Patient Heterogeneity in Health Economic Decision Models for Chronic Obstructive Pulmonary Disease
Are Current Models Suitable to Evaluate Personalized Medicine?

Hoogendoorn, Martine; Feenstra, Talitha L.; Asukai, Yumi; Briggs, Andrew H.; Borg, Sixten; Dal Negro, Roberto W.; Hansen, Ryan N.; Jansson, Sven Arne; Leidl, Reiner; Risebrough, Nancy; Samyshkin, Yevgeniy; Wacker, Margarethe E.; Rutten-van Mölken, Maureen P M H

Published in:
Value in Health

DOI:
10.1016/j.jval.2016.04.002

2016

Document Version:
Peer reviewed version (aka post-print)

Link to publication

Citation for published version (APA):

Creative Commons License:
CC BY-NC-ND

General rights
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

• Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
• You may not further distribute the material or use it for any profit-making activity or commercial gain
• You may freely distribute the URL identifying the publication in the public portal

Take down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.
Patient heterogeneity in health economic decision models for chronic obstructive pulmonary disease (COPD): are current models suitable to evaluate personalized medicine?

Running title: patient heterogeneity in COPD models

Martine Hoogendoorn ¹, Ph.D.
Talitha L. Feenstra ², ³, Ph.D.
Yumi Asukai ⁴, M.Sc.
Andrew H. Briggs ⁵, DPhil.
Sixten Borg ⁶-⁸, M.Sc.
Roberto W. Dal Negro ⁹, MD, Ph.D.
Ryan N. Hansen ¹⁰, Pharm.D., Ph.D.
Sven-Arne Jansson ¹¹, Ph.D.
Reiner Leidl ¹², Ph.D.
Nancy Risebrough ¹³, Ph.D. ?
Yevgeniy Samyshkin ⁴, M.Sc.
Margarethe E. Wacker ¹², M.Sc
Maureen P.M.H. Rutten-van Mölken ¹, Ph.D.

¹ Institute for Medical Technology Assessment (iMTA), Erasmus University Rotterdam, Rotterdam, The Netherlands
² Department for Prevention and Health Services Research, National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands
³ Department of Epidemiology, University Medical Centre Groningen, Groningen, The Netherlands
⁴ IMS Health, Health Economics and Outcomes Research and Real-World Evidence Solutions, London, UK
⁵ Institute of Health & Wellbeing, University of Glasgow, Glasgow, UK
⁶ The Swedish Institute for Health Economics, Lund, Sweden
⁷ Health Economics Unit, Department of Clinical Sciences in Malmö, Lund University, Sweden
⁸ Evidera, London, UK.
9 National Center for Respiratory Pharmacoconomics and Pharmacoepidemiology (CESFAR), Verona, Italy.
10 Pharmaceutical Outcomes Research and Policy Program, School of Pharmacy, University of Washington, Seattle, WA, USA
11 Department of Public Health and Clinical Medicine, Occupational and Environmental Medicine, The OLIN Unit, Umeå University, Umeå, Sweden
12 Helmholtz Zentrum München, Institute of Health Economics and Health Care Management, Member of the German Center for Lung Research, Comprehensive Pneumology Center Munich, Neuherberg, Germany
13 ICON Health Economics, Toronto, Canada

Correspondence and request for reprints:
Martine Hoogendoorn
Institute for Medical Technology Assessment
Erasmus University Rotterdam,
P.O. Box 1738
3000 DR Rotterdam
The Netherlands
Phone: *31 10 4088871
Email: hoogendoorn@imta.eur.nl

Acknowledgements/Financial support
This study was financially supported by Boehringer Ingelheim International, GlaxoSmithKline The Netherlands, Novartis International and Takeda Pharmaceuticals International

Key words:
COPD, model, patient heterogeneity, validation

Patient heterogeneity in health economic decision models for chronic obstructive pulmonary disease (COPD): are current models suitable to evaluate personalized medicine?
Abstract

Objectives: To assess how suitable current COPD cost-effectiveness models are to evaluate personalized treatment options for COPD by exploring the type of heterogeneity included in current models and by validating outcomes for subgroups of patients.

Methods: A consortium of COPD modelling groups completed three tasks. First, they reported all patient characteristics included in the model and provided the level of detail in which the input parameters were specified. Second, groups simulated disease progression, mortality, quality-adjusted life-years (QALYs) and costs for hypothetical subgroups of patients that differed in terms of gender, age, smoking status and lung function (FEV\textsubscript{1}% predicted). Finally, model outcomes for exacerbations and mortality for subgroups of patients were validated against published subgroup results of two large COPD trials.

Results: Nine COPD modelling groups participated. Most models included gender (seven), age (nine), smoking status (six) and FEV\textsubscript{1}% predicted (nine), mainly to specify disease progression and mortality. Trial results showed higher exacerbation rates for females (found in one model), higher mortality rates for males (two models), lower mortality for younger patients (four models), and higher exacerbation and mortality rates in patients with severe COPD (four models).

