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### Towards health status guided care in COPD

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# TOWARDS HEALTH STATUS GUIDED CARE IN COPD

Using the Clinical COPD Questionnaire (CCQ)

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**Janwillem Kocks**

**Stellingen**  
behorende bij het proefschrift

## **TOWARDS HEALTH STATUS GUIDED CARE IN COPD**

Using the Clinical COPD Questionnaire (CCQ)

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Janwillem Kocks

1. Van de vele factoren die van invloed zijn op de gezondheidstoestand van mensen met COPD, is de longfunctie er slechts één en heeft een marginale rol (dit proefschrift).
2. Het meten en weten van de gezondheidstoestand van patiënten verandert het consult (dit proefschrift).
3. Voor het meten van de functionele status bij COPD patiënten zijn vele methodes beschikbaar, slechts weinigen zijn echter betrouwbaar en bruikbaar genoeg voor de dagelijkse praktijk (dit proefschrift).
4. Een verandering in CCQ score van 0,4 punten is klinisch relevant voor de patiënt (dit proefschrift).
5. De gezondheidstoestand is betrouwbaar te meten in individuele patiënten op het spreekuur door middel van de CCQ (dit proefschrift).
6. Als metingen niet gebruikt kunnen worden om COPD behandeling te sturen, is hun waarde voor de dagelijkse patiëntenzorg beperkt (vrij naar: van den Bemt; Int J Clin Pract 2010)
7. De CCQ is geschikt om dagelijks de gezondheidstoestand te meten tijdens exacerbaties van COPD. De hoogte van de CCQ score heeft een voorspellende waarde voor het optreden van behandelfalen. Na een exacerbatie voorspelt de CCQ de tijdsduur tot de volgende exacerbatie en overlijden (dit proefschrift).
8. De CCQ zal in de toekomst gebruikt worden om behandelingen van individuele patiënten te sturen op de klachten van de patiënt.
9. Werk breidt zich uit tot het de tijd die beschikbaar is voor voltooiing, vult (vrij naar: CN Parkinson in *Parkinson's Law: The Pursuit of Progress*. London, 1958).
10. Kookboekgeneeskunde is goed, maar het variëren op het basisrecept maakt de arts tot behendig clinicus.
11. Het zou onderzoekers veel tijd, frustratie en energie schelen als ze zich zouden verdiepen in de mogelijkheden die ICT hen biedt.
12. Kwaliteit is meetbaar, maar enkel met goede instrumenten; de uitslagen zijn interpreteerbaar, maar enkel met de nodige inhoudelijke kennis.
13. Bij een nieuw gadget is het met name van belang dat de eigenaar de meerwaarde ervan inziet.
14. Te veel mensen krijgen de hele dag door zo veel informatie dat ze hun gezond verstand verliezen (vrij naar: Gertrude Stein 1874-1964)
15. Kleren maken de dokter (Ned Tijdschr Geneesk. 2010;154:A2898)

# **Towards health status guided care in COPD**

using the Clinical COPD Questionnaire (CCQ)

RIJKSUNIVERSITEIT GRONINGEN

# Towards health status guided care in COPD

using the Clinical COPD Questionnaire (CCQ)

Proefschrift

ter verkrijging van het doctoraat in de  
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aan de Rijksuniversiteit Groningen  
op gezag van de  
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## **Chapter 1**

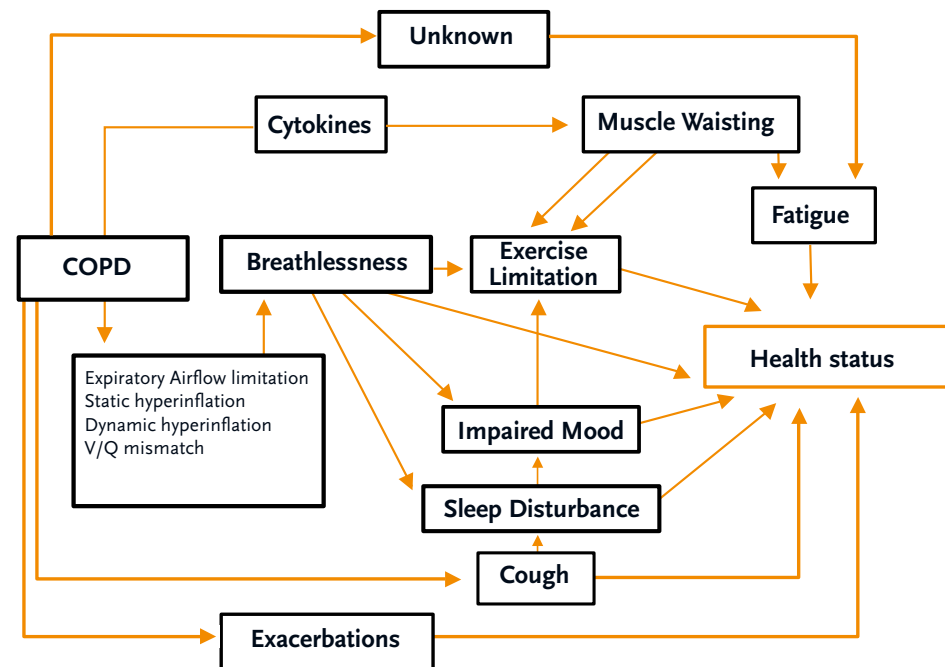
### General introduction

## Chronic Obstructive Pulmonary Disease (COPD)

Patients with Chronic Obstructive Pulmonary Disease (COPD) - if they actually have symptoms of their COPD- suffer from dyspnoea, cough, limitation in functional status and impaired mental health [1]. Many people only start to experience problems in their daily living in more advanced stages of the disease. The number of people worldwide with COPD will increase in the coming years, and so will the COPD related morbidity and mortality [2]. A patient is diagnosed with COPD once they experience symptoms and have airflow obstruction following the definition of the Global Initiative for Chronic Obstructive Lung Disease (GOLD). GOLD defines COPD as 'a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases' [2].

The degree of airflow limitation or impairment in lung function has only a weak relation with the number of problems a patient encounters because of the COPD because these symptoms often have no immediate relationship to expiratory airflow limitation [3,4]. The pathways that lead from COPD to the effects on life are displayed in Figure 1. The consequences on a patient's life of symptoms, functional status, and mental health is reflected in a patient's health status [5-7].

**Figure 1.** A model of COPD progression and consequences. The multiple consequences of COPD, including breathlessness, exercise limitation, muscle wasting, fatigue, and exacerbations Adapted from [3].



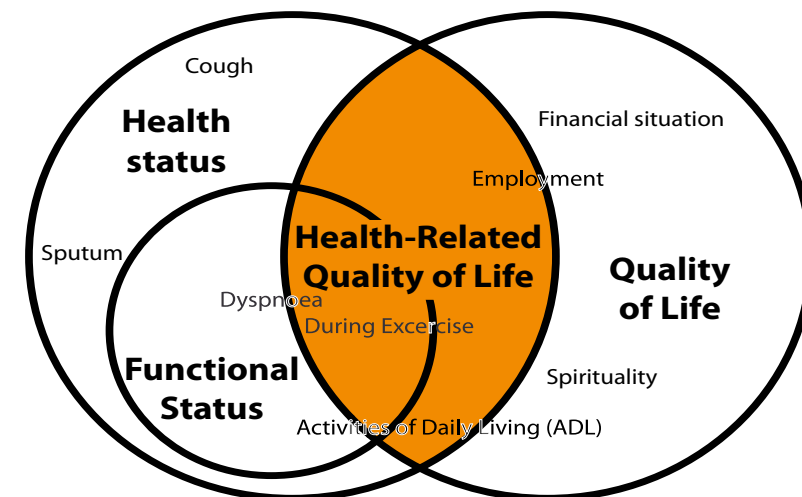
## Quality of life, health related quality of life, health status and functional status

Quality of life, health related quality of life, health status and functional status are different concepts. Quality of life can be defined as a person's self-determined satisfaction with issues important to them, and it can be influenced by a number of factors including financial status, housing, employment, spirituality, social support network, and health [8,9]. To narrow this broad concept and relate it to a person's health, investigators started to use the term "Health Related Quality of Life" for quality of life as it is affected by health and health care [8]. In its most general definition, "health status" assesses the effect of a person's health on the ability to perform and enjoy the activities of daily life [8]. Functional status is defined as a 'multidimensional concept characterizing one's ability to provide for the necessities of life; that is, those activities people do in the normal course of their lives to meet basic needs, fulfill usual roles, and maintain their health and well-being [10]. The relationships between the terms used to describe health status and quality of life are shown in Figure 2.

The terms are frequently used interchangeably in the scientific literature. For example, one questionnaire, the Saint George's Respiratory Questionnaire (SGRQ) is described as measurement of quality of life [11], health related quality of life [12], and health status measure [13], while the developer consequently used the term "health status" for the SGRQ. The different terms reflect different scopes of what is measured, therefore the appropriate term should be used to prevent wrong conclusions.

Finally, Patient Reported Outcomes (PROs) are measures that capture outcomes of health care from the patient's perspective, thus quality of life, health related quality of life and health status measures are all PROs.

**Figure 2.** Conceptual model of the overlapping realms of common terms describing patient-assessed health outcomes. Shaded area represents health-related quality of life; adapted from Curtis et al. [8].



Over the last decades there has been a growing interest in the development of patient reported outcome instruments and their utilisation in both research and clinical practice.

### How to measure health status?

In routine clinical practice, health care professionals ask their patients how they are doing, the patient's response informs the health care professional about parts of the patient's health status. These answers might not completely reflect what is really important to the patient and health care professional. A thorough clinical history gives a better insight of a patient's health status than (just) the question "how are you?". But highly structured history taking and recording requires much more effort than using standardised patient completed questionnaires. Reviewing standardised questionnaires about the impact of the disease over longer periods takes less effort than reviewing notes in medical records and the information is more comprehensive [14].

Many instruments have been developed in the last decades to measure health status, first for the use in clinical trials, and later for the use in clinical practice as well. These instruments can roughly be divided in tools that measure general health status like the MOS 36-item short-form health survey SF-36 [15], or disease specific health status, for COPD for example the Saint Georges' Respiratory Questionnaire [16], Chronic Respiratory Questionnaire [17], or the Clinical COPD Questionnaire [18]. The advantage of general health status questionnaires is that the scores can be compared with other diseases, the greatest disadvantage is that these general questionnaires are less sensitive for changes in the impact of a specific disease like COPD [19]. Therefore, in COPD, disease specific questionnaires are more often used to assess health status. Most tools developed in the last years are self completed questionnaires, and the few questionnaires that were interview based have been changed and validated into self completed versions [20].

The methods of development and validation of questionnaires has grown to a professional level during the last decades. In the past, questionnaires were developed mainly without the consultation of patients, but newly developed questionnaires require patient's perspectives and a rigorous development and validation process to be qualified as good enough for research outcomes for pharmaceutical claims [21].

Carefully developed and validated questionnaires are precision measurement instruments that are able to capture patient's health state in a reliable, reproducible way and are responsive to changes in a patient's health state [22].

Health status questionnaires measure various aspects of the impact of the disorder on patient's health status i.e. functional status, symptoms and mental health. Specific aspects like dyspnoea or functional status can be measured using questionnaires especially designed for this single aspect. In COPD, tools for symptom measurements have been developed [23-27] which specifically measure symptoms, often during the recovery of exacerbations. There is a broad range of functional status measures [28] and questionnaires to assess mental health [29].

The separate fields of health status can also be measured in comprehensive measures. The advantage of one single instrument is that one overall score represents the health status of a patient, and the domains reflect the profile of health status (e.g. symptoms, functional status and mental state).

### Why measure health status?

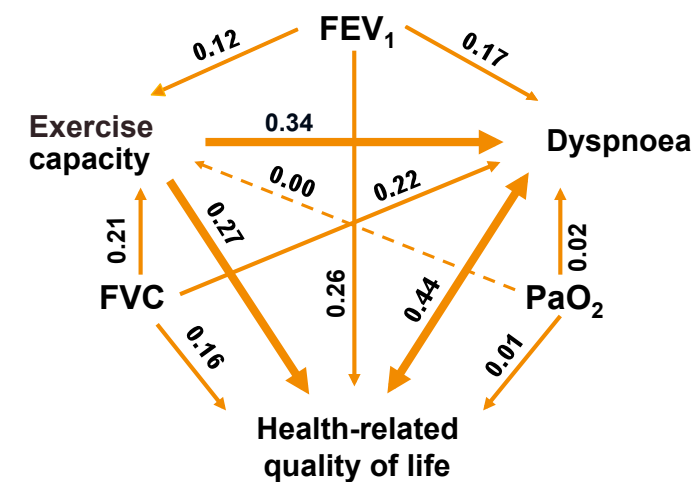
Health status measurement is a way of quantifying, in a standardised and objective manner, the impact of COPD on patients' daily life, health, and wellbeing [7].

In clinical studies, patients have traditionally been categorised according to FEV<sub>1</sub> and effectiveness of therapy has routinely been assessed as change of lung function. The COPD research community and regulatory agencies have underlined its importance as an objective index of that measures both symptomatic relief and disease progression [28]. However, FEV<sub>1</sub> has a very poor correlation with most measures of COPD that matter to patients, such as exercise tolerance, symptoms, and also HRQOL (Figure 3).

Therefore, currently most researchers regard changes in patient centred outcomes, such as symptoms, exacerbations, functional status and health status, more important than changes in lung function [28], because these better reflect the complexity and the impact of the disease and several aspects of health status also predict clinical meaningful outcomes in COPD [31,32]. Functional status as part of health status has been shown to predict exacerbations [33,34], hospital admissions [33-37] and mortality [38,39]. Mental status can be measured with different tools and usually at least partially reflect anxiety and depression which are predictors of worse outcome in COPD [40-44].

For clinical practice, health status gives the opportunity to quickly assess the impact of COPD, evaluate treatment and follow disease progression in a standardised way.

**Figure 3.** Squared correlation coefficients ( $R^2$ ) between health related quality of life (HRQL), dyspnoea scale, and pulmonary physiological parameters [30].



It has been shown repeatedly that clinicians underestimate the impact the disease, treatment, and natural history on patients' quality of life [45,46]. Therefore, the regular measurement and review of quality of life may go a long way towards closing the gap between the patient's experience of disease and the clinicians evaluation of the same problems. Studies have shown that patient satisfaction is improved and patient opinions are more positive when quality of life questionnaires form part of routine practice [45,47]. Patient satisfaction is very important since patients who report high satisfaction display superior compliance [48,49], more promptly seek medical care [50] and retain a higher amount of information than those who are less satisfied [51].

Secondly, health status can facilitate patient-doctor communication and can detect new problems [52].

### How to interpret health status scores?

Interpretation of health status scores depends on the setting in which the health status is measured. In clinical trials, health status is used in groups of patients, while in clinical practice health status is used for a single patient. The group versus individual scores require a different interpretation.

#### Clinical trials

In clinical trials, health status scores need to be interpreted at two moments, at the baseline visit (cross-sectional) and after the intervention (longitudinal). The scores at baseline can be compared between groups or different studies to describe the severity of the patients included in the study.

More interesting however is the change in scores after the intervention. These changes can be statistically different within the treatment group and between treatment groups. Statistically significant changes can be very small and might not be clinically relevant. To make the results amenable to clinical use, the concept minimal clinical important difference (MCID) has been introduced. The MCID has been defined as 'the smallest difference in a score in the domain of interest which patients perceive as beneficial and which would mandate in the absence of troublesome side effects and excessive costs a change in the patient's management' [53].

If the mean score of the population improves more than the MCID, and the improvement is statistically significant, the intervention can be considered successful. An other and probably better way of using the MCID is to calculate the percentage of patients improving more than the MCID, to show effectiveness of the interventions.

#### Clinical practice

Scores of health status questionnaires developed for research should be interpreted with caution in clinical practice. To monitor individual patients, the quality of the questionnaire - the measurement standards - needs to be higher than in groups of patients [54]. If questionnaires have been proven to have these high measurement standards, they can be used to evaluate treatment in individual patients.

Next to the total score, the domains and individual items may give interesting information. The domains and items that are less often discussed during normal consultation, like problems in the mental domain may be captured using health status questionnaires and improve doctor patient communication [55].

Figure 4. IPCRG COPD Wellness tools comparison [58].

### "Wellness in COPD" tool table/grid

| KEY            |   |             |                         |                               |                    |                 |
|----------------|---|-------------|-------------------------|-------------------------------|--------------------|-----------------|
| Very poor      | Not good enough, if this criterion is important | Good enough | Recommended             | Highly recommended            |                    |                 |
| Tool/ Criteria | Validity/ Reliability                           | Responsive  | Primary Care Population | Practical/ Easy to Administer | Tested in Practice | Other Languages |
| AQ20           | ☺   | ☺           | ☺                       | ☺                             | ☺                  | ☹               |
| BPQ-5          | ☺   | ☺           | ☺                       | ☺                             | ☹                  | ☹               |
| CARS           | ☺   | ☹           | ☹                       | ☺                             | ☹                  | ☹               |
| CAT            | ☺   | ☺           | ☺                       | ☺                             | ☺                  | ☺               |
| CCQ            | ☺   | ☺           | ☺                       | ☺                             | ☺                  | ☺               |
| CRQ            | ☺   | ☺           | ☺                       | ☺                             | ☺                  | ☺               |
| MRC-D          | ☺   | ☺           | ☺                       | ☺                             | ☺                  | ☺               |
| RIQ-MON10      | ☺   | ☺           | ☺                       | ☺                             | ☹                  | ☹               |
| SGRQ           | ☺   | ☺           | ☺                       | ☺                             | ☺                  | ☺               |

AQ20=Airways questionnaire  
 BPQ-5=Breathing problems questionnaire - short  
 CARS=Copd activity rating scale  
 CAT=Copd assessment test  
 CCQ=Clinical copd questionnaire  
 CRQ=Chronic respiratory disease questionnaire  
 MRC-D=Medical research council, dyspnoea  
 RIQ-MON10=10 item respiratory illness questionnaire - monitoring  
 SGRQ=St. george's respiratory disease questionnaire

## How health status fits in primary care

The majority of COPD patients is treated in primary care [2,56]. Primary care professionals are used to work based on a patient's history, rather than laboratory tests. Once a patient is correctly diagnosed with COPD after spirometric evaluation, structured follow-up is thought to be the cornerstone of COPD treatment [57]. With the increased structured care for COPD patients in primary care, follow-up tools that are standardised are needed. Next to lung function measurement, symptoms, smoking habits, exercise tolerance, and comorbidity are also recommended in guidelines [57]. Recently, the International Primary Care Respiratory Group (IPCRG) therefore issued a review of tools that measure 'COPD wellness' as a practical guide for healthcare professionals working in their everyday clinical practice [58]. The result is displayed in Figure 4. The tool with the highest rating is the Clinical COPD Questionnaire (CCQ).

## The Clinical COPD Questionnaire (CCQ)

The CCQ has been developed as a COPD specific health status measure according to the high standards of questionnaire development and validation and was first published in 2003 [18]. The CCQ was developed for both research and clinical use and has been translated into more than 50 languages and is used worldwide in clinical research and routine practice (www.ccq.nl). It has shown good measurement properties [18,59,60].

The CCQ consists of 10 questions rated on a seven point Likert scale. Higher scores represent worse health status. Questions are divided into three domains: symptoms (4 questions), functional status (4 questions), and mental state (two questions) (Figure 5). This thesis focuses on the use of health status measurement, and specifically health status measured by the CCQ in the setting of daily clinical practice.

## Current use of health status measurement in clinical practice

Currently, health status – if used – is mostly used as follow-up measure in COPD. Studies evaluating the effect of implementation of health status measurements in routine practice show promising results regarding the feasibility and their influence on the consultation, but until now have not been able to show great benefit on long term health outcomes for patients with COPD [47,55,61-64]. The most seen positive effects are effects on communication between patients and health care providers and satisfaction with care. Little impact has so far been demonstrated on health status after implementation of health status in routine care. These ambiguous results might be due to differences in the way studies were performed. Studies that test the clinical effectiveness of health status instruments have used a large variety of tools, settings and outcome parameters [47,55,61,62,64-70]. Both general and disease specific quality of life and health status questionnaires have been used, and data were collected by postal questionnaire/survey or collected in the waiting room before the consultation. The format used to present data to clinicians ranged from showing only raw scores to showing graphs with group comparisons with or without interpretation.

In contrast to more familiar laboratory results or lung function parameters, clinicians are not used to interpret health status data. Healthcare professionals need education and

Figure 5. The Clinical COPD Questionnaire, UK English week version.

Patient number: \_\_\_\_\_  
Date: \_\_\_\_\_

| <b>CLINICAL COPD QUESTIONNAIRE</b>   |                    |                       |                  |                    |              |                    |                                  |
|--|--------------------|-----------------------|------------------|--------------------|--------------|--------------------|----------------------------------|
| Please <b>circle</b> the number of the response that best describes how you have been feeling during the <b>past week</b> .<br>(Only <b>one</b> response for each question). |                    |                       |                  |                    |              |                    |                                  |
| On average, <b>during the past week</b> , how often did you feel:  | never              | hardly ever           | a few times      | several times      | many times   | a great many times | almost all the time              |
| 1. Short of breath <b>at rest</b> ?  | 0                  | 1                     | 2                | 3                  | 4            | 5                  | 6                                |
| 2. Short of breath <b>doing physical activities</b> ?  | 0                  | 1                     | 2                | 3                  | 4            | 5                  | 6                                |
| 3. <b>Concerned</b> about getting a cold or your breathing getting worse?  | 0                  | 1                     | 2                | 3                  | 4            | 5                  | 6                                |
| 4. <b>Depressed (down)</b> because of your breathing problems?   | 0                  | 1                     | 2                | 3                  | 4            | 5                  | 6                                |
| In general, <b>during the past week</b> , how much of the time:  |                    |                       |                  |                    |              |                    |                                  |
| 5. Did you <b>cough</b> ?  | 0                  | 1                     | 2                | 3                  | 4            | 5                  | 6                                |
| 6. Did you <b>produce phlegm</b> ?   | 0                  | 1                     | 2                | 3                  | 4            | 5                  | 6                                |
| On average, <b>during the past week</b> , how limited were you in these activities <b>because of your breathing problems</b> :   | not limited at all | very slightly limited | slightly limited | moderately limited | very limited | extremely limited  | totally limited /or unable to do |
| 7. <b>Strenuous physical activities</b> (such as climbing stairs, hurrying, doing sports)?   | 0                  | 1                     | 2                | 3                  | 4            | 5                  | 6                                |
| 8. <b>Moderate physical activities</b> (such as walking, housework, carrying things)?  | 0                  | 1                     | 2                | 3                  | 4            | 5                  | 6                                |
| 9. <b>Daily activities at home</b> (such as dressing, washing yourself)?   | 0                  | 1                     | 2                | 3                  | 4            | 5                  | 6                                |
| 10. <b>Social activities</b> (such as talking, being with children, visiting friends/relatives)?   | 0                  | 1                     | 2                | 3                  | 4            | 5                  | 6                                |

support to learn how to interpret the scores of health status instruments, if they are to be successfully integrated into routine practice. In studies, the education of the clinicians varied from single group trainings to multiple individual training sessions. A review of health status studies by Greenhalgh *et al.* concluded that information should be fed back throughout the decision making process to all clinicians involved in the patient's care, and in a format they can make sense of and integrate in clinical decision making. Health status scores should therefore be presented in a coherent, clinically-relevant format, with clear guidelines for interpretation [61].

In conclusion, in COPD health status gives additional information next to physiologic parameters, it can be easily assessed with existing methods like the CCQ, but the impact on clinical practice is still limited. Until now, health status had been used in clinical practice as evaluative and informative tool and not as a tool to guide treatment.

### Main research question of this thesis

How is health status currently used and what is needed to use health status measurement in routine clinical practice as an evaluating tool (passive) towards a treatment guiding tool (active).

### Outline of this thesis

The factors known to influence a patient's quality of life and their interrelationships are described in *chapter two*. We describe the possible role for health status measures in improving COPD treatment in *chapter three*. To assist the primary care physician in assessing functional status, we have reviewed the tools used in research and scored their validity and feasibility in the primary care setting in *chapter four*. To interpret the scores, the availability of the Minimal Clinical Important Difference (MCID) is needed. The assessment of the CCQ's MCID is described in *chapter five*. Next to traditional, statistically defined assessments, we developed a new method to assess the individual validity of a questionnaire. This method is very close to the normal practice and how clinicians think. This method and the results for the CCQ are described in *chapter six*. Course and predictive value of patient reported outcomes including health status in an evaluative and predictive role within a randomised controlled trial are described in *chapter seven*. The previous chapters described what was needed to design a study that will prospectively test whether health status guided care in COPD had benefits compared to FEV<sub>1</sub> guided care. The protocol of this study: the Moving towards Algorithm-based Restructuring of COPD care by Health status (MARCH) study is described in *chapter eight*.

The last chapter, *chapter nine*, summarizes the results of all chapters and discusses how to proceed in guiding care based on health status measures.

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## Chapter 2

# Factors that influence disease specific quality of life or health status in patients with COPD. A review and meta-analysis of pearson correlations

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## Abstract

**Introduction:** A major goal in COPD management is to ensure that the burden of the disease for patients with COPD is limited and that patients will have the best possible quality of life and health status.

**Aim:** The aim of this review was to explore all the possible factors that could influence disease specific quality of life and health status in patients with COPD.

**Methods:** A systematic review of the literature and a meta-analysis was performed to explore the factors that could have a positive or negative effect on quality of life and/or health status in patients with COPD.

**Results:** Quality of life and health status is determined by certain factors including gender, disease severity indexes, lung function parameters, body mass index, smoking, symptoms, comorbidity, depression, anxiety, and exacerbations. Factors such as dyspnea, depression, anxiety and exercise tolerance were found to be more correlated with health status than the widely used spirometric values. FEV<sub>1</sub> had a weak to a modest Pearson weighted correlation coefficient ranging from -0.110 to -0.510 depending on the questionnaire used.

**Conclusion:** The broad range of determining factors suggests that in order to reach the management goals in COPD, health status should be measured next to lung function in each patient with COPD.

## Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a prevalent disease in the general population and a great burden for the patients suffering from COPD. This burden for the patients is very different between patient groups. Some patients can live their lives almost untouched by the disease while other patients are almost completely handicapped. The burden of the disease does not follow the classic GOLD severity grades based on spirometry as postulated by the current guidelines of COPD [1]. It is widely accepted that the burden of the disease is determined by more than pulmonary function measured by the Tiffeneau index and the FEV<sub>1</sub>. One way to indicate the burden of the disease of patients is the assessment of health related Quality of life and Health status. Quality of life in general refers to the patient's ability to enjoy normal life activities (Websters New World Medical Dictionary). Health-related quality of life (HRQoL) is more specific and is related to the part of the QoL that is determined by health. It may include dimensions such as general health status, mental, psychological and sleep status, ability to proceed with daily life and social activities. Disease specific quality of life is the quality of life related to a certain disease. COPD related Quality of life is considered to be the potential impact of COPD on HRQoL.

Health status represents an overall evaluation of the state of the health of a person. Finally health status related to a specific disease is almost interchangeable with disease specific quality of life.

Health status measurement is currently becoming an important issue for day to day management of COPD patients in both primary and secondary health care [2-9]. Studies report that a shorter survival is related to worse health status/HR-QoL [10-12]. Since health status is considered as a major goal in managing the disease [13] physicians should be focused on the improvement of health status. The implementation of short instruments to measure health status have significantly improved their usage in daily clinical practice [14-24]. However, the currently available health status questionnaires have a number of differences in the concepts included and various items are unique in some questionnaires [25-26].

The theoretical model of factors that potentially have an influence on health status includes factors such as age, gender, disease severity, lung function, the body mass index (BMI), smoking status, symptoms, exercise capacity, comorbidity, depression, anxiety and exacerbations [27-38].

The aim of the present review and meta-analysis is to present and also to discuss the published data of factors that could possibly play a role in COPD related quality of life or health status. Existing literature provides information on various factors that could be positively or negatively associated with COPD related quality of life although until now no literature exists that aggregates this knowledge in one report.

## Materials and methods

A systematic literature search was performed from 1984 until September 2009 in Pubmed, Embase and Cochrane Collaboration containing the following keywords: COPD, health status or quality of life, in conjunction with questionnaires, age, gender, BMI, smoking, COPD severity, FEV<sub>1</sub>, symptoms, exercise capacity, comorbidity, depression, anxiety, and exacerbations. Further articles were identified from the reference lists of the included articles.

In our review we included studies that used general health status questionnaires such Short Form Health Survey Questionnaire (SF-12) and SF-36, Quality of Well Being scale (QWB), Sickness Impact Profile scale (SIP), Nottingham Health Profile scale (NHP), European Quality Of Life questionnaire (EuroQOL) and studies that used specific health status and QoL questionnaires such as Chronic Respiratory Questionnaire (CRQ), St George's Respiratory Questionnaire (SGRQ), Clinical COPD Questionnaire (CCQ), Quality of Life in Respiratory Illness questionnaire (QoL-RIL), Airways Questionnaire 20 (AQ-20) for the assessment of COPD.

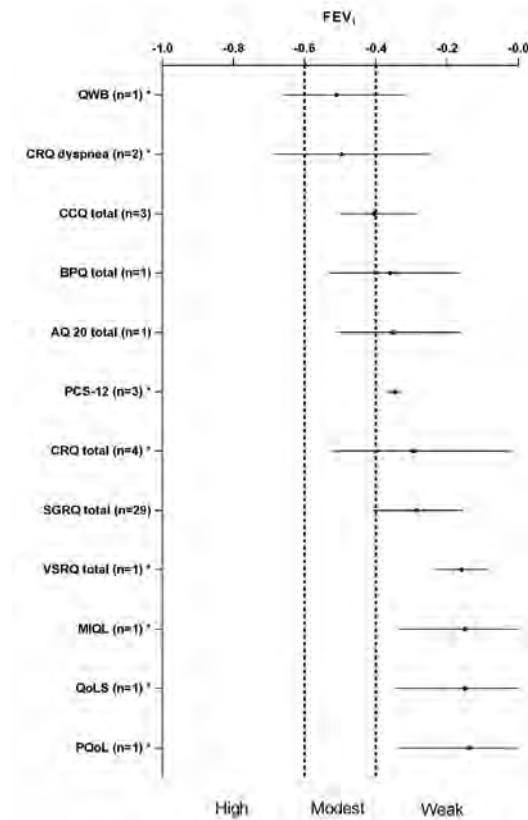
The number of potentially relevant studies identified and screened for retrieval were n=2391 (regarding COPD and factors and quality of life), n=1497 (regarding COPD and factors and health status). Studies were excluded because title or abstract showed that they were not relevant or they were duplications in keywords searching n=3717. The most frequently excluded studies were interventional studies that were not in the goals of this manuscript. Studies that reported quality of life questionnaires comparisons but not reported factors informations were also excluded. Studies retrieved for evaluation and included in this review n=171. Studies reported Pearson or Spearman Correlation Coefficients that are included in the meta-analysis n=66.

