GOLD D Patients in Primary Care: A Group Whose Clinical Outcomes Can Easily Be Improved

Authors: de Jong, Corina; Kocks, Janwillem; Van der Molen, Thys

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<td>GOLD D in Primary Care</td>
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<td>Principal investigator(s)</td>
<td>Prof. Dr. Thys van der Molen MD</td>
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<tr>
<td>Sponsor</td>
<td>University Medical Center Groningen, Department of General Practice</td>
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<tr>
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<td>Certe (in kind)</td>
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<td>Independent expert (s)</td>
<td>Frederik van Gemert</td>
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### PROTOCOL SIGNATURE SHEET

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# LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>ABR</td>
<td>Algemene Beoordeling en Registratie (General Assessment and Registration form)</td>
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<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>ATS</td>
<td>American Thoracic Society</td>
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<tr>
<td>CAT</td>
<td>COPD Assessment Test</td>
</tr>
<tr>
<td>CCMO</td>
<td>Centrale Commissie Mensgebonden Onderzoek (Central Committee on Research Involving Human Subjects)</td>
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<tr>
<td>CCQ</td>
<td>Clinical COPD Questionnaire</td>
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<tr>
<td>COPD</td>
<td>Chronic Obstructive Pulmonary Disease</td>
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<tr>
<td>EU</td>
<td>European Union</td>
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<tr>
<td>ERS</td>
<td>European Respiratory Society</td>
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<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Force Expiratory Volume in one second</td>
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<td>GOLD</td>
<td>Global Initiative for Chronic Obstructive Lung Disease</td>
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<tr>
<td>METC</td>
<td>Medisch ethische toetsing commissie (medical research ethics committee; MREC)</td>
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<tr>
<td>QALY</td>
<td>Quality adjusted life year</td>
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<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
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<tr>
<td>SD</td>
<td>standard deviation</td>
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<td>Sponsor</td>
<td>The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study, but does not commission it, is a subsidising party rather than a sponsor.</td>
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<tr>
<td>TiC-P</td>
<td>Trimbos/iMTA questionnaire for Costs associated with Psychiatric Illness</td>
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<tr>
<td>UNLOCK</td>
<td>Uncovering and Noting Long-term Outcomes in COPD to Enhance Knowledge</td>
</tr>
<tr>
<td>WBP</td>
<td>Wet Bescherming Persoonsgevens (Personal Data Protection Act)</td>
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<tr>
<td>WMO</td>
<td>Wet Medisch-wetenschappelijk Onderzoek met Mensen (Medical Research Involving Human Subjects Act)</td>
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SUMMARY

A study was recently published into the revised multidimensional Global Initiative for Chronic Obstructive Lung Disease (GOLD) A–D classification of chronic obstructive pulmonary disease (1). This revealed that the prevalence of group D patients receiving inhaled medication was low, with almost 50% not being treated at all. Although this group is frequently encountered in primary care, further information is scarce. Moreover, adequate treatment of this group in an integrated care environment should enhance their overall health status and reduce the rate of exacerbations.

Consequently, this study has two aims that will be assessed across two work packages. Work package 1 will involve a descriptive analysis of group D patient characteristics (age, gender, current medication, smoking status and comorbidities) in comparison to those in groups A, B and C. Furthermore, we will assess how representative the data are in comparison with other countries in the Uncovering and Noting Long-term Outcomes in COPD to Enhance Knowledge (UNLOCK) initiative.

Work package 2 will then involve specifically evaluating the health statuses and exacerbation rates among group D patients before and after treatment for 12 months in an integrated care system. The focus in work package 2 will be on patient-centred treatment that is individualised using the GOLD A–D classification. During the 12-month follow-up period, we will collect information on the following variables: lung function, health status, medication use (type of medication, daily dose, device used, and adherence), inhalation technique, number of exacerbations, health care costs (direct primary and secondary health care usage and medication costs as well as indirect costs related to lost work), quality adjusted life years, and full blood counts (especially eosinophil and neutrophil). For comparison, we will collect data from group A, B and C patients. We hypothesise that accurate treatment of GOLD D patients in an integrated primary care system will improve patient outcomes over 12 months.
1. **INTRODUCTION AND RATIONALE**

Chronic obstructive pulmonary disease (COPD) is characterised by progressive non-reversible airway obstruction, with structural and functional changes in the lungs and other organs. It results in a disabling symptom complex of breathlessness, reduced exercise capacity, fatigue, muscle wasting and disturbances in sleep and mood (2). In 2008, more than 3 million people died of COPD, accounting for nearly 6% of all deaths, making it the fourth leading cause of death. Moreover, the problem is increasing, and it is expected to become the third leading cause of death by 2025 (3).