Conclusions: The majority of currently available COPD cost-effectiveness models are able to evaluate the cost-effectiveness of personalized treatment based on gender, age, smoking and FEV\textsubscript{1}% predicted. Treatment in COPD is however, more likely to be personalized based on clinical parameters. Two models include several clinical patient characteristics and are therefore most suitable to evaluate personalized treatment, although some important clinical parameters are still missing.
Introduction

Personalized medicine has the potential to improve the (cost-)effectiveness of treatments and contribute to health care cost containment. Hence, interest in personalized medicine has increased exponentially in the past decade [1]. The concept of personalized medicine has different definitions [2, 3]. Some definitions focus on the use of genetics, proteomic, cytomic and/or metabolic biomarkers to define patient geno- and phenotypes most likely to benefit most from a certain treatment. Other definitions are broader and refer to customizing treatment to the individual characteristics, needs, and preferences of a patient during all stages of care, including prevention, diagnosis, treatment, and follow-up [3]. The expectations of personalized medicine are high, but so far, cost-effectiveness of such technologies on average has not been found to be any better than that of non-personalized interventions [4, 5]. Thus, economic evaluation studies are needed to show whether the personalized approach indeed leads to greater efficiency in health care compared to the one size fits all approach. If based on health economic models, such economic evaluations of personalized treatment strategies based on demographic and clinical patient characteristics, require models that are able to address the heterogeneity due to those patient characteristics appropriately. However, the majority of currently available cost-effectiveness models are cohort Markov or state-transition models that have only limited capability for addressing patient heterogeneity. The majority of published cost-effectiveness analysis similarly focused on results for the average patient. Current guidelines for health economic modelling recognize the importance of patient heterogeneity, but there is a lack of consensus on how to best address this in a modelling framework [6].

One of the major chronic diseases for which treatment is increasingly personalized is chronic obstructive pulmonary disease (COPD). In 2011 the new Global initiative for Obstructive Lung Disease (GOLD) guidelines proposing a new classification system for COPD patients based on lung function, symptoms and exacerbations. Although this new classification is a step forward to personalized treatment for COPD, proposed treatment guidelines for the subgroups of patients still need to be validated [7]. Manufacturers of drugs and devices focus are increasingly focused on specific phenotypes of patients, such as the patients with frequent exacerbations, a rapid decline in lung function, persistent systemic inflammation, raised eosinophil concentrations, bacterial colonization etc [8, 9]. In addition, caregivers providing multidisciplinary integrated care programs develop different treatment modules for subgroups of patients who need physical reactivation,
smoking cessation support, nutritional interventions, treatment of depression etc. In contrast, the majority of decisions about the reimbursement of new treatments is still made for large groups of patients and based on evaluations that do not consider patient heterogeneity. This is expected to change rapidly because biologics for COPD are under development [10] and payers are likely to limit the reimbursement of these expensive drugs to specified subgroups. Moreover, new drugs for COPD that have recently been launched or are still under development are often quite similar to the currently marketed drugs which makes it increasingly difficult to demonstrate their value for money, unless one can specify the subgroup for which they are particularly beneficial.

In the past years several health economic decision models for COPD have been published. In 2011 our modelling group took the initiative to establish a network of people involved in COPD modelling around the world (COPD modelling teams, pharmaceutical companies interested in COPD modelling, epidemiologists, clinicians etc). Up to now, we have organized three one-day meetings in 2011, 2012 and 2014 with the aim to compare the different available models with respect to model structure and input parameters and to cross validate the models against each other [11]. Proceedings of the third meeting regarding patient heterogeneity are described in the current paper.

The aim of the paper is to assess how suitable current models are to evaluate the cost-effectiveness of personalized treatment options for COPD. Firstly, we explored which type of patient heterogeneity is included in currently available COPD cost-effectiveness models to see whether the models are able to evaluate subgroups of COPD patients that are considered clinically relevant. Second, we investigated the impact of patient characteristics on the outcomes. Finally, we validated the outcomes of specific subgroup analyses with the models against subgroup results of clinical trials to assess whether the models are suitable for performing subgroup analyses. These questions are relevant because most of the models are initially built to evaluate treatment options for a large group of COPD patients.

Methods

Procedure

In March 2014 the COPD modelling groups that participated in previous meetings as well as new groups identified through publications or other participants within the network were contacted to
explore their interest in participation in the third COPD modelling meeting and in running the model simulations required for this heterogeneity analysis. Modelling groups were first asked to specify which patient characteristics are currently included in their model and which input parameters are specified by subgroup. Second, they were asked to run their model for hypothetical patients that differed in terms of patient and disease characteristics to explore the impact of these characteristics on the outcomes of the models. Third, they were asked to simulate the outcomes for subgroups of patients that had similar characteristics as the subgroups of two large randomized controlled clinical trials to validate the model outcomes. Results were returned to the organizers of the meeting in a structured format in Microsoft Excel two weeks before the meeting. The combined results of the models were circulated to all participants of the COPD modelling meeting one week before the meeting to give participants time to reflect on the outcomes. The results were presented during the meeting and explanations for the differences in outcomes between the models were discussed.

**Participating models**

Nine different COPD models participated in the model simulations. Six of these nine models also participated in the previous meeting in 2012 [12-17]. A short description of these six models can be found in the publication about the proceedings of this second COPD modelling meeting [11]. Three new models also participated. The simulation model of Asukai et al was published in 2013 [18]. The other two models have not yet been published, but have been presented at international conferences. The model of Briggs et al (GALAXY COPD model) was presented at the ISPOR Annual International meeting 2013 and the ISPOR 17th Annual European Congress 2014 [19, 20]. The model of Dal Negro et al was also presented at the ISPOR 17th annual European Congress 2014 [21].

**Content of the modelling challenge**

For the first part of the modelling challenge groups reported all patient characteristics that are currently included in their models. Furthermore, groups provided the level of detail in which the following input parameters had been specified in the models: disease progression, exacerbation frequency, mortality, case-fatality of an exacerbation, utilities during stable disease, utilities during exacerbations, maintenance costs and exacerbation-related costs.
In part two, modelling groups simulated the outcomes for hypothetical subgroups of patients that differ in terms of gender, age, smoking status and level of FEV$_1$% predicted to see how patient heterogeneity affected effects and costs within one model and between models. Gender, age, smoking status and FEV$_1$% predicted were chosen because these are the factors that are included in most models (Table 2). In the first simulation, outcomes for a 65-year old, ex-smoking, male patient with severe COPD were calculated. In each of the following four simulations one of the patient characteristics was changed: female instead of male patient, 75-year old instead of 65-year old patient, smoking instead of ex-smoking patient and patient with moderate COPD instead of severe COPD. The outcomes of each of these four simulations were compared with the results of the first simulation.

