Author's response to reviews

Title: Tiotropium's cost-effectiveness for the treatment of COPD: a cost-utility analysis under real-world conditions.

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Author's response to reviews: see over
Dear editor,

We are happy with the appreciation of the reviewers. The remaining questions are answered point by point.

One of the reviewers suggested to write an editorial. Instead of an editorial, we have written a methodological note to avoid confusion on the methodological approach. It is entitled “Calculating real-world cost effectiveness: combining strengths of both RCTs and routine data.” It is included in our responses to the reviewers’ questions and as a separate file.

We hope you consider both our manuscript and methodological note for publication in BMC pulmonary medicine.

Thanking you in advance,
With kind regards,
Mattias
Reviewer: Nikos Maniadakis
Reviewer's report:
The authors have done a lot of work and have improved the paper significantly.

We are very happy that the reviewer appreciates the efforts and changes.
**Reviewer:** Huib Kerstjens  
**Reviewer's report:**
In general, I think the authors have very thoroughly and seriously addressed the comments, and have made many valuable additions to the text. I think the above also applies to the responses to reviewer 2, who unfortunately you were not able to obtain an analysis of the responses from. I am least sure (not capable) of judging the answer to major point 5, but think the difference between the two pints is not pivotal: in both cases, the incremental cost-effectiveness ratio is quite unfavourable.

The reviewer is indeed right that the result remains unfavourable, no matter how the calculation was made. However, we would like to stress that we follow the state-of-the-art Belgian guidelines. The Belgian guidelines for economic evaluations state that “The central estimate of the ICER results directly from the probabilistic sensitivity analysis as the mean of the simulated ICERs. This is not necessary equal or close to the ratio of the mean incremental cost and mean incremental effect, which is the deterministic version of the ICER. A deterministic ICER can be presented if the Monte Carlo simulations fall in different quadrants of the cost-effectiveness plane.” We added this text and reference to the Belgian guidelines in our manuscript.

Having said that to my opinion the response are quite adequate, I also have a more general remark to make. I believe the results might well spark quite some controversy and correspondence. Basically, the authors apply the results obtained from a very large RCT (UPLIFT, n=6000) to an extremely large data-set (n=50,000) that however is totally uncontrolled. Nothing is known about any relevant characteristics of the group such as basic severity (GOLD stage). There was most probably not even a verification of the diagnosis of COPD (tiotropium is used off lable also for asthma, and probably also for chronic bronchitis without COPD).

In our discussion we wrote the following: “A disadvantage of our database is that no parameter was present indicating the COPD stage. As a result, no subgroup analyses could be made according to these stages. In our approach, the population was initially analysed as a whole (i.e. all patients fulfilling our inclusion criteria). In subgroup analyses, the population was divided depending on the number of hospitalisations related to exacerbations (i.e. one, two, three or more exacerbation-related hospitalisations) in combination with the number of exacerbations. These subgroup analyses showed that, in the first place, for a selected group of patients with a relative high base risk on events, the results were more cost effective. …”

In other words, the use of extremely large, real world data should be balanced against the scientific soundness of the exercise. I think that it would be useful to the pulmonary field to have a discussion on this and this manuscript might spark it. But BMC pulmonary will receive letters! Perhaps an editorial could even fuel it and indicate that this critical consideration was taken into account.

This is indeed a correct remark of the reviewer. Also in our meetings with external experts, we had to explain very good the applied methodology. Sometimes there was
confusion with some experts who thought we extracted the treatment effect from our observational data. This is absolutely not the case!
To avoid the same kind of confusion, we would like to write a short editorial (or maybe it should be called “methodological note”) on the used approach.

- **Title:** “Calculating real-world cost effectiveness: combining strengths of both RCTs and routine data.”

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Randomised controlled trials (RCT) are acknowledged being the best available tool for evaluating the risks and benefits of medical interventions.[1] RCTs, however, also have limitations. In particular, they include highly selected populations and their external validity for the general population is usually not straightforward.

