Early Health Technology Assessment of Using NeoDoppler Technology to Monitor Cerebral Blood Flow Velocity in Pediatric Cardiac Surgery

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Abbreviations

AV-ratio	Cerebral arterial-to-venous volume ratio
CBF	Cerebral blood flow
CBFV	Cerebral blood flow velocities
CDA	Clinical decision analysis
CEA	Cost-effectiveness analysis
CED	Coverage with either evidence development
CE-plane	Cost-effectiveness plane
CHDs	Congenital heart defects
CICU	Cardiac intensive care unit
CPB	Cardiopulmonary bypass
CTC	Conditional treatment continuation
CUA	Cost–utility analysis
DHCA	Deep hypothermic circulatory arrest
EarlyHTA	Early health technology assessment
EEG	Electroencephalography
H	Headroom analysis
HrQoL	Health-related quality of life
HSCC	Health and social care cost
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
ISPOR	International society for pharmacoeconomics and outcomes research
LFCPB	Low flow cardiopulmonary bypass
LOS	Length of stay
LYG	Life years gained
MEAs	Managed-entry agreements
MRP	Maximum reimbursable price
NICU	Neonatal intensive care unit
NIRS	Near-infrared spectroscopy
PVN	Predictive value negative
PbR	Payment-by-result
pCO_2	Partial pressure of carbon dioxide
PICO	Population, intervention, control, and outcomes
PICU	Pediatric intensive care unit
PM	Precision medicine
PVP	Predictive value positive
PSA	Probabilistic sensitivity analysis
QALYs	Quality-adjusted life years
rSO2	Regional cerebral oxygen saturation
ROI	Return of investment
RWD	Real world data
RWE	Real world evidence
SMDM	Society for medical decision making
TCD	Transcranial doppler ultrasound
VBC	Value-based care

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1. Introduction

Congenital heart defects (CHDs) contributes to one-third of common congenital defects (Sidra Kaleem Jafri et *al.*, 2017). The incidence of CHDs in neonatal vary from 4/1,000 to 50/1,000 in different studies (Julien I. E. Hoffman *et al*., 2002). There are several types of CHDs, ranging from minor to severe involving atrial septal defect, patent ductus arterioles, pulmonary stenosis, ventricular septal defect, tetralogy of fallout, and hypoplastic left heart syndrome. Some studies indicate that genetics (e.g. chromosomal defects), smoking during pregnancy, medicines, and mother's medical condition (e.g. diabetes, phenylketonuria, and rubella) increase the risk of getting CHDs (Joseph B. Clark *et al*., 2012; Jenkins KJ *et al*., 2007). The risk of CHDs can be estimated by screening with for instance fetal echocardiogram during pregnancy and pulse oximetry in newborn. Surgical correction in early childhood is one of the treatment strategies (Dean B Andropoulos *et al.*, 2004). The need for surgery depends on the symptoms. Most neonatal with complex CHDs need surgery before they are one year old. There are three common bypass techniques used in pediatric cardiac surgery, low-flow cardiopulmonary bypass (CPB), high-flow deep hypothermic CPB, or circulatory arrest (DHCA) (Sara Lozano *et al.*, 2004). Pediatric cardiac surgery techniques, such as deep hypothermic circulatory arrest (DHCA) and low-flow bypass, may lead to adverse neurologic event. Cardiac surgery may result in cerebral oxygen imbalance including 1) dysautoregulation of cerebral blood flow 2) suboptimal CO_2 management, and 3) inadequate oxygen delivery. It could contribute to neurological and brain injury (Harvey L. Edmonds, 2005). The rate of neurological complications is about 23% after heart surgery in children (without monitoring) (Sara Lozano, 2004). Therefore, in clinical practice, neurological monitoring during heart surgery is a strategy to prevent adverse events and improve neurological outcomes.

Currently, there are some medical devices used in cardiac surgery to monitor cerebral blood flow (CBF) during circulatory arrest and low-flow cardiopulmonary bypass (CPB). They work together as a multimodality neurological monitoring system to prevent adverse events (e.g. neurological complications) intraoperation. The evidences indicate that it is a tool to improve neurological outcome before, during, or after cardiac surgery. The existing brain monitoring devices have certain technical limitations could lead to errors and pitfalls. (Retrieved from NHLBI; Erle H. Austin III *et al.*,1997; Sushmita Purkayastha *et al.*, 2012; Angelo Polito *et al.*, 2006; Y Durandy *et al.*, 2011). NIRS monitoring system has been adapted as standard of care in several countries. However, stand-alone use as a diagnostic tool to prevent neurologic outcomes is controversial (Jennifer C. Hirsch *et al.*, 2009). In

1997, Austin EH, and Edmonds HL provided a retrospective cohort study results. It indicates a multimodality neuromonitoring system combined with NIRS, TCD, and EEC could be useful in pediatric cardiac surgery. The monitoring system has a potential to reduce the risk of adverse neurologic event caused by surgery. It could optimize the health outcomes in post-operation (Erle H. Austin III *et al.*, 1997; Joseph B. Clark *et al.*, 2012).

CIMON Medical develops NeoDoppler technology to evaluate cerebral blood flow variations for expectation on early detection and diagnosis of clinical conditions. The intended use of innovative technology is to detect potential problems such as cerebral perfusion and cerebral emboli in patient management during operation and correct the deficiencies by proper clinical interventions. The innovation ameliorates some limitations of brain monitoring devices that have been used in pediatric cardiac surgery. In a previous study (Sigrid Dannheim Vik and Hans Torp et al., 2020), NeoDoppler technology measures cerebral blood flow velocity continuously and simultaneously in different depths of the brain. The results showed good agreement with conventional ultrasound system on the accuracy of continuous cerebral circulation monitoring in neonates. Therefore, the aim of this study is to evaluate the clinical application of NeoDoppler technology as an assistant tool of neurophysiological monitoring system. As a role of innovation, what are the technical requirements for NeoDoppler to gain cost-effective compared with a multi-monitoring system?

In the first part of our study is to estimate the cost-effectiveness of a multi-monitoring system compared with no multi-monitoring system during surgery. The estimated endpoints are survival rate, neurocomplication, and length of stay at the hospital. In the second part of our study, Early Health Technology Assessment (EaryHTA), we estimate the possibility of NeoDoppler technology (innovation) for being cost-effectiveness compared with a multi-monitoring system. We use device's accuracy approach to estimate in which conditions that NeoDoppler technology will become more cost-effective or cost saving than a multi-monitoring system. The generate effects (survival rate, neurocomplication, and length of stay) and/or less costs of health service can predict how much room for maximum reimbursement price (MRP) on innovation. The results are presented in the headroom analysis. Finally, return of investment (ROI) in innovative technology calculates from value of revenues (V) method. There are some assumptions applied to our study based on the information obtained from our literature search.

2. Outline of Thesis

In introduction, we describe the essential cardiac surgery for congenital heart defects (CHDs) in neonates. A brain monitoring system has an important function in intraoperative. In background section, we present two types of brain monitoring system. They have been adopted in certain healthcare sections. We also introduce innovative NeoDoppler technology, which has the same intended use as existing brain monitoring systems. We state the benefits of medical innovation in healthcare service. How innovation can create a value-based care and gains the chance of reimbursement from payers. In theoretical framework, we employ widely used models of health economics evaluation to explain the research questions in our study. In methods and material section, PICO (population, intervention, control, and outcomes) model is a guidance in our research framework, which is an evidence-based practice. Foreground research questions are formulated by PICO format. There are four main elements, population, intervention, control, and outcomes addressed in our study (Sadaf Aslam and Patricia Emmanual, 2010).

P: Population of interest. Specific population can be identified by age, sex, and medical history.
I: Intervention or treatment of interest. It includes new therapy, diagnostics test, or procedure.
C: Control or comparison intervention. It can be standard of care, existing intervention, or placebo.
O: Outcome of interest. It should consider measurable and appropriate to research question.

Lastly, all analysis results are presented in two main parts. The first part is cost-effectiveness analysis for a multi-monitoring system. The second part is EarlyHTA for innovative NeoDoppler technology. Discussion and conclusion are conducted in the last section of thesis.

3. Background

3.1 Medical Device

In recent years, many countries face a challenge of growing in healthcare expenditure because of increasing elder population and higher medical standards to expect from patients. Innovation of medical devices play an important role on the quality of healthcare service. It may simulate the reform of health care system because of budget control and cost containment from governments. Health technology assessment is one of methods to evaluate the possible impact on health expenditure and to

reduce the cost and allocate the resource in an efficiency way. Patient access scheme considers no delay on the availability of innovation (C. Lee Ventola, 2008). As for medical device companies, the incentives of innovation and investment on research and development could reflect from government's policy and strategy (G. Gregory Raab and David H. Parr, 2006). "Medical Innovation" includes modifying, upgrading, and improving existing devices to fulfill the unmet needs. (Karen B Ekelman, 1988). Innovation could lower the costs in many health care circumstances to relevant stakeholders such as patients, healthcare providers and payers. The great benefits drive an innovation in medical technology. Diagnosis devices with great promise can provide physician more useful information on the decision of treatment in individual patient. Innovation can be a value-based care (VBC) approach by making a better clinical outcomes.