### Statistical analysis

Meta-analysis was conducted only in the studies that had Pearson's or Spearman's correlations. In some questionnaires a high score indicates a good health status, in others a high score indicates a bad health status. To enable a good comparison between the correlation coefficients of the different questionnaires, correlation coefficients were multiplied by -1 when the direction of the scoring was from bad (low score) to good (high score). The following questionnaire scores were transformed: Chinese 35-Item Quality of Life Instrument, CRQ, European quality of life questionnaire (EuroQoL), EuroQoL-Five-Dimension visual analogue scale (EQ-5D VAS), Mental component summary (MCS-12) and Physical component summary (PCS-12) of SF-12, Multidimensional Index of Life Quality (MIQL), Perceived Quality of Life Scale (PQoL), Quality of life in respiratory illness questionnaire (QoLRIQ), Quality of Life Scale (QoLS), Quality of well being scale (QWB), Visual Simplified Respiratory Questionnaire (VSRQ). As a result, a high score on a questionnaire indicates much impairment/worse health status.

Pooled estimates of the correlation coefficients were calculated by transforming the correlation coefficients to Fisher's z values. The resulting values were weighted with the inverse of the variance of the correlation coefficients. The 95% confidence intervals of the pooled weighted Fisher's z values were also calculated after which all the values were backtransformed to the metric of the correlation coefficients [39].

Figure 1. Pearson weighted correlations, FEV<sub>1</sub> and various health status/Quality of life questionnaires.



\* The score was transformed so that a high score on a questionnaire indicates much impairment/worse health status. In brackets is indicated the number of studies. From references: 17,32,35,42,49,50,61,62,67,70, 76,80,82,84,87,96,98,104,109,111,113,117, 118,119,121,124,126,127,129.

## Results

### Factors that influence COPD-health related quality of life and health status

In the following section we present the factors that have been mentioned in the literature related with QoL and health status in COPD patients. In Table 1 Pearson weighted correlations and confidence intervals between various factors and questionnaires are reported. In order to make this table readable we only show the relations between questionnaires and factors when at least three studies reported on these outcomes. All Pearson weighted correlations are shown in Appendix I. Figure 1 shows Pearson weighted correlations between FEV<sub>1</sub> and various quality of life or health status questionnaires. Figure 2 shows the highest Pearson weighted correlations between different factors and questionnaires. Some factors as gender and COPD severity are not included in the figures or the appendix because such studies did not provide correlations but only comparisons between groups. Studies that used the SF-36 questionnaire were not included in figures or appendix because the large amount of different domains. However their impact in health status is reported in the text.

**Table 1.** Meta-analysis results from correlations from 3 and more studies are reported. Pearson weighted correlations between questionnaires and factors, upper and lower limits, total number of patients included in the meta-analysis and the lower and upper number of patients that was mentioned in the studies.

| Questionnaire<br>(Number of studies)   | Factor             | Weighted<br>Pearson | Weighted<br>Pearson<br>upper 95 | Weighted<br>Pearson<br>lower 95 | Total number of<br>patients in the<br>studies. Lower<br>and upper<br>number |
|--|--------------------|---------------------|---------------------------------|---------------------------------|---|
| SGRQ total (29)<br>{17,32,35,42,49,50,61,62,67,70,76,80,82,84,87,96,98, 104,109,111,113,117,118,119,121,124,126,127,129} | FEV <sub>1</sub>   | -0.285              | -0.156                          | -0.404                          | 5288 (30-751)   |
| CCQ total (3)<br>{75,79,19}  | FEV <sub>1</sub>   | -0.405              | -0.285                          | -0.513                          | 562 (58-329)  |
| CRQ* (4)<br>{105,114,116,129}  | FEV <sub>1</sub>   | -0.294              | -0.023                          | -0.525                          | 206 (44-62)   |
| SGRQ total (5)<br>{72,98,99,100,104}   | BODE               | 0.441               | 0.572                           | 0.289                           | 583 (64-253)  |
| SGRQ total (19)<br>{17,35,42,49,53,58,61,67,70,76,87,96,104,109,111,113,117,121,124}                                     | Dyspnea            | 0.507               | 0.622                           | 0.371                           | 2510 (30-560)   |
| SGRQ total (15)<br>{35,50,58,61,70,76,84,104,109, 111,121, 113,117,127,144}  | 6 MWD              | -0.342              | -0.221                          | -0.453                          | 2454 (30-1217)  |
| SGRQ total (6)<br>{17,50,56,96,113,150}  | HADS<br>anxiety    | 0.462               | 0.610                           | 0.283                           | 589 (41-218)  |
| SGRQ total (6)<br>{17,50,56,96,113,150}  | HADS<br>depression | 0.528               | 0.662                           | 0.321                           | 589 (41-218)  |

\* The score was transformed so that a high score on a questionnaire indicates much impairment/worse health status. In ( ) brackets the total number of studies assessed. In { } brackets the references numbers.

### Demographic & anthropometric factors

#### Age

Results about age are controversial. Higher age has been reported as a negative predicting factor for health status of patients with COPD in 16 studies [7,20,28,29-32,38,40-48]. In another 8 studies we found no significant correlation between age and health status [49-56]. In 8 studies it was reported that younger patients had worse health status [33,57-63]. The meta-analysis includes only a small number of studies that reported correlations since the large majority of studies only reported comparisons between age groups. In the meta-analysis, age was found to be weakly associated with impairment of health status (Table 1, Figure 2).

#### Gender

Female patients with COPD report worse health status than male patients in 18 studies [7, 29,30,33,35,37,38,41,43,48,51,64-70] both on total scores and on physical condition scores as assessed by the SF-36 [29,35]. We found 10 studies that reported no gender differences in health status [40,50,52-55,71-74]. Only one study reported the opposite, that is worse health status in men [28].

#### Body weight and Body Mass Index

Body weight and Body Mass Index (BMI) is related to health status and underweight patients had worse health status than normal weight patients [28,43,53,75-79]. Four studies reported that health status tends to be worse also in overweight patients [53,63,75,80]. Some studies reported no correlation between health status and BMI [31,49,58]. The Pearson weighted correlation ranged from weak to modest, depending also in the questionnaire used. Strongest correlations reported with SGRQ and CCQ (Figure 2). Also low lean body mass abnormalities and a low fat free mass index have been associated with an activity impairment and worse health status [53,81]. In one study worse health status was associated with less type I fibers proportion in peripheral muscles [80].

#### Life style parameters

##### Smoking status

Current smoking and a higher number of pack years have a weak negative influence on health status [7,28,31,46,55,61,79,82-87]. There are some studies that reported no correlation [40,43,51,53] and one study reported that smokers had a better health status [29]. Second hand smoke was also reported to be associated with poorer health status in COPD patients [88].

##### Social class

Some studies report a relation between socioeconomic status and health status [83,89] but others do not confirm that finding [40,52].

#### Disease driven determinants

##### Severity of COPD (GOLD/ATS/BTS/Canadian staging/BODE index)

The majority of the published studies suggest that COPD severity measured by recommendations from ATS, BTS, GOLD, and severity score is related to health status [8,29-31,38,40,43,46,67,75,90-102].

Health status with minor exceptions becomes stronger associated to disease severity as disease pass to a more severe stage [8,29-31,38,40,43,46,67,75,90-102]. One study by Yeo *et al.* [103] reported no significant association between health status and GOLD stages. COPD severity when assessed by the composite BODE index (Body mass index(B), degree of airway obstruction (O), level of functional dyspnea (D), exercise capacity (E) shows a better correlation with health status. This relation is stronger than the relation with pulmonary function parameters and GOLD stages [72,98-100,104] (Table 1, Figure 2). A new composite index the DOSE index (dyspnea (D), airflow obstruction (O), smoking status (S), and exacerbation frequency (E)] showed a modest correlation with QoL in COPD patients [79].

### Physiology (lung function values, PaO<sub>2</sub>, PCO<sub>2</sub>)

Most studies show a non significant or a weak association between FEV<sub>1</sub> and health status [28,30-31,33,35,42,43,45,47-49,53,56-59,61-64,67,68,70,76,82,84,87,89,98,104-127]. Some of the studies revealed a moderate association between health status and FEV<sub>1</sub> [7,19,32,50,60,75,80,123,128-132]. The differences in the strenght of the correlatation might be due to the different questionnaires used (Table 1, Figure 1). The strongest correlations were shown mainly with QWB, CRQ dyspnea and CCQ questionnaire while in all other questionnaires the correlations were rather weak.

Other lung function values that were investigated included IC/TLC ratio [35], FEV<sub>1</sub>/FVC [31,42,80,105], FVC [33,42,61,64,107], VC [31,50,61,112,133], IC [67,114], RV/TLC [63]. Most of them showed a weak association with health status. MIP (maximal inspiratory respiratory muscle pressure) [31,58,64] and MEP (maximal expiratory respiratory muscle pressure) [64] are also weakly associated with health status. Carbon monoxide diffusing capacity was also found to be weakly associated with health status [31,50,63,64]. PaO<sub>2</sub> was either not significantly associated or modestly positively associated [47, 49,50,56,80,81,83,89,104, 108,109,117,128,129,134]. A weak negative association or a not significant association was also reported with PCO<sub>2</sub> [32,35,47,50,56,109].

### Symptoms and exercise performance

The key symptom in COPD is dyspnea. Dyspnea mainly measured either with the TDI (transitional dyspnea index) or with the BDI (baseline dyspnea index) was found to be strongly negatively associated with health status and has the highest correlations with health status questionnaires [20,28-30,35,42,45,48-53,57,58,60,61,63,65,67,70,75,76,79,81,87,93,94,96,97,101,104-114,117,123,124,131,133,135-141] (Table 1, Figure 2). Sputum production, chronic cough [29,102] wheezing [54,57] and fatigue [58,110,139,142] were also negatively associated with health status.

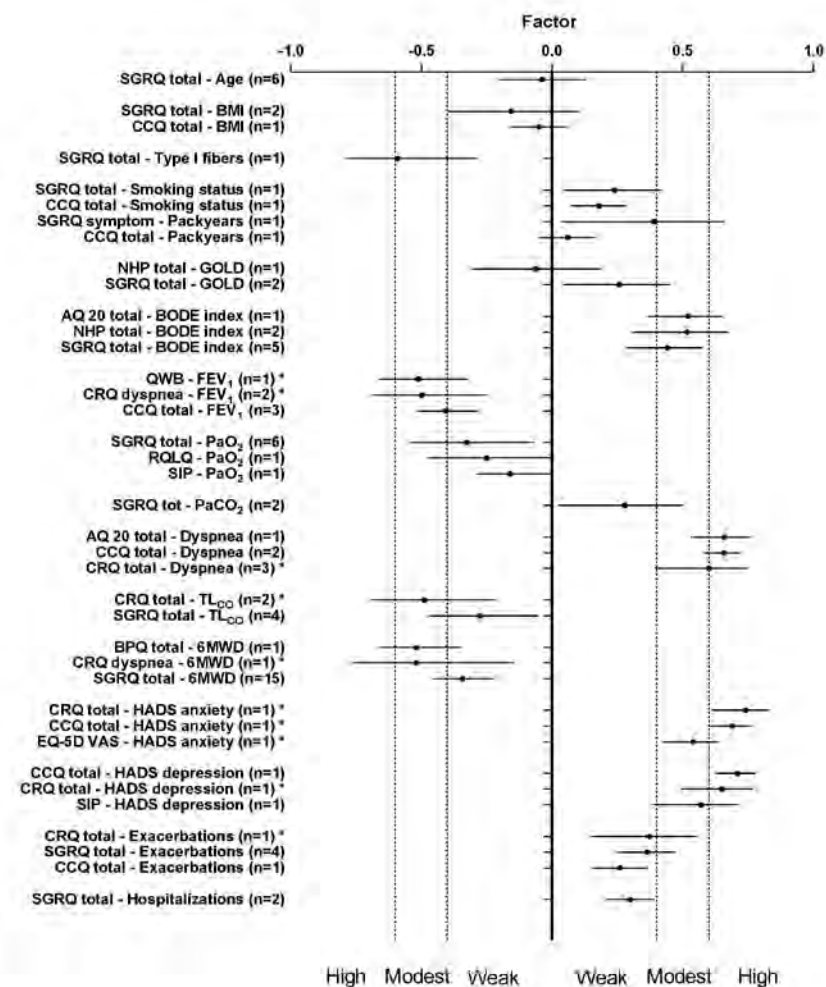
Impairment of exercise performance-tolerance was associated with impairment in health status and mainly with the functional status or activity domains. The most used instrument to assess the exercise tolerance was the 6 MWD test and this was weakly to modestly correlated with health status measurement questionnaires [35,50,52-54,58-61,64,70,73,76,81, 83,84,87,104,105,109,111,113,114,116,117,121,127, 133,138, 143,144] (Table 1, Figure 2). Only one study reported no association between health status and exercise capacity [145].

### Comorbidity -Depression, anxiety

Comorbidity influences health status of patients with COPD [28,35,38,41,48, 51,62,91,92, 103,115,146,147]. Heart disease, hypertension, locomotive disorders, diabetes and sleep disturbances are among the most common comorbidities reported to be associated with impaired health status [38,41,51,87,92,103,146,147]. We found only two studies in which comorbidity was not associated with impaired health status [53,99].

Depression and anxiety strongly impair health status and quality of life in patients with COPD as reported in several studies [34,50,56,61,62, 63,67,73,92,96,103,89,83,115,131,133,138,148, 149,150,151-154]. The depression and anxiety has been assessed in the majority of the studies by Hospital Anxiety and Depression Scale (HADS) and by Beck Depression Inventory Scale (BDI) and Anxiety Scale (BAI). The meta-analysis revealed depression and anxiety had among the highest correlations with various questionnaires for the assessment of health status (Table 1, Figure 2).

**Figure 2.** Highest Pearson weighted correlations between various Health status/ Quality of life questionnaires and factors that influence QoL or health status are figured.



\* The score was transformed so that a high score on a questionnaire indicates much impairment/worse health status. In brackets is indicated the number of studies. From references 17,19,28,30, 32,33,34,35, 42,43,45,48,49,50, 56,58,60,61,62,64,70,72,75,76,79,80,84,89,98,99,100,104,105,107,109,111,113,114,116,117,118,121,123,124,127,128,129,133,134,144, 159.

### Other factors

Previous exacerbations and hospital admissions have a weak negative impact in health status [11,33,35,40,42,43,46,49,57,62,123,124,126,133,155-168]. Lower education and the non compliance to medication and medical interventions are also associated with worse health status [7,28,29,43,46,169]. An increased number of medicinations for controlling COPD [42,170,171] and a longer duration of the disease associated with a worse health status [42,46,120]. Living alone was associated with poorer QoL [132].

A seasonal-dependent variation, with a better health status in spring/summer than in winter has been reported [157]. In one study home warmth of at least 21° C for at least 9 hours per day was associated with better health status [172]. There is also a variability in the health status between northern and southern countries and between urban and not areas with worse health status reported in southern countries and urban areas [28,42,173].

Finally, psychological, psychosocial factors and coping strategies are associated with health status [33,48,52,120,174,175,176]. The patients illness perception is also associated with several domains of QoL [176]. One study mentioned that the patients coping strategies and health status were not significantly related [177]. Holm *et al.* reported a worse family relationship quality was associated with more psychological distress and dyspnea resulting in a worse QoL [178]. One study reported employment status and more specific COPD patients that were disabled for work had worse quality of life compared to paid workers [125].

### Discussion

Health status in patients with COPD is influenced by many different factors. However the level of influence on health status of each factor is difficult to estimate because the many different questionnaires used and because some factors influence different parts or domains of the available questionnaires. This meta-analysis shows that the most significant factors that determine QoL/health status in COPD patients are dyspnea, depression, anxiety, and exercise tolerance. This meta-analysis also indicated that spirometry values are only weakly associated with health status. This finding supports the idea that health status should therefore be measured next to spirometry.

Results about age are controversial. Poorer health status was reported in both older and younger patients. Although from the meta-analysis a trend for worse health status in older COPD patients was found the correlation was rather weak. The impairment of health status in older people is to be expected because ageing by itself deteriorates health status of the general population and also impairs lung function [179]. The presence of significant comorbidities or/and increased number of medication taken in older people deteriorate health status even further [7,59,67,92,103,171]. The fact that in some studies younger people report worse health status could be explained by a larger gap between experienced and expected health status [59].

Female patients with COPD report a poorer health status [7,29,30,33,35,37,38,41,43,48,51,64-70]. Foy *et al.* investigated the effect of rehabilitation on health status in males and females and suggest that gender differences in physiologic and psychological impairment explain differences in health status [66]. Other suggestions are an increased burden of symptoms, [65] different coping mechanisms [37], more intense restriction of activity [33], an airway predominant phenotype [180], or a greater psychosocial impairment [69] in females.

Women are also known to be more susceptible to depression, a disease that deteriorates health status in COPD patients [66,181].

Many studies assessed the effect of underweight on the health status in patients with COPD. Underweight patients have impairment in health status mainly because of the deterioration of dyspnea [53]. This is well known in COPD patients. Overweight patients have also impaired health status [53,75]. Shoup *et al.* reported overweight patients with COPD had increased dyspnea and worse scores on both impact and total domain [53]. Obesity leads to worse respiratory symptoms and less exercise capacity, factors that are impaired in COPD patients [182].

Smoking and pack-years are considered important factors for health status [7,31,106]. Ex-smokers and smokers had significant differences in health status mainly because of the improvement in a range of respiratory symptoms after smoking cessation [29,85,86]. Ferrer *et al.* reported that in smokers mainly the impact and symptoms score were impaired [7]. Only Wijnhoven *et al.* reported that current smoking was associated with better QoL [29]. The authors in that study suggested that this contradicting result could be due to confounding by severity. In that study patients who continued to smoke were those with a less severe disease [29]. Although we expected smoking would be among the best predictors for health status the correlation was only weak but the number of studies was rather small to make firm conclusions.

The majority of the studies mentioned that the severity of the disease is associated with health status [8,29-31,38,40,43,46,67,75,90-102]. Ferrer *et al.* reported that health-related QoL varied greatly within each stage of severity even after stratification for comorbidity [92]. In the one study that reported no significant correlation between severity of disease and health status a trend was reported to higher scores in severe COPD that indicated a poorer quality of life [103]. The BODE index has been found to have stronger correlations with health status than FEV<sub>1</sub> (Table 1). This strong correlation is very understandable since the BODE index is composed by factors such as dyspnea and exercise capacity that are domains of many health status questionnaires.

Although spirometry is traditionally seen as the most important determinant of the diagnosis and severity of COPD, this meta-analysis showed that the relation between health status and all spirometric values mainly FEV<sub>1</sub> is weak (Figure 1). This indicates that assessment of COPD severity in clinical practice could benefit from additional measurement of health status.

Pearson weighted correlations from numerous studies revealed dyspnea as a very important determinant of health status (Figure 2, Table 1, Appendix). The strong relation between dyspnea and health status could be in part artificial because all reported questionnaires have questions or a domain about symptoms including dyspnea. Stucki *et al.* reported in a comparison of 11 instruments used for the assessment of health status in COPD that there was a large heterogeneity between questionnaires but dyspnea was the only factor present in all of them [26].

Comorbidity and especially depression, and anxiety have among the highest influence on the impairment of health status [34,50,56,61,62,63,67,73,92,96,103,89,83,115,131,133,138,148,149,150,151-154]. An increased number of chronic diseases is associated with a worse

health-related quality of life in the general population [183]. Few studies mentioned all the related comorbidities in COPD patients with an impaired health status [38,41,51,92,103,146,147]. Special attention has been given to depression and anxiety in a significant number of papers. Depression and anxiety have a significant impact in health status. All the questionnaires showed a good correlation with depression and anxiety questionnaires but only the Clinical COPD Questionnaire (CCQ) was reported to have such a good correlation that it could be used to predict depression and anxiety [34]. Anxiety significantly influences the health status of patients with COPD and it is strongly dependent on patients' dyspnea [61]. The high correlations found in this meta-analysis with depression and anxiety highlights their important role in health status impairment and underlines the need of their estimation in daily clinical practice.

Surprisingly both emotional and rational coping strategies impaired health status [52,174]. Osman *et al.* reported that younger patients suffered more because of the psychological impact of their disease [33]. Patients that deny their disease are less influenced by the disease [52]. Patients with positive beliefs and with less strong emotional reaction to the illness have better QoL [176].

Since improvement of health status is a pivotal treatment goal, physicians should be informed about a patient's individual health status. Since health status is only for a very small part determined by spirometric values the need for simultaneous assessment of health status by a proper instrument is crucial. However, it is rather difficult to select an instrument that is appropriate for use in clinical practice. Cazzola *et al.* (on behalf of ATS/ERS task force on outcomes of COPD) suggested instruments for generic health status (SF-36, SIP, NHP), lung-disease specific health status and HRQoL: (CRQ, SGRQ, QoL-RIQ), short-disease-specific health status and HRQoL: (CRQ-SAS, AQ-20, BPQ), disease-specific health status and HRQoL for patients with respiratory failure (Maugeri Foundation respiratory failure questionnaire) and COPD control questionnaire: CCQ [25]. Only few of these instruments like the Clinical COPD Questionnaire, and AQ20 are applicable in daily clinical practice. In the future the newly developed COPD Assessment Test (CAT) [184] might be an alternative although data to compare the psychometric properties with other questionnaires are too limited to include in this review. Further an important problem indeed of almost all instruments to assess health status is that include items directly related to the disease such as dyspnoea or other symptoms, as is the case with many disease specific QoL questionnaires fact that will automatically result in strong associations.

## Conclusions

Quality of life and health status is determined by a significant number of factors from which the strongest are dyspnea, depression, anxiety, and exercise tolerance This meta-analysis concluded that health status of COPD patients is only weakly associated with spirometric values. We considered it advisable to measure health status in addition to spirometry in order to be better informed about the influence of the disease on typical health status issues as symptoms, impairment and mental state.

## Conflicts of interest

The authors declare that there are no conflicts of interest regarding this paper.

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**Abbreviations reported in Appendix:** SGRQ=St George's Respiratory Questionnaire, QoL-35 Chinese=Chinese 35-item Quality of life instrument, CCQ=COPD control questionnaire, RQLQ=Modified asthma respiratory quality of life questionnaire, AQ20=Airways questionnaire 20, QWB=quality of well being scale, SIP=sickness impact profile, NHP=Nottingham Health Profile scale, EuroQOL=European quality of life questionnaire, PQoL= PerceivedQuality of Life Scale, Perceived Quality of Life Scale (PQoL), QoLS=Quality of Life Scale (QoLS), VSRQ= Visual Simplified Respiratory Questionnaire, EQ-5D-VAS = EuroQol-Five-Dimension visual analogue scale, CRQ= Chronic Respiratory Questionnaire, MCS=Mental component summary, PCS=physical component summary, QoL-RIL=quality of life in respiratory illness questionnaire, MILQ=Multidimensional Index of Life Quality, BPQ=BreathingProblems Questionnaire, COPDSS=COPD Severity Score, MHI-5=Mental Health Inventory Scale- 5, MSAS=Memorial Symptom Assessment Scale, CPX =Maximum ergometer, BODE INDEX= Body mass index, bronchial obstruction, dyspnea, exercise, DOSE index = dyspnea (D), airflow obstruction (O), smoking status (S), and exacerbation frequency (E), FEV1=forced expiratory volume in one second, FVC= forced vital capacity, VC=vital capacity, RV=residual volume, IC/TLC=inspiratory to total lung capacity, TLCO=carbon monoxide difusing capacity, MIP= inspiratory respiratory pressure, , MEP =expiratory respiratory pressure, 6MWD=6-min walk distance, STAI questionnaire=State Trait Anxiety Inventory , SDS= Self-rated depression scale, HADS=Hospital Anxiety and Depression Scale MACL=Mood Adjective Check List, PSQI =Pittsburg Sleep Quality index, BMI =body mass index. BAI=Beck Anxiety Inventory, BDI=Beck Depression Inventory, STAI=State Trait Anxiety inventory, SDS=Self Rated Depression Scale, CDML=Capacity of daily living during the morning, GCSQ=Global Chest Symptom Questionnaire.

See next page for **Appendix**





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## Chapter 3

# Do health status measures play a role in improving treatment in COPD?

*Adapted version from:*  
*Expert opinion on Pharmacotherapy, 2006*

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## Outline

During the past few decades, health status has become increasingly important in the clinical research of Chronic Obstructive Pulmonary Disease. The use of health status questionnaires in routine practice can enhance understanding about the impact of the disease on the patient, improve standardisation and increase compliance through increased patient satisfaction. However, before health status measurement in individual patients can be used in routine practice, questionnaires have to be validated on an individual level. In this article, the authors suggest a new method of assessing this individual validity, to enhance the use of health status instruments in daily clinical practice, and thus improve treatment in COPD.

## Introduction

Over the last two decades there has been a growing interest in the development of quality of life (QoL) instruments and their utilisation in routine practice. During this period, several other terms have emerged to describe the aspect of a patient's QoL that is influenced by their health (i.e., Health Related QoL [HRQoL or HRQL], health status and patient reported outcomes [PRO]). HRQoL is interpreted as the part of a person's overall QoL that is determined primarily by the person's health status, and which can be influenced by clinical interventions [1]. However, health status is considered to more closely reflect the direct influence of disease on functional status, symptoms and mental health. The term PRO has partly replaced the term QoL in some parts of the world, mainly in the US. In this article, the terms QoL, HRQoL and health status will be used interchangeably, as it is the author's opinion that the differences in these terms are not relevant to the aim of this paper.

The most frequently used method to assess a patient's health status is to ask the patient about their current health during a normal clinical consultation. The advantage of this method is that it is fast, simple and conforms to what is expected within a consultation. The disadvantage is that this method is not standardised and probably unreliable. It is known that doctors tend to overestimate patients health when health status is not measured in a standardised way [2,3]. Certainly on a group level, carefully developed questionnaires to measure health status are more valid.

## Chronic obstructive pulmonary disease

### Overview

The Global Initiative for Obstructive Lung Disease (GOLD) and the combined American Thoracic Society (ATS)/European Respiratory Society (ERS) statement on chronic obstructive pulmonary disease (COPD) define it as a disease state characterised by airflow limitation that is not fully reversible [4,5]. COPD affects several organs and systems, and has a considerable impact on health status. Impaired exercise tolerance, fatigue, muscle weakness, depression and sleeping disorders are all features of the disease [4,5]. Several guidelines have been developed for the diagnosis and treatment of COPD. For decades, forced expiratory volume in 1 second (FEV<sub>1</sub>) was the only known predictor of mortality in patients with COPD [6,7], and has often been used to stratify groups of patients by their disease severity [4,5]. Although lung function is needed to diagnose COPD, it yields little information on the symptoms and impact the disease has on the patient. Furthermore, there is only a low correlation between lung function and health status in patients with COPD [8-10], this measure alone cannot properly reflect problems the patient encounters in daily life. Because health status and symptoms are undervalued in guidelines that are based on the lung function alone, it is hard for healthcare professionals to apply these guidelines in daily clinical practice. Moreover, most physicians worldwide do not have access to, or do not use, spirometry, making it impossible to apply the current guidelines.

### Multidimensional severity index

Self-reported patient variables have been found to give additional information to lung function. For example, the self-report of dyspnoea was a better predictor of mortality and morbidity than airway obstruction [11]. Health status [12,13] and exercise capacity [14] are also

associated with morbidity and mortality. Recently Celli *et al.* [15] developed a multidimensional scale that is a combination of body mass, obstruction, dyspnoea and exercise capacity (BODE). The BODE score proved to be a better predictor of mortality than FEV<sub>1</sub> alone, which illustrates the importance of multidimensional indicators of disease severity.

## Health status

### Health status measurement and effects on consultation

Health status instruments are developed to evaluate treatment, assess severity and measure the impact of disease on health status. Questionnaires must be validated for this purpose on a group level and produce reliable information that can be used for scientific purposes. These instruments are not widely used in routine clinical practice, but they are of clear advantage, as information can be collected systematically in the waiting room prior to a consultation. Further, standardised information about the impact of the disease over longer periods of time takes less effort than reviewing notes in medical records, and the information is more comprehensive [16].

It has been repeatedly shown that clinicians underestimate the impact of the disease, treatment and natural history on a patient's QoL [2,3]. Therefore, the regular measurement and review of QoL may go a long way towards closing the gap between the patient's experience of disease and the clinician's evaluation of the same problems. Studies have shown that patient satisfaction is improved, and patient opinions are more positive, when QoL questionnaires form part of routine practice [2,17]. Patient satisfaction is very important, as patients who report high satisfaction display superior compliance [18,19], seek medical care more promptly [20] and retain a larger amount of information compared with those who are less satisfied [21].

Patient satisfaction is often related to patient–doctor communication. An example of improved communication is the way impairment in mental health is discussed during consultation. When a patient completes the questionnaire, and the physician reviews the results during the consultation, impairment of mental status is often discussed, whereas without the use of this tool, physicians are less likely to bring up this subject [2,22-24]. Another advantage of using these questionnaires in daily clinical practice is that over long periods of time it prevents misunderstandings about the treatment and its usefulness in relation to perceived quality of life. They may also improve compliance because the perception of the patients' well being by physicians and patients themselves can easily diverge [25].

### Health status in routine practice

Health status or disease-related QoL studies carried out in routine practice show promising results regarding the feasibility of health status instruments and their influence on the consultation, but show little or no benefit on health outcomes for patients with COPD. Jacobs *et al.* [17] investigated the feasibility of systematically monitoring disease-related QoL and its relationship with general practitioners' (GPs') interventions. Over 15 months, 175 patients underwent 537 consultations. Directly before each consultation, patients completed a self-reported questionnaire about their disease-related quality of life. GPs reviewed the scores during the consultation, and recorded their diagnostic and therapeutic interventions after the consultation. The relationship between the patients reported disease-related QoL and the GPs chosen interventions were analysed. Multivariate regression revealed reported

physical complaints that were positively associated with changes in medication prescription and health education. Reported emotional complaints were related to a greater number of follow-up appointments. Both physicians and patients were positive about the QoL monitoring programme [17]. In another study, Rubenstein *et al.* [26] used computer generated feedback in primary care, which was based on patients' disease/management complaints and preprogrammed disease management suggestions. Results showed increased diagnosis of impaired emotional well-being, improved management of functional problems, social functioning and emotional well-being. This resulted in a non-measurable positive influence on patients' well being. Finally, Fihn *et al.* [27] conducted a randomised effectiveness trial of 15,346 American veterans, in which synthesised accumulated information, including PRO, was reported to primary care providers (n = 895). Both a generic QoL (SF-36) and health status questionnaire were used, including the Seattle Obstructive Lung Disease Questionnaire, for COPD patients. The questionnaires were completed at home by the patients and mailed back to the hospital. A graph displaying plotted physiological and questionnaire data, and a randomly selected 'management tip', was delivered to the physician, along with the medical record. Throughout the study, local investigators held sessions to train providers in the interpretation of health status measurements. In this 2-year trial, the outcomes (improvement in overall health status and change from baseline in overall satisfaction) did not improve.

