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Long-term exercise maintenance via telerehabilitation for people with COPD

Feasibility, effectiveness, benefits and challenges

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Abbreviations

30s-STS	30 second Sit-To-Stand chair test
6MWD	6-Minutes Walking Distance
6MWT	6-Minutes Walk test
ACE	Acute COPD Exacerbation
ANOVA	Analysis of Variance
ATS	American Thoracic Society
BMI	Body Mass Index
CAT	COPD Assessment Test
CCQ	Clinical COPD Questionnaire
CHF	Chronic Heart Failure
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CRQ-D	Chronic Respiratory Questionnaire – Dyspnoea domain
ED	Emergency Department
EQ-5D	EuroQol 5-Dimension Questionnaire
EQ-VAS	EuroQoL Visual Analogue Scale
ERS	European Respiratory Society
ESWT	Endurance Shuttle Walk Test
FEV_1	Forced Expiratory Volume in one second
FTSST	Five Times Sit to Stand Test
FVC	Forced Vital Capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GP	General Practitioner
GSES	Generalised Self-Efficacy Scale
HADS	Hospital Anxiety and Depressions Scale
heiQ	Health Education Impact Questionnaire
HRQoL	Health Related Quality of Life
LIPA	Light Intensity Physical Activity
m	Meter
MAST	Model for Assessment of Telemedicine
MCID	Minimal Clinical Important Difference
MCTT	Maugeri Centre for Telehealth and Telecare
min	Minute
MLHFQ	Minnesota Living with Heart Failure Questionnaire
mMRC	modified Medical Research Council scale
MRC	Medical Research Council scale
MVPA	Moderate to Vigorous Physical Activity
PA	Physical activity
PASE	Physical Activity Profile
PGIC	Patient Global Impression of Change scale
PhD	Philosophiae Doctor
PR	Pulmonary rehabilitation
PRAISE	Pulmonary Rehabilitation Adaptive Index for Self-Efficacy
PT	Physiotherapist
QALY	Quality-Adjusted Life Year
RCT	Randomized Control Trial
SD	Standard Deviation
SF-36	Short Form 36-health survey
SGRQ	Saint George's Respiratory Questionnaire
TUG	Timed Up & Go test

List of papers

I. Zanaboni P, **Hoaas H**, Lien LA, Hjalmarsen A, and Wootton R. Long-term exercise maintenance in COPD via telerehabilitation: A two-year pilot study. J Telemed Telecare. 2016;0(0):1-9.

II. **Hoaas H**, Andreassen H, Lien L, Hjalmarsen A, and Zanaboni P. Adherence and factors affecting satisfaction in long-term telerehabilitation for patients with chronic obstructive pulmonary disease: a mixed methods study. BMC Med Inform Decis Mak. 2016;16(1):26.

III. **Hoaas H**, Morseth B, Holland AE, and Zanaboni P. Are Physical Activity and Benefits Maintained After Long-Term Telerehabilitation in COPD? International Journal of Telerehabilitation. 2016;8(2):39-48.

IV. Zanaboni P, Dinesen B, Hjalmarsen A, **Hoaas H**, Holland AE, Oliveira CC, and Wootton R. Long-term integrated telerehabilitation of COPD Patients: a multicentre randomised controlled trial (iTrain). BMC Pulm Med. 2016;16(1):126.

V. **Hoaas H**, Zanaboni P, Hjalmarsen A, Morseth B, Dinesen B, Burge A, Cox N, and Holland A. Seasonal variations in objectively assessed physical activity among patients with COPD in two Nordic countries and Australia: a cross-sectional study. International journal of chronic obstructive pulmonary disease [under revision].

Abstract

Background and aims: The availability of pulmonary rehabilitation (PR) and exercise maintenance programs for people with chronic obstructive pulmonary disease (COPD) is low, despite being beneficial and recommended. Telerehabilitation can support the delivery of such programs to patients' homes. However, there is little knowledge of its benefits for people with COPD. This thesis aimed to investigate feasibility, effectiveness, benefits and challenges of a long-term exercise maintenance program via telerehabilitation in COPD.

Methods: An innovative 2-year telerehabilitation intervention comprising of treadmill exercise at home, telemonitoring by a physiotherapist via videoconferencing, and self-management via a website was investigated in a pilot study and an international randomized control trial.

Results: No adverse events related to the intervention occurred. After one year, 6-minutes walking distance was improved. Physical capacity, lung capacity, symptom level, and quality of life were maintained over the long-term. Participants were satisfied with the intervention and found the technology user-friendly. Satisfaction was supported by experienced health benefits, increased self-efficacy and emotional safety.

Discussion and conclusions: Long-term exercise maintenance in COPD via telerehabilitation is safe and feasible. Results are encouraging and suggest that telerehabilitation can prevent deterioration in lung function, symptom burden and health-related quality of life, and maintain functional walking capacity over the long-term. Telerehabilitation can overcome geographical distance, provide specialist access in areas where this is not available, and provide regularity of follow-up by the same healthcare personnel over a longer period. Challenges included maintenance of motivation for exercise, and challenges with transport of equipment and teaching in how to use the technology in the participants' homes. Long-term telerehabilitation could be offered as an alternative or supplement to centre-based PR.

1 Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive lung disease that is characterised by airflow limitations and respiratory symptoms (Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2018). The disease contributes significantly to morbidity and mortality worldwide (World Health Organization, 2017). Pulmonary rehabilitation and exercise training are considered core components in the management of COPD and are recommended for all people with COPD (Spruit et al., 2013b, Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2018, Troosters, 2018). However, the availability of pulmonary rehabilitation and exercise maintenance programs is low and dropout rates are a high (Spruit et al., 2013b, Rochester et al., 2015, Troosters, 2018). The development of telerehabilitation interventions attempts to meet the need for increased applicability and accessibility of pulmonary rehabilitation in a cost-effective way (Vitacca and Holland, 2018, Clini et al., 2018b). Telerehabilitation is defined as the delivery of medical rehabilitation service at a distance, regardless of patients' geographical location, using electronic information and communication technologies (Rosen, 1999, International Organisation for Standardization, 2016 p.4). Telerehabilitation differs from telemonitoring, which only provides remote monitoring of patients. Telerehabilitation has the potential to deliver effective pulmonary rehabilitation and long-term exercise maintenance to people with COPD in their homes. There is still little evidence of the benefits of telerehabilitation for people with COPD (Spruit et al., 2013b). Previous studies reported promising results for telerehabilitation in COPD in regards of feasibility, safety, physical activity and health-related quality of life (Holland et al., 2013a, Tabak et al., 2014c, Burkow et al., 2013, Marquis et al., 2015, Paneroni et al., 2015). However, all interventions had a short-term duration. Long-term adherence of exercise routines are often difficult for those with COPD (Hellem et al., 2012), and new ways of extending short-term benefits of pulmonary rehabilitation are warranted (Spruit et al., 2013b). The overall aims of this thesis were to investigate and discuss feasibility, effectiveness, benefits and challenges of a long-term exercise maintenance program via telerehabilitation for people with COPD. These topics were addressed in the five papers presented in this thesis.

1.1 COPD: definition, diagnosis, and epidemiology

Chronic obstructive pulmonary disease (COPD) is a common and prevalent, not curable, yet preventable and treatable disease (Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2018). The disease is characterized by persistent respiratory symptoms and progressive expiratory airflow limitation due to airway and/or alveolar abnormalities that is usually caused by exposure to noxious particles or gases (Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2018). COPD is considered a complex, heterogeneous, multicomponent disease and disease severity is affected by exacerbations, extrapulmonary manifestations and comorbidities (Vanfleteren, 2018).

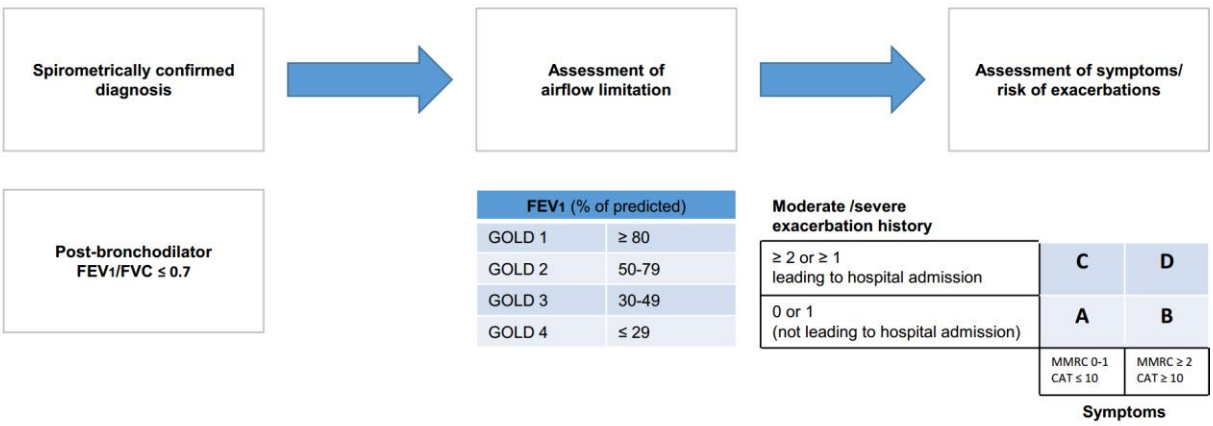
The diagnosis of COPD should be considered in any patient who experiences dyspnoea, chronic cough or sputum production, and/or a history of exposure to risk factors for the disease (Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2018, Celli et al., 2004). The diagnosis is confirmed by spirometry, and a presence of persistent airflow limitation is revealed with a post bronchodilator forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) ≤ 0.70. The severity of the disease increases with a reduction in FEV_1, and COPD is categorized into four stages according to the GOLD classification (Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2018) (Table 1).

Table 1 The GOLD classification of COPD

In patients with $FEV_1/FVC \leq 0.70$ post bronchodilator		
GOLD 1	Mild	$FEV_1 \geq 80\%$ predicted
GOLD 2	Moderate	$50\% \leq FEV_1 < 80\%$ predicted
GOLD 3	Severe	$30\% \leq FEV_1 \leq 50\%$ predicted
GOLD 4	Very severe	$FEV_1 < 30\%$ predicted

Based on increasing knowledge about COPD and its extrapulmonary effects, a new approach to the grading system was proposed with the ABCD assessment tool in 2011 (Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2018). Disease severity was determined by combining assessment of the patient’s level of symptoms with spirometric classification and/or risk of exacerbations. However, the ABCD assessment tool was not better in predicting mortality or other important health outcomes than the spirometric grading system (Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2018, Franssen and Han, 2013). A further refinement of the ABCD assessment tool was presented in the 2017 GOLD Report. Spirometric grades were separated from the ABCD groups (Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2018). In this revised version, spirometry should be used to determine the patient's severity of airflow limitation (four GOLD stages as the earlier GOLD classification). Then dyspnoea or symptoms should be assessed, using the modified Medical Research Council dyspnoea score (mMRC) or the COPD Assessment Test (CAT), respectively. In addition, history of moderate and severe exacerbations (including hospitalisations) should be recorded to evaluate future risk of exacerbation. Based on information regarding symptom burden and exacerbation risk, the patient is categorised into one of the ABCD groups. This refined approach acknowledges the limitations of spirometry alone for deciding treatment options on an individual patient level, and highlights the importance of perceived symptoms and risk of exacerbations in making treatment decisions. However, spirometry remains the main criterion for making a diagnosis of COPD (Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2018).

Figure 1 The ABCD assessment tool



FEV_1= Forced expiratory volume in one second. MMRC= Modified medical research council. CAT= COPD assessment test. Figure from the Global Initiative for Chronic Obstructive Lung Disease (GOLD) (2018).

Under-diagnosis of COPD is widespread and affects prevalence data (Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2018). According to the World Health

Organization (2017), 251 million people were suffering from COPD in 2016 worldwide, and 5% of all deaths globally were estimated to be caused by COPD in 2015. However, COPD is likely underestimated as cause of death (May and Li, 2015). Estimates from population studies suggests that 8% of Norwegians aged above 40 years have COPD. This is equivalent to at least 200 000 people (Leivseth et al., 2017). However a prevalence up to 350 000 Norwegians suffering from COPD has been reported (Gulsvik et al., 2012).

The most common symptoms for COPD are chronic and progressive dyspnoea, cough and sputum production. Symptoms vary from day-to-day, and may develop years before an airflow limitation is present (Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2018).

People with COPD experience frequent exacerbations, between one to four per year (Miravitlles et al., 2004). Exacerbation of COPD is defined as “an acute worsening of respiratory symptoms that results in additional therapy” and can occur in all grades of COPD (Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2018). Exacerbations are associated with a more rapid decline in lung function, particularly among those with mild COPD (Makris et al., 2007, Dransfield et al., 2017), reduced health-related quality of life (Roche et al., 2017), and increased risk of future exacerbations (Sadatsafavi et al., 2018). Exacerbations may lead to hospitalisations, but about half of the cases are unreported by patients, despite considerable encouragement to do so (Wedzicha and Donaldson, 2003). Prevention of severe exacerbations is important and has potential in modifying the disease trajectory (Sadatsafavi et al., 2018).

Systemic manifestations such as increased lung inflammation, which in turn is associated with low body mass index, skeletal muscle wasting and loss of fat free mass are common in COPD (Barnes and Celli, 2009, Sinden and Stockley, 2010). Systemic inflammation may lead to or worsen comorbidities such as ischaemic heart disease, heart failure, osteoporosis, anaemia, lung cancer, depression and diabetes (Barnes and Celli, 2009). People with COPD are prone to comorbidities (Vanfleteren et al., 2013), and have an average of seven comorbidities compared to three for other persons (Baty et al., 2013). Common comorbidities are lung cancer, cardiovascular diseases, osteoporosis, depression, anxiety, metabolic syndrome, diabetes, obstructive sleep apnoea, and gastroesophageal reflux.

Comorbidities contribute to the severity of disease in individual patients (Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2018).

A significant economic burden is associated with COPD (World Health Organization, 2017). Both maintenance treatment and treatment of acute exacerbations are associated with high healthcare costs (Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2018, May and Li, 2015). One COPD-related hospitalisation is estimated to £1807/ €2250/ NOK 20820 (Punekar et al., 2015). In the European Union, respiratory diseases are estimated to seize about 6% of the total healthcare budget, with COPD accounting for 56% of the cost of respiratory diseases (Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2018).

1.2 Exercise capacity limitations and effects of exercise in COPD

Reduced physical capacity, dyspnoea and (leg) fatigue are hallmarks of COPD and limits exercise capacity. Exercise capacity is reduced due to ventilatory and gas exchange limitations, cardiac and respiratory muscle dysfunction, reduced functions of skeletal muscles, or any combination of the above (Cooper and Storer, 2010, Spruit et al., 2013b). Muscle weakness in the skeletal muscles is common in COPD. This weakness is associated with reduced capillarisation and a shift from type I to type IIa fibres. Consequently, the muscles are more disposed to fatigue. Lactic acid production and metabolic acidosis is encountered at low workloads, which leads to an increase drive to breathe and dynamic hyperinflation that result in increased work of breathing (Romer, 2010). Even though the cause of exercise intolerance among those with COPD is multifactorial and related to disease severity, abnormal dynamic ventilatory mechanisms, especially dynamic hyperinflation, are believed to play a central role (Laveneziana et al., 2007, O'Donnell and Laveneziana, 2007). The term dynamic hyperinflation refers to the increase in end-expiratory lung volume and air trapping that occurs when airflow limitations prevent complete exhalation during exercise, hypoxia or anxiety. As a result, exhalation may not be completed prior to the onset of the next breath, causing progressive hyperinflation of the lungs. This air trapping causes the lungs to be slightly more inflated than normal, putting the diaphragm muscle at a mechanical disadvantage due to length-tension effect, which in turn decreases its function and increases the work of breathing. Dynamic hyperinflation is experienced as dyspnoea on exertion

(McCormack, 2017). People with COPD are less physically active than healthy age-matched controls (Pitta et al., 2005, Park et al., 2013). Inactivity leads to further physical deconditioning, increased ventilatory requirements and increased breathlessness (Cooper and Storer, 2010). Psychological conditions, such as anxiety, depression and poor motivation might also limit the ability to exercise in individuals with COPD (Spruit et al., 2013b).

Exercise can increase physical capacity, also for those affected by COPD (Cooper and Storer, 2010). Exercise does not improve lung function or gas exchange in this group of patients. The aim is rather to reverse the systemic consequences of the disease. Endurance training improves cardiovascular function through increased maximum oxygen uptake. Exercise also increases endurance (longer duration at same work load) and increases the ability to tolerate higher intensity of exercise due to reduced heart rate, lactate levels and ventilatory requirements on a given work load (Cooper and Storer, 2010, Casaburi and Zuwallack, 2009). Strength training of skeletal muscles contributes to an increase in muscle strength and endurance (Cooper and Storer, 2010). Other favourable exercise responses in the skeletal muscles are increased capillary density and type I (aerobic) muscle fibres. This increases oxygen extraction and decreases lactic acid production, thus reducing the ventilation requirements. As patients improve their physical capacity, less demands are made on the ventilation at a given work load and respiratory rate reduces, prolonging the time allowed for expiration and reducing dynamic hyperinflation, thsu reducing breathlessness (Casaburi and Zuwallack, 2009).

1.3 Pulmonary rehabilitation

1.3.1 Current concept of pulmonary rehabilitation

Definition

Pulmonary rehabilitation is an evidence-based treatment option for people with respiratory diseases and is recognised as a core component in the management of COPD (Troosters, 2018). The American Thoracic Society (ATS) and the European Respiratory Society (ERS) updated the definition of pulmonary rehabilitation in 2013 as following: *"Pulmonary rehabilitation is a comprehensive intervention based on a thorough patient assessment followed by patient tailored therapies that include, but are not limited to, exercise training, education, and behaviour change, designed to improve the physical and psychological* *condition of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviours."(Spruit et al., 2013b).*

For whom?

All patients with chronic respiratory disease might be eligible for pulmonary rehabilitation provided that there are clear clinical needs in terms of lack of physical capacity, symptoms or lack of physical activity (Spruit et al., 2013b, Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2018, Troosters, 2018). As pulmonary rehabilitation is considered an integral part in the management of COPD, it might be offered at any stage of the disease. There is evidence that both patients with less and more severe degree of airflow limitation might benefit (Spruit et al., 2013b). According to ATS/ERS recommendations, pulmonary rehabilitation should not be initiated during hospitalisation due to a COPD exacerbation, but rather initiated within 3 weeks following hospital discharge. Pulmonary rehabilitation shortly after discharge from a COPD exacerbation is associated with a reduction in readmissions and improved quality of life. However, these are conditional recommendations with very low quality of evidence, and should be reconsidered as new evidence becomes available (Wedzicha et al., 2017).

Goals and benefits

Based on thorough initial and ongoing assessment, the pulmonary rehabilitation program itself should be individualised and fitted to the clinical needs and goals of each patient (Spruit et al., 2013b, Singh, 2018, Nici, 2009). Nevertheless, the overarching goal is to minimise symptom burden, maximise exercise performance, promote autonomy, increase participation in everyday activities, enhance health-related quality of life, and support long-term health-enhancing behaviour change (Spruit et al., 2013b).