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) has made great inroads into increasing the awareness and decreasing the burden of COPD, by promoting effective prevention and management. Much has changed since its inception in 1998 and the publication of the first GOLD report. Initially, their approach was to implement a simple staging strategy to classify disease severity based solely on lung function impairment using the forced expiratory volume in 1 second (FEV₁). It was assumed that most patients followed a simple path of disease progression in which the severity in airflow limitation reflected disease severity. However, lung function is only moderately related to disease burden in COPD (4), which meant that a revised version was needed (GOLD update 2013).

The new GOLD classification incorporates both the severity of symptoms and the number of exacerbations, and allocates patients to groups A–D based on risk (airflow limitation and number of admissions or exacerbations) and symptom scores (Clinical COPD Questionnaire [CCQ], Modified Medical Research Council Dyspnea Scale [mMRC], or COPD Assessment Test [CAT]) (see Figure 1).

Interestingly, GOLD group D is notable for combining high risk with a high symptom score, encompassing former GOLD III or IV patients (severe airflow limitation). Moreover, group D is especially prevalent in primary care, with unpublished data from the Groningen integrated care system, the Asthma/COPD Service (Certe AC Service), showing that 25% of patients with COPD meet the criteria for GOLD group D. Despite such empirical evidence, studies in this particular cohort are scarce.

In 2005, the integrated AC Service care system was developed by Certe in the north of the Netherlands in an effort to provide expert specialist diagnosis and treatment advice for primary care physicians.
This service strongly adheres to the World Health Organization definition of integrated care as ‘a concept bringing together inputs, delivery, management and organization of services related to diagnosis, treatment, care, rehabilitation and health promotion’. It is a means of improving access, quality, user satisfaction, and efficiency in services (5), and its effectiveness can be demonstrated by decreased exacerbation rates (6–8). The Certe AC Service is an expert-supported integrated care system initiated in primary care to provide standardised diagnostic support and advice from secondary care (pulmonologists) that is then fed back to primary care.

![Gold D in primary care](image)

Patients seen by the Certe AC Service are typically reviewed annually. A trained nurse takes the patient’s history, performs lung function tests (including reversibility), and evaluates their inhaler technique, before sending the data to one of thirteen participating pulmonologists. A pulmonologist then makes a diagnosis and provides treatment advice, which may include formal referral to the pulmonologist and/or control visits by the Certe AC Service. The lung function data, diagnosis and treatment advice are then returned to the General Practitioner (GP) using an electronic support system based on guidelines from the Dutch College of General Practitioners (NHG). All data produced by the Certe AC Service is transparent and available to relevant care providers.
The Certe AC Service evaluated 11,473 unique patients in the north of the Netherlands between April 2007 and December 2012 (9). Published data has shown improvements in the health statuses of patients with COPD following intervention by the Certe AC Service that led to a change in medication (10); additionally, it has shown a stabilising effect on the health statuses of those where a change in medication was unnecessary. Some 29% of COPD patients that entered the Certe AC Service with one or more exacerbation in the preceding year had fewer exacerbations the year following (10). However, publications from other integrated care systems have failed to show similar effects (11, 12).

Previously, we reported that 23% of GOLD D patients in the Certe AC Service did not use pulmonary medication at baseline, indicating significant undertreatment (13). However, since very little is known about this group in primary care, the optimal treatment remains unclear. By assessing patient characteristics and evaluating their treatment over a prolonged period, it is hoped that we can validate the GOLD patient classification and improve patient-centred management. Important factors will undoubtedly include adequate pharmacological treatment, optimising inhalation techniques and encouraging smoking cessation. Indeed, the use of adequate medication is expected to improve both symptoms and exacerbation rates, with the latter being particularly important given that subsequent hospitalisation negatively influences health status, quality of life, lung function, mortality, and health care costs (6, 14–18).