In part three, the validity of the subgroup analyses with the models was investigated by comparing the model outcomes against published subgroup results of two large randomized controlled clinical trials, the four-year UPLIFT trial and the three-year TORCH trial [22, 23]). In the UPLIFT trial almost 6000 patients with moderate-to-very severe COPD were randomized to placebo, defined as all regular respiratory medication except inhaled anticholinergics, or tiotropium 18 µg plus all regular respiratory medication except other inhaled anticholinergics [22]. In the TORCH trial slightly more than 6000 patients with moderate-to-very severe COPD were randomized to placebo, defined as all COPD medications except for long-acting bronchodilators and inhaled corticosteroids, salmeterol 50µg, fluticasone 500 µg or the combination of salmeterol 50 µg and fluticasone 500 µg [23]. For both the UPLIFT and the TORCH trial several subgroup analyses have been published mainly by gender, age, smoking status and level of FEV$_1$% predicted [24-27]. The modelling groups were asked to adjust the starting population of the model to the baseline characteristics of the specific subgroups within the placebo group of the trial in terms of percentage of males, mean age, percentage current smokers and mean FEV$_1$% predicted (or distribution over the GOLD severity stages moderate, severe or very severe COPD). The baseline characteristics of the subgroups in the trial are given in Table 1. For comparison with the UPLIFT placebo arm, groups were asked to run the simulations assuming that patients received all regular respiratory medication except for inhaled anticholinergics. Simulation of the TORCH placebo arm was done assuming that patients did not use long-acting bronchodilators and/or inhaled corticosteroids.
Outcomes

For part two of the challenge, the following outcomes were reported: disease progression defined as decline in lung function, mortality, quality-adjusted life years per patient, and total costs per patient. These outcomes were calculated for both one-year and lifetime horizons. For part three of the challenge, the total number of exacerbations per patient-year and all-cause mortality were calculated including the uncertainty around the outcomes if possible. The time horizon of the model simulations was similar to the duration of the clinical trials: three years for the TORCH trial and four years for the UPLIFT trial.

Results

Table 2 shows the patient characteristics included in the nine participating cost-effectiveness models. The majority of models include gender, age, smoking status and FEV$_1$% predicted. Newer models also included patient characteristics such as previous exacerbations, BMI and co-morbidities (Asukai_simulation model, Briggs). Table 3 shows the level of specification for the most important input parameters. The level of detail in which the input parameters are specified varies greatly between the models. Table 4 shows the results for the model simulations of hypothetical patients that differ in terms of gender, age, smoking status and FEV$_1$% predicted. The validation of subgroup analysis in the models against the outcomes of the subgroup analyses in the clinical trials is presented in figures 1 to 4. Below, the results will be discussed separately for the four patient characteristics that most of the models have in common: gender, age, smoking status and FEV$_1$% predicted. For each characteristic we first present the results for the simulations of hypothetical patients followed by the simulations of the subgroups in the clinical trials.

Gender

Seven models included gender as patient characteristic (Asukai_Markov, Asukai_simulation, Briggs, Dal Negro, Hoogendoorn, Samyshkin and Wacker). Gender was mainly included to specify disease progression (six models) and mortality (six models) (Asukai_Markov, Asukai_simulation, Briggs, Dal Negro, Hoogendoorn, Samyshkin) (Table 3). Results of the comparison of hypothetical subgroups of
patients showed however, that three of the models that included gender reported a disease progression rate that was similar for males and females (Asukai_Markov, Dal Negro, Hoogendoorn) (Table 4), while three models had faster disease progression rates for females (Asukai_simulation, Briggs, Samyshkin). Five models had a higher one-year mortality rate for male patients compared to female patients (Asukai_markov, Asukai_simulation, Brigs, Hoogendoorn, Wacker), while in one model mortality in males and females was comparable (Samyshkin). A few models specified utilities during stable disease and/or COPD-related maintenance costs by gender (Table 3) (Asukai_simulation, Briggs, Hoogendoorn). The simulation model of Asukai et al specifying utility weights by gender reported a lower number of QALYs for a female compared to a male patient, despite a lower female mortality, while the model of Briggs et al had a slightly higher number of QALYs for females. Of the two models specifying maintenance costs by gender one used higher costs for females (Hoogendoorn), while the other model (Briggs) included lower costs for females compared to males. Validation of the model results with respect to gender against empirical data showed that in the UPLIFT study male patients had less exacerbations (RR=0.89 (95% CI: 0.81; 0.98)) compared to female patients, while this was only found in the model of Briggs (Figure 1A). The other models reported rates equal for females and males. Four-year all-cause mortality in the UPLIFT trial was reported to be higher for males (RR=1.49 (95% CI: 1.21;1.84)), which was found in two models (Hoogendoorn and Wacker) (Figure 1B).

