Complete manuscript title: **The potential added value of novel hearing therapeutics: An early health economic model for hearing loss**

Short running head: **An early health economic model for novel hearing therapeutics**

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Conflict of Interest and Source of Funding

Professor Schilder is recipient of National Institute of Health Research (NIHR) and European Horizon 2020 grants. In her roles of director of the NIHR University College London Hospitals Biomedical Research Centre and National Lead of the NIHR Clinical Research Network ENT Specialty, she acts as an advisor on clinical trial design and delivery to CRO, biotech and pharma companies.

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ABSTRACT

Objective:

To construct an early health economic model to assess the potential added value of novel hearing therapeutics, compared to the current standard of care. We use idiopathic sudden sensorineural hearing loss (ISSNHL) as a case example, because it is a lead indication for several emerging hearing therapeutics.

Methods:

A decision analytic model was developed to assess the costs and effects of using novel hearing therapeutics for patients with ISSNHL. This was compared to the current standard of care. Input data were derived from literature searches and expert opinion. The study adopted a healthcare perspective of the UK National Health Service (NHS). Four analyses were conducted: 1) headroom; 2) scenario; 3) threshold; 4) sensitivity.

Results:

The decision analytic model showed that novel therapeutics for ISSNHL have potential value both in terms of improved patient outcomes, as well as incremental net monetary benefit (iNMB). The base case analysis revealed an iNMB of £39032 for novel therapeutics compared with the current standard of care. Results of the threshold and scenario analysis revealed that age of treatment and severity of ISSNHL are major determinants of iNMB for novel therapeutics.

Conclusion:

This paper describes the first health economic model for novel therapeutics for hearing loss; and shows that novel hearing therapeutics can be cost-effective under NICE's cost-effectiveness threshold, with considerable room for improvement in the current standard of care. Our model can be used to inform the development of cost-effective hearing therapeutics; and help decision makers decide which therapeutics represent value for money.

INTRODUCTION

Hearing medicine has entered into an exciting phase, with innovations that promise to bring considerable benefits to patients with sensorineural hearing loss.[1-3] Recent discoveries in the genetic and molecular pathways underlying this type of hearing loss have led to the identification of therapeutic targets and the development of novel therapeutics, including drug, gene and cell therapies, many of which are entering the phase of clinical testing in humans.[1-3]

This field is driven by new biopharmaceutical companies, supported by sizeable investments from venture capitalists who recognise hearing loss as an important area of unmet clinical need with high growth potential.[1,4] 466 million people worldwide have disabling hearing loss and owing to our ageing population, it is estimated that by 2050, over 900 million people will be affected.[5] Hearing loss has been found to be a major risk factor for dementia[6] and its annual economic cost is estimated at $750 billion globally.[5]

Current treatments for sensorineural hearing loss focus on care rather than cure and are therefore not fully meeting the needs of patients.[2,3] Novel hearing therapeutics, aiming at curing hearing loss, if proven effective, could radically change hearing services within the next 5-10 years.[2,3] Healthcare systems will need to make difficult decisions on which therapeutics represent value for money and are worth commissioning. Early health economic modelling provides a tool to do so by providing an understanding on likely cost-effectiveness, and by informing product development, market access and pricing.[7]

This study aims to construct an early health economic model to assess the potential added value of novel hearing therapeutics, compared to the current standard of care. We use idiopathic sudden sensorineural hearing loss (ISSNHL) as a case example, because it is a lead indication for several emerging hearing therapeutics.[2]

MATERIALS AND METHODS

Ethics approval and consent to participate

Ethical approval was granted by University College London (UCL) Research Ethics Committee 12241/001. Informed consent was sought from all participants.

Target population

The target population simulated through our model consisted of patients with unilateral ISSNHL in the National Health Service (NHS) in England. ISSNHL is sub-type of sensorineural hearing loss that develops suddenly, within the course of 3 days, usually in one ear, and with no known cause (idiopathic).[8,9] It affects 5 to 27 per 100,000 people annually, with

about 66,000 new cases per year in the United States.[8] The most widely used treatments for ISSNHL are systemic and intratympanic steroids, with considerable limitations in their effectiveness and evidence base.[8,9] It is estimated that 35 to 68% of cases of ISSNHL fail to recover; and clinical experience suggests that this is an underestimation.[8,9] In case of non-recovery of hearing, patients are offered a hearing device.