In recent years, there has been a great interest in identifying COPD phenotypes, with a plethora of publications and reviews (19–24). Han et al define a clinical COPD phenotype as disease attributes that describe differences between individuals that relate to clinically meaningful outcomes, such as symptoms, exacerbations, response to therapy, and rate of disease progression or death (25). Their definition suggests that validation of a proposed phenotype is essential. Examples of recently described phenotypes include frequent exacerbators (26, 27), patients with rapid decline in FEV₁ (28, 29), patients with low body mass index (BMI) (30), and those with poor exercise capacity (31). However, despite the significant number of studies identifying possible phenotypes, most have not been validated. Indeed, only the frequent exacerbator phenotype has been adequately validated to date, being associated with rapid deteriorations (32) and reduced effectiveness of some drugs (27).
The Certe AC Service has a patient population that is comparable with that in primary care in the Netherlands (33), and the prevalence of asthma and COPD in the Netherlands is comparable with that in neighbouring countries (34). However, to assess whether the classification system is valid on a broader scale (i.e., generalizable) a multinational dataset is needed. Therefore, we intend to use the database of the Uncovering and Noting Long-term Outcomes in COPD to Enhance Knowledge (UNLOCK) initiative. This has established a common international dataset encompassing diagnostic and follow-up data related to COPD management in primary care. Currently, it includes databases from the United Kingdom, the Netherlands, Sweden, Norway, Spain, Belgium, Greece, Ukraine, Canada and Australia (35), with approximately 90,000 records of patients with COPD or asthma (as of March 2013). We will compare the data from the current study with the primary care COPD data from the UNLOCK initiative.

We intend to complete a 12-month observational study of GOLD D patients receiving integrated care in the Certe AC Service in two work packages. The aim is to provide information about the specific phenotypes identified in our database together with the factors associated with improved health and reduced exacerbation rates. We hypothesise that accurate treatment of GOLD D patients in an integrated primary care system will improve patient outcomes by 12 months.
2. OBJECTIVES

2.1 Work package 1

We will describe and compare the characteristics (age, gender, smoking status, medication use, and comorbidities) of group D patients with those of groups A, B and C, and assess the wider applicability (representativeness) of group D using the database of the UNLOCK initiative (35).

Primary objective: We aim to describe the baseline characteristics of GOLD D patients in the primary care setting.

Secondary objectives:

- We will compare the baseline characteristics of GOLD D patients with those of GOLD group A, B, and C patients.
- We will compare GOLD D patients as assessed using either CCQ $\geq 1$ or CAT $\geq 10$ criteria.
- We will evaluate how representative the Certe AC Service patients are of the wider COPD population by comparing their characteristics with those of patients in the UNLOCK initiative.

2.2 Work package 2

Work package 2 will evaluate the health statuses and exacerbation rates among GOLD D patients after treatment in the Certe AC Service for 12 months. This work package focusses on validating the phenotypes associated with clinically relevant improvements in health status, exacerbations, health care costs and medication use. We will use typical care data for GOLD group A, B and C patients for comparison.

Primary objective: We aim to identify the difference in health status between baseline and final follow up at 12 months, as measured by the CCQ and CAT.

Secondary objectives:

- We aim to identify the patient characteristics associated with changes in quality of life, thereby seeking to validate the known patient phenotypes, such as frequent exacerbators, patients with rapid decline in FEV1, patients with low body mass index, and those with poor exercise capacity.
• We will compare the following variables between the year preceding the study and the study period:
  
  o Differences in exacerbation rates;
  
  o Differences in health care costs;
  
  o Differences in medication use; and
  
  o Differences in patient characteristics between gold D and gold a, b and c patients.

• Using data based on their usual care, we also aim to identify the characteristics of patients that change classification within the study period, as follows:
  
  o Those changing from GOLD D to another GOLD group (A, B, or C) versus those that remain unchanged, and;
  
  o Those changing from GOLD group A, B or C to another GOLD group versus those that remain unchanged.
3. STUDY DESIGN

We plan to conduct a two-part observational study of patients with COPD, with a focus on validating the GOLD D classification and known phenotypes. First, we will perform a cross-sectional analysis of the baseline characteristics of GOLD A–D patients (work package 1). Second, we will conduct a prospective cohort study to assess the effects of Certe AC Service interventions (work package 2). A flow diagram of the study is summarised in Figure 2.

