed for the intervention, including physiotherapy.

Usual care group

The control group consists of 'usual care' [28], which is based on the 2007 national primary care COPD guidelines[27]. Instead of the multidisciplinary RECODE course, the practice nurse received a course on technical performance of spirometry in primary care only, in order to divert attention from any of the IDM topics mentioned in Table 1. If the results of our study show that the IDM program could substantially improve the health-related quality of life of COPD patients, we will make the entire set of interventions available to the control group after the study has been completed.

Outcomes

Time points

We follow patients at baseline, and at 6 and 12 months with a face-to-face interview. Blinded research nurses administer the questionnaires (Table 2) at specific time points. These interviews take place at the general practice or at the patients' homes, using the web-based application Zorgdraad. At 9, 18 and 24 months we sent questionnaires by post. In addition, retrospectively the researchers extract data from the patients' EMRs at 24 months over the complete trial period, regarding prescribed medication.

Primary endpoint is at 12 months, when we expect to detect the clinically relevant effect of the intervention[20;29]. Total study duration provides 24 months of follow-up, to assess whether benefits can be maintained.

A. Patients

At baseline, we assessed socio-demographic factors (age, gender, socioeconomic status measured through level of education), marital status, lung function and co-morbidity.

Primary outcome

The primary outcome measure in this study is health status as measured by the Clinical COPD Questionnaire (CCQ) at 12 months. This questionnaire is a disease-specific, 10-item questionnaire that calculates an overall score and three domain scores: symptoms, functional state and emotional state. Patients are required to respond to each item on a

Table 2. Overview of measurements per time point in the RECODE study

Outcomes	Baseline	6 m	9 m	12 m	18 m	24 m
Participants						
Demographic characteristics	X					
Lung function	X					
Co morbidity	X					
CCQ	X	X	X	X	X	X
SGRQ-C	X	X	X	X	X	X
EQ-5D	X	X	X	X	X	X
SF-36	X	X	X	X	X	X
Smoking behavior, guided smoking attempts	X	X	X	X	X	X
IPAQ	X	X	X	X	X	X
SMAS-30	X	X	X	X	X	X
MRC-Dyspnea scale	X	X	X	X	X	X
Exacerbations	X					X
Costs of health care utilization by patients, part A: Health care use Questionnaire, including direct non-medical costs borne by patients/families	X	X	X	X	X	X
Costs of productivity loss: Absence from work Questionnaire	X	X	X	X	X	X
Costs of health care utilization by patients, part B: Data extraction from medical records (health care utilization, medical treatment)						X
PACIC	X	X	X	X	X	X
Health care providers						
ACIC	X			X		
Satisfaction, involvement and implementation of the IDM program				X (IG)		
IDM program information						
Development costs of the IDM program						X (IG)
Implementation costs of the IDM program						X (IG)
Performance indicators of practices (see Table 4)	X					X

ACIC: Assessment Chronic Illness Care; CCQ: Clinical COPD Questionnaire; EQ-5D: EuroQol-5D; IPAQ: International Physical Activity Questionnaire; MRC: Medical Research Counsil scale; PACIC: Patient Assessment Chronic Illness Care; SF-36: ShortForm-36; SGRQ-C: Saint Georges Respiratory Questionnaire; SMAS-30: Self Management Scale-30. IG=intervention group only

7-point scale with 0 representing the best possible score and 6 representing the worst possible score. This instrument is proven to be sensitive and valid, and easy to administer in primary care. The minimal clinical important difference (MCID) is -0.4 points.[30;31]

Secondary outcomes

Secondary outcome measurements at 6, 9, 12, 18 and 24 months include (the questionnaire for each outcome is provided in brackets):

1. Measures of changes in health-related quality of life (disease-specific as well as generic), measured by :

a. CCQ

b. St. George Respiratory Questionnaire (SGRQ); designed to measure health impairment in patients with asthma and COPD. The first part produces the symptom score and the second part the activity and impact score. A total score can also be calculated. We use a Dutch version of the SGRQ, and consider a -4 unit change as the MCID for within-group comparison.[32]

c. The Euro Qol-5D-3L is a generic, preference-based health-related quality of life questionnaire, with many applications in respiratory disease. It consists of 5 dimensions to describe health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) each item with three levels of functioning (e.g., no problems, some problems, and extreme problems). We used the value set derived from the Dutch general population that, when applied to the dimensions of the health state, result in a preference-based utility score that typically ranges from states worse than dead (<0) to 1 (full health), anchoring dead at 0. Besides the descriptive system and the off-the-shelf value sets, the EQ-5D includes a visual analog scale (VAS) where an individual rates his own health on a scale from 0 (worse imaginable health) to 100 (best imaginable health).[33;34]

a. Short-Form Health Survey (SF-36) is a 36-item questionnaire that measures two components (physical and mental component). The physical component consists of four domains of health: physical functioning, role limitations due to physical health, bodily pain and general health perceptions. The mental component consists of role limitations due to emotional problems, vitality, social functioning and mental health.[35]

2. Measures of change in patients' lifestyle, illness behavior and knowledge:

a. Smoking behavior, guided smoking attempts;

b. Taking initiatives, investment behavior and level of self-efficacy, as measured by the Self-Management Scale-30 (SMAS-30)[36];

c. Physical activity, as measured by the International Physical Activity Questionnaire (IPAQ) short form. This is an instrument designed primarily for population surveil-

lance of physical activity among adults. The items in this short form are structured to provide separate scores on walking, moderate-intensity and vigorous-intensity activity. The total score is computed by multiplying the duration (in minutes) and frequency (days) of walking, moderate-intensity and vigorous-intensity activities by its energy requirement to yield a score in Metabolic Equivalent Time (MET) minutes.

3. Measures of change in intermediate patient-related outcomes:
a. Dyspnea, measured by the MRC Dyspnoea Scale[37]
b. Exacerbations: moderate (oral prednisone and/or antibiotic courses), severe (hospitalizations). These data were retrospectively extracted from EMRs at 24 months, over the entire follow-up period.

4. Measures of change in healthcare utilization and costs:
a. Development and implementation costs of the program: time and material resources associated with the training of the healthcare providers and the ICT support (measured at 24 months).
b. Costs of healthcare utilization by patients: including all COPD and non-COPD related cost of a) hospitalization, b) medication, c) caregiver contact, and d) revalidation. Retrospectively we extract data from EMRs at 24 months over the complete trial period, regarding prescribed medication.
c. Direct non-medical costs borne by patients/families, e.g. travel costs. Costs of productivity loss due to absenteeism/presenteeism at work. This was measured at baseline, and at 6, 9, 12, 18 and 24 months.

5. Measures of change in care delivery process: level of care integration according to patients, measured by the Patient Assessment Chronic Illness Care (PACIC).[38]This questionnaire was self-reported by patients in both groups and was administered at baseline, and at 6, 9, 12, 18 and 24 months.

B. Healthcare providers

The Assessment Chronic Illness Care (ACIC) questionnaire, which is a tool to measure the level of care integration according to healthcare providers[39], was sent to primary care providers at baseline and is evaluated at 12 months. Furthermore, we use a self-designed questionnaire at 12 months ("Satisfaction, involvement and implementation of the IDM program") for the primary care team, to measure the level of involvement and implementation of the practice teams with the RECODE intervention at 12 months. This questionnaire comprises questions on the number and type of healthcare providers which were involved in the program, the types of team meetings and local appointments, and the usage of tailored benchmark reports. Furthermore, we requested the number

of patients involved in the intervention, and the numbers of components implemented in daily practice. Overall, the healthcare providers are asked to rate the intervention on a 5-point scale, and we ask for details on possible bottlenecks and problems regarding implementation.

C. Current level of care of the practices at baseline

The current level of COPD care was assessed at baseline in all general practices to be able to report any difference in quality of care at 12-months follow-up. Therefore, from the EMRs we extracted the following performance indicators: registration of smoking status and stop-smoking advice, registration of body mass index, assessment of spirometry and inhalation technique in the last year, the number of patients with monitored functioning by means of the CCQ, MRC, or the number of patients with controlled physical activity in the last year.

Sample size calculation

The primary outcome is the difference in change in the CCQ score between baseline and 12 months between both groups. We used methods for standard sample size estimates for trials that randomised at the level of the individual[40] adjusting for clustering by inflating sample size estimates by the design effect given by $1+(n-1)\rho$, where n is the average cluster size, and ρ is the estimated intraclass correlation coefficient (ICC).[41] Sample size estimates are based on the mean difference in CCQ between intervention and control group. Using the minimal clinically important mean difference for the CCQ[30], and the upper value of 0.05 from a range of ICC values identified in studies involving the older person in primary care[42], power calculations indicate that 40 clusters of practices with an average of 27 participants per cluster are required. To allow for subgroup analysis in MRC scores 1-2 versus 3-5, in total 1080 participants are need to be randomized to achieve a power of at least 80% with alpha levels of 0.05, including a participant loss to follow-up of 10% or a loss of 4 clusters at 12 months.

Randomization

Cluster randomization was at the level of the primary care team. The first author recruited the practices, and the selected participants were checked by the GP against formal inclusion and exclusion criteria before the intervention started. To enhance comparability between the intervention and control group, the clusters were matched and randomized by a researcher who was blinded to the identity of the practices. Matching was into pairs according to the following criteria: (i) percentage of patients from ethnic minorities, (ii) type of practice, (iii) practice location (urban/rural), (iv) age of GP, and (v) gender of the GP. Subsequently, the matched practices were randomized to the intervention group or the control group by using a computer-generated random number list.

Informed consent

Informed consent was provided by the GPs and the patients. The informed consent was acquired before the course took place and the practices started with their intervention.

Blinding

Because of the nature of the intervention, it is not possible to blind patients and primary care providers to practice group allocation. Therefore, blinded research nurses assess the outcomes. Patients are instructed not to report on their type of management to the outcome assessors.

Data analysis at baseline

Non-participation analysis at baseline

We recruited potential participants with an invitation letter including a postal CCQ questionnaire. Returned questionnaires were analysed to investigate if there were differences between participants and patients who fulfilled inclusion criteria, but refused to participate in the trial (non-participants). We compared differences on CCQ scores, sex and age using independent t-tests and chi-square tests.

Analysis plan

Analysis of effectiveness at 12 and 24 months

The final analysis of the trial will be carried out on an intention-to-treat basis. The freedom of the clusters to fill in the precise implementation of the intervention will probably relate to the (cost)-effectiveness of the intervention and, therefore, the clustering of patients in GP practices should be taken into consideration in the analysis.[43] Therefore, the results will be investigated with respect to the differences in intensity between and within clusters over time using multi-level analysis.

Pre-planned subgroup analyses

We will study the influence of age, sex, disease burden (MRC score 1-2 vs. 3-5), disease severity (GOLD stage), and socioeconomic status. The trial was specifically powered on the MRC 1-2 vs. 3-5 subgroup analyses; see 'Sample size calculation'.

Economic evaluation at 12 and 24 months

The economic evaluation will be performed according to the internationally agreed guidelines[44] and the national guidelines for pharmacy-economic research.[45] We will calculate the costs from a healthcare perspective and a broad societal perspective, in order to facilitate decision making. The healthcare perspective will include all costs covered by

the healthcare sectors budget: development, implementation and healthcare utilization costs. The costs from societal perspective will include travel and productivity costs in addition to the costs from the healthcare perspective to capture (almost) all costs related to the intervention, irrespective of who actually bears them.

The healthcare utilization costs (excluding medication costs), travel costs and productivity costs of patients will be calculated using questionnaires at different time points (Table 2). These questionnaires will collect self-reported cost-related data by patients using a recall period of three months. Additionally, the type and amount of medication from the individual patients will be collected from the GP information systems. The unit costs per medication prescription will be based on the GIP Databank.[45] Time and material resources associated with the training of the healthcare providers, the multidisciplinary team meetings in the GP practices, and the ICT support will be estimated based on course attendance, computer-documented minutes of ICT use, treatment plans, and professional self-report. Finally, the productivity costs will be estimated using the friction method, which implies that the costs of absenteeism will occur only for a fixed (friction) period ending at the moment that the employee is replaced.[46]

Cost-effectiveness (CEA) and cost-utility analyses (CUA)

The relation between the costs and the estimated health outcomes is expressed in cost-effectiveness ratios: (1) costs per QALY, (2) costs per exacerbation prevented, (3) costs per patient with a clinically relevant improvement of at least 0.4 units on the CCQ, (4) costs per patient with a clinically relevant (4 units) improvement on the SGRQ, and (5) costs per patient with a 1 point improvement on the MRC dyspnea scale. Adopting such a wide range of outcome measures in the economic evaluation is in line with recent guidelines of a joint ATS/ERS task force on outcome measurements in COPD that recommend taking a multi-outcome approach.[47] At the same time, comparison with the cost-effectiveness of other interventions for other diseases is made possible through the calculation of costs per QALY. Uncertainty around cost-effectiveness ratios will be dealt with in probabilistic sensitivity analysis in which costs and health outcomes will be bootstrapped and plotted on cost-effectiveness planes from which cost-effectiveness acceptability curves will be drawn.[48-50] In additional 'net monetary benefits[51], will be calculated using different thresholds of the willingness to pay for a QALY and it will be investigated which patient, practice and team characteristics are related to the size of the net monetary benefits. The economic evaluation will compare differences in costs to differences in effects (CEA) and quality adjusted life-years (CUA). The analysis will have a 12 and 24-months time horizon. Sensitivity analyses will be performed on the perspective (societal versus healthcare) and the applied utility measure (Dutch EQ5D).

BASELINE RESULTS

Primary care practices

The characteristics of the enrolled 54 general practices, which formed 40 clusters, are shown in Table 3. Numbers of included patients per participating cluster ranged from 11 to 79 patients. Most practices were single-handed (44%) or one or more partner practices (41%). Of all the practices, 50% were healthcare centers. The enrolled practices included a total of 76 participating GPs; the majority (61%) were males with a mean age of 50 (range 35-62) years and 16 (SD 8.2) years of practicing.

Table 3. Characteristics of included primary care practices in the RECODE study

General practices	
Number of GP practices	54
Number of clusters	40
Number of included patients per participating cluster, range	11-79
Type of practice, %	
Single-handed practice	44
One or more partner practice	41
Healthcare centre	15
Practice location, % urban	72
Patient practice population, n (range)	3418 (1750-16907)
Ethnic minorities, %	15
General practitioners	
Number of participating GP's	76
Gender GP, % male	61
Age GP, years (range)	50 (35-62)
Years practicing, years (SD)	16 (8.2)

Current level of care of the practices

We assessed the current level of COPD care at baseline in all general practices to be able to report any difference in quality of care after 12 months. Results at baseline are shown in Table 4. Almost half of the RECODE patients (53%) have a registered smoking status; however, a standard spirometry test in the last year was less common, with only (12%) of the patients receiving spirometry.

Patient recruitment

Figure 2 shows the study flow chart until baseline. In total, 2886 patients were selected in 40 clusters of which 617 (21%) patients were excluded by their GP. Most of these excluded patients were registered as a COPD patient in the EMR; however, after

Table 4. Description of current level of care of included GP practices: distribution of the performance indicators of the practices

Measurement category	Process indicator	% (SD)
Smoking	% RECODE patients with registered smoking status	53 (27.9)
	% RECODE patients that are registered smokers	35 (19.3)
	%RECODE patients, which are registered smokers with stop-smoking advice in the last year	35 (34.3)
BMI	% RECODE patients of which the BMI is measured in the last year	42 (23.8)
Treatment & monitoring	% RECODE patients with inhalation technique controlled in the last year	13 (20.3)
	% RECODE patients with a spirometry test in the last year	12 (14.9)
	% RECODE patients with monitored functioning with a structured method (CCQ or MRC) in the last year	28 (27.4)
	% RECODE patients with controlled physical activity in the last year	30 (24.9)

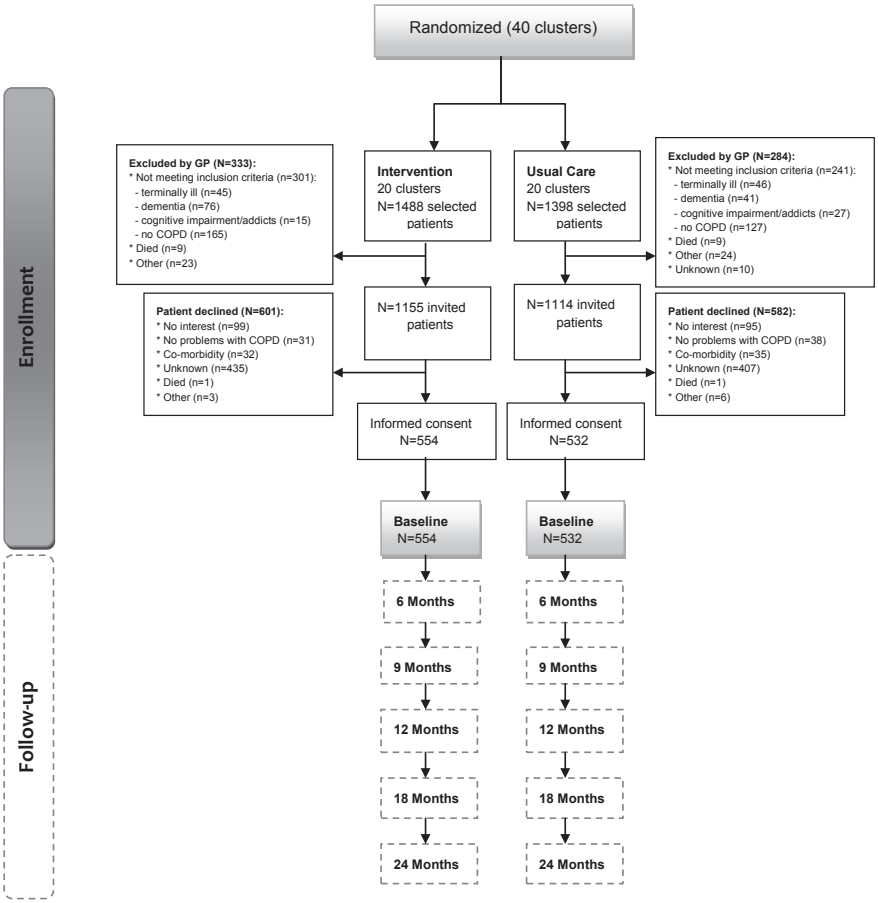


Figure 2. Flowchart of the recruitment to the baseline assessment of the RECODE study

evaluation they turned out to be mislabelled by their GP. After exclusion, 2269 patients were invited to participate, of which 48% participated (response 48%). Most patients indicated no reason for refusing (71%), while others expressed no interest (16%), did not consider themselves to be a COPD patient (6%), or reported not having troublesome COPD symptoms (6%). In total, we have been able to allocate 1086 COPD patients at baseline: 554 participants to the intervention group and 532 participants to the control group. Patients were included from September 2010 until September 2011.