The benefits of pulmonary rehabilitation for people with COPD are substantial. Pulmonary rehabilitation has been proven to improve dyspnoea, health status and exercise tolerance in stable patients with COPD, and graded evidence level A (Celli and Goldstein, 2018). In addition, it reduces hospitalisation in patients with recent exacerbations ($\leq$4 weeks from prior hospitalization) (Evidence level B) (Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2018). With an estimated cost per quality-adjusted life year (QALY) of

£2000 – £8000, pulmonary rehabilitation ranks as one of the most cost-effective treatment strategies for people with COPD (Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2018). However, short-term benefits appear to diminish over the succeeding 6-12 months without any maintenance strategy (Spruit et al., 2013b).

Program components

Due to the complex nature of COPD, its multisystem manifestations, comorbidities, and frequent exacerbations, it is recommended that pulmonary rehabilitation is provided by a dedicated, interdisciplinary team consisting of physicians and other health professionals. The latter may include physiotherapists, respiratory therapists, nurses, psychologists, behavioural specialists, exercise physiologists, nutritionists, occupational therapists, and social workers (Spruit et al., 2013b).

Exercise and education aimed at supporting health behaviour change are the two core components of pulmonary rehabilitation (Desveaux et al., 2015, Burtin and Zuwallack, 2018). A variety of exercise training methods can be implemented to achieve improvements in cardiorespiratory endurance, strength and flexibility. These include endurance training, interval training, strength training, upper limb training, and transcutaneous neuromuscular electrical stimulation (Spruit et al., 2013b, Burtin and Zuwallack, 2018). Exercise training might be performed as outdoor walking with or without poles (Nordic walking), on a treadmill, stationary cycling, resistance training, aquatic exercises, group-based aerobic training and calisthenics. Moreover, a variety of training intensities and durations might be effective, depending on the specific patient deficits (Spruit et al., 2013a, Burtin and Zuwallack, 2018). Inspiratory muscle training may also be added to the program for motivated patients with COPD and impaired respiratory muscle function (Langer, 2018).

Pulmonary rehabilitation programs provide a good opportunity to deliver education and help people with COPD develop the skills and confidence they need to adopt a healthier lifestyle. Traditionally, education was provided as information and advice, assuming that knowledge would lead to behaviour change. However, patients often failed to adopt or maintain new behaviours. Today, it is recommended to integrate collaborative self-management skills by targeting not only knowledge, but also motivation to engage in behaviour change. Features supporting self- management include: involving the patient in decision making, assessment of the unique needs and barriers for the individual patient, agreement of goals, enhancing skills, problem solving, follow-up and support, and increasing access to resources (Bourbeau et al., 2018). Other components of the program might be nutrition, occupational therapy, guidance on disease management skills including medication management and smoking cessation, physical activity coaching, and breathing exercises and mucus clearance techniques (Spruit et al., 2013a, Clini et al., 2018a).

Organisation

Pulmonary rehabilitation programs can be organised successfully in several locations (Troosters et al., 2014, Rochester and Clini, 2018). Outpatient programs where patients visit hospital outpatient departments, community facilities or physiotherapy clinics, two to three times per week for a duration of 6 to 12 weeks, are the most common settings. Inpatient rehabilitation can be offered in hospitals or specialised rehabilitation centres where patients participate in to the program up to 6 days per week for 2 to 4 weeks (Spruit et al., 2013a, Rochester and Clini, 2018). More recently, pulmonary rehabilitation delivered in a home-based setting has shown similar effects as centre-based pulmonary rehabilitation (Holland et al., 2017). In addition, a variety of telerehabilitation interventions can be used to deliver pulmonary rehabilitation successfully. However, home-based pulmonary rehabilitation and telerehabilitation is not widely used in clinical practice and mostly been conducted in the context of clinical trials (Rochester and Clini, 2018). The updated knowledge related to telerehabilitation is extensively discussed in detail in paragraph 1.4.

1.3.2 Challenges of conventional centre-based pulmonary rehabilitation

As described in a previous paragraph, pulmonary rehabilitation has an evidence level "A" (Celli and Goldstein, 2018). Nevertheless, there are still some challenges to be met. Telerehabilitation and new technologies may be viable solutions to face some of these challenges (Donner et al., 2018, Clini et al., 2018b).

Applicability, scope and accessibility

Researchers underlines the need to increase the applicability, scope and accessibility of pulmonary rehabilitation programs in the future (Clini et al., 2018b). The number of suitable patients participating in pulmonary rehabilitation is surprisingly and strikingly low (Rochester et al., 2015, Keating et al., 2011). First, there is a large variation in referral rates to pulmonary rehabilitation, ranging from 0% to 85%. The most common barriers to referral among physicians seems to be the low knowledge of the content and benefits of pulmonary rehabilitation, and the referral process (Milner et al., 2018). Second, up to half of referred patients does not attend at all. Identified barriers for participation are disruption to established routines, travel and transportation difficulties, lack of encouragement from the participant's physician, lack of perceived benefit and inconvenient timing of the program (Keating et al., 2011). Methods and programs to increase the number of patients assessing pulmonary rehabilitation, including those living in remote areas, are encouraged (Clini et al., 2018b). Another future target is to offer pulmonary rehabilitation in a larger scale, including also those patients affected by milder disease, comorbidities, exacerbations, critical illness, and other "non-COPD" chronic respiratory diseases (Clini et al., 2018b). Available resources and availability of pulmonary rehabilitation programs vary across different healthcare settings (Spruit et al., 2013b, NHS Right Care, 2012). A Canadian study found that only 1.2% of the COPD population had access to pulmonary rehabilitation programs (Brooks et al., 2007). In Sweden, the availability of pulmonary rehabilitation programs also is reported to be low. Pulmonary rehabilitation was not available to people with COPD in 24% of all primary care centres (Arne et al., 2016). A systematic review found that less than 1.2% of individuals with COPD had access to pulmonary services on an international basis (Desveaux et al., 2015). The ATS/ERS has acknowledged the need to increase availability of pulmonary rehabilitation (Spruit et al., 2013b).

Dropout and adherence

For patients who attend pulmonary rehabilitation programs, dropout and lack of adherence to the program and to long-term health-enhancing behaviour after the program are a known challenge (Spruit et al., 2013b, Rochester et al., 2015, Hayton et al., 2013). Dropout rates vary between studies, ranging from 10-32% (Spruit et al., 2013b). A study investigating attendance and adherence among people with COPD attending pulmonary rehabilitation found that 29%

of the participants completed less than 2/3 of the sessions. The study concluded that age, smoking status, availability of social support, travel distance, and markers of disease severity, use of long-term oxygen therapy in particular, were strong predictors of attendance and adherence to pulmonary rehabilitation (Hayton et al., 2013). A qualitative study exploring perspectives related to adherence to pulmonary rehabilitation among of people with COPD suggested that adherence could be enhanced by building confidence in the patient, fostering tangible results, and recognising and responding to the patient readiness and access issues (Guo and Bruce, 2014). To improve adherence and increase benefits, a report from a recent international workshop emphasised the need for improving delivery and outcome assessment of the education component of pulmonary rehabilitation (Blackstock et al., 2018).

Maintenance of long-term benefits

Benefits of pulmonary rehabilitation appear to wean off over 6-12 months without any maintenance strategy (Spruit et al., 2013b, Spruit and Singh, 2013). The decline in health status may partially reflect disease progression or exacerbations but, at large, it is probably due to a drop-off in adherence to exercise prescription, and the optimal maintenance intervention to sustain benefits still remains unknown (Spruit and Singh, 2013, Brooks et al., 2002, Griffiths et al., 2000). Ongoing encouragement after pulmonary rehabilitation by more frequent contact with health professionals through visits to the institution and by telephone contact does not appear to be enough to avoid the decline in health status (Brooks et al., 2002). Even among those patients who initiate a formal post-rehabilitation maintenance program, the dropout rate is reported to be 36.7% one year after completing pulmonary rehabilitation (Heerema-Poelman et al., 2013).

Physical inactivity among people with COPD

People with COPD are less physically active than healthy age-matched controls (Pitta et al., 2005, Park et al., 2013), and physical inactivity and sedentary behaviour are associated with an increased risk of all-cause mortality in this group (Troosters et al., 2013, Watz et al., 2014, Waschki et al., 2011, Furlanetto et al., 2017). Inactivity is also thought to lead to a more rapid progression of the disease and the development of comorbidities in these individuals (Troosters et al., 2013, Van Remoortel et al., 2013, Watz et al., 2014, Waschki et al., 2011).

Improving physical activity levels during and after pulmonary rehabilitation is a challenge (Burtin et al., 2015, Cindy Ng et al., 2012), and studies are aiming to test behaviour-targeted interventions for improving physical activity (Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2018). A recent review concluded that the addition of physical activity counselling to exercise training in pulmonary rehabilitation is beneficial in increasing physical activity (Lahham et al., 2016).

Individualising and tailoring of pulmonary rehabilitation

Professionals in the field have suggested a more personalised approach to refine pulmonary rehabilitation to target the unique needs of the complex and individual patient. One size does not seem to fit all in the vast and heterogeneous population of people with COPD. (Ambrosino and Clini, 2015, Spruit et al., 2013b, Vanfleteren et al., 2017). To accomplish this, the patient should be involved in decision making, evaluation of his goals and needs, as well as making priorities for follow-up in a coordinated way (Vanfleteren et al., 2017). It is important to identify the right patient to the right rehabilitation program. A study including 2068 patients with COPD identified groups of patients with a very good, good, moderate or poor response to the pulmonary rehabilitation program. Ongoing pulmonary rehabilitation programs may need to be redesigned to better fit the poor responders (Spruit et al., 2015).

1.3.3 Pulmonary rehabilitation in Norway

There is a large variation in where and how pulmonary rehabilitation programs are organized in Norway. Most programs are offered by the specialist health service, like hospitals or private rehabilitation centres. In 2015, 75% of people with COPD receiving pulmonary rehabilitation was enrolled in a program offered by a public funded hospital. However, pulmonary rehabilitation is also offered by some primary care services, which represents a recent political goal (Leivseth et al., 2017).

Pulmonary rehabilitation is provided in form of both inpatient programs and outpatient programs. Geographical conditions often make inpatient programs the only choice for patients living in remote areas, while outpatient programs are offered mostly to patients living close to a rehabilitation centre or hospital. Group-based programs are most utilised (Hjalmarsen, 2012 p. 66).

Specialist competence and availability of pulmonary rehabilitation programs is lower in Norway than in England and the Netherlands. Often only patients with a severe degree of COPD are offered a rehabilitation program (Askvik, 2015). In 2015, about 2500 Norwegians with COPD participated in pulmonary rehabilitation (of whom, 1343 women and 1181 men). Four out of five were aged 60 years or older (Leivseth et al., 2017). There was a considerable geographical variation in the number of people enrolled in pulmonary rehabilitation across the country, and there seems to be an unwarranted variation in the service (Leivseth et al., 2017). Moreover, people with COPD does not receive enough information about pulmonary rehabilitation and its benefits (Nasjonalt servicemiljø for medisinske kvalitetsregistre, 2017).

The Norwegian Heart and Lung Association offers group-based exercise maintenance programs led by volunteers across the country (Landsforeningen for hjerte- og lungesyke). However, the availability of maintenance programs after rehabilitation is low, especially in the remote areas and Northern Norway.

1.4 Telerehabilitation

The term telerehabilitation is relative new, but is an important subdiscipline of telemedicine (Brienza and McCue, 2013). Telerehabilitation involves clinical rehabilitation through information and communication technology, regardless of the patient’s geographical location (Rosen, 1999). Telerehabilitation differs from telemonitoring, which refers to monitoring of patients at a distance using information technology. Initially, the focus of telerehabilitation was to mimic real-time face-to-face interactivity in a telesetting, typically by video conferencing. However, advancements in technology now make it possible to initiate new types of interventions (Brienza and McCue, 2013). Examples are programs provided by web-based platforms, peer-group support through web-based network (Donner et al., 2018), pre-filmed videos (Burkow et al., 2015, Burkow et al., 2013), interactive group sessions (Cox et al., 2018a, Hansen et al., 2017), exergames, serious games and gamification (Brox et al., 2011, Brox et al., 2017, Tabak et al., 2015), and virtual reality (Wardini et al., 2013). Further, monitoring of health parameters and/or physical activity through direct feedback via mobile apps (Lunde et al., 2018), Internet and mobile-based interventions (Antypas and Wangberg, 2014b) or activity armbands (Tabak et al., 2014b) has the potential to foster increased physical activity in home dwelling patients. Costs may be reduced and effectiveness may be improved compared with conventional in-person rehabilitation, especially for prolonged interventions for people with chronic conditions (Brienza and McCue, 2013). In addition to increase accessibility in both remote areas and urban settings, telerehabilitation holds a potential to provide effective rehabilitation in the patient's natural environment. Brienza and McCue (2013) provided evidence that suggests that rehabilitation services can be more effective when they are provided in the natural environment where the client lives, works, and/or interacts socially and recreationally rather than in a clinical environment. Others have also advocated that telerehabilitation in the home may contribute to long-term adoption of healthy behaviours (Donner et al., 2018). Other pros for telerehabilitation suggested by a recent interdisciplinary workshop with health experts in the field of pulmonary rehabilitation are summarised in table 2.

Table 2 Pros for telerehabilitation for the individual patient

• Access to rehabilitation service regardless of location and time of the day
• Access to regularly updated standardised information and education material so the patient can learn in his own pace
• Access to specialised healthcare professionals
• Access to advice to share with partners and caregivers
• Content can be customised to individual needs

Table from Donner et al. (2018).

1.4.1 Telerehabilitation interventions for people with COPD

The knowledge base on telerehabilitation has moved forward since our research group started to plan, design and test a pilot intervention in 2011 (Zanaboni et al., 2016b), and since the start of this PhD work in February 2014. In order to provide an up-to-date state of knowledge, structured literature searches were performed during Summer 2018. The last search was performed on 29th August 2018. Literature published after this date is not discussed in this thesis. Searches were performed in PubMed, Embase, and Cochrane Central Register of Controlled Trials. Search terms were "telerehabilitation" or "internet" or "e-health" or "video conference" and "chronic obstructive pulmonary disease" and "pulmonary rehabilitation". Reference lists of the retained articles were also screened to identify studies that were not originally captured in the electronic database searches.

From the literature searches 3 systematic reviews, 1 study protocol for a systematic review (Cox et al., 2018b), 8 published randomised controlled trials (RCT), 7 intervention studies on telerehabilitation, and 3 study protocols for RCTs were found. In addition, one upcoming Danish RCT investigating the feasibility and effect of a follow-up telerehabilitation program for COPD against standard follow-up was identified from ClinicalTrials.gov (Identifier: NCT03443817). Finally, 4 qualitative or mixed-methods studies were found. Details of the study protocols, RCTs, intervention studies, mixed method studies and qualitative studies are summarised in table 3, 4, 5 and 6, respectively. Study protocols that were followed by articles reporting the main results, were not reported in table 3, but in table 4. Studies involving telemonitoring alone, self-management alone, and interventions promoting physical activity alone were not included. Studies delivering telerehabilitation in community-based centres or inpatient facilities and not in the individuals homes were also excluded. Studies whose results were only published in conference proceedings were not covered.

A systematic review by Lundell et al. (2015) showed that telemedicine may lead to increased physical activity level for people with COPD, but no beneficial effect was found on exercise capacity and dyspnoea. However, the majority of the studies included consisted of simple interventions and results should be considered with cation given a heterogeneity among the studies. Another systematic review by Chan et al. (2016) compared exercise telemonitoring and telerehabilitation with conventional cardiac and pulmonary rehabilitation. However, only one study on pulmonary rehabilitation was included in this review (Paneroni et al., 2015). Consequently, more studies comparing telerehabilitation for patients with COPD with usual care need to be conducted (Chan et al., 2016). Another systematic review by Almojaibel (2016) including seven studies provided a narrative synthesis of the use of video components to provide real-time interactive pulmonary rehabilitation at home for people with COPD. Although this review included pilot studies with small sample sizes and without a control group, findings suggested that the provision of pulmonary rehabilitation via specially designed or commercially available telecommunication equipment is feasible, well-accepted by the participants, and safe. Telerehabilitation was associated with positive clinical outcomes including improvements in exercise capacity, quality of life, dyspnoea level, and sense of social support (Almojaibel, 2016). A recent review by Bairapareddy et al. (2018), attempted to review the evidence behind telerehabilitation to inspire healthcare personnel and decisions makers in India to test telerehabilitation for people with COPD. Twelve studies with different study designs, most of them with small sample sizes and only three RCTs were included. Eight of the studies comprised supervised exercise training via video conferencing. Authors concluded that telerehabilitation was effective in improving dyspnoea, functional work capacity, and quality of life in people with COPD (Bairapareddy et al., 2018).

Table 3 Protocols on randomized controlled trials on telerehabilitation for people with COPD

Author	n	Intervention	Comparison	Timeframe	Measurement points	Outcomes
Zanaboni et al. (2016a)	120	Remotely supervised exercise training via iPad and video conferencing software, comprising treadmill training ≥30 min and strength exercises 3-5 sessions per week in the home. Intensity and mode (interval or continuous training) is adjusted individually depending in the patient's condition. Telemonitoring by pulse oximeter. Website with training diary, symptom diary, and individual goal setting. Individual follow-up.	1) Individualised unsupervised training program on a treadmill at home performed as described to the telerehabilitation group. Training sessions to be recorded on a paper-based diary. 2) Standard care.	2 years, at least one weekly follow-up in the first 8 weeks, and at least 1 monthly follow-up in the following period.	Baseline, 6 months, 1 year and 2 years.	Hospitalisations, ED presentations, mortality, time free from first event, health status, quality of life, anxiety and depression, self-efficacy, subjective impression of overall change, physical performance, level of physical activity, cost-effectiveness, and experiences in telerehabilitation.
Hansen et al. (2017)	134	Remotely supervised exercise training via web camera and computers in groups of 4-8, comprising 35 min exercise and 25 min patient education in the home.	Standard outpatient group-based PR comprising 60 min exercise 2 times/week and 60-90 min patient education 1 time/week.	10 weeks, 3 weekly follow-ups.	Baseline, end of intervention, and 3, 6 and 12 months post-intervention.	Endurance and walking capacity, lower extremity muscle strength, health status and symptoms, quality of life, anxiety and depression, level of physical activity, and health economic analysis.
Cox et al. (2018a)	142	Remotely supervised exercise training via iPad and video conferencing software in groups of 4-6, comprising 30 min stationary cycling and/or walking + strength training in the home. Telemonitoring by pulse oximeter. Individualised education and self-management training. Home exercise program 3 times/week documented in a diary. After 8 weeks: supervised exercise maintenance program.	Standard outpatient group-based PR, comprising 30 min aerobic training and strength training. Groups of 8-12. Individualised education and self-management training. Home exercise program 3/week to be documented in diary. After 8 weeks: supervised exercise maintenance program.	8 weeks, 2 weekly follow-up.	Baseline, end of intervention and 12 months post-intervention.	Change in dyspnoea score, endurance and walking capacity, level of physical activity, quality of life, self-efficacy, anxiety and depression, adherence, and health economic analysis.

PR: Pulmonary rehabilitation.