Age

All nine participating models included age as characteristic mainly to specify disease progression (seven models) and mortality (nine models). In one model, disease progression was lower for a 75-year old compared to a 65-year patient (Asukai_Markov). In the models of Dal Negro and Hoogendoorn disease progression increased with increasing age, while in the remaining models disease progression was about equal for both ages (Table 4). In all models one-year mortality was higher for a 75-year old compared to a 65-year old (1.5-3.3 times higher). Only one model reported higher QALYs for an older patient (Briggs). Three of the four models that specified costs by age (Briggs, Dal Negro, Hoogendoorn and Wacker) reported higher costs for an older patient (Briggs, Dal Negro and Hoogendoorn). Validation of the model results with respect to age against the outcomes of the UPLIFT study showed that in all models except one, the exacerbation rate in the subgroup of
patients younger than 50 years was equal to the rate in the total population (mean age 65 years), which was in accordance with the trial results (Figure 2A). Only in the model of Briggs the subgroup of patients below 50 years of age had a significantly lower exacerbation rate compared to the total population. In the subgroup of younger patients in the UPLIFT study four-year all-cause mortality was significantly lower compared to the total population (RR=0.43 (95% CI: 0.25; 0.74), which was also found in four models (Briggs, Hansen, Hoogendoorn, Wacker) (Figure 2B).

Smoking status
Six of the nine models included smoking status as patient characteristic (Asukai_Markov, Asukai_simulation, Briggs, Hansen, Hoogendoorn and Wacker). In all six models disease progression was specified by smoking status (Table 3) as smokers having a higher disease progression compared to ex-smokers (Table 4). Three models specified mortality by smoking status (Briggs, Hoogendoorn, and Wacker). One-year mortality in these models was higher for smokers (Table 4). Only in the model of Briggs et al smoking status was modelled to have an association with other input parameters such as utilities and costs (Table 3). As a result, the one-year QALYs and costs were (almost) equal for a smoking compared to an ex-smoking patient in the models (Table 4). The UPLIFT study showed no difference in exacerbations between smokers and ex-smokers, which was in line with the results of most models, except for two (Briggs and Wacker) that reported a higher exacerbation rate for ex-smokers. Four-year mortality in the UPLIFT trial was also not found to be different between smokers and ex-smokers. Three models however, reported a significantly higher mortality rate for ex-smokers compared to smokers (Hansen, Hoogendoorn and Wacker), most likely because ex-smokers in the UPLIFT trial were older than the smokers and not because of their difference in smoking status. This is confirmed by Table 4, which isolates the impact of smoking status from the impact of age.

FEV1% predicted
All nine models included FEV1% predicted. In all models except the Markov model of Asukai disease progression was specified by FEV1% predicted. All models used FEV1% predicted to specify exacerbation frequency, mortality, utilities and maintenance costs. In all nine models one-year mortality and costs were lower for a patient with moderate COPD (FEV1% predicted about 65%) compared to a patient with severe COPD (FEV1% predicted about 40%), while the number of QALYs
was higher in all models (Table 4). Five models also specified utilities during exacerbations by FEV₁% predicted (Briggs, Borg, Dal Negro, Hansen, Wacker). Exacerbation costs were specified by FEV₁% predicted by four models (Briggs, Dal Negro, Hansen, Wacker) (Table 3).

Validation of the model results with respect to FEV₁% predicted against the outcomes of the three-year TORCH study showed that in three models (Borg, Briggs and Wacker) the exacerbation rate in patients with severe COPD was significantly higher than in patients with moderate COPD (Figure 4A) which was in line with the trial results. In the TORCH trial, mortality in patients with severe COPD was higher than in patients with moderate COPD (RR=1.33 ((95% CI:1.09;1.63). Four models reported a higher mortality rate in severe COPD (Borg, Hansen, Hoogendoorn and Wacker).

Discussion

By comparing patient heterogeneity in currently available COPD cost-effectiveness models this study aimed to assess how suitable current models are to evaluate the cost-effectiveness of personalized treatment options for COPD. The patient characteristics that almost all nine models included were gender, age, smoking status and FEV₁% predicted.

Results with respect to gender showed that the empirical data supported a difference in exacerbations between female and male patients. Several studies in the literature confirm that female patients have a higher exacerbation rate compared to males [28-31]. Only one of the current COPD models included this relationship. Two models reported a significantly higher mortality rate in male patients, which was also found in the UPLIFT trial. However, it should be noted that in the trial female patients were on average three years younger and had a slightly higher FEV₁% predicted, but they were also more likely to smoke. The difference in mortality is less clear from the literature. Some studies reported lower mortality rates for females [32-34], while others found no difference [35-38]. Only two models specified quality of life by gender, while several studies found a lower quality of life for female patients [39-41].

All models included a strong association between age and mortality, which was in line with studies found in the literature [32, 33, 35-38]. Validation against trial results also showed a difference in
mortality between young and old patients for the trial as well as most models. The majority of models did not specify quality of life by age, while several studies have shown that older COPD patients have lower quality of life [39, 42]. Three models specified COPD-related costs by age. Several studies investigated the association between age and COPD-related costs and found no significant impact of age on costs [43-46]. This may be because age and FEV\(_1\)% predicted are correlated and in three of these studies FEV\(_1\)% was also included in the multivariate model and found to be a significant predictor.

The impact of smoking on disease progression was included in six of the models. Smokers were modelled to have a higher disease progression compared to ex-smokers, which was in line with the literature [47-49]. Three models included a higher all-cause mortality rate for smokers compared to ex-smokers in their input data (Table 4). No difference in mortality rate between smokers and ex-smokers was found in the UPLIFT trial. Validation of model outcomes against trial results showed that three models reported a higher mortality rate for ex-smokers. This was probably because ex-smokers in the trial were on average five years older than smokers and had a lower FEV\(_1\)% predicted. Of seventeen studies on predictors of mortality found in the literature four studies found a higher mortality rate for smokers, six studies found no association and ten studies did not investigate this association.