Non-participation analysis

As we invited all eligible participants for this trial with an invitation letter with an attached CCQ questionnaire, we were able to determine any differences between participants of the trial and COPD patients eligible but declining randomization, in order to assess external validity (Table 3). Of all eligible patients who were invited to participate, 1549 questionnaires had analyzable data. We received a higher response rate (961 vs. 588) of returned CCQ questionnaires in the group of patients willing to participate in the trial, compared to patients eligible but declining randomization. There was no difference in age between both groups. Significantly more men (54.7%) are participating in the RECODE trial compared to the proportion of men in patients who declined participation (46.9%). Furthermore, participants in the trial reported significantly more symptoms and disabilities on their functional and mental state, which was reflected in a mean total CCQ score of 1.8 (1.1), compared to 1.5 (1.1) in non-participants.

Table 5. Characteristics and comparison of participants and non-participants of the RECODE trial

	Participant (n=961)*	Non-participant (n=588)	p-value
Age, years (SD)	68.7 (11.0)	67.8 (11.5)	0.162
Males, %	54.7	46.9	0.003
CCQ			
Symptoms	2.4 (1.2)	1.9 (1.2)	<0.001
Functional state	1.8 (1.3)	1.5 (1.4)	<0.001
Mental state	0.9 (1.2)	0.7 (1.2)	<0.001
Total score	1.9 (1.1)	1.5 (1.1)	<0.001

*Values are means (S.D.) unless stated otherwise. ** Of the 1086 RECODE patients, there were 961 CCQ questionnaires available at the time of initial invitation.

Baseline characteristics COPD patients

Table 6 presents the baseline demographic and clinical characteristics of the included COPD population. Enrolled subjects were mainly elderly (ex) smokers, and had moderate COPD which is reflected by a mean post-bronchodilator FEV1 of 68% predicted. We included COPD patients with substantial co-morbidities: 36.8% had a diagnosis of

hypertension, 16.1% suffered from major cardiovascular disease, 14.7% had diabetes and 9.9% had a combined diagnosis of depression. Mean SGRQ total score was 35.6 (20.5) and mean CCQ total score was 1.5 (0.97). The proportion of patients with dyspnea on moderate exertion or worse (MRC score >2) comprised one third of the study population.

Table 6. Baseline demographic and clinical characteristics of the patients with COPD included in the RECODE study

	Total (n=1086)
Men, %	53.9
Age, y	68.3 (11.2)
Employment, %	28.3
Low education, %	40.3
Pulmonary function[1]	
Predicted FEV1** %	67.8
FER*** %	57.7
GOLD-stage, %****	
I Mild	24.6
II Moderate	53.2
III Severe	19.4
IV Very severe	2.9
Smoking status, %	
Current	36.7
Former	53.2
Never	10.1
Co-morbidities	
Major cardiovascular disease, %	16.1
Hypertension, %	36.8
Diabetes, %	14.7
Depression, %	9.9
Charlson co-morbidity index	2.3 (1.3)
CCQ	
Symptoms	2.09 (1.21)
Functional state	1.40 (1.22)
Mental state	0.51 (0.98)
Total score	1.50 (0.97)
MRC	
score ≤2. %	66.6
score >2. %	33.4
MRC score (mean)	2.01 (1.28)

SGRQ	
Symptom	50.5 (20.9)
Activity	47.8 (29.5)
Impact	23.3 (19.6)
Total	35.6 (20.5)
EQ-5D	
Total score	0.74 (0.26)
EQ-VAS	67.0 (17.4)
SF-36	
Physical	38.3 (10.8)
Mental	48.6 (10.4)
IPAQ	
Total MET minutes	2925 (4683)
High physical activity, %	11.1
Moderate physical activity, %	0.6
Low physical activity, %	88.4
Self-management	
Taking initiatives	57.0 (17.9)
Investment behavior	60.4 (17.6)
Self-efficacy	65.3 (17.4)

*Values are means and corresponding standard deviations (SD) unless stated otherwise. **FEV1 predicted: Forced expiratory volume in 1 second, post-bronchodilator, predicted according to age and height. ***FER: forced expiratory ratio (FEV1 / FVC x 100%), FVC: forced vital capacity. ****Mild= FEV1 > 80%, Moderate= 50%≤ FEV1 < 80%, Severe= 30%≤ FEV1 <50%, Very severe= FEV1<30%

1. Lungfunction was missing in 66 patients (34 control patients; 32 intervention patients).

DISCUSSION AND COMPARISON WITH OTHER STUDIES

Optimal COPD management continues to be an important area of research, as the worldwide prevalence is growing and costs will rise in coming decades. Furthermore, in contrast to asthma patients, medication has demonstrated to have limited effect in the management of COPD patients. IDM for chronic diseases has the potential to influence health status, while reducing total costs.[6] However, the (cost) effectiveness of IDM in primary care COPD patients remains unknown, due to a paucity of randomized clinical trials in this field. This article presents the design and baseline results of the RECODE trial, which aims to assess the (cost) effectiveness of IDM for COPD patients in primary care.

We have chosen a cluster-randomized design to prevent cross-contamination of the IDM intervention within a practice. In order to enhance comparability between the intervention and control group at baseline, clusters were matched by stratification and randomized by a blinded researcher. We were able to allocate a broad sample of

1086 COPD patients (ranging from mild to very severe patients) with a response rate of participants of almost 50%. We can conclude from our non-participation analysis that we have recruited a sufficient proportion of patients with considerable complaints, and thus room for improvement. Furthermore, the included practices showed great diversity in the kind of practice, practice size and distribution of ethnic minorities, thereby contributing to high external validity.

To date, previous clinical trials of disease management or home-based rehabilitation trials in primary care have revealed encouraging results on quality of life.[52-56] Based on an earlier example of a published protocol[57], we compared several aspects of our current study to the previously conducted randomized trials which aimed to evaluate the effectiveness of such programs in primary care or in the home-based setting (Table 7).

Selection of patients

In respiratory medicine there is a lack of research on mild to moderate COPD patients, despite that over 80% of COPD patients suffer from this stage of disease and are often treated in primary care. Moreover, it has been shown that treatment decisions for asthma and COPD patients are usually based on studies including a very small and highly selected proportion of the real patient population; this indicates the need for more real-life studies targeted at the true population, and applying less exclusion criteria.[58] Former trials included a highly selected severely ill patient population[52;53] or recruited their patients in secondary care[56]; overall, this is not an uncommon phenomenon in primary care COPD trials.

Limited follow-up

Most studies presented data up to 12 months follow-up, while limited information is available on studies with long-term (18 or 24 months) follow-up. Gottlieb et al. evaluated the effect of an intensive exercise and educational program in patients with moderate COPD during 18 months of follow-up.[54] Although an effect was found on walking distance and quality of life, the effect on quality of life disappeared over 18 months. However, this result should be interpreted with caution, as the intensive rehabilitation program lasted only 7 weeks, which was followed by a maintenance phase including a monthly session focusing on ways of incorporating exercise in daily life. Furthermore, the authors acknowledged many dropouts before randomization, at randomization and during rehabilitation, potentially introducing bias and indicating substantial loss of power.[54] Another study evaluated the efficacy of a community-based COPD management program in less advanced (GOLD 2 and 3) COPD patients during 24 months follow-up. The SGRQ score initially improved in the intervention group compared to the control group. At 12 months, scores in the intervention group had returned to baseline, whereas in the usual care group it remained stable up to 12 months and worsened thereafter.[56]

Table 7. Characteristics of trials evaluating IDM programmes in primary care or home-based setting.

	RECODE	Rea 2004	Boxall 2005	Fernandez 2009	Wetering 2010	Gottlieb 2011
Recruitment	P	P+S	P+S	S	S	P
Pilot study	+	-	-	-	-	-
Population	GOLD stage 1-4	GOLD stage 1-4	GOLD 4	GOLD 4	GOLD 2-3	GOLD 2
Intervention	Multidisciplinary team training, designing practice and patient relevant treatment plans including education, smoking cessation, physiotherapeutic reactivation, dietary intervention (24 mo)	Exacerbation action plan, structured follow-up by nurse, GP. Education about smoking cessation, medication (12 mo)	Home rehabilitation programma (12 wks), under supervision of physiotherapist. Educational sessions for patients and carers, including structured follow up by physiotherapists, nurses, occupational therapy	Home-rehabilitation programme (11 mo) under supervision of physiotherapist. Three education sessions	Intensive exercise programme (4mo), individualized education programme, smoking cessation, dietary intervention (if needed). 20mo maintenance phase, exercise at home (under supervision).	Intensive exercise and educational programme (7wks) led by multidisciplinary team. Smoking cessation counseling.
Included HCP	3-5	3	3	2	3	?
Randomization	Clustered	Clustered	Individual	Individual	Individual	Individual
Blinding outcome assessor	+	-	-	-	+	-
Stratification/matching	+	-	-	-	-	-
Powercalculation based on	MRC score >2	Hospital days	6MWD	Not mentioned	SGRQ	Not mentioned
Cost-effectiveness analysis	+	-	-	-	+	-
Included patients	1086	135	60	50	199	61
Follow-up (months)	24	12	3	12	24	18

Methodological aspects

Due to the nature of the intervention, blinding of participants and patients to the intervention is usually impossible. However, blinding of an outcome assessor can substantially diminish the risk of bias. All the above-mentioned studies, except for the trial of Wetering et al.[56], failed to introduce blinded outcome assessors or did not report this as such. In the study of Rea et al.[55], randomization was also clustered, comparable to our study; however, statistical analysis was at the level of the patient, thereby not taking the clustering coefficient in account. Furthermore, the authors failed to allocate five practices to the correct treatment group.

Planned subgroups

Finally, this study differs from the other studies in that we based our sample size estimates on the a priori planned subgroup of patients with a MRC dyspnea score >2. We earlier reported that we found the greatest improvements on quality of life in these patients.[25] It is probably that lung function is still relatively well maintained at this stage, while patients experience considerable dyspnea and an impaired quality of life.[20] As a result of this pre-planned subgroup power analysis and to compensate for the intra-clustering, we allocated almost 1100 patients in the present trial according to protocol. As can be seen in Table 7, this number is much higher than that of earlier studies in this field.

CONCLUSION

It is acknowledged that not all patients who potentially benefit from an exercise training program, pulmonary rehabilitation, or smoking cessation intervention are actually receiving this type of support in daily practice. It is likely that costs will be lower when patients are detected and persuaded to change their lifestyle at an earlier stage, possibly reducing health decline and disease progression in the long term. To the best of our knowledge, this is the first and largest cluster randomized trial to evaluate the cost and clinical effectiveness of IDM in primary care COPD patients. The results of this study will provide insight into the clinical and cost-effectiveness of IDM in primary care COPD patients, also on the long term.

REFERENCES

(1) Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Available from: http://www.goldcopd.org. Accessed 2012 Dec 31

(2) Celli BR, Thomas NE, Anderson JA et al. Effect of pharmacotherapy on rate of decline of lung function in chronic obstructive pulmonary disease: results from the TORCH study. *Am J Respir Crit Care Med* 2008;178:332-338.

(3) Agusti A, Calverley PM, Celli B et al. Characterisation of COPD heterogeneity in the ECLIPSE cohort. *Respir Res* 2010;11:122.

(4) Rabe KF, Wedzicha JA. Controversies in treatment of chronic obstructive pulmonary disease. *Lancet* 2011;378:1038-1047.

(5) Nici L, Zuwallack R. An official American Thoracic Society workshop report: the Integrated Care of The COPD Patient. *Proc Am Thorac Soc* 2012;9:9-18.

(6) Weingarten SR, Henning JM, Badamgarav E et al. Interventions used in disease management programmes for patients with chronic illness-which ones work? Meta-analysis of published reports. *BMJ* 2002;325:925.

(7) Lacasse Y, Goldstein R, Lasserson TJ, Martin S. Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2009;CD003793.

(8) Berry MJ, Rejeski WJ, Adair NE, Zaccaro D. Exercise rehabilitation and chronic obstructive pulmonary disease stage. *Am J Respir Crit Care Med* 1999;160:1248-1253.

(9) Nici L, Donner C, Wouters E et al. American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation. *Am J Respir Crit Care Med* 2006;173:1390-1413.

(10) Landry MD, Hamdan E, Al MS, Brooks D. The precarious balance between 'supply' and 'demand' for health care: the increasing global demand for rehabilitation service for individuals living with chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis* 2008;3:393-396.

(11) Yohannes AM, Connolly MJ. Pulmonary rehabilitation programmes in the UK: a national representative survey. *Clin Rehabil* 2004;18:444-449.

(12) Brooks D, Sottana R, Bell B et al. Characterization of pulmonary rehabilitation programs in Canada in 2005. *Can Respir J* 2007;14:87-92.

(13) Tiep BL. Disease management of COPD with pulmonary rehabilitation. *Chest* 1997;112:1630-1656.

(14) Ries AL, Kaplan RM, Limberg TM, Prewitt LM. Effects of pulmonary rehabilitation on physiologic and psychosocial outcomes in patients with chronic obstructive pulmonary disease. *Ann Intern Med* 1995;122:823-832.

(15) Griffiths TL, Burr ML, Campbell IA et al. Results at 1 year of outpatient multidisciplinary pulmonary rehabilitation: a randomised controlled trial. *Lancet* 2000;355:362-368.

(16) Vale F, Reardon JZ, ZuWallack RL. The long-term benefits of outpatient pulmonary rehabilitation on exercise endurance and quality of life. *Chest* 1993;103:42-45.

(17) Guyatt GH, Berman LB, Townsend M. Long-term outcome after respiratory rehabilitation. *CMAJ* 1987;137:1089-1095.

(18) Strijbos JH, Postma DS, van Altena R., Gimeno F, Koeter GH. A comparison between an outpatient hospital-based pulmonary rehabilitation program and a home-care pulmonary rehabilitation program in patients with COPD. A follow-up of 18 months. *Chest* 1996;109:366-372.

(19) Kruis AL, Chavannes NH. Potential benefits of integrated COPD management in primary care. *Monaldi Arch Chest Dis* 2010;73:130-134.

(20) Chavannes NH, Grijsen M, van den Akker M et al. Integrated disease management improves one-year quality of life in primary care COPD patients: a controlled clinical trial. *Prim Care Respir J* 2009;18:171-176.

(21) Chavannes N. Integrated Chronic Obstructive Pulmonary Disease Management in Primary Care. *Dis Manage Health Outcomes* 2008;16:315-318.

(22) Adams R, Chavannes N, Jones K, Ostergaard MS, Price D. Exacerbations of chronic obstructive pulmonary disease--a patients' perspective. *Prim Care Respir J* 2006;15:102-109.

(23) Lemmens KM, Nieboer AP, Huijsman R. A systematic review of integrated use of disease-management interventions in asthma and COPD. *Respir Med* 2009;103:670-691.

(24) Steuten LM, Lemmens KM, Nieboer AP, Vrijhoef HJ. Identifying potentially cost effective chronic care programs for people with COPD. *Int J Chron Obstruct Pulmon Dis* 2009;4:87-100.

(25) Kruis AL, van AJ, Erkelens MR et al. Sustained effects of integrated COPD management on health status and exercise capacity in primary care patients. *International Journal of Copd* 2010;5:407-413.

(26) Miller MR, Hankinson J, Brusasco V et al. Standardisation of spirometry. *Eur Respir J* 2005;26:319-338.

(27) Smeele IJM, van Weel C, van Schayck CP et al. Dutch College of General Practitioners Guideline for COPD Diagnosis. *Huisarts Wet* 2007;50:362-379.

(28) Smelt AF, van der Weele GM, Blom JW, Gussekloo J, Assendelft WJ. How usual is usual care in pragmatic intervention studies in primary care? An overview of recent trials. *Br J Gen Pract* 2010;60:e305-e318.

(29) Kocks JW, Tuinenga MG, Uil SM, van den Berg JW, Stahl E, van der Molen T. Health status measurement in COPD: the minimal clinically important difference of the clinical COPD questionnaire. *Respir Res* 2006;7:62.

(30) van der Molen T, Willemse BW, Schokker S, ten Hacken NH, Postma DS, Juniper EF. Developm ent, validity and responsiveness of the Clinical COPD Questionnaire. *Health Qual Life Outcomes* 2003;1:13.

(31) Jones PW. St. George's Respiratory Questionnaire: MCID. *COPD* 2005;2:75-79.

(32) Lamers LM, McDonnell J, Stalmeier PF, Krabbe PF, Busschbach JJ. The Dutch tariff: results and arguments for an effective design for national EQ-5D valuation studies. *Health Econ* 2006;15:1121-1132.

(33) The Euro Qol Group. Euro Qol-a new facility for the measurement of health-related quality of life. 199-208. 1990. Amsterdam, the Netherlands, Health Policy.

(34) Aaronson NK, Muller M, Cohen PD et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. *J Clin Epidemiol* 1998;51:1055-1068.

(35) Schuurmans H, Steverink N, Frieswijk N, Buunk BP, Slaets JP, Lindenberg S. How to measure self-management abilities in older people by self-report. The development of the SMAS-30. *Qual Life Res* 2005;14:2215-2228.

(36) Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. *Thorax* 1999;54:581-586.

(37) Glasgow RE, Wagner EH, Schaefer J, Mahoney LD, Reid RJ, Greene SM. Development and validation of the Patient Assessment of Chronic Illness Care (PACIC). *Med Care* 2005;43:436-444.

(38) Bonomi AE, Wagner EH, Glasgow RE, VonKorff M. Assessment of chronic illness care (ACIC): a practical tool to measure quality improvement. *Health Serv Res* 2002;37:791-820.

(39) Devane D, Begley CM, Clarke M. How many do I need? Basic principles of sample size estimation. *J Adv Nurs* 2004;47:297-302.

(40) Donner A, Birkett N, Buck C. Randomization by cluster. Sample size requirements and analysis. *Am J Epidemiol* 1981;114:906-914.