Table 4 Randomized controlled trials on telerehabilitation for people with COPD

Author	n	Intervention	Comparison	Timeframe	Results
Bernocchi et al. (2018)	112	Telemonitoring of vital signs with pulse oximeter and electrocardiograph in older patients with combined COPD and CHF. Unsupervised personalised exercise program with minimum of 45-55 min on a mini-ergometer and callisthenics 3/week + free walking 2/week. Weekly telephone call from nurse and PT.	*Standard care including medications and oxygen prescriptions, visit from GP, and in-hospital check-ups on demand.	4 months, 2 weekly follow up (once by nurse, once by PT)	Significant improvement in 6MWD, time to hospitalisation/death, MRC, PASE, Barthel, MLHFQ, CAT compared to control after 4 months of interventions * Benefits were maintained at 2 months post intervention for all outcomes.
Bourne et al. (2017)	90	6-week online program called myPR comprising educational videos and exercise videos that consisted of 10 exercises. For each week the length of each of the 10 exercises increased by 30 seconds, starting from 60 seconds the first week. Patients were instructed to access myPR at least twice and up to 5/week.	Standard outpatient group-based PR comprising educational sessions and 10 exercise stations, which were identical to the exercises carried out by the patients using myPR.	6 week, 2 weekly sessions + 3 additional weekly exercise sessions at home.	No difference was seen in 6MWD and CAT score between groups. Non-inferiority was demonstrated between the impacts of online and conventional PR on clinical scores for breathlessness or HRQoL between groups.
Vasilopoulou et al. (2017)	147	Following completion of an initial 2-month conventional PR program, a 12-month home-based maintenance telerehabilitation was provided. The program comprised an individualised action plan, exercise training (video on tablet computer demonstrating arm and leg exercises and walking drills), access to a call centre 5 days/week, psychological support, and dietary and self-management advice via weekly contact with personnel from an interdisciplinary team through phone or video conference. Telemonitoring by spirometry and pulse oximeter.	1) 12-months hospital-based outpatient maintenance rehabilitation program twice weekly including exercise training, physiotherapy, dietary and psychological advice. 96 sessions. 2) 12-months usual care treatment without initial PR.	12 months, 144 sessions in total.	Both maintenance telerehabilitation and hospital-based PR were independent predictors of a lower risk for ACE and hospitalisations. In addition, these groups improved functional work capacity and HRQoL from baseline to 12 months. Only maintenance telerehabilitation was an independent predictor of ED visits.
Chaplin et al. (2017)	103	Web-based PR program including individualised webpage with personalised action plan for managing exacerbations, goalsetting, educational content, and home exercise program consisting of daily walking and strength training to be reported	Conventional PR, 7 weeks (4 weeks supervised/3 weeks unsupervised), twice weekly, 2 hourly sessions (1 hour for exercise training consisting of walking and strength training and	6-8 weeks	Significant improvements in ESWT and CRQ-D form baseline in both groups. No significant differences between groups in any outcome. Dropout rates were higher in the web-based program (57% vs 23%).

		at website. Weekly contact by phone or email with healthcare personnel. Motivational interviewing techniques were used.	1 hour for education in topics including medication, relaxation skills, chest clearance etc.)		
Tsai et al. (2017)	37	Remotely supervised exercise training via laptop computer with an in-built camera in groups up to 4, comprising lower limb cycle ergometer, walking training for a total of 40-55 min and lower limb strengthening exercises (sit to stand and squats), 3 times/week.	Usual care consisting of usual medical management including optimal pharmacological intervention and provision of an action plan. This group did not participate in any exercise training. No education component in either groups.	8 weeks	Significant improvements in ESWT and self-efficacy, and a trend towards improvement in HRQoL when compared with control.
Paneroni et al. (2015) (Controlled clinical trial)	36	Interactive television monitor and remote control system called the IGEA-SAT platform, comprising strength exercises for 40 min, stretching/relaxation for 20 min, cycle ergometer training for 40 min 6 times/week, and an educational component. Diary to report dyspnoea, leg fatigue sensation and 02 saturation before and after exercise. Follow-up by physiotherapist by phone or video conference.	Retrospectively matched group who had undertaken centre-based conventional PR similar to the telerehabilitation program.	28 sessions (in maximum period of 40 days)	No difference in 6MWD, MRC and SGRQ compared to control. Telerehabilitation was well accepted by the participants.
Tabak et al. (2014c)	34	Physical activity coach by smart phone for ambulant activity registration and real-time feedback, complemented by a web portal with a daily symptom diary.	Usual care (no PR).	4 weeks	No difference in physical activity levels compared to control. A non-significant improvement for health status was found between groups. Activity coach was wore more than prescribed.
Tabak et al. (2014a)	29	Telerehabilitation program consisting on an activity coach for ambulant activity monitoring and real-time coaching of daily activity behaviour, web-based exercise program for home exercise (endurance and strength training, mobilisation, relaxation, breathing exercises and mucus clearance), self-management of COPD exacerbations via a triage diary on the web portal, and teleconsultations.	Usual care (contact with medical doctor as usual and attend physiotherapy sessions if this was prescribed as part of the usual care).	9 months	Participants were satisfied with the program. The self-management module was highly used, while use of the exercise module was critically low. No significant improvements in exercise capacity or HRQoL in neither groups, or in between group differences in hospitalisations.

CHF: Chronic heart failure. PT: Physiotherapist. GP: General practitioner. PR= Pulmonary rehabilitation. 6MWD: six minutes walking distance. MRC: Medical research council scale. MMRC= the modified medical research council scale PASE: physical activity profile. Barthel: The Bartel index of activities of daily living. MLHFQ: the Minnesota living with heart failure questionnaire. CAT: the COPD assessment test. HRQoL= Health related quality of life. ACE= Acute COPD exacerbations. ED= Emergency department. CRQ-D= Chronic Respiratory disease Questionnaire -Dyspnea domain. ESWT= Endurance shuttle walk test. SGRQ= the Saint George's respiratory questionnaire. CCQ= Clinical COPD Questionnaire.

Table 5 Intervention studies on telerehabilitation for people with COPD

Author	n	Intervention	Timeframe	Results
Zanaboni et al. (2016b)	10	One weekly individual supervised exercise training via iPad and video conferencing software, comprising interval training on a treadmill ≥30 min and strength exercises in the home. Recommended unsupervised training additionally 2 times per week. Telemonitoring by pulse oximeter. Website with training- and symptom diary.	2 years	No dropouts. Improvements in 6MWD, CAT, and EQ-5D after one year. After two years, the different outcomes were in line with baseline. Patients succeeded in maintaining exercise over 2 years.
Hoaas et al. (2016b)	9	Participants participating in the study of Zanaboni et al. (2016b) described above was reassessed after 1 year post intervention. After the intervention period, participants kept all equipment for exercise training on a treadmill, self-monitoring with a pulse oximeter and access to a web-based diary for reporting symptoms and exercise training. No other maintenance strategy was provided.	1 year	Physical activity levels and adherence to registration of symptoms and training sessions in the web based diary decreased significantly. Other outcomes including health status, quality of life, anxiety and depression, self-efficacy, and healthcare utilization did not change significantly.
Marquis et al. (2015)	26	Remotely supervised exercise training via video conferencing, comprising endurance exercise on a stationary bike lasting 10-40 min 3/week and strengthening exercises with weights and rubber bands. Sessions were supervised three times during Weeks 1 and 2, two during Weeks 3–5, and one during Weeks 6–8. Telemonitoring by pulse oximeter and heart rate sensor. Self-managements education comprising written pamphlets and PowerPoint presentation on computer every week.	8 weeks	Significant improvements in 6MWD, cycle endurance test time and CRQ from baseline to post-intervention. Users were very satisfied with the program and adherence was high.
Minet et al. (2015)	50	Remotely supervised exercise training via a video conferencing system called the “Patient Briefcase” early after hospitalisation three times per week 30-45 min each time, comprising thorax mobilisation exercises, walking on the sport, seated exercises and strengthening exercises etc, and up to two sessions of supervised counselling in energy conservation	3 weeks	74% completed the program. Significant improvements in TUG, FTSST and CCQ.
Holland et al. (2013a)	8	Remotely supervised exercise training via video conference software on a stationary bicycle for 30 min twice a week in groups of 2. Telemonitoring by pulse oximeter. Informal discussions about aspects of self-management of COPD.	8 weeks	Participants attended 76% of possible sessions. No significant adverse events. Three participants did not complete the program due to exacerbation of COPD (2) and unstable diabetes (1). Clinically significant improvements in 6MWD, CRQ dyspnea and CRQ fatigue in participants completing the program.
Tousignant et al. (2012)	3	Remotely supervised exercise training via video conference on a stationary bicycle for 10-45 min and strengthening exercises, 3/week. Supervision was	8 weeks	Clinically significant improvements in 6MWD for 2 of the 3 participants. All participants improved the scores on the CRQ.

		gradually decreased to be replaced by unsupervised exercise training. Telemonitoring by pulse oximetry.		
Marquis et al. (2014)	23	Participants participating in the study of Marquis et al (2015) described above was reassessed after 24 weeks post intervention. After the intervention period, the stationary bicycle was removed from the home, but participants kept the exercise program and written pamphlets on self-management. No formal maintenance strategy was provided. Participants were simply encouraged to buy their own stationary bicycle, continue their programs.	6 months	Improvements in exercise tolerance and quality of life obtained in the previous/before going intervention, decreased significantly after 6 months without any maintenance strategy provided.

COPD= Chronic obstructive pulmonary disease. 6MWD: six minutes walking distance. CAT: the COPD assessment test. EQ-5D: EuroQol 5-Dimension Questionnaire. CRQ= Chronic respiratory disease questionnaire. TUG : Timed up & go test,. FTSST: The five times sit to stand test. CCQ: the Clinical COPD questionnaire.

Table 6 Qualitative studies or mixed method studies on patients with COPD perspective on telerehabilitation

Author	n	Intervention	Timeframe	Results
Burkow et al. (2013)	5	Multidisciplinary led group-based PR program in the home of the patients. Delivered via patients' own television connected to a computer and a remote control. Program included pre-filmed education videos and follow-along exercising videos, weekly educational sessions and supervised exercising in groups (30 min) via videoconferencing, a health diary for reporting daily symptoms and sensor data (oxygen saturation, heart beat), and weekly individual consultations.	6 weeks	Individual semi-structured interviews indicated that the home PR program were acceptable and positively received by the participants. The group setting at home gave the participants a possibility to share experience and to learn from questions raised by others. The participants valued the socially supportive environment facilitated by multiparty videoconferencing. The individual consultations were well perceived, but the need to discuss personal health issues varied among the participants.
Burkow et al. (2015)	10	Multidisciplinary led, PR program delivered via the participants TV connected to a small computer with internet connection, headset and remote control to navigate in menus and enter data. Exercise training twice each week lasting 30 min and weekly self-management education lasting 60 min in groups of 5, additional training via online follow-along exercise video, educational videos, and individual online consultations. Digital health diary for reporting daily symptoms, pulse oximetry and step counts.	9 week	Multidisciplinary PR delivered in online groups may be feasible for patients with different severity levels of COPD. The program supported learning from both healthcare personnel and peers, for group exercising and for social support. High usability of the technology. Significant improvements in HRQoL. The cost per patient of the home rehabilitation programme was lower than the reimbursement rate for outpatient rehabilitation.
Tsai et al. (2016)	19	Remotely supervised exercise training via real-time video conferencing in groups up to 4, comprising 60 min cycling on a stationary cycle ergometer, strengthening exercises for lower limbs, and ground-based walking training within their home.	8 weeks, 3 weekly sessions	Key themes emerged from semi-structured interviews (n=11) were: positive virtual interaction through technology; use of equipment; convenience; and health benefits. Participants were highly satisfied with the program. In addition, participants' partners reported a high level of satisfaction with the program.
Hoaas et al. (2016a)	10	Weekly individual supervised exercise training via video conferencing as described in Zanaboni et al. (2016b) in table 5 above. Telemonitoring via pulse oximeter, and access to web-based diary for reporting exercise performance and daily symptoms.	2 years	Participants registered 3.0 symptom reports/week and 1.7 training sessions/week in the diary. Adherence rate decreased during the second year. Four major themes regarding factors affecting satisfaction, adherence and potential improvements of the intervention emerged from two focus group interviews: (i) experienced health benefits; (ii) increased self-efficacy and independence; and (iii) emotional safety due to regular meetings and access to special competence; (iv) maintenance of motivation. Participants were highly satisfied with the technical components.

PR= Pulmonary rehabilitation. COPD= Chronic obstructive pulmonary disease.

1.5 Aims and objectives

The overall purpose of our research was to increase access to pulmonary rehabilitation and support long-term maintenance of exercise through telerehabilitation. Such needs were especially relevant for Arctic regions, characterised by remote and scattered populations, harsh winters and long travel distances to healthcare facilities. Northern Norway thus represented an attractive setting for research in telerehabilitation. Adherence to long-term regular exercise is often difficult for people with COPD (Hellem et al., 2012) and developing new ways to prolong the benefits obtained from pulmonary rehabilitation is an important goal (Spruit et al., 2013b).

The main objective of this thesis was to investigate the feasibility, clinical effects, adherence, benefits and challenges of providing long-term exercise maintenance to people with COPD in their homes via telerehabilitation. To achieve this, we evaluated the feasibility and effects of a two-year pilot study on a long-term exercise maintenance program provided via telerehabilitation. We also evaluated the adherence to this program and explored participants' perspectives. After completing this pilot study, the participants kept the equipment, but were no longer supervised via telerehabilitation. Participants were reassessed at the end of the post-intervention year to evaluate if adherence to self-management and home exercise routines would decline. An international, multicentre RCT was then designed to compare long-term telerehabilitation with unsupervised exercise training at home and with standard care. One hundred and twenty people with COPD from Norway, Denmark and Australia were randomly assigned to telerehabilitation, unsupervised treadmill exercise training at home or control, and followed up for two years. We also wanted to investigate whether there were differences in physical activity levels among the participants across the three different countries, and establish if any variations in physical activity would be attributable to seasonal variations. Understanding such variations across countries can assist the interpretation of data from international multicentre RCTs.

The specific objectives of this theses were addressed in five scientific papers.

Paper I

- To investigate feasibility, long-term exercise maintenance, clinical effects, quality of life and use of hospital resources of a two-year telerehabilitation intervention tested in a pilot study with ten people with COPD.

Paper II

- To investigate the adherence to a two-year telerehabilitation intervention tested in a pilot study with ten people with COPD.
- To identify the main factors affecting satisfaction and adherence to the long-term telerehabilitation intervention for people with COPD.
- To identify potential factors that might increase adherence.

Paper III

- To investigate if the benefits achieved after a two-year of telerehabilitation intervention for people with COPD would deteriorate in the post-intervention year with access to exercise equipment but without supervision via telerehabilitation.

Paper IV

- To compare long-term telerehabilitation comprising exercise training at home, telemonitoring, and self-management designed for people with COPD with unsupervised exercise training at home on a treadmill, and with standard care (Study protocol).

Paper V

- To investigate potential differences in physical activity levels between Norwegian, Danish and Australian people with COPD.
- To establish if potential variations in physical activity levels were attributable to seasons.

2 Materials and methods

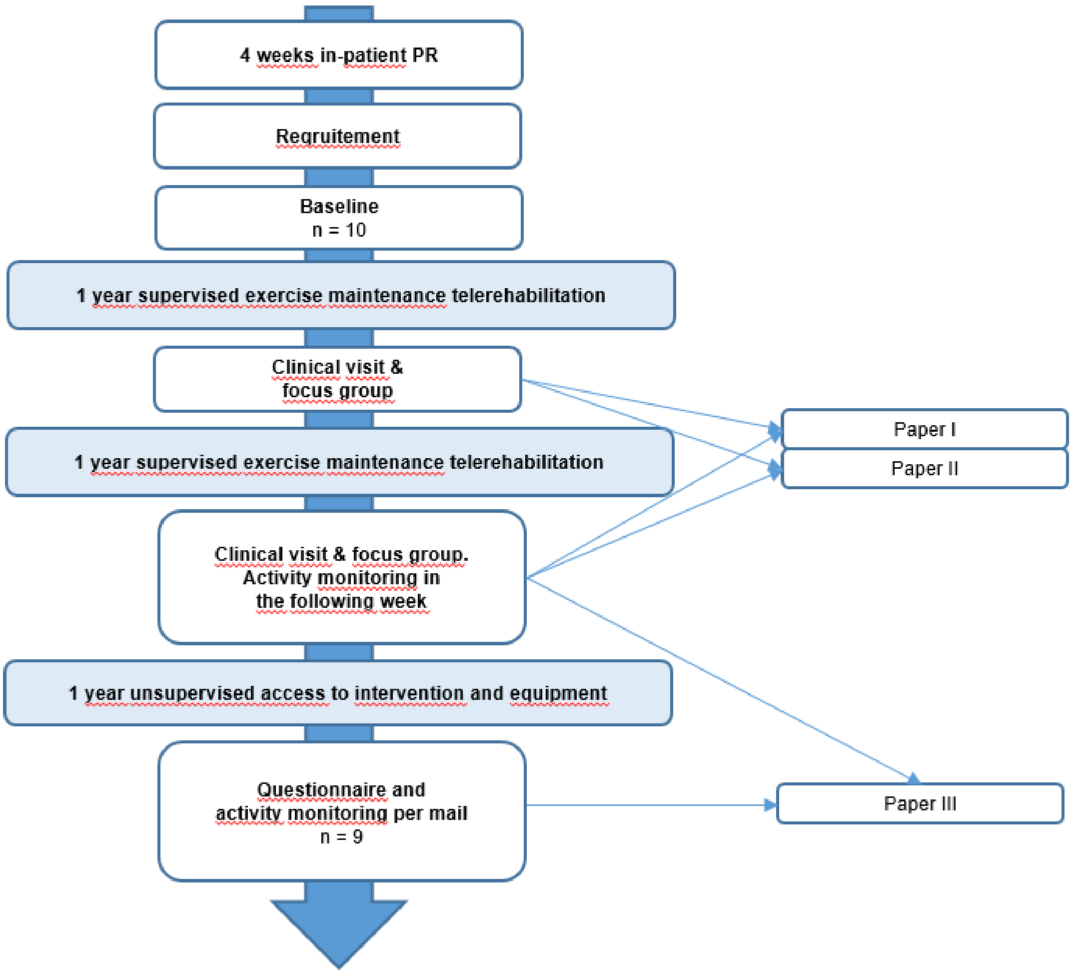
2.1 Design and study material

The five papers in this thesis included research on patients with COPD. An overview of the timeline of the two studies performed (pilot study and RCT), sample sizes, and related papers is presented in figure 2 and figure 3.

