Cost-Effectiveness of Binocular Treatment for Amblyopia: A Markov MODEL Framework

POSC154

Tai TA[1], Commane J[1], Raunak K[1], Bouchet C[2], O'Brien P[1], Felizzi F[2]

[1]Novartis Global Services Center, Dublin, Ireland; [2]Novartis Pharma AG, Basel, Switzerland

Background

- Amblyopia ("lazy eye") is characterized by a decrease in best corrected visual acuity (VA) in one eye (unilateral) or, less frequently, both eyes (bilateral) with no detectable cause on physical examination. It is caused by eye(s) not being able to develop a strong connection to the brain during visual development early in life. Amblyopia often starts in childhood and children with best corrected VA worse than 20/30 or interocular difference of two lines or more in VA would be defined as amblyopia[1-3]. In addition to decreased VA, amblyopic patients may also suffer from impaired binocular functions such as poor stereoacuity[4].
- Amblyopia is the most common cause of vision loss in children and young adults and with an estimated prevalence of 1-5%[1]. It was estimated that amblyopia affects 99.2 million people by 2019 worldwide, increasing to 221.9 million affected by 2040[5].
- Amblyopia has an impact on daily activities and quality of life (QoL)[6-7]. In addition, patients with amblyopia are reported to have increased risk of developing bilateral visual impairment (BVI) from age-specific, non-amblyopia-related causes such as cataract and age-related macular degeneration (AMD). BVI is associated with significant QoL deterioration, higher mortality and higher healthcare resource utilisation[8-11].
- The traditional, monocular, therapies (patching or atropine) improve VA of the amblyopic eye by penalizing the fellow eye. However, these types of therapies focus on the amblyopic eye only and binocular outcomes (e.g. stereopsis) are rarely restored[12-14]. Furthermore, patching is associated with poor compliance which may imply a suboptimal treatment effect[15].
- A novel digital, binocular, therapy has the potential to improve binocular functions including binocular VA and stereoacuity by stimulating both eyes simultaneously[12]. It is also anticipated to have better compliance than patching or atropine. It is important to understand the cost-effectiveness of funding such a novel therapy in treating amblyopia patients.

Objective

- The objective of this research is to conceptualize a cost-effectiveness model that captures the natural history of amblyopia and the treatment effects on binocular functions to guide the funding decisions for novel amblyopia treatments.

Methods

- Previously published economic evaluations of amblyopia treatments were reviewed (**Table 1**). The majority of the studies focused on screening strategies and were based on simple decision-tree structures. More importantly, most of the models were one-eye models which fail to capture VA of both eyes and thus may inaccurately estimate the impact on QoL. In addition, these studies did not consider stereopsis, compliance and relapse which are important attributes of amblyopia and its treatments.
- A de-novo model was conceptualized aiming to capture following important attributes of disease and treatment:
  - Change in VA of each eyes
  - Utility impact by VA of both eyes
  - Utility benefit from improvement in stereoacuity
  - Disease relapse
  - Non-compliance
  - Long-term risk and costs of developing BVI

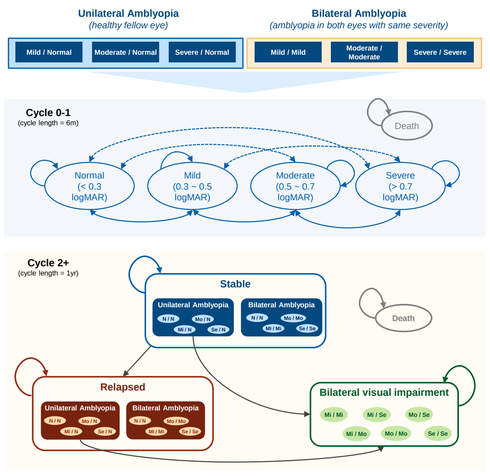
Table 1. Review summary of published economic evaluations