![Flow diagram of the study](image)

**Figure 2: Overview of the planned study implementation according to the two work packages**

GOLD A, B, C and D patients are included at baseline. The numbers provided in the first (blue) column refer to the expected number of patients during the 16-month inclusion period. Group D patients will be entered in the follow-up study (pink columns). There will be assessments at 6 and 12 months, and short phone interviews at 3 and 9 months. At 12 months, usual care data for groups A, B and C will be provided by Certe. Work package 1 = blue; work package 2 = pink

This study will be conducted in Groningen, The Netherlands, and managed by the Department of General Practice (part of the Groningen Research Institute for Asthma and COPD, University Medical Center Groningen, University of Groningen, The Netherlands) and the local Certe laboratory (Damsterdiep 191, 9713 EC Groningen, The Netherlands). Certe will be responsible for providing the patients and performing measurements, while the Department of Primary Care will manage all other aspects of the study. General practitioners involved in pulmonary screening as part of the Certe AC
Service will be contacted, informed about the study, and their consent gained. After their consent, patients diagnosed with COPD at baseline will be asked to participate and their consent will be obtained prior to inclusion. All consenting patients will then be entered into work package 1 and their baseline data obtained. GOLD D patients are eligible for participation in work package 2, they will be informed of this and asked to participate in this 1-year follow-up study.

The first follow-up visit is planned for 6 months after study inception, and the final visit at 12 months. Furthermore, short phone interviews lasting 5–10 minutes will take place at 3 and 9 months, focussing on health care costs using a validated questionnaire. Although the baseline and final visits are largely based on standard Certe procedure, visit 1 and the phone interviews are not, and have been specifically added for study. At 12 months, Certe will provide usual care data for the participants of groups A, B and C.
4. STUDY POPULATION

4.1 Inclusion criteria

To be eligible for inclusion in this study, participants must meet the following criteria:

- Age > 40 (all patients)
- Diagnosed COPD (work package 1)
- Diagnosis compatible with GOLD D classification (work package 2)

4.2 Exclusion criteria

Any participants who meet the following criteria will be excluded from this study:

- Asthma diagnosis, asthma/COPD overlap syndrome or other respiratory illnesses
- Inability to complete questionnaires due to language or cognitive difficulties

4.3 Sample size calculation

The minimal clinically relevant difference in the CCQ and CAT scores after 12 months is the primary outcome of the study. We will need 51 patients to achieve a power of 0.8 at the 5% significance level ($\alpha = 0.05$) given a minimal clinically relevant difference in the CCQ of 0.4 and a standard deviation (SD) of 0.9. We will need 43 patients to achieve a power of 0.8 at the 5% significance level ($\alpha = 0.05$) given a minimal clinically important difference in the CAT of 2 and a published SD of 7.4. Adjusting the higher number of 51 to allow for potential attrition of 10% over 1 year, we aim to include 56 patients that meet the criteria for the GOLD group D phenotype.

Given that the Certe AC Service manages 84 GOLD D patients per year, and anticipating that 50% of those patients will be unwilling to participate, we intend to allow a 16-month inclusion period.
5. METHODS

5.1 Study parameters/endpoints

5.1.1 Main study parameter/endpoint

The main outcomes are as follows:

- The baseline characteristics of GOLD D patients in the primary care setting, to include age, gender, lung function (FEV₁, forced expiratory ratio [FER], reversibility), smoking status, comorbidities, CCQ score, mMRC score, medication use and health care usage.

- The difference in health status between baseline and final follow up at 12 months, as measured by the CCQ and CAT.

5.1.2 Secondary study parameters/endpoints

The secondary outcomes are as follows:

- The baseline characteristics of GOLD D patients compared with those of GOLD group A, B, and C patients; these will include age, gender, lung function (FEV₁, FER and reversibility), smoking status, comorbidities, CCQ scores, mMRC scores, medication use and health care usage.

- The numbers of GOLD D patients with a CCQ ≥ 1 or a CAT ≥ 10.

- How representative the sample is of the wider population will be measured by comparison of patient characteristics between the Certe AC Service and UNLOCK initiative, including age, gender, lung function (FEV₁, forced expiratory ratio [FER], reversibility), smoking status, comorbidities, CCQ score, mMRC score, medication use and health care usage.

- The patient characteristics associated with changes in quality of life (measured by Quality-adjusted life years [QALYs]). These will be compared to those in known patient phenotypes (such as the frequent exacerbators), thereby validating or discounting those phenotypes.
Differences in exacerbation rates, health care costs (via the Trimbos/iMTA Questionnaire for Costs associated with Psychiatric Illness [TiC-P]), medication use (dose and frequency), and patient characteristics (age, gender, lung function (FEV₁, FER, reversibility), smoking status, comorbidities, CCQ score, mMRC, medication use and health care use) between gold d and gold a, b, and c patients.