Previous studies described promising results for telerehabilitation in COPD in regards to feasibility, safety, physical activity and health-related quality of life (Holland et al., 2013a, Tabak et al., 2014c, Burkow et al., 2013, Marquis et al., 2015, Paneroni et al., 2015). However, all interventions had a short-term duration. A 10-year survival study conducted in Northern Norway found that people with very severe COPD could be favourably treated with a long-term extensive rehabilitation program in an outpatient setting (Hjalmarsen et al., 2014). Alternatives for long-term rehabilitation and maintenance programs for this patient group are lacking in Northern Norway. Long-term adherence to exercise routines is often difficult for those with COPD (Hellem et al., 2012), and new ways of extending short-term benefits of pulmonary rehabilitation are warranted (Spruit et al., 2013b). We therefore wanted to test an innovative long-term telerehabilitation intervention in a pilot study to obtain documentation on feasibility, long-term exercise maintenance and other benefits. The telerehabilitation intervention included a customised website used for self-monitoring and telemonitoring, an application for video conferencing, a treadmill, a tablet computer and a pulse oximeter. The intervention was developed and implemented in a two-year pilot study with a test-retest design. Based on the results and experience from the pilot study, a RCT was planned and implemented. When properly designed, conducted and reported, RCTs are considered the gold standard for evaluating the effect of treatments. However, it has been argued that the controlled setting of a RCT and possible patient selection bias can make it difficult to extrapolate findings to the general target population and real life situations (Pringle and Churchill, 1995, Mørch, 2010). A systematic review of reviews assessing telemedicine (Ekeland et al., 2012) concluded that larger and rigorous studies are crucial to evaluate the effectiveness of telemedicine interventions. However, summative methodologies and formative, naturalistic methodologies are also acknowledged as important to produce knowledge in the field of telemedicine. Our RCT (iTrain study) was an international multicentre trial conducted across sites in Norway, Denmark and Australia. The specific methods used in the pilot study and the iTrain study are described in detail in the following sections.

2.1.1 Study 1: the pilot study

Figure 2 Timeline pilot study



Participants

Ten participants were recruited from the rehabilitation clinic LHL-klinikkene Skibotn, about two hours driving North from Tromsø. Inclusion criteria were: confirmed diagnosis of moderate to severe COPD in accordance with the GOLD guidelines (Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2018), aged 40 to 75 years, Norwegian speaking and resident in Northern Norway, and completion of a 4 week inpatient pulmonary rehabilitation program during the previous six months. Their clinical status was considered stable and their physical condition optimised before enrolment in the pilot study. They were also experienced with treadmill training from the recent rehabilitation stay. Exclusion criteria were: unwillingness or inability to give informed consent, presence of comorbidity or physical condition which might interfere with performing home rehabilitation in a safe manner, or home environment not suitable for installation and use of telerehabilitation equipment (including space and Internet connection). Recruitment process was swift. All eligible patients who were approached agreed to participate.

Outcome measures

Baseline measures were collected from the participants' final assessments of their recent rehabilitation stay. Patients' characteristics, including age, gender, use of long-term oxygen treatment, distance from closest hospital, living arrangements, education level and experience with internet, were also collected at baseline. All participants attended clinical visits at LHL-klinikkene Skibotn for outcome measurements one year and two years after baseline. The clinical visits were organised as two overnight stays due to long travel distance for most participants. Focus groups were conducted at both clinical visits. Participants wore physical activity monitors in the week following the clinical visit at two years (end of intervention). At one year post-intervention, the participants wore physical activity monitors for one week and answered the study questionnaires, which were collected via mail. In addition, data on hospitalisation and outpatients visits were collected form the Norwegian Patient Registry for the two years prior to enrolment, the two years of the intervention period, and the following post-intervention year. An overview of the outcomes measured in the pilot study is provided in table 7.

The long-term exercise maintenance intervention via telerehabilitation

The intervention consisted of exercise training in the home, telemonitoring, and self-management support via video conferencing with an experienced physiotherapist.

Equipment was installed in the participant's home shortly after recruitment and included a treadmill, a pulse oximeter, a tablet computer to access a website for self-management and telemonitoring, an app to perform videoconference sessions with a physiotherapist, and a tablet holder mounted on the treadmill to allow safe use of the tablet while exercising. The equipment is showed in figure 3. A training session on the use of the equipment including a test videoconference session was conducted during a home visit.

During the study, participants were asked to fill in a daily electronic form for self-management of symptoms including oxygen saturation at rest and the breathlessness, cough and sputum scale (Leidy et al., 2003). Each participant received an individual exercise program consisting of interval training on the treadmill, recommended three times per week. The program was accessible from on the website after login. Interval training consisted of a 10-minutes warm-up, followed by three or four exercise bouts lasting between 3 to 4 minutes with a perceived exertion of 5-6 on the Borg CR10 scale (Borg and Borg, 2010), interposed by 2 to 3 minutes active recovery periods with a perceived exertion of 3-4. The training session ended by a 5 minutes cool-down. This gave a total exercise time of ≥30 minutes. Number and length of intervals were adjusted according to the individual participant's condition. Adjustments of speed and/or incline of the treadmill, and exercise duration were adjusted individually during the study. Participants were also encouraged to perform strength training exercises and other physical activity on their own. After each training sessions, participants were asked to fill in an electronic form including: training duration, perceived exertion, oxygen saturation (lowest value during exercise) and heat rate (highest value during exercise). Both the participants and the physiotherapist could access historical data for the daily diary and the training diary from the website. Participants were followed-up via videoconferences on a weekly basis for two-years. The physiotherapist supported and educated the participants in health-enhancing behaviour, focusing on motivation for exercise training, but also self-efficacy strategies were emphasised so that the participants could gain insight into their own health and management of their disease. In the beginning all participants were supervised during one weekly exercise session on the treadmill, but after a while some participants requested to talk to the physiotherapist after they had exercised to that they could have a quiet talk about the exercise and other topics without being "out of breath" during the exercise. Some also requested less frequent videoconference follow-ups as they felt they were more independent in the training and had nothing new to discuss with the physiotherapist.

Statistical analyses

Quantitative data were analysed using IBM SPSS Statistics Version 22. A value of $p \leq 0.05$ were considered statistically significant.

Descriptive analyses were reported as mean ± standard deviation (SD) and range (min-max) for continuous data, and as counts and percentages for categorical data. In addition, results in *Paper III* were also reported as mean difference with 95% confidence interval (CI). Normality were assessed by the Shapiro–Wilk test. Descriptive statistics were used to describe the study population, results for clinical effects, patient-related outcomes and for adherence to the intervention.

The specific statistical analyses related to the pilot study are presented as follows.

Paper I:

To investigate feasibility, long-term exercise maintenance, clinical effects, quality of life, and use of hospital resources during the two-year intervention an analysis of variance (ANOVA) with repeated measures was performed. A Bonferroni post hoc test was used to discover which specific means differed in case the overall ANOVA result was significant.

Paper III:

Changes in physical activity and other outcomes from the second year of telerehabilitation to the post-intervention year were tested with the paired-samples t-test.

Mixed methods and triangulation of data collection techniques

Mixed methods and triangulation of data collection techniques were also used in the pilot study and presented in *Paper II*. This study was focused on adherence and patients' experience, aiming to explore the perspectives of people with COPD participating in long-term telerehabilitation and to identify factors affecting satisfaction and potential improvements of the intervention. Four methods for data collection were utilised. Adherence to the telerehabilitation intervention was measured through the analysis of logs reporting the frequency of registrations in the daily diary and the training diary on the website. Factors affecting satisfaction and adherence, together with potential for service improvements, were explored through focus groups and individual open-ended questionnaires. User-friendliness and technical improvements were examined through standardised questionnaires and open-ended questionnaires. The conduction of focus group and related analysis will be elaborated in the following paragraph.

Focus groups and data analysis

Thoughts and reflections about use of a new intervention may be best captured by individual interviews or focus groups (Kitzinger, 2007). In focus groups, experiences are discussed openly. Different opinions and points of view can be forwarded, negotiated and new insight may be produced from the group interaction. In this way, this might be a good approach to discuss and discover alternatives for improving interventions (Flick, 2009). However, more in-depth information about each participant's experience may be lost.

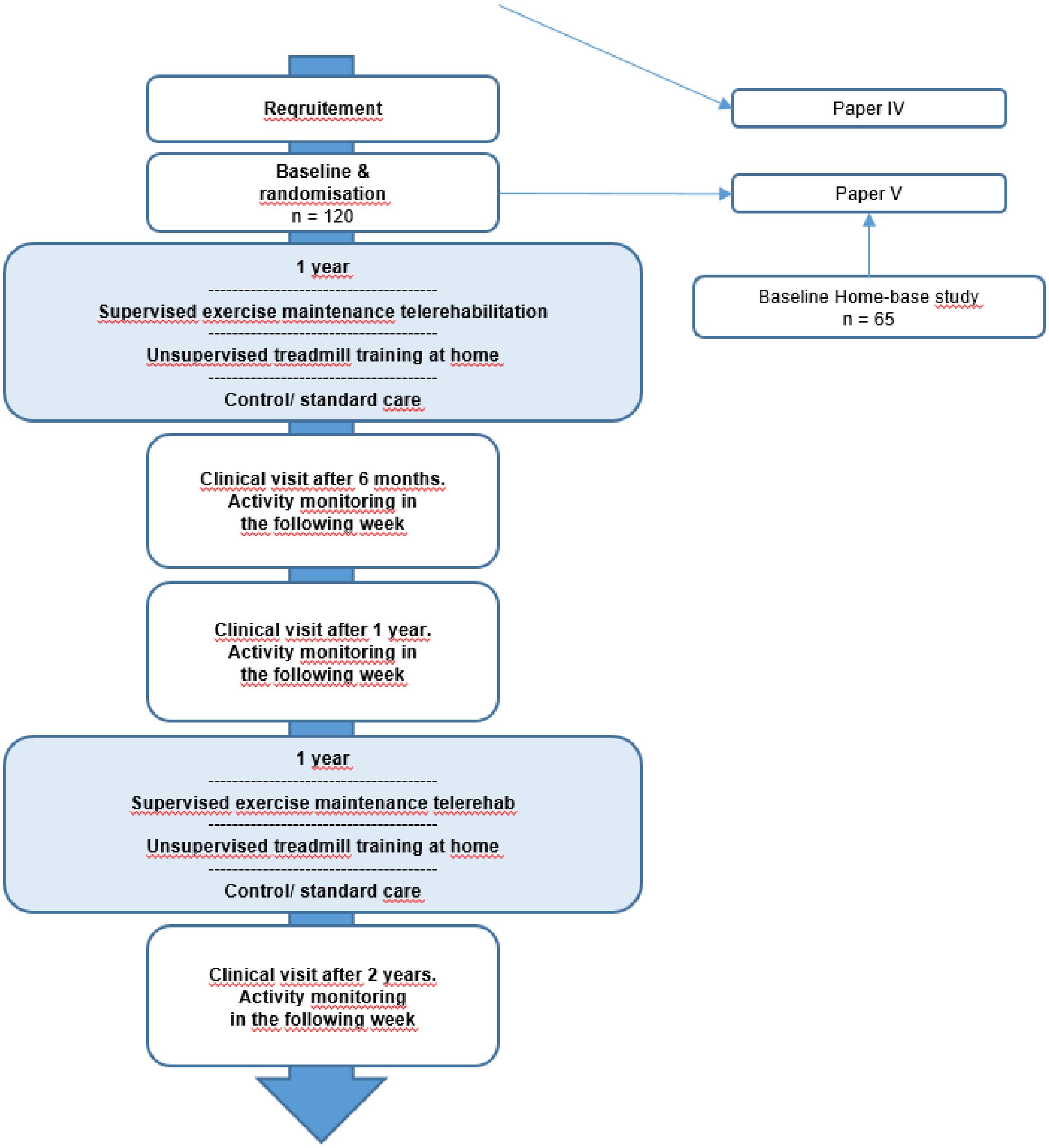
Two semi-structured focus groups were conducted during the two clinical visits after the first year of the intervention and after the second year. A semi-structured interview guide was used at both occasions. The first focus group was focused mainly on user-friendliness and experience with the technical equipment. Issues from the interview guide were: potential benefits from telerehabilitation in health and everyday life, challenges, motivation, experience with the different equipment (treadmill, pulse oximeter, iPad, website, videoconferences), and suggestions for improvements. Issues from the interview guide were: potential benefits from telerehabilitation on health and everyday life, challenges, motivation, experience with the equipment (treadmill, pulse oximeter, iPad, website, videoconferences), and suggestions for improvements. Issues covered in the second focus group included the experiences with participation, experiences with the exercise training, improvements of the equipment, webpage and videoconferences, and organisation of telerehabilitation (who should be offered this service, when, content, healthcare personnel included, groups-based vs individual-based).

Analysis of the qualitative data focused on identifying topics rather than on differences and similarities between individual respondents, thus confirming to a thematic analysis technique (Braun and Clarke, 2006). Further, the material was analysed using systematic text condensation, which is inspired by Giorgi and modified by Malterud

(Malterud, 2001, Malterud, 2011). Details on the steps of analysis in systematic text condensation with examples are available in *Paper II*.

2.1.2 Study 2: the iTrain study

Figure 3 Timeline iTrain study



Participants

The iTrain study aimed at enrolling 120 participants. Norwegian participants were recruited from the Department of Pulmonary Medicine at the University Hospital of North Norway in Tromsø and Harstad, and the Medical Department at the Finnmarkssykehuset in Kirkenes. Danish participants were recruited from the Pulmonary ward at South West Hospital and the Esbjerg Healthcare Centre in Esbjerg. Australian participants were recruited from the Alfred Health in Melbourne. Inclusion criteria were: confirmed diagnosis of moderate, severe or very severe COPD, based on a an FEV_1/FVC ratio ≤70% and an airflow limitation of FEV_1% of predicted ≤80% (Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2018), at least one COPD-related hospitalisation or COPD-related emergency department (ED) presentation in the prior 12 months, age between 40-80 years, and capable of providing informed written consent. Exclusion criteria were: attendance at a rehabilitation program in the 6 months prior of enrolment, participation in another clinical study that might have an impact on the primary outcome, physical incapable of performing the study procedures, presence of comorbidities that might prevent the participant to perform exercise training in the home, home environment not suitable for installation and use of telerehabilitation equipment. The second inclusion criteria was modified from the pilot study according to the primary outcome of the iTrain study, which was the combined number of hospitalisations and ED presentations. Patients with a recent history of hospital access are more likely to experience re-hospitalisations in the following period. Consequently, a change in the primary outcome can be expected in this population. The first exclusion criteria was modified from the pilot study because clinical benefits from a recent pulmonary rehabilitation program might be maintained in the first months of participation in the RCT, thus affecting the study outcomes. Potential participants were not excluded on the basis of their existing home Internet access, as this could be provided by the study. Recruitment process was challenging in all countries. We assessed 198 Norwegian patients for eligibility and approached them by mail correspondence and/or phone. Out of these, 38 did not meet the inclusion criteria, 28 did not answer, and 89 declined to participate. In the end, 43 patients were included in the study. The first Norwegian participant was enrolled in October 2014, while the last participant was enrolled two years later, in October 2016. Overall, the last participant in the whole study was enrolled in Australia in December 2016.

Randomisation

Participants were randomly assigned to three arms (telerehabilitation, treadmill or control) in a 1:1:1 ratio after baseline measures and followed up for two years. Randomisation was stratified by centre and disease severity (FEV_1 ≥50% vs. FEV_1 ≤50%). The randomisation process was web-based and concealed from the researchers by the program.

Outcome measures

Appropriately trained study personnel blinded to group performed all clinical assessments at baseline, 6 months, 1 year and 2 years.

The primary outcome was the combined number of hospitalisation and ED presentations. Differences in the rate of events between the study arms will be measured at all assessment time points. Data on hospitalisations and ED presentations, together with out-patient visits, were requested to national registries in Norway, regional systems in Denmark, and hospital records in Australia.

An overview of outcome measures used in both the pilot study and the iTrain study is given in table 7. During the planning of the iTrain study, two other questionnaires were considered. We wanted to use the Pulmonary Rehabilitation Adapted Index of Self-Efficacy (PRAISE) (Vincent et al., 2011) to investigate self-efficacy and the Health Education Impact Questionnaire (heiQ) (Osborne et al., 2007) to evaluate patient education. However, validated versions of the PRAISE tool were not available for all languages and access to the heiQ stranded on administrative delay at the university that provided the contracts to use the questionnaire. Use of these tools could have provided valuable insight in disease specific self-efficacy for those with COPD and possible benefits of our telerehabilitation intervention as a patient education program.

Most assessment tools used to evaluate the iTrain study are frequently used in pulmonary rehabilitation research, except from the Patient Global Impression of Change scale (PGIC) (Hurst and Bolton, 2004) and the Generalised Self-Efficacy Scale (GSES) (Schwarzer and Jerusalem, 1995), which we used instead of the PRAISE tool to investigate self-efficacy. The System Usability Scale (Brooke, 1996) and frequency of registrations in web-based diaries have been used in other studies on telerehabilitation for people with COPD (Burkow et al., 2015, Tabak et al., 2014c), but might be unfamiliar to most in the pulmonary rehabilitation field. Patients’ characteristics, such as clinical history, age, gender, body weight status, use of long-term oxygen treatment, distance from closest health facility and living arrangements, were also collected.

Table 7 Objectives and assessment tools used in the studies

Objectives	Assessment tool	Pilot study	iTrain study
Feasibility	Completion rate	x	x
Exercise maintenance and adherence to intervention	Frequency of training sessions reported in the web-based diary	x	x
Self-management maintenance and adherence to intervention	Frequency of daily registrations reported in the web-based diary	x	x
Functional walking capacity	6-minutes walk test (6MWT) (Holland et al., 2014)	x	x
Lung capacity	Spirometry	x	x
Body weight status	Body Mass Index	x	
Symptom burden	COPD Assessment Test (CAT) (Jones et al., 2009)	x	x
Health-related quality of life	EuroQoL 5 dimensions (EQ-5D) (EuroQol Group, 1990)	x	x
Level of dyspnoea	Modified British medical research council questionnaire (Fletcher, 1960, Stenton, 2008)		x
Self-efficacy	Generalised self-efficacy scale (GSES) (Schwarzer and Jerusalem, 1995)	Post-intervention	x
Subjective impression of change	Patients Global Impression of Change scale (PGIC) (Hurst and Bolton, 2004)	After two years	After 6 months
Anxiety and depression	Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983)	Post-intervention	x
Level of physical activity	Daily number of steps, minutes of moderate to vigorous physical activity and sedentary time during one week measured with the Sensewear Activity monitor	Post-intervention	x

Healthcare utilisations	Number of COPD-related hospitalisations, ED presentations and out-patient visits	x	x
Mortality and adverse events	Mortality rate and number of adverse events such as treadmill injuries		x
Time free from first event	Days to first hospitalisation		x
Cost-effectiveness	Cost-utility analysis (cost per QALY)		x
User-friendliness	System Usability Scale (Brooke, 1996)	End of first year	
Technical improvements	Individual open-ended questionnaire	x	
Motivational factors for maintaining exercise	Individual open-ended questionnaire	Post-intervention	
Experiences with telerehabilitation	Focus groups or qualitative interviews with semi-structured questions	Focus groups (end of first year and end of second year)	Individual interviews with 5-8 patients in the telerehabilitation arm at each site before telerehabilitation, after 1 year and after 2 years.

The long-term exercise maintenance intervention via telerehabilitation

The intervention used in the iTrain study was an improved version of the intervention from the pilot study. This paragraph will shortly describe the improvements and changes that were implemented for the iTrain study.

As in the pilot study, the intervention used in the iTrain study consisted of exercise training at home, telemonitoring, and self-management support via videoconferences with an experienced physiotherapist (Figure 4).