These ambiguous results might be due to differences in the way studies were performed. Studies that test the clinical effectiveness of health status instruments have used a large variety of tools, settings and outcome parameters [17,26-34]. Both general and disease-specific QoL questionnaires have been used, and data are collected by postal questionnaire/survey or in a healthcare setting. The format used to present data to clinicians ranged from showing only raw scores to showing graphs with group comparisons.

In contrast to more familiar laboratory results or lung function parameters, clinicians not familiar with interpreting health status data. Healthcare professionals need education and support to learn how to interpret the scores of health status instruments, if they are to be successfully integrated into routine practice. In many studies, the education of the clinicians varied from single group training to multiple individual training sessions. Greehalgh's review [30] of health status studies concluded that information should be fed back throughout the decision-making process to all clinicians involved in the patient's care, and in a format they can make sense of and integrate in clinical decision making. Therefore, health status scores should be presented in a coherent, clinically-relevant format, with clear guidelines for interpretation. Furthermore, it is important to ensure that clinicians understand that most of these instruments have only been validated on a group level.

## Expert opinion and conclusions

Before health status scales can become widely used in routine clinical practice, two important aspects should be studied: firstly, the individual validity of a scale, and secondly the usefulness of the scales in daily clinical practice decision making. The first challenge is to establish the validity of these questionnaires on an individual level. Validity was defined by Cook and Cambell in 1979 as the 'best available approximation to the truth or falsity of a given inference, proposition or conclusion' [35]. In other words, how much does the result of this single questionnaire measurement reflect the real health status of this individual patient, and is this valid enough to influence decision making during the consultation? What change

in the unit should prompt action? The authors argue that this validation is of fundamental importance. If health status is to be taken into account when individual clinical decisions are made about treatment, physicians should be informed about the validity of such measures in individual cases. There are established methods for validating questionnaires at a group level, but no consensus exists as to how one should validate questionnaires on an individual level.

#### Assessing individual validity

The score on a health status scale should measure symptoms and impact of disease in a standardised way, so it is essential that the participating patient understands the questions that are asked, and answers the questions in the way the questionnaire developer intended. Moreover, the score must reflect reality. It is this reflection of reality that is hard to measure. The authors suggest that, in order to validate a questionnaire on the individual level, a gold standard of this 'reality' should be obtained by a maximum effort to assess the real health status of a patient. In order to achieve this, a multidimensional construct of the health status of the individual COPD patient should be made. This includes an assessment of the patient's health status by their healthcare professional, measurement of the patient's functional status, for example by the 6-minute walking distance test, and, most importantly, an in-depth interview of the patient by an independent healthcare professional. The interview should aim to describe the way in which the patient thinks, performs and reacts to their disease. Comparing the opinion of healthcare professionals directly with the patient's scores has a known error, as shown before; doctors underestimate the problems that patients experience.

The 6-minute walking distance test reflects how far someone can walk at his own pace in 6-minutes, and can give an indication about the way a patient can manage their energy. The test may not reflect generalised activity on normal days. Health status questionnaires may more successfully capture this information, which may explain the differences shown between these measurements, even in the most relevant functional domain of questionnaires.

Finally, the in-depth interview will provide key information concerning the patient's disease-related behaviour, such as how the patient performs daily activities. Ideally, with these multidimensional data, an independent team of clinicians should be able to fill in the questionnaire, with a reliable and acceptable level of agreement with the patient's own score. The difference between the patient's results and the team results should not be greater than the minimal clinical important difference (MCID) of the questionnaire under study.

Therefore, the number of times that the sum of the difference between the team and the patients score is larger than the MCID of the questionnaire, is a reflection of the validity of the instrument.

When the individual validity of a questionnaire has been established in this way and is satisfactory for use in daily clinical practice, the next step is to determine how to use the questionnaire in this setting. Standardised measures generated by questionnaires should allow us to standardise the intervention choice, supported by computer generated management tips. This differs from the randomly generated tips investigated by the previously mentioned study of Fihn *et al.* [27]. However, these computer-supported intervention tips should be fully developed and tested before they can be applied in daily clinical practice.

#### Conclusions

HRQoL, health status and PRO questionnaires are now widely accepted in clinical research. They also have shown very promising qualities for use in daily clinical practice. However, before health care professionals can use these sophisticated tools in routine clinical care, their feasibility in daily clinical practice, their validity on an individual level and their effectiveness in conjunction with management suggestions should be further investigated.

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## Chapter 4

# Functional status measurement in COPD: A review of available methods and their feasibility in primary care

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## Abstract

**Background:** Guidelines advocate to designate the improvement of functional status as a major goal in COPD treatment. Many tools are available to assess functional status and related constructs. This review aims to categorize available tools based on their construct, and to rate the tools for use in the primary care setting.

**Methods:** PubMed was searched with the keywords: 'Functional status' or 'physical capacity' or 'functional capacity' and 'COPD'. All tools were categorized and rated on their measurement properties, feasibility, and usage in primary care COPD patients. The tools were divided into four constructs: functional capacity, functional performance, functional reserve, and capacity utilization, and used the following modes of measurement: laboratory tests, semi laboratory tests, field tests, and patient reported outcomes.

**Results:** The PubMed search resulted in 364 articles. Thirty-two tools were identified and rated.

**Conclusions:** In primary care, the six minute walking distance test is the most reliable semi-laboratory functional capacity test, but is not very practical. The pedometer is the best functional performance field test and the Medical Research Council dyspnea questionnaire (MRC) and the Clinical COPD Questionnaire (CCQ) functional status domain are the best patient reported outcome tools to assess functional performance.

## Introduction

The amount of physical activity and functional status of COPD patients predict exacerbations [1,2], hospital admissions [2], and mortality [3]. Therefore guidelines advocate to designate the improvement of functional status as one of the major goals in the treatment of patients with COPD [4,5]. Most guidelines however do not precisely define functional status nor define how to assess functional status. For routine clinical practice it is important to understand that functional status can be measured by several completely different methods representing also different constructs. The 'construct' of a measurement or questionnaire is what the tool intends to measure.

Functional status, functional capacity, exercise capacity, and exercise tolerance are often used interchangeably, but represent different constructs. To straighten the discussion Leidy defined a theoretical framework of functional status, exercise capacity and functional capacity [6]. She defines functional status as a 'multidimensional concept characterizing one's ability to provide for the necessities of life; that is, those activities people do in the normal course of their lives to meet basic needs, fulfil usual roles, and maintain their health and well-being' [6]. The framework labels and clearly defines four distinct, but related, constructs of functional status: *functional capacity*, *functional performance*, *functional reserve*, and *capacity utilization*. *Functional capacity* is defined as 'one's maximum potential to perform activities' and can be tested for example using cycle ergometry. *Functional performance* is defined as the physical, psychological, social, occupational, and spiritual activities people actually do in the normal course of their lives to meet basic needs, fulfil usual roles, and maintain their health and well being. *Functional reserve* is the difference between capacity and performance, and *capacity utilization* is the effort used to reach the functional performance. This framework is graphically represented in Figure 1.

**Figure 1.** Theoretical framework of functional status constructs by Leidy [6] Reprinted with permission from N. Leidy. Functional status and the forward progress of merry-go-rounds: Toward a coherent analytical framework. *Nurs Res* 1994; 43:196–202.

## Functional Status



It is important to keep this framework in mind when selecting tools for research or clinical practice. For research purposes the improvement in functional capacity may be most important and directly related to the intervention, but for clinical management an indication of the limitations patients experience in daily life, the functional performance is more informative.

For research purposes, measurement properties, like validity and responsiveness are of great importance to detect even the smallest effects of treatment. These high standards often lead to intensive, time consuming and costly tests. For clinical practice, high measurement standards are equally important, but next to good measurement properties, feasibility is of equal importance. Tools that are not easy to administer will not be implemented in routine practice [7,8]. Furthermore measurement tools should therefore be feasible and easy to interpret.

Next to categorization in different measurement constructs the tools can also be categorized according to measurement methods and the resources needed to perform the measurement. In this article we categorized measurement tools into 1) laboratory tests (e.g. cycle ergometry [9]), 2) semi laboratory tests (e.g. 6 minute walking distance test [10]), 3) field tests (e.g. accelerometer [11]) and 4) patients reported outcomes (e.g. MRC [12], SGRQ [13]). Putting the measurement tools into a framework based on the construct they measure and the resources needed, clinicians might be better able to make a choice between the tools to use in routine practice. However since the number of tools is large and each tool has its own measurement properties we conducted a literature search to compare the tools with each other.

This review will summarize and rate the tools to measure functional status in a framework based on the construct they measure and resources needed to create an overview of functional status measurements in primary care clinical practice.

## Methods

### Literature search

We searched PubMed on the following keywords: 'Functional status' or 'physical capacity' or 'functional capacity' and 'COPD'.

The literature search was limited by searching the last 15 years, i.e. from January 1995 until July 2010. Studies published in languages other than English were excluded. No attempt to assess the quality of the studies was made as this was beyond the scope of this article.

The resulting titles, abstracts and texts were screened by three authors (JWHK, GMA, TvdM) for tools that were used in patients with COPD to assess exercise capacity, functional status or functional capacity.

This resulted in the identification of a set of relevant tools. Following the identification of these tools, the article describing the development or implementation of the corresponding tool was reviewed for further information. To complete the set of articles found in PubMed, articles that referenced the development article were searched using the "citing articles" function on ISI web of science.

### Data collection and scoring of tool properties

For all tools, information was obtained about the time to complete, time for the patient to recover after performing the test, the test properties (reproducibility, reliability, validity, and responsiveness), the existence of the minimal clinically important difference (MCID) and about data in different COPD severity groups. Based on this information scoring of the tools was done according to the previously used IPCRG rating system [14].

This system was developed to quickly compare the usefulness for clinical practice of 'COPD wellness tools'. The tools utilized the following scores: 😞=very poor/unknown; 😐=Not good enough, if this criterion is important; 😊=Good enough; 😄=Recommended; 😍=Highly recommended.

For all tools, scores were given for the following categories:

**Validity/reliability:** articles reporting the development of the tool and further validation of instruments were used to rate the validity and the reliability of a tool. For questionnaires, a high Cronbach's alpha (> 0.9) is suggested for the use in individual patient care [15]. If a tool scored high on these items, preferably in several papers, the rating was "highly recommended".

**Responsiveness:** if a tool has been shown to be able to measure changes in the patient's situation, for example during exacerbations or upon efficacious treatment, the tool was rated recommended. If a tool appeared to be very responsive in multiple events (exacerbations, smoking cessation, pulmonary rehabilitation etcetera) the rating was "highly recommended".

**Primary care population:** if a tool was developed in patients with mild to moderate COPD, or the tool has successfully been used in this population, the tool was rated recommended or highly recommended based on the number and size of the studies.

**Practical/easy to administer:** a tool was rated "highly recommended" when the application of the tool results in a completion within 5 minutes, the scores/values are easy to calculate and interpret, no or very little additional resources are needed (rooms, (electronic) devices), and the patient recovery time is limited.

**Tested in practice (COPD):** if according to published articles tools are used in clinical practice or if guidelines recommend their use, these tools received (highly) recommended ratings.

**MCID known:** if the minimal clinically important difference is published, the rating was "highly recommended". If the tool is part of a larger questionnaire, and the total questionnaire's MCID is known, but not the part/domain's MCID, the tool was rated "recommended".

## Results

The PubMed search resulted in 364 articles. Thirty-two tools were identified. The tools were divided into four categories: 1) laboratory tests; 2) semi laboratory tests; 3) field tests; and 4) patient reported outcomes. The tools and ratings are presented in Table 1. References mentioned in the table are development articles, further validation articles, manuals or reviews describing the properties of the tools.

Table 1. Measurements and scores.

| Category | Dimension of functional status | Tool                     | Validity/Reliability | Responsive | Primary Care Population | Practical/Easy to Administer | Tested in Practice (COPD) | MCID known |
|----------|--------------------------------|--------------------------|----------------------|------------|-------------------------|------------------------------|---------------------------|------------|
| 1. Lab   | Cap                            | Cycle ergometry [9]      |                      |            |                         |                              |                           |            |
| 1. Lab   | Cap                            | Shuttle walk test [9]    |                      |            |                         |                              |                           |            |
| 1. Lab   | Cap                            | Treadmill test [9]       |                      |            |                         |                              |                           |            |
| 1. Lab   | Per                            | Direct video observation |                      |            |                         |                              |                           |            |
| 2. Semi  | Cap                            | 6 MWD [10]               |                      |            |                         |                              |                           |            |
| 2. Semi  | Cap                            | Master 2 step test [16]  |                      |            |                         |                              |                           |            |
| 2. Semi  | Cap                            | Sit to stand test [17]   |                      |            |                         |                              |                           |            |
| 2. Semi  | Cap                            | Stair climbing [18]      |                      |            |                         |                              |                           |            |
| 2. Semi  | Cap/per                        | Glittre ADL [19]         |                      |            |                         |                              |                           |            |
| 3. Field | Cap/per                        | Energy Expenditure [20]  |                      |            |                         |                              |                           |            |
| 3. Field | Per                            | Pedometer [21]           |                      |            |                         |                              |                           |            |

|          |     |  |  |  |  |  |  |  |
|----------|-----|--|--|--|--|--|--|--|
| 3. Field | Per | Accelerometer [11]   |  |  |  |  |  |  |
| 3. Field | Per | Heart rate monitoring [22]   |  |  |  |  |  |  |
| 4. PRO   | Per | Activity Self-Efficacy Questionnaire (ASEQ) [23]                               |  |  |  |  |  |  |
| 4. PRO   | Per | COPD Activity Rating Scale (CARS) [24]   |  |  |  |  |  |  |
| 4. PRO   | Per | Clinical COPD Questionnaire functional status domain (CCQ-fun) [25,26]         |  |  |  |  |  |  |
| 4. PRO   | Per | Capacity of Daily Living during the Morning questionnaire (CDLM) [27]          |  |  |  |  |  |  |
| 4. PRO   | Per | Canadian Occupational Performance Measure (COPM) [28,29]                       |  |  |  |  |  |  |
| 4. PRO   | Per | Chronic Respiratory Questionnaire dyspnoea domain (CRQ-dys) [30,31]            |  |  |  |  |  |  |
| 4. PRO   | Per | Daily record cards [32]  |  |  |  |  |  |  |
| 4. PRO   | Per | Nottingham Extended Activities of Daily Living Questionnaire (EADL) [33,34,35] |  |  |  |  |  |  |
| 4. PRO   | Per | Functional Performance Inventory (FPI) [36]                                    |  |  |  |  |  |  |

|        |     |  |  |  |  |  |  |  |  |
|--------|-----|--|--|--|--|--|--|--|--|
| 4. PRO | Per | Functional Status Questionnaire (FSQ) [37]                                     |  |  |  |  |  |  |  |
| 4. PRO | Per | General Practice Physical Activity Questionnaire (GPPAQ) [38]                  |  |  |  |  |  |  |  |
| 4. PRO | Per | London Chest Activity of Daily Living scale (LCADL) [35]                       |  |  |  |  |  |  |  |
| 4. PRO | Per | Modified Activity Record Questionnaire (MARQ) [39]                             |  |  |  |  |  |  |  |
| 4. PRO | Per | Manchester Respiratory Activities of Daily Living Questionnaire (MRADLQ) [40]  |  |  |  |  |  |  |  |
| 4. PRO | Per | Medical Research Council dyspnoea questionnaire (MRC) [12]                     |  |  |  |  |  |  |  |
| 4. PRO | Per | Pulmonary Functional Status and Dyspnea Questionnaire (PFSDQ) [41,42]          |  |  |  |  |  |  |  |
| 4. PRO | Per | Pulmonary Functional Status Scale (PFSS) [43]                                  |  |  |  |  |  |  |  |
| 4. PRO | Per | Saint George's Respiratory Questionnaire activity domain (SGRQ-act) [13]       |  |  |  |  |  |  |  |
| 4. PRO | Per | Short Questionnaire to Assess Health-enhancing physical activity (SQUASH) [44] |  |  |  |  |  |  |  |

Description of label: =very poor/unknown; =Not good enough, if this criterion is important; =Good enough; =Recommended; =Highly recommended.

Lab=laboratory tests; semi= semi laboratory tests; field= field tests; and PRO= patient reported outcomes; cap=functional capacity, per= functional performance.

References refer to manuals, development- or validation studies.

## Discussion

This review is the first that systematically organizes tools measuring functional status in COPD within a framework assessing the exact construct that they measure as well as the resources needed for its use. The measurement properties of each tool were graded based on the existing literature and feasibility was graded on predefined criteria.

To assess functional status in COPD patients, this study revealed that although there is a variety of tools to assess functional status in COPD no one meets all criteria to be considered highly recommended for primary care. The six minute walking distance test is the most reliable, but not a very practical semi-laboratory functional capacity test; The pedometer is the best functional performance field test and the MRC and the CCQ functional status domain are the best patient reported outcome tools.

The number of published studies measuring functional status increased rapidly in the past years. In 2000 18 articles were found using our search strategy and in 2009 40. This increase in publications reflects the increasing awareness that more than the lung function is impaired in COPD patients, and functional status is one of the important dimensions the disease impairs. Only two conceptual frameworks in which functional status is described are currently available: Leidy's model [6] and a model described by Larson [45]. Giving the increased attention to functional status, more conceptual frameworks will be developed in which this is described. An example is the new conceptual framework that is being developed as part of the PROactive program (personal communication M. Puhan, [www.proactivecopd.com](http://www.proactivecopd.com)).

The framework we created is based on an existing framework developed by Leidy and we extended this with aspects on the resources needed to perform the test. Leidy divided functional status into functional capacity, functional performance, functional reserve and capacity utilization. Since functional reserve is the difference between capacity and performance, no specific tests have been developed to measure this theoretical construct. Capacity utilization which represents the effort that the patient needs to reach the functional performance, might be one of the most important constructs but is not represented as a separate tool in the literature.

We therefore ended up dividing the measurement tools into functional capacity and functional performance tools. Two tools however, the Glittre ADL [19] and Energy Expenditure [20] were categorised as being both capacity and performance tests. The 6 minute walking distance test (6MWD) shows characteristics of both functional capacity and functional performance, although the test is considered a test for functional capacity [10]. The 6MWD has shown good correlations with functional performance measures such as motion sensors [46,47] and is indeed more related to functional performance, measured with patient reported outcomes, than exercise capacity, measured by cycle ergometry in patients with severe emphysema [48].

Next to categorization in constructs, we divided the tools into methods based on resources needed i.e. laboratory tests, semi laboratory tests, field tests, and patient reported outcome tests. Using this framework we rated the most important measurement features which include validity and reliability, responsiveness, the validation in primary care COPD patients, the feasibility, the usage in primary care, and the availability of the MCID.

Despite the difficulty categorizing certain tests, the combination of Leidy's framework and our resources framework gives a good overview of available current functional status measurement tools and a guide for choosing tools feasible in primary care.

This study focussed on tools for patients with mild to moderate COPD and in Table I the rating for this patient group is shown. Internationally, differences between countries regarding where patients are treated (primary or secondary care) vary considerably. In some countries, all stages of COPD are mainly treated in primary care. In others, such as in the Netherlands most patients with severe COPD are managed in secondary care. Secondly most tools have been developed in more severe COPD patients, therefore we explicitly focussed in our rating system on mild to moderate COPD patients because in milder patients the measurement properties are more difficult to obtain from literature. Nevertheless, within the group of mild patients (defined by lung function), the patients with more impaired functional status may benefit most from interventions [49].

The categorization can help to select the most appropriate measurement in specific situations. In clinical settings, it is important that physicians realize what they measure in a patient, why they measure it and how valid this measurement is. For example, a capacity test like cycle ergometry is very valid and can reveal true (limitations in) maximum capacity. In COPD, the limitation of capacity can be linked to the loss of pulmonary function. When the capacity limitation cannot be explained by pulmonary function loss this might be a reason to re-examine the patient for co-morbidities, for example. Although laboratory capacity tests might be very useful in hospital based clinical settings, for primary care, the field tests and patient reported outcomes are more feasible. Field tests and PRO's however always test performance and not capacity. Clinical conclusions drawn from these tests might therefore differ from conclusions based on (laboratory based) capacity tests. An additional complication of functional status PROs is that although categorized as performance tests, most PRO's measure patient perceived performance limitations and/or symptom burden during performance. Correlations between motion sensors measuring actual performance and functional status PROs are therefore moderate [11]. Only the SQUASH measures the amount of physical activity, the MRADLQ measures whether or not activities are performed (with or without help), but both show poor measurement properties.

Not all tests are standardized, making it difficult to compare them between settings and studies. For example, the stair climbing test was performed in a hospital setting with 16 flights of stairs and stopped after exhaustion or chest pain and at their own pace [18] or at maximal speed [50] or after 35 seconds counting the maximum number of stairs [51]. Although the test is cheap and, when having stairs in your practice, can be easily performed, it lacks standardization. However, for individual follow up of patients in the same setting it might be useful.

Standardized health status questionnaires with a separate functional status domain were included in this review (SGRQ, CRQ, CCQ). These domains are often separately described in studies. However, it is not advised to create a "new" questionnaire that only uses the separate domain, because that creates new tests and alters the validity [52]. The advantage of a domain within a health status scale is that with one tool, different aspects of the health impairment caused by the disease are measured.

Like many medical tests and functional status examination tests can be used to support the diagnostic trajectory but can also be used for monitoring purposes only. In clinical practice capacity tests like the cycle ergometry are often used as a diagnostic tool [9] whereas PRO

outcomes are suggested as evaluation tools. Since patient reported outcomes are "precision instruments" [52] and instruments are being developed [26,53] and validated [54] for use in daily clinical practice these instruments are more often used for evaluating purposes.

Although information coming from questionnaires is often more comprehensive and more reliable than from oral history taking, the benefits from this for clinical practice have to be established.

A limitation of this study is that the grading of the tools was done based on the literature review by JWHK and GMA. Although we had pre-defined criteria to rate the measurements, it was in several occasions difficult to rate according to the 5 grades of the smilies. For example: When a measurement was used in a large study population which included a low number of GOLD I and II patients, we discussed between the authors if "primary care population" should be rated as "good enough", or "recommended". This resulted in a less objective rating as for example "MCID known", but the agreement between the authors improved the validity in scoring. Where JWHK and GMA disagreed on the scoring, TvDM reviewed the literature as well and discrepancies were discussed. The ratings on "Practical/Easy to Administer" and "Tested in Practice (COPD)" are based on the literature and not on real life experience. Our method was different from that used in an overview of COPD wellness tools for the IPCRG where researchers and clinicians were asked to rate the several COPD wellness tools. The latter method might have resulted in different scoring because of unpublished experiences. We limited our search to PubMed, which will have resulted in most, but not all available articles [55]. We have used our search to identify tools, not to review individual studies. We are confident that important tools that are used in scientific work were included in this review.

In conclusion, for primary care, the six minute walking distance test is the most reliable, but not very practical semi-laboratory functional capacity test. The pedometer is the best functional performance field test. And the MRC and the CCQ functional status domain are the best patient reported outcome tools to measure functional performance in primary care.

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## Chapter 5

# Health status measurement in COPD: the minimal clinically important difference of the Clinical COPD Questionnaire

*Adapted version from:*  
*Respiratory Research, 2006*

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## Abstract

**Background:** Patient reported outcomes (PRO) questionnaires are being increasingly used in COPD clinical studies. The challenge facing investigators is to determine what change is significant, ie what is the minimal clinically important difference (MCID). This study aimed to identify the MCID for the Clinical COPD Questionnaire (CCQ) in terms of patient referencing, criterion referencing, and by the standard error of measurement (SEM).

**Methods:** Patients were  $\geq 40$  years of age, diagnosed with COPD, had a smoking history of  $>10$  pack-years, and were participating in a randomized, controlled clinical trial comparing intravenous and oral prednisolone in patients admitted with an acute exacerbation of COPD. The CCQ was completed on Days 1-7 and 42. A Global Rating of Change (GRC) assessment was taken to establish the MCID by patient referencing. For criterion referencing, health events during a period of 1 year after Day 42 were included in this analysis.

**Results:** 210 patients were recruited, 168 completed the CCQ questionnaire on Day 42. The MCID of the CCQ total score, as indicated by patient referencing in terms of the GRC, was 0.44. The MCID of the CCQ in terms of criterion referencing for the major outcomes was 0.39, and calculation of the SEM resulted in a value of 0.21.

**Conclusion:** This investigation, which is the first to determine the MCID of a PRO questionnaire via more than one approach, indicates that the MCID of the CCQ total score is 0.4.

## Background

Chronic Obstructive Pulmonary Disease (COPD) is a major cause of morbidity and mortality in industrialized countries. COPD affects several organs and systems, and has a considerable impact on health status. Impaired exercise tolerance, exacerbations, fatigue, muscle weakness, depression and sleeping disorders are all features of the disease, and although spirometry is useful for assessing the effects of COPD on the lungs, it yields limited information relevant to health status or symptoms. Nevertheless, health status has become a central feature of studies in COPD in recent years because: (i) treatments for the condition are largely symptomatic, and (ii) European clinical trials are now required to incorporate a symptomatic measure [1,2]. The importance of the evaluation of health status in COPD has been demonstrated by two studies that show correlations between health status and other clinical outcomes. Poor scores on the St George's Respiratory Questionnaire (SGRQ), an instrument that measures disease specific health status, were associated with mortality, hospital readmission and increased healthcare resource consumption [3,4].

A number of questionnaires for the assessment of health-related quality of life and health status which cover a broader view of patients' well-being have been introduced into clinical practice since the late 1980s. These include COPD specific tools, such as the Chronic Respiratory Questionnaire (CRQ) [5], the SGRQ (which is for both asthma and COPD) [6], the generic instruments such as the Medical Outcomes Study Short-Form 36 (SF-36) [7], the Breathing Problems Questionnaire (BPQ) [8] and the Quality of Life for Respiratory Illness Questionnaire (QOL-RIQ) [9]. These instruments all capture valuable data, but have levels of complexity that make them difficult to use in the routine clinic setting. This has led to the need for a shorter and validated method to measure health status in order to assess clinical control in clinical trials as well as in daily clinical practice. The Clinical COPD Questionnaire (CCQ) (Figure 1) has been developed to address this need [10].

One of the problems facing researchers using new assessments of patient reported outcomes (PRO) questionnaires is the determination of what constitutes a change that can be considered significant [11]. This minimal clinically important difference (MCID) has been defined as 'the smallest difference in a score in the domain of interest which patients perceive as beneficial and which would mandate in the absence of troublesome side effects and excessive costs a change in the patient's management' [12]. The MCID can be determined by the judgment of the patient on the basis of a Global Rating of Change (GRC) questionnaire (patient referencing), by the clinician (clinician referencing – again with a global questionnaire), or by comparing scores on a health status instrument with a pre-specified health criterion (criterion referencing). These categories have been applied variously to other instruments such as the SGRQ and CRQ [4,6,12-14]. The aim of the present study was to identify the MCID for the CCQ in three different ways: patient referencing, criterion referencing, and by calculating the standard error of measurement (SEM), a method that seeks correlations between single standard error units and established MCID approximations [15,16].

Figure 1. The Clinical COPD Questionnaire, UK English week version.

Patient number: \_\_\_\_\_  
Date: \_\_\_\_\_

| <b>CLINICAL COPD QUESTIONNAIRE</b>   |                    |                       |                  |                    |              |                    |                                  |
|--|--------------------|-----------------------|------------------|--------------------|--------------|--------------------|----------------------------------|
| Please <b>circle</b> the number of the response that best describes how you have been feeling during the <b>past week</b> .<br>(Only <b>one</b> response for each question). |                    |                       |                  |                    |              |                    |                                  |
| On average, <b>during the past week</b> , how often did you feel:  | never              | hardly ever           | a few times      | several times      | many times   | a great many times | almost all the time              |
| 1. Short of breath <b>at rest</b> ?  | 0                  | 1                     | 2                | 3                  | 4            | 5                  | 6                                |
| 2. Short of breath <b>doing physical activities</b> ?  | 0                  | 1                     | 2                | 3                  | 4            | 5                  | 6                                |
| 3. <b>Concerned</b> about getting a cold or your breathing getting worse?  | 0                  | 1                     | 2                | 3                  | 4            | 5                  | 6                                |
| 4. <b>Depressed (down)</b> because of your breathing problems?   | 0                  | 1                     | 2                | 3                  | 4            | 5                  | 6                                |
| In general, <b>during the past week</b> , how much of the time:  |                    |                       |                  |                    |              |                    |                                  |
| 5. Did you <b>cough</b> ?  | 0                  | 1                     | 2                | 3                  | 4            | 5                  | 6                                |
| 6. Did you <b>produce phlegm</b> ?   | 0                  | 1                     | 2                | 3                  | 4            | 5                  | 6                                |
| On average, <b>during the past week</b> , how limited were you in these activities <b>because of your breathing problems</b> :   | not limited at all | very slightly limited | slightly limited | moderately limited | very limited | extremely limited  | totally limited /or unable to do |
| 7. <b>Strenuous physical activities</b> (such as climbing stairs, hurrying, doing sports)?   | 0                  | 1                     | 2                | 3                  | 4            | 5                  | 6                                |
| 8. <b>Moderate physical activities</b> (such as walking, housework, carrying things)?  | 0                  | 1                     | 2                | 3                  | 4            | 5                  | 6                                |
| 9. <b>Daily activities at home</b> (such as dressing, washing yourself)?   | 0                  | 1                     | 2                | 3                  | 4            | 5                  | 6                                |
| 10. <b>Social activities</b> (such as talking, being with children, visiting friends/relatives)?   | 0                  | 1                     | 2                | 3                  | 4            | 5                  | 6                                |

## Patients and Methods

### The CCQ

The CCQ is a 10-item, self-administered questionnaire that can be completed in less than 2 minutes. Items are divided into three domains: symptom, functional state and mental state; patients are required to respond to each item on a seven-point Likert scale where 0 = asymptomatic/no limitation and 6 = extremely symptomatic/total limitation. The final score is the mean of all ten items, and scores for the three domains can be calculated separately if required. Two versions are available: a 7-day version, which asks patients to recall their COPD status over the past week, and a 24-hour version, which is usually used as a diary. The CCQ has been validated and has shown strong discriminative properties, test–retest reliability and responsiveness [10].