Value-Based Care (VBC)

VBC is one of measurement for reimbursement. The valued-based payment models base on the results of quality measures. It is a reimbursements reform from fee-for-service (FFS) model. It focuses on resource utilization (e.g., length of stay), patient outcomes (e.g., mortality) and safety (e.g., complications) in order to ensure high-quality care delivered and manage costs. (Michael E. Porter, 2006). Performance-based agreement is one of the managed-entry agreements (MEAs). It can be coverage with either evidence development (CED) or payment-by-result (PbR) at patient level or population level. Performance-Based MEAs address the uncertainty and share the risk between payers and producers. It is a way of managing budget impact for payers and increasing the likelihood of reimbursement for producers. The payment occurs along the evidence development and real world data gathering, which gives the room for renegotiate the novel price and allows re-evaluation of the price for reimbursement (Jacoline C. Bouvy *et al.*, 2018; Justin S Yu *et al.*, 2017). Producers will be accountable for effectiveness and keep following up on patients' outcomes though post-market surveillance. It may generate extra cost and time-consuming to monitor. On the other hand, performance-based MEAs also benefit patients on accessing to innovative technology earlier. It creates incentives for innovation and improvement of healthcare service sustainably. The transparency of novel pricing and payment models based on patient outcomes data can ensure to fit for purpose and legal frameworks (Martin Wenzl and Suzannah Chapman, 2020; Josh J Carlson *et al.*, 2014). The main challenges could be stakeholder alignment, measurement outcomes, and information technology (IT). Stakeholder alignment includes both consumer side and manufacturer side. In the customer alignment, there are different needs from patients, health care providers, payers, and policy makers. As for manufacturer, they may take business model, launch strategy, and potential revenues into account. All stakeholders would have certain level of engagement on clinical measures, performance and efficiency, cost of

care, and social impact. They would have different goals of assessment on the potential benefits of innovation (Patricia Vella Bonanno *et al.*, 2017). Return of investment (ROI) and profitability of products are the primary purpose for a company. To maximize profits for future research and development drives companies growing and steadying on the market. For decision makers, optimizing health expenditure can benefit most public health and achieve health economics. In addition, either industry or other stockholders, the accessible, affordable, high quality and patient-orient healthcare services should be the common values and core values for all of them. Innovation contributes to shape the health care system making it sustainably to society (Jacoline C. Bouvy *et al.*, 2018).

Other barriers for MEAs are outcome selection and measurement in determining the coverage and reimbursement. There are three aspects in the reimbursement strategy. First, clinical outcomes of patients, the endpoints should be sufficient and acceptable by payers as an evidence-based approach. It could be short-term effect such as current health or long-term health as consequence of the intervention. Second, whether innovation can provide a better workflow for professionals and cost-saving by improving the performance and efficiency. Third, quality of life during the life expectancy is also important in humanistic aspect. It could have influence on mental health, financial issue, productivity of work, and societal impact in later life. Thus, outcomes measurement should have a clearly define (TylerO'Neill *et al.*, 2019). The agreement on chosen outcomes presents the value for money to related stakeholders. Another challenge is how to collect data in defined outcomes. Information technology (IT) is responsible for data administration. The system should include several departments to register patient medical data such as patients electronic health records, pharmacy and hospital information, and ambulatory care. These key elements are linked together to establish a comprehensive healthcare information system for data source, collection, store, access, later analysis and evaluation purpose under patients privacy and protection law. MEAs has been adapted widely in some countries of OECD, European Union, or the United States nowadays. (Martin Wenzl and Suzannah Chapman, 2020; Stefanos Zenios *et al.*, 2010).

Brain Monitoring System

Near-Infrared Spectroscopy (NIRS)

Children undergoing heart surgery is at a high risk of experiencing neurological outcome. Brain monitoring technology to ensure adequate blood flow and cerebral oxygenation interoperation has progressed in the last decades. Intraoperative regional cerebral oxygen saturation (rSO_2) value and the duration of low rSO_2 are associated with brain injury and negative neurologic outcome. NIRS can direct measure regional tissue oxygen saturation (rSO_2) values and indirect obtain the blood flow

index by NIRS software calculation. rSO_2 indicates the balance between oxygen supply and demand in the detecting area (Hiroyuki Uchino, 2015). The treatment of increasing oxygen delivery and decreasing the consumption of oxygen by monitoring the values of CPB flow, depth of anesthesia, and hemoglobin can play a role of preventing brain injury from surgery (J. M. Murkin and M. Arango, 2009). The diagnosis devises are considering as NIRS stand alone, or NIRS additional TCD and other medical devices. In Giuseppe Filiberto Serraino and Gavin J Murphy, 2017, they presented a systematic review and meta-analysis from several randomized trials. It indicates while using NIRS-based algorithms in adult surgery to optimize cerebral oxygenation did not improve the clinical outcomes in patients comparing to non-NIRS-based protocols. In the study, Samra *et al*, 2000, it indicates that the sensitivity of NIRS is 80% with a specificity 82% in a cutoff point 20 % relative decrease in rSO_2 in patients undergoing carotid endarterectomy (CEA). The false positive rate is 66.7% and the false negative rate is 2.6% (Robert S. Bonser *et al*., 2011). There are certain limitations of NIRS be mentioned in some papers, NIRS obtains the value from NIRS calculation, a cerebral arterial-to-venous volume ratio (AV-ratio), which is an indirect measurement (H. Marc Watzman *et al.*, 2000). Their study indicates a fixed ratio(s) do not have obvious difference in certain pathophysiological conditions for instant normoxia, and hypoxia. The poor response may lead concern on NIRS's accuracy by using the method (H. Marc Watzman *et al*., 2000). NIRS technology only can detect frontal cerebral cortex of brain and unavailable in measuring other deeper areas (Andropoulos, Dean B *et al*., 2004). At the upper and lower values of the spectrum, the results will being inaccuracy and less quality (Andropoulos, Dean B *et al*., 2004). Another technical boundary is that the response time up to several minutes when a sudden change in cerebral blood flow occur. It may delay the real-time clinical intervention and treatment. Moreover, cerebral oximetry can be vary in different values of hemoglobin and partial pressure of carbon dioxide (pCO_2), for instance hemodilution, and hypocapnia. There are no sufficiency references for value correction (Y Durandy *et al*., (2011).

Transcranial Doppler Ultrasound (TCD)

Cardiopulmonary bypass (CPB) flow management is important in brain protection in anesthesia for pediatric cardiac surgery. Cerebral autoregulation plays a function of maintaining cerebral blood flow (CBF). The function would be affected by CPB, which needs deeper hypothermia in the clinical practice. Hypothermia has been used to reduce CPB flow in order to slow metabolism for neuroprotection and able to operate in bloodless area. Transcranial Doppler Ultrasound (TCD) is introduced to measure cerebral blood flow velocities (CBFV). Blood flow velocity is related to hematocrit, viscosity, carbon dioxide, and blood pressure (Suzanne Verlhac, 2011). The impact of temperature on blood flow velocity do not have a clear relationship for instance in hypothermia and further studies required

(Sushmita Purkayastha *et al.,* 2012). There are also certain limitations of TCD mentioned in Sushmita Purkayastha *et al*., 2012. Firstly, well knowledge of the three-dimensional cerebrovascular anatomy and highly operator-dependent are required to understand the meaning of sonograms shown by the windows. Secondly, ultrasound energy transmission is influenced by the bone thickness and porosity in the detection region. Thirdly, TCD technology can only obtain the value of cerebral blood flow velocity from large basal arteries and undetectable in local area. Furthermore, in M. Akif Topcuoglu, 2012, it indicates the signals variation are risen by several factors, for instance intracranial distal and extracranial proximal arteries, and cardiac physiology. Therefore, given correct interpretation of sonograms is highly needed for further clinical intervention and treatment.

NIRS and TCD work together which can help guide bypass flow rates and monitor cerebral perfusion in low flow cardiopulmonary bypass (LFCPB) (Hiroyuki Uchino, 2015). In the paper Erle H. Austin III *et al.,* (1997) identified the treatment algorithm according to the data of neurological monitoring system. Monitoring cerebral perfusion is the way of giving real-time clinical intervention intra-operation. NIRS and TCD work together with other medical devises as a diagnostic tool for brain monitoring.

Innovative, NeoDoppler technology

NeoDoppler technology is a novel system continuously monitoring cerebral blood-flow. The core of the innovation is a coin-sized ultrasound probe that can measure blood circulation continuously by illuminating a 1x4 cm cylindric area of the tissue under the probe and capture all blood flow signals in this volume simultaneously. It catches the multiple sample volumes. The design of the probe is user friendly. NeoDoppler technology does not require a trained operator to position a small sample volume inside one specific blood vessel. The probe adhesives to the infant's fontanel during the monitoring, handheld not required. The material of medical device where applied to skin, sensitivity and toxicology analysis are take into consideration. The response time less than 10 seconds, NIRS and TCD are more than 10 seconds, which provides physicians real-time information on clinical intervention intraoperation. NeoDoppler technology response time is fast and less than 0.5 sec. Several arteries are picked up from the fontanelle position due to the broad beam, no need for detailed anatomical knowledge for NeoDoppler technology. However, the disadvantage of NeoDoppler technology is also limited to the large basal arteries for measuring on cerebral blood flow velocity.