The requirement for participants to have a recent COPD-related hospitalisation implied that more severe and unstable patients were included in the iTrain study than in the pilot study. Moreover, none of the participants had attended a rehabilitation program in the period prior of enrolment. Their physical conditions were therefore not optimised and most of them were not familiar with treadmill exercise. Consequently, we needed to have an even broader exercise prescription in this study. Initial exercise training on the treadmill was individualised and adjusted based on the participants' performance on the 6-minutes walk test (6MWT) at baseline. According to patients' preference and previous experience, an exercise program with continuous or interval training was prescribed. Regardless of the exercise mode, treadmill training lasting for at least 30 minutes, three times per week, was recommended. Additionally, strength exercises were recommended with a frequency of 2-3 sessions a week. Progression in the program was made according to the patients' conditions. Details of the training prescription can be found in Appendixes.

Based on the experience from the pilot study, new functionalities were implemented in the website. As in the earlier version, participants could access their individual exercise program, fill in a daily diary and a training diary, and access their past data. In addition, they could exchange electronic messages with the physiotherapist, have an overview of the upcoming scheduled videoconferencing sessions, their individual goal setting and goal attainment. The items used in the daily diary and in the training diary were mostly the same than in the earlier version. A general wellbeing scale, based on a five-point Likert scale illustrated by emoticons, was added to the daily diary. Moreover, a field with open-ended text where participants could provide additional comments was added to both the daily diary and the training diary. The information reported by the participants was monitored and interpreted by the physiotherapist on a weekly basis. Another new functionality was the addition of a page where the physiotherapist could take electronic notes regarding the participants. This information was not accessible to the participants.

The app used to conduct videoconferences between the tablet computer provided to each participant and the physiotherapist was changed to Acano™. The frequency of contacts was modified from that used in the pilot study based on previous feedback from the participants and the physiotherapist. In the iTrain study, at least one individual videoconference session per week was scheduled during the first 8 weeks after enrolment, and at least one individual videoconference session per month was scheduled in the following period. Participants who experienced a hospital admission or exacerbation of disease were invited to continue their participation with at least one videoconference contact per week in the month after discharge as a reinforcement strategy. Physiotherapists were provided with common project guidelines for exercise prescription, theoretical background on how to support and educate participants in health-enhancing behaviour and goalsetting, and practical instructions for the conduction of videoconferences (weekly interpretation of participants' registrations on the website, topics to be discussed, writing of electronic notes, etc.). Topics discussed between the participant and the physiotherapist included individual goals, self-management education, exercise completion and progression, pursed lip breathing, and airway clearance techniques. Project guidelines are available in the Appendixes.

Figure 4 Telerehabilitation equipment used in participants' home

Photo by Jarl-Stian Olsen, Norwegian Centre for E-health Research.

Costs of the telerehabilitation equipment

Total cost of the telerehabilitation equipment for each Norwegian patient was approximately NOK 12 000 (€ 1 235). This price includes the costs for the treadmill, transportation of treadmill, the pulse oximeter, the iPad, and the iPad holder. The videoconference software Acano^{TM} and user accounts were provided for free by the Norwegian Health Network (Norsk helsenett, 2018). The Norwegian physiotherapist used approximately 20% of her work time over the study period to supervise the participants in the telerehabilitation arm and support the iTrain study.

Treadmill arm

Participants in the treadmill arm of the iTrain study were provided with a treadmill for unsupervised exercise training at home. They were recommended the same exercise training as the telerehabilitation group and taught how to progress the program themselves. Details of the training prescription can be found in Appendixes. Participants were asked to record each training session on a paper-based diary. This intervention arm allowed us to compare the effects of providing exercise equipment only, to those who were followed-up via telerehabilitation. In particular, according to the findings from the post-intervention year of the pilot study, we wanted to investigate whether the provision of exercise equipment and one-time instruction could be enough to produce clinical benefits for the patients and whether this intervention could be cost-effective.

Control arm

Participants in the control arm were offered standard care. Any participant in the study could undertake a conventional pulmonary rehabilitation program at any time during the 2-year study period if their usual healthcare personnel considered this necessary. All participants were provided brochures containing information about pulmonary rehabilitation, physical activity and exercise, diet, self-management, motivation and lifestyle changes, smoking cessation, and oxygen therapy.

Sample size calculation

The sample size requirements for this study were intended to provide adequate power for the analysis of the primary outcome, which was the combined number of hospitalisations and ED presentations. We calculated that a sample size of 65 person-years per group would allow a power of 95% to detect an incidence rate ratio of 0.60, with a type-I error (α) of 0.05. Assuming that up to 20% of participants could drop out uniformly over the intervention period, we aimed at enrolling 40 patients (corresponding to 80 person-year) per each of the three arms for the 2-year study duration. In total, we aimed at enrolling 120 patients (corresponding to 240 person-years).

Statistical analyses

The statistical analyses related to the iTrain study are reported in *Paper IV.* Descriptive statistics at baseline will be reported as means ± SD for normally distributed continuous variables, or medians with 25–75th percentiles in the case of skewed distribution. Normality of distribution will be tested by means of the nonparametric Kolmogorov-Smirnov test. An intention-to-treat analysis will be performed on all randomised subjects to provide unbiased comparisons among groups and avoid the effects of dropout. The primary outcome and related secondary outcomes will be measured through the Incidence Density, defined as the number of events in a group divided by the total person-time accumulated during the study in that group. Differences between study arms will be tested by the Comparison of Incidence Rates. A two-sided test and a significance level of $\alpha = 0.05$ will be used. All events from the day after randomisation to patient exit/death will be included. Other secondary outcomes will be measured as changes from baseline to all assessment time points. Changes of the secondary outcomes will be tested by use of linear mixed models. A p-value <0.05 will be considered significant for all tests. All statistical analyses will be performed by using IBM SPSS Statistics. Preliminary results for the patients enrolled in the telerehabilitation arm were analysed and summarised with descriptive statistics.

The statistical analyses related to the cross-sectional study are reported in *Paper V.* To investigate whether there were differences in physical activity levels between Norwegian, Danish and Australian people with COPD and to establish if any variation in physical activity levels was attributable to seasons (winter, spring, summer, autumn) an one-way ANOVA was performed. A Tukey post-hoc test was used to discover which specific means differed where the overall ANOVA result was significant. Between country differences were also adjusted for disease severity (FEV_1 %) using one-way ANCOVA. The combined effect of seasons and countries on physical activity was analysed with two-way ANOVA. Log transformation (used for energy expenditure) and cubic root transformation (used for steps, LIPA and MVPA time) were applied to the physical activity variables with a non-parametric distribution in order to obtain normally distributed data so that parametric methods for statistical analyses could be performed. No transformation nor statistical analyses were applied to time in MVPA bouts due to the high number of zero values.

2.1.3 The cross-sectional study

During my PhD, I submitted an application to the ERS for a Short-term research fellowship, which was approved and successfully funded in 2016. This fellowship project was conducted at La Trobe University in Melbourne, supervised by Anne Holland. The fellowship work plan included an introduction to research projects in home-based pulmonary rehabilitation and telemedicine conducted at the university, appropriate training on extracting and analysing data on physical activity from the iTrain study across the three sites (Norway, Denmark, Australia), and preparation of a joint publication. By the time I was in Australia, not all the baseline visits of the iTrain study were conducted. Supervised by Holland, a cross-sectional study was conducted to explore seasonal variations in objectively assessed physical activity among people with COPD in two Nordic countries and Australia. Available data from the iTrain study were merged together with data from COPD patients with similar characteristics enrolled in the Homebase study (Holland et al., 2013b, Holland et al., 2017) performed at Alfred Health in Melbourne, Australia. Results was reported in *Paper V*, which was submitted in November 2018 and is currently under review.

Minimal clinically important differences

Minimal clinically important differences (MCID) are patient derived scores that reflect changes in a clinical outcome variable that is perceived as useful and important for the patient in his everyday life (Cook, 2008). Some findings presented in this thesis were interpreted in light of the MCID in addition of the statistical significance. The rationale for this was that even though studies might not show statistical significant changes in some outcomes, the changes might be of larger clinical significance. For those with COPD, perceived improvements in physical capacity, physical activity, and quality of life might feel useful in everyday life hence be of clinical significance. The MCID for these three outcome measures are provided below.

We have used the 6MWT (Holland et al., 2014) to evaluate physical capacity. In the past, the MCID for the 6MWT was considered 54 meters (Carlin et al., 2010 p. 387, American Thoracic Society, 2002). In the most recent guideline on field walking tests from the ERS/ATS, a MCID of 30 meters in the 6MWT was suggested for adult patients with chronic respiratory disease (Holland et al., 2014). The MCID for the 6MWT was reported and interpreted in *Paper I*.

Daily step count was used as a main outcome measure when evaluating physical activity. An increase between 600 and 1100 steps/day is considered a MCID in daily step count after pulmonary rehabilitation (Demeyer et al., 2016). The MCID for daily step count was reported and interpreted in *Paper III and Paper V*.

The CAT was used to evaluate symptom burden and health-related quality of life. Recently, a new MCID for the CAT ranging between -3.0 and -2.0 points was proposed (Smid et al., 2017) and was used as a criterion for a positive change in this thesis. It is also reported and interpreted in *Paper I and Paper III.*

2.2 Ethical aspects

All patients participating in the studies reported in this thesis were given written and oral information when invited to participate in accordance with the Declaration of Helsinki. They were informed that participation was voluntary and that they could withdraw from the study without giving any reason at any time of the follow-up period. All participants signed a written informed consent to participate. The pilot study was approved by the Regional Committee for Medical and Health Research Ethics (2011/2154 REK nord). The iTrain study received approval from the Regional Committee for Medical and Health Research Ethics in Norway (2014/676 REK nord), the Alfred Hospital Human Research Ethics Committee (289/14), and the North Denmark Region Committee on Health Research Ethics (N-20140038).

The pilot study was funded by the Northern Norway Regional Health Authority (grant number HST1014-11). The iTrain study was funded by the Research Council of Norway (Project Grant 228919/H10) and the Northern Norway Regional Health Authority (Project Grants HST1117-13, HST118-13 and HNF1384-17).

3 Results

This section summarises and repeats the results presented in *Papers I, II, III, IV* and *V*. In addition, some unpublished preliminary descriptive results from the iTrain study are presented. A publication including the results on the primary and secondary outcomes from the first year is expected in the beginning of 2019. Where appropriate, results from the different papers are grouped into common topics. Details can be found in the attached papers.

3.1 Feasibility

On average, the ten patients enrolled the pilot study participated to the intervention for 740 ± 26 days. They experienced voluntarily and non-voluntarily relapses due to holidays, travelling, sickness, or hospital admissions. However, they all rejoined the program after these breaks, and no dropout occurred *(Paper I).*

In total, 120 participants were enrolled in the iTrain study. Forty-three of these were enrolled from Norway. For the whole iTrain study, the dropout rate was 7.5% after one year. Three of the five Norwegian participants who dropped out during the first year were enrolled in the telerehabilitation group of the study. The other two who dropped out, were enrolled the control group. Both reported a dissatisfaction with randomisation to control as the reason for dropping out, reflecting their frustration since the current offer is very limited and they missed the chance of receiving some kind of support. Such dissatisfaction was also expressed at randomisation by many of those enrolled into the control group, reflecting their desire for this type of interventions. No adverse events (deaths, injury or other events) specifically related to the provision of the telerehabilitation intervention or treadmill exercise training at home occurred. However, some participants experienced exacerbations of COPD or other comorbid diseases that contributed to dropouts or deaths *(Unpublished results).*

Due to the low number of dropouts and adverse events specifically related to the intervention, long-term exercise maintenance via telerehabilitation is considered feasible and safe.

3.2 Clinical effects

Ten people with COPD took part in the pilot study. They were on average aged 55.2 ± 6.1 years. The mean FEV1 (% of predicted) was 49.1 ± 20.9).

After one year of telerehabilitation, the 6 minutes walking distance (6MWD) improved with a mean of 40 meters compared to baseline (post-pulmonary rehabilitation). After two years, 6MWD decreased to a value in line with baseline. Mean FEV_1 % of predicted, mean total score for the CAT, mean utility score from the EQ-5D and mean EQ-VAS followed the same pattern, with improvements after one year and values in line with baseline measurements after two years (Table 7). Statistical analyses of these outcomes with a repeated measures ANOVA did not show any statistical significant differences between time points. Nevertheless, long-term exercise maintenance via telerehabilitation succeeded in maintaining clinical effects like functional walking capacity, lung function, level of symptoms, and quality of life over a two-year period *(Paper I).*

Table 8 Results for clinical effects in the pilot study

Outcomes	Baseline	1 year	2 years
6MWD, m	493 ± 106	533 ± 124	473 ± 108
FEV_1 % of predicted	49.1 ± 20.9	54.9 ± 28.8	45.2 ± 20.6
Total CAT score	21.5 ± 6.3	17.7 ± 5.5	20.3 ± 6.7
EQ-5D, utility score	0.624 ± 0.218	0.660 ± 0.210	0.557 ± 0.211
EQ-VAS	48.6 ± 21.9	64.2 ± 20.4	52.3 ± 23.9
BMI, kg/m^2	27.9 ± 7.3	26.7 ± 5.5	26.4 ± 5.3

Data are mean ± standard deviation. 6MWD: 6-minute walking distance, m: metres, FEV_1 % of predicted: forced expiratory volume in 1 second, percentage, CAT: COPD Assessment Test, EQ-5D: EuroQoL 5 dimensions, EQ-VAS: EuroQoL visual analogue scale, BMI: body mass index.

Results from the iTrain study are not published at the time of completion of this thesis. However, some preliminary results on the secondary outcome measures for the telerehabilitation group only are provided in table 8. This allows to provide a comparison with the results from the pilot study. Forty participants of the iTrain study were randomised to the telerehabilitation group. The mean age was 64.9 ± 7.1 years, mean FEV_1 % of predicted was 40.4 ± 16.5, 30% were had severe to very severe COPD, 57.5% were men, 30% used long-term oxygen treatment, mean body mass index was 27.0 ± 5.6, and mean number of comorbidities were 2.6 ± 1.2.

The telerehabilitation group improved their walking capacity with a mean of 53 meters from baseline to 6 months. This improvement was maintained until the 1-year follow-up. Values for FEV_1 % of predicted, total score for the CAT, utility score from the EQ-5D and EQ-VAS at 6 months and 1 year were in line with baseline measurements (Table 8). Statistical analyses of these outcomes are not computed yet. Nevertheless, long-term exercise maintenance via telerehabilitation improved functional walking capacity, and succeeded in maintaining lung function, level of symptoms, and quality of life over a period of one year *(Unpublished results).*

Table 9 Preliminary results for clinical effects in the telerehabilitation group of the iTrain study

Outcomes	Baseline	6 months	1 year
6MWD, m	367 ± 125	420 ± 126	415 ± 146
FEV_1 % of predicted	40.4 ± 16.5	44.5 ± 18.4	40.1 ± 19.4
Total CAT score	19.6 ± 6.2	18.2 ± 6.9	18.6 ± 7.0
EQ-5D, utility score	0.739 ± 0.110	0.733 ± 0.149	0.688 ± 0.197
EQ-VAS	51.9 ± 21.0	58.4 ± 16.6	56.8 ± 18.8

Data are mean ± standard deviation. 6MWD: 6-minute walking distance, m: metres, FEV_1 % of predicted: forced expiratory volume in 1 second, percentage, CAT: chronic obstructive pulmonary disease assessment test, EQ-5D: EuroQoL 5 dimensions, EQ-VAS: EuroQoL visual analogue scale, BMI: body mass index.

3.3 Adherence to the telerehabilitation intervention

On average, the participants in the pilot study reported 3.0 diary registrations/week and 1.7 training sessions/week via the website during the whole period of the two-year intervention. This corresponds to an average adherence rate of 43.3% and 56.2%, respectively. On average, participants had 3.4 diary registrations/week during the first year, while adherence decreased to 2.6 diary registrations/week during the second year. Adherence to training sessions was maintained at an average of 2.1 training sessions/week during the first year, before it decreased to 1.2 sessions/week during the second year *(Paper II).*

The participants reported fewer training sessions and diary registrations during December (Christmas) and July/August (summer holidays). During holiday periods, they did not receive video conference follow-up by the tele-physiotherapist and were also encouraged to take some time-off *(Paper II).*

Individual adherence rates to self-management via daily diary for the ten participants in the pilot study ranged from 8.2% to 98.3%, while individual adherence rates to exercise ranged from 16.3% to 99.1% *(Paper II).*

3.4 Participants perspectives

Four major themes regarding factors affecting satisfaction and adherence, and potential for service improvement emerged from the analysis of the data collected from two focus group interviews with the participants in the pilot study: i) experienced health benefits; ii) increased self-efficacy and independence; iii) emotional safety due to regular meetings and access to specialist competence; and iv) maintenance of motivation *(Paper II).*

Themes emerged are elaborated in the paragraphs below. More elaboration and quotes that illustrates the themes can be found in *Paper II*.

3.4.1 Experienced health benefits

All participants in the pilot study mentioned a positive change in perceived level of health throughout the two-year intervention period. Experienced health benefits were interpreted as one of the main factors affecting satisfaction. Despite having a chronic disease, the participants felt in good health most of the time. They described a broad perspective of health and health benefits consequent to their participation in the study, including physical, psychological, and social achievements *(Paper II).*

3.4.2 Increased self-efficacy and independence

The participants proudly described an increased competence in a variety of different fields. These mastery experiences seemed to have created a higher degree of self-efficacy and confidence in self-management of their exercise regime, everyday life, and disease.

More independence was also described in the relationship with the therapist. Participants reflected on how the technology made it easier for them to withdraw themselves without confrontation from the collaboration with the tele-physiotherapist if the follow-up did not "fit" their goals, mood or values, or if the relationship felt too challenging *(Paper II).*

3.4.3 Emotional safety due to regular meetings and access to specialist competence

Participants expressed that they felt safe and well taken care of in the pilot study. They valued especially their relationship with the tele-physiotherapist and the regularity of the videoconferences *(Paper II).*

3.4.4 Maintenance of motivation during the intervention

Motivation for exercise training declined for most participants in the pilot study over the two-year period. Consequently, maintenance of motivation was interpreted as a challenge. How physical performance developed during the intervention period represented one of the main factors affecting motivation.

When searching for motivational strategies in the focus group interviews, we found that participants used both a promotion and a prevention focus. There was no connection between high adherence and a specific motivational strategy *(Paper II).*

3.4.5 Motivational factors for maintaining exercise post intervention

After the two-year intervention, participants were recommended to continue exercising on the treadmill without supervision. Two themes affecting motivation for maintaining exercise were identified in the open-ended questionnaires collected at one year post-intervention: i) experiences of health improvements and ii) regularity, feedback and affiliation. Most participants described previous or current experiences of health improvements related to exercising as reasons why they continued to exercise *(Paper III).*

3.4.6 User-friendliness and technical improvements

Participants in the pilot study had an average score of the System Usability Scale of 83.5 (min 32.5, max 100). This indicates that they were highly satisfied with the telerehabilitation intervention and considered it user-friendly. Participants' main complaint was the stability of the videoconference connection. They also had different suggestions for technical improvements of the intervention *(Paper II).* These suggestions were improved and implemented to some extent in the iTrain study.