Study	Intervention	Model type	Model description
König HH, 2000[16]	Screening	Decision-tree	These studies were conducted by the same study team. Patients were modelled until diagnostic examination (negative/positive). Long-term outcomes and natural history of disease were not considered and the model outcome was costs per case detected.
König HH, 2002[17]	Screening	Decision-tree	
König HH, 2002[18]	Screening	Decision-tree	
König HH, 2004[19]	Treatment	Decision-tree + Markov	This study concerned a decision tree with one decision-node to distinguish between treatment success (VA≥0.5) and non-success (VA<0.5), followed by a Markov model, which simulated long-term risk of developing BVI. The model considered one eye only; utility was estimated based on VA of better eye, compliance / relapse / stereopsis were not considered.
Membreno JH, 2002[20]	Treatment	Decision-tree	This study employed a decision-tree model to determine which VA level (out of five levels) patients would fall into after treatment (or no treatment), each VA level is associated with corresponding utility and costs. The model considered one eye only; long-term outcomes and other disease events were not considered.
Joish VN, 2003[21]	Screening	Decision-tree	Patients were modelled until diagnostic examination (negative/positive). Long-term outcomes and natural history of disease were not considered.
Carlton J, 2008[11]	Screening	Markov	The model employed 20 health states, with VA in two eyes considered. Long-term risk of developing BVI and associated costs were included. Other disease attributes including stereopsis, compliance and relapse were not considered.
Rein DB, 2012[22]	Screening	Patient-level simulation	Those with positive screening results would receive treatment and experience either treatment success or non-success. Long-term risk of developing BVI was considered.

Results

- A Markov model structure was selected due to its flexibility to, in our case, accommodate VA of each eye and model the natural history of amblyopia. **Figure 1** describes the structure of the conceptualized Markov model and **Table 2** lists the model settings and inputs.
  - Health states were defined by the combination of VA in two eyes. VA was categorized into four severity levels: normal vision ws defined as logMAR less than 0.3 with mild vision loss defined as logMAR between 0.3 and 0.5. Moderate and severe vision impairment were logMAR of 0.5 to 0.7 and larger than 0.7, respectively.
  - While amblyopia is often considered as unilateral with prevalence of bilateral amblyopia reported to be one-third to half of that of unilateral amblyopia[23-24], other studies suggest that bilateral amblyopia takes 36~55% of amblyopia population[25-26]. In our model, both unilateral and bilateral amblyopia were considered. For bilateral amblyopia patients, VA of both eyes were assumed to be the same based on internal evidence[26].
  - In this model, treatment duration was assumed to be 6 months which is a common length of follow-up in amblyopia trials. During the 6 months of treatment (i.e. first model cycle), patients may remain in the current VA state or transition to other VA states.
  - Due to lack of comparative treatment effect data from head-to-head trials, treatment effect (reduction in logMAR) was sourced from individual trial of each treatments.
  - Transition probabilities were estimated by mean reduction in logMAR. Specifically, reduction in logMAR was assumed to be normally distributed and a normal cumulative density function was used to estimate the probability of moving across change cut-offs, which were then converted to the probability of transitioning by one, two or three health states (**Table 2**).
  - During treatment, a proportion of patients were assumed to exhibit poor compliance (defined as less than 50% of the prescribed time) which reduces the treatment effect.
  - After the first cycle, treatment ceased and patients may maintain their VA or experience a relapse (VA worsens), following the natural history of amblyopia.
  - It is assumed that only unilateral amblyopia patients would develop BVI as patients with bilateral amblyopia already have BVI by definition. Patients with BVI were assumed to have lower QoL and higher mortality. Patients who had severe vision loss in both eyes were assumed to incur higher costs and healthcare resource utilisation as they are considered to be nearly blind. Vision worsening in the fellow eye may improve vision in the amblyopic eye; however, this was not modelled here as it may unnecessarily complicate the model.
  - Traditionally, QoL is believed to be mainly impacted by VA of the fellow-eye. Thus, the majority of the utility studies were based on better-seeing eye only. However, studies argue that both eyes are equally important in determining QoL[27]. Hodgson 2017[34] paper was selected because the regression algorithm included VA in both eyes though with the caveat of population being based on wet AMD. No similar study conducted for amblyopia population was identified.
  - The impact of improvement in stereoacuity was not modelled through health states; instead, a utility increment was assigned, estimated by the change in percentage of patients having nil stereoacuity from baseline. The utility of nil stereoacuity was estimated from published SF36 scores, mapped onto EQ5D using a published algorithm.
- Using the base-case model inputs (**Table 3**), the incremental cost-effectiveness ratio (ICER) ranges from being dominant to £1,223 per QALY compared with patching and atropine across different pricing scenarios. These estimates fall within the range considered as cost-effective in the UK (£30,000 per QALY). The main drivers of the results are utility values, proportion of poor compliance and treatment effect. ICERs are increased if alternative utility sources (based on better-seeing eye) are used, but remain under threshold. In the most pessimistic scenario assuming same treatment effect in VA and same compliance as comparators, the ICERs are close to £30,000 per QALY.