In our study, we considering the innovation could solve certain limitations from NIRS and/or TCD. The main goal is to improve the device's accuracy and in line with treatment algorithm. Treatment

algorithm based on the monitoring data has to achieve the best intervention strategy. Sensitivity and specificity of diagnosis devices contribute to false positives and false negatives. They perform the accuracy of diagnosis devices (Thomas Jue and Kazumi Masuda, 2013). As an innovative device, what are the requirements for NeoDoppler technology to become more cost-effective than existing multi-monitoring system? Thus, there are some research questions generated in our study.

3.2 Research Questions

The First Part: Cost-Effectiveness Analysis for an Existing Multi-Monitoring System

1. Is multi-monitoring system improve survival, reduce neurocomplication, and short the length of stay at the hospital? What are the ICER(s) of these three estimated health outcomes?
2. Which of the parameter(s) has an impact on uncertainty of the ICER(s)?

The Second Part: EarlyHTA for NeoDoppler Technology

3. In which conditions NeoDoppler technology could have potential of being cost-effective compared to multi-monitoring system. (The conditions are estimated in the accuracy of innovation, for instance pTP and PVP parameters.)
4. In two-way sensitivity analysis, in what values of probability of sensitivity and probability of specificity parameters will reach the values of pTP and PVP parameters in the conditions of research question 3.
5. What are the maximum reimbursement prices in these conditions?
6. Based on the headroom results in the research question 5, what are the value of revenues (V) one year after the product has been launch?

4. Theory

4.1 Economic evaluation of diagnosis perspectives

From the Developer Point of View

Nowadays, accuracy medical test is more hope for precision medicine. It is also more complicate in term of the role of guiding the treatment and patient management. These developments built upon each other complementarily to better meet the clinical needs. (Lucy Abel *et al.*, 2019). The main purpose of clinical trials are to evaluate the reliability and validity of medical devices. Conducting a trial is costly and time-consuming and resources required, which may not applicable for small bio-technology or medical device companies. However, EarlyHTA method is likely to be used in the earlier stage of research and development (R&D) (Lucy Abel *et al.*, 2019). The primary outcomes and relevant parameters are selected from literature review and expert opinion for building the cost-effectiveness model. It provides the basic information of the uncertainty of model parameters and the potential cost-effectiveness in the intended clinical pathway. It also reduces the risk of carrying out the clinical htrial that expected results not foreseeable. The strategy of establishing an economic model is to identify frequency of diagnostic test and potential patient group that is cost-effective or subgroup that is the most cost-effective. Moreover, the possibility of further applications are executable in the future research such as clinical trials (Maarten J. IJzerman, 2017). The strategy of model can be refined as the opinion from clinical experts and more evidence generated. As stated by the result of modeling, a developer would decide to process for further development, advance the technology, alternate the intended use and care pathway, or abandon its development (Emma Cosh *et al.*, 2007). The return of investment (ROI) is also predictable from earlyHTA method. Revenue forecasting is important for investors as a part of business plan. It will help them to make better strategy for further decision and achieve successful business.

From other Stakeholders' Point of View

The innovation of medical technology contributes to clinical efficacy, health outcomes, and quality of medical service such as pediatric cardiac surgery. Healthcare policy considers all the related stakeholders. Economic evaluation of innovation medical device take into account the benefits of stakeholders and meet their requirement. Health technology evaluation maximizes welfare and improve health economics by reducing disease burden and societal cost (Jane W *et al.*, 2006; Juhyeok Park *et al.*, 2019). From patient perspective, for the short-term effect, it increases the likelihood of requiring longer length of treatment (adverse event), hospitalization time (LOS) and the relevant cost including

medicine. Considering the longer-term effect of lower school performance, learning and behavioral problem, poor social skills, productivity loss, and health-related quality of life follow by cardio surgery for those who had experiences in infants (Glyn D. and Chandra, 2007). For family members of patient, the quality of life also has several impact on their mental and physical status.1) Emotional impact: The level of emotional impact often related to the severity of the patient. Family members contribute to informal care, decision making, and financial issue would lead to feel of lacking of control and helplessness. It burdens their well-being and mental stability. 2) Financial impact: The cost of treatment and hospitalization, travel expense, hiring a caregiver (out-of-pocket cost), opportunity cost and reduce the working hour in order to provide informal care and support to patients. 3) Reduce of leisure time: It could be the effect of the time spending on care of patients, financial problem, or having extra working hours to cover the costs. 4) Social impact could be the consequence by lacking of understand their circumstance (Catherine Jane Golic *et al.*, 2013). From payers' point of view, meaningful clinical benefits obtain from accuracy diagnosis combining with treatments. As for reimbursement strategy, high budget impact may cause by the uncertainty on heterogeneity in real world data (RWD). Whether innovation is dominate or more effects gained, it would be the main concern for reimbursement decision. It also relates to value-based agreement between payer and producer for market entry management (TylerO'Neill et al., 2019).

4.2 Economic Evaluation of Diagnostics

The clinical performance of medical device can be evaluated by specific parameters as sensitivity, specificity, predictive value of a positive (PVP), and predictive value of a negative (PVN) through the probability approach. The method of validating the medical device is to compare the results with gold standard and both with a meaningful number of patients in statistics. The agreement of the test device based on the results of true positive or true negative. The sensitivity and specificity are calculated from the number of true positive or true negative. Clinical decision-making considers the cut-off points of a medical device comparing with alternatives. The cut off points will lead to different results of PVP and PVN (Barnett S. Kramer *et al.*, 1999). The more stringent criterion would contribute to having a higher PVP, but also greater number of false negative occurred. The degree of diagnosis and monitoring performance has effects on the expected outcomes. The sensitivity and specificity estimate the performance of new diagnosis device by comparing the results with gold standard. The accuracy of devices are validated by measuring the sensitivity and specificity. The sensitivity is defined as the probability of being test positive among patients with the disease. The

specificity is the probability of being test negative among patients without the disease. The formula presented as below: (David Simon *et al.*, 1990, and Rajul Parikh, 2008)

· $TestSensitivity = (TP)/(TP + FN)$ (3)

* TP: true positive
* FN: false negative
* Notation: p (T+|D+), it indicates the test positives are conditional on the patients who have disease.

· $TestSpecificity = (TN)/(TN + FP)$ (4)

- TN: true negative
- FP: false positive
- Notation: p(T-|D-), it indicates the test negatives are conditional on the patients who do not have disease.

· $Probabilityoftestpositive = sensitivityxprevalence + (1 - specificity)x(1 - prevalence)$ (5)

· $Probabilityoftestnegative = 1 - (sensitivityxprevalence + (1 - specificity)x(1 - prevalence))$ (6)

Furthermore, predictive value positive (PVP) and predictive value negative (PVN) present how the new device performs as good as gold standard. The higher value shows the better quality of the device. It the number closes to 100%, the performance of the new device as the same as gold standard. PVP is the probability of a patient who has disease and test positive. PVN is the probability of a patient who does not has disease and test negative. The calculation of PVP and PVN are derived from Bayes' formula: (David Simon *et al.*, 1990, and Rajul Parikh, 2008)

Bayes' theorem: $P(A|B) = P(B|A)P(A)/P(B)$ (7)

· $PVP = (sensitivityxprevalence)/((sensitivityxspecificity) + (1 - specificity)x(1 - prevalence))$
$= truepositiverate/(truepositiverate + falsepositiverate)$ (8)

Notation: p ($D^+|T+$), it indicates the probability of a patient who has disease is conditional on the test positive

$$\cdot \quad PVN = specificityx(1 - prevalence)/((specificityx(1 - prevalence) + (1 - sensitivity)xprevalence)) = truenegativerate/(truenegativerate + falsenegativerate) \quad (9)$$

Notation: p ($D^-|T^-$), it indicates the probability of a patient who does not has disease is conditional on the test negative.

Table 1 Contingency table for test results

	Gold standard **Positive**	***Gold standard*** **Negative**
Test outcome **Positive**	True Positive (TP)	False Positive (FP)
Test outcome **Negative**	False Negative (FN)	True Negative (TN)

4.3 Pros and Cons of Using Sensitivity, Specificity, PVP, and PVN to Estimate the Accuracy and Reliability of Diagnosis Device

As a diagnosis device, reproducibility and accuracy are important for the quality of the test. The same test results are repeatable and highly agreement with reference device (e.g. standard of care). The strategy of performing diagnostic tests on patients' management and better treatment outcomes approach for both clinician and patients are its main values. The accuracy can be determined from different measures, which are sensitivity, specificity, PVP, and PVN. As for sensitivity and specificity, the perfect values for both are 100%, which means the test among all patients with or without the target condition are all true positives or true negative, respectively. The type I error (false positives) and type II error (false negatives) are not performed in the tests ideally. In the reality, the limitations of test device lead to the barrier of measurement (Thomas R. Vetter *et al.*, 2018). Therefore, the acceptability of the values of sensitivity and specificity is not straightforward. It could depend on the situations and the strategy of testing. The higher sensitivity but lower specificity (higher false positives) may be acceptable, if it functions as a triage, because other testing will perform the following

test (second test) for patients who have positives. The main goal is the primary testing accessing for everyone with a low cost for each test. Vice versa, in the condition of considering of side effects (complications) caused by the testing device, the lower risk but lower accuracy of sensitivity and specificity may be preferred. It is the trade-off between the probability of type I or type II error and the risk of side effects (Karlijn J van Stralen *et al.*, 2009). The values of sensitivity and specificity provide the information of the probability of testing result in true positives or true negatives among patients who actually have or have not target condition. However, PVP and PVN indicate the probability of a patient who truly has or has not target condition by testing result in positive or negative given. Basing on the results of PVP and PVN, the decision on requiring of further tests, beginning the treatment selected, or physician will make no need on either one of them (Karlijn J van Stralen *et al.*, 2009).

