Author's response to reviews

Title: The Cost-Effectiveness of the Argus II retinal prosthesis in Retinitis Pigmentosa patients

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Author's response to reviews: see over
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Maastricht, the Netherlands

Dear Editor and Reviewers,

Thank you for giving us the opportunity to revise our manuscript titled as ‘The Cost-Effectiveness of the Argus II retinal prosthesis in Retinitis Pigmentosa patients’.

On behalf of all co-authors, I hereby submit our revised manuscripts to the ‘BMC Ophthalmology’ for consideration for publication.

Please find below our point by point response to the comments made on the submitted version of the manuscript. The comments were very useful to us and have improved the paper.

In the revised manuscript all changes are made by using track changes.

We look forward to hear from you.

Regards,

Anil Vaidya (on behalf of co-authors)
Editorial Comments:

"Please address the reviewer's suggested revisions"

Authors’ response: Thank you for your comments. We have addressed the reviewers’ remarks in the revised manuscript. Our point by point response to the remarks is appended below.

Reviewer: Ashish Ahuja

Reviewer report

Major Compulsory Revisions

Are the methods appropriate and well described?

There are multiple fundamental assumptions that aren’t justified:

a. You stated the following assumption but gave no reason or basis: “We assumed that over a decade the visual impairment will progress to the level of legal blindness in these patients”

Authors’ response:

Thank you for your comment and for pointing this out, we agree with the reviewer and following reference has been added to support our assumption in the manuscript.


Changes in text:

We assumed that over a decade the visual impairment will progress to the level of legal blindness in these patients. Therefore, we simulated a hypothetical cohort of 1000 RP male and female patients aged 46 years [12].
b. You stated that “The model analysis began in the first state (legally blind RP patients with no light perception) for all the individuals”, but inclusion criteria on study actually requires some level of light perception (in order to make sure the optic nerve could at least transmit signals).

Authors’ response:

Thank you for your comment. We agree with the reviewer that some level of light perception is required for signal transmission. We have changed first Markov state to ‘legally blind RP patients with minimal light perception’ and have amended the text in the manuscript accordingly.

Changes in text:

A Markov model with annual cycles was developed with four health states:

1. RP patients with minimal light perception, MLP
2. Visual acuity + (light perception, LP)
3. Visual acuity ++ (counting fingers, CF)
4. Visual acuity +++ (reading letters, RL)

The model analysis began in the first state (legally blind RP patients with minimal light perception) for all the individuals.

c. You stated, “The model assumed to have Argus II fitted patients moving from Low visual acuity to higher visual acuity health states at an annual rate of 10%. This transition was deemed reasonable after personal communication with experts.” Again, given the fact that all results in the paper are dependent on modeling, any assumptions
made have to be well justified. It is not sufficient to pin the 10% rate on personal communication without even specifying the source. In this case a peer reviewed source is likely needed.

Authors’ response:

Thank you for your comment. Argus II is a newly approved device and to the best of our knowledge, there is no peer reviewed source available for reference.

Transition probabilities from minimal light perception to various Markov states are calculated from the FLORA study data. This study has produced data from 30 patients fitted with ARGUS II device and is the only data source for these transition probabilities. FLORA patients are under follow-up and the annual inter-state transition rate of 10% is based on this follow up and discussion with the clinicians dealing with these patients. FLORA study results are indicative of such improvements and these results are presented by the experts in scientific congresses.

Furthermore, all the assumptions were subjected to a sophisticated and rigorous method of probabilistic sensitivity analysis (PSA) by performing Monte Carlo simulations. In this way all the model parameters were varied in a reasonable range simultaneously. Computer drew an estimate of each parameter from the assigned range and the distribution to perform the PSA.

d. “This is another example of unjustified model parameters. There are a couple of grammatical errors in the sentence as well. “As there is no robust data available regarding the reduction in the cost of care for RP patient with improving visual acuity, we assumed a stepped reduction in cost of care for patients according to progressive Markov states, i.e. reduction of 20% for patients with mild visual acuity improvement (light perception),
30% in patients with moderate visual acuity improvement (counting fingers) and 40% in patients with good visual acuity improvement (reading letters).” Since these assumptions will likely drastically affect the model, if they are not well justified the central results of the paper are unfounded.

Authors’ response:

Thank you for your comment. Grammatical error has been corrected. We based this assumption on a peer reviewed article published by Hernández-Pastor et al (2010). On the basis of data given in this article for AMD patients, we assumed the similar reduction in non-medical costs (i.e. assistance from paid professionals for daily activities and social benefits received for visual disabilities) for RP patients. We have revised our manuscript accordingly and have given reference of the above mentioned article. These assumptions were also subjected to PSA.