Decision analytic model

A decision analytic model was constructed following ISPOR-SMDM Best Practice Guidelines[10] to assess the potential costs and effects of using novel hearing therapeutics in adult patients with ISSNHL. This was compared to the current standard of care. The model consists of a decision tree to map the early management of ISSNHL and a state-transition model to simulate long-term follow-up. The structure of the decision tree and state transition model was based on best available evidence[8,9,11-13] and validated by expert opinion. Model assumptions are summarised in Supplemental Digital Content 1 and were reviewed by expert participants (n=26). Information on expert participants can be seen in Supplemental Digital Content 2.

Decision tree

A decision tree was constructed to map the costs and outcomes of the acute treatment pathway for patients presenting with SSNHL, at four different severities, mild (25-40 decibel [dB] loss), moderate (41-70 dB loss), severe (71-95 dB loss) and profound (>95 dB loss), for both the current NHS standard of care and for novel hearing therapeutics (see Figure 1). The decision tree only includes parameters that differ in effect, incidence and costs between strategies, and that therefore contribute to a difference in the cost-effectiveness. Non-

differentiating variables were not included in the model following consultation with experts. For example, an initial hearing test for either the existing or the novel strategy will occur at the same incidence, with the same effect, at the same costs and will therefore not differ between strategies.

For the current NHS standard of care, patients with SSNHL are mapped to receive oral steroids, followed by three intratympanic steroid injections, 1 to 2 weeks apart in the event that hearing does not recover to baseline (baseline defined as hearing level within 10dB of the unaffected ear). Patients whose hearing does not recover to baseline following intratympanic injections undergo Magnetic Resonance Imaging (MRI) and laboratory testing to exclude identifiable causes of SSNHL. Patients that do not recover to baseline either stay at their initial level of hearing loss or improve to a less severe level of hearing loss.

For the new strategy, steroids have been replaced by a novel hearing therapeutic that can return hearing back to baseline. The final outcomes of the decision tree include: recovery to baseline, or, mild, moderate, severe or profound ISSNHL.

State-transition model

The decision tree is followed by a state-transition model, to simulate the long-term costs and impacts on quality of life due to ISSNHL (see Figure 2). In the state-transition model, patients enter the hearing health state that corresponds to their hearing level at the end of the decision tree. Following the first cycle, patients are able to move to a 'hearing loss with amplification health state'. This includes a hearing aid for patients with mild hearing loss;

patients with moderate, severe or profound hearing loss are able to receive a hearing aid, a contralateral routing of signal (CROS) aid or a bone conduction hearing device (BCHD).

Patients with amplification were able to move back to their unamplified hearing loss state, recognising compliance issues with hearing devices. Patients from all health states were able to move to "death" (all-cause mortality). The state-transition model adopted a cycle length of one year and spanned the patient's lifetime until death, owing to the life-long costs and effects of hearing loss.

Probabilities

Data on transition probabilities were derived following scientific and grey literature searches and reviewed by expert participants (n=26). Supplemental Digital Content 3 shows the probabilities used in the decision tree and the state-transition model, together with their standard errors and sources.[11-16] All-cause mortality rates were obtained from the Office for National Statistics and were age dependent (Supplemental Digital Content 4).[14]

Outcome measures

Effectiveness was measured in quality adjusted life years (QALYs) based on lifetime follow-up. A QALY is a generic measure of health that factors both length and quality of life into a single measure. It is calculated by the number of years spent in a health state, multiplied by its utility score. A utility score represents the health-related quality of life (HRQoL) and ranges from 0 to 1, where 0 represents total loss of health-related quality of life, i.e., death, and 1 represents perfect health.[17]

Utility scores for HRQoL and their standard errors were obtained from systematic literature searches and reviewed by expert participants. HUI-3 was used since it has been found to be a more valid and responsive instrument to change in hearing loss HRQoL than EQ-5D. To account for declining quality of life with age, an annual disutility score was applied to utility scores.[18] Supplemental Digital Content 5 summarises the utilities used and their sources.[17-20] Effects were discounted at a 3.5% per annum rate as per NICE guidelines.[19]