In order to estimate the accuracy of new technology, how to choose a proper reference standard is critical for sensitivity and specificity determination. As the limitation of reference standards, their performance with 100% sensitivity and 100% specificity are unreachable in the most of diagnosis devices. It could lead to verification bias (Karlijn J van Stralen *et al.*, 2009). The outcome measurement usually requires a follow-up evaluation in a set trial or real-world data collection. The values of sensitivity and specificity are affected by subgroups, for instance, patient characteristics, disease or disorder severity, mix symptoms or complications, and congenital genetic mutation. As to PVP and PVN, they are both influenced by population prevalence. As the population prevalence increasing, PVP will be higher; otherwise, PVN will turn into lower value. The reason for this change is type I error (false positives) decreasing and enhancing the true positives results. Population prevalence could occur differently in subgroups that may lead to different values of PVP and PVN as the accuracy measurement (Thomas R. Vetter *et al.*, 2018).

According to Bayes' theorem, prevalence of the diseases or disorders would influence the degree of trust on the test result and multiple tests for treatment decision may be required if the accuracy of PVP and PVN have certain degree of uncertainty. Physicians assess all relevant information such as types of disease, symptoms and severity, prevalence, and diagnosis results, to select a treatment strategy for better patients' outcomes. Therefore, the strategy of using diagnostic device as a tool of triage, replacement, or add-on package for different purposes (Holger J Schünemann *et al.*, 2008; Karlijn J van Stralen *et al.*, 2009).

4.4 Cost-Effectiveness Analysis (CEA)

Economic evaluation is the comparative analysis of interventions in terms of both their costs and consequences. Generally, cost-effectiveness analysis (CEA) or cost–utility analysis (CUA) is employed to perform the economic evaluation. The different between CEA and CUA is measurement unit of consequence. CEA is natural units for the measure of benefit (e.g. life-years gained, complication rate, and length of stay). CUA is measuring quality-adjusted life-years (QALYs) as benefit. Incremental cost-effectiveness ratio (ICER) in equation (10) is defined as the result of CEA.

$$ICER = (C1 - C0)/(E1 - E0) \quad (10)$$

* C1: The cost of intervention
* C0: The cost of comparator
* E1: The effect of intervention
* E0: The effect of comparator

The effects are quantified in life years gained (LYG), quality-adjusted life years (QALYs), or other clinical outcomes depending on the sufficiency of data from literature review. (Briggs A. et al., 2006) Standard CEA compares the different of costs and benefits between alternatives. An incremental cost-effectiveness ratio (ICER) calculated from the incremental cost and benefits indicates the additional cost per extra unit of effect gained in intervention that is more effective. ICER is compared with the threshold given by decision makers. The threshold presents the value of willing-ness to pay for per additional unit of effect. The relevant comparator is considered from standard care or alternatives used in common practice. The appropriate time horizon reflects the difference of estimated cost and effect required. The long of horizon could be lifetime to predict the long-term effect or days to years for directly and short term effect. CEA model uses mathematical simulation models and address the uncertainty of parameters. It provides the evidence of decision problem for decision-making (Drummond MF *et al.*, 2015).

Decision analytic models

Decision tree is one of the forms of cohort model to structure a decision model. Decision tree estimate the short-term time horizon. It reflects the probabilities of events and the accuracy of diagnosis medical devices including sensitivity and specificity. The natural history and the impact of interventions are presented in the model structure. The longer term forecast obtained by extrapolating the data from randomized trials and a baseline defined. The probability of a pathway is a joint probability P (A and

B). The notation of joint and conditional probabilities of two events present in equation (11). The expected value are the chances outcomes multiplied by their probabilities and summed:

$$P\ (A \text{ and } B) = P\ (A|B) \times P(B) \qquad (11)$$

*P (A and B) indicates joint probability: The probability of event A and event B occur at the same time.
*P (A|B) indicates conditional probability: The probability of event A occurring when event B has happened.
*P (B): The probability of event B has happened.

The expected value in the context of decision trees are the payoffs weighted by their probabilities. By using Macro function and recording feature in Excel to generate 1000 Monte Carlo simulations than plotted on cost-effectiveness plane (CE-plane) shows the overall uncertainty of model.

4.5 Cost-Effectiveness Plane (CE-Plane)

CE-plane presents the difference in effectiveness on y-axis against the difference in cost on x axis per individual. The slope of the line joining any point on the plane to the origin is equal to the incremental cost-effectiveness ratio ($(ICER) = (C1 - C0)/(E1 - E0)$ (William C. Black, 1990). The plane consists four separate quadrants as Figure 1. In the SE quadrant, it is less costly and more effects gained. If the ICER ratio(s) are located in the SE quadrant, it implies the new technology dominates to comparator and cost-saving. In the NW quadrant. It is the opposite of SE quadrant. It is more costs and less effect. If the ICER ratio(s) are plotted in NW quadrant, it indicates the comparator is dominate than new technology. In the NE and SW quadrants, there are trade-off decision should be made basing on the threshold ratio (λ). The threshold ratio is the maximum value of willingness-to-pay given by payers. In the NE quadrants, the new technology could generate more effects but costly than comparator. In the SW quadrants, the new technology is less costly but also less effective than comparator (Briggs A. *et al.*, 2006). The incremental cost-effectiveness ratio (ICER) = $\triangle C/\triangle E$ per simulation is plotted in four quadrants in a CE-plane. The output of these simulations provides the joint distribution of expected costs and outcomes for each strategy being compared. The decision of adopting or favoring the intervention depends on the value of threshold (λ) given and the probability of cost-effectiveness where the ICER less than the acceptable threshold ratio. The value of threshold (λ) is not given in the analysis due to lack of information from our search (willingness-to-pay in U.S.A healthcare system). If λ equal to zero given by decision makers, it implies that only the cost reduction is important for comparing two alternatives. The decision makers may not willingness-to-pay the more

money for an extra effect gained in new intervention if exist standard care are considered very cost-effective (Briggs A. *et al.*, 2006). In our study, the distribution of ICER ratio(s) in three estimates outcomes (survival rate, neurocomplication, and length of stay) are plotted in the CE-Plane shown in Figure 13, 14, and Figure 15.

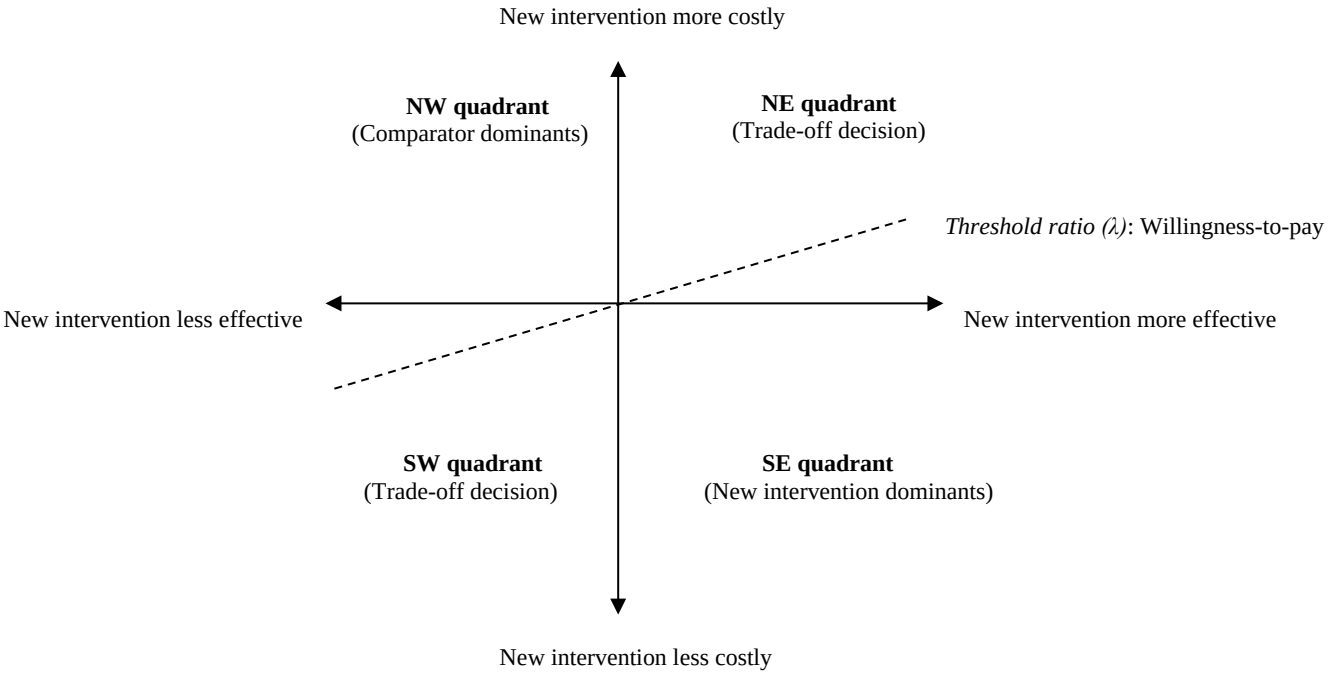


Figure 1 Cost-effectiveness plane.

