Author's response to reviews

Title: Using and interpreting cost-effectiveness acceptability curves: An example using data from a trial of management strategies for atrial fibrillation

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Author's response to reviews: see over
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Dear Editor

Please find attached a revised version of our article entitled "Using and interpreting cost-effectiveness acceptability curves: An example using data from a trial of management strategies for atrial fibrillation". This version has been revised in light of reviewers' comments received earlier this year, as detailed below.

I can confirm that the material submitted within this paper has not been published elsewhere and is not under consideration for publication elsewhere. The word count for the revised manuscript is 3124.

I trust that the revised manuscript satisfactorily deals with the issues raised by the reviewers and complies with the requirements for submissions. I look forward to hearing from you concerning this matter in due course.

Yours faithfully,

Elisabeth Fenwick
Responses to reviewer’s comments

Reviewer 1
General comments
We have added a reference to bootstrapping techniques for those who wish to learn more about bootstrapping.

Minor essential revisions
1) We have added ‘average’ to the formula as suggested.
2) We have replaced the sentence with ‘However, while these independent incremental cost-effect pairs provide some information about the joint uncertainty in the estimate of incremental cost-effectiveness it is not clear how to present a summary measure of this uncertainty.’
3) We believe that we have already explained the issue of the decreasing slope within the section on constructing a CEAC. We have included the suggested reference which provides further details about the shape of the CEAC.
4) We have added the sentence ‘The proportion of the re-samples falling in the northeast or southeast quadrants (i.e. were cost-effective when lambda was infinite) was found to be 98.3%. Hence as lambda tends to infinity, the probability that rate-control is cost-effective compared to rhythm control tends to 0.983 (Figure 3).’
5) We have added the phrase ‘given the decision makers selected value of lambda’ to page 13.

Discretionary revisions
i) We have changed the sentence to ‘However, this does not take any uncertainty in the estimates of costs and effects into consideration and decision makers will be interested to ascertain how sure they can be that this is the correct conclusion to make.’
ii) We have replaced the sentence with ‘The presence of this uncertainty means that there is inevitably some possibility that decisions made on the basis of the available (uncertain) information will be incorrect and introduces the possibility of error into decision-making.’
iii) We have changed the sentence to ‘Since the maximum acceptable ceiling ratio will generally not be stated explicitly, a sensitivity analysis should be undertaken with the probability determined for a range of lambdas.’
iv) No action taken.
Reviewer 2

General comments
1) The aim of the paper is to provide a straightforward explanation of CEACs for a clinical audience who are not yet familiar with the technique. As such, the paper explains how to calculate cost-effectiveness acceptability curves and how to interpret them appropriately using a topical and relevant example.
2) We have added a sentence 'This definition involves a Bayesian definition of probability i.e. the probability that the hypothesis is true ('rate-control strategy is cost-effective') given the data, although the CEAC can be given a Frequentist interpretation' and a reference to O’Hagan et al (2000) as suggested by the referee.
3) The CEACs generally shown in the literature are textbook examples varying over the range 0% - 100% as lambda increases. In contrast, there is little decision uncertainty surrounding AFFIRM and hence the CEAC is fairly stable at high levels of probability. We believe that it is precisely because of this that AFFIRM is an interesting example. The effectiveness results for AFFIRM showed no statistically significant difference between rate-control and rhythm-control strategies for the management of patients with atrial fibrillation. However, the cost-effectiveness results show that there is very little uncertainty that the decision to adopt rate-control compared to rhythm-control for patients with atrial fibrillation is correct (with decision uncertainty less than 1.67% regardless of the maximum acceptable ceiling ratio).
4) We believe that the paper provides a straightforward explanation of CEACs using a topical and relevant clinical example, illustrating how to calculate CEACs and how to interpret them appropriately, that will be of value to a clinical audience.

Major compulsory revisions
1) We have added confirmation that the results are from a two-sided test.
2) We agree that there is no trade-off required in the NE quadrant. However, for AFFIRM it is the trade-off in the southwest quadrant that is of interest. 'With AFFIRM there was no statistically significant difference in effectiveness between rate-control and rhythm-control strategies for the management of patients with atrial fibrillation. However, the CEAC shows that the decision uncertainty surrounding the adoption of rate-control strategies is less than 1.67% regardless of the maximum acceptable ceiling ratio. Thus, there is very little uncertainty that the decision to adopt rate-control compared to rhythm-control for patients with atrial fibrillation is correct from a cost-effectiveness point of view.'
3) We have amended the sentence to 'The use of stochastic (e.g., bootstrapping)
and probabilistic techniques (e.g., Monte Carlo simulation), for trial analyses and modelling studies respectively, to generate the sampling distribution of the joint mean cost and efficacy has enabled quantification of the uncertainty surrounding the estimates of costs and effects.'

In addition, we have changed the sentence to clarify that bootstrapping was used in this study 'Figure 2 illustrates the incremental cost-effectiveness plane for the cost and effectiveness data bootstrapped from the AFFIRM trial.'

4) This has been clarified in response to reviewer 1 point (2) by addition of the sentence 'We have replaced the sentence with 'However, while these independent incremental cost-effect pairs provide some information about the joint uncertainty in the estimate of incremental cost-effectiveness it is not clear how to present a summary measure of this uncertainty.'

5) We have clarified the discussion and added the references suggested by the reviewer 'These methods include the use of Fieller’s theorem and non-parametric bootstrapping (19;20). However, these solutions do not resolve the problems associated with a small or non-existent effect difference which would cause the ICER to be undefined and may make the variance intractable (18).'

6) We have amended the sentence 'When analysing a clinical trial, this distribution is most commonly estimated using non-parametric bootstrapping however it can be generated from a probabilistic analysis of a decision model which translates the uncertainty in input parameters into uncertainty in costs and effects'

7) The issue of CEACs not representing cumulative distribution functions was added to the paper in response to previous comments from referees.

8) The text has been amended accordingly.