Change in text:

Cost of care in Age related Degeneration (AMD) has been reported by Hernández-Pastor et al.[17]. As there is are no robust data available regarding the reduction in the cost of care for RP patient with improving visual acuity, on the basis of Hernández-Pastor’s article we assumed a stepped reduction in cost of care (assistance from paid professionals for daily activities and social benefits received for visual disabilities) for patients according to progressive Markov states.

e. You stated, “Patients who experienced Serious Adverse Events (SAEs) after The Argus II implantation were assigned a utility reduction of 0.16 which is equivalent to the lost utility value estimated for severe dry eye in an article by Schiffman et al [17].”
But are the lists of SAE are in these two studies the same? Are these two studies normalized with respect to each other?

Authors’ response:

Thank you for your comment. In the article by Schiffman et al. severe dry eye is a ranked as a very severe eye condition having a utility reduction of 0.16 against 0.07 and 0.1 utility reductions for mild and moderate dry eye respectively. Since very few SAEs were observed in Argus II fitted patients and utility reduction for individual SAE was not feasible to incorporate in the model, a conservative disutility estimate of 0.16 was assigned to SAEs in the model. Disutility of 0.16 is an estimate on higher side when the maximum utility of Argus II fitted patients could be 0.54. In future, when more data are available from a bigger sample size, it is likely that this value will go down and model results will become more favorable to the ARGUS II device. This assumption was also subjected to PSA.

f. You stated, “Arbitrarily, a ±25% of range was given to the point estimates of the model parameters.” I don’t understand how an arbitrary value can be given with no further justification.

Authors’ response:

Thank you for your comment. We agree with the reviewer and further explanation of this has been added to the manuscript text.

Change in text:

The BETA Pert distribution for model parameters (based on mode and ±25% range) was used as confidence intervals or standard errors were not reported in the source literature. The reported deterministic values were varied in ±25% range to calculate the minimum and maximum for BETA Pert distribution.
**Minor Essential Revisions** (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct) There are no units at all on the last two plots.

Authors’ response:

Thank you for your comment. WTP unit and incremental cost unit (Euro) has been added to the plots.

**Reviewer: Paul Yang**

**Reviewer report**

**Major Compulsory Revisions**

1) Background, 2nd paragraph, 3rd sentence. "In patients who have lost their sight, admission to nursing homes occurs three years earlier." Please qualify this statement. Clearly, not all patients have the same level of vision loss, and not all patients require nursing home care.

Authors’ response:

Thank you for your comment. This paragraph is about building a case for need of cost effective interventions for visually impaired patients. Two references given at the end of the paragraph are the articles by Taylor and Hamn reporting relatively higher costs incurred by the visually impaired patients to the health systems and to the society. Furthermore, this background information has no direct consequence to the assessment of cost effectiveness of ARGUS II as this has been done using a Markov model fed with published model parameter values.
2) Materials and Methods, 2nd paragraph. If the average age of diagnosis is 35.1 years, why did the authors choose a hypothetical cohort aged 46 years?

Authors’ response:
Thank you for your comment and for pointing this out, we agree with the reviewer and following reference has been added to support our assumption in the manuscript.


The average age of RP diagnosis is reported to be 35.1 years in the published literature. We assumed that over a decade the visual impairment will progress to the level of legal blindness in these patients. Therefore, we simulated a hypothetical cohort of 1000 RP male and female patients aged 46 years. [12].

This assumption has been supported by the article by Birch et al. (above).

3) Model Structure, 2nd paragraph, 4th sentence. "The reference hypothetical cohort....remained in the state of legally blind RP with no light perception for the entire model time horizon." From personal experience and the experience of my colleagues, the majority of patients with RP age 46 years of age have much better vision than "no light perception." If the data exists to back up the author's assumption, then it should be referenced here. Just one longitudinal study of x-linked RP (Grover, et al., 2000. Ophthalmology 107(2):386-396), reveals that these patients have much better vision than no light perception.

Authors’ response:
Thank you for your comment. Please refer to our response to your point number 2.

Furthermore we have assessed the cost effectiveness of ARGUS II over a time horizon of 25 years. Changing initial age of RP patients from 46 (for example 50 or 55) will not affect model results.
Has it been shown that the Argus II implant can reduce depression and anxiety?

Authors’ response:

Thank you for your comment. Visual impairment has been shown to be associated with depression and anxiety. Published evidences suggest that cost of care is higher in visually impaired patients and depression and anxiety are associated with increased costs of care.