4.6 Early Health Technology Assessment (EarlyHTA)

In the product life cycle, early health economic modeling applies in earlier stages of technology development to estimate under which conditions the new technology is cost-, which are useful when designing a clinical study. Headroom analysis is a method to inform developers on the potential medical device development. This method provides the information of commercial viability and estimates potential value to the healthcare provider (Cosh, E. *et al.*, 2007; Girling, A. *et al.*, 2012; Hartz, S. and John, J., 2008; Ijzerman, M. J. *et al.*,2017; Janneke P.C. Grutters *et al.*, 2019). It performs the impact on health service cost and reflection of health benefits derived from the new intervention. The formula presents the net-benefit shown in Equation (12). The Headroom, H, can indicates the maximum reimbursable price (MRP) and the ceiling of unit cost of the new technology, taking development and

production costs into account (A.M. Chapman *et al.*, 2013). MRP reflects the value of innovation or the new technology that can provide better health care by increase effects and/or reduce the costs. From Equation (12), given a threshold ratio (λ), MRP will increase with an increase in net benefits and a reduction in health and social care cost (HSCC). In this scenario, it is a cost saving approach for innovation or new technology. If the HSCC is a positive number, which indicates innovation or new technology less costly than comparator(s). In contract, if HSCC is a negative number, innovation or new technology is more costly. Similarly, if there are zero net benefits generated and higher costs, the MRP will be negative, there will not be any reimbursement on innovation or new technology. In other scenarios, the values of net benefit and the values of HSCC will result in a negative or positive number of MRP. For example, if the value of difference in HSCC is large than threshold ratio (λ) multiplied by the difference of net benefit as the equation (12) then the MRP will be a positive number. Otherwise, MRP would be a zero or a negative number. It could provide an information on trade-off between HSCC and net benefits when the decision of reimbursement or no reimbursement made.

$$MRP = \triangle HSCC + (\lambda \triangle netbenefit) \quad (12)$$

* Headroom (H): Maximum reimbursement price (MRP)
* Threshold ratio (λ): Willingness-to-pay
* ▵HSCC: Net reduction in health and social care cost (ignore the price of the device)
* ▵Net benefit: incremental effects (e.g., survival rate, neurocomlication, and length of stay)

Return on investment (ROI) is estimated by the value (V) of the revenues to predict whether the projected market revenues given a time horizon will cover further development costs including a clinical trial. The formula of the value (V) of the revenues is shown in Equation (13). The estimate values of M depends on the market size (Girling, A. *et al.*, 2015). Referring to equation (13), the degree of the difference of headroom (H) and unit cost (U) will influence on the predicted revenues when the number of units sold is given for a specific time period. Therefore, if the innovation or new technology has a higher value of MRP based on the analysis in equation (12) and lower unit costs then the ROI would be increased to innovators.

$$V = M(H - U) \quad (13)$$

*M: The projected number of items sold over the time horizon given
*H: Maximum reimbursable price
*U: Estimated cost of production per unit

4.7 Sensitivity Analysis

There are four main types of uncertainty relating to resource data (e.g. additional health benefits and variation of costs) or methodological assumptions, which are stochastic uncertainty indicating the random variability in patients outcomes , parameter of interest uncertainty, patients' heterogeneity , and model structural uncertainty. As the consequences of these uncertainties, the uncertainty and bias in cost-effectiveness results will be occurred. For decision makers, identifying key parameters and their potential impact on expected cost-effectiveness and budget allocation are important before reimbursing a new technology or requiring further evidence. Sensitivity analysis is a method to evaluate the degree of uncertainties basing on the model built in critical methodological assumptions presented by probabilistic sensitivity analysis (PSA) or deterministic sensitivity analysis (Briggs *et al.*, 2006).

Deterministic Sensitivity Analysis

Deterministic sensitivity analysis can be conducted as one-way or multiway sensitivity analysis (e.g. two-way sensitivity analysis) to estimate the quantitative relationship between changes input parameter(s) with output expected cost, effect, and net benefit (expected outcome, ICER in this study). It identifies which the parameter(s) has greater uncertainty to decision. The uncertainty around expected values can be address. The appropriate distribution for parameter(s) is required as probability sensitivity analysis (Drummond MF, 2015). One-way sensitivity analysis predicts the impact of each single input parameter on cost-effectiveness result based on the mean value by changing a range of proportion in the mean value of parameter (SE +/- 5% and 10% in this study). The upper and lower bounds can also be set at extreme value but reasonable to estimate the difference on cost and effect in the range of data set. Two-way sensitivity analysis changes the mean values of two parameters at the same time to estimate the combined effect of uncertainty in expected value. The magnitude of uncertainty surround the decision may be changed from one-way sensitivity to two-way sensitivity considering the correlation between parameters (Drummond MF, 2015).

Probability Sensitivity Analysis (PSA)

PSA assesses the joint uncertainty of parameter(s) through a series of sampling (e.g. 1,000 simulations) generated by Monte Carlo simulation given a range of plausible standard error and appropriate distributions assigned in parameters. Every running result (expected net-benefit) is calculated from a set of random samples to obtain an average of expected costs and an average of expected effects in

each alternative. The correlation between input parameter(s) and ICER in expected each outcome are presented in a decision-analytic modelling (Briggs *et al.*, 2006). The appropriate distributions for parameters are applied in probability sensitivity analysis.

4.8 Model Validation

According to the International Society for Pharmacoeconomics (ISPOR) and Outcomes Research and the Society for Medical Decision Making (SMDM) (David M.Eddy, 2012), we validate the model in two types based on the existed resource, face validity and cross validation, to verify the model accuracy and make transparency. In face validation, the experts in the cost-effectiveness method in healthcare field are involved in the review of dada sources, model structure and limitations, equations, input parameters and values, expected outcomes, and assumptions applied in the analysis.

5. Methods and Material

In the method section, cost-effectiveness analysis and headroom analysis are applied to our study. In our search, whether the multimodality neuromonitoring system using in surgery can be cost-effective remaining uncertainty. Therefore, in the first part, we estimate the potential CEA of multimodality neuromonitoring system comparing with control group. Here we assume the control group is WITHOUT using multimodality neurological monitoring intraoperation. In the second part, headroom analysis, we estimate in what conditions NeoDoppler technology, innovation diagnosis device, has potential of being cost-effective comparing with multimodality neurological monitoring, which is the comparator in our study. The two methods, CEA and headroom analysis, will be described in the following with relevant data input. The input data for CEA are extracted from Erle H. Austin III *et al.* (1997) and Sara K. Pasquali *et al.* (2014). Considering the availability of data resources, this study will focus on the United State setting.

5.1 Population

In our study, the patients are infants less than a year old with congenital heart defects in need of cardiac surgery. According to Erle H. Austin III *et al.* (1997), 250 pediatric patients had congenital cardiac defects and underwent cardiac surgery. Patients underwent different types of surgical procedures and monitored with multi-monitoring system. The patients' age are from less than 7 days to more than 5 years old. Basing on their surgical results, all patients were divided into three groups. 1) Group 1: No worthy data change and no clinical intervention. 2) Group 2: Worthy data change and

clinical intervention 3) Group 3: Worthy data change and no clinical intervention. The percentages of patients under one year old are 40% in the group 1, 61% in the group 2, and 41% in the group 3. In the group 2 and group 3, the patient characteristics were similar in the distribution of desaturation, perfusion, and anesthesia. In our model, because we estimate patients under 1 year old, but the health outcome data from Erle H. Austin III et al. (1997) is lacking of information on the age distribution of neurologic complication and death number in the three groups. Therefore, in our study we ignore the health outcomes data related to ages and adapt the data from Erle H. Austin III *et al*. (1997) into our model. We also assume the control arm has the same patient characteristics as intervention arm.

5.2 Intervention

Multimodality neurological monitoring system is used during pediatric heart surgery and in line with available clinical algorithm. The monitoring system is in conjunction with NIRS, TCD, and other diagnosis devices.

5.3 Comparator

In the control group, the non-monitoring intervention arm is to be chosen.