### Patients

From June 2001 until May 2003, data were collected from 210 patients admitted to the Isala klinieken at Zwolle, The Netherlands with an acute exacerbation of COPD. These patients were participating in a randomized, controlled clinical trial designed to compare the effects of treatment with intravenous and oral prednisolone in patients with an acute exacerbation of COPD. Patients were at least 40 years of age and had COPD as indicated by the criteria of the American Thoracic Society [17]. All patients had a smoking history of more than 10 pack-years, and gave informed and written consent before enrolment.

Patients with a history of asthma were excluded, as were those with known hypersensitivity to prednisolone, chest X-ray not consistent with exacerbation of COPD, arterial PaCO<sub>2</sub> above 9.3 kPa or acidosis (pH <7.26). Participation in another clinical trial in the four weeks preceding randomization, presence of severe co-morbidity, and inability to follow the investigator’s instructions were also grounds for exclusion. Patients received either a 5-day course of continuous intravenous prednisolone (60 mg/24 hours diluted in 96 ml saline 0.9%) together with three-times daily one placebo tablet, or a 5-day course of three-times daily one tablet of 20 mg prednisolone with a continuous placebo infusion (100 ml saline 0.9%/24 hours). Active and placebo medication had a similar appearance. After 5 days all patients received oral prednisolone at a dosage of 30 mg once daily, which was subsequently reduced by 5 mg daily until 0 mg or a prior maintenance dosage was reached [18].

### Data collection

#### Patient referencing

The CCQ was completed on Days 1 to 7 and during an outpatient visit on Day 42. A GRC assessment was also taken on Days 2 and 3 to evaluate self-perceived changes in disease control since the first day of admission to hospital. Responses were scored from +7 (a very great deal better) to –7 (a very great deal worse); 0 indicated no change (Juniper *et al.* 1994). Scores of -3, -2, +2 and +3 were considered to represent minimal but nevertheless clinically important changes. To establish the MCID by patient referencing, the mean change in CCQ score from admission to Day 2 or 3 of the group with minimal change on the GRC questionnaire (-3, -2, +2 and +3) was calculated.

### Criterion referencing

Health events were classified as major (hospital readmission for a pulmonary cause or death) or minor (worsening of COPD symptoms requiring treatment with an oral corticosteroid and/or antibiotics). Major health events only were included in the present analysis, with data pertaining to health events in all patients who completed the CCQ on Day 42 of the follow-up period. Data were obtained from general practitioners and hospital records.

### SEM

SEMs were calculated using the following equation [19]:

$$SEM = \sigma_x \sqrt{1 - r_{xx}}$$

Where (i)  $r_{xx}$  = the reliability/intra class coefficient of the CCQ = 0.94 [10]; and (ii)  $\sigma_x$  = standard deviation of the total CCQ on Day 42 (baseline) = 0.87.

### Follow-up

Patients were followed for 12 months after completion of the CCQ on Day 42 in order to collect data on health events that could be matched to CCQ responses. Electronic medical dossiers at the trial centre were checked and data were provided by general practitioners, with information requested including dosages and lengths of courses for oral corticosteroids and/or antibiotics, hospital admissions for COPD exacerbations, admission to nursing homes, and death.

### Statistical analysis

All analyses were performed with SPSS software version 12.0 (SPSS Inc., Chicago). A paired samples t-test was used to test the differences between CCQ total and domain scores on admission and on Days 2 and 3. The Wilcoxon signed ranks test was used for the mental state domain, since scores in this domain were skewed.

For criterion referencing, means and standard deviations of total, functional and symptom CCQ scores were calculated. Unpaired t-tests were used to compare differences between groups. For CCQ scores in the mental state domain, the non-parametric Mann-Whitney U test was used. P values less than 0.05 were considered to be statistically significant.

## Results

Of the 210 patients who were recruited to the clinical study on which this analysis is based, 168 completed the CCQ questionnaire on Day 42, 58 had global ratings of change for Day 2, 59 on Day 3 and completed the CCQ on Day 1, 2 and 3. Of the 168 patients who were followed up in the criterion referencing population, 24% were current smokers; the median smoking history across all these patients was 36.5 pack-years (range: 11 to 130 pack-years). Ages ranged from 43 to 84 years, with a median age of 71 years. Most patients were experiencing moderate (47.6%) or severe (33.3%) disease according to Global Obstructive Lung Disease (GOLD) criteria [20]. The 42 patients that could not be included in the criterion referencing study (14 withdrew their informed consent, 12 died before day 42, 9 were lost to follow-up, 5 had no CCQ data, one had no exacerbation and one reported side effects of study medication), were slightly older with a median of 74 years, but were similar in respect to percentage predicted forced expiratory volume in one second (FEV<sub>1</sub>), current smoking and number of pack-years.

As might be expected as a result of study intervention, the FEV<sub>1</sub> increased significantly in the criterion referencing population from 37.7% to 43.2% (means,  $p=0.000$ ) between hospital admission (Day 1) and Day 42.

### Patient referencing

Tables 1 and 2 show mean CCQ changes between day 1 and days 2 and 3, respectively, grouped according to response on the GRC scale. Twenty-one patients responded with no change and 3 reported worsening on Day 2. On Day 3, 1 patient reported worsening whereas 10 patients reported no change. The first category, which shows changes of +1 (no discernable or only very slight improvement), included only very small numbers of patients on both Days 2 and 3 and is below the threshold for clinical change specified in the protocol. No significant change in CCQ scores for any domain was seen for this category. However, at the threshold for clinically relevant change (score change of +2 or +3), some significant improvements in CCQ scores became apparent: on Day 2, CCQ changes of 0.70 for the symptom domain and 1.0 for the mental domain fell outside the respective 95% confidence intervals and attained statistical significance. A trend towards significant change for the total CCQ score on Day 2 (0.40;  $p = 0.098$ ) translated into statistically significant improvement on Day 3 (0.44;  $p = 0.008$ ) that was associated with a GRC improvement of +2 or +3. Statistical significance was maintained on Day 3 for the symptom domain, but was lost for the mental domain. Furthermore, the number of patients available for CCQ scoring in the GRC +2 or +3 category increased from 15 on Day 2 to 20 on Day 3. These observations therefore suggest that the MCID of the CCQ total score, as indicated by patient referencing in terms of the GRC, is 0.44.

As might be expected, significant improvements in all CCQ domains were seen in the GRC category of +4 to +5 (Table 1 and Table 2). These GRC scores represent higher levels of patient-perceived clinical improvement that are reflected by significant improvements in CCQ scoring (CCQ changes ranged from 1.25 to 1.46 across domains on Day 3), but are too great to be considered as minimally clinically relevant. Too few patients were represented in the maximal GRC change category (+6 to +7) on Days 2 and 3 for CCQ results to be trustworthy, but there was an overall trend towards further increases in CCQ scores.

### Criterion referencing

Differences in mean CCQ scores on Day 42 between patients who experienced major health events (death, rehospitalization and death and/or rehospitalization) during the subsequent 12 months are presented in Table 3. There were no significant differences that could be related to clinical outcomes in the mental domain of the CCQ, but changes of interest were seen for functioning and symptoms, and for total CCQ scores.

Day 42 total CCQ score difference was -0.8 between patients who died and those who survived over the next 12 months ( $p < 0.001$ ). CCQ differences for rehospitalization were not as marked, however, with borderline significance being noted for the difference of -0.47 in the function domain ( $p = 0.047$ ) only. For the combined major outcome of death and/or rehospitalization, a difference -0.39 for the total CCQ score, attained statistical significance (Table 3). Thus, the MCID by inspection for the CCQ in terms of criterion referencing for the major outcomes covered in this analysis is 0.39.

### SEM

Calculation of the SEM using the described method resulted in a SEM of 0.21.

**Table 1.** Minimal Clinically Important Difference (MCID) for the Clinical COPD Questionnaire (CCQ) by patient referencing.

| CCQ score category           | Score difference: Day 1 minus Day 2 |                         |         |
|------------------------------|-------------------------------------|-------------------------|---------|
|                              | Mean $\pm$ SD                       | 95% confidence interval | p value |
| <b>GRC +1 (n = 3)</b>        |                                     |                         |         |
| Total                        | 0.30 $\pm$ 0.30                     | -0.45, 1.05             | 0.225   |
| Symptoms                     | -0.25 $\pm$ 1.64                    | -4.32, 3.82             | 0.816   |
| Function                     | 1.17 $\pm$ 0.80                     | -0.83, 3.16             | 0.128   |
| Mental                       | -0.5 $\S$                           |                         | 0.157   |
| <b>GRC +2 to +3 (n = 15)</b> |                                     |                         |         |
| Total                        | 0.40 $\pm$ 0.90                     | -0.09, 0.91             | 0.098   |
| Symptoms                     | 0.70 $\pm$ 1.09                     | 0.98, 1.30              | 0.026*  |
| Function                     | 0.17 $\pm$ 1.37                     | -0.93, 0.59             | 0.645   |
| Mental                       | 1.0 $\S$                            |                         | 0.007*  |
| <b>GRC +4 to +5 (n = 14)</b> |                                     |                         |         |
| Total                        | 1.31 $\pm$ 1.09                     | 0.69, 1.94              | 0.001*  |
| Symptoms                     | 1.13 $\pm$ 1.52                     | 0.25, 2.0               | 0.016*  |
| Function                     | 1.48 $\pm$ 1.25                     | 0.76, 2.20              | 0.001*  |
| Mental                       | 0.5 $\S$                            |                         | 0.018*  |
| <b>GRC +6 to +7 (n = 2)</b>  |                                     |                         |         |
| Total                        | 1.95 $\pm$ 0.07                     | 1.31, 2.59              | 0.016*  |
| Symptoms                     | 2.75 $\pm$ 1.77                     | -13.13, 18.63           | 0.272   |
| Function                     | 1.50 $\pm$ 1.06                     | -8.03, 11.03            | 0.295   |
| Mental                       | 1.25 $\S$                           |                         | 0.317   |

Differences between CCQ scores for Days 1 and 2 grouped according to Global Rating of Change (GRC) as scored by patients on a scale of -7 to 7. Note that paired-sample t-tests were used for total CCQ scores and for symptom and functional domains; Wilcoxon signed rank test was used for the mental domain.

\* Statistically significant (2-tailed):  $p < 0.05$ .  $\S$  Difference in median scores  
COPD = chronic obstructive pulmonary disease; SD = standard deviation.

## Discussion

The methods used in the present analysis to determine the MCID for the CCQ yielded similar findings with patient and criterion referencing (0.44 and 0.39 units respectively). However the SEM was much lower (0.21). In light of these observations, we suggest that the MCID of the CCQ instrument is approximately 0.4 points. Thus, a change in score of 0.4 or more from baseline indicates the smallest change indicated by the CCQ in health status that can be considered to be clinically significant.

The first method used, patient referencing, was based on CCQ changes linked to a pre-specified global rating of change of +2 to +3 points over the first 3 days of treatment. In both this group and that with the next level of improvement (GRC change of +4 to +5), sufficient numbers of patients were available for clear patterns of change in the CCQ to be evident.

**Table 2.** Minimal Clinically Important Difference (MCID) for the Clinical COPD Questionnaire (CCQ) by patient referencing.

| CCQ score category           | Score difference: Day 1 minus Day 3 |                         |         |
|------------------------------|-------------------------------------|-------------------------|---------|
|                              | Mean $\pm$ SD                       | 95% confidence interval | p value |
| <b>GRC +1 (n = 4)</b>        |                                     |                         |         |
| Total                        | 0.05 $\pm$ 0.49                     | -0.73, 0.83             | 0.852   |
| Symptoms                     | 0 $\pm$ 1.02                        | -1.62, 1.62             | 1.0     |
| Function                     | 0 $\pm$ 1.02                        | -1.62, 1.62             | 1.0     |
| Mental                       | 0.25 $\S$                           |                         | 0.414   |
| <b>GRC +2 to +3 (n = 20)</b> |                                     |                         |         |
| Total                        | 0.44 $\pm$ 0.66                     | 0.13, 0.75              | 0.008*  |
| Symptoms                     | 0.74 $\pm$ 0.93                     | 0.30, 1.17              | 0.002*  |
| Function                     | 0.26 $\pm$ 0.995                    | -0.20, 0.72             | 0.253   |
| Mental                       | 0.25 $\S$                           |                         | 0.398   |
| <b>GRC +4 to +5 (n = 20)</b> |                                     |                         |         |
| Total                        | 1.36 $\pm$ 1.07                     | 0.86, 1.86              | <0.001* |
| Symptoms                     | 1.46 $\pm$ 0.99                     | 1.0, 1.92               | <0.001* |
| Function                     | 1.31 $\pm$ 1.65                     | 0.54, 2.08              | 0.002*  |
| Mental                       | 1.75 $\S$                           |                         | 0.023*  |
| <b>GRC +6 to +7 (n = 4)</b>  |                                     |                         |         |
| Total                        | 1.95 $\pm$ 0.87                     | 0.56, 3.34              | 0.021*  |
| Symptoms                     | 2.37 $\pm$ 1.13                     | 0.58, 4.17              | 0.024*  |
| Function                     | 2.31 $\pm$ 0.90                     | 0.88, 3.74              | 0.014*  |
| Mental                       | -0.25 $\S$                          |                         | 0.655   |

Differences between CCQ scores for Days 1 and 3 grouped according to Global Rating of Change (GRC) as scored by patients on a scale of -7 to 7. Note that paired-sample t-tests were used for total CCQ scores and for symptom and functional domains; Wilcoxon signed rank test was used for the mental domain.

\* Statistically significant (2-tailed):  $p < 0.05$ .  $\S$  Difference in median scores  
COPD = chronic obstructive pulmonary disease; SD = standard deviation.

The very small numbers of patients and consequent inconclusive results in the groups showing least (GRC change +1) and most (GRC change +6 to +7) clinical improvement was of little importance in the setting of the present analysis, as the change in health status of these patients was either too small or too large to be of interest.

Patient referencing has been used extensively by other investigators calculating MCIDs of PRO instruments, and our results are in broad agreement with these other findings. Furthermore, although this approach has not been formally validated, there is ample evidence that the global assessments used correlate well with PRO questionnaires.

Jaeschke and colleagues [12] performed an analysis in 55 patients with COPD who had participated in two clinical trials and in 20 patients with heart failure. Changes in CRQ [5]

**Table 3.** Minimal Clinically Important Difference (MCID) for the Clinical COPD Questionnaire (CCQ) by criterion referencing.

| CCQ score category  | Score difference |                         |         |
|---|------------------|-------------------------|---------|
|   | Mean             | 95% confidence interval | p value |
| <b>Death (n = 25) or survival (n = 143)</b>   |                  |                         |         |
| Total   | -0.80            | -1.23, -0.37            | <0.001* |
| Symptoms  | -0.62            | -1.13, -0.12            | 0.015*  |
| Function  | -1.32            | -1.90, -0.74            | <0.001* |
| Mental  | 0.5§             |                         | 0.211   |
| <b>Rehospitalization (n = 56) or not (n = 112)</b>                                    |                  |                         |         |
| Total   | -0.18            | -0.52, 0.16             | 0.290   |
| Symptoms  | -0.07            | -0.46-0.31              | 0.706   |
| Function  | -0.47            | -0.93, -0.007           | 0.047*  |
| Mental  | 0§               |                         | 0.505   |
| <b>Death/rehospitalization (n = 70) versus survival/no rehospitalization (n = 98)</b> |                  |                         |         |
| Total   | -0.39            | -0.71, -0.07            | 0.017*  |
| Symptoms  | -0.27            | -0.63, 0.10             | 0.153   |
| Function  | -0.77            | -1.19, -0.34            | 0.001*  |
| Mental  | 0§               |                         | 0.987   |

Differences between baseline (Day 42) CCQ scores are grouped according to major health events during 12-month follow-up. Unpaired-sample t-tests were used for total CCQ scores and for symptom and functional domains, with equal variances assumed; the Mann-Whitney U test was used for the mental domain.

\* Statistically significant (2-tailed);  $p < 0.05$ . § Difference in median scores  
COPD = chronic obstructive pulmonary disease.

and Chronic Heart Failure Questionnaire (CHQ) [21] scores were compared with retrospective global estimates of change by the patients themselves on a 15-point transition scale similar to our GRC (seven categories of improvement, seven of deterioration and one of no change). The authors set the threshold for clinical significance on this scale as ‘almost the same, hardly any better (or worse)’, ‘a little better (or worse)’ or ‘somewhat better (or worse)’, the last two of which approximate to the change of 2 to 3 on the scale used here. Although there was considerable variation between patients in MCID estimates, mean changes corresponding to the predefined threshold were 0.43 for dyspnea, 0.64 for fatigue, and 0.49 for emotional function. Jaeschke and colleagues [12] concluded that the mean change in score per question that corresponded to the MCID was consistently around 0.5.

Juniper *et al.* [22] adopted a similar approach to determine an MCID for the Asthma Quality of Life Questionnaire (AQLQ), except that their threshold for minimally significant change was more similar to ours than that adopted by Jaeschke *et al.* AQLQ scores that corresponded to ‘a little better (or worse)’ and ‘somewhat better (or worse)’ were used. In this analysis, each of 39 patients attending an asthma clinic was followed for 8 weeks. For overall asthma-specific quality of life and for all individual domains (activities, emotions and symptoms), the MCID per item was close to 0.5 (0.42 to 0.58). Differences of approximately 1.0

corresponded to moderate change, and large changes were accompanied by score changes of around 1.5.

It is worth noting at this point that more noticeable global changes as shown by the GRC were accompanied in our analysis by larger CCQ changes. By Day 3, a GRC of +4 to +5 was associated with mean increases in CCQ scores of 1.25 to 1.46 for the separate domains, and an increase in total mean score of 1.36. These changes were consistent across domains and were all statistically significant.

Further data in patients with asthma are available from a 1-year study in which 719 adults received nedocromil sodium or placebo and were assessed with the SGRQ [23]. Differences in scores from baseline to 12 months were compared with patients’ own retrospective estimates of treatment efficacy, and there was a rank order correlation between change in health-related quality of life and overall judgement of treatment efficacy. Patients who judged treatment to be ‘slightly effective’ showed a mean 4.0-unit change on the SGRQ [24]. In another study [25], 87 patients who judged treatment with salmeterol to be ‘satisfactory’ showed a mean change in SGRQ of 2.0 points over 16 weeks. This term, however, was deemed ambiguous. [13] The lowest response category compatible with efficacy, ‘effective’, corresponded with a mean SGRQ change of 4.3 units in 109 patients.

Although it is not possible to compare these authors’ results with those reported here because of the different PRO questionnaires and health status scales examined, it is clear that all these investigators were readily able to identify MCIDs by patient referencing methods. Furthermore, patterns of findings across the different studies are remarkably consistent, and show not only the smallest discernible changes, but also consistent increases in health status scores in parallel with patients’ own perceptions of greater clinical improvement.

The criterion referencing approach compares health status scores to a specified health-related variable on the understanding that PRO questionnaire scores should be worse in patients who have major health events than in those who do not. Upon examination of CCQ scores categorized according to the major health outcomes of death, rehospitalization, and death and/or rehospitalization, we found the smallest statistically significant score change associated with one of these outcomes to be 0.39. Score changes that exceeded this value were found to be consistently significant, while lower scores failed to attain significance.

It should also be noted that MCIDs determined by this method might be expected to have predictive value, as the CCQ score differences were noted at baseline point of study Day 42 and corresponded to subsequent health outcomes reported 1 year later. Thus, it can be concluded that when a difference in CCQ score between two patients with COPD exceeds 0.39 points, the patient with the higher score has an increased risk of dying and/or being readmitted to hospital during the course of the following year. Overall, the smallest CCQ differences were found to be those between patients who were readmitted to hospital and those who were not, whereas the score differences between patients who died and those who survived were the largest. This predictive value concurs with results of other studies, such as Domingo-Salvany *et al.* [3] who reported a link between reduced duration of survival for male patients with COPD and poor health-related quality of life. In addition, Osman and colleagues [4] found poor SGRQ scores to be associated with increased risk of hospital readmission for COPD.

The similarity between MCIDs determined by patient and criterion referencing for the CCQ as noted in the present analysis has been apparent in research into other health-related quality of life scales. SGRQ scores at baseline differed by 4.8 units between patients who were admitted to hospital or died and those who experienced neither of these outcomes

in the year following discharge from hospital for an acute exacerbation of asthma in a study in 238 individuals [4]. Similarly, in a study in patients with COPD, SGRQ scores were related to Medical Research Council dyspnea gradings [26]. In 32 patients with a grading of 5 (housebound), SGRQ scores were 3.9 units worse than in patients who had major impairment but who were not housebound (grade 4).

The SEM has not been used in many studies for establishing the MCID of PRO questionnaires. For the CRQ, one-SEM appears to be closely related to the MCID of the CRQ [15]. In this study the SEM was found to be 0.21, which is lower than the other two methods used for establishing the MCID of the CCQ. This might be because of the high reliability/intra-class coefficient. Some researches take a more conservative approach to the assessment of the MCID using the SEM. They use the 1.96 SEM, which represents a 95% confidence interval [19]. Using this conservative measure, the MCID is 0.41, a similar result to that produced by the two other methods.

Thus, the present investigation, which is the first to determine the MCID of a PRO questionnaire via more than one approach, indicates that the MCID of the CCQ total score is 0.4. Our findings also demonstrate the predictive value of such differences in terms of longer term major health outcomes in patients with COPD.

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## Chapter 6

# Health status in routine clinical practice: validity of the Clinical COPD Questionnaire at the individual patient level

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## Abstract

**Background:** There is a growing interest to use health status or disease control questionnaires in routine clinical practice. However, the validity of most questionnaires is established using techniques developed for group level validation. This study examines a new method, using patient interviews, to validate a short health status questionnaire, the Clinical COPD Questionnaire (CCQ), at the individual patient level.

**Methods:** Patients with COPD who visited an outpatient clinic completed the CCQ before the consultation, and the specialist physician completed it after the consultation. After the consultation all patients had a semi-structured in-depth interview. The patients' CCQ scores were compared with those of the treating clinician, and with mean scores from 5 clinicians from a pool of 20 who scored the CCQ after reading the transcript of the in-depth interviews only. Agreement was assessed using Lin's concordance correlation coefficient (CCC), and Bland and Altman plots. Interviews with patients with low agreement were reviewed for possible explanations.

**Results:** A total of 44 COPD patients (32 male, mean age 66 years, FEV<sub>1</sub> 45% of predicted) participated. Agreement between the patients' CCQ scores and those of the treating clinicians (CCC=0.87) and the mean score of the reviewing clinicians (CCC=0.86) was very high. No systematic error was detected. No explanation for individuals with low agreement was found.

**Conclusion:** The validity of the CCQ on the individual patient level, as assessed by these methods, is good. Individual health status assessment with the CCQ is therefore sufficiently accurate to be used in routine clinical practice.

## Background

Health status measurement by questionnaires can be used in routine clinical practice to enhance communication, monitor disease progression and response to treatment, screen for undetected disability, improve patient satisfaction, and assess disease severity [1,2]. Questionnaires available for use in routine clinical practice must be short, and easy to administer, score and interpret; in addition, guidelines for their interpretation should be available [3, 4]. Questionnaires should also be reliable and validated for the patient who completes the questionnaire.

Methods to develop and validate health status or quality of life questionnaires are well established. These validation processes focus on their use in clinical trials in groups of patients. However, despite their increasing use in everyday practice, we found only one proposed guideline for the validation of questionnaires in the individual patient. In 1995 McHorney and Tarlov suggested a number of measurement standards for individual patient application of questionnaires, such as high internal consistency reliability (above 0.9) and a small standard error of measurement, besides usual qualities such as construct validity and sensitivity to clinical change [3]. Although these proposed standards are mainly based on current knowledge and 'common sense', practically no questionnaires have been validated for individual health status assessment according to these standards [3].

Reliability levels of 0.90-0.95 are difficult to meet for many existing questionnaires. Secondly, since reliability is related to questionnaire length and measuring a unidimensional construct, newly developed questionnaires aiming to achieve these levels of reliability should be long and unidimensional (i.e. they measure only one aspect of the disease). However, clinicians might be more interested in being informed about several aspects of the disease (e.g. emotions, functional status and symptoms) and may prefer short questionnaires. Therefore, it may be interesting to ignore these suggested guidelines and assess whether a questionnaire is valid according to the dynamics of routine clinical practice.

To address this question we published a proposal for a new methodology [5]. In this methodology the patient's health status in daily life (as measured by an in-depth interview) is used as the gold standard, and the outcome of the in-depth interview is compared with the patient's score on the questionnaire completed in the clinic before the in-depth interview took place. We applied this new methodology in patients with chronic obstructive pulmonary disease (COPD), a condition that has a large impact on health status [6], even in mild disease [7].

One of the health status questionnaires used in COPD in clinical trials and clinical practice is the Clinical COPD Questionnaire (CCQ) [8]. This is a short 10-item questionnaire with answers based on a 7-point Likert scale. The final score is calculated by simply summing the item scores and dividing them by the number of items. The CCQ has three domains: symptoms (4 items), mental health (2 items) and functional status (4 items). The CCQ has shown to be reliable health status measure, is responsive to treatment and is stable over time if no changes occur [8,9].

This article describes the validation, at the individual patient level, of the CCQ.

## Methods

### Patients

Patients with physician-diagnosed COPD, and confirmed by lung function measurement, visiting an outpatient clinic were invited to participate in the study. Patients were excluded if they had suffered a myocardial infarction within 3 months prior to enrolment. All patients gave written informed consent.

### Measurements

Lung function was taken from the patient's charts, including height and weight. Exercise capacity was assessed by the 6-minute walking distance test performed according to the ATS criteria [10]. Pulse oxygenation and BORG scores for dyspnoea [11] were measured before and after the walking test. Health status was measured using the CCQ. Dyspnoea during exercise was measured with the MRC dyspnoea score. The BODE score (a multidimensional index) was calculated [12].

### CCQ

The CCQ is a 10-item health status questionnaire measuring symptoms, functional status and mental status in patients with COPD. The questionnaire is self-administered, and can be completed in 2 min. The CCQ has a high internal consistency reliability (0.91 [8]) and a small standard error of measurement (0.21 [13]) The minimal clinically important difference (MCID) was calculated using three different methods and is set at 0.4 points [13].

### Study design

Patients completed the CCQ prior to the routine consultation with their pulmonary clinician. Directly after the consultation, the pulmonary clinician (without knowledge of the patient's scores) completed the CCQ as he thought the patient should have completed the CCQ. After the consultation, patients performed the 6-minute walking distance test.

One of the investigators (SLS or BdV), who did not know the patient, held a semi-structured in-depth individual interview with the patients on the day of the consultation. Patients were asked to comment on every separate concept of the questionnaire. They were asked what thoughts they had during completion of the individual questions, and were asked to give examples of their symptoms and disabilities in daily life.

### Group of reviewing clinicians

All interviews were recorded and fully transcribed. All references to scores on individual items of the questionnaire (in numbers or words) were covered by black bars to blind these results for the reviewing clinicians.

Twenty sets were created containing: i) patient characteristics: gender, age, marital status, forced expiratory volume in one second (FEV<sub>1</sub>) %predicted, body mass index, 6-minute walking distance, oxygenation at start of the 6-minute walking distance, and the number of pack years; ii) the transcribed and blinded interview; and iii) a blank CCQ.

Each set of interviews contained 11 randomly assigned interviews. The order in which interviews were in the packaged set was randomised to prevent fatigue of the reviewers and learning effects in the interviews performed later in sequence.

These sets were sent to 20 pulmonary physicians and general practitioners who have a special interest in pulmonary diseases. The clinicians were instructed to complete the CCQ of a patient the way they thought the patient should have rated the CCQ, based on the patient characteristics and interview.

This method resulted in each patient/interview being reviewed and scored by five separate clinicians.

### Data processing

The agreement between patient CCQ scores and the treating physician and reviewing clinicians scores was presented in Bland and Altman plots. The Shapiro-Wilk normality test was used to assess normality.

The pairwise agreement (concordance) between patient's score, treating clinician's score and the mean of the scores of the five reviewing clinicians, was studied by two coefficients: the intraclass correlation coefficient (ICC) and Lin's concordance correlation coefficient (CCC). Both range from 0 = no agreement, to +1 = perfect agreement.

Lin *et al.* have proposed a unified approach for assessing agreement for continuous and categorical data [14]. For the pairwise agreement used in our study, the unified estimate reduces to the original CCC proposed by Lin [15]. The CCC contains a measurement of precision and of accuracy for a better understanding of the sources of disagreement.

The equation from Lin (1989) is

$$\rho_c = \frac{2s_{xy}}{s_x^2 + s_y^2 + (\bar{x} - \bar{y})^2}$$

where  $\bar{x}$  and  $\bar{y}$  are the mean values of the measures at 2 times, by 2 raters, or by 2 methods. Lin further proposes two absolute indices, the Total Deviation Index (TDI) and the Coverage Probability (CP), which are independent of the total data range. The MCID is used for the Coverage Probability.

The cut-off points described for rating agreement based on the ICC are  $\leq 0.4$  as poor to fair, 0.41-0.6 as moderate, 0.61-0.8 as good, and 0.81-1.0 as excellent. Because the CCC and ICC measure the same construct, the cut-off points can be assumed to be similar.

A significance level of 0.05 was considered statistically significant.

All analyses (excluding the CCC) were performed using SPSS for Windows version 14. The CCC was calculated using SAS version 9.1 for Windows and the macro available at (<http://tigger.uic.edu/~hedayat/>)

## Results

A total of 44 patients participated in the study, in equal numbers at the two locations. Most patients had severe COPD. Table 1 presents the characteristics of the study participants.

The relation between the patient's scores and the reviewer's scores is shown in the Bland and Altman plots (Figure 1). No systematic errors can be seen as there is no trend visible. The Bland and Altman plots of the separate domains show more deviation from the origin than the total score, where the functional status and mental status have the largest deviation.