Cost of care in Age related Degeneration (AMD) has been reported by Hernández-Pastor et al [17]. As there is no robust data available regarding the reduction in the cost of care for RP patient with improving visual acuity, on the basis of Hernández-Pastor’s article we assumed the same for RP. All these assumptions were subjected to a sophisticated and rigorous method of probabilistic sensitivity analysis (PSA) by performing Monte Carlo simulations. In this way all the model parameters were varied in a reasonable range simultaneously. Computer drew an estimate of each parameter from the assigned range and the distribution to perform the PSA.

5) Costs, 2nd paragraph, 4th paragraph. "...there is no robust data available regarding reduction in cost...we assumed a stepped reduction in cost of care..." I applaud the author's frank declaration of these uncertainties and assumptions, and understand that these are highly complex issues not previously studied. However, the assumed cost savings of 20-40% seem to be pulled out of thin air, and this casts serious doubt regarding any cost saving conclusions based on these unsupported assumptions.

Authors’ response:

Thank you for your comment.

We based this assumption on a peer reviewed article published by Hernández-Pastor et al (2010). On the basis of data given in this article for AMD patients, we assumed the similar reduction in non-medical costs (i.e. assistance from paid professionals for daily activities and
social benefits received for visual disabilities) for RP patients. We have revised our manuscript accordingly and have given reference of the above mentioned article. These assumptions were also subjected to PSA.

6) Utility Values and QALYs, 1st paragraph, 7th sentence. "Patients who experienced SAEs after the Argus II implantation were assigned...equivalent to...severe dry eye..." I would argue that post-operative complications after lensectomy, vitrectomy, scleral dissection, and implantation of artificial material into the eye is not an equivalent lost utility value to that of severe dry eye.

Authors’ response:

Thank you for your comment. Very severe complications following the device implantation are dealt in the model by explanting the device and by assigning a utility value same as the patients without the device (first Markov state).

In the article by Schiffman et al. severe dry eye is a ranked as a very severe eye condition having a utility reduction of 0.16 against 0.07 and 0.1 utility reductions for mild and moderate dry eye respectively. Since very few SAEs were observed in Argus II fitted patients and utility reduction for individual SAE was not feasible to incorporate in the model, a conservative disutility estimate of 0.16 was assigned to SAEs in the model. Disutility of 0.16 is an estimate on higher side when the maximum utility of Argus II fitted patients could be 0.54. In future, when more data are available from a bigger sample size, it is likely that this value will go down and model results will become more favorable to the ARGUS II device.

This assumption was also subjected to PSA.

7) Discussion, 6th paragraph, 1st sentence. "Markov model...begins at the age of 46 years as most of the RP patients are legally blind by this age." Just because patients are legally blind,
does not mean they are eligible for the Argus II prosthesis. A more accurate model is to use
the average age at which patients become eligible for the Argus II.

Authors’ response:

Thank you for your comment. Please refer to our response to point 2 and 3.

The average age of RP diagnosis is reported to be 35.1 years in the published literature. We
assumed that over a decade the visual impairment will progress to the level of legal blindness
in these patients. Therefore, we simulated a hypothetical cohort of 1000 RP male and female
patients aged 46 years. [12].

This assumption has been supported by the following article:

Birch DG, Anderson JL, Fish GE: Yearly rates of rod and cone functional loss in retinitis

Furthermore we have assessed the cost effectiveness of ARGUS II over a time horizon of 25
years. Changing initial age of RP patients from 46 (for example 50 or 55) will not affect
model results.

8) Discussion, 7th paragraph, 3rd sentence. "...explantation...return to legally blind Markov
state..." Aren't all health states legally blind, whether it's no LP, LP, or CF?

Authors’ response:

Thank you for your comment and for pointing this out, we agree with the reviewer and term
'legally blind' has been removed from there and text is amended throughout the manuscript.

9) Discussion, 7th paragraph, 5th sentence. "This may not happen in practice....most of the
patients are expected to adapt to the device and explantation would be a rare event..." Even if
patients do adapt to the device, this is an independent variable to the causes of explantation
that have to do with extrusion, infection, or infection risk. Implanted artificial material within
the eye, even when initially judged to be stable, have a low but indefinite risk that they may
migrate, extrude, or become infected. Examples include scleral buckles and glaucoma implant devices.

Authors’ response:

Thank you for your comment. Base on the available data (FLORA) the transition probability of explantation had been calculated and applied to the model for the time horizon of 25 years. Therefore, the model accounts for explantation risk in the patients over the life time.