5.4 Innovation Medical Device

NeoDoppler technology directly monitor and measure the value of cerebral blood flow though the probe detection. Automatic spectral tracing and calculation for flow indexes. Ultrasound energy transmission is not influenced by the bone thickness and porosity in the detection region. The signals variation are risen by several factors, for instance intracranial distal and extracranial proximal arteries, and cardiac physiology. Therefore, given correct interpretation of sonograms is highly needed for further clinical intervention and treatment. NeoDoppler technology sufficient signal quality for automatic analysis in most cases. Insufficient signal quality are automatically detected. In these cases, NeoDoppler technology can be operated in «expert mode» with manual assessment of the sonograms.

5.5 Clinical Outcomes

In this study, we estimate the immediate effects during/after surgery such as survival rate, neurologic complications, length of stay (LOS),)and costs of neurologic complication, and ICER in each health outcome. Moreover, patients who require congenital heart surgery are expected to have preoperative LOS, ICU LOS, and total hospital LOS (Joyce T. Johnson *et al.*, 2018). Therefore, LOS is one of the endpoints in our analysis. The results are presented in the CE-plane and CEAC. MRP and ROI will calculate from Headroom analysis and Value of revenues (V), respectively. The values of estimated

outcomes in the control group including the mortality rate, abnormal neurologic outcome, normal neurologic outcome are, and length of stay (LOS) are derived from Sara Lozano *et al.* (2004). Sensitivity analysis is conducted to estimate the impact of parameters. In the first part of CEA, the parameters are considered as pTN, pTP, pPrev, nnC, pSpec, and pSens tested in one-way or two-way sensitivity analysis to estimate the key parameters and uncertainty surrounding by the model-base analysis. For the second part of potential CEA for NeoDoppler technology, the parameters of pTP and pVP are tested in one-way and two-way sensitivity analysis in order to estimate the potential cost-effectiveness comparing with multimodality neurological monitoring. Furthermore, two-way sensitivity are performed in both headroom analysis and revenues. In the headroom, we give a series value of cost-saving of healthcare service and incremental effect to estimates the maximum reimbursement price. Later, the predicted revenues are able to obtain by varying the values of headroom and the numbers of unit sold at the first year of product launch.

5.6 Perspectives

The analysis is conducted from healthcare provider and payer perspectives considering the United State setting. From healthcare provider perspective, in neonatal congenital heart surgery, perioperative care requires highly intensive resource use such as intensive care unit (ICU), and specialized professionals. In pediatric hospitals, in order to maximize the value of care and minimize the resource use, based on the outcomes specialization, patient could be admitted to neonatal intensive care unit (NICU), cardiac intensive care unit (CICU), or pediatric intensive care unit (PICU). The costs and resource use are vary in three units because the models of care are different among them. Patients' allocation in which care unit considers surgical volume, institution preference, and financial control.

5.7 Time Horizon

The assessment of estimate outcomes is during the postoperative care in the hospital from Erle H. Austin III *et al.* (1997). In our study, the time horizon is set to two months including length of stay in pre-operation and post-operation for estimating the immediate effect caused by surgery.

5.8 Model Structure

Clinical decision analysis (CDA) aims to provide the evidenced-based technology and reduce the uncertainty. The methodology for decision making in clinical practice to apply proper clinical interventions during surgery. The aim goal is to reduce the incident of neurologic complications and improve the clinical outcomes caused by surgery. Medical device plays an important role of diagnosis in early, real-time, and accuracy data to professionals. In this study, decision tree model is developed

using Microsoft Excel shown in Figure 2 and Figure 3. Decision tree model is easy to understand and visualize the sequential decisions and outcome dependencies. The model is suit for few decisions and outcomes in short period of time, which also limit the tree depth. It is a nonparametric method that means assumption not required. Uncertainty can be assessed in the sensitivity analysis basing on the decision tree built. The accuracy of the model could be influenced by increasing the number of decisions and outcomes to be estimated. On the other hand, the optimal tree may difficult to find. In general, thinking out the advantages above, a decision tree model is applicable in our analysis.

In the first part of our study, cost-effectiveness analysis, we construct the two arms in the decision tree model, intervention and control basing on the assumptions. Intervention arm is defined as surgery WITH neurophysiologic monitoring system. Control arm is defined as surgery WITHOUT neurophysiologic monitoring system. In Figure 2, decision tree model starts with intervention arm and control arm. In the intervention arm, it is built basing on the probability of test positive (pTP) and test negative (pTN). The values of pTP and pTN parameters in our decision tree model are calculated from sensitivity, specificity, and prevalence in formula (5) and (6) respectively. The sensitivity value is obtain from formula (3) and specificity value from formula (4). In both pTP and pTN groups, we use formula (8) and (9) to analyze the predictive value positive (PVP) and predictive value negative (PVN) conditional on with or without clinical guideline followed interoperation. The estimated health outcomes are survival rate, neurocomplication rate, and length of stay in both intervention arm and control arm. In the second part of our study, Headroom analysis, we create another arm to estimate the maximum reimbursement price for NeoDoppler technology by using multi-monitoring system as a comparator. The parameters, pTP, pTN, PVP, and PVN conditional on with or without clinical guideline followed interoperation are built in the same structure in the decision tree model. It is presented in Figure 3. The health outcomes are survival rate, neurocomplication rate, and length of stay to be estimated in both intervention arm and comparator arm.

The probabilities in the decision tree model have three different shape nodes. The square decision node indicates the decision point between the control group and the intervention group. The circle is the chance node where several outcomes are possible. The conditional probabilities relate to circle nodes for each outcome. The probabilities of events sum up to one from the same circle node and mutually exclusive. At the end of model, there is triangular terminal node. It is the endpoint of each path of the probability model, which is unconditional probabilities among the paths. The expected effect of each arm is obtained by multiply all the conditional probability with the value of outcome and sum up all the values.

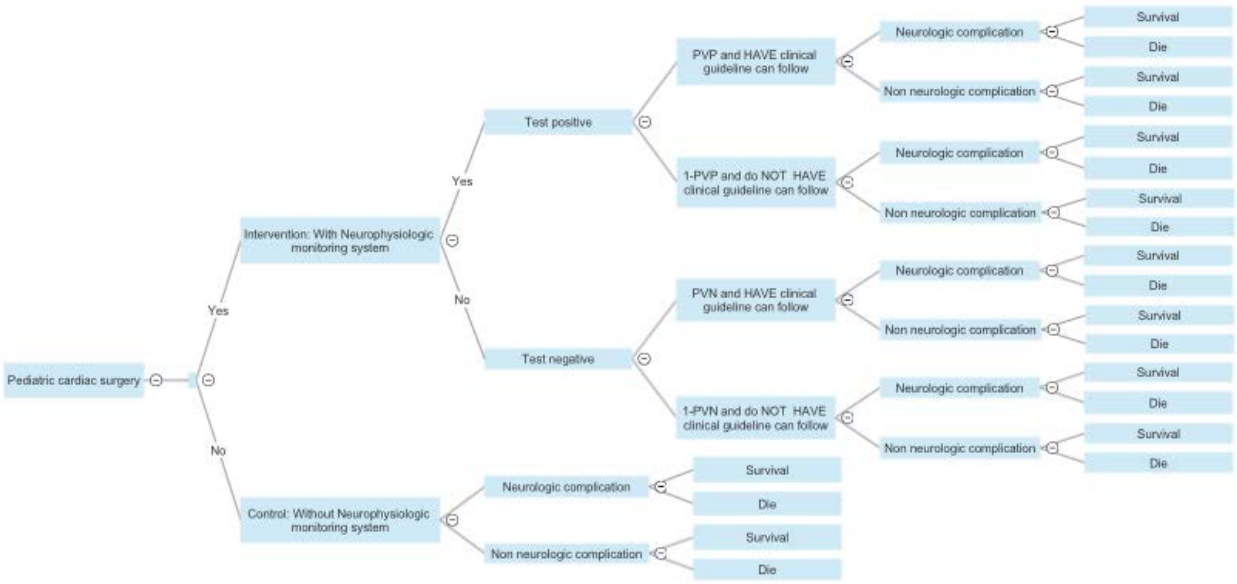


Figure 2 Decision tree model for cost-effectiveness analysis of multi-neuromonitoring system compared with no multi-neuromonitoring system, where PVP is defined as predictive value positive and PVN is defined as predictive value negative.