(41) Smeeth L, Ng ES. Intraclass correlation coefficients for cluster randomized trials in primary care: data from the MRC Trial of the Assessment and Management of Older People in the Community. *Control Clin Trials* 2002;23:409-421.

(42) Snijders TABBRJ. *Multilevel Analysis: An Introduction to Basic andAdvanced Multilevel Modeling*. London: 2011.

(43) Ramsey S, Willke R, Briggs A et al. Good research practices for cost-effectiveness analysis alongside clinical trials: the ISPOR RCT-CEA Task Force report. *Value Health* 2005;8:521-533.

(44) College voor Zorgverzekeringen. *Dutch guidelines for pharmacoeconomic research, evaluation and update.* Diemen: Dutch Health Insurance Council, 2006.

(45) Koopmanschap MA, Rutten FF, van Ineveld BM, van RL. The friction cost method for measuring indirect costs of disease. *J Health Econ* 1995;14:171-189.

(46) Cazzola M, MacNee W, Martinez FJ et al. Outcomes for COPD pharmacological trials: from lung function to biomarkers. *Eur Respir J* 2008;31:416-469.

(47) Al MJ. Cost-effectiveness acceptability curves revisited. *Pharmacoeconomics* 2013;31:93-100.

(48) Fenwick E, O'Brien BJ, Briggs A. Cost-effectiveness acceptability curves--facts, fallacies and frequently asked questions. *Health Econ* 2004;13:405-415.

(49) Fenwick E, Claxton K, Sculpher M. Representing uncertainty: the role of cost-effectiveness acceptability curves. *Health Econ* 2001;10:779-787.

(50) Stinnett AA, Mullahy J. Net health benefits: a new framework for the analysis of uncertainty in cost-effectiveness analysis. *Med Decis Making* 1998;18:S68-S80.

(51) Boxall AM, Barclay L, Sayers A, Caplan GA. Managing chronic obstructive pulmonary disease in the community. A randomized controlled trial of home-based pulmonary rehabilitation for elderly housebound patients. *Journal of Cardiopulmonary Rehabilitation* 2005;25:378-385.

(52) Fernandez AM, Pascual J, Ferrando C, Arnal A, Vergara I, Sevila V. Home-based pulmonary rehabilitation in very severe COPD: is it safe and useful? *Journal of Cardiopulmonary Rehabilitation & Prevention* 2009;29:325-331.

(53) Gottlieb V, Lyngso AM, Nybo B, Frolich A, Backer V. Pulmonary rehabilitation for moderate COPD (GOLD 2)--does it have an effect? *COPD* 2011;8:380-386.

(54) Rea H, McAuley S, Stewart A, Lamont C, Roseman P, Didsbury P. A chronic disease management programme can reduce days in hospital for patients with chronic obstructive pulmonary disease. *Internal Medicine Journal* 2004;34:608-614.

(55) van Wetering CR, Hoogendoorn M, Mol SJ, Rutten-van Molken MP, Schols AM. Short- and long-term efficacy of a community-based COPD management programme in less advanced COPD: a randomised controlled trial. *Thorax* 2010;65:7-13.

(56) Trappenburg JC, Koevoets L, de Weert-van Oene GH et al. Action Plan to enhance self-management and early detection of exacerbations in COPD patients; a multicenter RCT. *BMC Pulmonary Medicine* 2009;9:52.

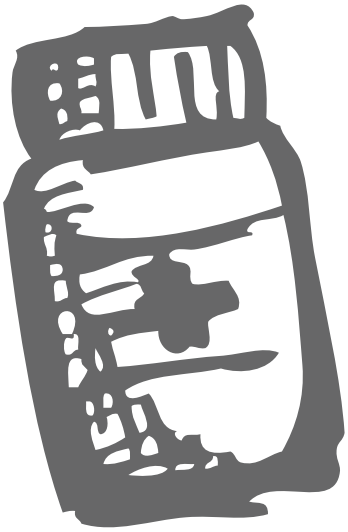
(57) Herland K, Akselsen JP, Skjonsberg OH, Bjermer L. How representative are clinical study patients with asthma or COPD for a larger "real life" population of patients with obstructive lung disease? *Respir Med* 2005;99:11-19.

CHAPTER 9

Effectiveness of integrated disease management for primary care COPD patients: results of a cluster randomised trial.

Annemarije L. Kruis, Melinde R.S. Boland, Willem J.J. Assendelft, Jacobijn Gussekloo, Apostolos Tsiachristas, Theo Stijnen, Coert Blom, Jacob K. Sont, Maureen P.H.M. Rutten-van Molken, Niels H. Chavannes

BMJ 2014;349:g5392



ABSTRACT

Objective To investigate the long term effectiveness of integrated disease management delivered in primary care on quality of life in patients with chronic obstructive pulmonary disease (COPD) compared with usual care.

Design 24 month, multicentre, pragmatic cluster randomised controlled trial.

Setting 40 general practices in the western part of the Netherlands.

Participants Patients with COPD according to GOLD (Global Initiative for COPD) criteria. Exclusion criteria were terminal illness, cognitive impairment, alcohol or drug misuse, and inability to fill in Dutch questionnaires. Practices were included if they were willing to create a multidisciplinary COPD team.

Intervention General practitioners, practice nurses, and specialised physiotherapists in the intervention group received a two day training course on incorporating integrated disease management in practice, including early recognition of exacerbations and self management, smoking cessation, physiotherapeutic reactivation, optimal diagnosis, and drug adherence. Additionally, the course served as a network platform and collaborating healthcare providers designed an individual practice plan to integrate integrated disease management into daily practice. The control group continued usual care (based on international guidelines).

Main outcome measures The primary outcome was difference in health status at 12 months, measured by the Clinical COPD Questionnaire (CCQ); quality of life, Medical Research Council dyspnoea, exacerbation related outcomes, self management, physical activity, and level of integrated care (PACIC) were also assessed as secondary outcomes.

Results Of a total of 1086 patients from 40 clusters, 20 practices (554 patients) were randomly assigned to the intervention group and 20 clusters (532 patients) to the usual care group. No difference was seen between groups in the CCQ at 12 months (mean difference –0.01, 95% confidence interval –0.10 to 0.08; P=0.8). After 12 months, no differences were seen in secondary outcomes between groups, except for the PACIC domain "follow-up/coordination" (indicating improved integration of care) and proportion of physically active patients. Exacerbation rates as well as number of days in hospital did not differ between groups. After 24 months, no differences were seen in outcomes, except for the PACIC follow-up/coordination domain.

Conclusion In this pragmatic study, an integrated disease management approach delivered in primary care showed no additional benefit compared with usual care, except improved level of integrated care and a self reported higher degree of daily activities. The contradictory findings to earlier positive studies could be explained by differences between interventions (provider versus patient targeted), selective reporting of positive trials, or little room for improvement in the already well developed Dutch healthcare system.

Trial registration Netherlands Trial Register NTR2268.

BACKGROUND

Chronic obstructive pulmonary disease (COPD) is a disabling respiratory disease affecting millions of people worldwide.[1] Although no medical treatment can modify the course of the disease, multiple interventions are available to improve the wellbeing of patients and to reduce unnecessary hospital admissions due to exacerbations. However, these interventions are underused or suboptimally implemented.[2] Irregular exacerbations, fluctuating symptoms, and various disabilities require a collaborative interaction between actively involved patients and a proactive multidisciplinary team.[3] Such interaction is promoted by integrated disease management programmes developed in response to the evidently unsuccessful reactive response to disease progression.[2]
Recently, we published a Cochrane systematic review showing clinically relevant effects on disease specific health related quality of life and exercise capacity of COPD patients following an integrated disease management programme for at least three months.[4] The review also showed that integrated disease management reduced respiratory related hospital admissions and days in hospital. This led to potential savings in healthcare costs, as shown in a second review.[5] Interestingly, the effects and cost savings increased with severity of COPD. As COPD is a disease with increasing prevalence, and general practitioners and family physicians treat most patients, well designed studies of pragmatic integrated disease management programmes in primary care are essential. However, in COPD trials, the participants commonly comprise a small and selected fraction of the real world population, resulting in leading medical journals calling for studies in more representative patient populations.[6;7] The few studies of integrated disease management in primary care recruited patients in secondary care,[8-11] consisted of palliative programmes for severe patients,[12;13] had a short duration of intervention,[9-12;14] or did not correct for cluster analysis.[15] The true effect of integrated disease management in primary care thus remains inconclusive. Therefore, the aim of this large pragmatic RECODE (randomized clinical trial on effectiveness of integrated COPD management in primary care) cluster randomised trial was to assess whether integrated disease management implemented in primary care is effective in improving the quality of life of COPD patients.

METHODS

This study was performed in accordance with the study protocol.[16]

Study design and patients

We did a 24 month, cluster randomised controlled trial in which general practitioners were randomly assigned to the intervention (integrated disease management) or usual

care. General practitioners were recruited from the western part of the Netherlands. Patients in both groups received an information leaflet stating that the aim of the study was to improve treatment of COPD in primary care and that general practitioners were randomised to two groups. All general practitioners and all participants gave written informed consent. Eligible participants had a diagnosis of COPD, according to GOLD (Global Initiative for COPD) guidelines.[1] For all included patients, we attempted to verify the diagnosis by lung function tests. If spirometry data were not of sufficient quality or not available, patients were invited to participate for a lung function assessment, according to the American Thoracic Society/European Respiratory Society guidelines for spirometry.[17] Exclusion criteria were terminal illness, cognitive impairment, hard drug or alcohol misuse, and inability to fill in questionnaires. Recruitment of practices started in September 2010 and was finished in September 2011.

Intervention

The intervention was delivered at the cluster level. General practitioners, practice nurses, and specialised physiotherapists in the intervention group received a two day training course on incorporating integrated disease management in practice. Optionally, an additional team member (such as a dietitian or pulmonary specialist) could attend the course if they expressed interest. Elements of the course included performing/interpreting spirometry, assessment of disease burden, review of advice from international guidelines, motivational interviewing to stimulate a healthier lifestyle, and smoking cessation. Furthermore, the healthcare providers were trained in adopting self management action plans, including early recognition and treatment of exacerbations, encouragement of regular exercise and guideline based physical reactivation, cooperation with secondary care, and instructions in nutritional support. The secondary aim of the course was to provide a network platform for team members.

At the end of the second day, each practice team designed a specific time contingent plan in a group discussion with their multidisciplinary members. They decided which elements of integrated care they wanted to start implementing first, who would be responsible for which part of the interventions, and which steps to take to integrate integrated disease management into their daily practice. The practice plan they agreed to depended not only on the chairperson and the capacity of the team but also on the COPD care already provided at baseline and the priorities and feasibility in their practice. They received advice on the content and feasibility of their plan from the experts who guided the training. After six and 12 months, the intervention practices had a refresher course.

During the course, the team learnt the details of a web based decision support system for audit and feedback with patients' and professionals' portals, named Zorgdraad ("care ties"). The teams received practice tailored benchmark reports at baseline and at six and

12 months. All practices were free to determine and follow their individual plans and could choose to implement the Zorgdraad programme. The intensity of the integrated disease management programme for individual patients depended on health status, personal needs, and preferences, as well as on the capacity of the general practice team. As a result, patients with severe disease or at high risk were encouraged to receive multiple interventions, whereas other (for example, stable) patients had only regular control visits. All patient care was covered by the basic health insurance package that is compulsory in the Netherlands, except physiotherapy, which was additionally reimbursed for all RECODE patients with a Medical Research Council dyspnoea score above 2. Healthcare providers in the control group were asked to continue their usual care, based on Dutch general practice COPD guidelines, in line with GOLD guidelines.[1] The practice nurses in the usual care group received a course on technical performance of spirometry only, to divert attention from topics related to our intervention.

Randomisation and masking

To enhance comparability, a blinded researcher (NHC) stratified and matched participating clusters according to the following criteria: percentage of patients in practice from ethnic minorities, type of practice (single handed, one or more partner practice, or healthcare centre), practice location (urban/rural), age of general practitioner, and sex of general practitioner. Following this procedure, the same blinded researcher randomised matched clusters in pairs by using a computer generated list in four blocks of 10. Because of the nature of the intervention, participating healthcare providers and patients could not be blinded. Therefore, blinded research nurses assessed outcomes to minimise detection bias. Patients were instructed not to report on their type of management to these research nurses.

Outcomes

All outcomes were assessed at the level of the individual participant and are reported in Supplementary table 1. The primary outcome was change in health related quality of life on the Clinical COPD Questionnaire (CCQ)[18] at 12 months. Secondary outcomes were change in health related quality of life as measured by the St George's Respiratory Questionnaire (SGRQ)[19], Euro Qol-5D (EQ-5D)[20], and Short Form 36 (SF-36)[21]. In addition, we measured MRC dyspnoea[22], Self-Management Ability Scale-30 (SMAS-30)[23], daily physical activities (International Physical Activity Questionnaire; IPAQ[24]), level of care integration according to patients, measured by the Patient Assessment Chronic Illness Care (PACIC)[25], smoking behaviour, and healthcare usage (including hospital admissions and moderate/severe exacerbations). Blinded research nurses administered these questionnaires at baseline and at six and 12 months. Postal questionnaires were sent at nine, 18, and 24 months. We extracted data on moderate exacerbations over

Table 1 Baseline characteristics of chronic obstructive pulmonary disease patients included in RECODE study. Values are numbers (percentages) unless stated otherwise

	Intervention (n=554; 20 clusters)		Usual care (n=532; 20 clusters)	
Characteristic		**Observations**		**Observations**
Mean (SD) age (years)	68.2 (11.3)	554	68.4 (11.1)	532
Male sex	280 (50.5)	554	305 (57.3)*	532
Employment	140 (27.7)	505	142 (28.8)	493
Low education	195 (39.2)	498	195 (41.5)	491
Mean (SD) FEV1 % predicted	67.7 (20.3)	522	67.9 (20.5)	498
GOLD stage:				
I—mild	116 (25.3)	458	97 (23.7)	409
II—moderate	241 (52.6)	458	220 (53.8)	409
III—severe	87 (19.0)	458	81 (19.8)	409
IV—very severe	14 (3.1)	458	11 (2.7)	409
Current smoker	179 (34.8)	515	196 (38.7)	506
Relevant comorbidities:				
Major cardiovascular disease	81 (14.6)	522	94 (17.7)	515
Hypertension	196 (35.4)	522	204 (38.3)	515
Diabetes	81 (14.6)	522	79 (14.8)	515
Depression	54 (9.8)	522	54 (10.1)	515
Mean (SD) CCQ score:				
Total	1.5 (1.0)	553	1.5 (1.0)	527
Symptoms	2.1 (1.2)	554	2.1 (1.2)	531
Functional	1.5 (1.2)	553	1.3 (1.2)*	531
Mental	0.5 (1.0)	554	0.5 (1.0)	527
Mean (SD) SGRQ score:				
Total	36.7 (21.1)	551	34.5 (19.8)	529
Symptoms	51.6 (20.8)	554	49.3 (20.9)	530
Activities	49.4 (29.9)	551	46 (29)	531
Impact	24 (20.2)	554	22.7 (19)	530
Mean (SD) MRC total score	2.0 (1.3)	553	2.0 (1.3)	529
MRC score >2	194 (35.1)	553	167 (31.6)	529
Mean (SD) EQ-5D score	0.74 (0.25)	546	0.73 (0.28)	528
Mean (SD) EQ-5D VAS score	66.6 (17.6)	554	67.3 (17.3)	532
Mean (SD) SF-36 score, physical component	38 (10.9)	512	38.6 (10.7)	503
Mean (SD) SF-36 score, mental component	48.3 (10.5)	512	48.9 (10.3)	503

Mean (SD) SMAS score				
Taking initiatives	56.8 (17.8)	518	56.9 (17.4)	509
Investment behaviour	61.4 (16.8)	517	59.3 (17.9)	511
Self-efficacy	65.7 (17.2)	516	64.3 (17.6)	512
Mean (SD) IPAQ, total MET minutes	2925 (4574)	546	2925 (4798)	526
IPAQ, high/moderate	54 (10.0)	541	70 (13.4)	523
IPAQ, low	487 (90.0)	541	453 (86.6)	523
Mean (SD) PACIC score:				
Total	2.3 (0.9)	436	2.2 (0.8)	437
Activation	2.3 (1.3)	435	2.1 (1.2)	435
Delivery system design	2.9 (1.2)	432	2.8 (1.1)	436
Goal setting	2.1 (1.0)	431	2.0 (0.8)	433
Problem solving	2.2 (1.2)	430	2.1 (1.0)	433
Follow-up/coordination	1.8 (0.9)	433	1.8 (0.8)	431
Mean (SD) exacerbations:				
Moderate exacerbation rate (12 months)	0.4 (0.8)	554	0.3 (0.8)	532
Severe exacerbation rate (3 months)	0.02 (0.2)	554	0.02 (0.2)	532
Hospital admission days (3 months)	6 (2.1)	554	8.6 (4.7)	532

CCQ=Clinical COPD Questionnaire; GOLD=Global Initiative for Chronic Obstructive Pulmonary Disease; EQ-5D=Euro Qol-5D; FEV_1=forced expiratory volume in 1 second; IPAQ=International Physical Activity Questionnaire; MRC=Medical Research Council; MET=Metabolic Equivalent of Task; PACIC=Patient Assessment Chronic Illness Care; SF-36=Short Form 36; SGRQ=St George's Respiratory Questionnaire; SMAS=Self-Management Ability Scale.
*Statistically significant difference between intervention and usual care groups.

the complete trial period from electronic medical records at 24 months. We defined a moderate exacerbation as a worsening of daily symptoms that led a patient's physician to prescribe systemic corticosteroids, antibiotics, or both, without hospital admission. A severe exacerbation occurred when worsening symptoms required a hospital admission.

Statistical analysis

We based sample size estimates on the mean difference in CCQ score between intervention and control groups at 12 months. We used methods for standard sample size estimates for trials that randomise at the level of the individual,[26] adjusting for clustering by inflating sample size estimates by the design effect given by $1+(n-1)\rho$, where n is the average cluster size and ρ is the estimated intra-class correlation coefficient.[27] Using the minimal clinically important mean difference of 0.4 for the CCQ,[28] with a standard deviation of CCQ equal to 0.49 at 12 months, and the upper value of 0.05 from a range of intra-class correlation coefficient values identified in primary care studies,[29] power

calculations indicated that we needed 40 clusters of practices with an average of 27 participants per cluster. To allow for subgroup analysis of MRC scores 1-2 versus 3-5, a total of 1080 participants were needed to achieve a power of at least 80% with α levels of 0.05, including a loss to follow-up of 10% of participants or a loss of four clusters at 12 months.