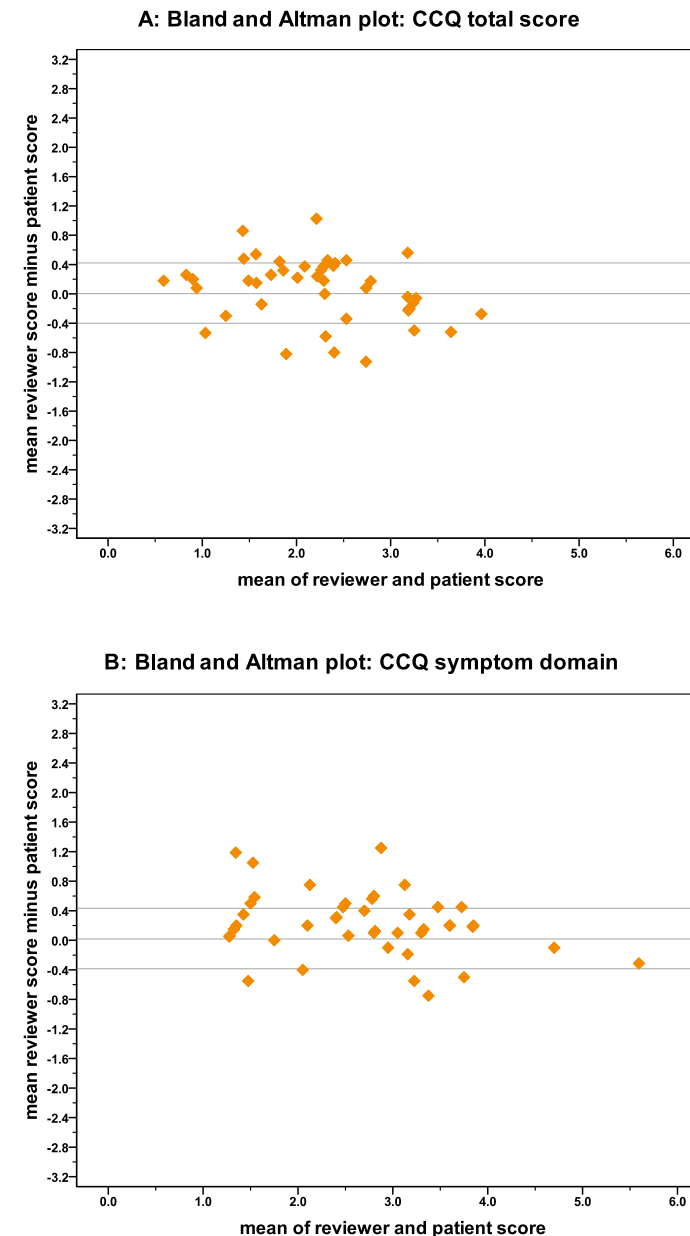
**Table 1.** Characteristics of the study population.

|                                    |                    | Number | (%)    | Mean | (±SD)  | IQR<br>(25th-75th) |
|------------------------------------|--------------------|--------|--------|------|--------|--------------------|
| <b>Gender</b>                      | Male               | 32     | (72.7) |      |        |                    |
|                                    | Female             | 12     | (27.3) |      |        |                    |
| <b>Age (years)</b>                 |                    |        |        | 66.1 | (7.4)  |                    |
| <b>Marital status</b>              | Married            | 33     | (75.0) |      |        |                    |
|                                    | Not Married        | 7      | (15.9) |      |        |                    |
|                                    | Divorced           | 1      | (2.4)  |      |        |                    |
|                                    | Widow              | 3      | (6.8)  |      |        |                    |
| <b>Educational level</b>           | No primary school  | 3      | (6.8)  |      |        |                    |
|                                    | Primary school     | 10     | (22.7) |      |        |                    |
|                                    | High school        | 24     | (54.5) |      |        |                    |
|                                    | College/University | 5      | (11.4) |      |        |                    |
|                                    | Missing            | 2      | (4.5)  |      |        |                    |
| <b>Pack years</b>                  |                    |        |        | 29.3 | *      | (15.7-46.8)        |
| <b>FEV<sub>1</sub> % predicted</b> |                    |        |        | 44.8 | (13.8) |                    |
| <b>Tiffenau</b>                    |                    |        |        | 41.2 | 11.1   |                    |
| <b>GOLD stage</b>                  | I                  | 0      | (0.0)  |      |        |                    |
|                                    | II                 | 13     | (29.5) |      |        |                    |
|                                    | III                | 26     | (59.1) |      |        |                    |
|                                    | IV                 | 5      | (11.4) |      |        |                    |
| <b>BODE score</b>                  |                    |        |        | 2.9  | (1.8)  |                    |
| <b>CCQ Total score</b>             |                    |        |        | 2.2  | (0.9)  |                    |
| <b>Current exacerbation</b>        |                    | 5      | (11.4) |      |        |                    |

IQR: Inter Quartile Range, FEV<sub>1</sub>: Forced Expiratory Flow in one second

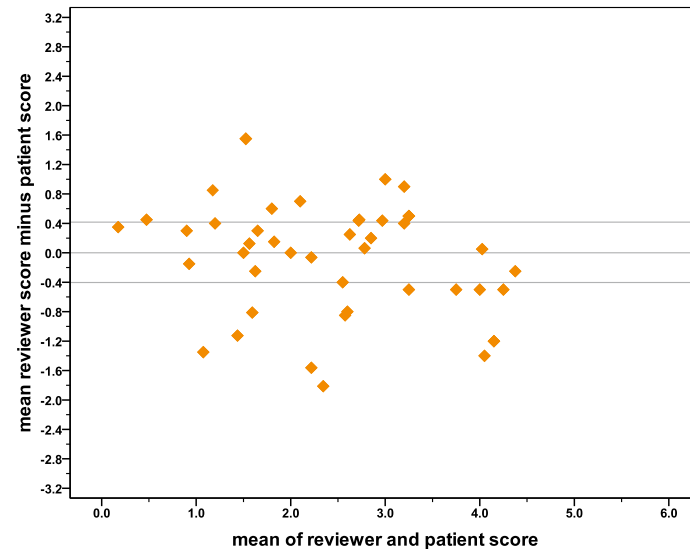
The Shapiro-Wilk normality test revealed that the total scores of the patients, the treating clinicians and the reviewing clinicians are normally distributed, guaranteeing correct confidence intervals. Table 2 shows that the agreement between patients' CCQ score and the scores of the treating clinicians (CCC=0.87) and the mean score of five reviewing clinicians (CCC=0.86) was excellent. The agreement between the treating clinicians and reviewing clinicians was good (CCC=0.74). In all three cases the accuracy was considerably higher than the precision. The CCQ scores of the patients were within the limits of the MCID of the scores of the treating clinician in 62% and the mean score of the reviewing clinicians in 63%. The proportion of cases within the MCID of 0.4 (CP<sub>0.4</sub>) between treating clinician and reviewing clinicians was lower (0.50).

There were no differences in patient characteristics between patients with a score difference smaller than the MCID, and those larger than the MCID between patient and reviewing clinicians. No recurrent themes emerged from the interviews to explain low agreement.

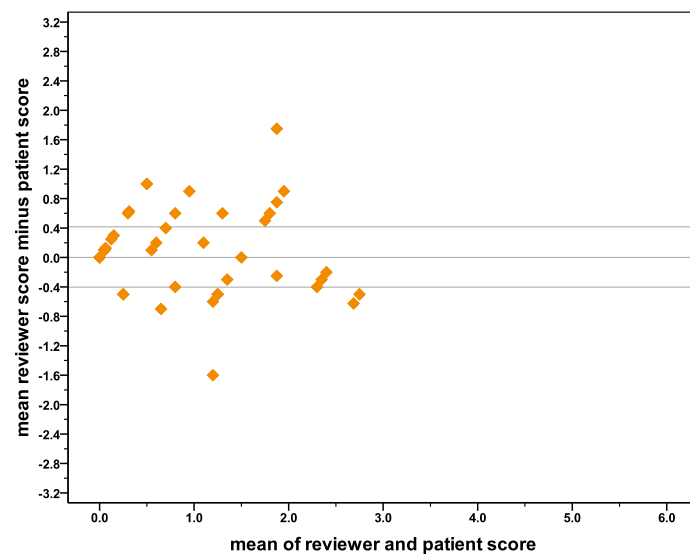
**Figure 1.** Bland and Altman plots showing the relationship between the scores of the patients and the reviewers.

A: Clinical COPD Questionnaire (CCQ) total score; B: CCQ symptoms domain score; C: CCQ functional status domain score; D: CCQ mental status domain score.

C: Bland and Altman plot: CCQ functional status domain



D: Bland and Altman plot: CCQ mental status score



C: CCQ functional status domain score; D: CCQ mental status domain score.

Table 2. Agreement between patient, treating clinician and reviewing clinicians.

| Agreement between:  | Statistics      | CCC  | Precision | Accuracy | TDI <sub>0.9</sub> | CP <sub>0.4</sub> |
|---|-----------------|------|-----------|----------|--------------------|-------------------|
| <b>Patient &amp; Treating clinician</b>                   | Estimate        | 0.87 | 0.88      | 0.98     | 0.7                | 0.62              |
|   | 95% Conf. Limit | 0.79 | 0.81      | 0.94     | 0.9                | 0.53              |
| <b>Patient &amp; Mean reviewing clinicians</b>            | Estimate        | 0.86 | 0.87      | 0.99     | 0.7                | 0.63              |
|   | 95% Conf. Limit | 0.79 | 0.80      | 0.94     | 0.9                | 0.54              |
| <b>Treating clinician &amp; Mean reviewing clinicians</b> | Estimate        | 0.74 | 0.76      | 0.97     | 1.0                | 0.50              |
|   | 95% Conf. Limit | 0.61 | 0.63      | 0.89     | 1.1                | 0.42              |

95% Conf. Limit: 95% confidence limit. CCC: Concordance Correlation Coefficient, TDI<sub>0.9</sub>: A total deviation index of 0.9 (TDI 0.9) represents the distance (percentile) that captures 90% of the differences in scores between the treating clinician and the patient. A TDI 0.9 of 0.7 means that in 90% of the cases the patient and treating clinician score the patient status within 0.7 distance. CP<sub>0.4</sub>: Coverage Probability, proportion of cases within the Minimal Clinically Important Difference of 0.4.

## Discussion

This study uses a new method to assess the individual validity of a health status questionnaire. The method was applied in the management of COPD, with the Clinical COPD Questionnaire (CCQ) health status questionnaire. This study shows that there is a very good agreement in CCQ outcomes between the individual patient score and 20 reviewing clinicians who did not know the patient but scored the CCQ based on an in-depth interview. In combination with the previously known high reliability and stability, this confirms the validity of the CCQ at the individual patient level.

This new method to assess the validity of health status questionnaires in clinical practice is feasible for a short questionnaire, but requires much effort due to the patient interviews and the subsequent review by clinicians. However, by using transcripts of interviews with each individual patient, this method provides accurate and transparent information about the actual performance of a patient who is asked to complete a questionnaire in daily clinical practice. The use of qualitative methods to assess the individual accuracy of a questionnaire in routine practice provides more insight into individual validity than pure statistical methods assessing the internal consistency and stability of a questionnaire.

The validity of the CCQ at the group level has already been assessed [8,9,16,17]. In two of these studies internal stability and consistency was very high, thus meeting the requirements for individual use of the questionnaire [8,9]. However, in a recent study this high level was not met [16], possibly due to the different study population and methods used in that study. Nevertheless the high concordance between the results of the approach according to the standards as proposed by McHorney and Tarlov [3] and our new method using patient interviews, confirms the acceptability of this new method.

The high CCC indicates that there was no systematic error in measuring. The Bland and Altman plots also confirm this finding. The absence of a systematic error is in contrast to previous findings of a difference in patient-proxy ratings of quality of life [18] and differences in patient-clinician ratings [19]. Proxies and clinicians tend to rate the quality of life worse than the patients [18,20]. The domains of the questionnaires that cover emotions tend to differ more between proxies and patients than the domains measuring symptoms [18]. In the current studies we also see that the mental status domain shows the least concordance; however, there is no systematic under- or over-estimation compared to the patient's score.

For the Bland and Altman plots we chose a difference in scores of 0.4 (the MCID), as cut-off point for agreement. Over 60% of the 44 patient-reviewer scores differed less than the MCID. Of the patients-reviewer scores, 90% (the TDI0.9) were within 0.7 points. We chose the MCID because this difference in score would (according to the definition) potentially cause a clinician to change the management: *“the smallest difference in a score in the domain of interest which patients perceive as beneficial and which would mandate in the absence of troublesome side-effects and excessive costs a change in the patient's management”* [21]. Compared to others, we chose a very strict cut-off point. In Wilson's method for proxy ratings, a moderate difference is used [18]. For the CCQ, this moderate difference would be around 1.3 [13], which is far more than the 0.7 points in which 90% of scores were in the current study.

A limitation of this study is that this new method of assessing the validity of a health status questionnaire on the individual patient level could be improved by additional information about the individual patient's scoring stability and responsiveness to changes. The stability of scoring of the studied population could be assessed using the test-retest method. Although the test-retest reliability of the CCQ was very high in two studies [8,9], and so was the ability to measure treatment effects [17,22] we did not confirm this in the present group of patients.

The current study could not identify patient factors that were associated with low agreement between patient and reviewers. A possible explanation for low agreement in some individuals might be that most patients completed the questionnaire for the first time. During the interview, patients sometimes answered *“now I'm re-thinking about this, my score would have been...”*. Although some patients with a low agreement gave the impression of lower intelligence, this could not be substantiated by a lower educational level.

In the present study we found a better agreement in scores between patients and the treating clinicians than others [19]. In contrast to other patient-proxy agreement studies, only two clinicians participated in the recruitment of the patients and the scoring of the CCQ, as the main research question was the patient-reviewer agreement. These two clinicians previously used the CCQ in their practice or in pulmonary rehabilitation programs. One clinician stated that he changed his history taking during the study, because he was unable to answer specific questions on multiple occasions, especially about the mental state domain. The experience in measuring health status and the change in history taking might contribute to the high agreement between the scores of the patient and treating clinician.

## Conclusion

In conclusion, this study shows that this new method to assess the individual validity of a questionnaire by using patient interviews is feasible, and confirms results from previous studies using statistical methods. Secondly, there seems to be a good validity of the CCQ on the individual patient level as established with this new methods. The CCQ can therefore be used in routine clinical practice to assess the health status of patients with COPD.

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## Chapter 7

# Day to day measurement of patient reported outcomes (PROs) in exacerbations of COPD

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## Abstract

**Background:** Exacerbations of Chronic Obstructive Pulmonary Disease (COPD) are a major burden to patients and to society. Although improving management of exacerbations is important, guidance on optimal treatment is still scarce. To facilitate decision-making, several models have assessed predictive properties of clinical measurements, but daily measurement of health status has not yet been tested in these decision models.

**Methods:** Data from two randomised control trials (n=210, n=45 patients) were used to describe the feasibility of daily collecting of, and the day-to-day course of patient-reported outcomes during admission to the hospital or out-patient treatment. Besides clinical parameters, the BORG dyspnoea score, the Clinical COPD Questionnaire (CCQ), and the St. George's Respiratory Questionnaire were used in Cox regression models to predict treatment failure, defined by death and/or intensive care unit admissions and/or the necessity to intensify pharmacologic treatment in the hospital study.

**Results:** All patient-reported outcomes show a distinct pattern of improvement. In the multivariate models, absence of improvement of CCQ symptom score and impaired lung function were independent predictors of treatment failure. Long term mortality was predicted by age, FEV<sub>1</sub> predicted, smoking status and CCQ score. Health status and gender predicted time to next exacerbation. In out-patient exacerbations, health status was less impaired than in hospitalized patients, while the rate and pattern of recovery was remarkably similar.

**Conclusion:** It is possible and feasible to perform daily measurement of patient-reported outcomes. Since the results of patient-reported outcomes predict treatment failure, daily measurement could help decision-making for patients hospitalised due to an exacerbation of COPD.

## Introduction

Exacerbations are major events for Chronic Obstructive Pulmonary Disease (COPD) patients, are associated with high in-hospital mortality ranging from 10-60% [1], cause sustained reduction in quality of life [2,3], and repeated exacerbations cause increased decline in lung function [4].

When a COPD patient is hospitalised due to an exacerbation, the clinician evaluates the severity and starts appropriate treatment. To assess the severity of an exacerbation, treatment guidelines suggest checking medical history, clues in the physical examination (e.g. use of accessory respiratory muscles), and measurement of arterial blood gas and blood tests [5]. However, because the way clinicians interpret this information varies [6,7], the clinical decisions may also vary. To facilitate decision-making, models have been developed that predict outcome in COPD exacerbations at the emergency department [8] and the intensive care unit (ICU) [9]. Some of these models also use patient-reported outcomes, e.g. the modified Medical Research Council scale for the 'usual' severity of dyspnoea [10]. Health status/health-related quality of life (HRQoL), an important patient-reported outcome, has not been included in current models even though HRQoL measurements at first consultation for an exacerbation may yield important information for stratification of patients [3]. Health status questionnaires are not used in the current models, probably because of their length and the perceived complexity of their use when a patient is admitted because of an exacerbation.

The present study assesses the feasibility of daily patient reported outcome measurements during exacerbations, describes the course of patient reported outcomes during the exacerbation, and assesses whether patient reported-outcomes can help decision-making in exacerbation of COPD.

## Methods

The present study uses data from a prospective, randomised, double-blind, double-dummy, placebo-controlled, parallel-group clinical study assessing the non-inferiority of oral to intravenous corticosteroids during a hospitalisation because of an exacerbation of COPD [11] and a second study [12] evaluating the effect of 14 days of combined high dose budesonide/formoterol, prednisolone, or placebo during an out-patient treated COPD exacerbation [13].

The methods are described elsewhere [11,13] but, in brief, are as follows. The primary outcome was treatment failure, defined as death from any cause, admission to the ICU, readmission to the hospital because of COPD, or the necessity to intensify pharmacologic treatment. The intensification of pharmacologic treatment was defined as the prescription of open-label corticosteroids, theophylline, or antibiotics. Treatment failure was subdivided into early failure (the first 2 weeks after randomisation), and late failure (from 2 weeks to 3 months). Patients referred to the hospital for an exacerbation of COPD were enrolled in the study. Inclusion criteria were age >40 years, a history of at least 10 pack years of cigarette smoking and evidence of airflow limitation. Airflow limitation was defined as a ratio of FEV<sub>1</sub> to forced vital capacity of less than 70% and an FEV<sub>1</sub> of <80% predicted (at least GOLD severity stage II). An exacerbation of COPD was defined as a history of increased

breathlessness and at least two of the following symptoms for at least 24 h: increased cough frequency or severity, increased sputum volume or purulence, and increased wheeze. Excluded were patients who had signs of a very severe exacerbation upon admission (arterial pH < 7.26 or PaCO<sub>2</sub> > 9.3 kPa), with significant or instable co-morbidity, who had a history of asthma, had participated in another study within the 4 weeks before admission, were previously randomised in this study, had clinically significant findings on chest radiography other than fitting with signs of COPD, a known hypersensitivity to prednisolone, or who were known to be totally non-compliant. Patients received either a 5-day course of 60 mg intravenous, or oral prednisolone together with placebo medication. Active and placebo medication had a similar appearance. After 5 days all patients received oral prednisolone in a dosage of 30 mg once daily which subsequently was tapered with 5 mg daily until 0 mg or prior maintenance dosage. All patients received nebulised ipratropium bromide and salbutamol (albuterol) 4 times daily together with oral amoxicilline/clavulanate.

The studies were approved by the hospital medical ethics committees and all patients gave written informed consent.

#### Measurements

Lung function was measured according to ATS/ERS guidelines at admission, and on day 3, 5 and 7. An absolute difference of 100 ml has been suggested to be clinically relevant [14]. Arterial blood gases were obtained on the day of admission, and on days 2, 3, 5 and 7.

C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were measured at admission.

Lung function was assessed twice during the run in period in the out-patient treated at home and at day 1,7 and 14 of the exacerbation.

#### Patient reported outcomes

The BORG dyspnoea score measures dyspnoea on a scale from 0 (“nothing at all”) to 10 (“maximal”) [15,16]. The minimal clinically important difference (MCID) of the BORG score is 1 point [17]. The BORG score was measured on days 1-5 and day 7.

The Clinical COPD Questionnaire (CCQ) is a 10-item health status scale measuring symptoms, functional status and mental state of COPD patients. Scores range from 0 (best) to 6 (worst) [18]. The MCID is 0.4 [19]. The CCQ was administered on days 1-5 and 7 using the diary version. In the out-patient exacerbation study the CCQ was administered at baseline, two months after stopping inhaled corticosteroids, on the first exacerbation day, and on days 3,7 and 14.

The St. George’s Respiratory Questionnaire (SGRQ) is a 50-question, 76-item health status scale for both asthma and COPD patients. The SGRQ has 3 subscales: symptoms, activities and impact. The score ranges from 0 (best) to 100 (worst) [20]. The MCID is 4 points [21]. The standard SGRQ (3-month recall period) was administered on days 1 and 7.

#### Statistical analysis

Differences in patient characteristics between the two studies were tested by chi<sup>2</sup> or independent t-tests.

To compare the course of the patient-reported outcomes and the FEV<sub>1</sub>, all scores were transformed to the number of times the mean score changed the MCID. For example, a mean change of e.g. SGRQ score of 3 points resulted in a ‘number of MCID change’ of (3 units /4 units=MCID) 0.75. We computed this number of MCID changes in all patient-

**Table 1:** Patient characteristics at start of the exacerbation.

|                              | Hospital    | Out-patient  |
|------------------------------|-------------|--------------|
| Number of patients           | 210         | 45           |
| Age, yr                      | 70.6 (8.4)  | 64.1 (8.1)   |
| Male gender                  | 158 (75.2)  | 37 (82.2)    |
| FEV <sub>1</sub> % predicted | 36.9 (14.7) | 52.1 (12.9)  |
| GOLD stage                   |             |              |
| I                            | 4 (2)       |              |
| II                           | 33 (16.1)   | 26 (57.8)    |
| III                          | 99 (48.3)   | 17 (37.8)    |
| IV                           | 69 (33.7)   | 2 (4.4)      |
| Packyears                    | 35 (24-50)  | 38 (26-48.5) |
| Current smokers              | 49 (23.7)   | 21 (46.7)    |
| BORG score                   | 4.6 (2.0)   | N/A          |
| CCQ total score              | 3.3 (0.93)  | 2.6 (0.79)   |
| SGRQ total score             | 63.1 (13.9) | N/A          |

FEV<sub>1</sub>: Forced expiratory flow in one second, GOLD: The Global Initiative for Chronic Obstructive Lung Disease, CCQ: Clinical COPD Questionnaire, SGRQ: St. George’s Respiratory Questionnaire, IQR: Inter quartile range. Values are given as mean (standard deviation) unless stated otherwise

reported outcomes and FEV<sub>1</sub> for each day during the hospitalisation to represent the change graphically. To evaluate the responsiveness, the number of patients that changed more than the MCID after 7 days of treatment was calculated.

Cox regression models were used to assess predictors for treatment failure. Based on their clinical relevance and on the literature the following variables were included in the univariate Cox models: treatment arm, age, gender, smoking status, pack years, baseline FEV<sub>1</sub>% predicted, number of hospitalisations during the year prior to the exacerbation, long-term oxygen use, BMI, SGRQ and CCQ total and domain scores, and the BORG dyspnoea score. Blood gases, CRP, ESR, and the change between day of admission and the next day for blood gases, BORG dyspnoea score, and CCQ total and domain scores were also tested. Next, multivariate Cox regression models were estimated. In these models treatment arm, FEV<sub>1</sub>% predicted, age, gender, smoking status and all variables with a p-value < 0.1 in the univariate model were entered. Because the CCQ, the SGRQ and the BORG score measure a similar construct, these were not entered in the models simultaneously but their effects were estimated in 3 separate multivariate Cox models. Data were analysed on an intention-to-treat basis.

Statistical analyses were performed using SPSS version 14.

**Table 2.** Responsiveness of patient-reported outcomes and lung function. Change in patient-reported outcomes and lung function between admission and day seven, including the percentage of patients improving more than the minimal clinically important difference ( $\Delta > \text{MCID}$ ).

|                                | n   | MCID | Change<br>Score | Change<br>% from<br>baseline | $\Delta > \text{MCID}$<br>% |
|--------------------------------|-----|------|-----------------|------------------------------|-----------------------------|
| BORG dyspnoea                  | 182 | 1    | -1.76 (2.27)    | -32.2 (52.4)                 | 72.1                        |
| CCQ hospital                   | 181 | 0.4  | -1.03 (1.04)    | -29.7 (31.2)                 | 73.5                        |
| SGRQ                           | 179 | 4    | -3.99 (13.23)   | -5.09 (22.8)                 | 50.3                        |
| FEV <sub>1</sub> (ml) hospital | 179 | 100  | 111 (9.0)       | 13.9 (10.1)                  | 48.6                        |

n: number of patients that completed the measurement on both admission and day 7, MCID: Minimal Clinically Important Difference, CCQ: Clinical COPD Questionnaire, SGRQ: St. George's Respiratory Questionnaire, FEV<sub>1</sub>: forced expiratory volume in one second. Values are presented as mean (standard deviation).

## Results

Patients who were admitted to hospital were generally older, had more airways obstruction, and had higher CCQ scores. The outpatient group contained more current smokers (Table 1). On the first day of admission, 198 patients completed the BORG score, 196 the CCQ, 197 the SGRQ and 193 performed spirometry. Reasons for not completing the patient-reported outcomes were: too dyspnoeic to complete the questionnaires, not in the mood for completing the questionnaires, having no reading glasses, logistical reasons or the reason is unknown.

### Course of patient-reported outcomes

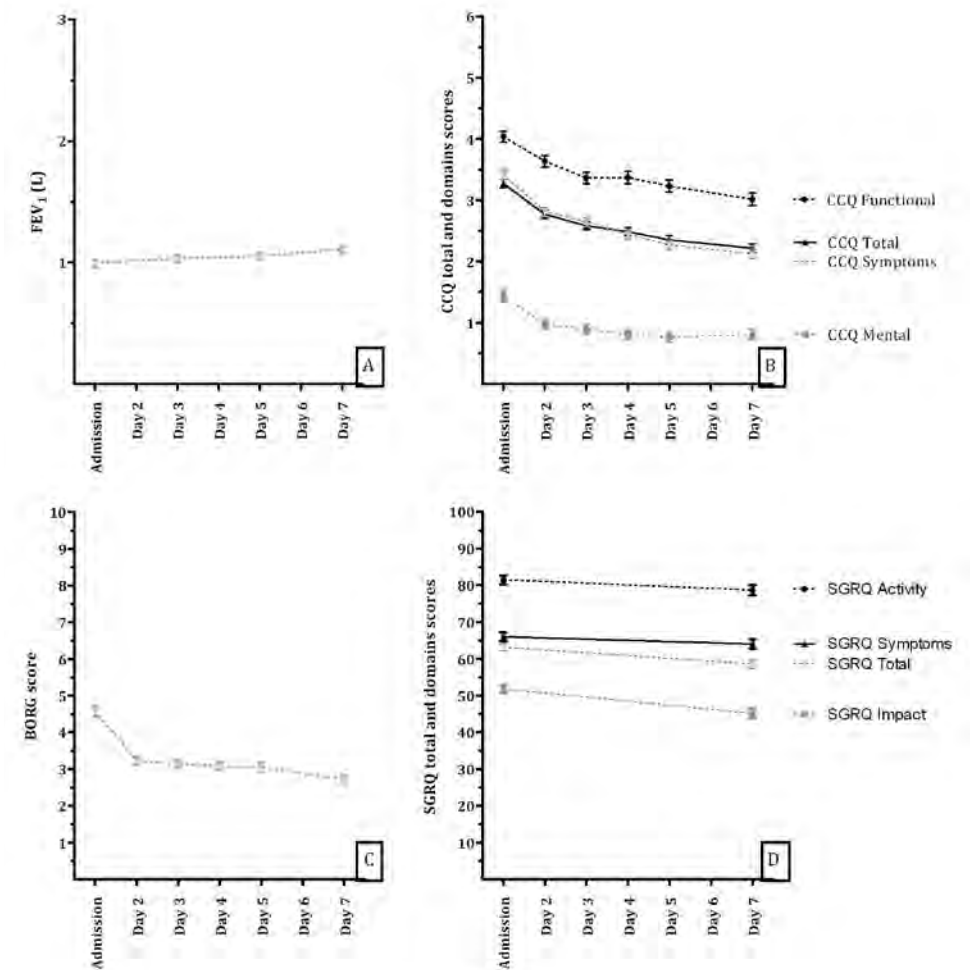
Figure 1 shows the course of the FEV<sub>1</sub>, BORG, CCQ total and domain scores and the SGRQ total and domain scores in their normal values. The FEV<sub>1</sub> improves only slightly (Figure 1A). The BORG score for dyspnoea decreased (i.e. improves) quickly during the first day of treatment in hospital, then stabilises (Figure 1C). The CCQ shows rapid improvement on the first day, and continues to improve on the following days (Figure 1B). Within the SGRQ, the activity and impact scores improve most (Figure 1D). To compare the course and responsiveness of the measurements, the absolute mean scores were changed into the number of MCIDs of the measurements (Figure 2).

The improvement between admission and day 7 represents the responsiveness of the FEV<sub>1</sub> and the patient-reported outcomes and is expressed as: 1) mean change in absolute score, 2) percentage change, and 3) percentage of patients improving more than the MCID of the measurement (Table 2).

### Course of CCQ in in-hospital and out-patient treatment

The mean CCQ scores of the two study populations are shown in Figure 3. CCQ scores increased significant between stable status (before and after the two month run-in period) and exacerbation in the home-treated group. The slope of the patients treated in hospital is

**Figure 1.** Course of the mean FEV<sub>1</sub>, BORG, CCQ total and domain scores and the SGRQ total and domain scores.



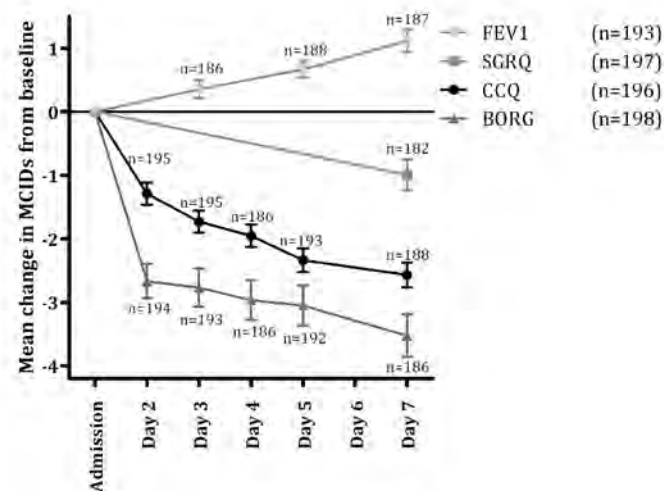
FEV<sub>1</sub>: Forced expiratory flow in one second, CCQ: Clinical COPD Questionnaire, SGRQ: St. George's Respiratory Questionnaire.

-0.16 points/day in the first 7 days, while the mean change (i.e. improvement) for the home treated patients is -0.12 points/day. The rate of improvement does not differ significantly.

### Treatment failure

Of the 210 patients, 38 had early treatment failure, i.e. within the first 14 days after admission. The models including the patient-reported outcomes are shown in Table 3. In the models with the BORG score and with the SGRQ, the patient-reported outcome did not predict treatment failure. However, in the model with the CCQ, treatment failure was predicted by the change in CCQ symptom score on the first day and FEV<sub>1</sub>% predicted on admission.