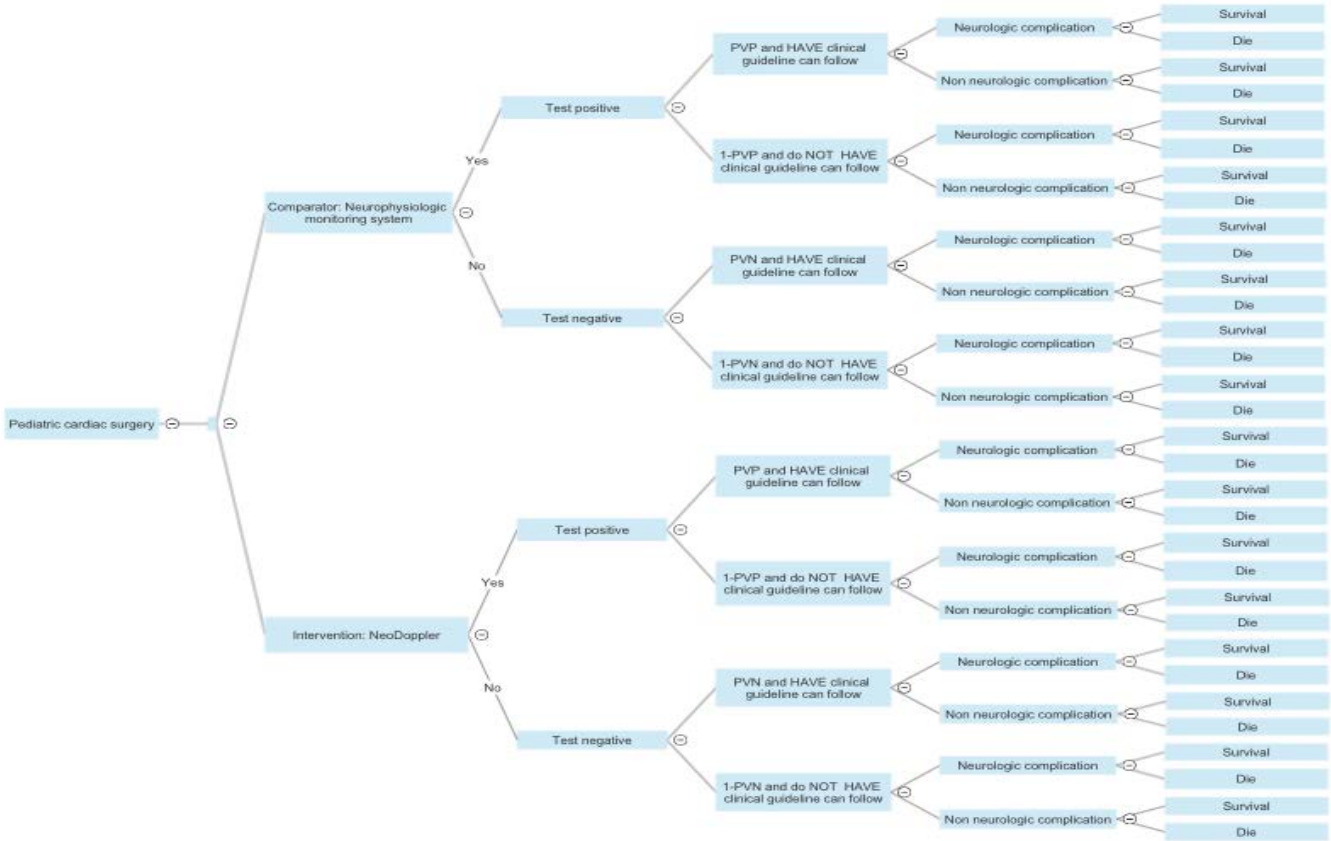


Figure 3 Decision tree model for potential cost-effectiveness and headroom analysis of Neodoppler technology compared with multi-neuromonitoring system.

5.9 Data Input

In our study, a review of the literature was performed. We use a systematic search of PubMed and Embase for relevant articles of neuromonitoring studies in pediatric cardiac surgery by the following terms: multimodality neuromonitoring, near-infrared spectroscopy, transcranial Doppler, NeoDoppler technology, pediatric cardiac surgery, congenital heart disease, and others. There are few books will be used as references for instance, Fetal and Neonatal Brain Injury edited by David K. Stevenson *et al.* (2003), and Neurology of the Newborn by Joseph J. Volpe (2008).

5.9.1 Health outcomes and transition probabilities

In our study, all data were collected from literature review and input parameters for the models in Figure 2 and Figure 3 are listed in Appendix A. In our model, we estimate the patients' age are under one year old. We simplify and adapt the health outcome data from Erle H. Austin III et al. (1997) in our analysis. We also assume the control arm has the same patient characteristics as intervention arm in the decision tree model.

The comparison table of abnormal neurologic outcome and normal neurologic outcome are shown on a review article (Sara Lozano et al. 2004). According the data form Sara Lozano (2004), the incident rate of abnormal neurologic outcome is 23% and 77% in normal neurologic outcome. The average hospital length of stay for patients with abnormal neurologic is 17.7 days and 10.3 days for normal neurologic outcome. Mortality rate in abnormal neurologic group is 42.8% much higher than 2.6% in normal neurologic group. In the model, we use the data as my control group. In the control group, we assume there were no mutil-neuromonitoring system introduced in the cardiac surgery before 1999 and in the review article the multimodality neurophysiologic monitoring algorithm were defined. The tables are adapted from the original abstract (Mossad et al 1999). In the intervention group, the probability are extracted from Erle H. Austin III *et al.* (1997). This study evaluates the advantages of neurophysiologic monitoring system applied to intraoperation in 250 neonates. The probability of noteworthy changes in the monitoring system is 70% (176 of 250) and 30% non- noteworthy changes. Real-time clinical intervention were given based on the data from monitoring system. The intervention algorithm were established as a reference. There were three groups, no noteworthy data change, noteworthy data changed and clinical intervention followed, and noteworthy data changed but no clinical intervention performed to the treatment. In the noteworthy changes group, the probability of given intervention is (130/176), neurologic sequelae (7/130), and death (8/130). The probability of no intervention is (46/176), neurologic sequelae (12/46), and death (17/46). In the non-noteworthy changes group, The probability of no intervention is (74/74), neurologic sequelae (5/74), and death

(5/74). The mortality rate of no change of data group and data changed but no intervention group, we assume the mortality rate in abnormal neurologic outcome is 42.8%. The mortality rate in normal neurologic outcome is 2.6% applied to input parameters which both probabilities are adapted from the review article, Sara Lozano et al. (2004). Because we do not know the death number from neurologic sequelae or overlap with other complications in the paper (Austin et al. 1997), but we know the mortality rate is 42.8% in abnormal neurologic outcome (Sara Lozano et al.). Therefore, we use this information to calculate the death number from non-neurologic outcome in no change, intervention, and no intervention groups. Then we convert the number to estimate the death number from neurologic outcomes in the three groups.

In the data changed and intervention group, the total number of patients with neurologic sequelae is 7 of 130 and total death number is 8 of 130. First, we estimate the result of 3 death patients by calculating from neurologic sequelae multiple 7 by 42.8%. Second, we can obtain the death patients from non-neurologic sequelae are 5 calculated from 8 total death minus 3 death from neurologic sequelae. So the mortality rate in abnormal neurologic outcome is 0.428 (3/7) and in normal neurologic outcome is 0.04 (5/123). The clinical outcomes and their probabilities shown in Table 2.

Table 2 Clinical outcomes after surgery and their incidence rate (%)

Neurophysiologic monitoring system used during surgery			
	No worthy data change & No clinical intervention	Worthy data change & Clinical intervention	Worthy data change & No clinical intervention
Number of patients	74	130	46
Total patients number	250		
Surgery outcomes (unit: the number of patients)			
Neurologic sequelae	5	7	12
Non neurologic sequelae	69	123	34
Deaths in neurologic sequelae	2	3	5
Deaths in non-neurologic sequelae	3	5	12
Total deaths	5	8	17
Total survivals	69	122	29
Surgery outcomes (unit: proportion)			
Neurologic sequelae rate	(0.07)	(0.05)	(0.26)
Non neurologic sequelae rate	(0.93)	(0.95)	(0.74)
Death rate in neurologic sequelae	(0.43)	(0.43)	(0.43)

Death rate in non-neurologic sequelae	(0.03)	(0.04)	(0.03)
Survival rate in neurologic sequelae	(0.57)	(0.57)	(0.57)
Survival rate in non-neurologic sequelae	(0.97)	(0.96)	(0.97)

1. In Sara Lozano and Emad Mossad (2004), the incidence rate of abnormal neurologic outcome caused by surgery is 0.23. The mortality in abnormal neurologic group is 0.428. The length of stay are 17.7 days (±1.8) in patients with abnormal neurologic outcome and 10.3 days (±0.7) in patients with normal neurologic outcome.
2. The calculation also uses the data from Sara Lozano and Emad Mossad (2004) to estimate the probability of each surgery outcome in the table 2.
3. The values are round up and applied to the model for analysis.
4. The unit for incidence rate is percentage.

In our contingency table 3, the true positive, 130 patients, is defined as data change from monitoring system and available treatment guidelines followed. The 46 patients are false positives defined as data change from monitoring system and no treatment guidelines can followed. The treatment guidelines in this group is defined as no need to have clinical intervention or unavailable treatment guideline. On the other hand, in the true negative and false negative, we assume 69 patients without neurologic sequelae outcome in no data change group are true negative. In contrast, patients with neurologic sequelae outcome in no data change group is false negative, which are 5 patients in total. Basing on our assumption above, the sensitivity (pSens) of the detection from multi-monitoring system is approximately 0.96 (130/135). The specificity (pSpec) of the detection is 0.6 (69/115). The probability of test positive (pTP) and the probability of test negative (pTN) are 0.53 and 0.47 based on the prevalence rate 0.23. In our study, we assume prevalence rate equal to incidence rate caused by surgery, which is WITHOUT neurophysiologic monitoring system intervention. The predictive value positive (PVP) and predictive value negative (PVN) are estimated to be 0.42 and 0.98, respectively.