Cost information

Cost analysis was performed from a NHS healthcare provider perspective (only healthcare costs were included). Unit costs were calculated in British Pounds (GBP) and were primarily obtained from NHS reference costs.[21] Other sources included NICE guidelines,[9] the British National Formulary (BNF),[22-24] University College London Hospitals (UCLH) NHS Foundation Trust,[25] Cambridge University Hospital NHS Foundation Trust,[26] University Hospitals Birmingham NHS Foundation Trust,[27] the literature[28] and NHS England.[29] Supplemental Digital Content 6 and 7 provide a detailed breakdown of costs used for the decision tree and state-transition model respectively. All unit costs were reviewed and agreed upon by experts.

In the state-transition model, costs were incurred for transitioning into an amplification state and for staying in an amplification state. These costs depended on the type of amplification used, which included: a hearing aid, and/or a CROS aid, and/or a BCHD. The proportion of patients of each severity, receiving each type of device was determined following expert input and is summarised in Supplemental Digital Content 8.

The cost for a BCHD also included costs for common complications, including skin complications and implant failures. Complication rates were obtained from the literature[30,31] and from experts and were taken as 20% and 4% for skin complications and implant failures, respectively (Supplemental Digital Content 8).

The minimum possible cost incurred for patients for the novel therapeutic included a hearing test and an ENT follow-up appointment. Costs were discounted at a rate of 3.5% as per NICE guidelines[19] and all unit costs were adjusted to 2018 according to the consumer price index (Supplemental Digital Content 9).

Validation

We verified the model's validity using the AdViSHE checklist.[38] This checklist covers five aspects of validation: conceptual model, input data, computerised model and operational validation and other validation techniques. The conceptual model, input data and model outcomes were tested on its face and operational validity by consulting with 26 participants, including ENT surgeons (n=11), audiologists (n=4), health economic modelling experts (n=4), discovery scientists (n=2), industry representatives (n=2) and patients with ISSNHL (n=3). No other health economic models on ISSNHL were found for cross-validation. The computerised model was validated by sub-unit, extreme value testing and testing of traces to detect possible coding errors. The model was checked for inaccuracies by an expert in economic modelling.

Analysis

The model was developed and built using Microsoft Excel. Adults with ISSNHL were sent through the model to determine mean expected costs and effects (QALYs) per patient, from onset of ISSNHL until death, for the current standard of care and the novel therapeutic. Four different but related analyses were conducted: Headroom analysis, scenario analysis, threshold analysis and sensitivity analysis, taking into account NICE's cost-effectiveness threshold of £20,000/QALY.[19]

The headroom analysis explored the room for improvement in the current treatment of ISSNHL; specifically the maximum added value of a novel therapeutic. The headroom analysis assumed patients entering the model at 50 years of age,[11] receiving a 100% effective and a zero cost novel therapeutic. Effectiveness is defined as percentage of patients whose hearing recovered to baseline. Therefore 100% effectiveness indicates that 100% of patients returned to their baseline hearing. The scenario analyses explored the effects on cost-effectiveness of: different starting ages of patients, different severity of ISSNHL at onset, combined use of steroids with the novel therapeutic. The threshold analysis was used to determine the maximum cost of the novel therapeutic in order to be cost-effective, at different levels of effectiveness. In the sensitivity analysis, the effect of varying uncertain parameters on the outcome was assessed including: utility of hearing loss states (without amplification); utility gain following amplification; adoption rates of a hearing aid, CROS aid or BCHD.

Results were expressed using the incremental net monetary benefit (iNMB) of the novel therapeutic. The iNMB represents the added value of an intervention, compared to the

current standard of care, in monetary terms. The iNMB was calculated using the formula:

iNMB = ($QALY_n$ x threshold value – $Costs_n$) – ($QALY_c$ x threshold value – $Costs_c$)

[n = novel therapeutic, threshold value = 20,000/QALY, c = current treatment]. A positive iNMB indicates that the novel therapeutic is cost-effective compared to the current standard of care. The higher the iNMB, the greater the added value of the novel therapeutic in monetary terms.