With respect to FEV\(_1\)% predicted the models are in line with the empirical data and the literature. All models include an association between FEV\(_1\)% predicted and exacerbation frequency, quality of life, mortality and costs. In some models the differences in exacerbations and mortality are however very small and not significant due to the large uncertainty around the estimates. The literature also showed that disease progression in terms of lung function decline seems to decrease when the FEV\(_1\) decreases [47, 48, 50]. This association was not included in all models, because five of the models used the Lung Health Study as (one of the) data source(s) for disease progression, which is a study in mild-to-moderate COPD patients showing the opposite relation (decline increases when FEV\(_1\) decreases) [49]. It is not surprising that the model performance with respect to patient heterogeneity was best for FEV\(_1\)% predicted, because in almost all models the FEV\(_1\)% predicted is the key parameter. Five out of the nine models are cohort Markov models with Markov states defined
according to the 2007 GOLD classification, i.e. the severity of COPD was defined by the FEV\textsubscript{1} % predicted.

Outcomes of the different models were compared to published subgroup results of two large trials: the UPLIFT and TORCH trial. Some of the COPD models were built to extrapolate the results of clinical trials (Asukai-Markov, Samyshkin) and were populated with input data from these trials, while other models are population models using a wide range of different data sources as input (Hoogendoorn, Hansen and Wacker). For the latter models comparison with trial results may therefore be less valid because it is well known that patients included in clinical trials are a subgroup of the total COPD population. This was, for example, shown in a study of Kruis et al that found that patients participating in large clinical trials sponsored by pharmaceutical companies are on average younger, more likely to be male, have a lower FEV\textsubscript{1} % predicted and tend to have more exacerbations compared to patients in primary care [51]. In the current analysis this selection bias issue was most likely the explanation that no difference in mortality was found between smokers and ex-smokers in the UPLIFT trial. Patients who continue to smoke are probably less likely to be included in clinical studies, because they progress faster to more severe stages, have more co-morbidities and are more likely to die due to other smoking-related diseases. On the other hand, among the patients who continue to smoke despite having COPD there may be relatively more patients that are less susceptible to smoking-related diseases. The true impact of trial populations being a selective group of patients on the outcomes of this study is difficult to assess. In the current study we mainly focused on the differences in outcomes between subgroups within one model or trial and therefore the impact might be limited.

The results of this study showed that all currently available models are capable of running simulations for different age- and COPD severity classes. The majority of the models also have the ability to run analyses separately for males and females and for smokers and ex-smokers. The validity of these subgroup analyses within the models is questionable, because important input parameters have not been specified by gender, age or smoking status. For example, the specification of higher exacerbations for females or lower quality of life with older age, is not included in the majority of models. Most models are developed to evaluate treatment options for the total general COPD population or the average COPD trial population.
Although it is not unlikely that future treatment will be increasingly tailored to age, gender and smoking status, treatment is more likely to be personalized on the basis of clinical parameters especially when considering ethical debates and societal preferences. Exacerbations for example are highly associated with the number of previous exacerbations [29-31, 52]. Mortality in COPD is associated with age and FEV$_1$, but also with co-morbidities, BMI, dyspnea and several other clinical parameters [32, 34, 36, 38, 53]. BMI also seems to be associated with quality of life in COPD [39, 54] and co-morbidities may affect COPD-related costs [44, 45, 55, 56]. Only the more recently developed models of Asukai (simulation) and Briggs included these types of clinical parameters and are therefore more suitable to evaluate personalized treatment that the other models. Recent reviews on phenotyping in COPD showed that currently about four different phenotypes have been defined in COPD that may require a different treatment strategy: emphysema, COPD with chronic bronchitis, COPD combined with asthma (ACOS) and COPD with frequent exacerbations [57-60]. Information on effectiveness and cost-effectiveness of treatment options for these subgroups is needed to guide clinical guideline development and decisions for reimbursement. Three of the nine models included information on one of the phenotypes, i.e. COPD with frequent exacerbations, but none of the current models is able to evaluate treatment options for the other three phenotypes. Future models should include all clinical patient characteristics currently considered to influence disease severity, prognosis and treatment response in COPD.

The current study had some limitations. Firstly, not all models could perform uncertainty analysis around the results for exacerbations and all-cause mortality. Therefore, it was not always possible to determine whether predicted differences between subgroups are important within the range of uncertainty estimated. The information in the published papers of the two clinical trials was also sometimes not sufficient to calculate whether the difference between subgroups was statistically significant or not. Results of the trials by smoking status and by COPD severity did not present standard deviations or standard errors around the mean exacerbation rate [24, 27]. The exacerbation rates in the UPLIFT trial in smokers and ex-smokers were, however, almost equal, 0.77 versus 0.83, a difference that is most likely not significant [27]. By contrast, the difference in exacerbation rate in the TORCH trial between people with severe and moderate COPD was large, 1.24 versus 0.82 and therefore this difference seems significant given the population size [24].
A second limitation was that the starting population of the models was only adjusted with respect to gender distribution, age, smoking distribution and FEV$_1$%predicted to mirror the population of either the TORCH or the UPLIFT trial. The most recent models include much more characteristics (e.g. BMI, co-morbidities) that could have been adjusted, to create model-populations that were even more similar to the trial-populations. However, this would have made a comparison with the other models impossible.

A third limitation of the current study was that we only assessed whether there were significant differences in outcomes between the subgroups simulated with the models and whether that result was in line with the trial results and the literature. We did not focus on the results of the models in absolute terms. However, the results of the different models showed substantial variation, especially for mortality. A more detailed external validation of model results against the outcomes of the trials for the total population will be topic of another paper.

Finally although this study aimed to compare cost-effectiveness models, it mainly focused on the comparison of clinical outcomes, not on costs. Only table 4 presents information on costs. Validation of costs was not possible because the trials did not present costs specified by subgroups. Clinical outcomes are important outcomes for cost-effectiveness models as well, because they have a high impact on quality of life and costs.