Any change in GOLD classification, as defined via established GOLD criteria.

5.2 Study procedures

- An overview of when the different assessments will take place is provided in Table 1.

<table>
<thead>
<tr>
<th></th>
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<th>6 month follow up</th>
<th>9 month phone interview</th>
<th>12 month follow up</th>
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<td>History (including smoking status)</td>
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<td>Spirometry (FEV₁, FER)</td>
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<tr>
<td>Reversibility</td>
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<tr>
<td>CCQ *</td>
<td>X</td>
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<td></td>
<td>X</td>
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<tr>
<td>CAT</td>
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<td>ACQ</td>
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<td>Exacerbations *</td>
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<td>Full blood count</td>
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Table 1: Overview of the different assessments at baseline and follow up

* Also available for groups A, B and C at 12 months from usual care.

- Comorbidity will be measured with the Charlson Comorbidity Index.
- History assessments will clarify age of COPD onset, family history, smoking status, current and past symptoms and symptoms provoked by stimuli.
- Spirometry will be used to assess the following parameters: FEV₁, FEV₁% predicted, FVC, FVC% predicted, and reversibility (after 400 mg salbutamol).
• We will collect the type of medication used, the daily dose, the device used and adherence when assessing general medication use. The information will be gathered through the GP database. In case of missing data, the local pharmacy will be requested to provide additional information.

• Health status will be assessed via three questionnaires: the CCQ (36), the CAT (37) and the Asthma Control Questionnaire (ACQ) (38).

• Inhaler technique will be assessed according to the Certe AC Service protocol.

• QALYs will be calculated using the EQ-5D.

• Full blood counts taken will focus on the eosinophil and neutrophil counts.

• Health care costs will be measured with an adapted version of the TiC-p questionnaire covering the direct health care costs of primary and secondary health care usage, medication costs and indirect costs related to lost work.

• Exacerbations will be defined as any worsening of the patient's symptoms from his or her usual stable state, beyond normal day-to-day variations, and that warrants additional treatment. The treatment should consist of either oral corticosteroids, antibiotics, or hospital admission. This data will be based on personal recall.

5.3 Withdrawal of individual participants

If they wish to do so, participants can leave the study at any time, for any reason, and without any consequences. Participants may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow up for any other reason.

5.4 Follow up of participants who are withdrawn from treatment

If premature withdrawal occurs for any reason, the investigator will ask the patient to provide a reason for the premature withdrawal and record this information.
6. SAFETY REPORTING

6.1 Section 10 WMO-reportable event

In accordance to Section 10, Subsection 1, of the WMO (Medical Research Involving Human Subjects Act, 1998), the investigator will inform the participants and the reviewing accredited medical research ethics committee (METC) if anything occurs where the disadvantages of continued participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardise the health of the participants. The investigator will take care that all participants remain informed. As this is a non-interventional observational study of current best practice in our region, no such events are anticipated. However, any treatment related event will be reported in line with the appropriate guidelines.

6.2 Adverse events and serious adverse events

6.2.1 Adverse events

Adverse events (AEs) are defined as any undesirable experience occurring to a participant during the study, whether or not they are considered related to the study. All AEs reported spontaneously by the participant or observed by the investigator (or his or her staff) will be recorded.

6.2.2 Serious adverse events

A serious adverse event (SAE) is any untoward treatment-related occurrence or effect with the following consequences:

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatient hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;
- or, any other important medical event that may not result in death, be life threatening, or require hospitalisation, may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardise the participant or may require an intervention to prevent one of the outcomes listed above.

The sponsor will report SAEs through the web portal ToetsingOnline to the accredited METC that approved the protocol, within 15 days after the sponsor has first knowledge of the SAE.

SAEs that result in death or that are life threatening will be subject to expedited reporting. The preliminary report will be provided no later than 7 days after the responsible investigator has first knowledge of the adverse event, with another 8 days allowed for completion of the full report.