**Figure 2.** Mean change in minimal clinically important differences of FEV<sub>1</sub>, BORG, CCQ, and SGRQ.



FEV<sub>1</sub>: Forced expiratory flow in one second, CCQ: Clinical COPD Questionnaire, SGRQ: St. George's Respiratory Questionnaire. n: number of patients completed the measurement. Error bars represent the standard error of measurement (SEM).

To facilitate the decision rule for clinicians, we calculated the hazard ratios (HR) for patients that do not improve in their symptoms measured by the CCQ. A lack of improvement in CCQ symptoms score in the first day of hospitalisation had a HR of 2.6 (95% CI 1.2-5.8) and in that model the FEV<sub>1</sub> predicted had a HR of 0.95 (95% CI 0.91-0.99) in predicting time to treatment failure within 14 days after admission.

All other clinical variables tested, including blood gases, were not predictive of time to treatment failure within 14 days, whether tested as continuous variable or dichotomously as normal or abnormal.

#### Time to re-exacerbation

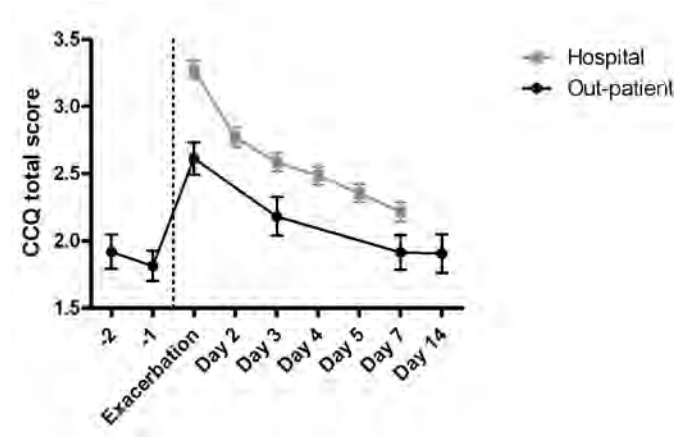
Sixty-six percent of 164 patients with a complete dataset in the hospital admission study had a re-exacerbation within the first year, beginning at 6 weeks after hospitalization. Time to first re-exacerbation was predicted by CCQ total score at six weeks (HR 1.23 [1.03-1.46]) and male gender (HR 1.80 [1.11-2.94]). Patients in the highest tertile of the CCQ score had a hazard ratio of 1.88 (CI 1.18-3.0) compared to the lowest tertile (Figure 4).

Lung function, smoking status, age, GOLD stage and SGRQ score did not predict time to re-exacerbation.

#### Mortality

The 5-year mortality of the hospital based study population was 54.9% with a median follow-up of 4.8 (inter quartile range 4.2-5.2) years after initial admission. At day 42 the factors predicting increased all cause mortality were age (HR 1.07 [1.04-1.11]), FEV<sub>1</sub>% pre-

**Figure 3.** Course of Clinical COPD Questionnaire scores in the hospital and the out-patient population.



dicted (HR 0.98 [0.97-1.00]), current smoking (HR 1.79 [1.05-3.05]) and CCQ score (HR 1.4 [1.11-1.69]). When entering CCQ functional status instead of total CCQ score, FEV<sub>1</sub>% predicted no longer contributed significantly to the model.

The SGRQ at day 42 after admission did not predict mortality (HR 1.01 [0.99-1.02]).

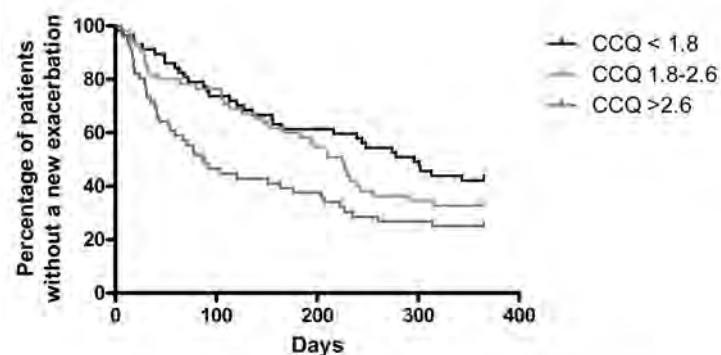
After adjusting for age, smoking status, gender and FEV<sub>1</sub>% predicted, patients in the highest tertile of the CCQ score had a hazard ratio for mortality of 3.10 [1.64-5.87] compared to the lowest CCQ tertile (Figure 5).

#### Discussion

Daily measurement of patient-reported outcomes is feasible in patients hospitalised for an exacerbation of COPD. In this study, health status measured by the Clinical COPD questionnaire predicted treatment failure and may therefore help in decision-making.

Most patients were able to complete the patient-reported outcomes, even at admission when their health was severely impaired (93-94%). Patients completed the questionnaires themselves, assisted by the researchers only when needed; support was strictly limited to reading out the questions. The choice of instruments used in the present study was based on feasibility, known responsiveness to treatment, and usage in previous trials. The SGRQ is the gold standard in health status measurement in clinical trials. However, the SGRQ's length and complex scoring algorithm makes it less feasible in routine practice. In the present study the standard 3-month version was used. During hospitalisation the SGRQ was administered twice within 7 days. Formally, 7 days is too soon when considering the recall period of the SGRQ. Others have resolved this problem by discarding the SGRQ's symptom domain [2]. As a result, a total score should no longer be calculated without this domain and the scores are therefore no longer comparable with other studies. A slightly shorter version of the SGRQ has been developed for COPD, but without a defined recall period

**Figure 4.** Cox survival curve of re-exacerbation within a year beginning at 6 weeks after hospitalization. Groups divided by CCQ score tertiles (CCQ <1.8; 1.8-2.6;>2.6).



[22]. Although this resolves the recall period issue, the shorter questionnaire was not available at the time of the present study.

The 4 measurements (FEV<sub>1</sub>, BORG, CCQ and SGRQ) show a different course of improvement during the first week of recovery. The FEV<sub>1</sub> improves 13% compared with baseline, and almost 50% of all patients improve above the FEV<sub>1</sub>'s MCID. This improvement is more than previously described [23,24], but still not large (111 ml).

The BORG score showed most improvement on the first day and remained stable during the following days. In a similar study, after 3 days Maltais *et al.* found a change in score of 2.6 ( $\pm$  2.3 SD) points after oral treatment with prednisolone [24], compared to 1.4 points within 3 days in our study.

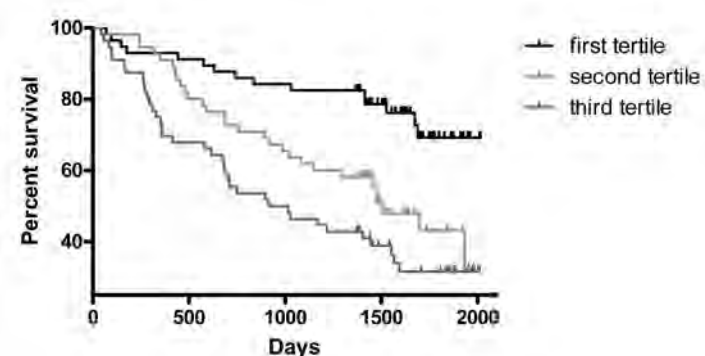
The CCQ total score improved by more than one MCID within the first day and continued to improve up to day 7. The SGRQ was measured only at admission and on day 7 and the mean score almost reached the SGRQ's MCID.

During exacerbations, the health status of patients admitted to hospital is worse than that of those treated at home. The most important difference between the two groups is their health status and lung function on the first treatment day of treatment. However both treatment groups show a remarkably similar pattern in health status improvement.

To our best knowledge, no other studies have shown a detailed course of change in health status during an exacerbation in COPD in both hospital and out-patient settings.

The domains that measure functional status, i.e. the CCQ functional state domain and the SGRQ activity domains, were the most impaired. The scores on the symptom domains of both health status scales were less, but still very high. The least impaired was the mental status domain and the SGRQ impact domain. However, 23 patients still scored above 3 points on the CCQ mental state domain at admission and 9 patients scored above 3 points on day 7. A CCQ score > 3 is a strong predictor (odds ratio 15.17 [3.19 -72.07]) for depressive symptoms assessed with the Hospital Anxiety and Depression Scale (HADS) in primary care patients [25]. This is an important finding because depression is associated with worse outcome in COPD [26]. These patients may need extra attention.

**Figure 5.** Proportion of patients alive after hospitalization for the exacerbation of COPD. (CCQ score <1.8; 1.8-2.7;>2.7).



Selecting patients suitable for early supported discharge schemes could reduce the costs of COPD, because hospital admissions are responsible for more than half of the COPD-related healthcare expenses. In the present study the mean hospital admission was 11.8 days. Early supported discharge schemes are safe and reduce the length of hospital stay [27]. Selecting patients suitable for early discharge schemes might be supported by day-to-day health status measurement. The mean CCQ score of hospitalised patients reached the same level as the CCQ score at the start of the exacerbations in patients treated at home after 3 days (Figure 3). Although many factors (e.g. the situation at home) should be considered when discharging patients [5], the CCQ could help identify patients for early discharge.

This is the first study to measure health status daily during the initial recovery of a COPD exacerbation. Most studies that evaluated health status following or during exacerbations did this at admission and after 2 weeks to 3 months [3]. Health status provides more information than symptoms alone. In our study dyspnoea measured using the BORG score did not predict treatment failure, whereas SGRQ impact scores did in the univariate analysis. Although the dyspnoea improved rapidly after the initiation of treatment, which is accordance with other studies [28,29], improvement in dyspnoea did not predict which patients would suffer treatment failure. Although dyspnoea is one of the key symptoms in an exacerbation and will guide the clinician's opinion on the severity and improvements during an exacerbation, a composite measure reflected in one score might be more reliable in determining the improvements.

Treatment failure in our study was predicted by a range of factors in the univariate analyses: the FEV<sub>1</sub> percentage from predicted, oxygen use at home, pCO<sub>2</sub> and acidosis at admission, SGRQ total and impact score, and CCQ changes within one day. Several of these factors have been reported as predictors for in-hospital mortality or treatment failure [30,31]. Additional factors are gender [9], physical activity, MRC dyspnoea score, O<sub>2</sub> oxygen tension, BMI, neurological impairment and use of inspiratory accessory muscles. Many of the earlier studies report different predictors, probably due to different populations, measurements



**Table 3.** Cox regression models describing the prediction of treatment failure.

| Variabele             | Univariate analysis |                   |       | Multivariate analysis CCQ |                   |       | Multivariate analysis SGRQ |                   |       | Multivariate analysis BORG |                   |       |
|-----------------------|---------------------|-------------------|-------|---------------------------|-------------------|-------|----------------------------|-------------------|-------|----------------------------|-------------------|-------|
|                       | HR                  | 95% CI            | p     | HR                        | 95% CI            | p     | HR                         | 95% CI            | p     | HR                         | 95% CI            | p     |
| treatment arm         | 0.980               | ( 0.519 - 1.851 ) | 0.950 | 1.086                     | ( 0.472 - 2.502 ) | 0.846 | 1.228                      | ( 0.549 - 2.749 ) | 0.616 | 1.159                      | ( 0.690 - 3.666 ) | 0.276 |
| fev pred              | 0.967               | ( 0.939 - 0.996 ) | 0.024 | 0.949                     | ( 0.907 - 0.993 ) | 0.024 | 0.971                      | ( 0.935 - 1.009 ) | 0.129 | 0.636                      | ( 0.927 - 1.001 ) | 0.590 |
| age                   | 1.007               | ( 0.969 - 1.047 ) | 0.720 | 1.003                     | ( 0.952 - 1.056 ) | 0.918 | 1.019                      | ( 0.963 - 1.078 ) | 0.512 | 1.010                      | ( 0.956 - 1.068 ) | 0.715 |
| male gender           | 1.026               | ( 0.486 - 2.169 ) | 0.945 | 1.239                     | ( 0.429 - 3.575 ) | 0.692 | 1.094                      | ( 0.369 - 3.249 ) | 0.871 | 0.763                      | ( 0.264 - 2.209 ) | 0.618 |
| smoking status        | 0.831               | ( 0.381 - 1.812 ) | 0.641 | 0.632                     | ( 0.217 - 1.839 ) | 0.400 | 0.534                      | ( 0.195 - 1.461 ) | 0.222 | 0.513                      | ( 0.183 - 1.435 ) | 0.203 |
| packyears             | 0.990               | ( 0.974 - 1.007 ) | 0.258 |                           |                   |       |                            |                   |       |                            |                   |       |
| previous admission    | 1.328               | ( 0.878 - 2.009 ) | 0.180 |                           |                   |       |                            |                   |       |                            |                   |       |
| previous admission >2 | 2.283               | ( 0.810 - 6.438 ) | 0.119 |                           |                   |       |                            |                   |       |                            |                   |       |
| O2 use at home        | 2.923               | ( 1.449 - 5.897 ) | 0.003 | 0.952                     | ( 0.312 - 2.905 ) | 0.932 | 1.821                      | ( 0.702 - 4.725 ) | 0.218 | 2.430                      | ( 0.923 - 6.398 ) | 0.072 |
| BMI                   | 0.986               | ( 0.925 - 1.052 ) | 0.671 |                           |                   |       |                            |                   |       |                            |                   |       |
| BMI <21               | 0.872               | ( 0.340 - 2.233 ) | 0.775 |                           |                   |       |                            |                   |       |                            |                   |       |
| O2 sat                | 1.000               | ( 0.969 - 1.032 ) | 0.997 |                           |                   |       |                            |                   |       |                            |                   |       |
| O2 sat t1-t2          | 0.957               | ( 0.879 - 1.042 ) | 0.307 |                           |                   |       |                            |                   |       |                            |                   |       |
| pH                    | 0.038               | ( 0.001 - 1.323 ) | 0.071 |                           |                   |       |                            |                   |       |                            |                   |       |
| pH t1-t2              | 0.000               | ( 0.000 - 1.463 ) | 0.059 |                           |                   |       |                            |                   |       |                            |                   |       |
| Pa, O2                | 0.939               | ( 0.804 - 1.097 ) | 0.429 |                           |                   |       |                            |                   |       |                            |                   |       |
| Pa, O2 t1-t2          | 0.837               | ( 0.686 - 1.021 ) | 0.079 |                           |                   |       |                            |                   |       |                            |                   |       |
| Pa, CO2               | 1.451               | ( 1.123 - 1.874 ) | 0.004 | 1.207                     | ( 0.855 - 1.705 ) | 0.286 | 1.396                      | ( 0.998 - 1.953 ) | 0.052 | 1.304                      | ( 0.933 - 1.822 ) | 0.120 |
| Pa, CO2 t1-t2         | 1.003               | ( 0.717 - 1.403 ) | 0.986 |                           |                   |       |                            |                   |       |                            |                   |       |
| HBCO                  | 0.946               | ( 0.711 - 1.260 ) | 0.705 |                           |                   |       |                            |                   |       |                            |                   |       |
| HbCO t1-t2            | 1.153               | ( 0.830 - 1.602 ) | 0.395 |                           |                   |       |                            |                   |       |                            |                   |       |
| Hypoxaemia            | 1.071               | ( 0.477 - 2.405 ) | 0.869 |                           |                   |       |                            |                   |       |                            |                   |       |
| Hypercapnea           | 0.544               | ( 0.165 - 1.793 ) | 0.317 |                           |                   |       |                            |                   |       |                            |                   |       |
| Acidotic              | 0.378               | ( 0.145 - 0.988 ) | 0.047 |                           |                   |       |                            |                   |       |                            |                   |       |
| CRP                   | 1.000               | ( 0.996 - 1.004 ) | 0.921 |                           |                   |       |                            |                   |       |                            |                   |       |
| ESR                   | 1.007               | ( 0.995 - 1.018 ) | 0.255 |                           |                   |       |                            |                   |       |                            |                   |       |
| Glucose               | 0.988               | ( 0.953 - 1.023 ) | 0.493 |                           |                   |       |                            |                   |       |                            |                   |       |
| SGRQ total score      | 0.978               | ( 0.959 - 0.999 ) | 0.037 |                           |                   |       | 0.979                      | ( 0.954 - 1.004 ) | 0.098 |                            |                   |       |
| SGRQ symptoms         | 0.989               | ( 0.972 - 1.008 ) | 0.250 |                           |                   |       |                            |                   |       |                            |                   |       |
| SGRQ impact           | 0.980               | ( 0.961 - 1.000 ) | 0.045 |                           |                   |       |                            |                   |       |                            |                   |       |
| SGRQ activity         | 0.987               | ( 0.972 - 1.003 ) | 0.100 |                           |                   |       |                            |                   |       |                            |                   |       |
| CCQ total             | 0.217               | ( 0.943 - 1.757 ) | 0.294 |                           |                   |       |                            |                   |       |                            |                   |       |
| CCQ symptoms          | 0.927               | ( 0.678 - 1.267 ) | 0.633 |                           |                   |       |                            |                   |       |                            |                   |       |
| CCQ functional status | 1.264               | ( 0.942 - 1.695 ) | 0.119 |                           |                   |       |                            |                   |       |                            |                   |       |
| CCQ mental status     | 1.144               | ( 0.932 - 1.402 ) | 0.198 |                           |                   |       |                            |                   |       |                            |                   |       |
| CCQ t t1-t2           | 0.062               | ( 0.072 - 0.929 ) | 0.017 |                           |                   |       |                            |                   |       |                            |                   |       |
| CCQ s t1-t2           | 0.624               | ( 0.471 - 0.828 ) | 0.001 | 0.636                     | ( 0.427 - 0.947 ) | 0.026 |                            |                   |       |                            |                   |       |
| CCQ f t1-t2           | 0.783               | ( 0.610 - 1.004 ) | 0.054 |                           |                   |       |                            |                   |       |                            |                   |       |
| CCQ m t1-t2           | 1.077               | ( 0.860 - 1.349 ) | 0.518 |                           |                   |       |                            |                   |       |                            |                   |       |
| CCQ s t1-t2 >0        | 0.339               | ( 0.171 - 0.671 ) | 0.002 |                           |                   |       |                            |                   |       |                            |                   |       |
| BORG                  | 1.151               | ( 0.989 - 1.340 ) | 0.070 |                           |                   |       |                            |                   |       |                            |                   |       |
| BORG t1t2             | 1.171               | ( 0.997 - 1.375 ) | 0.055 |                           |                   |       |                            |                   |       |                            |                   |       |
| BORG t1t2>0           | 0.278               | ( 0.038 - 2.029 ) | 0.207 |                           |                   |       |                            |                   |       | 1.143                      | ( 0.924 - 1.415 ) | 0.218 |

**Table 4.** Kocks JWH et al. Health status in exacerbations of COPD - Cox Regression models: Time to exacerbation.

| Variabele             | Univariate analysis |                   |       | Multivariate analysis CCQ |                   |       | Multivariate analysis SGRQ |                   |       | Multivariate analysis BORG |                   |       |
|-----------------------|---------------------|-------------------|-------|---------------------------|-------------------|-------|----------------------------|-------------------|-------|----------------------------|-------------------|-------|
|                       | HR                  | 95% CI            | p     | HR                        | 95% CI            | p     | HR                         | 95% CI            | p     | HR                         | 95% CI            | p     |
| treatment arm         | 1.243               | ( 0.857 - 1.804 ) | 0.252 | 1.170                     | ( 0.793 - 1.727 ) | 0.428 | 1.056                      | ( 0.673 - 1.657 ) | 0.812 | 1.179                      | ( 0.783 - 1.177 ) | 0.431 |
| fev1pred              | 0.992               | ( 0.980 - 1.004 ) | 0.212 | 0.996                     | ( 0.983 - 1.009 ) | 0.561 | 0.994                      | ( 0.979 - 1.008 ) | 0.377 | 0.992                      | ( 0.979 - 1.005 ) | 0.249 |
| age                   | 1.018               | ( 0.996 - 1.042 ) | 0.114 | 1.016                     | ( 0.989 - 1.042 ) | 0.245 | 1.007                      | ( 0.977 - 1.038 ) | 0.646 | 1.015                      | ( 0.988 - 1.044 ) | 0.278 |
| male gender           | 1.624               | ( 1.026 - 2.517 ) | 0.038 | 1.636                     | ( 0.985 - 2.718 ) | 0.057 | 1.766                      | ( 0.968 - 3.221 ) | 0.064 | 1.566                      | ( 0.937 - 2.216 ) | 0.087 |
| smoking status        | 0.769               | ( 0.492 - 1.201 ) | 0.249 | 0.888                     | ( 0.557 - 1.418 ) | 0.620 | 0.698                      | ( 0.400 - 1.221 ) | 0.208 | 0.892                      | ( 0.553 - 1.439 ) | 0.640 |
| packyears             | 1.004               | ( 0.995 - 1.013 ) | 0.384 |                           |                   |       |                            |                   |       |                            |                   |       |
| previous admission    | 1.295               | ( 0.910 - 1.765 ) | 0.101 |                           |                   |       |                            |                   |       |                            |                   |       |
| previous admission >2 | 1.305               | ( 0.573 - 2.972 ) | 0.527 |                           |                   |       |                            |                   |       |                            |                   |       |
| o2 use at home        | 1.373               | ( 0.753 - 2.503 ) | 0.301 |                           |                   |       |                            |                   |       |                            |                   |       |
| BMI                   | 0.975               | ( 0.936 - 1.016 ) | 0.226 |                           |                   |       |                            |                   |       |                            |                   |       |
| BMI <21               | 1.137               | ( 0.649 - 1.199 ) | 0.654 |                           |                   |       |                            |                   |       |                            |                   |       |
| SGRQ total score      | 0.995               | ( 0.984 - 1.007 ) | 0.440 |                           |                   |       | 0.995                      | ( 0.983 - 1.007 ) | 0.423 |                            |                   |       |
| SGRQ symptoms         | 1.000               | ( 0.988 - 1.013 ) | 0.938 |                           |                   |       |                            |                   |       |                            |                   |       |
| SGRQ impact           | 0.995               | ( 0.985 - 1.006 ) | 0.358 |                           |                   |       |                            |                   |       |                            |                   |       |
| SGRQ activity         | 0.997               | ( 0.989 - 1.006 ) | 0.558 |                           |                   |       |                            |                   |       |                            |                   |       |
| CCQ total             | 1.233               | ( 1.047 - 1.452 ) | 0.012 | 1.213                     | ( 1.007 - 1.462 ) | 0.042 |                            |                   |       |                            |                   |       |
| CCQ symptoms          | 1.215               | ( 1.049 - 1.407 ) | 0.009 | 1.178**                   | ( 1.008 - 1.376 ) | 0.040 |                            |                   |       |                            |                   |       |
| CCQ functional status | 1.158               | ( 1.017 - 1.319 ) | 0.027 |                           |                   |       |                            |                   |       |                            |                   |       |
| CCQ mental status     | 1.041               | ( 0.907 - 1.194 ) | 0.570 |                           |                   |       |                            |                   |       |                            |                   |       |
| BORG                  | 0.981               | ( 0.912 - 1.054 ) | 0.595 |                           |                   |       |                            |                   |       | 0.996                      | ( 0.924 - 1.074 ) | 0.912 |

\*\* using CCQ symptoms instead of total score

**Table 5.** Kocks JWH et al. Health status in exacerbations of COPD - Cox Regression models: Mortality .

| Variabele             | Univariate analysis |                   |       | Multivariate analysis CCQ |                   |       | Multivariate analysis SGRQ |                   |       | Multivariate analysis BORG |                   |       |
|-----------------------|---------------------|-------------------|-------|---------------------------|-------------------|-------|----------------------------|-------------------|-------|----------------------------|-------------------|-------|
|                       | HR                  | 95% CI            | p     | HR                        | 95% CI            | p     | HR                         | 95% CI            | p     | HR                         | 95% CI            | p     |
| treatment arm         | 1.042               | ( 0.673 - 1.612 ) | 0.855 | 1.079                     | ( 0.689 - 1.691 ) | 0.740 | 0.987                      | ( 0.597 - 1.632 ) | 0.959 | 1.015                      | ( 0.642 - 1.606 ) | 0.949 |
| fev1pred              | 0.986               | ( 0.972 - 1.001 ) | 0.062 | 0.989                     | ( 0.971 - 1.006 ) | 0.199 | 0.976                      | ( 0.958 - 0.995 ) | 0.012 | 0.980                      | ( 0.964 - 0.996 ) | 0.015 |
| age                   | 1.046               | ( 1.016 - 1.076 ) | 0.002 | 1.083                     | ( 1.046 - 1.121 ) | 0.000 | 1.080                      | ( 1.037 - 1.125 ) | 0.000 | 1.088                      | ( 1.048 - 1.130 ) | 0.000 |
| male gender           | 1.199               | ( 0.710 - 2.025 ) | 0.498 | 0.888                     | ( 0.498 - 1.582 ) | 0.686 | 1.156                      | ( 0.595 - 2.248 ) | 0.668 | 0.940                      | ( 0.529 - 1.672 ) | 0.833 |
| smoking status        | 1.166               | ( 0.709 - 1.919 ) | 0.545 | 1.922                     | ( 1.113 - 3.316 ) | 0.019 | 2.186                      | ( 1.155 - 4.136 ) | 0.016 | 1.797                      | ( 1.042 - 3.100 ) | 0.035 |
| packyears             | 1.001               | ( 0.991 - 1.011 ) | 0.870 |                           |                   |       |                            |                   |       |                            |                   |       |
| previous admission    | 1.330               | ( 0.935 - 1.892 ) | 0.112 |                           |                   |       |                            |                   |       |                            |                   |       |
| previous admission >2 | 1.755               | ( 0.763 - 4.036 ) | 0.186 |                           |                   |       |                            |                   |       |                            |                   |       |
| o2 use at home        | 1.787               | ( 0.945 - 3.382 ) | 0.074 | 1.537                     | ( 0.702 - 3.361 ) | 0.282 | 1.798                      | ( 0.431 - 4.422 ) | 0.201 | 1.976                      | ( 0.881 - 4.436 ) | 0.099 |
| BMI                   | 0.965               | ( 0.918 - 1.015 ) | 0.168 |                           |                   |       |                            |                   |       |                            |                   |       |
| BMI <21               | 1.852               | ( 1.022 - 3.357 ) | 0.042 | 1.896                     | ( 0.958 - 3.752 ) | 0.066 | 1.359                      | ( 0.602 - 3.066 ) | 0.460 | 1.561                      | ( 0.793 - 3.069 ) | 0.197 |
| SGRQ total score      | 1.001               | ( 0.987 - 1.015 ) | 0.905 |                           |                   |       | 1.005                      | ( 0.989 - 1.021 ) | 0.530 |                            |                   |       |
| SGRQ symptoms         | 0.999               | ( 0.986 - 1.011 ) | 0.821 |                           |                   |       |                            |                   |       |                            |                   |       |
| SGRQ impact           | 1.003               | ( 0.991 - 1.015 ) | 0.586 |                           |                   |       |                            |                   |       |                            |                   |       |
| SGRQ activity         | 0.998               | ( 0.988 - 1.008 ) | 0.688 |                           |                   |       |                            |                   |       |                            |                   |       |
| CCQ total             | 1.410               | ( 1.176 - 1.691 ) | 0.000 | 1.383                     | ( 1.103 - 1.733 ) | 0.005 |                            |                   |       |                            |                   |       |
| CCQ symptoms          | 1.242               | ( 1.048 - 1.472 ) | 0.012 |                           |                   |       |                            |                   |       |                            |                   |       |
| CCQ functional status | 1.443               | ( 1.236 - 1.685 ) | 0.000 | 1.402**                   | ( 1.169 - 1.681 ) | 0.000 |                            |                   |       |                            |                   |       |
| CCQ mental status     | 1.027               | ( 0.874 - 1.207 ) | 0.746 |                           |                   |       |                            |                   |       |                            |                   |       |
| BORG                  | 0.982               | ( 0.900 - 1.071 ) | 0.677 |                           |                   |       |                            |                   |       | 1.017                      | ( 0.927 - 1.115 ) | 0.723 |

\*\* using CCQ functional status instead of total score

and analyses. None of the studies have reported the use of daily measurement of health status. In our multivariate models, only the FEV<sub>1</sub> percentage from predicted and the change in CCQ symptom score were significant independent predictors. The number of known potential predictors is large and (with the addition of health status) more specific, the CCQ even larger. Additional studies using a broad range of measurements, and probably additional variables, are needed to create a decision aid for clinicians that is useful and predictive for outcomes. The factors should be easy to assess and be available in most hospitals. Health status measurement is a good candidate because it is both feasible and inexpensive.

The 5-year mortality rate of 55% is high compared to two recent long-term studies. Mortality rate in the study by Soler *et al.* [32] was 38.2% after hospital admission for a COPD exacerbation and 27% in Nishimura's [33] study. Patients in those studies were around similar age, had a higher FEV<sub>1</sub>% (46.4 and 41.1 respectively) compared to 36.9% in our study. In Nishimura's study 33% were current smokers versus 49% in the current study. Smoking status and more severe obstruction might explain the high mortality rate in the current study. Unfortunately, the patient reported outcomes measures were different in the described studies, therefore the health status level can not be compared.

The strength of this study is that we could collect daily patient-reported outcomes in a well-controlled environment. However, this study uses data from a single-centre study and patients with respiratory failure were not included. This limits the generalisability for patients with more severe exacerbations. Future studies should confirm our findings and assess the predictive value of daily health status measurement in a prospective algorithm in a broader group of patients. Secondly, because it was not possible to calculate the Charlston's comorbidity index we could not include this index of co-morbid diseases in our models, although co-morbid diseases are predictors of worse outcome in exacerbations. The SGRQ is not intended for use in COPD exacerbations, although it has been used in other types of exacerbations [3].

In conclusion, it is possible and feasible to perform daily measurement of patient-reported outcomes. The absence of improvement on the first day in the CCQ symptoms score (an easy to measure variable even during an exacerbation) predicts treatment failure. There is a marked difference in health status between patients treated at home or in the hospital for an exacerbation of COPD, while the rate of health status recovery is similar. Health status as measured by the CCQ after a COPD exacerbation predicts mortality and time to next exacerbation. Patient-reported outcomes could therefore help decision-making in patients with an exacerbation of COPD.