In conclusion, this study showed that the majority of currently available COPD cost-effectiveness models include the relevant patient characteristics gender, age, smoking status and FEV$_1$% predicted and are therefore able to evaluate the cost-effectiveness of personalized treatment based on these parameters. Most models however, do not include all important associations between these characteristics and input parameters. Furthermore, treatment in COPD is more likely to be personalized on the basis of clinical parameters. Two models also included several clinical patient characteristics, such as previous exacerbations, BMI and co-morbidities and seem to be more suitable to evaluate personalized treatment. Inclusion of other clinical parameters, such as emphysema, chronic bronchitis and co-existence of asthma is relevant to make the models suitable to evaluate the cost-effectiveness of treatment options for currently defined phenotypes in COPD.
References


21. Dal Negro RW. Current annual cost calculation is the best predictor of mortality at three years in COPD. *Value in Health* 2014; 17(7): A590-591.


Table 1: Baseline characteristics of subgroups within the placebo group of the UPLIFT and TORCH trial used as starting population of the model simulations [24-27]

<table>
<thead>
<tr>
<th>Trial</th>
<th>UPLIFT trial</th>
<th>TORCH trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subgroup</td>
<td>By gender</td>
<td>By age</td>
</tr>
<tr>
<td></td>
<td>Males</td>
<td>Females</td>
</tr>
<tr>
<td>N</td>
<td>2222</td>
<td>784</td>
</tr>
<tr>
<td>Males %</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>65 (8)</td>
<td>62 (9)</td>
</tr>
<tr>
<td>Current smokers %</td>
<td>26</td>
<td>40</td>
</tr>
<tr>
<td>Post-bronchodilator FEV1% predicted, mean (SD)</td>
<td>47 (13)</td>
<td>49 (13)</td>
</tr>
<tr>
<td>GOLD II: moderate COPD</td>
<td>44%</td>
<td>48%</td>
</tr>
<tr>
<td>GOLD III: severe COPD</td>
<td>45%</td>
<td>43%</td>
</tr>
<tr>
<td>GOLD IV: very severe COPD</td>
<td>10%</td>
<td>7%</td>
</tr>
</tbody>
</table>
Table 2: Patient characteristics included in nine COPD cost-effectiveness models

<table>
<thead>
<tr>
<th>Characteristic:</th>
<th>Asukai_ Markov model</th>
<th>Asukai_ Simulation model</th>
<th>Borg</th>
<th>Briggs</th>
<th>Dal Negro</th>
<th>Hansen</th>
<th>Hoogendoorn</th>
<th>Samyshkin</th>
<th>Wacker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Age</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Smoking</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>FEV1 % predicted</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Height</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Previous exacerbations</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>BMI</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Number of ER visits/ hospitalizations</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Rapid decline in FEV1</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Dyspnea (mMRC)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Disease specific quality of life (SGRQ)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Utility (EQ-5D)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Activity (6 MWD)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Residual volume</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>DLCO</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Lung transplantation</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