The primary effectiveness analysis was an intention to treat analysis of the difference in mean CCQ score between groups at 12 months. Because of repeated measurements for all patients, we used linear mixed model analyses to assess differences within and between groups for all continuous outcomes, correcting for baseline scores, age, sex, proportion of patients with MRC score above 2, and clustering of patients per general practice. We used baseline scores as a dependent variable, the cluster was represented by a random effect, and the within patient covariance structure was unstructured. For dichotomous outcomes, we used logistic link generalised linear mixed models for repeated measurements to analyse differences within and between groups at all time points, correcting for the same covariates. We compared differences in two year moderate and severe exacerbation counts by using the negative binomial model[30], correcting for age, sex, MRC score above 2, exacerbation rate in the year before baseline, and clustering of patients per practice. This model returns incidence rate ratios, which in this case are exacerbation rates. On the basis of the literature, we did a priori defined subgroup analyses on the primary outcome of CCQ at 12 months[16].

RESULTS

Patients

Figure 1 shows the screening, randomisation, and follow-up of patients[31]. Supplementary figure 1 shows the drop-out at the several time points. Table 1 summarises the baseline characteristics of the patients. Supplementary table 2 demonstrates the characteristics of the general practices. Dropout rates at 12 months (9% intervention *v* 11% usual care) and 24 months (24% *v* 26%) were similar in the two groups. Patients who dropped out at 24 months were significantly older (P=0.002) and had worse scores on the CCQ, EQ-5D, PACIC, SF-36, SGRQ, and MRC questionnaires at baseline. Thirty two patients died in the intervention group and 28 in the usual care group. Causes of death were comparable between groups (P=0.54): COPD related (28% intervention; 36% usual care), cardiovascular disease (16%; 14%), and malignancies (16%; 21%). In 40% of the intervention patients and in 29% of the usual care patients, the cause of death was unknown.

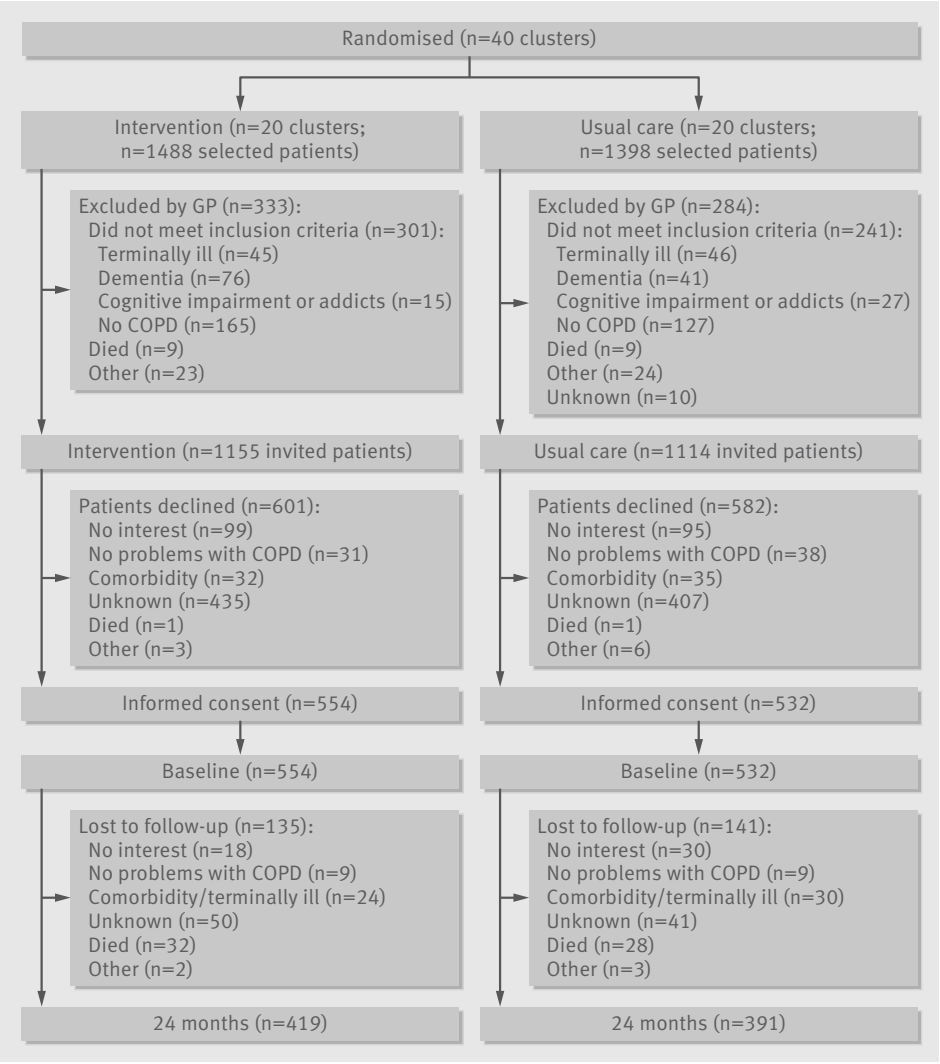


Figure 1. Flow diagram of RECODE study

Primary outcome

We found no statistically significant difference between the intervention and usual care groups in the CCQ score at 12 months (mean difference –0.01, 95% confidence interval –0.10 to 0.08; P=0.8) (Table 2; Figure 2)

Secondary outcomes and subgroup analyses

At 6, 9, 18, and 24 months, we found no statistically significant difference between intervention and usual care in the CCQ score (Figure 2). At 12 months, the change from baseline in SGRQ, EQ-5D, SF-36, MRC, and SMAS scores was not significantly different

Table 2 Clinical outcomes: within and between group differences at 12 months, corrected for age, sex, baseline score, and MRC score >2. Values are mean (95% CI) unless stated otherwise

Outcome	Intervention (n=554; 20 clusters)	Usual care (n=532; 20 clusters)	Mean difference (95% CI)	P value
CCQ total score	–0.03 (–0.09 to 0.03)	0.03 (–0.03 to 0.09)	–0.01 (–0.10 to 0.08)	0.80
CCQ—symptoms domain	–0.07 (–0.15 to 0.02)	–0.10 (–0.19 to 0.01)	0.03 (–0.09 to 0.15)	0.59
CCQ—functional domain	0.16 (0.08 to 0.25)	0.21 (0.12 to 0.29)	–0.04 (–0.16 to 0.07)	0.48
CCQ—mental domain	–0.09 (–0.16 to –0.02)	–0.06 (–0.14 to 0.01)	–0.03 (–0.13 to 0.07)	0.57
SGRQ total score	–0.40 (–1.46 to 0.65)	0.33 (–0.78 to 1.43)	–0.73 (–2.25 to 0.78)	0.34
SGRQ—symptoms domain	–0.75 (–2.43 to 0.93)	0.22 (–1.52 to 1.96)	–0.97 (–3.33 to 1.39)	0.42
SGRQ—activities domain	0 (–1.51 to 1.50)	1.25 (–0.32 to 2.82)	–1.25 (–3.41 to 0.90)	0.26
SGRQ—impact domain	–0.31 (–1.46 to 0.85)	–0.35 (1.96 to 5.33)	0.04 (–1.61 to 1.70)	0.96
MRC dyspnoea score	0.23 (0.14 to 0.33)	0.19 (0.09 to 0.29)	0.04 (–0.09 to 0.18)	0.52
EQ-5D	–0.04 (–0.06 to –0.02)	–0.01 (–0.03 to 0.01)	–0.03 (–0.06 to 0)	0.07
EQ-5D VAS score	–1.71 (–2.95 to 0.46)	–1.92 (–3.21 to –0.63)	0.21 (–1.44 to 1.87)	0.80
SF-36—physical domain	–1.1 (–1.82 to –0.38)	–0.48 (–1.23 to 0.26)	–0.61 (–1.61 to 0.39)	0.23
SF-36—mental domain	0.73 (–0.07 to 1.54)	0.09 (–0.74 to 0.92)	0.64 (–0.45 to 1.73)	0.25
SMAS—taking initiatives	–1.27 (–2.5 to 0)	–1 (–2.3 to 0.33)	–0.28 (–2.00 to 1.43)	0.75
SMAS—investment behaviour	–1.5 (–2.75 to –0.25)	–1.43 (–2.73 to –0.12)	–0.07 (–1.78 to 1.63)	0.93
SMAS—self-efficacy	–1.17 (–2.39 to 0.05)	–0.38 (–1.65 to 0.89)	–0.79 (–2.47 to 0.88)	0.35
IPAQ—total MET minutes	–44 (–475 to 387)	–438 (–886 to 11)	393 (–179 to 965)	0.18
IPAQ—high/moderate (%)	32.2	22.1	10.1	<0.001
PACIC—total score	–0.02 (–0.11 to 0.08)	–0.08 (–0.18 to 0.02)	0.06 (–0.06 to 0.19)	0.31
PACIC—activation	–0.03 (–0.16 to 0.1)	–0.5 (–0.19 to 0.08)	0.03 (–0.14 to 0.19)	0.76
PACIC—delivery system design	–0.20 (–0.32 to –0.8)	–0.27 (–0.40 to –1.30)	0.07 (–0.10 to 0.23)	0.43
PACIC—goal setting	0.04 (–0.06 to 0.13)	–0.08 (–0.18 to 0.03)	0.11 (–0.10 to 0.25)	0.10
PACIC—problem solving	0.02 (–0.09 to 0.14)	–0.02 (–0.14 to 0.1)	0.04 (–0.10 to 0.19)	0.58
PACIC—follow-up/coordination	0.13 (0.04 to 0.21)	–0.02 (–0.11 to 0.07)	0.15 (0.04 to 0.26)	0.01
Current smokers (%)	48.6	51.7	3.1	0.56
Hospital admission days	10.5 (7.6 to 13.3)	10.7 (7.4 to 14.0)	0.2 (–4.3 to 4.3)	0.92
Moderate exacerbations (rate)	0.58 (0.45 to 0.75)	0.48 (0.37 to 0.62)	1.22 (0.97 to 1.54)*	0.09
Severe exacerbations (rate)	0.13 (0.08 to 0.21)	0.10 (0.06 to 0.18)	1.20 (0.78 to 1.84)*	0.42

CCQ=Clinical COPD Questionnaire; EQ-5D=Euro Qol-5D; IPAQ=International Physical Activity Questionnaire; MET= Metabolic Equivalent of Task; MRC=Medical Research Council; PACIC=Patient Assessment Chronic Illness Care; SF-36=Short Form 36; SGRQ=St George's Respiratory Questionnaire; SMAS=Self-Management Ability Scale.
Values are corrected for clustering, age, sex, score at baseline, and MRC score >2.
*Means rate ratio.

between the intervention and usual care groups (Table 2). The proportion of patients with moderate or high activity levels at 12 months as measured with the IPAQ improved significantly in the intervention group compared with the usual care group (mean difference 10.1; P<0.001). The PACIC domain "follow-up and coordination," measuring

improvement in follow-up structure of COPD patients, was significantly higher in the intervention group at 12 months (mean difference 0.15; P=0.01). The proportion of current smokers, as well as moderate and severe exacerbation rates and hospital admission rates, did not differ (Table 2).

After 24 months of follow-up, the PACIC follow-up and coordination domain remained significantly higher in the intervention group (data not shown; mean difference 0.15; P=0.03). The other secondary outcomes did not differ significantly between groups at 24 months. Subgroup analyses showed no statistically significant effect of the intervention in any of the a priori defined subgroups (Table 3). We performed additional, a posteriori defined subgroup analyses, which demonstrated no significant effect of the intervention. (Supplementary table 3)

DISCUSSION

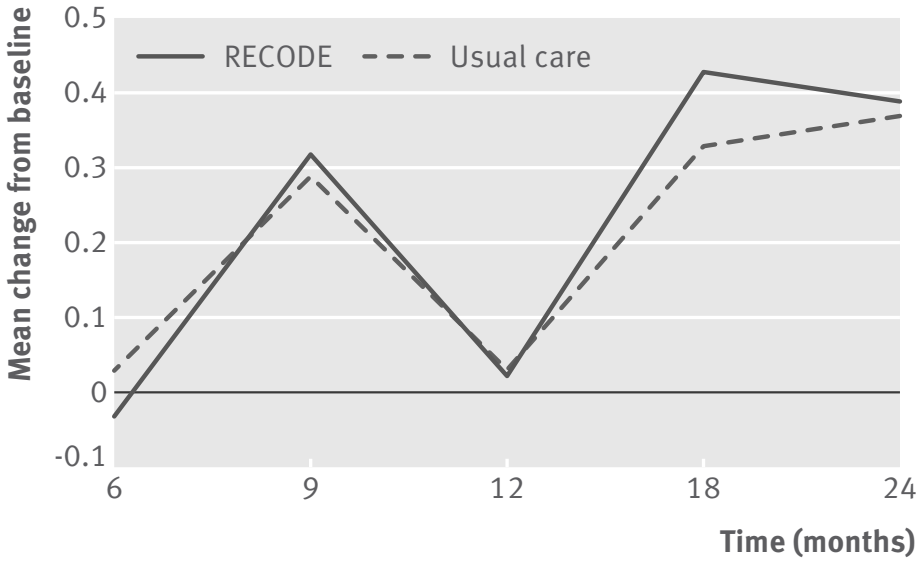


Figure 2. Change in Clinical COPD Questionnaire (CCQ) score at 6, 9, 12, 18, and 24 months, corrected for age, sex, baseline, CCQ score, and MRC score above 2.
Error bars represent standard errors. Score lower than 0 means improvement compared with baseline

This cluster randomised trial examined a pragmatic set of interventions aiming to establish an integrated disease management programme, delivered by a multidisciplinary team to primary care patients with COPD. We found no differences between groups

Table 3 Subgroup analyses: difference between intervention and usual care groups in change from baseline to 12 months' follow-up in CCQ score for pre-specified subgroups. Values are mean (SE) unless stated otherwise

Group	Intervention (20 clusters)		Usual care (20 clusters)		Intervention–usual care	P value	Subgroup by treatment interaction P value
	No	Mean (SE)	No	Mean (SE)			
Full cohort	554	0.02 (0.03)	532	0.03 (0.03)	–0.01 (0.04)	0.82	
Sex:							0.3
Male	280	0 (0.06)	305	0 (0.06)	0 (0.05)	0.99	
Female	274	0.01 (0.04)	227	0.03 (0.03)	–0.02 (0.05)	0.66	
Age:							0.15
<65 years	212	0.17 (0.09)	199	0.15 (0.09)	0.02 (0.05)	0.71	
³65 years	342	0 (0.04)	333	0.03 (0.03)	–0.03 (0.05)	0.54	
GOLD stage:							0.47
I-II	357	–0.29 (0.07)	317	–0.33 (0.07)	0.04 (0.05)	0.46	
III-IV	101	0.03 (0.06)	92	0.03 (0.04)	0 (0.07)	0.96	
MRC score:							0.2
£2	359	0.03 (0.04)	362	0.03 (0.03)	0 (0.05)	0.97	
>2	194	1.10 (0.07)	167	1.13 (0.06)	–0.03 (0.06)	0.63	

Lower CCQ score means better quality of life. Values are corrected for clustering, age, sex, score at baseline, and MRC score >2.

in quality of life, exacerbation related outcomes, self management, or MRC dyspnoea scores. However, significantly more patients in the intervention group had a self reported higher degree of daily activities, and the level of follow-up and coordination of the COPD patients improved.

Interpretation of findings

The results from our study were contrary to our expectations and to the positive results of the Cochrane systematic review.[4] Several reasons might explain the difference in findings.

Firstly, our intervention was implemented at the level of the healthcare provider, whereas earlier studies were of patient targeted interventions. We specifically chose to study a pragmatic intervention that was developed on the basis of positive results of a controlled primary care study and implementation project.[32;33] In these times of heavy workload in primary care, we gave the integrated disease management teams responsibility to develop their individual practice plans tailored to their own needs, to ensure ongoing implementation after the study was finished. This is clearly in contrast to other integrated disease management studies that applied patient targeted interventions and operated under more intensively supported, time consuming, and strictly regulated conditions.[4] Therefore, a suboptimal intensity, but more realistic, implementation of the

intervention may have contributed to the difference in effect between this study and earlier studies.

Secondly, in the intervening years, COPD care in the Netherlands has substantially evolved, which was partially unforeseen. Probably one of the most important triggers for general practitioners to start implementing integrated disease management was the start of a bundled payment system in 2010, which was our first study year. Although nationwide implementation of integrated disease management of COPD is still lacking, several regional projects have been started during recent years.[34;35] Nowadays, COPD care has a better prepared delivery system with structured collaboration between healthcare professionals, more and better equipped nurses, and the development of clinical information systems to support the professional and the patient.[36] Therefore, the considerable drive by health policies and providers to improve COPD care could have stimulated general practitioners in the usual care group to start implementing integrated disease management as well. The absence of effect due to already high levels of care was pointed out in other well designed Dutch and English primary care trials, studying components of COPD care.[36-38] In contrast, a community based integrated intervention for early prevention and management of COPD in a Chinese setting, with a potentially larger room for improvement, showed a significant effect on smoking cessation rates and improvements in knowledge.[39]

Thirdly, studies with positive results are more likely to be published, and in high impact journals. In contrast to trial settings, healthcare providers trying to implement COPD programmes in daily life often experience problems with poor adherence or non-response, owing to lack of time, motivation, or cooperation of patients. This mismatch was illustrated by Bjoernshave et al, who showed that the populations included in the Cochrane systematic review of pulmonary rehabilitation were highly motivated and not representative of the target population, as 75% of the initially suitable patients were omitted owing to exclusion or drop out.[40] Additionally, positive trial results have a higher chance of being referred to in guidelines. For example, the recent American Thoracic Society/European Respiratory Society statement[41] recommends offering pulmonary rehabilitation to patients with milder COPD on the basis of results of two positive trials,[8;42] whereas negative trials were not taken into consideration when these recommendations were formulated.[14;43]

Strengths and weaknesses of study

To best of our knowledge, this is the largest trial to date assessing the effectiveness of integrated disease management in primary care. Important features of this study are the long term follow-up and the inclusion of a sizeable real world, heterogeneous study population,[6;7] which provided sufficient power to study differences in effect in subgroup analyses. Additionally, this pragmatic study included a wide range of outcomes relevant

to primary care, including objective outcomes (moderate and severe exacerbation rates) and subjective measures (quality of life).[7] We applied sophisticated regression techniques to facilitate the analysis of clustered longitudinal data.