Further, four key factors of potential improvements in long-term telerehabilitation were identified: i) adherence to different components of the telerehabilitation intervention is dependent on the level of focus provided by the health personnel involved; ii) the potential for regularity that lies within the technology should be exploited to avoid relapses after vacation; iii) motivation might be increased by tailoring individual consultations to support experiences of good health and meet individual goals and motivational strategies; iv) interactive functionalities or gaming tools might provide peer-support, peer-modelling and enhance motivation *(Paper II).*

3.4.7 Patients global impression of change

The average score from the PGIC questionnaire (Hurst and Bolton, 2004) reported in the pilot study after two years was 5.5±1.2. Nine out of 10 participants expressed a change-score ≥ 5, which is considered a significant and favourable change in their conditions, including activity, limitations, symptoms, emotions, and overall quality of life *(Paper I).*

In the iTrain study, the PGIC questionnaire was collected only after six months. Fifty-three % of the telerehabilitation group reported a change-score ≥5, while 24% and 13% in the treadmill and the control group reported a such a significant positive change score *(Unpublished results).*

3.5 Healthcare utilisation and cost-effectiveness

Overall, healthcare utilisation during the two years of the pilot study was reduced by 32% compared to the two years prior to enrolment. However, only two participants had a history of hospitalisation at baseline. Most participants were therefore not classified at high risk of hospitalisations or readmissions *(Paper I).*

There was no statistical significant difference in healthcare utilisation between the second year of the intervention in the pilot study and the following post-intervention year. However, the average number of COPD-related hospitalisations per patient doubled during the post-intervention year compared with the previous year when the participants were still in the intervention. The average number of COPD-related outpatient visits almost tripled during the year following the intervention. Hence, the estimated COPD-related hospital costs also increased *(Paper III).*

Per December 2018, data on hospital accesses were requested to the national registries in Norway, Denmark and Australia *(Paper IV)* but not yet delivered. A publication reporting the results on the primary outcomes is expected in early 2019.

3.6 Maintenance of physical activity after the intervention

Physical activity data were available for 7 out of 9 participants at one year from completion of the two-year pilot study. On average, total energy expenditure decreased from 9451 kJ per day at the end of the intervention to 8270 kJ per day one year post intervention ($p=0.011$). The number of steps decreased from an average of 3806 steps/day to 2817 steps/day ($p=0.039$). There was a 21% decline in time spent in light physical activity ($p=0.009$). On average, total time spent in moderate to vigorous physical activity dropped by 51% between time points, from 88 ± 66 minutes per day to 43 ± 34 minutes per day, although this was not statistically significant. Time spent in bouts of moderate to vigorous physical activity decreased by 53% ($p=0.110$). At the end of the intervention, 6 of the 7 participants had ≥150 weekly minutes of bouts of moderate to vigorous physical activity, whereas only two participants maintained that level one year after the intervention. Adherence to registration of symptoms and training sessions decreased significantly without supervision *(Paper III).*

3.7 Seasonal variations and physical activity levels among people with COPD in two Nordic countries and Australia

In total, 168 subjects with moderate to severe COPD from Norway, Denmark and Australia were included in the cross-sectional study. Demographics for the three groups were generally similar, although the percentage of participants in GOLD stage 3 and 4 (severe and very severe airflow limitation) was higher among Danish participants. Australian participants had the highest number of comorbidities and Danish participants had a lower functional walking capacity.

After controlling for disease severity, awake sedentary time was greater in Danish participants compared to the other countries (median 784 min/day [660-952] vs 775 min/day [626-877] for Norwegians vs 703 min/day [613-802] for Australians, p=0.013). Time spent in moderate to vigorous physical activity was lower for the Danish participants (median 21 min/day [4-73] vs 30 min/day [7-93] for Norwegians vs 48 min/day [19-98] for Australians, p=0.024). Participants tended to walk more during summer (median 3502 [1253-5407] steps/day) than in spring (median 2698 [1613-5207] steps/day), winter (median 2373 [1145-4206] steps/day) and autumn (median 1603 [738-4040] steps/day), regardless of geography. The median difference between summer and other seasons exceeded the minimal clinically important difference of 600 steps/day. However, the differences were not statistically significant (p=0.101) *(Paper V).*

4 Discussion

We designed an innovative two-year telerehabilitation intervention bringing pulmonary rehabilitation into the patients' homes, thus allowing remote supervision at distance. To our knowledge, this is the first telerehabilitation interventions with such a long-term follow-up.

Despite the evidence and knowledge still is limited, this thesis has showed that long-term exercise maintenance via telerehabilitation for people with COPD is safe and feasible.

Deterioration in the disease is expected over time (Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2018, Hjalmarsen et al., 2014). Results from our studies are encouraging and suggest that telerehabilitation can prevent deterioration in lung function, symptom burden and health-related quality of life in addition to improve and maintain functional walking capacity over the long-term. Other RCTs on short-term telerehabilitation programs (Bernocchi et al., 2018, Bourne et al., 2017, Chaplin et al., 2017, Tsai et al., 2017, Paneroni et al., 2015) have reported effectiveness in a variety of outcome measures including functional walking capacity, dyspnoea, symptom burden, health-related quality of life, self-efficacy, physical activity profile, and time to first hospitalisation and mortality. In addition, one RCT investigating a 12-months home-based maintenance telerehabilitation program following an initial 2-month conventional pulmonary rehabilitation program (Vasilopoulou et al., 2017) reported improved functional walking capacity, higher health-related quality of life, and lower risk of acute COPD exacerbations and hospitalisations. The evidence of cost-effectiveness of telerehabilitation interventions is still limited. In addition, real-life experience of full-size routine programs is also very limited.

The advantage of long-term telerehabilitation over the existing offer of exercise maintenance programs after conventional pulmonary rehabilitation in Norway is threefold. Telerehabilitation has the ability to overcome geographical distance, provide specialist access in areas where this is not available, and provide regularity of follow-up by the same healthcare personnel over a long period. Our research has also revealed some factors that are important for successful use and acceptance of telerehabilitation interventions. Satisfaction was supported by experienced health benefits, increased self-efficacy and emotional safety. We identified four key factors of potential improvements in long-term maintenance telerehabilitation: i) adherence to different components of the telerehabilitation intervention is dependent on the level of focus provided by the health personnel involved; ii) the potential for regularity that lies within the technology should be exploited to avoid relapses after vacation; iii) motivation might be increased by tailoring individual consultation to support experiences of good health and meet individual goals and motivational strategies; iv) interactive functionalities or gaming tools might provide peer-support, peer-modelling and enhance motivation.

Challenges included motivation for exercise over the long-term especially without supervision from healthcare personnel. Our experience from running the pilot study and the iTrain study also revealed challenges with transport of equipment and teaching in how to use the technology in the participants' homes, mostly due to long travel distances and limited time available for us since we were not located in the same area than all participants. Local health personnel seems vital in implementing full-scale programs outside urban settings, especially if these include the use of training equipment such as treadmills or bicycles in the participants' homes.

4.1 Feasibility of the intervention

Findings reported in this thesis and its related papers showed that long-term exercise maintenance via telerehabilitation comprising supervised treadmill exercises in the participants' homes via individual real-time videoconferencing was feasible and safe for people with COPD. The equipment, technology and supervision model used was acceptable for participants with moderate to severe COPD.

Participants in the pilot study expressed that the program provided emotional safety due to regular meetings and access to specialist competence. A study comprising a model for supervision and monitoring during exercise training similar to ours suggested that the monitoring provided via pulse oximetry and an experienced physiotherapist was sufficient to allow safe and effective exercise training for people with COPD at home (Holland et al., 2013a). Moreover, no important adverse events related to the program or exercise training itself occurred during our studies. However, two of the Norwegian participants that dropped out from the telerehabilitation group experienced cognitive or psychological comorbid diseases causing them to withdraw from video conference follow-up during the first year of the intervention. The third participant from Norway that dropped out during the first year died after a COPD exacerbation. All participants recruited in the iTrain study had a history of at least one COPD-related hospitalisation prior to enrolment, hence being at high risk of future exacerbations of the disease (Sadatsafavi et al., 2018). Re-hospitalisation and death rates one year after a COPD-related hospitalisation are reported as high as 25% and 21%, respectively. After five years, re-hospitalisation and death rates are 44% and 55%, respectively (McGhan et al., 2007). More recently, a study on 35 994 individuals with COPD reported that the first severe exacerbation during an average follow-up of 3.21 years was associated with a 75% increase in the risk of future severe exacerbations, which was reduced to 11% for the fourth severe exacerbation (Sadatsafavi et al., 2018). Furthermore, researchers have suggested that there is substantial heterogeneity in the rate of severe COPD exacerbations among individual patients so that the rate of exacerbations may vary from year to year (Han et al., 2017, Sadatsafavi et al., 2018). When conducting research on such frail individuals with a progressive chronic disease as those included in the iTrain study, one could expect some deterioration of symptoms and disease severity despite the long-term intervention provided. With this, our findings regarding adverse events are not surprising.

4.1.1 Patients are ready to use telerehabilitation interventions

During the randomisation process in the iTrain study, we identified a desire for telerehabilitation interventions among the volunteer participants as many expressed dissatisfaction with being randomised to the control group, and some even dropped out from the study due to their disappointment. A recent survey (Seidman et al., 2017) among people attending conventional pulmonary rehabilitation supports our observation, as the majority of patients expressed a substantial technology engagement, access to devices and willingness to use telerehabilitation, especially those younger than 70 years and regular users of technology. However, despite many had access to technology and rated their computer and Internet skills as adequate, few did actually use technology to search health information online (Seidman et al., 2017). Interestingly, in our studies, previous computer skills did not seem to be a barrier for use of the telerehabilitation program when face-to face education and a written education manual was provided, as participants with low computer literacy also managed to use the intervention intuitively.

To sum up, our findings related to feasibility of long-term exercise maintenance via telerehabilitation in COPD are in tandem with other short-term intervention studies on telerehabilitation for those with COPD (Burkow et al., 2015, Burkow et al., 2013, Holland et al., 2013a, Marquis et al., 2015, Minet et al., 2015, Tsai et al., 2016) and one other long-term maintenance telerehabilitation program (Vasilopoulou et al., 2017).

4.2 Effects of the intervention

4.2.1 Clinical effects

In the absence of any maintenance strategy, benefits of pulmonary rehabilitation seems to diminish after 6 to 12 months (Spruit et al., 2013b). The reason for this decline includes decrease in adherence to therapy, especially long-term regular exercise, progression of underlying disease and comorbidities, and exacerbations (Carr et al., 2007). Our telerehabilitation intervention aimed to support patients with COPD in maintaining exercise routines over a two-year period. The findings described in this thesis and related papers revealed that functional walking capacity, lung capacity, health status, symptom burden and quality of life were all maintained over the long term.

Both participants in the pilot study and participants in the telerehabilitation group of the iTrain study improved their walking distance with more than 30 meters after the first year of telerehabilitation, which is considered to be a clinically important difference (Holland et al., 2014). A study investigating longitudinal change in 6MWT on a Norwegian cohort of patients with COPD found that walking distance was maintained after 1 year, but decreased significantly after 3 years. The decrease over time was only evident for patients with severe and very severe COPD. Furthermore, participation in pulmonary rehabilitation, self-reported vigorous physical activity and an increase in FEV_1 were significant predictors of a positive change in walking distance (Frisk et al., 2014).

A surprising difference in the results between our two studies was that participants in the pilot study, despite considered optimised in health status after the recent pulmonary rehabilitation program, seemed to improve more in lung capacity, symptom burden and health-related quality of life after one year than their counterparts in the iTrain study. One explanation might be that the attendance to a conventional inpatient pulmonary rehabilitation program before enrolment made it easier for the tele-physiotherapist to support participants in self-management strategies and health enhancing behaviour. Participants in the iTrain study were older, had a more severe disease, and were not educated in self-management and health enhancing behaviour. Even though the tele-physiotherapists provided a dialogue on self-management routines and individual goal attainment, the focus was oriented towards exercise routines and the participants did not receive the full interdisciplinary education which is common and highly recommended in conventional centre-based programs (Blackstock et al., 2018). The effects of our telerehabilitation intervention might have been larger if it had been provided by an interdisciplinary team as piloted in other studies (Burkow et al., 2015, Burkow et al., 2013, Vasilopoulou et al., 2017). However, physiotherapists are an important member of the pulmonary rehabilitation team and are present in most programs (Desveaux et al., 2015). One easy way to provide a more formal education in telerehabilitation interventions is to use pre-filmed educational videos. One study showed that education via pre-filmed videos were acceptable to patients participating in a pulmonary rehabilitation program and were as effective in improving patients' knowledge of COPD as spoken talk (Ward et al., 2018).

To date, only eight RCTs evaluating telerehabilitation against conventional pulmonary rehabilitation or standard care have been published. The evidence base of the clinical effects of telerehabilitation in COPD still is limited. However, the published studies yield positive benefits in regards of functional walking capacity, dyspnoea, symptom burden, health-related quality of life, self-efficacy, physical activity profile, lower risk of acute COPD exacerbations and hospitalisations, and time to first hospitalisation and death (Bernocchi et al., 2018, Bourne et al., 2017, Chaplin et al., 2017, Tsai et al., 2017, Paneroni et al., 2015, Vasilopoulou et al., 2017). The optimal telerehabilitation intervention for people with COPD has not been identified yet, and may vary across settings (Vitacca and Holland, 2018).

4.2.2 Healthcare utilisation and cost-effectiveness

Exacerbations and re-hospitalisations are expected to increase along the disease trajectory. Results from the pilot study were encouraging and suggested that telerehabilitation could maintain benefits over time, prevent deterioration and limit the use of hospital resources. Results from the iTrain study on the primary outcomes (hospitalisations and ED admissions) and on cost-effectiveness (cost-utility analysis) will represent new knowledge. However, these data have not been analysed yet. More RCTs providing evidence of cost-effectiveness are needed.

4.2.3 Adherence

Program effectiveness depends on adherence (Sabaté, 2003). Adherence was used in this thesis to describe the degree to which a participant correctly followed the recommended use of the website for self-management and conduction of their prescribed exercise regime. According to the World Health Organization, only about 50% of patients with chronic diseases follows their treatment recommendations (Sabaté, 2003).

In the pilot study, the average adherence rate for diary registrations and training sessions was 43.3% and 56.2%, respectively. Compared to a nine-month intervention consisting of a web-based home exercise program, an activity coach for ambulant activity registrations and feedback, self-management via a web-based triage diary, and teleconsultations (Tabak et al., 2014c), adherence in the current study was higher for the training sessions, but lower for the web-based diary. Reasons might be that our intervention had a stronger focus on exercise rather than on monitoring symptoms and early recognition of exacerbations. A more active education on the recognition of early symptoms of exacerbation and the importance of treatment together with a provision of a straightforward treatment regimen might support participants' adherence to fill in the diary. On the other hand, the patients in our pilot study were in a quite stable condition of their disease, and registering symptoms every other day (50% adherence) throughout a period of two years might be enough to detect early changes in symptoms and start treating exacerbations as soon as possible. An average adherence rate of 56.2% for the training sessions equals to 1.7 training sessions per week. Compared to recommendations of 3 training sessions per week, this rate is probably too low to maintain the experienced health benefits and increased physical performance. Even though the average adherence rate was kept lower than recommended, we consider the intervention successful as all participants maintained their exercise and self-management routines for the 2-year period. No other studies have succeeded in such a result. However, we believe that while a lower adherence for the diary registrations does not have any negative impact, it is important to focus on patient's compliance to exercise, which is the key feature of conventional centre-based pulmonary rehabilitation programs as well as of the current telerehabilitation intervention.

Adherence rate for training sessions increased during the first three months of the pilot study to a level close to the recommendation. This could be due to a learning effect or an increase in motivation. Adherence was also affected by seasonality. The participants were encouraged to take time-off and did not receive follow-up via videoconferencing from the tele-physiotherapist during holidays. This influenced the lower adherence in these periods. As the participants appreciated the regularity of the telerehabilitation intervention and found it difficult to start exercising again after holidays, we would recommend to exploit the potential for regularity that lies within the technology. Future long-term telerehabilitation interventions could benefit from prescheduled peer-group meetings or exercise sessions via videoconferencing, mobile text message reminders aimed to motivate individual training, online follow-along exercise videos or other gaming elements for exercise training during holidays to avoid relapses.

The wide range of individual adherence rates in the pilot study (from 99.1% to 16.3% for the training sessions) shows that, as for conventional pulmonary rehabilitation programs, one size does not fit all.

4.3 Benefits and potential improvements

Findings from our mixed methods study suggest that the potential of long-term telerehabilitation over the existing offer of exercise maintenance programs after conventional pulmonary rehabilitation in Norway is threefold. Telerehabilitation has the ability to overcome geographical distance. A travel time to a rehabilitation facility greater than 30 minutes is a known barrier to attending pulmonary rehabilitation and exercise programs for patients with COPD (Rochester et al., 2015). Another advantage of long-term telerehabilitation lies in the specialist access and the potential regularity of follow-up by the same health personnel over a long period.

Participants perceived the exercise and monitoring equipment and the technology used in our interventions as user-friendly. Their main complaint was the stability of the videoconference connection. Access to an adequate data network might be a major challenge especially for remote places where such services might not be fully developed. Others have also emphasised that the effective delivery of telerehabilitation requires an adequate data network (Holland et al., 2013a). However, the quality and speed of many broadband suppliers have improved during the last few years, even in Northern Norway. Yet, more than an adequate data network is required for an effective telerehabilitation intervention. As few telerehabilitation interventions have evolved beyond the pilot phase, understanding the determinants of success is key to design better interventions. We received feedback on functionality in the focus groups during the pilot study, and made changes to the webpage used for the iTrain study so that it was better suitable to the needs of the participants and physiotherapists involved. Through this work and related research, we identified four key factors related to potential improvements for future telerehabilitation interventions: i) adherence to different components of the telerehabilitation intervention is dependent on the level of focus provided by the health personnel involved; ii) the potential for regularity that lies within the technology should be exploited to avoid relapses after vacation; iii) motivation might be increased by tailoring individual consultations to support experiences of good health and meet individual goals and motivational strategies; iv) interactive functionalities or gaming tools might provide peer-support, peer-modelling and enhance motivation. Only one group of healthcare personnel, namely physiotherapists, provided our telerehabilitation intervention. This represents a limitation to our intervention. To adhere stronger to the definition of pulmonary rehabilitation, we recommend that future telerehabilitation programs should be patient-tailored and provided by an interdisciplinary team of engaged healthcare personnel. Tailoring could be provided by visualisation of individual goals and goal attainment or maintenance of exercise-, self-management or physical activity routines (Froisland et al., 2012), by including motivational messages (Higgins, 1998, Antypas and Wangberg, 2014a), by providing social support via group exercises (Burkow et al., 2015), by online gaming tools (Tabak et al., 2015), chat rooms or discussion forums (Antypas and Wangberg, 2014b). Persuasive technology designs may also enhance adherence and provide tailored elements (Blackstock et al., 2016, Oinas-Kukkonen and Harjumaa, 2009). Persuasive technology is computer software or information systems designed to reinforce, change or shape attitudes and/or behaviours without using coercion or deception (Oinas-Kukkonen and Harjumaa, 2009). Such technology designs can reduce complex behaviour into simple tasks that help users to perform the target behaviour and visualise the benefit/cost ratio of a behaviour. People have a tendency to become more motivated to change behaviour if the effort to make the change complies with what we gain. For example, a website for smoking cessation can provide calculations on how much money a user could save by quitting. Furthermore, persuasive technology can guide users through a learning process by offering self-reflection questions or suggestions for actions based on results from a quiz. Visualisation of the users' performance or status can support them in achieving goals. Systems that offer reminders, praise, and rewards might also have the capability to persuade their users (Oinas-Kukkonen and Harjumaa, 2009).