*FEV1=forced expiratory volume in one second, BMI=body mass index, ER=emergency room, mMRC=modified Medical Research Council dyspnea scale, SGRQ=St. George’s Respiratory Questionnaire, EQ-5D=EuroQol questionnaire with 5 dimensions, 6MWD=six-minute walking distance, RV=residual volume, DLCO= Diffusion Lung Capacity for carbon monoxide
<table>
<thead>
<tr>
<th>Model:</th>
<th>Type of input parameter</th>
<th>Exacerbation frequency specified by:</th>
<th>FEV1% pred.</th>
<th>Gender, age, smoking, FEV1 % pred. + all other listed in table 2</th>
<th>Age, FEV1% pred.</th>
<th>Age, RV, DLCO, BODE, % FEV decline, co-morbidities</th>
<th>Age, RV, DLCO, BODE, % FEV decline, co-morbidities</th>
<th>Age, FEV1% pred.</th>
<th>Age, FEV1% pred.</th>
<th>Age, FEV1% pred.</th>
<th>Exacerbation-related costs specified by:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asukai_Markov model</td>
<td>Disease progression specified by:</td>
<td>Exacerbation frequency specified by:</td>
<td>Gender, age, FEV1 % pred.</td>
<td>FEV1% pred.</td>
<td>Gender, age, smoking, FEV1 % pred. + all other listed in table 2</td>
<td>Age, RV, DLCO, BODE, % FEV decline, co-morbidities</td>
<td>Age, RV, DLCO, BODE, % FEV decline, co-morbidities</td>
<td>Age, FEV1% pred.</td>
<td>Age, FEV1% pred.</td>
<td>Age, FEV1% pred.</td>
<td>Exacerbation severity</td>
</tr>
<tr>
<td>Asukai_Simulation model</td>
<td>Disease progression specified by:</td>
<td>Exacerbation frequency specified by:</td>
<td>Gender, age, smoking, FEV1 % pred.</td>
<td>FEV1% pred.</td>
<td>Gender, age, smoking, FEV1 % pred. + all other listed in table 2</td>
<td>Age, RV, DLCO, BODE, % FEV decline, co-morbidities</td>
<td>Age, RV, DLCO, BODE, % FEV decline, co-morbidities</td>
<td>Age, FEV1% pred.</td>
<td>Age, FEV1% pred.</td>
<td>Age, FEV1% pred.</td>
<td>Exacerbation severity</td>
</tr>
<tr>
<td>Borg</td>
<td>Disease progression specified by:</td>
<td>Exacerbation frequency specified by:</td>
<td>Gender, age, smoking, FEV1 % pred.</td>
<td>FEV1% pred.</td>
<td>Gender, age, smoking, FEV1 % pred. + all other listed in table 2</td>
<td>Age, RV, DLCO, BODE, % FEV decline, co-morbidities</td>
<td>Age, RV, DLCO, BODE, % FEV decline, co-morbidities</td>
<td>Age, FEV1% pred.</td>
<td>Age, FEV1% pred.</td>
<td>Age, FEV1% pred.</td>
<td>Exacerbation severity</td>
</tr>
<tr>
<td>Briggs</td>
<td>Disease progression specified by:</td>
<td>Exacerbation frequency specified by:</td>
<td>Gender, age, smoking, FEV1 % pred.</td>
<td>FEV1% pred.</td>
<td>Gender, age, smoking, FEV1 % pred. + all other listed in table 2</td>
<td>Age, RV, DLCO, BODE, % FEV decline, co-morbidities</td>
<td>Age, RV, DLCO, BODE, % FEV decline, co-morbidities</td>
<td>Age, FEV1% pred.</td>
<td>Age, FEV1% pred.</td>
<td>Age, FEV1% pred.</td>
<td>Exacerbation severity</td>
</tr>
<tr>
<td>Dal Negro</td>
<td>Disease progression specified by:</td>
<td>Exacerbation frequency specified by:</td>
<td>Gender, age, smoking, FEV1 % pred.</td>
<td>FEV1% pred.</td>
<td>Gender, age, smoking, FEV1 % pred. + all other listed in table 2</td>
<td>Age, RV, DLCO, BODE, % FEV decline, co-morbidities</td>
<td>Age, RV, DLCO, BODE, % FEV decline, co-morbidities</td>
<td>Age, FEV1% pred.</td>
<td>Age, FEV1% pred.</td>
<td>Age, FEV1% pred.</td>
<td>Exacerbation severity</td>
</tr>
<tr>
<td>Hansen</td>
<td>Disease progression specified by:</td>
<td>Exacerbation frequency specified by:</td>
<td>Gender, age, smoking, FEV1 % pred.</td>
<td>FEV1% pred.</td>
<td>Gender, age, smoking, FEV1 % pred. + all other listed in table 2</td>
<td>Age, RV, DLCO, BODE, % FEV decline, co-morbidities</td>
<td>Age, RV, DLCO, BODE, % FEV decline, co-morbidities</td>
<td>Age, FEV1% pred.</td>
<td>Age, FEV1% pred.</td>
<td>Age, FEV1% pred.</td>
<td>Exacerbation severity</td>
</tr>
<tr>
<td>Hoogendoorn</td>
<td>Gender, age, smoking, FEV₁% pred.</td>
<td>FEV₁% pred.</td>
<td>Gender, age, smoking, FEV₁% pred.</td>
<td>FEV₁% pred.</td>
<td>Exacerbation severity</td>
<td>Gender, age, FEV₁% pred.</td>
<td>Exacerbation severity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------</td>
<td>-----------------------------------</td>
<td>------------</td>
<td>-----------------------------------</td>
<td>------------</td>
<td>----------------------</td>
<td>--------------------------</td>
<td>-------------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Samyshkin</td>
<td>Gender, age, FEV₁% pred.</td>
<td>FEV₁% pred.</td>
<td>Gender, age, FEV₁% pred.</td>
<td>FEV₁% pred.</td>
<td>Exacerbation severity</td>
<td>FEV₁% pred.</td>
<td>Exacerbation severity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wacker</td>
<td>Smoking, FEV₁% pred.</td>
<td>FEV₁% pred., lung transplant</td>
<td>Gender, age, smoking, FEV₁% pred., lung transplant</td>
<td>FEV₁% pred., lung transplant</td>
<td>FEV₁% pred., Exacerbation severity, lung transplant</td>
<td>Age, FEV₁% pred., lung transplant</td>
<td>Age, FEV₁% pred., exacerbation severity, lung transplant</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* A disutility that depends on exacerbation severity is applied to the utility of stable disease.
Table 4: One-year model outcomes for a hypothetical reference patient (analysis 1) and for patients that differ on one patient characteristic compared to the reference patient (analysis 2 to 5)