The results for all analyses were obtained using probabilistic sensitivity analyses (PSA), taking the mean across 5000 simulations to account for uncertainty around parameters. 95% confidence intervals were calculated by multiplying the standard deviation derived from a PSA by 1.96.

RESULTS

Headroom analysis

The results for the headroom analysis are shown in Table 1, scenario '1'. The total costs and QALYs per patient from 50 years of age to death for the current standard of care are £6,963 [£5,032-£8,894] and 14.78 [12.09-17.47] respectively. The total costs and QALYs for the novel therapeutic are £158 [£158-£158] and 16.39 [13.53-19.25], respectively. This results in savings of £6,805 [£4,875-8,736] and an increment in QALYs of 1.61 [0.79-2.43] per patient. For the headroom scenario, the iNMB of a novel therapeutic is £39,032 [£21,103-£56,962].

Scenario analysis

Table 1 shows the results of the scenario analysis. When compared to the headroom scenario (scenario 1), adding oral and intratympanic steroids to the novel hearing therapeutic (scenario 2) has a minimal effect on the iNMB. Only treating 30 year old patients increases the iNMB to £48,125 [£25,848-70,403], whereas only treating 70 year old patients, decreases the iNMB to £24,666 [£13,716-35,615]. Increasing the severity of the hearing loss at onset increases the iNMB (scenarios 5, 6 and 7), owing to increasing costs of the current standard of care. All iNMBs carried wide confidence intervals (CI) that were greater than zero.

Threshold analysis:

The threshold analysis is illustrated in Figures 3 and 4. The lines in the graphs represent an iNMB of £0, identifying 1) the maximal cost for each level of effectiveness, and 2) the minimum effectiveness required at each cost point, for the novel therapeutic to be cost-effective, compared to the current standard of care. For example, if age of onset of ISSNHL is 70 years, and the therapeutic is 75% effective, maximum cost of the novel therapeutic in order to be cost-effective is £16,714, taking into account NICE's cost-effectiveness threshold of £20,000/QALY. Supplemental Digital Content 10 and 11 illustrate these results with confidence intervals.

Sensitivity analysis

The results of the sensitivity analysis are shown in the tornado plot in Figure 5. Varying the parameter 'unamplified utility score' produced the largest impact on iNMB of the novel therapeutic. This was followed by utility gain following a hearing aid/CROS aid.

DISCUSSION

This paper describes the first early health economic model for novel therapeutics for hearing loss; and uses ISSNHL as a case example.

Summary of findings:

The headroom analysis, revealed an iNMB of £39,032 compared to the current standard of care. This means that in a perfect scenario, where a novel ISSNHL therapeutic were 100% effective and cost £0, the added monetary value of the novel therapeutic to a 50-year old across their lifetime would be £39,032 compared to the existing standard of care. Along with cost and degree of effectiveness, the starting age of treatment and severity of ISSNHL at onset are major determinants of the iNMB for a novel therapeutic. Our scenario and threshold analyses illustrate the uncertainty of our findings with wide confidence intervals.

Implications

There is clear room for improvement in the current standard of care for patients with ISSNHL in the UK healthcare system; and novel therapeutics for ISSNHL can be cost-effective; making this an attractive area for discovery scientists, clinicians, investors and decision makers. Our model can be used by industry and decision makers to assess: 1) the maximum price-point of a novel ISSNHL therapeutic at different levels of effectiveness, and 2) the minimum effectiveness required at each price point, for the novel therapeutic to be cost-effective. Our model allows for these assessments to be tailored to age of onset of

ISSNHL and severity of ISSNHL, the two major determinants of cost-effectiveness as identified from our analysis.

By providing this information *before* a therapeutic has entered the market, this study will assist industry to develop ISSNHL therapeutics that are cost-effective in the UK healthcare system. With a growing number of hearing therapeutics on the horizon, our findings will help investors, policy makers, regulators and guideline developers decide which therapeutics represent value for money and are worth commissioning. Overall, this research will increase the likelihood of developing hearing therapeutics that can be adopted into the UK healthcare system and therefore used by patients.