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## Chapter 8

# Putting health status guided COPD management to the test: protocol of the MARCH study – using the CCQ in a prospective RCT

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## Abstract

**Background:** Chronic Obstructive Pulmonary Disease (COPD) is a disease state characterized by airflow limitation that is not fully reversible and usually progressive. Current guidelines base their management strategy mainly on lung function impairment, measured by the FEV<sub>1</sub>, while it is well known that the FEV<sub>1</sub> has a poor correlation with almost all features of COPD that matter to patients. Symptoms nor impact have been incorporated in treatment algorithms so far. Health status measures capture both symptoms and impact and could therefore be used as a standardized way to capture the information a doctor could otherwise only collect by careful history taking and recording, or might not collect at all. We hypothesize that a treatment algorithm that is based on a simple validated 10 item health status questionnaire, the Clinical COPD Questionnaire (CCQ), improves health status (as measured by the SGRQ), classical COPD outcomes like exacerbation frequency, patient satisfaction and health care utilization compared to usual care based on guidelines.

**Methods/Design:** This hypothesis will be prospectively tested in a randomized controlled trial (RCT) following 330 patients for two years. During this period general practitioners will receive treatment advices every four months that are based on the patient's health status in half of the patients (intervention group) or based on lung function alone, as advised by GOLD guidelines (usual care group), in the other half.

**Discussion:** While designing this study, especially the selection of outcomes and the development of the treatment algorithm were challenging and these are discussed in greater detail.

## Background

Chronic Obstructive Pulmonary Disease (COPD) is a disease state characterized by chronic airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases [1]. COPD has a considerable impact on health status [2]. Most guidelines, amongst which the Global initiative for Chronic Obstructive lung Diseases (GOLD) guidelines[3], and the Dutch GP guideline [3] have based severity categorization on lung function impairment, more specifically the FEV<sub>1</sub>. It is, however, well known that the FEV<sub>1</sub> has a poor correlation with almost all patient reported outcomes in COPD and therefore the impact the disease has on the patient [4]. This is in contrast to health status instruments, that have been developed specifically to assess severity and measure the impact of disease and to evaluate treatment. Potentially, the usage of validated health status instruments offers a wide range of advantages.

Information can be collected in a standardized manner prior to consultation. This may help decrease the known underestimation by clinicians of the impact of the disease and its treatment on the patients quality of life [5,6] and make it easier to review the patients condition over longer periods of time [7]. Studies have also shown that patient satisfaction is improved and patient opinions are more positive when quality of life questionnaires form part of routine practice [6,8]. High patient satisfaction is known to lead to superior compliance [9,10], to more promptly seeking medical care [11] and to retaining a higher amount of information [12].

Although it is now standard in clinical trails to include health status measurement using well validated questionnaires, their use is not by any means standard in routine clinical care.

The GOLD guidelines advocate a stepwise algorithm that, based on FEV<sub>1</sub> level, differentiates mainly pharmacological treatment recommendations. All non-pharmacological recommendations are identical for all levels of severity, limiting individual differentiation. We propose that health status instruments provide the opportunity for individually tailored advices on functional status, mental status and symptoms.

Health status or disease related quality of life studies carried out in routine clinical practice show promising results regarding the feasibility of health status instruments usage and their influence on the consultation but until now have not been able to show consistent benefits on health outcomes for patients with COPD [8,13,14]. These ambiguous results might be due to differences in questionnaires used and differences in the way studies were performed. Studies that test the clinical effectiveness of health status instruments have used a large variety of tools, settings, and outcome parameters [8,13-21]. However none of these studies used a clear algorithm of what to do with outcome of health status measures nor a clear advise regarding patient management.

We hypothesize that a treatment algorithm that is based on a simple validated measure of health status, the Clinical COPD Questionnaire (CCQ) improves health status (as measured on a separate scale) and secondary parameters like exacerbation frequency, patient satisfaction, and health care utilization, when compared to usual care based on FEV<sub>1</sub> level as per current GOLD guidelines.

The research questions addressed are:

- I Does a treatment algorithm that is based on CCQ measurements improve health status as measured by St. Georges Respiratory Questionnaire (SGRQ) over two years of use compared to usual care based on FEV<sub>1</sub>?

- 2 Does such a treatment algorithm improve other parameters of COPD care such as exacerbation frequency, patient satisfaction, and health care utilization compared to usual care based on FEV<sub>1</sub>?

This study combines the advantages of standardized health status measurement in routine clinical practice and of clear clinical treatment recommendations.

## Methods/Design

### Study design

The study will be a prospective randomized controlled trial with a follow-up duration of two year with two arms:

- (i) intervention group with CCQ guided treatment proposals (CCQ group) and
- (ii) guideline group where treatment advice is based on FEV<sub>1</sub> level according to Dutch National and GOLD guidelines (Usual Care, UC group).

The treatment algorithm for the intervention group has been developed in cooperation with the participating divisions of the Groningen Research Institute for Asthma and COPD (GRIAC) and has been tested on databases of previous studies in the Wilhelmina Hospital Assen (n=38) and the Isala hospital Zwolle (n=168) in order to assess its feasibility and to generate the cut-off points of the treatment algorithm.

The study flow-chart is represented in Figure 1. The study has been approved by the local ethic committees and is registered on the Dutch trial register (ISRCTN-register).

### Duration

Patients will be followed up for 2 years and during that period there will be 7 visits, including a baseline and a final visit (Figure 1).

### Selection and recruitment

Local general practitioners will be contacted to participate in the study. When a general practitioner agrees to participate, he/she is asked to review his/her patient database for possible participants. The resulting eligible patients are sent a patient information leaflet and an informed consent form by their general practitioner. They will be asked by letter to return the informed consent form to their general practitioner if they wish to participate in the study (opt-in method). The patients will then be invited for the baseline visit. The inclusion criteria are a spirometry confirmed doctor's diagnosis of COPD, age 40 years or above, a smoking history of at least 10 pack-yrs and a post bronchodilator FEV<sub>1</sub>/ forced vital capacity (FVC) <0.70. Exclusion criteria are a myocardial infarction less than 3 months ago, inability to read and understand the Dutch language, history of asthma or allergic rhinitis before the age of 40, regular use of oxygen, unstable or life-threatening co-morbid condition (as judged by the investigator) and dementia.

This study will take place in general practices in the Northern part of the Netherlands. All measurements including spirometry will take place in or near the GP practices when possible.

### Blinding strategy

The study will be performed as a double-blind study. Patients and doctors will be blinded as

well as the technicians that perform the measurements. A separate researcher will collect the data, and feed them in to a PC for a computerized treatment advice based on pre-defined criteria as per protocol. This advice will be sent to the doctor. Since the doctor will only see the resulting treatment advices, and not the measurement results they are derived from, and since in both groups the treatment advices are compliant with the same national guideline, albeit organized in a different fashion, blinding is maintained.

### Intervention

The actual intervention is the provision of treatment advices to the general practitioner. These treatment advices are derived from guidelines and an algorithm has been developed for each treatment group separately.

The FEV<sub>1</sub> algorithm resulted from the treatment steps in the GOLD criteria. The transformation from this treatment steps into the algorithm was straight forward.

The CCQ algorithm was a result of extensive discussions within the study development group. The primary objective during the developmental phase was that the algorithm should result in a strategy that would treat the patient's prime problem, reflected by the most impaired CCQ domain and not treat all the patient's CCQ impaired domains at once. At the next visit, it is assessed whether the specific domain problem is sufficiently improved, and it is judged whether this, or other, or no domain demonstrates relevant impairment. So, the domain that is most impaired will guide the treatment. The treatment intensity is guided by the CCQ total score, i.e. the overall impairment in health status. For example, a high score on CCQ total score (>3, i.e. maximally impaired) in combination with the highest score on the functional status domain will lead to a pulmonary rehabilitation program advice, while a total CCQ score between 1 and 2 in combination with the highest score on the functional status domain will lead to the provision of leaflets on healthy movement. Scores below 1 are deemed not to be impaired to a clinically meaningful degree. For reference purposes, it is useful to state that changes in CCQ of  $\geq 0.4$  are above the minimal clinically important difference.

The final algorithm is displayed in Figure 2.

### Measurements

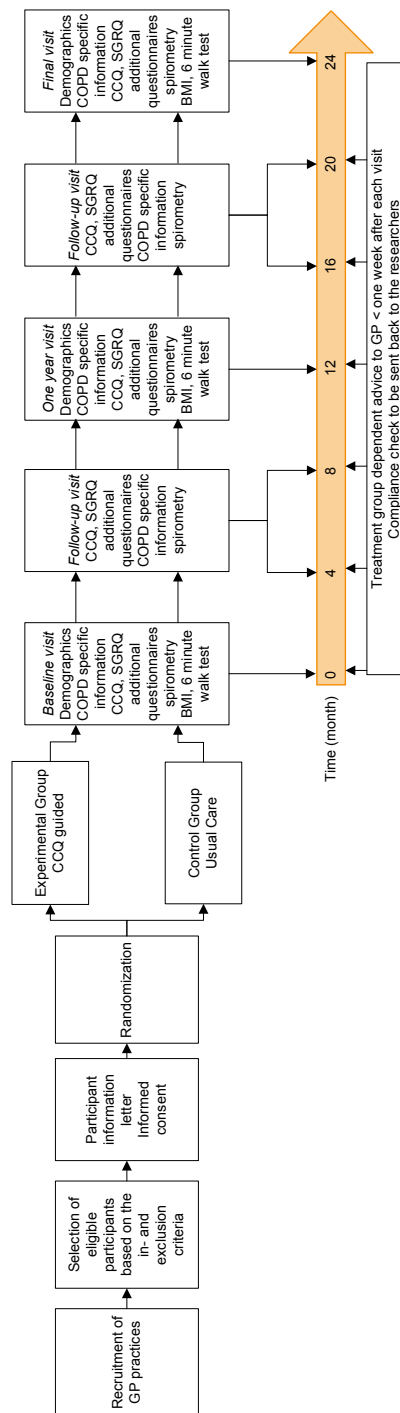
#### Baseline visit and last visit

At a visit, the disease should be stable; visits are postponed until six weeks after an exacerbation. The following parameters are gathered at study visits:

- Patient demographics: age, gender, marital status, educational level, employment status, postal code.
- COPD specific information: smoking status, pack years, duration of COPD.
- Previous participation in a formal smoking cessation program, pulmonary rehabilitation or reactivation program.
- Co-morbidities, using the Charlson comorbidity index [22].
- Medication use and exacerbations in the last year. Exacerbations are defined as an increase in or new onset of more than one respiratory symptom (cough, sputum, sputum purulence, wheezing, dyspnea) with a duration of three or more days requiring treatment with an antibiotic and/or systemic steroid.
- Spirometry, pre- and postbronchodilator FEV<sub>1</sub> in liters, FEV<sub>1</sub> % predicted, FVC % predicted, and inspiratory capacity. The bronchodilator will be administered as salbutamol 4 times 100 microgram per metered dose inhaler with chamber device.



Figure 1. MARCH study flow chart.



- Body Mass Index
- Functional exercise capacity as measured by the 6 minute walking test[23]. The patients are asked to walk a along a level 30 meter walkway for 6 minutes. Breaks are allowed if necessary and recorded. Total distance walked is recorded as well as heart rate, blood pressure, Borg dyspnea score and oxygen saturation immediately before and after the test.
- Patient reported outcomes:
  - The SGRQ is a 50-question, 76-item health status scale for COPD patients. The SGRQ has 3 subscales: symptoms, activities and impact. The score ranges from 0 (best) to 100 (worst). The minimal clinically important difference is 4 points [24,25].
  - The Clinical COPD Questionnaire is a 10-item health status scale measuring three domains: symptoms, functional status and mental state of COPD patients. Scores range from 0 (best) to 6 (worst). The minimal clinically important difference is 0.4 [26,27].
  - The CCQ has been validated on the individual patient level [28].
  - The modified Medical Research Council (mMRC) dyspnea scale [29]. This measures dyspnea on a scale of 0 (not breathless except when performing strenuous exercise) till 4 (too breathless to leave the house or breathless when dressing).
  - The EuroQoI-5D a self administered questionnaire for health outcome. Applicable to a wide range of health conditions and treatments [30].
  - The Hospital Anxiety and Depression Scale, a scale developed to identify anxiety disorders and depression among patients in non-psychiatric hospital clinics but also widely used outside the hospital. It is divided into an Anxiety subscale and a Depression subscale both containing seven items. Each question is answered on a 0 to three scale. A total score above 8 suggests the existence of pathology. A change of 1.5 in each domain score represents a clinically relevant change [31].

#### During each follow-up visit

The following will be collected during each follow-up visit: CCQ, spirometry, pulmonary medication use, generic questionnaire about treatment offered and received, and about unscheduled visits to the GP or hospital because of pulmonary problems, and patient reported outcomes: SGRQ, mMRC, EuroQOL-5D and HADS.

#### Advices to health care provider

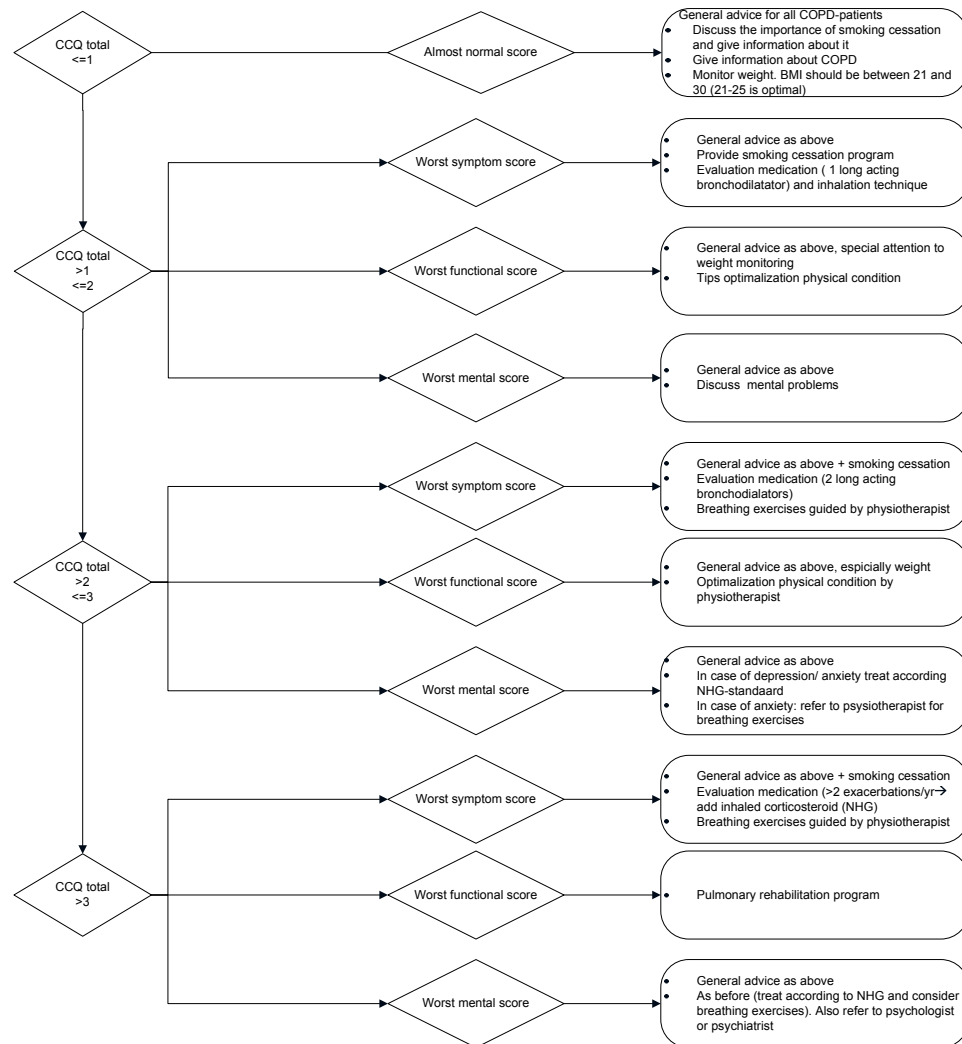
After each visit the GP will receive a treatment advice. Depending on the group to which the patient is randomized this will be based either on the CCQ (CCQ group) or on the Dutch National guidelines (UC group). In order to check for compliance the GP will be asked to report what treatment (pharmacological and importantly non-pharmacological) was offered to the patient and if the GP deviates from the advice he or she will be asked to provide the reason for deviating.

#### Outcomes

##### Primary outcomes

Change in SGRQ over time, both baseline versus two years and course of SGRQ score. Because the intervention is guided by the CCQ, a different health status instrument, the SGRQ, will be used as primary outcome measure. In the treatment of COPD patients in primary care, the improvement of health status and reduction of exacerbations are the main goals of treatment. In this perspective it is a logical choice to use a health status questionnaire as an outcome measure.

Figure 2. CCQ based treatment algorithm.



### Secondary outcomes

One of the secondary outcomes will be the exacerbation frequency, measured by medication use. This is one of the classical COPD outcomes and exacerbations have a large impact on patients' lives.

Other secondary outcome parameters will be changes in CCQ score, 6 minute walking distance test, HADS, mMRC, lung function, and differences between the two groups in hospital admissions and mortality.

### Economical outcome variables

Health care utilization and other direct medical costs will be recorded in a diary by the patient. Data will include medication usage, and all visits to the general practice, hospital, and other health care professionals involved in the management of COPD. Quality adjusted life years (QALY's) will be calculated using the EuroQOL-5D.

### Sample size calculation

Sample size calculations are based on difference in change in health status between both groups. Because the intervention is guided by the CCQ, an alternative health status scale, the SGRQ, is used for the power-calculation. Based on 80% power to detect the minimal clinically important difference (4 points on the SGRQ) between the two groups, a sample size of 150 persons per group is needed. The standard deviation of the SGRQ total score in different samples is around 10-17 (12 used in calculation) [32-36]. The alpha level was set at 0.05. Taking dropouts into consideration, a sample size of 165 patients/group = 330 patients in total is aimed for.

### Statistical analysis

The primary outcome measures is the change in SGRQ over time. The SGRQ results in a total score and 3 subscale scores: symptoms, activities and impact. The SGRQ change in scores over the treatment period of the control group will be compared to that of the experimental group. The scores will be tested for normality. In case of normality the difference will be univariately tested with a student T-test and multivariately with a linear regression model. In case of deviation from normality the variable will be transformed to normality via a Box-Cox transformation and thereafter analyzed via student T-test and linear regression models. The multivariate models will be corrected for the following confounders: educational level, age, gender, current smoking, and FEV<sub>1</sub>. The number of exacerbations will be reported as weighted exacerbations rates (total number of exacerbations divided by the total person-time of follow up per group) [37-39]. Statistical significance of weighted rate ratios will calculated using a Poisson regression model. The secondary research outcomes will be tested in a similar fashion as the primary research question. The primary analyses will be based on the intention-to-treat principle. As secondary analyses, a per protocol analysis will be performed to increase insight in the data.

### Discussion

The objective of the MARCH study is to study whether a treatment algorithm that is based on CCQ measurements alone improves health status as measured by SGRQ after two years of use compared to care based on FEV<sub>1</sub> levels as per regular (GOLD) guidelines.

This study is based on the assumption that treatment that is guided on the basis of problems that matter to patients (as reflected in a health status measurement) will have more positive effect on their life than treatment that is guided on a single measurement that has little relation with their problems (FEV<sub>1</sub>).

The selection of an appropriate primary outcome measure for the current study was an important issue when designing this study. The traditional primary outcome measure in COPD research is lung function, usually represented by the FEV<sub>1</sub>. The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) still routinely require this

in pharmaceutical trials. However,  $FEV_1$  has been found over and over again to have a very poor correlation with several markers of COPD that seem to matter most to patients, such as exercise tolerance, symptoms, and also health status. Therefore, currently most researchers regard changes in patient centered outcomes such as health status and also symptoms, exacerbations and functional status more important than changes in lung function [40]. Patient centered outcomes better reflect the complexity and the impact of the disease and several aspects of health status predict clinically meaningful outcomes in COPD [41,42]. For instance, functional status as measured in health status questionnaires has been shown to predict exacerbations [43,44], hospital admissions [43-47] and mortality [48,49]. In most large scale COPD studies, health status is measured, and improves with interventions, but it is seldom used as primary outcome. The situation is better in pulmonary rehabilitation studies where health status has been used as one of the primary end points.

Using health status as primary outcome measure in a study where the treatment in one arm is organized according to health status carries the risk of direct influence on the outcome. In order to reduce this potential methodological problem, a different health status questionnaire (SGRQ) is used in our study instead of the questionnaire that is used to guide the treatment (CCQ).

In the current study we decided to randomize on the patient level and not on the GP cluster level. This decision was made after careful evaluation of advantages and disadvantages of randomization on the individual and the cluster level. In this evaluation the following factors played a pivotal role. A large disadvantage of cluster randomization is the risk of selective inclusion, i.e. the physician is more likely to discover to which treatment group all his or her patients are allocated and this might, unconsciously, play a role in selecting patients for participation in the study. A second large disadvantage is the need for a much larger study population to maintain sufficient power. An additional power calculation for cluster randomization assuming 10 COPD patients per practice, and a correlation of SGRQ scores within primary care practices of 0.14 (based on previous unpublished studies in our group), the total number of patients needed to achieve a power of 0.8 is 462. This constitutes an increase in patient number of 40%.

A disadvantage of randomizing at the individual level is the risk of contamination, loss of allocation concealment. This risk is present on both the patient level and on the physician level. On the patient level this is caused by the fact that several patients from one GP practice participate in this study and often patients in one practice know each other. Therefore patients in the control group might know patients that have been randomized into the intervention group and via that route receive information from the intervention group which they then might decide to use for themselves. However, we do not consider this to be a large risk in our study because the experimental treatment does not differ markedly from the usual care treatment, the same treatment elements are used however they are differently organized. In other words none of the patients will receive completely new and unexpected advices and therefore we expect them to conform to the recommendations given by their physicians.

The second level on which contamination might pose a risk for the study is the physician level, physicians might learn from the intervention and adjust their way of working. We try to circumvent this risk by supplying the physician with clear and individually tailored written practical advices. Physician and patients are routinely asked to report which treatment was given to each of the participants in the study giving us an accurate picture of whether or not contamination was present and if so the size of the problem.

Health care providers are not used to interpreting health status data. They need education and support to learn how to interpret the scores of health status instruments if they are to be successfully integrated into routine practice. Greenhalgh's review of health status studies concluded that information should be fed back throughout the decision making process to all clinicians involved in the patient's care and in a format they can make sense of and integrate in clinical decision making [17]. Health status scores should therefore be presented in a coherent clinically relevant format, with clear guidelines for interpretation and preferably with to-the-point recommendations. Based on his suggestions we incorporated in our study a clear treatment advice for the participating clinicians in order to avoid these difficulties around the interpretations of health status scores. The health status based treatment algorithm is the core of the study.

The algorithm providing the treatment advices based on health status scores was designed using the following method. All treatments are based on the current Dutch general practitioners guideline. In this guideline, treatments are organized by severity of lung function impairment as expressed in  $FEV_1$ . In our algorithm in the experimental (CCQ) arm, we evaluated all standard treatments options (pharmacological, stop-smoking, reactivation, counseling etc) and reviewed the possible effects of the treatment on COPD symptoms, functional status or exercise capacity and mental state. Subsequently we arranged the interventions according to intensity of the treatment and resources needed, e.g. for functional status: physical activity advices, out-patient reactivation, and finally rehabilitation. This led to a re-ordering of the existing interventions based on domain and level of health status impairment. Feasibility was assessed using study databases, ensuring equal distribution of patients across all arms of the algorithm.

Vital for successful completion of the study is compliance of the care provider with the treatment advices. In the current Dutch GP practice the care for patients with chronic diseases is often transferred from the GP to the practice nurse. This applies also to implementing treatment advices. Practice nurses can achieve similar outcomes as doctors in chronic disease management [50]. Additionally, it has been demonstrated that practices in which the organization is optimal, guidelines are better adhered to [51]. Although this adds an extra layer in the process from measurement (lung function or health status) to effectuating the treatment, we are confident that in well organized practices with practice nurses our advices will lead to treatment changes.

## Conclusions

This article describes the design of a double-blind randomized controlled trial in general practice that aims at demonstrating that COPD care can be improved by implementing a treatment algorithm based on a simple health status questionnaire. Considerations in choosing the primary end point, the randomization procedure and the design of the algorithm are described and result in decisions that both support the scientific robustness and feasibility of this study.

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## **Chapter 9**

### **Summary and general discussion**

## Summary and general discussion

Patients with Chronic Obstructive Pulmonary Disease (COPD) generally have an impaired health status [1]. This impairment in health status has only a modest relation with their lung function, the parameter on which current guidelines diagnose the disease and guide the treatment [2,3]. Based on this inconsistency we investigated what is needed to develop a model of COPD management that is based on health status measurement rather than lung function.

The relationship between health status and different measures in COPD is further analysed in *chapter two*. This meta-analysis shows that the most significant factors that determine health status in COPD patients are dyspnea, depression, anxiety, and exercise tolerance. This meta-analysis also indicates that spirometry values are only weakly associated with health status. This finding supports the idea that in each COPD patient health status should be measured next to spirometry in the evaluation of the disease in patients with COPD.

*Chapter three* puts forward the opinion that health related quality of life, health status and patient reported outcomes are now widely accepted in clinical research and that they have shown very promising qualities for use in daily clinical practice. However, before healthcare professionals can use these tools in routine clinical care, their feasibility in daily clinical practice, their validity on an individual level and their effectiveness in conjunction with management suggestions should be further investigated. A new questionnaire validation method for the individual level is introduced and used in chapter six.

*Chapter four* reviews and systematically organizes tools to measure functional status in a framework that describes what construct they measure and the facilities needed for measuring functional status. The measurement properties of each tool were rated according to a novel rating system for primary care. In conclusion, for primary care, the six minute walking distance test is the most feasible and reliable semi-laboratory functional capacity test; the pedometer is the best functional performance field test and the MRC and the Clinical COPD Questionnaire (CCQ) functional status domain are the best patient reported outcome tools to measure functional performance in primary care.

*Chapter five* reports the study to determine the CCQ's minimal clinically important difference (MCID). This study suggests that the MCID of the CCQ instrument is approximately 0.4 points. Thus, a change in score of 0.4 or more from baseline indicates the smallest change indicated by the CCQ in health status that can be considered to be clinically significant.

*Chapter six* reports a new method to assess the individual validity of a health status questionnaire. The method was applied to the CCQ health status questionnaire. This study shows that there is a very good agreement in CCQ outcomes between the individual patient score and 20 reviewing clinicians who did not know the patient but scored the CCQ based on an in-depth interview. The combination with the previously known high reliability and stability confirms the validity of the CCQ at the individual patient level.

*Chapter seven* describes that the outcome of formal health status measurement within a randomized clinical trial in 210 hospital admitted patients and 45 patients that were treated at

home because of an exacerbation of COPD. This study concludes that (1) change in health status as measured by the CCQ, especially symptoms during the start of an exacerbation, predicts the occurrence of treatment failure; (2) health status as measured by the CCQ on day 42 after a COPD exacerbation predicts time to next exacerbation and long-term mortality; (3) health status can be measured during exacerbations of COPD on a daily basis; (4) there is a marked difference in health status between patients treated at home or in the hospital for an exacerbation of COPD, but the rate and pattern of recovery is remarkably similar. Health status provides strong additional information that might guide early intensification of treatment.

*Chapter eight* describes the protocol for the “**M**oving towards **A**lgorithm-based **R**estructuring of **C**OPD care by **H**ealth status (MARCH)” study, a prospective randomised clinical trial that will assess the effectiveness of health status guided COPD care.

## General discussion

We started the studies in this thesis based on the idea that the management of COPD based on lung function does not address the problems experienced by the patient. That same idea was one of the reasons to develop a few years before the start of this thesis the Clinical COPD Questionnaire (CCQ), a health status questionnaire that was suitable for routine clinical practice. The CCQ was developed according to the state of the art psychometric methods of questionnaire development, and was designed to fit on a single sheet of paper.

During the development of a protocol that assesses the effectiveness of guiding COPD based on health status, several research questions emerged. *What is known to impact the health status of patients? Can we use the CCQ to guide treatment? Can a questionnaire that has good measurement properties in groups of patients be used in individual patient management? Not only to evaluate the treatment, but also to guide the treatment? What differences in score should be a reason to react as a clinician? And are different scores actually meaningful in predicting COPD outcomes? If an intervention has effect on health status, does that mean the course of the disease is modified? What will be end-points in such a study?*

The studies in this thesis found answers on most of these questions, resulting in the MARCH study protocol.

The review of factors that influence health status revealed that the most significant factors that determine health status in COPD patients are dyspnea, depression, anxiety, and exercise tolerance. These factors are partly associated because these symptoms are part of most health status questionnaires [4]. Nevertheless, the most important finding is that the most influential factors for health status can be influenced by therapy. Dyspnoea and exercise tolerance can be improved by bronchodilation [5], oxygen therapy [5], physiotherapy [6] and pulmonary rehabilitation [5]. Depression and anxiety are both frequently present in COPD [7] and can be influenced by anti depressants and counselling [7,8]. Finally symptoms in general like sputum and cough can be improved greatly by smoking cessation [9]. Tailoring treatment to the individual patient can address these factors. This approach is already the cornerstone of the multicomponent pulmonary rehabilitation. In pulmonary rehabilitation,



most studies include health status measures and exercise capacity measures as guidance for therapy as well as primary end points. Following this line of thought, the most appropriate end points for a study that guides treatment based on health status will be similar to that of pulmonary rehabilitation and should also include health status as end point.

Previous studies that have evaluated the implementation of health status in routine clinical care have not shown great impact on how clinicians manage patient problems or on subsequent patient outcomes [10].

A review of health status studies in routine practice concluded that information should be fed back throughout the decision making process to all clinicians involved in the patient's care, and in a format they can make sense of and integrate in clinical decision making. Health status scores should therefore be presented in a coherent, clinically-relevant format, with clear guidelines for interpretation [11]. Furthermore, it is important to ensure that clinicians understand that most of these instruments have only been validated on a group level.

To establish guidelines for interpretation, the CCQ's minimal clinically important difference (MCID) was assessed. The MCID represents the minimal change that is perceived as clinically important. All measurement instruments, including blood pressure measurement and spirometry suffer from variation between serial measurements. These measurement errors are also present in questionnaires. Next to this error, changes in scores can be too small to be perceived as real changes. The changes on a group level in clinical studies can be statistically significant, while the change is too small to be perceived by patients and/or clinicians. We've established the CCQ's MCID using three measurement methods. We have used the "anchor based" approach, in which patients rated their global change during the recovery of an exacerbation, and compared this to their CCQ scores. Secondly we have used the "criterion based" approach, in which future events, for example hospitalisation and/or death was related to CCQ scores. Finally we have used the "distribution based" approach that employs statistics to assess the MCID. This was the first study of a health status scale that used three methods. A fourth method is available, clinician referencing. Clinician referencing uses the same method as patient referencing by rating the perceived overall improvement, rated by the doctor on a 15 point scale. The improvement as rated by the clinician in the same patients would have been interesting because in a different approach to determine the MCID using clinician's judgements in an expert panel, the clinicians appeared to need greater changes in scores to be clinically relevant than patients [12,13].