Administrative real-world data may not necessarily provide a solution. The main difficulty with routine data issued from the health system is to identify an appropriate control group. In the case of the tiotropium analysis, the control group would have consisted of COPD patients with similar patient characteristics (age, sex, COPD stadium, and other comorbidities) but with no tiotropium use. Identifying such patients was not possible since no such Belgian database included this kind of information. Using proxies for such identification purpose (e.g. use of antibiotics, steroids, etc.) would have resulted in a mixture of COPD and asthmatic patients.

Another approach would be to use patients taking tiotropium as their own control in a before/after analysis. In Belgium, tiotropium is reimbursed since March 1, 2004 and (in theory) it is only used for COPD patients. The number of exacerbations and hospitalisations could be compared with their situation before taking tiotropium. Nevertheless, other factors, such as the progression of the disease or changes in smoking behaviour, could have an influence on the observed differences. As mentioned by Lewsey et al.[1] routine data sets have generally been assembled for other purposes and may omit potentially confounding variables. Adjustments for such variables are obviously restricted to information recorded in the database and COPD stadium or smoking behaviour, for example, are not included in the Belgian databases. And even if such confounding factors were recorded, the ‘allocation’ of patients to treatments could reflect other factors whose effects cannot be fully captured in a covariate adjustment.[2] Finally, the administrative data were not intended to analyse treatment effects. As a result, the quality of the data may lead to questions about the
validity of findings.[1] Therefore, it is clear that the effectiveness of tiotropium cannot be estimated reliably based on the administrative data we had at our disposal.

Nevertheless, the analysis of administrative data can be very useful for the appropriate purposes. Policy makers try to make decisions for real-world populations. As an aspect of Health Technology Assessments (HTA) supporting rational decision making, economic evaluations often apply modelling techniques to avoid some of the shortcomings of RCTs. It allows to reflect the cost effectiveness for the right target population, include an appropriate comparator and time horizon, exclude protocol driven events and costs, …, and include a realistic baseline risk for certain events. Cost effectiveness is driven by the absolute treatment effect, which is the combination of both relative treatment effect and baseline risk for certain events.[3] The latter may be very different comparing real-world and RCT populations. Using the baseline risk for certain events from RCTs may provide unrealistic real-world cost-effectiveness results, e.g. when the absolute percentage of avoided events due to a certain intervention is higher than the absolute percentage of these events under real-world conditions without the intervention. The availability of reliable administrative data may avoid such unrealistic outcomes by providing input for a “what-if” cost-effectiveness analysis. In a first step, the real-world situation is reproduced based on the administrative data (figure 1). In a second step, relying on results from RCTs and/or meta-analysis, the hypothetical situation is set up “as if” the intervention (in this case tiotropium) would have been used. In the next step, the intervention’s cost effectiveness under real-world conditions can be calculated by comparing the two situations. This approach combines the strengths of both routine data (reproducing the real-world situation) and RCTs (providing an estimate of the treatment effect).

Figure 1: (appropriate) use of specific sources for economic evaluations.

Systematic literature review: (meta-analysis of) randomised controlled trials

(reliable) Administrative database: frequency specific events for the target population

TREATMENT EFFECT

BASELINE RISK

Economic evaluation: calculate the intervention’s cost-effectiveness for the target population

References:
Reviewer: Reijo Sund  
Reviewer’s report:  
I think that the authors have addressed this concern adequately in their response (and their calculation technique is correct). It is of course possible to request that the authors mention their calculation technique explicitly in the manuscript (possibly with a reference) as someone else may ask the same question as the Referee 2.

In the section ‘probabilistic modelling’ we added the following: (referring to the Belgian pharmacoeconomic guidelines)  
"Following the Belgian pharmacoeconomic guidelines, the central estimate of the ICER results directly from the probabilistic sensitivity analysis as the mean of the simulated ICERs. This is not necessary equal or close to the ratio of the mean incremental cost and mean incremental effect, which is the deterministic version of the ICER. A deterministic ICER is presented if the Latin Hypercube simulations fall in different quadrants of the cost-effectiveness plane.”


Otherwise my comments about the manuscript would be very similar to Referee 3, and the authors have responded to them already.

Thank you.