Individual interviews conducted with Norwegian participants in the iTrain study supported that the changes we made to the intervention were beneficial as all interviewees described the website and the technology used as user-friendly *(Unpublished results).* Technological improvements are further elaborated in *Paper III*.

We gained a lot of insight through the conduction of two focus groups where the feasibility of the intervention was discussed with the participants. To support future implementation of telerehabilitation interventions and ensure that such interventions are a viable option for all partners involved, we recommend involving all users (both patients and healthcare personnel) at an early stage of development.

4.3.1 Participants perspectives on factors affecting satisfaction and adherence

In the pilot study, participants highlighted health benefits, experienced in terms of increased physical performance and self-management, as the main factor affecting satisfaction. Despite having a chronic disease, the participants gave an optimistic and varied picture of their definitions of good health. It seems important to foster these positive perspectives of health in long-term telerehabilitation interventions. Good health is often seen as medicine's main goal (Nordenfelt, 2007). If individual experiences of good health represent a primary objective in long-term telerehabilitation services for patients with COPD, health professionals cannot rely on following up all patients in the same manner. It becomes important to find out what corresponds to the patients' "own peak" and what good health is for the individual patient. This corresponds well to recent holistic views of health and theories of health promotion (Tones and Tilford, 2001, Huber et al., 2011, Antonovsky, 1996, Nordenfelt, 2007, Walseth and Malterud, 2004). It has been argued that telerehabilitation might contribute to more individualised treatment processes and flexibility in the patients everyday life (Thorup, 2017). To fulfil this prophesy, it is important to consider how the technology can be tailored to the individual patient. A pilot study (Yan and Or, 2017) on acceptance of a computer-based self-monitoring system for diabetes mellitus and/or hypertension found that participants were more likely to form positive feelings and intentions towards the use of the e-health technology if they perceived the technology as useful for their disease self-management. Yan and Or, headlights the importance of performing careful studies on the participants' needs, preferences and expectations to provide information about what functions to incorporate in the technology (Yan and Or, 2017).

Participants in our pilot study expressed an increase in self-worth and acceptance of their condition. They became more aware of their own needs and how they could fend for themselves. Despite feeling vulnerable, patients with COPD often come to an acceptance of their situation, which lead them to be able to adapt to their physical limitations and make the most out of their situation (Hellem et al., 2012). Their condition is perceived as a "way of life" rather than an illness, where symptoms and health problems become the normality. This "passive acceptance" might hinder patients to address healthcare needs (Pinnock et al., 2011). In contrast, the participants in the pilot study developed a newfound control over their own health situation and a renewed interest in their own health. When taking actions in terms of exercising, they felt they could cope with the vulnerability and stigma from having a chronic and often self-inflicted disease. Increased awareness and interest in once own health after using telemedicine interventions have been reported in a systematic review (Morton et al., 2017).

Conventional pulmonary rehabilitation is patient-tailored, and core generic strategies such as goal setting, goal assessment, problem solving and decision-making are important elements in self-management for patients with COPD (Spruit et al., 2013b). Patients' goals and resources are often assessed against their specific context and opportunities in the environment (Solli, 2011). The pilot study did not have a formal functionality for goal setting and goal attainment included in the website. Maintenance of motivation was perceived by participants as a main challenge. They were motivated to exercise as long as they experienced progress in physical capacity and the exercise program could be progressed. However, motivation decreased once their threshold for progress in physical capacity was reached. This happened for most of the participants after the first year of follow-up. Adherence might benefit if patients with COPD are involved in their own rehabilitation process. An agreement of goals and methods between the patient and the helper is seen as an important key to the change process (Bordin, 1979). Further, patients with COPD might need support to define visible results and appraise their newly acquired competences to be able to implement them in everyday life (Guo and Bruce, 2014, Mousing and Lomborg, 2012). To have a stronger focus on long-term maintenance of motivation, a template for goal setting and goal attainment was added to the website used in the iTrain study.

A previous qualitative study revealed that patients with COPD expressed and alternated between four attitudes towards telerehabilitation: indifference, learning as part of situations in everyday life, feeling of security, and motivation to perform physical exercise (Dinesen et al., 2013). These experiences with telerehabilitation are to some extent congruent with our findings. In the aforementioned study, indifference was related to measuring stable values (of blood pressure, pulse, weight, spirometry and oxygen saturation). This implied that stable patients with COPD would not benefit as much from telerehabilitation as patients with more unstable conditions. Pulmonary rehabilitation is recommended for all patients with COPD, even patients in earlier stages (Spruit et al., 2013b). Patients in earlier stages are often medically stable, but they would still benefit from rehabilitation in terms of enhanced mastery of everyday life and increased physical performance. Visualisation and documentation of tangible signs of improvements and maintenance might reduce the feeling of indifference and make long-term telerehabilitation suitable and beneficial for patients in stable conditions as well. Future telerehabilitation services, particularly in chronic diseases, should therefore also be patient-tailored, focusing on documentation and evaluation of goals, progress and maintenance. Likewise, it is important to assess individual interpretations of good health and preferences in motivational strategies so that every participant can be followed up according to his or her own needs and values.

4.4 Challenges of telerehabilitation

A recent review of the literature evaluating telemonitoring for people with COPD performed by Vitacca et al. (2018) revealed several barriers and challenges to telemedicine development which may be relevant for telerehabilitation implementation as well. These include a variety of difficulties related to work organisation, cultural barriers and technical concerns (Table

8)(Vitacca et al., 2018). Challenges considered relevant for telerehabilitation are elaborated below. Some challenges are also described as suggestions for future research.

Table 10 Barriers and challenges to telemedicine development

Work organisation	**Cultural barriers**	**Technical concerns**
Short-term funding	Low level of interest	Face-to-face visits are preferred
Sustainability	Technology not being user-friendly and support the needs of the users	Follow-up plan customized to each patient
Integration of new technologies into routine service	Low acceptance	Complexity of the system
Time limitations	Individuals illness and health literacy	Many different software, hardware and telecommunication options
Requirements for technical competence	Too much responsibility for patients with chronic disease	Poor specification design for each condition
Lack of standardisation of best practice	Poor knowledge and culture for use of technology	Legal/confidentiality problems between subjects involved (poor standard of care, manipulation of data, poor protection of data)
Lack of interoperability among different solutions	Lack of knowledge of e-health among patients, citizens and healthcare personnel	The network may show difficulty to ascertain responsibilities and potential obligations of healthcare personnel
Limited evidence of cost-effectiveness	Scepticism from doctors	High start-up costs
		Absence of reimbursements

Table from Vitacca et al. (2018).

4.4.1 Practical challenges in the iTrain study

Recruitment and home visits were rather time consuming. Recruitment in Harstad required a 3-hours boat ride one way, and travelling to Kirkenes took 30 minutes on a plane. These trips often included an overnight stay. Paolo Zanaboni and I who delivered and provided the initial teaching on the equipment to participants in the iTrain study in Norway travelled more than 8 000 kilometres, using plane, ferry, speedboat, shuttle boat, bus and car. This corresponds to a travel distance from Tromsø to Rome, and back, by car. In some cases, the treadmills were delivered by a transport bureau, but sometimes we brought them with us in a van when conducting the home visit. If we needed to carry the treadmill up or down one or two floors, we were both present, otherwise only one person was sufficient to deliver the equipment. We calculated every visit to be at least one hour, but we often stayed longer. Some participants needed to be visited more than one time.

There were also some problems with the technical equipment. The Norwegian IT-support consultant and our technical support consultant in the iTrain study had 34 requests from physiotherapists and participants regarding technical problems or updates on the software related to the videoconference system or iPad *(Unpublished results).*

4.4.2 Legal issues: data security and confidentiality

Telerehabilitation systems might be rather complex, involving data transmittance, real-time video interactions between patients and healthcare personnel, and storage of data in archives or clouds. Some systems also utilise hardware and software provided by international companies (Donner et al., 2018). Legal principles applying to centre-based rehabilitation services are equally valid for telerehabilitation (Vitacca and Holland, 2018). Healthcare personnel providing rehabilitation services are either ways bound by the duty of confidentiality and are not allowed to disclosure medical information without the patients' consent (The Norwegian Directorate of Health, 2015, Præstegaard, 2017). However, telerehabilitation holds unique legal challenges related to use of technology compared to centre-based rehabilitation. These includes possible failure to provide an acceptable standard of care, failure to equipment and software, electronic data can be manipulated, risks related to data protection (poor confidentiality, authenticity, data report, procedure certification, security and privacy), misunderstanding among patient, family and healthcare personnel, and not clarified responsibilities among healthcare personnel (Donner et al., 2018, Vitacca and Holland, 2018). Electronic telerehabilitation equipment connected to the Internet used in private homes is more exposed to unauthorised access. One way to limit potential risk of unauthorised use is to implement log-on identification and automatic log-out mechanisms after a period without interaction between user and system (Henriksen et al., 2013). Other measures to increase security in telerehabilitation interventions are: encrypted storage of sensitive user data and encrypted transfer of data, messages, and videoconferences (Henriksen et al., 2013). Education in secure behaviour and awareness about privacy risks among users may decrease unwarranted incidents and threats related to confidentiality risks (Henriksen et al., 2013). In Norway, e-health services require a Security Level 4 to be used in clinical practice. Some telerehabilitation programs are group-based and participants might be able to hear and see other participants during a videoconference session. Such interventions require confidentiality not only between patient and healthcare provider, but also among all the participants. An agreement on not to disclose medical or personal information about other participants might be signed by enrolment to the program (Præstegaard, 2017). Enrolment of patients to telerehabilitation program should be governed by “informed consent”. This allows patients to be adequately informed about content of the service, how confidentiality is ensured, potential risks and how to reduce them (Vitacca and Holland, 2018). Careful considerations about data security and patient confidentiality are paramount for properly use of telerehabilitation services.

All participants in our research were thoroughly informed about what the interventions implied and provided signed written consent to participation. In our interventions, communication was performed with Advanced Encryption Standard encryption. This minimized the risk of videoconferences being hacked by others. Access to the website and videoconference system was anonymised by use of study identification numbers (e.g. no001), and the contact information of the study participants was only available to designated study personnel. Confidentiality is also better secured in individual videoconferences than in group videoconferences where participants’ relatives or other visitors might be listening in on the conversation in the group. All data collected in our studies were anonymised before publication in journals.

4.4.3 Economic considerations

The cost-effectiveness of telerehabilitation interventions is not fully evaluated yet. To evaluate the real cost-effectiveness it is important to understand and reveal all costs related to conventional centre-based rehabilitation and standard care, as well as describing the costs of the new intervention, as “standard care” might vary among European countries and even within each country (Vitacca et al., 2018).

To set up a telerehabilitation system in the homes of a patient, transportation of equipment and an initial home visit are often required. Funding and reimbursement for this and to the healthcare professionals providing the telerehabilitation service may not be well established in many countries (Vitacca and Holland, 2018).

4.4.4 Comorbidities and health limitations

Comorbidities are not a sufficient reason to exclude patients from pulmonary rehabilitation, exercise (Burtin and Zuwallack, 2018) or telerehabilitation. However, every comorbidity in the individual patient must be taken into account when prescribing exercise and other components of rehabilitation provided via centre-based programs or telerehabilitation. In the iTrain study, participants reported having on average 2.6±1.2 comorbidities. Of the 29 Norwegian participants enrolled in either, the telerehabilitation group or the treadmill group 38% experienced comorbidities or COPD exacerbations that hindered them to exercise on the treadmill for a shorter or longer period within the first year. Moreover, health limitations such as impaired cognition, sight and hearing impairment could impact on how the participant will be able to use a telerehabilitation intervention (Donner et al., 2018).

4.4.5 Health literacy and computer literacy

Health literacy is the degree to which an individual is able to obtain, process, communicate and understand basic health information and health services to make appropriate decisions regarding one's own health (Institute of Medicine, 2004). Low levels of health literacy is common in patients with COPD and is linked to impaired self-management behaviour (Kale et al., 2015). It can also moderate the learning process in pulmonary rehabilitation (Blackstock et al., 2018). How level of health literacy affects the ability to use e-health technology is not clear and further research is needed (Emtekær Hæsum et al., 2016). One systematic review synthesising users' experience of digitalised self-management interventions for chronic health conditions found that the intervention enhanced health literacy by helping the participants to be more aware of their condition, by making them more capable to take decisions about their own health, and by enabling participants to engage in discussions as an equal with the healthcare personnel (Morton et al., 2017). Participants in our pilot study also had this experience.

The participants' familiarisation with technologies may be a barrier to use telerehabilitation. A survey performed in 2010 showed that American adults with chronic diseases are significant less likely to have access to the Internet than healthy adults (62% versus 81%, respectively). People affected by multiple diseases are even less likely to have Internet access, as only 52% reports to go online (Fox and Purcell, 2010). However, telerehabilitation studies reported that participants perceived the equipment as easy to use (Tsai et al., 2016, Burkow et al., 2015, Holland et al., 2013a). Participants in our pilot study shared this opinion, even though they sometimes experienced problems with the network and website.

Successful use of e-health technology is also depended on the healthcare personnel's knowledge on how to use the equipment. Yet perhaps more important, is their reflections on how technology affects work practices in telerehabilitation. Implementing new technologies might influence professionalism, collaborative relationships, core tasks and how healthcare personnel prioritises and acts towards the patients (Esbensen and Nickelsen, 2017). This is elaborated in the following paragraph.

4.4.6 A new meeting arena between patient and healthcare personnel

Traditionally, rehabilitation has required the patient and healthcare personnel to be located at the same place, at the same time. With telerehabilitation, this requirement is no longer needed as the patient can access educational content and exercise programs on his own and complete a telerehabilitation program in his own pace where he wants. How does this change the interaction between patient and healthcare personnel? What can be gained and what can be lost on this digitalised pathway? A qualitative meta-synthesis (Andreassen et al., 2018) explored digitally mediated patient-healthcare personnel interactions and identified four key concepts that point at structural processes of change: respatialisation, reconnection, reaction and reconfiguration. Respatialisation referred to healthcare being relocated in space and time, and that this changed the meaning and experience of patients' homes (and the primary health space). Respatialisation comes with relational consequences, which might lead to instrumental, emotional and contested reconnections. Paradoxically, technology may empower patients to act autonomously, but it also may lead to new dependencies. The synthesis suggested that use of technology alters social identities and interaction chains.

Patients’ reactions to these altered states can be found on a continuum between domestication and resistance. Some patients adapts well to technology, some resigns and others refuses to use the it. Health work and labour processes are reconfigured through e-health. E-health can redefine professional roles and create new ways of working. Which in turn can lead to negotiations and conflict on who does what, what healthcare work consists of, and what it means to be a competent healthcare professional. E-health can create new forms of labour process that includes patients and sometimes their family as well. Use of technology can also reconfigure how patients and their relatives think and act related to the disease and influence relational practices in the families (Andreassen et al., 2018).

Similarly to the previous synthesis, a systematic review and meta-synthesis (Brunton et al., 2015) of qualitative studies exploring the experience of both patients, their carer and healthcare personnel with a variety of telehealth interventions in COPD identified conflicting consequences of telehealth. Findings revealed three overarching themes that may either hinder or promote positive user experience with telehealth: i) telehealth influence on the moral dilemmas of help seeking (which may enable dependency or self-care); ii) telehealth transform interactions (which may increase risk or reassurance); and iii) telehealth reconfigures work practices (which may cause burden or empowerment) (Brunton et al., 2015). Comprehensive monitoring and self-reporting of symptoms may, instead of promoting independence foster patient dependency on healthcare personnel for feedback and assessment among those with COPD (Goldstein and O'Hoski, 2014, Donner et al., 2018). In our pilot study, participants described how the technology could make it easier for them to withdraw themselves without confrontation from the collaboration with the physiotherapist. If the follow-up did not fit their goals, mood or values, or the relationship felt too challenging, they could become “unavailable” by “loosing network access”. Participants in our pilot study also perceived that monitoring via telerehabilitation contributed to emotional safety. Others have experienced monitoring as violation of privacy (Thorup, 2017).

When we are not communicating face-to-face, the non-verbal communication might be limited and the contextual relationship weakened. With this, the risk is that healthcare personnel fails to observe symptoms, signs or personal interests in the patient (Præstegaard, 2017) that might contribute to increased health and/or motivation to health enhancing behaviour. Other concerns are that telerehabilitation might contribute to increased loneliness as patients meet their therapists through the screen and remain isolated in their homes (Præstegaard, 2017).

4.4.7 Implementation into routine healthcare

Policy makers in Norway have shown a strong interest in offering e-health solutions and welfare technologies to the population to reduce the demand of expensive hospital admission whilst helping people to live independently for longer. Despite the current e-health strategy, few telemedicine solutions have been successfully integrated into routine healthcare and, to our knowledge, none for people with COPD (The Norwegian Directorate of E-health, 2018). A telemonitoring service for patients with COPD have been used in routine practices locally in one hospital (Knarvik et al., 2014, Zanaboni et al., 2014, Linjord, 2015), but no telemonitoring or telerehabilitation services have been implemented into routine healthcare at national level.

At the Maugeri Centre for Telehealth and Telecare (MCTT) (Scalvini et al., 2018) in Italy, multidisciplinary e-health services have been successfully implemented into routine healthcare after hospital discharge for people with COPD, chronic respiratory insufficiency, amyotrophic lateral sclerosis, neuromuscular diseases, chronic heart failure, post-stroke and post-cardiac surgery patients. People with COPD and chronic heart failure account for 80% of the patients treated. The content of the e-health service vary depending on the underlying chronic disease. Key elements are a structured physician-directed and nurse-managed telephone support and telemonitoring service provided to the patients’ homes. The service also involves several disease-specific educational sessions before discharge, aimed to educate patients in self-management of their disease and early recognition of signs and symptoms of exacerbations. Patients are contacted weekly after discharge to reinforce adherence to self-management routines and counsel the patient on weight management, physical activity, smoking cessation, dietary changes, stress management and other specific targets set for the individual patient. Patients can contact the staff through a 24h/day open call centre out of the scheduled weekly contacts if they have any enquiries. An individually tailored exercise program is prescribed and supervised by a physiotherapist via home visits, scheduled videoconferences and/or telephone appointments. Videoconferences are also used to deliver an educational program and for counselling by the nurse. Patients are supplied with telemonitoring equipment depending on disease-specific clinical requirements. This equipment transmits data instantly to the MCTT via a secure data connection. Results from a series of studies demonstrated that the e-health service provided by MCTT to people with COPD is feasible, more effective in reducing re-hospitalisations (-36%), acute exacerbations (-71%) and urgent calls to general practitioners (-65%) than a control group. Improvements in quality of life were also observed among people with COPD enrolled to the e-health program (Scalvini et al., 2018). Another example of routine practice is a 6-month telemonitoring service for patients with COPD called the Nuovi Reti Sanitarie (New Healthcare Network) in the Lombardy region in Italy (Luzzi et al., 2017).

Despite optimistic evidence on the efficacy and benefits of telerehabilitation, there seem to be some barriers to the implementation of such services in routine healthcare (See also table 8). One main barrier is related to policies and economic incentives. Such services must be institutionalised, recognised, defined in respect to requirements and quality assurance, and have proper economic incentive in form of reimbursements.