After 24 months, dropout rates were low but selectively higher in patients with worse baseline scores. This raises questions of generalisability, although after correction for baseline scores no evidence existed for health benefits of the intervention at all, indicating that dropout is unlikely to have biased the result.

Blinding of participants and clinicians for this type of intervention was impossible. In an attempt to minimise bias, blinded research nurses collected the data and patients were instructed not to talk about their type of intervention. Although pairing and randomisation of the practices was done by a member of the research team, he was provided only with the characteristics of the practices (age and sex of general practitioner, type of practice). He was blinded to the identity of the practices and had no contact with the general practitioners.

The included practices were diverse in terms of setting, practice size, distribution of ethnic minorities, and level of COPD care at baseline.[16] We corrected for most practice related factors by matching and stratification. However, a pre-existing high level of COPD care at baseline may have limited the potential for further improvement in already well developed practices. Additionally, because of the complex character of the intervention and the pragmatic study design, we were unable to assess the effect of individual components of the intervention.

Implications for practice

We found that an integrated disease management programme implemented in primary care did not improve quality of life and exacerbation related outcomes in a representative group of Dutch primary care patients with COPD. We observed an improved level of follow-up and structure of COPD care, as measured with the Patient Assessment Chronic Illness Care in the intervention group over the two year period, indicating important changes at an organisational level. However, this did not translate into differences in health outcomes. When interpreting the unforeseen findings of our study, policy makers and healthcare professionals should take into account the fact that primary care for COPD in the Netherlands is already at a high standard and has further evolved during the years of our intervention. Effect sizes might be greater in countries where primary care is less well developed.

On the basis of our experiences, an intervention directed at healthcare providers cannot be recommended for the generality of COPD patients. We advise application of more intensive, but still pragmatic programmes aiming at a selection of patients with a higher burden of disease and thus larger room for improvement. Exercise can be recognised as a compulsory element of integrated disease management.[4] However, healthcare provid-

ers and insurers should realise that patients with mild disease often lack the motivation or do not feel the need (yet) to commit to an intensive (and expensive) integrated care or exercise programme.[14] Therefore, resources are probably better spent if patients with a higher burden of disease are firstly thoroughly assessed and stratified for risk, after which a personalised treatment plan is made using a shared decision making process between patient and physician. The individual patient's needs, preferences, and personal goals should play a key role in this process. Finally, we should take into account the fact that COPD is only one of the several chronic conditions we manage in primary care. Therefore, a more fruitful approach might be to consider integrated care for a suite of long term conditions with a high burden of disease, of which COPD is one component. The absolute number of patients eligible for this selective approach is probably relatively low, which makes having proper case management interventions in place possible.

Conclusion

In this study, integrated disease management incorporated in primary care was not effective in improving quality of life. The contradictory findings to earlier positive studies could be explained by differences between interventions (provider- versus patient targeted), selective reporting of positive trials, or little room for improvement in the well developed Dutch healthcare system.

WHAT THIS PAPER ADDS

What is already known on this subject

In a Cochrane systematic review, integrated disease management programmes for chronic obstructive pulmonary disease (COPD) showed clinically relevant effects on quality of life and exercise tolerance and reductions in admissions and hospital days
However, most studies were in patients with severe COPD, and the studies in primary care recruited patients in secondary care, consisted of palliative programmes for severe patients, had a short duration of intervention, or did not correct for cluster analysis

What this study adds

Integrated disease management incorporated in primary care was not effective in improving quality of life or exacerbation related outcomes, such as hospital admissions and hospital days
The contradictory findings to earlier positive studies could be explained by differences between interventions (provider versus patient targeted), selective reporting of positive trials, or little room for improvement in the well developed Dutch healthcare system

A healthcare provider directed intervention cannot be recommended for the general population of COPD patients

REFERENCES

(1) Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease 2014. (Accessed April 2, 2014, at http://www.goldcopd.org).

(2) Morgan MD. Action plans for COPD self-management. Integrated care is more than the sum of its parts. *Thorax* 2011;66(11):935-6.

(3) Kruis AL, Chavannes NH. Potential benefits of integrated COPD management in primary care. *Monaldi Arch Chest Dis* 2010;73(3):130-4.

(4) Kruis AL, Smidt N, Assendelft WJ, Gussekloo J, Boland MR, Rutten-van MM, et al. Integrated disease management interventions for patients with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2013;10:CD009437.

(5) Boland MR, Tsiachristas A, Kruis AL, Chavannes NH, Rutten-van Molken MP. The health economic impact of disease management programs for COPD: a systematic literature review and meta-analysis. *BMC Pulm Med* 2013;13:40.

(6) Dahlen SE, Dahlen B, Drazen JM. Asthma treatment guidelines meet the real world. *N Engl J Med* 2011;364(18):1769-70.

(7) Ware JH, Hamel MB. Pragmatic trials--guides to better patient care? *N Engl J Med* 2011 5;364(18):1685-7.

(8) van Wetering CR, Hoogendoorn M, Mol SJ, Rutten-van Molken MP, Schols AM. Short- and long-term efficacy of a community-based COPD management programme in less advanced COPD: a randomised controlled trial. *Thorax* 2010;65(1):7-13.

(9) Cambach W, Chadwick-Straver RV, Wagenaar RC, van Keimpema AR, Kemper HC. The effects of a community-based pulmonary rehabilitation programme on exercise tolerance and quality of life: a randomized controlled trial. *Eur Respir J* 1997;10(1):104-13.

(10) Wijkstra PJ, Ten Vergert EM, van Altena R., Otten V, Kraan J, Postma DS, et al. Long term benefits of rehabilitation at home on quality of life and exercise tolerance in patients with chronic obstructive pulmonary disease. *Thorax* 1995;50(8):824-8.

(11) Mendes de Oliveira JC, Studart Leitao Filho FS, Malosa Sampaio LM, Negrinho de Oliveira AC, Hirata RP, Costa D, et al. Outpatient vs. home-based pulmonary rehabilitation in COPD: a randomized controlled trial. *Multidiscip Respir Med* 2010;5(6):401-8.

(12) Boxall AM, Barclay L, Sayers A, Caplan GA. Managing chronic obstructive pulmonary disease in the community. A randomized controlled trial of home-based pulmonary rehabilitation for elderly housebound patients. *J Cardiopulm Rehabil* 2005;25(6):378-85.

(13) Fernandez AM, Pascual J, Ferrando C, Arnal A, Vergara I, Sevila V. Home-based pulmonary rehabilitation in very severe COPD: is it safe and useful? *J Cardiopulm Rehabil Prev* 2009;29(5):325-31.

(14) Gottlieb V, Lyngso AM, Nybo B, Frolich A, Backer V. Pulmonary rehabilitation for moderate COPD (GOLD 2)--does it have an effect? *COPD* 2011;8(5):380-6.

(15) Rea H, McAuley S, Lamont C, Roseman P, Didsbury P, Stewart A. A chronic disease management program can reduce days in hospital for patients with COPD. *Respirology* 2002;7:A6.

(16) Kruis AL, Boland MR, Schoonvelde CH, Assendelft WJ, Molken MP, Gussekloo J, et al. RECODE: Design and baseline results of a cluster randomized trial on cost-effectiveness of integrated COPD management in primary care. *BMC Pulm Med* 2013;13(1):17.

(17) van der Molen T, Willemse BW, Schokker S, ten Hacken NH, Postma DS, Juniper EF. Development, validity and responsiveness of the Clinical COPD Questionnaire. *Health Qual Life Outcomes* 2003;1:13.

(18) Jones PW. St. George's Respiratory Questionnaire: MCID. *COPD* 2005;2(1):75-9.
(19) Lamers LM, McDonnell J, Stalmeier PF, Krabbe PF, Busschbach JJ. The Dutch tariff: results and arguments for an effective design for national EQ-5D valuation studies. *Health Econ* 2006;15(10):1121-32.
(20) Aaronson NK, Muller M, Cohen PD, Essink-Bot ML, Fekkes M, Sanderman R, et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. *J Clin Epidemiol* 1998;51(11):1055-68.
(21) Schuurmans H, Steverink N, Frieswijk N, Buunk BP, Slaets JP, Lindenberg S. How to measure self-management abilities in older people by self-report. The development of the SMAS-30. *Qual Life Res* 2005;14(10):2215-28.
(22) Vandelanotte C, De Bourdeaudhuij I., Phillippaerts R, Sjostrom M, Sallis JF. Reliability and validity of a computerized and Dutch version of the International Physical Activity Questionnaire (IPAQ). *J Phys Act* 2005;63-75.
(23) Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. *Thorax* 1999;54(7):581-6.
(24) Glasgow RE, Wagner EH, Schaefer J, Mahoney LD, Reid RJ, Greene SM. Development and validation of the Patient Assessment of Chronic Illness Care (PACIC). *Med Care* 2005;43(5):436-44.
(25) Kocks JW, Tuinenga MG, Uil SM, van den Berg JW, Stahl E, van der Molen T. Health status measurement in COPD: the minimal clinically important difference of the clinical COPD questionnaire. *Respir Res* 2006;7:62.
(26) Smeeth L, Ng ES. Intraclass correlation coefficients for cluster randomized trials in primary care: data from the MRC Trial of the Assessment and Management of Older People in the Community. *Control Clin Trials* 2002;23(4):409-21.
(27) Keene ON, Calverley PM, Jones PW, Vestbo J, Anderson JA. Statistical analysis of exacerbation rates in COPD: TRISTAN and ISOLDE revisited. *Eur Respir J* 2008;32(1):17-24.
(28) Campbell MK, Piaggio G, Elbourne DR, Altman DG. Consort 2010 statement: extension to cluster randomised trials. *BMJ* 2012;345:e5661.
(29) Chavannes NH, Grijsen M, van den Akker M, Schepers H, Nijdam M, Tiep B, et al. Integrated disease management improves one-year quality of life in primary care COPD patients: a controlled clinical trial. *Prim Care Respir J* 2009;18(3):171-6.
(30) Kruis AL, van AJ, Erkelens MR, Scheepers H, In ', V, Muris JW, et al. Sustained effects of integrated COPD management on health status and exercise capacity in primary care patients. *Int J Chron Obstruct Pulmon Dis 2010*;5:407-13.
(31) Gress S, Baan CA, Calnan M, Dedeu T, Groenewegen P, Howson H, et al. Co-ordination and management of chronic conditions in Europe: the role of primary care--position paper of the European Forum for Primary Care. *Qual Prim Care* 2009;17(1):75-86.
(32) Tsiachristas A, Hipple-Walters B, Lemmens KM, Nieboer AP, Rutten-van Molken MP. Towards integrated care for chronic conditions: Dutch policy developments to overcome the (financial) barriers. *Health Policy* 2011;101(2):122-32.
(33) Bischoff EW, Akkermans R, Bourbeau J, van WC, Vercoulen JH, Schermer TR. Comprehensive self management and routine monitoring in chronic obstructive pulmonary disease patients in general practice: randomised controlled trial. *BMJ* 2012;345:e7642.
(34) Trappenburg JC, Monninkhof EM, Bourbeau J, Troosters T, Schrijvers AJ, Verheij TJ, et al. Effect of an action plan with ongoing support by a case manager on exacerbation-related outcome in patients with COPD: a multicentre randomised controlled trial. *Thorax* 2011;66(11):977-84.

(35) Pinnock H, Hanley J, McCloughan L, Todd A, Krishan A, Lewis S, 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.

(36) Bjoernshave B, Korsgaard J, Nielsen CV. Does pulmonary rehabilitation work in clinical practice? A review on selection and dropout in randomized controlled trials on pulmonary rehabilitation. *Clin Epidemiol* 2010;2:73-83.

(37) Spruit MA, Singh SJ, Garvey C, Zuwallack R, Nici L, Rochester C, et al. An official american thoracic society/european respiratory society statement: key concepts and advances in pulmonary rehabilitation. *Am J Respir Crit Care Med* 2013;188(8):e13-e64.

(38) Vogiatzis I, Terzis G, Stratakos G, Cherouveim E, Athanasopoulos D, Spetsioti S, et al. Effect of pulmonary rehabilitation on peripheral muscle fiber remodeling in patients with COPD in GOLD stages II to IV. *Chest* 2011;140(3):744-52.

(39) Roman M, Larraz C, Gomez A, Ripoll J, Mir I, Miranda EZ, et al. Efficacy of pulmonary rehabilitation in patients with moderate chronic obstructive pulmonary disease: a randomized controlled trial. *BMC Fam Pract* 2013;14:21.

Chapter 10

General discussion

GENERAL DISCUSSION

In the last decade, integrated disease management (IDM) programmes for patients with chronic obstructive pulmonary disease (COPD) have been developed and implemented worldwide. In the studies included in this thesis, we evaluated IDM for COPD from different perspectives. More specifically, we aimed to study if IDM is effective in improving health outcomes in patients with COPD.

Main results

In Chapters 1 and 3, we provided a framework for our research question. In Chapters 2 and 6, we evaluated two individual components of IDM: optimal medication and self-management. In Chapter 4, in our Cochrane systematic review, we summarized all the published evidence on IDM. This review showed that, after following a programme of three months, both quality of life and exercise tolerance improved, while hospitalisations and hospital days were reduced. The number needed to treat in a programme to prevent one hospital admission was calculated to be 15. Therefore, we can conclude that it is feasible to apply these programmes in a clinical setting. In Chapter 7, we demonstrated the results of IDM in primary care COPD patients in a controlled clinical trial (the Bocholtz study) and implementation project (Kroonluchter). At 24 months follow-up, the improvements in quality of life and exercise tolerance were still well sustained. Based on those positive findings, we designed the RECODE trial to confirm our findings in a pragmatic cluster randomised trial in primary care (Chapter 8). In a team setting, we trained healthcare providers during a two-day course to deliver IDM. The training was based on the positive experiences of the Bocholtz and Kroonluchter projects, and included several evidence-based elements of COPD care (including smoking cessation, motivational interviewing and physiotherapeutic reactivation), targeted at individual treatment goals. However, contrary to our expectations, we found no difference between IDM and usual care in our outcomes at 12 and 24 months follow-up (Chapter 9). In addition, a survey was conducted to examine the experiences of healthcare providers who have been working for several years in well-established multidisciplinary teams across the UK (Chapter 5). They valued working in a team as very satisfying and useful, as their meetings not only served to improve communication but also facilitated education and teaching. Especially nurses and physiotherapists reported that they felt highly supported in their decisions by being able to discuss their patients in a holistic way.

Then, the question arises: what can we learn from all these studies and experiences? In this chapter we reflect on the different aspects of integrated care (i.e. type of intervention, study population, context and outcomes) that can contribute to the (more or less) success of a programme. In addition, we discuss the implications for routine clinical practice and make some recommendations for future research.

IDM: WHICH INTERVENTION OR COMPONENTS ARE MOST EFFECTIVE?

The twenty-six studies included in the Cochrane review (Chapter 4) evaluated the effect of IDM on a number of different outcomes. However, due to the variations in healthcare providers, components, settings, context and patient populations, this led to a large body of evidence in which different combinations were tested. Therefore, it is difficult to interpret which intervention is most successful and to provide a blueprint of an ideal programme. However, a number of key components can be identified in the literature, which should be considered to be included or excluded when implementing an IDM programme.

Exercise training or physiotherapeutic reactivation can be considered a cornerstone of IDM, as studies focusing mainly on exercise revealed clinically relevant improvements in health-related outcomes (Chapter 4). These beneficial effects were already widely acknowledged in pulmonary rehabilitation programmes.[1;2] However, these programmes were usually tested in more severe patients in tertiary care clinics. Besides application in highly specialized settings, such as rehabilitation centres, there is evidence that training is safe in the home-based or community setting.[3-9] This is in line with Chapter 7, in which we demonstrated that twice-weekly training in the community, if applied for at least three months, is both feasible and effective. Nevertheless, in daily practice the use of pulmonary rehabilitation is limited by insufficient motivation or compliance of patients, high drop-out rates, or financial problems (Chapter 3). Especially in the early stages, patients often consider that the disease is not disabling enough to necessitate rehabilitation. We observed this phenomenon in the RECODE study, in which the majority of patients were not referred for, or declined participation in an exercise programme, even though we had arranged sufficient funding and facilities (Chapter 9). Similarly, in the INTERCOM trial, in which COPD patients with less severe lung function impairment were trained in the community, the two-year drop-out rates among patients who started the programme were 25% in the intervention group compared with 16% in the usual care group.[3] Whether or not exercise training is effective in patients with milder disease still remains unclear, as some studies demonstrated benefits[3;10] while others revealed no effect.[11-13] In short, we can conclude that exercise training can be beneficial in patients with mild and moderate disease with considerable dyspnoea (Chapter 7); however, more focus is required on feasible and cost-effective strategies that will increase motivation and adherence to a programme in this patient group.