<table>
<thead>
<tr>
<th>Model:</th>
<th>Asukai Markov</th>
<th>Asukai Simulation</th>
<th>Borg^</th>
<th>Briggs</th>
<th>Dal Negro</th>
<th>Hansen</th>
<th>Hoogendoorn</th>
<th>Samyshkin</th>
<th>Wacker</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Male patient, 65 year, ex-smoking with severe COPD (=comparator)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Disease progression*</td>
<td>12.8%</td>
<td>0.4%</td>
<td>5.5%</td>
<td>-0.51% pred.</td>
<td>10.0%</td>
<td>5.2%</td>
<td>2.8%</td>
<td>11.9%</td>
<td>2.5%</td>
</tr>
<tr>
<td>- Mortality</td>
<td>4.0%</td>
<td>4.7%</td>
<td>7.2%</td>
<td>2.8%</td>
<td>10.0%</td>
<td>3.1%</td>
<td>7.1%</td>
<td>4.9%</td>
<td>12.4%</td>
</tr>
<tr>
<td>- QALYs</td>
<td>0.752</td>
<td>0.627</td>
<td>0.688</td>
<td>0.581</td>
<td>n/a</td>
<td>0.658</td>
<td>0.723</td>
<td>0.724</td>
<td>0.520</td>
</tr>
<tr>
<td>- Costs (2014 $)</td>
<td>1950</td>
<td>1560</td>
<td>2350</td>
<td>3830</td>
<td>2680-4020</td>
<td>2260</td>
<td>1680</td>
<td>2270</td>
<td>2480</td>
</tr>
<tr>
<td>2. Female patient, 65 year, ex-smoking with severe COPD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Disease progression*</td>
<td>12.8%</td>
<td>0.9%</td>
<td>-0.81% pred.</td>
<td>10.0%</td>
<td>-</td>
<td>2.8%</td>
<td>16.7%</td>
<td>2.5%</td>
<td></td>
</tr>
<tr>
<td>- Mortality</td>
<td>3.6%</td>
<td>3.3%</td>
<td>-</td>
<td>2.6%</td>
<td>10.0%</td>
<td>-</td>
<td>4.7%</td>
<td>4.9%</td>
<td>7.9%</td>
</tr>
<tr>
<td>- QALYs</td>
<td>0.754</td>
<td>0.406</td>
<td>-</td>
<td>0.623</td>
<td>n/a</td>
<td>-</td>
<td>0.723</td>
<td>0.721</td>
<td>0.530</td>
</tr>
<tr>
<td>- Costs (2014 $)</td>
<td>1950</td>
<td>1590</td>
<td>2350</td>
<td>3810</td>
<td>2680-4020</td>
<td>-</td>
<td>2050</td>
<td>2320</td>
<td>2540</td>
</tr>
<tr>
<td>3. Male patient, 75 year, ex-smoking with severe COPD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Disease progression*</td>
<td>11.4%</td>
<td>0.5%</td>
<td>5.6%</td>
<td>-0.57% pred.</td>
<td>20.0%</td>
<td>5.2%</td>
<td>3.6%</td>
<td>11.6%</td>
<td>2.1%</td>
</tr>
<tr>
<td>- Mortality</td>
<td>6.1%</td>
<td>13.8%</td>
<td>24.1%</td>
<td>5.5%</td>
<td>20.0%</td>
<td>9.3%</td>
<td>13.2%</td>
<td>12.2%</td>
<td>27.2%</td>
</tr>
<tr>
<td>- QALYs</td>
<td>0.742</td>
<td>0.598</td>
<td>0.624</td>
<td>0.593</td>
<td>n/a</td>
<td>0.643</td>
<td>0.723</td>
<td>0.696</td>
<td>0.470</td>
</tr>
<tr>
<td>- Costs (2014 $)</td>
<td>1900</td>
<td>1460</td>
<td>2090</td>
<td>4010</td>
<td>4020-5360</td>
<td>2200</td>
<td>2090</td>
<td>2180</td>
<td>2290</td>
</tr>
<tr>
<td>4. Male patient, 65 year, smoking with severe COPD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Disease progression*</td>
<td>12.8%</td>
<td>2.3%</td>
<td>-</td>
<td>-1.27% pred.</td>
<td>-</td>
<td>8.6%</td>
<td>3.6%</td>
<td>-</td>
<td>7.6%</td>
</tr>
<tr>
<td>- Mortality</td>
<td>4.0%</td>
<td>4.8%</td>
<td>-</td>
<td>3.6%</td>
<td>-</td>
<td>3.1%</td>
<td>8.1%</td>
<td>-</td>
<td>17.7%</td>
</tr>
<tr>
<td>- QALYs</td>
<td>0.752</td>
<td>0.627</td>
<td>-</td>
<td>0.548</td>
<td>-</td>
<td>0.657</td>
<td>0.723</td>
<td>-</td>
<td>0.500</td>
</tr>
<tr>
<td>- Costs (2014 $)</td>
<td>1950</td>
<td>1600</td>
<td>3840</td>
<td>-</td>
<td>2270</td>
<td>1680</td>
<td>-</td>
<td>2450</td>
<td></td>
</tr>
<tr>
<td>5. Male patient, 65 year, smoking with moderate COPD#</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Mortality</td>
<td>2.5%</td>
<td>3.3%</td>
<td>5.3%</td>
<td>1.7%</td>
<td>8.0%</td>
<td>2.5%</td>
<td>5.0%</td>
<td>3.0%</td>
<td>6.3%</td>
</tr>
<tr>
<td>- QALYs</td>
<td>0.781</td>
<td>0.653</td>
<td>0.741</td>
<td>0.623</td>
<td>n/a</td>
<td>0.702</td>
<td>0.737</td>
<td>0.772</td>
<td>0.570</td>
</tr>
<tr>
<td>- Costs (2014 $)</td>
<td>330</td>
<td>450</td>
<td>1060</td>
<td>3910</td>
<td>2010-2680</td>
<td>1580</td>
<td>1270</td>
<td>1540</td>
<td>1460</td>
</tr>
</tbody>
</table>

*Disease progression was defined as the percentage of severe COPD patients moving to very severe COPD except for the model of Briggs et al in which disease progression was defined as the decline in FEV₁% pred.
Figure 1: Comparison of model results for the subgroup gender with empirical results of the four-year UPLIFT trial for a) exacerbations and b) all-cause mortality. * indicates that the difference is statistically significant. Difference in the simulation model of Asukai could not be tested because no uncertainty was available around the estimates.
Figure 2: Comparison of model results for the subgroup age with empirical results of the four-year UPLIFT trial for a) exacerbations and b) all-cause mortality. * indicates that the difference is statistically significant. Difference in the simulation model of Asukai could not be tested because no uncertainty was available around the estimates.
Figure 3: Comparison of model results for the subgroup smoking status with empirical results of the four-year UPLIFT trial for a) exacerbations and b) all-cause mortality. * indicates that the difference is statistically significant. Difference in the simulation model of Asukai and the trial (exacerbations) could not be tested because no uncertainty was available around the estimates.
Figure 4: Comparison of model results for the subgroup FEV$_1$% predicted with empirical results of the three-year TORCH trial for a) exacerbations and b) all-cause mortality. * indicates that the difference between moderate and severe COPD is statistically significant. ** indicates that the difference is most likely statistically significant, but standard errors were missing. Difference in the simulation model of Asukai and the model of Dal Negro could not be tested because no uncertainty was available around the estimates.