Figure 1. Model structure



N: normal vision; Mi: mild vision loss; Mo: moderate vision loss; Se: severe vision loss

Table 2. Mapping of health state transition and change cut-offs

Health state transition in the model	Change in logMAR cut-offs*
Gaining / Losing 3 health states	Reduction / increase in logMAR ≥ 0.5
Gaining / Losing 2 health states	Reduction / increase in logMAR 0.3 to 0.5
Gaining / Losing 1 health state	Reduction / increase in logMAR 0.1 to 0.3
Remain in current state	Reduction / increase in logMAR < 0.1

* Proportion is estimated by normal cumulative density function

Table 3. Key model settings and inputs

Parameter	Value	
Settings		
Cycle length	6 month in first cycle, 1 year afterward	
Time horizon	Lifetime	
Perspective	UK NHS and PSS	
Discount rate	3.5% for both outcome and costs	
Inputs		
Baseline characteristics		
Proportion of unilateral amblyopia at baseline[23-26]	25%~55.1%	
Proportion of each VA level for unilateral amblyopia[26]	mild: 65%; moderate: 24%; severe: 12%	
Proportion of each VA level for bilateral amblyopia[26]	mild: 77%; moderate: 19%; severe: 4%	
Efficacy		
6-months logMAR reduction – patching[28]	mild: -0.274; moderate: -0.365; severe: -0.370	
6-months logMAR reduction – atropine[28]	mild: -0.18; moderate: -0.27; severe: -0.34	
6-months logMAR reduction – binocular treatment[12,*]	mild: -0.344; moderate: -0.435; severe: -0.44	
Relapse		
Annual relapse rate[29]	patching: 25%; atropine: 21%; binocular treatment: 21% (assume same as atropine)	
Bilateral visual impairment (BVI)		
Incidence[9]	55 ≤ age < 65	0.280%
	65 ≤ age < 75	0.960%
	75 ≤ age	2.660%
Hazard ratio of mortality[10]	1.29	
Compliance		
Proportion of poor compliance[15,30,ǂ]	patching: 25%; atropine: 12.9%; binocular treatment: 12.9% (assume same as atropine)	
Odds ratio of treatment effect in non-compliers[31]	0.18	
Stereoacuity		
Proportion of nil stereoacuity at baseline[14]	66%	
Proportion of nil stereoacuity after 6-month treatment[14]	patching and atropine: 44%; binocular treatment: 20% (assumption)	
Utility of nil stereoacuity[32,33]	0.953	
Utility of measurable stereoacuity[32,33]	0.955	
Utility		
Utility by combination of VA of two eyes[¶]	Hodgson 2017[34] was used in the base-case; other studies[37-38] were used in sensitivity analyses.	
Healthcare resource utilization and costs		
Treatment costs[36]	£0.17 per disposable patch; £131.89 per unit of atropine; binocular treatment: hypothetical price	
Physician visits[26,35]	Frequency: 1.6 visits during 6-month treatment period; once a year afterward Unit cost: £104.16 per visit	
BVI costs[11,§]	£9110.76 (inflated to 2020)	

VA: visual acuity; N: normal vision; Mi: mild vision; Mo: moderate vision; Se: severe vision; BVI: bilateral visual impairment
*Assume 0.7 line gain vs patching across all VA severity and assume +1 line = -0.1 logMAR
ǂDefined as less than 50% of the recommended dose
¶Model three from the reference was used
§Apply only to patients with severe VA in both eyes

Discussion

Our model is the first model that more comprehensively incorporates key aspects of amblyopia and its treatments. The majority of the published economic evaluations studies were studying screening strategies and model until diagnosis examination using decision-tree structure, thus natural history of disease and treatment outcomes were generally not included. The König 2004 and Carlton 2008 papers contain significant development in methodology; however, utility impact from binocular VA and binocular functions were missing and these factors are important for studying novel binocular treatments. In our model, health states were defined by different combinations of VA in two eyes and utilities were estimated as a function of VA in both eyes. There is a continuous debate between whether utility is mainly impacted by better-seeing eye or both eyes. Alternative sets of utilities (based on better-seeing eye) were tested in sensitivity analysis and binocular treatment remained to be cost-effective. In addition, the majority of the utility studies were conducted for vitreoretinal diseases; further research based on the amblyopia population is thus required. The effect of improvement in stereoacuity was incorporated by including a utility increment estimated based on the proportion of patients having improvement in stereoacuity. It can be argued that the benefit associated with improving stereoacuity might be double counted using this approach due to reported association between stereoacuity and VA[39]. Further research on alternative approaches and the dynamic stereoacuity-VA relationship would be beneficial.