In contrast, the evidence for exacerbation-related self-management for COPD patients is currently fragmented.[14] This was highlighted in Chapter 6, as well as in the subgroup analyses of our Cochrane review (Chapter 4). Although initially regarded as an effective way to reduce costs related to hospitalisations and hospital days, an increasing number of negative trials[15-19] now has raised serious concern as to whether self-management is

safe and effective. To explain this, in Chapter 6 we further explored the characteristics of the negative and positive studies. Although self-management is probably not suitable for all patients, it tends to be beneficial in a subgroup of 'successful self-managers', representing about 40% of patients with COPD.[16;18] This subgroup was characterised by being of relatively younger age, living with others, having severe airflow obstruction, and having cardiac comorbidity.[16;18] We concluded that patients in the negative trials might not be adequately supported. Therefore, it is important to involve a key-person at place that could offer support in making treatment decisions. In routine clinical practice, guidance could be accomplished by a well-trained practice nurse or, in the case of multiple chronic diseases, by a case manager. It is recommended to involve a dedicated family member (or friend) in the exacerbation action plan, so that patients do not feel alone when faced with difficult treatment decisions (Chapter 6). Early recognition and treatment of exacerbations is an important aim of a self-management action plan. Probably the most effective measure consists of exacerbation management in order to reduce a delay of treatment. This could be achieved by simply explaining to patients that a short course of oral steroids (including a leaflet with instructions) is particularly effective during the first 72 hours.[20] Practices that can facilitate prompt access to this simple care, within this time span, can achieve success in treating exacerbations as early as possible. Besides self-management, telehealth is suggested as another solution to involve patients in their own treatment decisions. However, two systematic reviews demonstrated conflicting results of this intervention in COPD patients.[21;22] Another recent trial found that telehealth integrated in clinical services did not improve health outcomes, whereas the workload and costs increased.[23] In addition, the largest pragmatic study to date tested a 'whole system demonstrator' in COPD, diabetes and heart failure patients, with no effect on quality of life, costs and psychological outcomes.[24] In our trial, although we did not implement a true telehealth intervention, we encouraged the intervention practices to use a supportive web-based system, intended to facilitate communication by use of a patient and professional portal. Although most practices were initially enthusiastic about using the system, the overall uptake among providers and patients remained low. The most often mentioned reasons for this low uptake were instability of the application, disinterest of patients for the portal, and a need to duplicate information into separate ICT systems. Therefore, we can conclude that the added value of telehealth in COPD for routine practice is limited, the applications need to be thoroughly developed and tested, and resources are probably better spent on evidence-based interventions such as smoking cessation or exercise.

What are further options to improve the care of COPD patients in the Netherlands? Other recent initiatives developed in the UK have received interest in the Netherlands, as they have the potential to decrease admissions or hospital days. For example, the so-called 'discharge care bundles' (administered by nurses on respiratory wards) consist of short

lists of evidence-based practices: smoking cessation, pulmonary rehabilitation referral, education for exacerbations, inhalation technique instructions, and a follow-up call after 48 hours of discharge to check the health status.[25] The initial results presented in a research update in the journal 'Thorax' seem promising, as readmissions have tended to decrease and the uptake of evidence-based interventions by patients has increased.[25] Other innovating approaches include the 'hospital-at-home' or rapid response teams, which can transfer the care for exacerbations from the hospital to the home.[26] In the Netherlands, within a study setting, the hospital-at-home concept has proven to be a safe alternative for usual care.[27] It would be interesting to examine the long-term value of these initiatives in routine practice. There might be a role for nurses employed by home care organisations, who could be trained to deliver this specialised type of home care. Unfortunately, implementation of these initiatives is hampered by lack of financial coverage by health insurance, as hospitals are currently unable to fund this type of outreach care. In addition, as the introduction of the hospital-at-home has implications for the treating professionals, we need to explore whether general practitioners or pulmonary specialists are willing to assume responsibility for outreach care at home.[28]
In addition, we need to explore how best to implement programmes in daily practice. For example, in our RECODE trial, we trained the healthcare providers without targeting the intervention directly at the patients; consequently, we had little influence on the teams' actions and relied on their own initiatives. This approach has now proven to be less successful compared with other studies in which the interventions were directed to patients; as illustrated by the Cochrane systematic review (Chapter 4), the Bocholtz and Kroonluchter studies (Chapter 7) and the INTERCOM trial.[3] However, some critical barriers might exist that hinder the translation of an intervention targeted at the healthcare provider to the actual implementation of integrated care. We have planned an additional study to investigate the diversity in uptake of our intervention (data therefore not yet available). Another critical factor for success may be the presence of a dedicated leader who feels responsible for the continuity of the programme. Organising weekly or monthly team meetings, in which the derived goals are discussed with all team members, is considered the key to successful long-term implementation (Chapter 5).

IDM: FOR WHOM IS IT EFFECTIVE?

Our Cochrane systematic review provides evidence that an intensive IDM programme of at least three months duration is effective in improving health outcomes in patients with more severe COPD. However, whether these programmes are also effective in primary care populations with a considerable proportion of mild and moderate patients remains less clear. We found conflicting results in our own studies (Chapters 7 and 9). Unfortu-

nately, there is a lack of research on this topic in primary care. Because previous studies were restricted to subsets of primary care patients, such as only moderate and severe patients[3;29;30], this makes interpretation less clear. Therefore, to confirm or refute our findings, more research is needed that covers the whole range of primary care patients, with sufficient numbers of patients in each disease category.

Unfortunately, it is a common phenomenon in the literature that the efficacy of therapies is usually tested in more severely affected patients, in COPD as well as in other chronic diseases. This is not surprising, as room for improvement is usually greater in patients with more symptoms and frequent exacerbations; moreover, this large room for improvement increases the chance of positive findings. This long-standing issue is further examined in Chapter 2; here we investigated whether patients included in the six largest pharmaceutically-sponsored studies were representative of patients treated in primary care. The study revealed that the tested populations were highly selected and differed from primary care patients in terms of lung function, gender, exacerbations and quality of life. In addition, other research[31] revealed a similar selection of patients included in a Cochrane systematic review on pulmonary rehabilitation.[1] Patients that were included were not representative of the target population, as nearly half of the contacted patients were not offered screening if they were eligible to participate in the programme, and one third of the contacted patients finally completed the programme.[31] In contrast, in our pragmatic RECODE trial, due to our limited number of exclusion criteria, only 11% of all registered primary care COPD patients were not eligible to participate.

In addition, selection bias among participants is further complicated by publication bias: positive studies have a higher chance of being published in higher impact journals and, therefore, receive more attention from the public, policymakers and guideline developers. Consequently, treatment recommendations and guidelines rely on selective information. As a result, general practitioners (who deal with the majority of COPD patients) are left to make treatment decisions based on studies not targeted at their own population. Therefore, current guideline developers and trialists should continue to emphasise the importance of more studies conducted among milder patient groups. This is required not only because mild and moderate patients form 75% of the total COPD population, but also because low physical activity, comorbidities, exacerbations, anxiety and depression are evidently also apparent in milder stages.[2;32]

Until there is more certainty regarding the effectiveness of IDM and its components in milder stages, it seems clinically plausible and potentially most (cost-)effective to start an IDM programme in primary care in a subset of patients with considerable complaints (i.e. frequent exacerbators, patients with more symptoms, patients with diminished exercise tolerance), who are sufficiently motivated. When these programmes have found their way in primary care, inclusion criteria could be broadened to include milder patients. However, this will only be of value if such grouping provides clinically meaningful

categories of patients that will guide treatment (by predicting treatment success) more effectively.[32]

IDM: TIMING, ROOM FOR IMPROVEMENT AND OUTCOMES

When interpreting the results of studies that examine the effectiveness of IDM, we should consider the moment when the studies were developed. The yield of a newly developed programme is evidently higher in less developed settings and during the first years of intervention. For example, when tested in 2003 in Canada, the integrated care programme of Bourbeau et al. showed dramatic improvements in health-related outcomes.[33] When (a few years later) the same intervention was replicated in the Netherlands[15] and in the USA[19], the results were less favourable. Thus, the success of a programme is probably not only dependent on the setting, but also on the relative timing of interventions amongst each other. Similarly, we had successful results in 2005 with our IDM programme, when COPD care was less well organised and with considerable underdiagnosis and undertreatment, whereas we demonstrated no effect in our trial starting in 2010.

The interpretation of early trial results is complicated also for other reasons. In all developed countries, the care for COPD patients has changed considerably over the last decade. In the Netherlands, the need for a transfer of care from a secondary to a primary setting became increasingly more apparent, which (in 2010) was followed by the introduction of a bundled payment system.[34;35] According to this system, insurers pay a single fee to a 'care group' (usually exclusively general practitioners) to cover a full range of COPD care services for a fixed period. For the various components of care, the care group either delivers the services itself or subcontracts to other care providers (physiotherapy, nutritional support, pulmonary specialists consultations). The price for the bundle of services is freely negotiated by insurers and care groups; similarly, the fees for the subcontracted providers are negotiated by the care group and the providers.[34]

A nationwide implementation of COPD IDM is still lacking, but several regional projects have been initiated.[35;36] Nowadays, almost all practices have some kind of structured COPD care, including a practice nurse that performs spirometry and provides regular follow-up and monitoring. Although difficult to distinguish, the increased awareness and willingness to implement integrated care was also clearly apparent to the general practitioners in our usual care group, as our trial was conducted between 2010 and 2013; this could have reduced the contrast between the groups in the RECODE trial. Other recent trials studying components of COPD care in English and Dutch primary care settings, with the same absence of effect, illustrate the influence of already high levels of usual care in these countries and settings.[15;17;23]

Recent developments in the Netherlands are likely to stimulate further implementation of integrated care for COPD. The Lung Alliance Netherlands started the National Action Programme on Chronic Lung Diseases, which aims to achieve less burden/deaths, and costs for asthma and for COPD. In 2015 the Dutch government plans to change the reimbursement structure of GP care, i.e. care for chronic diseases in primary care will be financed by only one payment per patient that covers all multidisciplinary care, and single consultations by practice nurses will no longer be reimbursed.[37] These new plans will further motivate GPs to form care groups and multidisciplinary settings for COPD. In addition, healthcare insurers are encouraged to provide additional financial incentives for new innovations such as self-management and e-health. Similarly, those developments will further stimulate integrated care, leaving even less room for contrast with usual care in a study setting.

In addition, when implementing or testing IDM or other complex interventions, we need to consider what the best outcomes are to measure an effective IDM approach. In our study carried out in the UK, experienced team members acknowledged that this remains very difficult (Chapter 5). The participants suggested outcomes that were mostly related to underlying changes of the system: e.g. satisfaction of the team or the patient, decreases in healthcare resources, or the number of interventions implemented. In clinical trials, the outcomes are usually both functional (such as quality of life), as well as objective (exacerbations, mortality). Satisfaction of patients with the overall system or the physician can have an influence on their functional outcomes. Therefore, concern about bias is diminished when findings from both objective and subjective measures are consistent.[38] In our RECODE trial, we attempted to provide insight into underlying behavioural and organisational changes, by using outcomes such as self-management (SMAS), smoking behaviour, and integration of care according to the patient (PACIC) and providers (ACIC). Usually, compliance or adherence with the intervention is not considered as an outcome by itself, although good compliance is a prerequisite for effectiveness in routine use.[39] For example, the number of interventions implemented per patient in an IDM programme (Chapter 5) could give some idea about the level of compliance. Unfortunately, in our Cochrane review, process outcomes were hardly reported (only in 3 of the 26 studies), making it difficult to establish why one intervention was successful or not. Therefore, we recommend that future studies include process outcomes so that data on the intensity, processes and organisational changes can be linked to the yield of a programme.

MOVING FROM EVIDENCE TO PRACTICE

Having studied several integrated care programmes for COPD, we remain somewhat puzzled whether IDM for COPD patients is effective in routine practice, or not. Firstly, our systematic review demonstrated that an intensive IDM programme of at least three months duration is beneficial in more severe COPD patients. By contrast, we found no effect of our RECODE programme in milder COPD patients in primary care. Therefore, we cannot recommend our programme for primary care. Secondly, despite the lack of evidence of our IDM programme, there are several evidence based components in this programme (i.e. exercise therapy and smoking cessation), that deserve to be implemented in every general practice, regardless of being delivered in an IDM programme. Unfortunately, when moving from evidence to practice, we have experienced several barriers that hamper the implementation of these effective components in routine care. For example, while reimbursement of evidence-based interventions in a study setting is usually not a problem, it is essential to drive implementation of programmes in routine practice. Although the Dutch government and healthcare insurers propagate better integration and substitution of care, their reimbursement policy is not always directed towards doing so. In the RECODE study, we experienced that professionals and patients felt frustrated and insecure due to sudden changes in reimbursement policies and political whims. For example, the cancellation of coverage of smoking cessation therapy after one year of implementation had a detrimental influence on motivation to quit smoking. Preventive interventions for COPD, such as exercise therapy and nutritional support, required a co-payment or an additional healthcare insurance, which is surprising since expensive drugs, for example biologic therapies, remain fully reimbursed. In fact, the level of evidence for the effectiveness of non-pharmacological interventions in COPD is generally higher than that for pharmacological treatment.[40] As overprescribing is obviously a waste of money, this could be saved and reinvested in commissioning high-value services such as (community-based) pulmonary rehabilitation.[41] Therefore, we should aim to invest in robust strategies for increasing referrals to exercise training, and encourage people with breathing problems to take exercise rather than to take more medicine (if not appropriately prescribed).

The future will show whether or not IDM programmes are really stimulated and facilitated by the insurance companies and the government. Healthcare professionals need to focus on strategies that will increase the motivation of patients to commit to elements of integrated care (such as an exercise programme or smoking cessation) and to strive for evidence-based prescribing of medication. More personalised treatment, in which we take into consideration the needs and preferences of patients, and provide them with education and support, could be the key to successful long-term implementation.

REFERENCES

(1) Lacasse Y, Goldstein R, Lasserson TJ, Martin S. Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2006;(4):CD003793.

(2) Spruit MA, Singh SJ, Garvey C, ZuWallack R, Nici L, Rochester C, et al. An official American Thoracic Society/European Respiratory Society statement: Key concepts and advances in pulmonary rehabilitation. *Am J Respir Crit Care Med* 2013;188(8):e13-e64.

(3) van Wetering CR, Hoogendoorn M, Mol SJ, Rutten-van Molken MP, Schols AM. Short- and long-term efficacy of a community-based COPD management programme in less advanced COPD: a randomised controlled trial. *Thorax* 2010;65(1):7-13.

(4) Cambach W, Chadwick-Straver RV, Wagenaar RC, van Keimpema AR, Kemper HC. The effects of a community-based pulmonary rehabilitation programme on exercise tolerance and quality of life: a randomized controlled trial. *Eur Respir J* 1997;10(1):104-13.

(5) Mendes de Oliveira JC, Studart Leitao Filho FS, Malosa Sampaio LM, Negrinho de Oliveira AC, Hirata RP, Costa D, et al. Outpatient vs. home-based pulmonary rehabilitation in COPD: a randomized controlled trial. *Multidiscip Respir Med* 2010;5(6):401-8.

(6) Wijkstra PJ, Ten Vergert EM, van Altena R., Otten V, Kraan J, Postma DS, et al. Long term benefits of rehabilitation at home on quality of life and exercise tolerance in patients with chronic obstructive pulmonary disease. *Thorax* 1995;50(8):824-8.

(7) Boxall AM, Barclay L, Sayers A, Caplan GA. Managing chronic obstructive pulmonary disease in the community. A randomized controlled trial of home-based pulmonary rehabilitation for elderly housebound patients. *J Cardiopulm Rehabil* 2005;25(6):378-85.

(8) Fernandez AM, Pascual J, Ferrando C, Arnal A, Vergara I, Sevila V. Home-based pulmonary rehabilitation in very severe COPD: is it safe and useful? *J Cardiopulm Rehabil Prev* 2009;29(5):325-31.

(9) Casey D, Murphy K, Devane D, Cooney A, McCarthy B, Mee L, et al. The effectiveness of a structured education pulmonary rehabilitation programme for improving the health status of people with moderate and severe chronic obstructive pulmonary disease in primary care: the PRINCE cluster randomised trial. *Thorax* 2013;68(10):922-8.

(10) Vogiatzis I, Terzis G, Stratakos G, Cherouveim E, Athanasopoulos D, Spetsioti S, et al. Effect of pulmonary rehabilitation on peripheral muscle fiber remodeling in patients with COPD in GOLD stages II to IV. *Chest* 2011;140(3):744-52.

(11) Gottlieb V, Lyngso AM, Nybo B, Frolich A, Backer V. Pulmonary rehabilitation for moderate COPD (GOLD 2)--does it have an effect? *COPD* 2011;8(5):380-6.

(12) Roman M, Larraz C, Gomez A, Ripoll J, Mir I, Miranda EZ, et al. Efficacy of pulmonary rehabilitation in patients with moderate chronic obstructive pulmonary disease: a randomized controlled trial. *BMC Fam Pract* 2013;14:21.

(13) Monninkhof E, van d, V, van der Palen J, van HC, Zielhuis G. Effects of a comprehensive self-management programme in patients with chronic obstructive pulmonary disease. *Eur Respir J* 2003;22(5):815-20.

(14) Wagg K. Unravelling self-management for COPD: what next? *Chron Respir Dis* 2012;9(1):5-7.

(15) Bischoff EW, Akkermans R, Bourbeau J, van WC, Vercoulen JH, Schermer TR. Comprehensive self management and routine monitoring in chronic obstructive pulmonary disease patients in general practice: randomised controlled trial. *BMJ* 2012;345:e7642.

(16) Bischoff EW, Hamd DH, Sedeno M, Benedetti A, Schermer TR, Bernard S, et al. Effects of written action plan adherence on COPD exacerbation recovery. *Thorax* 2011;66(1):26-31.

(17) Trappenburg JC, Monninkhof EM, Bourbeau J, Troosters T, Schrijvers AJ, Verheij TJ, et al. Effect of an action plan with ongoing support by a case manager on exacerbation-related outcome in patients with COPD: a multicentre randomised controlled trial. *Thorax* 2011;66(11):977-84.

(18) Bucknall CE, Miller G, Lloyd SM, Cleland J, McCluskey S, Cotton M, et al. Glasgow supported self-management trial (GSuST) for patients with moderate to severe COPD: randomised controlled trial. *BMJ* 2012;344:e1060.

(19) Fan VS, Gaziano JM, Lew R, Bourbeau J, Adams SG, Leatherman S, et al. A comprehensive care management program to prevent chronic obstructive pulmonary disease hospitalizations: a randomized, controlled trial. *Ann Intern Med* 2012;156(10):673-83.

(20) Walters JA, Gibson PG, Wood-Baker R, Hannay M, Walters EH. Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2009;(1):CD001288.

(21) Bolton CE, Waters CS, Peirce S, Elwyn G. Insufficient evidence of benefit: a systematic review of home telemonitoring for COPD. *J Eval Clin Pract* 2011;17(6):1216-22.

(22) Polisena J, Tran K, Cimon K, Hutton B, McGill S, Palmer K, et al. Home telehealth for chronic obstructive pulmonary disease: a systematic review and meta-analysis. *J Telemed Telecare* 2010;16(3):120-7.

(23) Pinnock H, Hanley J, McCloughan L, Todd A, Krishan A, Lewis S, 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.

(24) Cartwright M, Hirani SP, Rixon L, Beynon M, Doll H, Bower P, 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.