Other barriers for implementation of telerehabilitation in routine healthcare include the availability of equipment and functional procedures on how to deliver equipment and to teach how to use it (Donner et al., 2018). Challenges related to the delivery of equipment was also faced in our studies, as participants were spread over Northern Norway and cooperation with local helpers were not established. For those with respiratory diseases located away from urban settings, another barrier is how to conduct a thorough initial assessment of lung function and physical capacity. Rural dwelling patients might find it difficult to travel long distances to a specialised health facility to conduct these assessments. During the recruitment process in the iTrain study, five of the 89 who declined to participate specified long travel distance as main reason for not participating in the study. It could have been possible to cooperate with local general practitioners' offices and physiotherapists, but this would have added a high degree of complexity to establish contacts and routines for exchange of sensitive personal health information with numerous local healthcare services in the different communities.

4.5 Variations in physical activity across countries and seasons

The cross-sectional study aimed at investigating whether there were differences in physical activity levels between Norwegian, Danish and Australian people with COPD. Results revealed some differences across countries after controlling for disease severity. Danish participants, who spent significantly longer periods of the day in sedentary activities and less time walking at higher intensities, had significantly lower functional walking capacity (indicated by 6MWD) than participants from other countries. There is a strong association between physical activity and physical capacity (Pitta et al., 2005). Participants from Norway and Australia had a median walking distance of >400 meters on the 6MWD and achieved ≥30 minutes of moderate-to-vigorous activity, whereas Danish participants walked <400 meters and did not meet the value of ≥30 minutes of moderate activity which is recommended by the American College of Sports Medicine (Haskell et al., 2007). Such relationship between physical capacity and intensity of physical activity has been observed by Pitta et al (Pitta et al., 2005). However, high physical capacity does not always translate into higher levels of physical activity, as physical activity is also influenced by psychological factors like habit, self-efficacy and health beliefs (Thorpe et al., 2014, Burtin et al., 2015). Strategies to reduce sedentary time may be clinically relevant in COPD (Lahham et al., 2016), for example via reduction of cardiovascular risk (Maclay et al., 2007, Wilmot et al., 2012) and improvement of physical functioning (Gibbs et al., 2017). Strategies that target sedentary behaviour might have a potential for increasing overall physical activity. The cross-sectional study could not answer why Danish participants with COPD were more inactive than the other groups, except that their disease severity was greater and physical capacity poorer. In addition, they wore the activity monitor for longer each day and, by this, they might have recorded longer time in sedentary activities than their counterparts.

The cross-sectional study aimed also at establishing whether variations in physical activity levels were attributable to seasons. Although it did not reach statistical significance, there was a trend for the participants to walk more and with higher intensity during summer compared to spring, winter and autumn, regardless of geography. Climate and variations in weather conditions following the different seasons may influence levels of daily physical activity in COPD (Watz et al., 2014). Studies have reported lower number of steps during rainy and colder days, in winter and during extreme summer heat (Togo et al., 2005, Sewell et al., 2010, Alahmari et al., 2015, Balish et al., 2017). A change in daily step count has also been observed during transition between different seasons (Wan et al., 2017). Results did not reach statistical significance due to the modest sample size in each group. However, the overall difference between summer (3502 steps/day) and winter (2373 steps/day) exceeded the minimal clinically important difference (between 600 and 1100 steps/day) in daily step count after pulmonary rehabilitation (Demeyer et al., 2016). An improvement of more than 600 steps/day after pulmonary rehabilitation is also reported to reduce the risk of hospitalisation in patients with COPD (Demeyer et al., 2016). We therefore considered the difference of 1129 daily steps between summer and winter to be of clinical relevance. Weather conditions and seasonal variations may influence outcomes in clinical trials and health registries measuring physical activity over time, irrespective of the interventions delivered, and should be taken into account when interpreting results.

4.6 Methodological considerations

4.6.1 Study designs, study populations and transferability

Results and discussions in this thesis are primarily based on two studies: 1) a pilot study investigating the feasibility of a long-term telerehabilitation intervention, the usability of the technology, and exploring participants' experience with the intervention, and 2) a RCT comparing the clinical effects and cost-utility of a long-term telerehabilitation intervention against a unsupervised exercise training at home and standard care. The Model for Assessment of Telemedicine (MAST) is a recognised model to evaluate the effects of empirical studies on telemedicine. According to the MAST model, it is necessary to conduct formative evaluation studies (e.g. participatory design-studies, usability studies or feasibility studies) before multidisciplinary effect studies (e.g. RCT) are performed. This is particularly important if the technology in question is still in a developmental phase and not tested on patients or personnel before (Kidholm and Dinesen, 2017). With this, our choice of conducting a pilot study was appropriate as such long-term telerehabilitation intervention had never been trialled before. The next step in the MAST model is to conduct a multidisciplinary evaluation of the effects of the intervention compared with one or more comparators in relation to seven different domains. These include description of the users health problem and the intervention, safety, clinical effects, patients perspective, economic aspects, organisational aspects, and socio-cultural, ethical and legal aspects (Kidholm et al., 2012). How our research complies with the MAST model is described in table 11.

Table 11 Evaluation of the pilot study and iTrain study based on the MAST model

Domain	**Data collection method and outcome measures used**
Health problem and intervention	The main health problem is the current need for increased accessibility and applicability of pulmonary rehabilitation in patients with COPD. The description of the telerehabilitation intervention we evaluated, together with a thorough description of the characteristics of COPD in general and the patients enrolled in the studies, are provided in this thesis and the related papers.
Safety	Safety in form of dropout rates and adverse events are registered. Technical reliability of the technology and equipment used is registered and also described as a challenge in qualitative focus groups.
Clinical effects	Valid and reliable outcome measures commonly used to evaluate clinical effects in this patient group were used in the evaluation of the telerehabilitation intervention (table 7). Internal validity of the studies are discussed below.
Patients perspective	Qualitative focus groups with ten participants in the pilot study and individual interviews with 5-8 participants from each site in the telerehabilitation arm were performed in the iTrain study.
Economical aspects	Changes in use of healthcare utilisation (combined number of hospitalisations and ED presentations) is the primary outcome of the iTrain study. A cost-utility analysis will be performed as a secondary outcome to verify whether the telerehabilitation and the treadmill interventions are cost-effective.
Organisational aspects	Assessment of the resources that need to be mobilised and organised before implementation of our intervention in routine healthcare, and potential changes or consequences this might imply, were not evaluated.
Socio-cultural, ethical and legal aspects	This thesis discusses and reflects over how socio-cultural aspects and relations might change between patients and healthcare personnel through telerehabilitation. Ethical and legal issues were considered before starting the study and described in *Paper IV*.

The third step in the MAST model is assessment of transferability. Transferability of results of studies investigating e-health interventions from one setting to another is a general problem (Kidholm et al., 2012). One reason is that organisation of healthcare services and technical infrastructure might vary between countries, and this can create substantial differences in applicability and cost per patient by introducing the same service into different countries (Kidholm et al., 2012). A strength related to transferability in our studies was that the iTrain study was an international study conducted in three countries. Our intervention was tested for both stable patients familiar to pulmonary rehabilitation (pilot study) and for patients more recently affected by exacerbations, most of whom non-familiar with rehabilitation (iTrain study). By this, our intervention was tested in a heterogeneous group, representative for a larger population of patients with COPD. The broad patient selection supports the external validity of our research and the implementation of such interventions in a real-life setting. Limitations that might affect transferability were the low sample size in the pilot study and the problems encountered with recruiting patients in the iTrain study. However, eventually, the iTrain study enrolled 120 participants with a dropout rate of 7.5% after the first year. This is within our initial sample size calculations for allowing a power of 95% to detect an incidence rate ratio of 0.60 on hospitalisation which were the main outcome in the iTrain study, with a type-I error (α) of 0.05.

4.6.2 Internal validity

Internal validity refers to what degree the study is free from systematic errors (bias). Randomisation to intervention and control groups in traditional RCTs is considered the best way to control threats to the internal validity. Likewise, it is important to ensure that the intervention groups receive the intervention as designed and that control groups not inadvertently receive components of the intervention. Furthermore, an accurate, reliable and preferably blinded collection of data is an important way of controlling the internal validity (Domholdt, 2005). Participants in the iTrain study were stratified by centre and disease severity before randomisation to preserve homogeneity between arms. Randomisation was web-based and the randomisation sequence was concealed from the research team. To ensure that the intervention was delivered correctly and equally by each site, the physiotherapists conducting the individual videoconferences and follow-ups of participants were provided with common project guidelines for exercise prescription, goalsetting, and practical instructions regarding the videoconferences. They were all experienced in pulmonary rehabilitation. However, individual differences in the way participants were followed up might have occurred. This also represents an issue in conventional pulmonary rehabilitation. Furthermore, the internal validity of our research was supported by use of external research assessors blinded to group allocation to perform the study follow-ups. Participants might have received other forms of medical or rehabilitation follow-up during the intervention period that might have influenced the results. However, to ensure that no participants was denied access to the best healthcare practice, any participant in the trial could undertake a conventional pulmonary rehabilitation programme at any time during the two-year study period if it was considered clinically indicated by their usual treating team.

4.6.3 Reliability

Reliability is the extent to which measurements are repeatable and free from errors (Domholdt, 2005). Common, validated and standardised tests and outcome measures were used to evaluate the telerehabilitation intervention. Threats to the reliability were multiple and different research assessors conducting the spirometry and 6MWT at each site. We also suspect that the number of comorbidities was underreported in the iTrain study among Danish participants, as they had registered fewer comorbidities despite having a more progressed and severe disease *(Paper V).*

4.6.4 Methodological considerations regarding the mixed method study

As most of the results in the mixed method study implemented in the pilot study *(Paper II)* were based on qualitative data, strengths and weaknesses were assessed against the four criteria for trustworthiness in qualitative research proposed by Guba and discussed by Shenton: credibility; transferability; dependability; and confirmability (Shenton, 2004). All participants were given the opportunity to express their experiences and reflections regarding attendance in the study through a triangulation of methods in a familiar atmosphere. Authors' immediate understanding of the participants' answers were summarised consecutively during the focus groups, so that participants' interpretations were confirmed, thus increasing credibility. We conducted a pilot study with a small number of patients with COPD. Results might therefore not necessarily be transferred to other settings or patient groups. Nevertheless, the findings are somewhat congruent with the existing body of evidence. In terms of dependability, an effort was made to transparently describe the research process and the analysis procedure. The conduction of the two focus groups and the analysis of the material were made by more than one of the authors, thus increasing confirmability. On the other hand, the physiotherapist conducting the videoconferences was also present during the focus groups. The participants might therefore have held back some personal thoughts. However, our overall impression is that triangulation of data collection allowed the participants to provide their critical views as well, thus reducing the effect of investigator bias. Despite being conscious of our preconceptions and theoretical background during data collection and analysis process, these might have affected our interpretations.

4.7 Suggestions for future research

Now that the feasibility of telerehabilitation for people with COPD has been established, future research should focus on providing more evidence of the efficacy, cost-effectiveness and long-term effects. Then the next step would be to understand how to deliver such programs optimally. Questions that still remain are discussed below.

4.7.1 Standardisation of best practice

Future challenges include standardising best practice of telerehabilitation to allow meaningful comparison of outcomes across studies and further allow a consistent implementation in routine healthcare. As described in this thesis, there is a large heterogeneity among telerehabilitation studies in terms of technology used, healthcare personnel involved, disease severity of patients enrolled, exercise modes and equipment, content of the educational component, degree of supervision, and program length. In addition, there is a large variability among outcome measures used in telerehabilitation studies. These findings stress the importance of future agreement on performance metrics and outcome measures to evaluate telerehabilitation interventions, to be able to provide quality healthcare via telerehabilitation, start international benchmarking, and provide recommendations for international standards based on evidence and best practice (Huynh and Stickland, 2016). In addition, achieving consensus on the content and costs of “standard” pulmonary rehabilitation is important so that potential benefits and cost-effectiveness of telerehabilitation can be better quantified (Vitacca et al., 2018).

All content components from conventional pulmonary rehabilitation are not always provided in telerehabilitation interventions. For example, education and social support are important components of pulmonary rehabilitation, and telemedicine holds an opportunity to deliver these components in a new way (Blackstock et al., 2018). However, their effectiveness when delivered via telerehabilitation has not been thoroughly evaluated.

We found that physical activity and other outcomes obtained after participation in the two-year pilot study were not maintained in the following year without supervision from the tele-physiotherapist, even though the participants kept the exercise equipment. More studies on long-term outcomes of telerehabilitation compared with conventional pulmonary rehabilitation (and usual care) are needed.

More research is also warranted on the security and confidentiality of patient data related to telerehabilitation services in general (Vitacca et al., 2018).

Broadening the scope of pulmonary rehabilitation with features from telerehabilitation

Different functionalities from telerehabilitation such as pre-filmed educational videos, exercise videos, and virtual game systems as described by Wardini et al. (2013), might have the potential to prepare people with COPD for conventional centre-based rehabilitation, as extra sessions during program delivery, as home exercises, or as a maintenance program after centre-based rehabilitation programs. The effectiveness of such approaches warrants future research.

4.7.2 Selection of the best candidates for telerehabilitation

So far, we do not know if there are subgroups of patients who benefit more, or could be harmed, by participating to telerehabilitation programs, or when telerehabilitation should be offered (e.g. disease severity, acute vs stable disease) (Vitacca et al., 2018). In our two studies, we experienced that it was easier to recruit stable COPD patients who were familiar with rehabilitation and exercising than more fragile and severe patients with a recent hospitalisation due to exacerbation. Suggestions for selecting candidates from other studies are conflicting. A qualitative study exploring patients' perspectives in an intervention comprising telemonitoring and unsupervised home exercises found that a small number of patients experienced indifference towards the telemonitoring measurements as it did not make sense for them to measure stable values (e.g. blood pressure, pulse, weight, spirometry and oxygen saturation) over time (Dinesen et al., 2013). This implied that stable patients with

COPD would not benefit as much from telerehabilitation as patients with more unstable conditions. Rochester and Clini (2018) suggested that individuals with less disease severity, fewer comorbidities, lower levels of disability and lower risk of adverse medical events are more likely to be better suited to telerehabilitation.

No association between motivational strategies and adherence rate was found in the pilot study. Consequently, we were not able to make conclusions regarding the process of selecting the best candidates for telerehabilitation. However, our findings were based on a small sample size and better results could be obtained if testing the intervention on a bigger target population.

A preference-based randomised control trial enrolling patients with COPD to telerehabilitation or conventional pulmonary rehabilitation based on the individuals' preference might produce knowledge on which patients prefer telerehabilitation and if preference can guide selection to telerehabilitation. Alternatively, if those choosing telerehabilitation have other characteristics than those choosing a face-to-face service? The latter question could be answered through a survey that also collected characteristics of the respondents. For our research group, the next research step might be to do a study on responders versus non-responders in the telerehabilitation intervention group of the iTrain study using multidimensional response profiling as described by Spruit et al. (2015).

Further, little is known about the feasibility and effectiveness of telerehabilitation for patients with other respiratory diseases.

4.7.3 Health economic benefits

The literature search described in paragraph 1.4.1 detected three published RCTs (Bernocchi et al., 2018, Vasilopoulou et al., 2017, Tabak et al., 2014a) and three upcoming RCTs (Zanaboni et al., 2016a, Hansen et al., 2017, Cox et al., 2018a) evaluating health economic benefits related to telerehabilitation. Nevertheless, more research is needed to articulate and conclude of the cost-effectiveness of telerehabilitation.

4.7.4 Patients perspective

Some research has already described the perspectives of those with COPD in e-health technology (Vatnøy et al., 2017, Brunton et al., 2015) and in telerehabilitation (Hoaas et al., 2016a, Burkow et al., 2015, Burkow et al., 2013, Tsai et al., 2016). However, future research should further address needs, preferences, attitudes and knowledge of the target population. Such knowledge might guide innovation of the technology, content and implementation of service in a way that can support adherence and long-term health enhancing behaviour.

4.7.5 Healthcare professionals perspectives

A successful implementation process of new health interventions is dependent not only on the patients, but also on the health professionals involved. To date, few studies (Brunton et al., 2015, Horton, 2008, Fairbrother et al., 2013, Fairbrother et al., 2012, Mair et al., 2008, Hibbert et al., 2004, Ure et al., 2011) have described the perspectives of healthcare professionals involved in e-health interventions for people with COPD. Only one study has explored healthcare professionals' experience with telerehabilitation for people with COPD (Damhus et al., 2018). It is important to address the needs, preferences, attitudes and potential barrier to adaptation and acceptance of telerehabilitation from the views of the service providers to be able to innovate and implement an effective and beneficial telerehabilitation service.

4.7.6 Implementation of routine service

For those who consider implementing a telerehabilitation component in their current pulmonary rehabilitation program, the evidence is promising, although additional research is needed (Huynh and Stickland, 2016). Before widespread implementation occurs, more research is required on organisational aspects of the delivery of telerehabilitation services. Other aspects to be considered include purchase and maintenance of equipment (e.g. should equipment be bought by patients vs equipment offered by healthcare providers), reimbursements and how to provide competence and training to the healthcare personnel involved. Moreover, it is important to describe, organise and clarify the needs for cooperation and shared responsibilities between specialist care services and primary care services, which is vital before a full-scale implementation.

5 Conclusions

The innovative two-year exercise maintenance telerehabilitation intervention investigated in this thesis and related papers is the first telerehabilitation intervention with such long-term follow-up.

Long-term exercise maintenance via telerehabilitation for people with COPD is safe and feasible. Findings from our pilot study and preliminary results for the telerehabilitation group of the iTrain study, are encouraging and suggest that long-term telerehabilitation can prevent deterioration in lung function, symptom burden and health-related quality of life, in addition, it can improve and maintain functional walking capacity over a longer period. This adds to the growing evidence that short-term telerehabilitation can achieve meaningful clinical benefits for this group of patients. Moreover, benefits similar to those of standard rehabilitation can be expected by a telerehabilitation program.

The advantage of long-term telerehabilitation over the existing offer of exercise maintenance programs after conventional pulmonary rehabilitation in Norway was threefold. Telerehabilitation has the ability to overcome geographical distance, provide specialist access in areas where this is not available, and provide regularity of follow-up by the same health personnel over a longer period. People with COPD were satisfied with the long-term follow-up and found the technology user-friendly. Satisfaction was supported by experienced health benefits, increased self-efficacy and emotional safety.

Long-term adherence to exercise routines was possible with telerehabilitation. However, maintenance of motivation for exercising was still a challenge despite regular supervision via telerehabilitation. Barriers for implementing telerehabilitation in routine healthcare are related to policies and economic incentives. In addition, practical concerns such as availability of equipment, functional procedures on how to deliver equipment and to teach how to use it might be other barriers. Other challenges to consider before routine implementation of telerehabilitation include difficulties related to work organisation and cultural barriers.

The findings in this thesis support the suggestion that long-term telerehabilitation for people with COPD is an alternative or supplement to conventional centre-based pulmonary rehabilitation. Centre-based programmes is still considered the best practice for pulmonary rehabilitation. However, telerehabilitation holds a great potential to expand the availability of pulmonary rehabilitation programs to a greater number of people who would benefit both in Northern Norway and worldwide.

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PAPERS I-V

APPENDICES