Conclusion

The proposed model structure describes important clinical features of amblyopia, including stereopsis, natural history of disease, long-term risks, vision of both eyes and impact on QoL. This model can be useful for health technology assessment and decision-making.

References

1. Von Noorden GK, Campos E. Binocular vision and ocular motility. 6th edn. Mosby, St Louis, MO2002
2. Doshi NR and Rodriguez ML. *Am Fam Physician*. 2007; 75: 361-367.
3. "Lazy eye". NHS. Available at: https://www.nhs.uk/conditions/lazy-eye/ [Accessed: 01 Oct 2021]
4. Levi DM et al. *Journal of Vision*. 2007; 7: 21.1–17.
5. Fu Z et al. *Br J Ophthalmol*. 2019; 0: 1-7.
6. Webber A. *Clin Exp Optom*. 2018; 101: 443–450.
7. Carlton J, Kaltenthaler E. *Eye*. 2011; 25: 403–413.
8. Rahi J et al. *Lancet*. 2002; 360: 597–602.
9. Leeuwen RV et al. *Br J Ophthalmol*. 2007; 91: 1450-1451.
10. Ehrlich JR et al. *Lancet Glob Health*. 2021; 9: e418-e430.
11. Carlton J et al. *Health Technology Assessment*. 2008; 12(25).
12. Kelly KR et al. *JAMA Ophthalmol*. 2016; 134: 1402-1408.
13. Wallace DK et al. *J AAPOS*. 2011; 15: 455– 461.
14. Stewart CE et al. *J AAPOS*. 2013; 17: 166– 173.
15. Wallace MP et al. *Investigative Ophthalmology & Visual Science*.2013; 54: 6158-6166.
16. König HH et al. *Strabismus*. 2000; 8: 79-90.
17. König HH et al. *Investigative Ophthalmology & Visual Science*. 2002; 43: 3209-3215.
18. König HH, Barry JC. *Pediatrics*. 2002; 109: e59.
19. König HH, Barry JC. *British Journal of Ophthalmology*. 2004; 88: 606-612.
20. Membreno JH et al. *Ophthalmology*. 2002;109: 2265–2271.
21. Joish VN. *J AAPOS*. 2003; 7: 283-290.
22. Rein DB et al. *J Pediatr Ophthalmol Strabismus*. 2012; 49(3): 146–156.
23. Haase W and Muhlig HP. *Klin Monatsbl Augenheikd*. 1979; 174: 232–235.
24. Shapira Y et al. *Br J Ophthalmol*. 2018;102: 659–666.
25. Fu J et al. Ophthalmic *Epidemiol*. 2014; 21:197-203.
26. Novartis real-world study, data on file.
27. Hirneiss C. *Clin Ophthalmol*. 2014; 8: 1703-1709.
28. The Pediatric Eye Disease Investigator Group (PEDIG). *Ophthalmology*. 2003; 110: 1632-1637.
29. Holmes JM et al. *J AAPOS*. 2004; 8: 420-428.
30. Tejedor J, Ogallar C. *American Journal of Ophthalmology*. 2008; 145: 562-569.
31. Hussein M et al. *J AAPOS*. 2004; 8: 429-434.
32. Kuang TM et al. *Eye*. 2005; 19: 540-545.
33. Ara R, Brazier J. *Value in Health*. 2008; 11: 1131-1143.
34. Hodgson R et al. *Adv Ther*. 2017; 34: 2360-2370.
35. NHS National Schedule of Reference Costs 2018/19, Available at: https://improvement.nhs.uk/resources/reference-costs/#rc1718 [Accessed: 01 Aug 2021].
36. British National Formulary. Available at: http://www.medicinescomplete.com [Accessed: 01 Aug 2021].
37. Brown GC. *Trans Am Ophthalmol Soc*. 1999; 97: 473-511.
38. Brown MM et al. *Ophthalmology*. 2003; 110: 1076-1081.
39. Lee SY and Isenberg SJ. *Ophthalmology*. 2003 ; 110 : 2088-2092.

Declaration of Interest

This study was sponsored by Novartis Pharma AG.

Acknowledgments

The authors received creative support from Hareesh Cheela and Vellanki Saketh (Novartis Healthcare Pvt. Ltd., Hyderabad, India).

Funding

Novartis

Contact information

For any query, please contact Ting-An Tai at ting-an.tai@novartis.com.

Poster presented at Virtual ISPOR Europe, 30 November – 3 December 2021.