(25) Hopkinson NS, Englebretsen C, Cooley N, Kennie K, Lim M, Woodcock T, et al. Designing and implementing a COPD discharge care bundle. *Thorax* 2012;67(1):90-2.

(26) Jeppesen E, Brurberg KG, Vist GE, Wedzicha JA, Wright JJ, Greenstone M, et al. Hospital at home for acute exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2012;5:CD003573.

(27) Utens CM, Goossens LM, Smeenk FW, Rutten-van Molken MP, van VM, Braken MW, et al. Early assisted discharge with generic community nursing for chronic obstructive pulmonary disease exacerbations: results of a randomised controlled trial. *BMJ Open* 2012;2(5).

(28) Utens CM, Maarse JA, van Schayck OC, Maesen BL, Rutten MP, Smeenk FW. Care delivery pathways for Chronic Obstructive Pulmonary Disease in England and the Netherlands: a comparative study. *Int J Integr Care* 2012;12:e40.

(29) Zakrisson AB, Engfeldt P, Hagglund D, Odencrants S, Hasselgren M, Arne M, et al. Nurse-led multidisciplinary programme for patients with COPD in primary health care: a controlled trial. *Prim Care Respir J* 2011;20(4):427-33.

(30) Rea H, McAuley S, Lamont C, Roseman P, Didsbury P, Stewart A. A chronic disease management program can reduce days in hospital for patients with COPD. *Respirology* 2002;7:A6.

(31) Bjoernshave B, Korsgaard J, Nielsen CV. Does pulmonary rehabilitation work in clinical practice? A review on selection and dropout in randomized controlled trials on pulmonary rehabilitation. *Clin Epidemiol* 2010;2:73-83.

(32) Rabe KF, Wedzicha JA. Controversies in treatment of chronic obstructive pulmonary disease. *Lancet* 2011;378(9795):1038-47.

(33) Bourbeau J, Julien M, Maltais F, Rouleau M, Beaupre A, Begin R, et al. Reduction of hospital utilization in patients with chronic obstructive pulmonary disease: a disease-specific self-management intervention. *Arch Intern Med* 2003;163(5):585-91.

(34) Struijs JN, Baan CA. Integrating care through bundled payments--lessons from The Netherlands. *N Engl J Med* 2011;364(11):990-1.

(35) Tsiachristas A, Hipple-Walters B, Lemmens KM, Nieboer AP, Rutten-van Molken MP. Towards integrated care for chronic conditions: Dutch policy developments to overcome the (financial) barriers. *Health Policy* 2011;101(2):122-32.

(36) Gress S, Baan CA, Calnan M, Dedeu T, Groenewegen P, Howson H, et al. Co-ordination and management of chronic conditions in Europe: the role of primary care--position paper of the European Forum for Primary Care. *Qual Prim Care* 2009;17(1):75-86.

(37) Nederlandse Zorgautoriteit. Advies Bekostiging huisartsenzorg en multidisciplinaire zorg. Het 3-segmenten-model. Available from: www.nza.nl/104107/139830/465987/Advies_Bekostiging_huisartsenzorg_en_ge_ntegreerde_zorg.pdf. Accessed 28-5-2014

(38) Ware JH, Hamel MB. Pragmatic trials--guides to better patient care? *N Engl J Med* 2011;364(18):1685-7.

(39) Godwin M, Ruhland L, Casson I, MacDonald S, Delva D, Birtwhistle R, et al. Pragmatic controlled clinical trials in primary care: the struggle between external and internal validity. *BMC Med Res Methodol* 2003;3:28.

(40) Troosters T, Casaburi R, Gosselink R, Decramer M. Pulmonary rehabilitation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005;172(1):19-38.

(41) British Thoracic Society and Primary Care Respiratory Society UK. IMPRESS Guide to the relative value of COPD interventions. *British Thoracic Society Reports* 2012:4(2) Available from: http://www.impressresp.com/index.php?option=com_docman&task=doc_view&gid=52&Itemid=82. Accessed 28-5-2014.

CHAPTER 11

Summary

The treatment of Chronic Obstructive Pulmonary Disease (COPD) is difficult due to large variation in clinical presentations, underreported symptoms, frequent comorbidities, disappointing effects of medical treatment and problems with giving up smoking. Treatment is focused on care rather than cure, and consists on improving quality of life and daily functioning of patients. In this thesis we explored different aspects of optimal COPD care, including optimal medical treatment and self-management. More specifically, the primary aim was to study the potential role of integrated disease management (IDM) programs for COPD, specifically in primary care.

PART 1: PRIMARY CARE AND COPD MANAGEMENT

In **Chapter 2**, we studied the external validity of six large pharmaceutically sponsored studies that evaluated medical treatment for COPD, and are often reported in guidelines. As the majority of COPD patients are treated by general practitioners who use those guidelines, we aimed to examine if the patients included in these studies were representative to patients seen in primary care. We compared baseline characteristics of seven primary care databases (n=3508) from Europe to baseline data of the large studies. Overall, patients in the pharmaceutically sponsored studies were younger, predominantly male, with worse lung function and worse quality of life scores than the patients in routine primary care. In addition, there were large differences in GOLD stage distribution and in the number of patients with frequent exacerbations. We concluded that the proportion of primary care patients that were eligible for inclusion in a trial ranged from 17% to 42%. Thus, large pharmaceutically sponsored trials included selective patient populations, and it is unclear if these results are applicable to patients treated in primary care.

Pulmonary rehabilitation can improve quality of life and exercise capacity, but the uptake is low in routine practice due to high costs, low availability and problems with adherence to an active lifestyle after the programs have been finished. This has increased the interest to develop and test alternative delivery models of PR. In **Chapter 3**, we positioned our hypothesis, which could be the solution for these problems. We assumed that if elements of PR programs could be adapted to primary care, the benefits could be extended to a larger, and also milder, part of the COPD population. For example, COPD patients could be trained in primary care specialised physiotherapy practices, and practice nurses could instruct on selfmanagement or smoking cessation. When general practitioners and practice nurses are actively involved in these programs, it is reasoned lifestyle benefits could be sustainable, even after the program has been finished. Several small studies have showed beneficial effects, however there is a need for large cluster randomised trials in primary care to demonstrate the effectiveness.

PART 2: THE EFFECTIVENESS OF INTEGRATED DISEASE MANAGEMENT FOR COPD

In **Chapter 4** we presented the results of a Cochrane systematic review that evaluated the effectiveness of IDM on quality of life, exercise tolerance and exacerbation related outcomes (hospitalisations, hospital days). We included 26 studies (n=2997) of moderate to high quality, which included 2997 patients of 11 countries, in which IDM was evaluated compared to usual care. On average, patients were 68 years and had a diminished lung function (FEV1% predicted 44). Compared with controls, IDM showed significantly and clinically relevant improvements in quality of life (CRQ questionnaire mean difference (MD) 1.02 (95% confidence interval (CI) 0.67-1.36); SGRQ questionnaire MD -3.71 (95% CI -5.83- -1.59)) and exercise tolerance (6 minute walking distance MD 43.86 (95% CI 21.83-65.89)). In addition, hospitalisation days decreased by 4 days and the number of patients with at least one hospital admission decreased from 27 to 20 per 100 (OR 0.68). The number needed to treat in a program to prevent one hospital admission over a year period was calculated as 15. Unfortunately, due to heterogeneity between studies, no further recommendations could be made regarding the ideal composition of a program. Subgroup analyses demonstrated the studies incorporating exercise training had the largest benefits, compared to studies focusing mainly on exacerbation self-management.

Moving from evidence to practice, we aimed to evaluate the attitudes, perceptions and experiences of UK healthcare professionals that are highly experienced in providing IDM in a COPD multidisciplinary team. In **Chapter 5**, we presented the results of a cross-sectional descriptive online survey amongst 69 members of 10 multidisciplinary teams in the UK. Participation was valued as very useful. They reported the meetings served 1) to optimise management for complex patients; 2) to increase disease-specific knowledge of members; 3) to improve communication between providers across settings and disciplines. They acknowledged the meetings could be improved by proper documentation of derived agreements and more widely information sharing. General practitioners were usually not participating in the meetings, although all members expressed a large need to include them.

Self-management programs for exacerbations aim to teach patients to recognise initial symptoms, in order to start therapy at an early stage. Although initially regarded as effective, recently, there is expanded literature published on this topic with mixed results, leading to questions if self-management is a safe and effective treatment. In **Chapter 6**, we explored characteristics of negative and positive studies, in order to provide more insight for clinicians. Self-management seems to be successful in a subgroup of 40% of COPD patients. This subgroup was characterised by being of relatively younger age, living with others, having severe airflow obstruction, and having cardiac comorbidity.

We concluded that patients in the negative trials might not be adequately supported. Therefore, it is important to involve a case-manager or key-person at place, for example a dedicated spouse, friend or family member, which could offer support in making treatment decisions. Hence, it is clear these programmes need to be implemented in daily practice only when patients have the capacity for understanding their symptoms.

The effectiveness of IDM programs in primary care is discussed in the last three chapters. In **Chapter 7**, we presented the long-term results of two Dutch studies: the Bocholtz controlled clinical trial and the Kroonluchter implementation project. In both studies, multidisciplinary teams were formed and patients received different components of IDM based on individualized treatment goals. After 24 months of follow-up, beneficial effects on quality of life (Clinical COPD Questionnaire; CCQ) and exercise tolerance (6 minute walking distance; 6MWD) were still sustained. In patients with a baseline CCQ score above 1 and in patients with an MRC dyspnea score above 2, the long-term effect on CCQ score was doubled and even tripled, respectively, compared with patients who had lower scores. In patients with a baseline 6MWD under 400meters, the 6MWD difference remained substantially large during two years, with effect sizes exceeding 100 meters.

These successful results needed confirmation in a large cluster randomized trial, the RECODE study. Design and baseline results of the study are presented in **Chapter 8**. In this pragmatic study, healthcare providers (general practitioners, practice nurses, physiotherapists) in 20 intervention practices learned during a two-day multidisciplinary course tips and tricks of applying successful IDM in primary care. During the course, the team redesigned the care process and defines responsibilities of different caregivers. Practice-tailored feedback reports were provided at baseline, and at 6 and 12 months. The team learned the details of an ICT program that supports recording of process and outcome measures. Afterwards, they designed a time-contingent individual practice plan, agreeing on steps to be taken in order to integrate a COPD IDM program into daily practice. The control group continued usual care. Patients were followed up at 6, 9, 12, 18 and 24 months. The primary outcome was disease-specific health related quality of life, as measured with the CCQ. Secondary outcomes were generic health related quality of life, self-management, dyspnoea, exacerbation related outcomes, level of physical activity, smoking status, and level of integration of care.

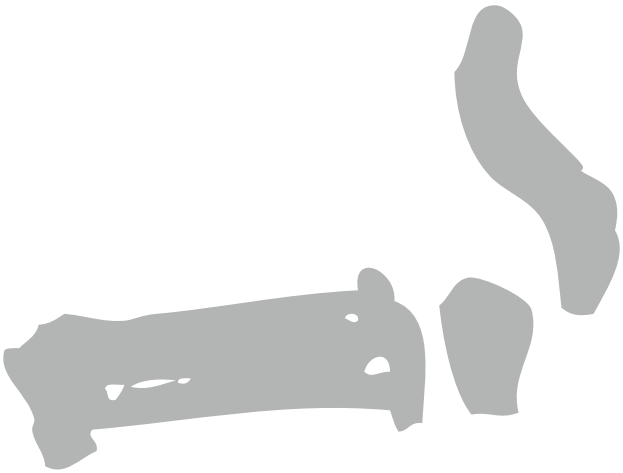
The results of the RECODE trial were described in **Chapter 9**. After 12 months, we concluded there was no difference between groups on the CCQ (Mean difference [MD] -0.01; 95% CI -0.1-0.08; p=0.8). After 12 months, we found no differences in secondary outcomes between groups, except for the PACIC domain 'follow-up/coordination' (indicating improved integration of care) (MD 0.15; p=0.01) and proportion of physically active patients (MD 10.1; p <0.001). After 24 months, there were no differences in outcomes, except for the PACIC instrument for 'follow-up/coordination'. The contradictory

findings to earlier positive studies could be explained by differences between interventions (provider- versus patient-targeted), selective reporting of positive trials, or little room for improvement in the well-developed Dutch healthcare system.

In **Chapter 10**, we reflected on our findings and discussed the implications for routine practice. Having studied several integrated care programmes for COPD, we remain puzzled whether IDM is potentially effective in routine practice. We concluded that the effectiveness of IDM seems highly dependent on the tested interventions, the setting, the population and the outcomes chosen. Our Cochrane review demonstrated that an intensive IDM program is effective in more severe COPD. Due to a minority of studies in milder patients and conflicting results in our studies, it remains less clear whether these programs are also effective in primary care populations with a considerable proportion of mild and moderate patients. Several elements of IDM have been proven to be more or less successful. Exercise training is beneficial, but the effects of exacerbation self-management and telehealth are less clear. Besides patient-related outcomes, we recommend to include process and compliance outcome measures in studies, so that data about the intensity, processes and organisational changes can be linked to the results of a program. Although the Dutch government and healthcare insurers propagate better integration and substitution of care, their reimbursement policy is not always directed towards doing so. The evidence for effectiveness of non-pharmacological interventions is generally higher than for pharmacological treatment. The money that could be saved by more evidence-based prescribing of medication could be invested in increased availability of exercise programs. As healthcare professionals, we need to focus on strategies to increase the motivation of our patients. We should try to make treatment plans as individual as possible, by adequately informing patients about their disease and about the possibilities there are for improvement of their daily functioning.

CHAPTER 12

Nederlandse samenvatting



De behandeling van Chronic Obstructive Pulmonary Disease (COPD) is lastig. Hier zijn diverse redenen voor: het klinische beeld wisselt sterk tussen patiënten, het effect van medicatie is beperkt en patiënten vinden het lastig om te stoppen met roken. COPD is niet te genezen en de behandeling is dan ook gericht op het optimaal omgaan met de klachten. In dit proefschrift bestudeerden we verschillende aspecten van optimale zorg voor COPD patiënten. Meerdere onderdelen van zorg kunnen gecombineerd worden in een geïntegreerd zorgprogramma, waarin hulpverleners de zorg op elkaar afstemmen en efficiënt samenwerken. Het hoofddoel van dit proefschrift was om een onderbouwing te geven van de effectiviteit van zo'n geïntegreerd zorgprogramma voor COPD patiënten in het algemeen, maar specifiek in de eerste lijn. Daarnaast werden ook enkele specifieke onderdelen van een zorgprogramma (medicatie en zelf-management) uitgelicht.

DEEL 1: DE EERSTE LIJN EN COPD MANAGEMENT

Medicamenteuze adviezen in richtlijnen voor huisartsen zijn gebaseerd op resultaten van grote farmaceutische studies. Het is de vraag of de patiënten die geïncludeerd werden in deze studies ook vergelijkbaar zijn met de patiënten die in de eerste lijn worden gezien. **Hoofdstuk 2** beschrijft een onderzoek naar de externe validiteit van zes grote farmaceutische studies, die veelvuldig geciteerd worden in richtlijnen. We vergeleken 3508 COPD patiënten uit zeven Europese huisartsdatabases met de patiënten die geïncludeerd waren in deze studies. De studies includeerden overwegend jongere mannen met meer pakjaren, veel klachten, een slechtere kwaliteit van leven en meer exacerbaties per jaar. Het percentage eerstelijns COPD patiënten dat in aanmerking kwam om deel te nemen als proefpersoon in zo'n studie loopt uiteen van 17 tot 48%. Gezien de sterke selectie in patiënten populaties, is het onduidelijk of de resultaten van deze studies ook toepasbaar zijn op eerstelijns COPD patiënten.

Longrevalidatie zorgt voor verbeteringen in patiënt-uitkomsten, echter de behandeling is duur, er is gebrek aan capaciteit, en patiënten hebben moeite om de levensstijl na afloop van het programma te continueren. In **Hoofdstuk 3** positioneerden wij in een beschrijvende review een hypothese, die een oplossing zou kunnen bieden voor deze problemen. Veel van de onderdelen van longrevalidatie kunnen worden aangeboden in een geïntegreerd eerstelijns COPD zorgprogramma, zoals bewegingsprogramma's bij fysiotherapeuten, stoppen met roken begeleiding en zelfmanagement bij de praktijkverpleegkundige en voedingsadvies bij de diëtiste. Het is belangrijk dat goed overleg plaatsvindt met de longarts, en door de huisarts en praktijkverpleegkundige actief bij het programma te betrekken en de patiënt in de eigen vertrouwde omgeving

te behandelen, is de kans groter dat de positieve veranderingen na het volgen van het programma langer beklijven. Enkele kleine studies laten positieve effecten zien van dergelijke eerstelijns geïntegreerde zorgprogramma's, maar een onderbouwing in een grote cluster gerandomiseerde trial ontbreekt nog.

DEEL 2: DE EFFECTIVITEIT VAN GEÏNTEGREERDE ZORGPROGRAMMA'S VOOR COPD PATIËNTEN

In **Hoofdstuk 4** beschrijven wij in een Cochrane systematische review de effectiviteit van geïntegreerde COPD zorgprogramma's op kwaliteit van leven, inspanningstolerantie en exacerbatie gerelateerde uitkomsten (zoals ziekenhuisopnames). Hiervoor analyseerden we alle gepubliceerde artikelen in de medische literatuur. We voegden de resultaten van 26 trials samen, van redelijke tot hoge kwaliteit, met in totaal 2997 deelnemers in 11 landen waarin zo'n multidisciplinaire aanpak werd vergeleken met standaardzorg. De patienten waren gemiddeld 68 jaar en hadden een fors verminderde longfunctie (voorspeld FEV1 van gemiddeld 44%). COPD patienten die behandeld werden in een zorgprogramma lieten verbeteringen zien op ziekte specifieke kwaliteit van leven (CRQ vragenlijst gemiddeld verschil (MD) 1.02 (95% betrouwbaarheidsinterval(BI) 0.67-1.36); SGRQ vragenlijst MD -3.71 (95% BI -5.83- -1.59)), en inspanningstolerantie (6 minuten wandeltest MD 43.86 meter (95% BI 21.83-65.89)). Het percentage mensen dat in het ziekenhuis terechtkwam daalde significant van 27 naar 20 per 100 (oddsratio: 0.68; 'number needed to treat': 15), en het aantal opnamedagen nam af met 4 dagen. Vanwege klinische heterogeniteit tussen de interventies was het niet mogelijk een uitspraak te doen over de ideale samenstelling van een zorgprogramma. Uit subgroep analyses bleek daarnaast dat interventies waarbij de nadruk op trainen lag, de grootste verbeteringen waarneembaar waren op kwaliteit van leven en inspanningstolerantie, vergeleken met studies waarbij de nadruk lag op zelfmanagement.