6.3 Follow up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures, as appropriate, and/or referral to a general physician or medical specialist.
7. STATISTICAL ANALYSIS

7.1 Work package 1

Description of the baseline characteristics of group D as well as those of groups A, B and C will be based on descriptive statistics. Means and SDs will be used for normally distributed continuous variables and medians and interquartile ranges for ordinal and non-normally distributed continuous variables. Differences between the Certe AC Service cohort and the UNLOCK cohort will be tested using independent t-tests for continuous variables, the Mann–Whitney U test for ordinal and continuous variables (if assumptions were violated), and the Chi-square test for dichotomous variables.

7.2 Work package 2

The difference in health status between baseline and 12 months will be tested using paired t-tests in case of continuous variables or the Wilcoxon signed rank test for ordinal or continuous variables when assumptions were not met. Identifying patient characteristics associated with changes in quality of life will be based on linear regression modelling using change scores as dependent variable and a backward Wald procedure (P-in: 0.2 and P-out: 0.05) to develop the final prediction model. Selection of potential factors will be based on literature and univariate association between each individual baseline characteristic and change score with $P < 0.2$ as the selection criterion.

Differences in number of exacerbations, health care costs and medication use between the year preceding the study and the study period will be analysed by paired t-tests or Wilcoxon signed rank tests, as appropriate. Identifying patient characteristics that dissociate between patients who change from group D to A, B or C within the study period and patients that remain in group D will be performed by comparing the baseline characteristics of 2 groups with an independent t-test, Mann–Whitney U test or Chi-square, as appropriate. This will be evaluated using similar methodology with usual care data for patients in GOLD groups A, B and C. For all analyses $P < 0.05$ will be considered statistically significant.
8. ETHERAL CONSIDERATIONS

8.1 Regulation statement

This clinical study was designed and shall be implemented and reported in accordance with the ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations, and with the ethical principles laid down in the Helsinki Declaration of 1975, as revised in 2000, 2008 and 2013.

8.2 Recruitment and consent

Recruitment starts with contacting general practitioners that are already involved with the Certe AC service. They will be informed about the study, and asked for permission to contact their patients. After their consent, patients diagnosed with COPD at baseline will be asked to participate. Patient information will be included in the invitation for the Certe AC service that is sent by the GP. During the visit to the Certe AC service the lung function analyst will answer any question from the eligible participants. Their consent will be obtained prior to study inclusion. All consenting patients will then be entered into work package 1 and their baseline data obtained. GOLD D patients are eligible for participation in work package 2, they will be informed of this and asked to participate in this 1-year follow-up study. Eligible patients may only be included in the study after providing written, informed consent approved by the relevant institutional review board or independent ethics committee. Where required by law or regulation, this will also be witnessed. The participant will indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (i.e., any procedure described in this protocol). The process of obtaining informed consent will be documented in the patient source documents.

8.3 Compensation for injury

The sponsor has a liability insurance.
9. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

9.1 Handling and storage of data and documents

Data will be handled by Certe and anonymised. The data key will be safeguarded by Certe and kept securely on their premises. The anonymous, coded data will then be provided to the Department of Primary Care for statistical analysis. Data codes will not be based on either the patient initials or their birth date. The handling of personal data will comply fully with the Dutch Personal Data Protection Act.

9.2 Amendments

Amendments may be made to the research after agreement from the accredited METC has been given. All amendments will be notified to the relevant METC.

9.3 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC annually. Information will be provided on the date of inclusion of the first participant, the number of participants included and that have completed the trial, the number and details of AEs and SAEs, other problems, and any amendments.

9.4 End of study report

The investigator will notify the accredited METC of the end of the study within 8 weeks of completion. The end of the study is defined as the completion of the last patient’s last follow-up visit. If the study is ended prematurely, the investigator will notify the accredited METC within 15 days, including the reasons for the premature termination. Within one year of the study ending, the investigator/sponsor will then submit a final study report with the results of the study, including any publications/abstracts, to the accredited METC.
9.5 Public disclosure and publication policy

9.5.1 Congress plans

1. European Respiratory Society Annual Congress 2016 – abstract: *An Observational Study of GOLD D Patients in Primary Care*


9.5.2 Publication plans

1. *An Observational Study of GOLD D Patients in Primary Care* will be submitted to the *International Primary Care Respiratory Journal (IPCRJ, Q1 journal)*

2. *A Prospective Observational Study of GOLD D Patients in an Integrated Care System* will be submitted to *Chest (Q1 journal).*
10. REFERENCES


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