Future research

The wide confidence intervals presented demonstrate that more reliable data on transition probabilities and utility scores for the current standard of care are warranted to make more reliable estimates. Varying 'unamplified utility score' and 'utility gain following a hearing aid or CROS aid' produced the largest impact on iNMB for the novel therapeutic. Research to more accurately delineate these parameters would help improve the accuracy of our model. The SeaSHeL study, led by the first author, is a recently launched ENT trainee and Audiologist collaborative UK prospective cohort study of adult patients presenting with SSNHL across 97 NHS Trusts.[39] The study will map the patient pathway and collect data on the characteristics and outcomes of adult patients presenting with ISSNHL in the NHS. We aim to utilise data from the SeaSHeL study to refine and validate our economic model.

It is important to recognise that cost-effectiveness alone does not determine whether a novel therapeutic can be successfully implemented into a healthcare system. Rather it is a key factor that influences the decisions of other agents within the healthcare market, including “market makers” (discovery scientists, industry, investors) driving the uptake of novel therapeutics; “bodies of strategic constraint” (regulators, funders, guideline and policy makers) trying to impose order and cost-control; and “users” (patients and clinicians) extracting opportunities for treatment.[40,41] Recognising the complexity of healthcare markets, our future work aims to characterise and understand the interacting factors and agents that motivate and shape the adoption of novel hearing therapeutics in the UK hearing market. Taken as a whole, this unique approach, combining sociological and economic perspectives can be used to pave the way for novel hearing therapeutics in the UK healthcare system; and its methodology can be used to facilitate the adoption of innovations in other disciplines.

Limitations

The precise treatment pathway for patients with ISSNHL (see Supplemental Digital Content 12) varies between regions within the UK and between countries, despite published guidelines. As a result our model cannot be fully representative of all treatment pathways. However, we expect similar trends in cost-effectiveness and our detailed account of the model allows for assessment of transferability to other situations. Owing to the hypothetical nature of the novel therapeutic, a drug safety profile of the novel therapeutic was not included, which would have an impact on the price of the novel therapeutic. The existing literature on ISSNHL is limited, mainly consisting of retrospective, heterogenous studies with different treatment regimens, including differences in time between hearing loss onset and

start of treatment, as well as differing definitions of hearing loss severity and outcome. Data were also limited for calculating utility gain following hearing amplification strategies. Moreover, no data were available on the proportion of patients with ISSNHL receiving differing hearing devices, and hearing device non-compliance rates. For these data, input was sought from expert participants who also fine-tuned the model and validated our assumptions. We recognise the limitations of using data from expert participants. This was mitigated by using multiple (n=26) expert participants to validate our model; and a sensitivity analysis was performed to assess uncertainty. We also acknowledge the wide confidence intervals in the scenario and threshold analyses, but highlight that these confidence intervals were all greater than zero, indicating that a novel SSNHL therapeutic would be cost-effective compared to the current standard of care.

Costs were based on NHS England healthcare prices and may therefore differ from other countries. The same applies to expert opinions, which were mainly of a UK perspective. Finally as with any health economic model, assumptions were made during its development (outlined in Supplemental Digital Content 1). To mitigate bias, these assumptions were reviewed and agreed upon by multiple expert participants (n=26).

Conclusions

This paper describes the first health economic model for novel therapeutics for hearing loss; and shows that novel hearing therapeutics can be cost-effective under NICE's cost-effectiveness threshold, with considerable room for improvement in the current standard of care. Our model can be used to inform the development of cost-effective hearing therapeutics; and help decision makers decide which therapeutics represent value for

money and are worth commissioning. Overall, this research will help pave the way for valuable, novel hearing therapeutics in the UK healthcare system.

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FIGURE LEGENDS:

Figure 1: A section of the decision tree showing the current standard of care for patients with moderate ISSNHL

Figure 2: State-transition model

Figure 3. Threshold analysis – starting age.

Figure 4. Threshold analysis - severity of hearing loss

Figure 5. Incremental NMB variation in sensitivity analysis.