Er is geen onderzoek beschikbaar waarin de opvattingen en ervaringen van hulpverleners die een geïntegreerd zorgprogramma verlenen in een multidisciplinair team wordt beschreven. Wat vinden zij van het werken in zulke teams, wat bespreken ze, en zijn er mogelijkheden tot verbetering? In **Hoofdstuk 5** beschrijven wij de resultaten van een enquête die is afgenomen onder 69 professionals werkzaam in 10 multidisciplinaire COPD teams in Engeland, die al jaren geïntegreerde zorgprogramma's verlenen. Zij gaven aan dat zij zeer tevreden waren over het werken in zulke teams. Hun wekelijkse overleggen dienden om samen tot een behandelplan te komen, om van elkaar te leren, en om de communicatie tussen de verschillende professies te verbeteren. Huisartsen waren veelal nog niet betrokken bij deze multidisciplinaire teams, maar alle teams

gaven aan hier veel behoefte aan te hebben. De overleggen konden verder verbeterd worden door de gemaakte afspraken uniform te registeren, en het delen van informatie tussen de disciplines te verbeteren.

Zelfmanagement programma's voor exacerbaties zijn erop gericht om patiënten beginnende symptomen te leren herkennen, zodat door vroegtijdig ingrijpen verergering en complicaties kunnen worden voorkomen. De programma's zijn veelvuldig bestudeerd en aanvankelijk met veel enthousiasme ontvangen. Echter, recentelijk zijn enkele grote studies verschenen met negatieve resultaten, zoals hogere sterftecijfers in de interventiegroep, waardoor het de vraag is of zelfmanagement programma's inderdaad effectief en veilig zijn. In **Hoofdstuk 6** beschrijven wij in een commentaar de eigenschappen van zowel positieve als negatieve studies, om op die manier inzicht te bieden in deze vraagstelling. Het blijkt dat zelfmanagement niet voor iedereen geschikt en veilig is, maar mogelijk effectief kan zijn in 40% van de COPD patiënten, mits voldoende ondersteund door een case-manager of voor de patiënt vertrouwd persoon, zoals bijvoorbeeld een familielid of vriend. De patiënt kan dan worden gesteund bij moeilijke beslissingen zoals wel of niet starten met medicatie voor een mogelijke exacerbatie. Ook zou de case-manager zelf een vinger aan de pols moeten houden, omdat het bekend is dat COPD patiënten gewoonlijk te laat of niet aan de bel trekken bij een exacerbatie. De geschiktheid van zelfmanagement voor COPD patiënten moet in de praktijk per patiënt zorgvuldig worden afgewogen, en alleen worden aangeboden aan patiënten die voldoende inzicht hebben in hun ziekte.

De effectiviteit van geïntegreerde zorg in de eerste lijn wordt besproken in de laatste 3 hoofdstukken.

In **Hoofdstuk 7** presenteren wij de gecombineerde lange termijn resultaten van een gecontroleerde klinische studie (de Bocholtz studie uit Limburg) en een implementatiestudie (het Kroonluchter programma uit Rotterdam). In beide studies werd een multidisciplinair team gevormd en kregen patiënten verschillende onderdelen van zorg aangeboden gebaseerd op hun persoonlijke behandeldoelen. Na 24 maanden bleek dat de verbeteringen op kwaliteit van leven en inspanningstolerantie die na 12 maanden al gemeten waren, gehandhaafd bleven. Bij patiënten met slechtere kwaliteit van leven (CCQ score >1) was het effect zelfs verdubbeld, en bij patiënten met aanzienlijke kortademigheid (MRC score >2), was het effect zelfs verdrievoudigd. Bij patiënten met beperkte inspanningstolerantie (6 minuten wandeltest < 400 meter), was de verbetering in conditie nog steeds meer dan 100 meter na twee jaar.

Met deze kennis en positieve ervaringen werd de RECODE trial ontworpen; opgezet als een grootschalig, cluster gerandomiseerd onderzoek voor de eerste lijn met 24 maanden follow-up. De opzet van dit onderzoek en de baseline resultaten staan beschreven in **Hoofdstuk 8**. Huisartspraktijken werden gerandomiseerd voor het verlenen van een geïntegreerd zorgprogramma dan wel de huidige zorg. Zij namen deel aan een tweedaagse nascholing, samen met hun praktijkverpleegkundige, fysiotherapeut gespecialiseerd in COPD zorg en eventueel een diëtist. Tijdens de nascholing werden alle onderdelen van een geïntegreerd zorgprogramma bijgebracht, en werden de teams en patiënten ondersteund door middel van een ICT applicatie (Zorgdraad). De controlegroep continueerde de huidige zorg. Patiënten werden gevolgd op 6, 9, 12, 18 and 24 maanden. De primaire uitkomstmaat was ziekte-specifieke kwaliteit van leven na 12 maanden, gemeten met de CCQ. De secundaire uitkomstmaten waren kwaliteit van leven, zelfmanagement, kortademigheid, dagelijkse activiteiten, mate van geïntegreerde zorg, rookstatus en exacerbaties.

De resultaten van de RECODE studie staan beschreven in **Hoofdstuk 9**. Door middel van randomisatie kwamen 20 huisartspraktijken (554 patiënten) in de interventiegroep en 20 huisartspraktijken (532 patiënten) in de controlegroep terecht. Er was geen verschil tussen beide groepen op de CCQ na 12 maanden (MD -0.01; 95% BI -0.01-0.08; p=0.08). Na 12 maanden waren er geen verschillen tussen beide groepen in de secundaire uitkomstmaten, behalve in de mate van coördinatie/follow-up van geïntegreerde zorg, zoals gemeten met de PACIC (MD 0.15; p = 0.01). Daarnaast gaf een hoger percentage patiënten na 12 maanden aan dat zij meer waren gaan bewegen (MD 10.1; p <0.001). Na 24 maanden was alleen de coördinatie en follow-up van geïntegreerde zorg nog significant verschillend, zoals gemeten met de PACIC. Onze negatieve bevindingen zijn tegenstrijdig met de studies die we evalueerden voor onze systematische review. Dit kan verklaard worden door verschillen in interventies (gericht op patiënten of op hulpverleners zoals bij RECODE), selectieve rapportage van positieve studie resultaten, of weinig ruimte voor verbetering in het al goed ontwikkelde gezondheidszorg systeem in Nederland.

Hoofdstuk 10 bevat de algemene discussie. Na het bestuderen van verschillende geïntegreerde zorgprogramma's, blijven we vertwijfeld achter of deze effectief zijn in de dagelijkse praktijk. De opbrengst is niet alleen afhankelijk van gekozen interventie en populatie, maar ook van de kwaliteit van de huidige zorg. Uit onze Cochrane review blijkt dat geïntegreerde zorgprogramma's in ieder geval effectief zijn voor patiënten met matig ernstig tot zeer ernstig COPD. Er is gebrek aan onderzoek en bewijs in patiënten in de eerste lijn die minder ernstig COPD hebben, en onze studies brachten tegenstrijdige resultaten. Verschillende onderdelen van geïntegreerde zorg zijn de laatste jaren meer

of minder effectief gebleken. Bewegingstherapie zou niet mogen ontbreken, maar voor exacerbatie actieplannen en telehealth is minder vaststaand bewijs. Om meer inzicht te bieden in waarom de ene interventie wel effectief is en de andere niet, lijkt het zinvol om niet alleen patiënt-gerelateerde uitkomsten te meten, maar ook bij te houden hoe de compliantie van patiënten en proces veranderingen op organisatie niveau zijn. Alhoewel de overheid en zorgverzekeraars (de onderdelen van) geïntegreerde zorgprogramma's sterk aanbevelen, is hun beleid hier niet altijd op gericht. Niet medicamenteuze interventies zoals bewegingstherapie en stoppen met roken zijn voor COPD patiënten effectiever dan medicatie, maar worden niet altijd zonder meer vergoed, hetgeen voor veel onrust en gebrek aan motivatie zorgt. Het geld dat zou kunnen worden bespaard door kritisch medicatie voor te schrijven, zou kunnen worden besteed aan het vergroten van de capaciteit voor preventieve bewegingsprogramma's. Wij als hulpverleners zouden daarnaast veel energie moeten steken in het vergroten van de motivatie van onze COPD patiënten. Door patiënten continu te informeren over hun ziekte en mogelijkheden voor verbetering, kunnen we de behandeling zo individueel mogelijk maken, en deze afstemmen op hun behoeften.

DANKWOORD

Er zijn veel mensen die hebben bijgedragen aan de totstandkoming van dit proefschrift. In de eerste plaats wil ik alle patiënten bedanken die deelnamen aan de RECODE studie en die veel tijd en energie kwijt waren aan de afname van onze vragenlijsten. Daarnaast uiteraard alle huisartsen die mee hebben gedaan, en in de interventiegroep ook hun praktijkverpleegkundigen, fysiotherapeuten, diëtisten en longartsen die de nascholing wilden volgen en aan de slag gingen met de interventie: zonder jullie geen studie en daarom heel veel dank.

Mijn promotoren Pim, Maureen en Jacobijn: heel erg bedankt dat jullie mij gesteund hebben en de vrijheid hebben gegeven om het onderzoek te combineren met de opleiding. Dankzij jullie waardevolle input en inzichten heb ik veel geleerd. Niels, als copromotor en jouw eerste promovenda was ik verzekerd van een enorm goede begeleiding: jouw reactietijd is onvoorstelbaar, ik had mij geen betere copromotor kunnen wensen. Erg veel dank voor alle kansen, de gezellige avonden op congressen en de nodige dosis humor waarmee we alles konden relativeren.

Het RECODE team heeft drie jaar lang gezorgd dat onze studie een succes werd. Melinde, als mede-promovendus bij RECODE heb ik veel aan je gehad, vooral toen ik de opleiding deed. We vulden elkaar aan en ik heb het samenwerken erg gezellig gevonden, vooral tijdens de congressen! Apo, ik bewaar goede herinneringen aan het "bouwen van casefinders"; maar gelukkig hoeft het nooit meer. De onderzoeksmedewerkers en secretaresses Astrid, Aysun, Wilma, Wilma, Leolien, Anita, en in het bijzonder Irene: dank voor alle interviews en jullie tomeloze inzet. Ineke, bedankt voor je hulp aan het baseline paper. Het team van Zorgdraad en in het bijzonder Coert voor hun bijdrage aan de studie en het bouwen van de applicatie. Erwina, heel erg bedankt voor je hulp en inzet om bij half Den Haag een spirometrie test af te nemen.

Beste Nynke, met jou een Cochrane review schrijven was geweldig, heel veel dank voor alle gezellige uren en dat je me daar zo bij geholpen hebt.

Dear Sarah and Michael, thanks for giving me the opportunity to work with you in London, I learned a lot, thanks so much!

Alle collega's op de afdeling PHEG: veel dank voor hun betrokkenheid, en in het bijzonder mijn mede-promovendi/AIOTHO's Marjolein, Iris, Annelore, Krista, Antonette, Marije en Rosalinde met wie ik het laatste jaar een kamer heb gedeeld. Beste Anne, samen hebben we een lang traject gebikkeld (en we zijn nog niet klaar), het was fijn om dat met jou te delen. Mede HAIO's Willemijn, Mascha, Lysbert, Annejet, Muriël, Amy, Margot en Jisva: veel dank voor jullie interesse en de gezelligheid.

Ik ben de SBOH en de Huisartsopleiding Leiden erg dankbaar voor het volgen van een AIOTHO traject, en daarnaast Gerard Smit, mijn opleider in het eerste jaar die het mogelijk maakte om de opleiding en onderzoek succesvol te combineren.
Alle vriendinnetjes en in het bijzonder Cordial Bizar, HW4c en de meiden van Formula: veel dank voor de mooie avonden en weekenden. Lieve Dag en Suus, met jullie aan mijn zij als paranimf en mede-AGIKO's maakt het promoveren voor mij extra bijzonder en hopelijk wat meer ontspannen, alvast bedankt voor jullie hulp!
Mijn schoonfamilie was altijd enorm betrokken en geïnteresseerd, waar ik heel dankbaar voor ben. Lieve oma, ik ben erg blij dat je mijn promotie mag meemaken, deze studie zit er weer op! Lieve Fleur en Marc, ondanks dat we alle drie ander werk hebben wordt elk succes gevierd op de groepsapp, ik ben blij met zo'n lieve zus en broer die er altijd voor me zijn. Lieve mama, jouw steun en betrokkenheid is enorm, heel veel dank. Lieve pap, jij bent mijn grote voorbeeld, ik hoop dat ik later zo'n huisarts word als jij. Heel erg bedankt allebei dat jullie er altijd voor me zijn.
Lieve Wout, samen zijn, lekker kletsen en leuke dingen doen zijn de zaken die uiteindelijk het allerleukste zijn en waar ik heel veel van geniet. Ik hoop dat ons nog heel veel leuks met veel lachen staat te wachten!

CURRICULUM VITAE

Annemarije Kruis was born on January 31st, 1985 in Stolwijk, the Netherlands. After graduating her secondary school at Coornhert Gymnasium Gouda in 2003, she started studying medicine at the Leiden University Medical Centre. In 2007, she started a research elective for 6 months in Stellenbosch/Cape Town, South Africa at the department of Pediatrics. At the end of her study medicine in 2010, she went to Curaçao for a clinical elective at the department of Gynaecology in the St Elisabeth Hospital. In that same year, she graduated as MD cum laude, and started her PhD project at the department of Public Health and Primary Care of the Leiden University Medical Center (supervisors N.H. Chavannes, W.J.J. Assendelft, J. Gussekloo, M.P.M.H. Rutten-van Mölken). In 2011, she started the vocational training for general practitioner at the same department, in a combined vocational and research-training program. In the last year of her PhD trajectory, she worked for 3 months at the Department of Primary Care and Public Health of the Imperial College in London on a project on trends in asthma admissions (supervisor M. Soljak) and a project of the value of COPD multidisciplinary teams (supervisor S. Elkin). She will finish her vocational training in March 2016.

BIBLIOGRAPHY

Peer-reviewed publications in international journals

Kruis AL, Soljak M, Chavannes NH, Elkin SL. COPD multidisciplinary team meetings in the UK: health care professionals perceptions of aims and structure. *COPD: in press.*

Kruis AL, Boland MR, Assendelft WJJ, Gussekloo J, Tsiachristas A, Stijnen T, Sont JK, Rutten-van Mölken MP, Chavannes NH. Effectiveness of integrated disease management for primary care chronic obstructive pulmonary disease patients: restults of cluster randomised trial. *BMJ* 2014; 349:g5392.

Kruis AL, Ställberg B, Jones RCM, Tsiligianni IG, Lisspers K, van der Molen T, Kocks JWH, Chavannes NH. Primary care COPD patients compared to large COPD studies: an UNLOCK validation study. *PLoS One* 2014; 9(3):e90145.

Boland MR, Tsiachristas A, **Kruis AL**, Chavannes NH, Rutten-van Mölken MP. Are GOLD ABCD groups better associated with health status and costs than GOLD 1234 grades? A cross-sectional study. *Prim Care Respir J* 2014;23(1):30-7.

Kruis AL, van Schayck OC, in't Veen JC, van der Molen T, Chavannes NH. Successful patient self-management of COPD requires hands-on guidance. *Lancet Respir Med* 2013;1(9):670-2.

Kruis AL, Smidt N, Assendelft WJJ, Gussekloo J, Boland MR, Rutten-van Mölken M, Chavannes NH. Cochrane corner: is integrated disease management for patients with COPD effective? *Thorax 2014. doi: 10.1136/thoraxjnl-2013-20497*

Kruis AL, Smidt N, Assendelft WJJ, Gussekloo J, Boland MRS, Rutten-van Mölken MP, Chavannes NH. Integrated disease management interventions for patients with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2013;10:CD009437

Boland MR, Tsiachristas A, **Kruis AL**, Chavannes NH, Rutten-van Mölken MP. The health economic impact of disease management programs for COPD: a systematic literature review and meta-analysis. *BMC Pulm Med* 2013;13:40.

Kruis AL, Boland MR, Schoonvelde CH, Assendelft WJ, Rutten-van Mölken MP, Gussekloo J, Tsiachristas A, Chavannes NH. RECODE: design and baseline results of a cluster ran-

domized trial on cost-effectiveness of integrated COPD management in primary care. *BMC Pulm Med* 2013;23:13-17.

Kruis AL, Chavannes NH. A nurse-led multidisciplinary COPD programme: potential flaws in the results? *Prim Care Respir J* 2011 (4):357.

Kruis AL, Chavannes NH. Potential benefits of integrated COPD management in primary care. *Monaldi Arch Chest Dis* 2010;73(3):130-134.

Kruis AL, Adrichem van J, Erkelens MR, Scheepers H, Veen in 't H, Muris JWM, Chavannes NH. Sustained effects of integrated COPD management on health status and exercise capacity in primary care patients. *Int J Chron Obstruct Pulmon Dis* 2010;5:407–413.

DC Stefan, **AL Kruis**, HS Schaaf, G Wessels. Incidence of tuberculosis in oncology patients. *Ann Trop Paediatr* 2008; 28(2): 11-116.

PEER-REVIEWED PUBLICATIONS IN NATIONAL JOURNALS

Kruis AL, Chavannes NH. Geleidelijk stoppen met roken werkt ook. Huisarts en Wetenschap 2013;6:303.

Kruis AL, Boland MRS, Rutten-van Mölken MPMH, Chavannes NH. Welke klinische fenotypen zijn relevant voor de eerstelijnsbehandeling van COPD? Spreekuur 2013;4(3):1-2.

Kruis AL. Vitamine D tegen COPD-aanval? Huisarts en Wetenschap 2012;55(4):144.

Boland MRS, Tsiachristas A, **Kruis AL**, Chavannes NH, Rutten-van Mölken MPMH. Is disease management van COPD kosteneffectief? Spreekuur 2012;3(14).