The three methods to determine the CCQ's MCID showed little differences. For individual patients, larger differences in scores could be needed before they perceive a meaningful difference. Indeed, in individuals, the MCID can be used as a guidance, but because the MCID is developed in groups of patients, the MCID in individual patients could be different. We suggest that clinicians should be extra alert when scores change above the 0.4 points.

For clinicians, reference values for patient groups or cut-off values for good or bad health status would improve the usability of scores. For asthma, a lung disease that is characterised by a variable airway obstruction, levels of disease control have been defined in international guidelines [14]. These levels of control are used to establish cut of scores of questionnaires in asthma [15]. The difficulty in determining these kind of cut-of scores in COPD is that, even if patients are treated optimally, the underlying problem, the "airflow limitation that is not fully reversible" will stay present. As a consequence, one could not expect that a patient

with very severe airway obstruction will have total disease control/no complaints at all. Nevertheless, maximal effort should be put in improving this patient's health status.

As long as FEV<sub>1</sub> is used to categorise disease severity, it will be difficult to establish cut-of points for health status questionnaires in COPD. New ways of categorising patients based on, for example, symptoms, exacerbation frequency, functional status and more lung function parameters are suggested [16,17], and these might be more suitable as gold standard for discussing at which threshold of problems change of intervention should be contemplated, given the individual's disease severity.

If the patient is monitored using health status questionnaires, a "personal best" score can be used. This personal best score can be used to, for example, intensify treatment when the scores become higher over time.

Next to interpretation on reference values, interpretation of health status scores on most questionnaires can be done at 3 levels: individual item level, domain or sub score level, and total score. To improve communication and discuss topics otherwise less often discussed, screening on item level is useful, for example on the mental domain. To guide treatment, one might start with interventions directed at the most impaired domain. For evaluation in time, the total domain might be most informative.

We've developed a new method to assess the validity of health status questionnaires on an individual level. This new method relies on the judgement of clinicians after reading the transcripts of interviews. The clinicians that reviewed the interviews needed between one and three hours to read and rate the interviews. Because we expected that the reviewing of the transcript was time-consuming, we selected clinicians with an interest in health status measurements. It turned out that the mean differences between doctors were not very large. However, between the individual clinician that rated health status higher and the clinician that rated health status the worst, there was a difference of -0.49 and +0.44 from the mean (Figure 1). This was not related to the clinician's self-assessment of experience with health status measurement in daily clinical practice. We are confident that the clinicians rated the CCQ as they really expected the patient to complete the CCQ.

As a result of this thesis we can answer a number of questions we started with. *What will be end-points in a study comparing lung function driven treatment compared to health status driven treatment?* A study that assesses the effects of guiding treatment of COPD patients based on health status should have primary end points that reflect the problems that patient with COPD encounter during their daily lives. *Can we use the CCQ to guide treatment? Can a questionnaire that has good measurement properties in groups of patients be used in individual patient management? Not only to evaluate the treatment, but also to guide the treatment? And are different scores actually meaningful in predicting COPD outcomes?* The CCQ is a valid instrument to be used in clinical practice in individual patients, there are guidelines for the interpretation of changes in the CCQ and the CCQ is able to predict future events. What we have not yet answered is if we can guide treatment based on health status, and if this has effects on patients outcomes and health status. And if an intervention has effect on health status, does that mean the course of the disease is modified?

## Future studies and perspectives

The CCQ has gone through a process of development and validation on the group level. Additionally, the Minimal Clinically Important Difference was determined, and the questionnaire was validated in individual patients. After that the usefulness in the clinical setting was evaluated, and the next step is to change the use from an evaluating tool towards a guiding tool in COPD care.

This thesis answered important questions that - in our opinion - needed to be answered before the MARCH study could be designed. The MARCH study is a prospective randomised controlled trial to study the effects of health status guidance in COPD care.

This trial will make use of the CCQ as guiding tool for treatment. Previous trials failed to show significant effects of health status usage in clinical practice. Trials studying the effects of health status measurement were often randomised on a patient level, which can cause contamination effects (the clinicians learn from the intervention and use that knowledge in the control group). Thus, the new trial design could benefit from cluster randomisation [18].

Another difference between previous trials and this new trial would be the specific guidance offered to individual caregivers based on the results of a patient's individual test, which contrasts with the routine so far of only showing the results of questionnaires.

In the Northern part of the Netherlands, a diagnostic and monitoring service is available for GPs as part of an integrated care program. Patients complete the CCQ, the Asthma Control Questionnaire and a short medical history questionnaire and perform spirometry. These results are evaluated by pulmonary physicians and they advise on diagnosis and treatment. A recent study evaluating a partly similar service in the southern part of the Netherlands showed little benefit to COPD patients compared to usual care [19]. In this study half of the monitoring visits resulted in disease management recommendations by a respiratory expert, and 46% of these recommendations were implemented by the GPs. Especially lifestyle recommendations had poor adherence. These results emphasise that this new trial should also use process indicators to measure the effects between the origin of the intervention (give advice based on the health status scores) and the primary outcome (health status improvement) [10].

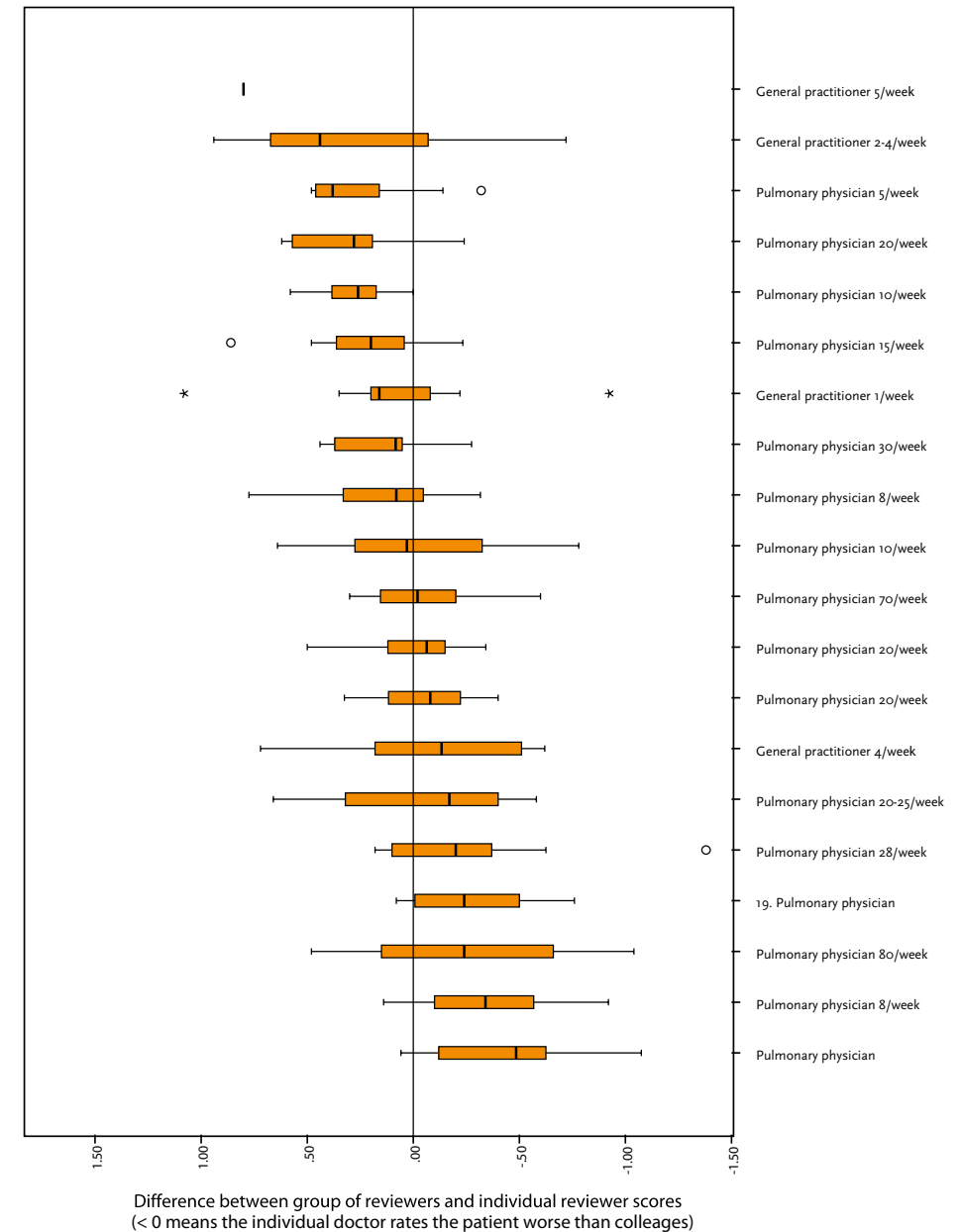
### Other future studies

Because health status instruments are more often used to monitor effects in routine care, large amounts of real life data will be available. Many of these programs use the CCQ and the MRC. If these data can be brought together, these data can be used to create patient profiles. These patient profiles can be followed in time and the real life effects of interventions can be studied using modelling techniques. With sufficient patients and interventions, this may lead to decision support systems that incorporate health status as measurements and help doctors to choose therapies based on performance in real life, rather than trials based on strict in- and exclusion criteria.

In chapter seven, we showed that the CCQ was able to predict if patients would experience treatment failure during the admission due to an exacerbation of COPD. After three days, hospitalised patients had a CCQ score that was similar to the scores of patients treated outside the hospital for their exacerbation. These two findings pose the question whether the CCQ can be used to determine which patients could be discharged earlier than normal.

New prospective studies that incorporate the CCQ in this clinical decision process are needed to assess the value of health status measurements in early discharge schemes.

Figure 1. Difference in CCQ between individual reviewer scoring and the group of reviewers assessing the same patient.



A lower score than 0 signifies that the reviewer rates patients worse than his/her colleagues on average. Numbers/week are the number of COPD patients the physician treats per week.

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## **Chapter 10**

### Nederlandse samenvatting

## Nederlandse samenvatting

Chronic Obstructive Pulmonary Disease (chronische obstructieve longziekte), oftewel COPD, is een verzamelnaam voor longaandoeningen die zich kenmerken door een niet of niet geheel omkeerbare luchtwegvernauwing. Deze obstructie is gewoonlijk progressief en wordt meestal geassocieerd met een abnormale ontstekingsreactie van de longen op prikkelers van buitenaf, zoals roken of kleine gasdeeltjes. Er lijkt ook een genetische gevoeligheid te zijn. Naast longklachten veroorzaakt COPD bij een aantal patiënten ook problemen buiten de longen, de systemische afwijkingen, zoals een verminderde spiermassa, gewichtsverlies en uiteindelijk pulmonale hypertensie. Ook depressie is een veelvoorkomende aandoening bij COPD.

Nederland heeft meer dan 350.000 mensen met de diagnose COPD en uit onderzoek blijkt dat dit aantal de komende jaren sterk zal toenemen.

In nationale en internationale richtlijnen voor het behandelen van COPD wordt voor het bepalen van de ernst van COPD uitgegaan van de longfunctie. De hoeveelheid lucht die mensen kunnen uitademen is bepalend voor de ernst van de ziekte. Hoe minder lucht een patiënt per seconde kan uitblazen, hoe intensiever de behandeling die voorgesteld wordt in de richtlijnen. De hoeveelheid lucht die mensen in een seconde kunnen uitademen blijkt echter maar weinig relatie te hebben voor de hoeveelheid klachten die zij door hun COPD ervaren.

De hoeveelheid klachten en de gevolgen daarvan op het leven wordt de gezondheidstoestand of 'health status' genoemd. Door het voeren van een uitgebreid gesprek met de patiënt is de gezondheidstoestand te bepalen. Het nadeel hiervan is dat de mate van klachten in het verloop in de tijd lastig te vervolgen is. Hiernaast kan de ene patiënt bepaalde klachten belangrijker vinden dan een andere patiënt en is om een goed en compleet beeld te krijgen is een gesprek van 30-45 minuten nodig. Voor een meer gestandaardiseerde methode om informatie over de gezondheidstoestand van patiënten te krijgen kan men gebruik maken van vragenlijsten. Huidige, gedegen ontwikkelde en gevalideerde vragenlijsten zijn gebaseerd op gesprekken met patiënten, het onderzoeken van de literatuur en het raadplegen van professionals. Na het verzamelen van mogelijke vragen moeten die vragen die het belangrijkste zijn voor de meeste patiënten en professionals worden uitgekozen en getest. Dit onderzoek, het valideren, gebeurt in groepen patiënten.

Door het gebruik van deze goed gevalideerde vragenlijsten kan men in een korte tijd betrouwbare informatie krijgen over de klachten van een patiënt en kunnen de klachten in de loop van de tijd worden gevolgd. Ook het effect van behandelingen kan worden gemeten.

Inmiddels zijn er verschillende vragenlijsten ontwikkeld voor het meten van de gezondheidstoestand van patiënten met COPD. De meeste vragenlijsten zijn ontwikkeld voor het gebruik in onderzoek, maar enkele zijn ook ontwikkeld met het idee om deze in de dagelijkse praktijk te gebruiken. De Clinical COPD Questionnaire (CCQ) is één van de vragenlijsten die bedoeld is voor het gebruik in onderzoek en in de dagelijkse praktijk. In een overzicht van vragenlijsten die gemaakt is voor de International Primary Care Respiratory Group (IPCRG) krijgt de CCQ de maximale score op betrouwbaarheid en toepasbaarheid in de huisartsenpraktijk.

De CCQ is ontwikkeld tussen 1999 en 2003. Hij is ontwikkeld volgens de methodes die

Figure 1. De Clinical COPD Questionnaire, Nederlandse weekversie.

Patiënt nummer: \_\_\_\_\_  
Datum: \_\_\_\_\_

| COPD VRAGENLIJST   |                       |                     |                    |                  |             |                  |                                    |
|--|-----------------------|---------------------|--------------------|------------------|-------------|------------------|------------------------------------|
| Omcirkel het nummer dat het beste beschrijft hoe u zich de afgelopen week heeft gevoeld.<br>(Slechts één antwoord per vraag) |                       |                     |                    |                  |             |                  |                                    |
| Hoe vaak voelde u zich in de afgelopen week ...  | nooit                 | zelden              | af en toe          | regelmatig       | heel vaak   | meestal          | altijd                             |
| 1. Kortademig <b>in rust</b> ?   | 0                     | 1                   | 2                  | 3                | 4           | 5                | 6                                  |
| 2. Kortademig <b>gedurende lichamelijke inspanning</b> ?   | 0                     | 1                   | 2                  | 3                | 4           | 5                | 6                                  |
| 3. <b>Angstig/bezorgd</b> voor de volgende benauwdheidsaanval?   | 0                     | 1                   | 2                  | 3                | 4           | 5                | 6                                  |
| 4. <b>Neerslachtig</b> vanwege uw ademhalingsproblemen?  | 0                     | 1                   | 2                  | 3                | 4           | 5                | 6                                  |
| In de <b>afgelopen week</b> , hoe vaak heeft u ...   |                       |                     |                    |                  |             |                  |                                    |
| 5. <b>Gehoest</b> ?  | 0                     | 1                   | 2                  | 3                | 4           | 5                | 6                                  |
| 6. <b>slijm</b> opgehoest?   | 0                     | 1                   | 2                  | 3                | 4           | 5                | 6                                  |
| In welke mate voelde u zich in de afgelopen week beperkt door uw ademhalingsproblemen bij het uitvoeren van ...              | helemaal niet beperkt | héél weinig beperkt | een beetje beperkt | tamelijk beperkt | erg beperkt | héél erg beperkt | volledig beperkt/ of niet mogelijk |
| 7. <b>zware lichamelijke activiteiten</b> (trap lopen, haasten, sporten)?  | 0                     | 1                   | 2                  | 3                | 4           | 5                | 6                                  |
| 8. <b>Matige lichamelijke activiteiten</b> (wandelen, huishoudelijk werk, boodschappen doen)?                                | 0                     | 1                   | 2                  | 3                | 4           | 5                | 6                                  |
| 9. <b>Dagelijkse activiteiten</b> (u zelf aankleden, wassen)?  | 0                     | 1                   | 2                  | 3                | 4           | 5                | 6                                  |
| 10. <b>Sociale activiteiten</b> (praten, omgaan met kinderen, vrienden/familie bezoeken)?                                    | 0                     | 1                   | 2                  | 3                | 4           | 5                | 6                                  |

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later ook door de Amerikaanse en Europese registratiecommissies zijn opgesteld voor het ontwikkelen van vragenlijsten. De vragenlijst bestaat uit 10 vragen. Deze vragen zijn onder te verdelen in drie categorieën of domeinen: symptomen, functionele status en mentale status. Mensen scoren van 0 (geen klachten of beperkingen) tot 6 (heel veel klachten of volledig beperkt). Het gemiddelde van de scores is de totale score van de CCQ. Voor de domeinen geldt het gemiddelde van de scores binnen dat domein. Figuur 1 laat de Nederlandse weekversie van de CCQ zien. De CCQ is inmiddels vertaald in ruim 60 talen en wordt over de hele wereld gebruikt voor onderzoek en in de dagelijkse praktijk.

*Hoewel het logisch lijkt om de behandeling van COPD te richten op de klachten van patiënten, in plaats van op de hoeveelheid lucht die ze in één seconde kunnen uitblazen, is dit tot op heden nog niet standaard.*

In dit proefschrift wordt onderzoek beschreven naar de voorwaarden en mogelijkheden om de behandeling van COPD te sturen op basis van de klachten van mensen gemeten met de Clinical COPD Questionnaire (CCQ) in plaats van op longfunctie alleen.

In *hoofdstuk één* wordt de achtergrond geschetst zoals ook hierboven kort staat beschreven. In *hoofdstuk twee* worden de relaties tussen verschillende metingen die gedaan worden bij patiënten met COPD en de kwaliteit van leven of gezondheidstoestand beschreven. Conclusies uit dit hoofdstuk zijn dat de longfunctie van mensen een slechte relatie heeft met de hoeveelheid klachten die veroorzaakt worden door COPD op vele gebieden. Het advies is daarom om in ieder geval naast het meten van de longfunctie ook de gezondheidstoestand van patiënten te meten.

In het verleden is er onderzoek gedaan naar de effecten van het gebruik van vragenlijsten in de dagelijkse praktijk bij verschillend aandoeningen. De effecten van het gebruik van vragenlijsten wisselt nogal in deze onderzoeken. Een mogelijke verklaring hiervoor is dat niet de juiste vragenlijsten worden gebruikt en dat behandelaars de resultaten onvoldoende kunnen interpreteren en dus gebruiken in hun besluitvorming. In dit hoofdstuk, *hoofdstuk drie*, bespreken we ook een nieuwe methode om te bepalen of een vragenlijst niet alleen betrouwbaar is voor groepen patiënten maar ook voor individuele patiënten.

In *hoofdstuk vier* worden verschillende methodes om de functionele status (dat wat patiënten nog kunnen en doen) te meten beoordeeld op hun betrouwbaarheid en bruikbaarheid in de huisartsenpraktijk. Een van de belangrijkste behandeldoelen bij COPD is het verbeteren van de functionele status. Er zijn vele verschillende methodes om te meten wat mensen nog kunnen doen, maar ook hoeveel en wat ze doen in het dagelijks leven. Uit dit overzicht blijkt dat voor de eerste lijn de 6 minuten wandeltest de meest toepasbare en betrouwbare semilaboratorium test is voor het meten van wat mensen nog kunnen. De stappenteller is de eenvoudigst toe te passen meting om te bepalen hoeveel mensen bewegen in het dagelijks leven. De CCQ en de MRC vragenlijsten zijn het meest betrouwbaar en het best toe te passen in de huisartsenpraktijk om de functionele status te meten. Met dit overzicht in de hand kunnen huisartsen, fysiotherapeuten en onderzoekers verschillende meetmethodes vergelijken en de juiste methode kiezen voor hun situatie.

Vragenlijsten kunnen gemaakt zijn voor het opsporen van ziektes of het ondersteunen van een diagnose, maar kunnen ook gemaakt zijn voor het vervolgen van patiënten door de tijd.

Bij het vervolgen van patiënten is het van belang om te weten of een verandering in score ook echt klinisch relevant is. Net als laboratoriumtesten hebben vragenlijsten een meetonzekerheid, waardoor een kleine verandering in score, door de patiënt niet als verandering ervaren hoeft te worden. In *hoofdstuk vijf* worden drie verschillende methodes gebruikt om te bepalen welke verandering in score patiënten ook daadwerkelijk opmerken. Patiënten die opgenomen waren in het ziekenhuis voor een exacerbatie (min of meer acute verergering) van hun COPD hebben dagelijks de CCQ ingevuld. Daarnaast hebben ze andere vragen beantwoord, waaronder dagelijks een algemene vraag over hoeveel beter of slechter zij op het moment van invullen waren ten opzichte van het moment van opname. Hierdoor was het mogelijk om te bepalen hoeveel verandering er in de CCQ score was bij mensen die aangaven dat ze een verbetering in hun gezondheidstoestand hadden bemerkt. Hiernaast is het verschil in scores vergeleken tussen mensen die in het jaar na de opname opnieuw werden opgenomen of overleden. Als derde methode is met behulp van de statistiek bepaald welke score buiten de meetonzekerheid zou vallen. Deze drie methodes kwamen allemaal ongeveer op een verandering in score van 0.4 punten op de CCQ terecht. Hiermee is dan ook de Minimal Clinically Important Difference, het minimale klinisch belangrijke verschil, de (MCID) van de CCQ gedefinieerd.

De meeste vragenlijsten zijn onderzocht in groepen mensen. De eisen aan de kwaliteit van de vragenlijst (hoe betrouwbaar meet de vragenlijst wat het zou moeten meten) zijn voor groepen van mensen minder hoog dan voor het gebruik in individuen. Dit komt doordat als een iemand de vragenlijst “verkeerd” invult, dit door de grote groep wordt uitgemiddeld. Wanneer deze ene patiënt echter op het spreekuur komt met de “verkeerd” ingevulde vragenlijst, dan kunnen de uitkomsten van de vragenlijst tot een verkeerd beleid leiden. Om deze reden is het belangrijk om de betrouwbaarheid op het individuele niveau te bepalen. De bepaling van individuele validiteit van de CCQ wordt in *hoofdstuk zes* beschreven. In de bestaande literatuur is alleen een statistische methode beschreven om te bepalen of een vragenlijst aan deze hoge kwaliteitseisen voldoet. De CCQ voldoet daaraan, maar de statistische methode doet weinig recht aan de dagelijkse praktijk. Daarom hebben we een nieuwe methode ontwikkeld waarin een interview over wat mensen nog kunnen en doen als ‘gouden standaard’/de waarheid gebruikt. Vierenveertig patiënten vulden de CCQ in vlak voordat zij bij de longarts op de polikliniek kwamen. Na het bezoek vulde de longarts de CCQ in over de patiënt zoals hij dacht het de patiënt het ingevuld zou moeten hebben. Daarna werd de patiënt voor gemiddeld 45 minuten geïnterviewd waarin de CCQ werd doorgesproken. Wat dachten mensen op het moment dat ze de vragenlijst invulden. Hoeveel doen ze daadwerkelijk nog in het dagelijks leven? Wat kunnen ze nog doen zonder benauwd te worden? Deze interviews werden uitgetypt en alle scores werden zwart gemaakt. Twintig long- en huisartsen hebben elk elf van deze interviews beoordeeld. Zij moesten na het lezen van het interview de CCQ invullen over deze patiënt, zoals zij vonden dat de patiënt het in had moeten vullen. De scores van de beoordelende long- en huisartsen hebben we vergeleken met de scores van de patiënt. Het resultaat van dit onderzoek was dat de scores tussen de beoordelende long- en huisartsen goed overeen kwamen met de scores van de patiënten. Bij een enkeling wijken deze scores erg af. Hoewel we dit (statistisch) niet aan het opleidingsniveau van de patiënt konden relateren, geeft het lezen van de interviews wel het idee dat de scores van patiënten met een (erg) laag intelligentieniveau minder overeenkomen met wat de hulpverleners verwachten op basis van het interview. De CCQ kan dus op basis van de statistiek (zoals reeds eerder beschreven in de literatuur)

en op basis van deze studie waarin de dagelijkse praktijk wordt nagebootst, betrouwbaar worden gebruikt in individuele patiënten in de dagelijkse praktijk.

In *hoofdstuk zeven* wordt het gebruik van vragenlijsten tijdens een opname voor een exacerbatie van COPD beschreven. Het blijkt haalbaar te zijn om dagelijks de gezondheidstoestand te meten tijdens een ziekenhuisopname. De gezondheidstoestand gemeten met de CCQ blijkt te voorspellen hoe snel mensen komen te overlijden, naar de intensive care overgeplaatst moeten worden of na ontslag opnieuw opgenomen moeten worden. Dit is in tegenstelling tot veel gebruikte metingen zoals het zuurstofgehalte in het bloed of benauwdheidsgevoel die dit niet voorspellen. Daarnaast kan de CCQ samen met de longfunctie en het wel of niet roken voorspellen hoe snel mensen opnieuw een exacerbatie krijgen en hoe groot de kans is op overlijden in de volgende 5 jaar. Het blijkt ook dat de patiënten in het ziekenhuis gemiddeld op de derde dag van de opname een vergelijkbare CCQ score hebben als patiënten die thuis worden behandeld aan het begin van de exacerbatie. Misschien kan een deel van deze mensen op de derde dag al naar huis om daar verder behandeld te worden. Concluderend kan een hulpverlener veel extra en zinvolle informatie krijgen als hij of zij de gezondheidstoestand met bijvoorbeeld de CCQ meet bij COPD patiënten tijdens een exacerbatie.

In het laatste hoofdstuk, *hoofdstuk acht*, is de opzet van de MARCH studie beschreven waarin het concept van het behandelen van COPD op basis van de health status daadwerkelijk getest gaat worden. In deze studie zullen de onderzoekers huisartsen twee jaar lang adviseren welke behandeling zij de patiënten volgens een vast schema zouden moeten geven. Bij de ene helft van de patiënten zal de huisarts het advies ontvangen zoals het staat in de richtlijnen gebaseerd op de longfunctie; bij de andere helft van de patiënten op basis van de gemeten health status door middel van de CCQ. Gedurende twee jaar zal bepaald worden of het behandelen op basis van de gezondheidstoestand gemeten met de CCQ voor de patiënt beter is dan het behandelen op basis van de longfunctie.

Nu met dit proefschrift de voorwaarden zijn geschapen om health status in de dagelijkse praktijk toe te passen, is nieuw onderzoek mogelijk en nieuwe ontwikkelingen denkbaar. De eerste aanzet vanuit dit proefschrift is het uitvoeren van de MARCH studie. Hoewel de CCQ wereldwijd al in de dagelijkse praktijk gebruikt wordt voor het vervolgen van patiënten, zal met de MARCH studie het concept dat health status gestuurde zorg beter is dan zorg gestuurd op longfunctie meer onderbouwd kunnen worden.

In hoofdstuk zeven blijkt dat de CCQ in staat is om te voorspellen wie goed of slecht reageert op de gebruikelijke behandeling van een exacerbatie. Mogelijk kan de CCQ bijdragen aan het bepalen wie snel verbetert, en dus ook eerder, maar ook veilig, met ontslag naar huis zou kunnen bij een ziekenhuisopname vanwege een COPD exacerbatie. In een nieuw op te zetten studie naar vervroegd ontslag uit het ziekenhuis zou de CCQ met andere gegevens gebruikt kunnen worden.

Op dit moment zijn er al studies gaande naar zelfmanagement bij COPD patiënten. In deze studies wordt de CCQ ook gebruikt om beginnende exacerbaties op te merken door patiënten zelf. In de toekomst zal zelfmanagement een steeds belangrijker plaats innemen. Vragenlijsten zullen, zeker in het begin, gebruikt kunnen worden om patiënten bewust te laten worden van klachten en daarop te anticiperen.



In de afgelopen jaren zijn internationaal bij veel patiënten al de MRC kortademigheid vragenlijst en de CCQ gemeten. Deze gegevens worden om dit moment door de 'UNLOCK' groep vanuit het IPCRG bij elkaar gebracht. Dit biedt nieuwe mogelijkheden om het inzetten van bijvoorbeeld de CCQ te onderzoeken.

Met gegevens uit deze grote databases over de dagelijkse praktijk kunnen vervolgens door rekenkundige modellen patiëntprofielen worden gemaakt. De effectiviteit van verschillende behandelingen in de dagelijkse praktijk bij bepaalde type patiënten kunnen vervolgens leidend worden binnen beslissingsondersteuning tijdens consulten. Er zal altijd een spanning blijven bestaan tussen de hoeveelheid gegevens dat een goed beslissingsondersteuningssysteem zal nodig hebben en de hoeveelheid gegevens die in de dagelijkse praktijk verzameld kunnen worden. Het optimum vinden hierin is noodzakelijk.

Samenvattend is het meten van health status in de dagelijkse praktijk mogelijk, het is betrouwbaar en het geeft belangrijke extra informatie. De toekomst moet uitwijzen of het sturen van de behandeling van COPD op basis van health status inderdaad beter is dan het huidige beleid.

Dankwoord

Een grote groep mensen is betrokken geweest bij het tot stand komen van dit proefschrift. Ik wil enkelen van hen hier persoonlijk bedanken.

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## Publication list

## Publication list

Kocks JWH, Asijee GM, Tsiligianni IG, van der Molen T. Functional status measurement in primary care: A review of available methods and feasibility. *Prim Care Respir J* 2011, in press.

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## Curriculum Vitae

Janwillem Kocks was born on May 27th 1980 in Zwolle, the Netherlands. He attended the secondary school at the Carmel College Salland in Raalte and passed his exam in 1998. He attended Medical School at the University of Groningen from 1998 and obtained his medical degree in 2004.

In January 2005 he started his PhD research at the department of general practice at the University Medical Center Groningen and the Groningen Research Institute on Asthma and COPD (GRIAC) resulting in this thesis. He combined his PhD training with the specialist training for general practitioner and graduated as general practitioner in March 2009. Since then he is working as general practitioner in the Academic General Practice in Groningen. After completion of this thesis he will continue to combine working as general practitioner at the Academic General Practice and his research at the University Medical Center, Groningen Department of General Practice.

Furthermore, during his study he was active in several educational committees, including an international summer school on pediatrics. He started his company Miegum in 2001, developing internet based software applications. He founded, amongst others, the Dutch AIOtho network (general practitioners trainees combining their training with research). He is web editor of the International Primary Care Respiratory Group (IPCRG) and member of the UMCG Compagnonscursus (specialist and general practitioners conference) committee.

He lives together with Jiska Meijer and their two sons, Nander and Borrit.

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