Table 3 Contingency table and data for sensitivity and specificity estimation

	Worthy data change (+) & follow treatment guidelines	***No worthy data change (-) & follow treatment guidelines***	Total patients
Worthy data change (+) & follow treatment guidelines	130	46	**176**
No worthy data change (-) & follow treatment guidelines	5	69	**74**
Total patients	**135**	**115**	**250**
Sensitivity	0.96	-	-
Specificity	-	0.6	-

1. The probability of test positive (pTP), probability of test negative (pTN), predictive value positive (PVP), and predictive value negative (PVN) are calculated from the values of sensitivity (pSens) and specificity (pSpec) in table 3.
2. Prevalence rate (pPrev) 0.23 %. is derived from Sara Lozano and Emad Mossad (2004), which we assume it is equal to the incidence rate of abnormal neurologic outcome caused by surgery 0.23 %. The value is applied to the calculation for pTP, pTN, PVP, and PVN.
3. Unit for contingency table and data: the number of patients; probability for sensitivity and specificity.

5.9.2 Measurement Costs

The cost data are extracted from Sara K. Pasquali *et al.* (2014). They use the data are from The Society of Thoracic Surgeons Database including the estimated costs of pediatric surgery, excess cost of neurocomplications, and prolonged of stay in several types operation from 2006 to 2010. All the clinical and costs data are in U.S.A setting. There are several types of operations depends on the deficiencies. In their study, the median cost of operations are vary from US$ 25,499 lowest to US$ 165,168 Norwood highest. Most general operations and cost are listed in the Table 4. There are studies shown newborn undergo heart surgery often come with certain types of complications, for example neurologic, respiratory, renal failure, infectious, and pleural effusion/chylothorax. The total cost is increased depending on the types complications occurred. The related costs of complications are listed in Table 4. Neurologic complication average excess cost per case in all operations is estimated at US$ 50,649 (US$ 29,498 - US$ 77,724 in 95% CI). In our model, in the neurocomplication groups, the excess cost are added to the operation costs. In the non-neurocomplication groups, only operation cost takes into account. In order to obtain the mean value, first we use Stata SE to graph the distribution of costs and look at the skewness of the distribution in nature unit. Secondly, we transform the nature unite into log form and graph the distribution. If it is normal distribution, we estimate the mean value 10.99033 from log form of median values and convert to the original value. The original mean value US$ 59,474 is employed to our model. The results are presented in Appendix B.

The complex of operation may have higher rate of complication occurred and postoperative LOS. In addition, certain operations cost are much higher than others for instance Norwood and ASD repair, the median value are US$ 165,168 and US$ 25,499 respectively. The median cost of additional day of LOS per case estimate as US$ 19,273 across operations. When the median cost of additional day of LOS are adjusted by all complications in sensitivity analysis, the median cost is US$ 17,836. In Sara Lozano (2004), the average hospital stay for patients with abnormal neurologic is 17.7 days and 10.3 days for normal neurologic outcome. Therefore, in our model, we assume the adjusted excess cost of neurological complication US$ 50,649 includes the costs of prolonged LOS to 7 additional days.

Table 4 Operation costs and neurologic complication costs

Operation Costs (unit: USD)		
Type of operation	**Mean**	**Median**
ASD repair	59,474	25,499
VSD repair		33,679
TOF repair		44,318
Fontan		51,464
BDG		44,893
CAVC repair		49,445
ASO		94,902
Truncus repair		133,006
Norwood		165,168
Certain Complications Costs (unit: USD)		
Type of complications	**Mean**	**Note**
Respiratory	68,053	Excess cost per case (we assume the costs including length of stay costs). Only neurologic complication costs $US 53,611 is taken into account in our analysis.
Renal failure	67,192	
Neurologic	53,611	
Infectious	50,381	
Pleural effusion/chylothorax	30,632	

* Mean value of costs in operation is transformed from log form of median values by using Stata SE software to avoid underestimate due to the skewness of the distribution.

5.10 Adverse Event Caused By Medical Devices

The principle of NIRS may lead to skin sensitivity and injury from probe or the light used. It likelihood occurs in premature and neonates. TCD is a low power technology. The complications consider less effect on patients when use it properly following the instruction and not directly apply to the eyes (Glyn D Williams and Chandra Ramamoorthy, 2007).

5.11 Probabilistic Sensitivity Analysis

The uncertainty of each parameter or joint uncertainty of two parameters can address by using possibility sensitivity analysis. Beta distribution is for binomial data on the interval 0-1 and characterized by α and β parameters for probability of input parameters. For gamma distribution is assigned to the events of length of stay (LOS). Considering no negative value of cost, gamma distribution on the interval 0 to positive infinity is applied in the sensitivities model. The standard error were estimated by multiplying the parameter values by 0.5% for pPrev, sSens, and pSpec, 20% for costs, and 10%

for the rest of parameters. First, we use Monte Carlo methods to generate 10,000 simulations by propagating these distributions. The results of 1000 Monte Carlo simulations in probabilistic analysis is presented in the cost-effectiveness plane for comparing two alternatives, intervention and control groups. Second, we perform deterministic one-way and two-way sensitivity analysis by changing the value of probability of specific parameter to estimate the model sensitivity. In deterministic one-way sensitivity, we estimate the impact of six parameters, sensitivity (pSens) specificity(pSpec), cost of neurologic complication (ncC), prevalece (pPrev), test positive (pTP), and test negative (pTN) on expected values, ICER, costs, and effects in three expected outcomes, survival rate, neurocomplicaiton rate , and LOS. The changes of deterministic value of each parameter are given in -60%, -40%, -20%, -10%, 10%, 20%, 40%, and 60%. We consider the parameter of sensitivity is approximately 0.96 in our estimation. Therefore, there are additional changes in -2% , -3%, 2%, and 3% tested instead of 10%, 20%, 40%, and 60% applied to one-way sensitivity analysis in order to take the imitations of diagnosis devices into consideration. Moreover, the extra test of changing in + 80% will be in pTP and pTN, but -80% pTP because of the number of probability shall not over 1. The percentage of standard errors stay the same as original setting corresponding to the changes of deterministic values. The results are presented in linear graphs. Furthermore, we estimate the five parameters given ± 20% changes shown in Tornado diagram with original ICER of estimated outcomes as the start point in the horizontal axis and parameters shown in the vertical axis. For two-way sensitivity, there are two parts in our study. In the first part, we simultaneously vary the values of input parameters, pSens and pSpec, to assess the correlation of these parameters and pTP, pTN, PVP, and PVN, respectively. Regarding the second part, we estimate the maximum reimbursement price by giving a series value of pTP, PVP, and ciPne at the threshold US$ 50,000. The prediction of possible revenues are tested in two different unit costs, US$ 97.68 to US$ 564 per patient in the assumptions.

5.12 Potential Cost-Effectiveness for NeoDoppler Technology

We start with testing several scenarios to estimate the probability for the NeoDoppler Technology to be cost-effective by compared with standard monitoring devices. Therefore, in the two best scenarios, we vary the values of pTP, PVP, and ciPne parameters to increase the accuracy of diagnosis and how the assumptions influenced the ICER(s) in estimated endpoints (survival rate, neurocomlication rate, and length of stay). The ciPne parameter is defined as the probability of neurocomplication in clinical intervention. We also test several scenarios only vary the values of pTP and PVP parameters to increase the accuracy of diagnosis to analyze the ICER(s) of the endpoints. The probability values are from 0.23 to 0.5 for pTP and 0.19 to 1 for PVP parameters in the scenarios. In two best scenarios, in addition to the probability values 0.05 and 0 are applied to ciPne parameter. The values of incremental

cost of health service and health effect are obtained from the deterministic analysis. The incremental costs and incremental effects are applied in the headroom analysis. In the headroom analysis, maximum reimbursement prices (MRP) for the NeoDoppler technology are calculated based on Equation (10).

5.13 Headroom Analysis and Revenues for NeoDoppler Technology

In the headroom analysis, first, we estimate the magnitude of headroom by applying the increment costs and the health effects resulting from potential cost-effectiveness analysis for NeoDoppler Technology to obtain the maximum reimbursement prices (MRP) in the scenarios of each endpoint (survival rate, neroucomplication rate, and length of stay). Later, we assess the value (V) of the revenues by using MRP conjunction with market size to evaluate the return of investment for covering the research and development (R&D) costs. We assess value of the revenues (V) in different values of headroom based on the assumption following 1) the willingness-to-pay for headroom analysis is US$ 50,000 2) The production cost for Neodoppler technology per patient is from US$ 97.68 to US$ 564 range. 3) The predicted market size is 100 NeoDoppler gtechnology-monitoring systems and 5,000 disposable probes to be sold at the first year in the United State. Monitoring system in intended for multiple patients use working together with disposable probes. 4) The lifetime of monitoring system or the maximum of usage is not take into account in our study. 5) The time horizon of market revenues is 1 year to be set. The value (V) of the revenues and two-way sensitivity are analyzed basing on certain assumptions made.

Furthermore, we test the two conditions of best scenarios for NeoDoppler technology basing on our model. In the first condition, we consider the probability of test positive would be 0.23, which is equal to incident rate so the relative risk (RR) is 0.43 for pTP parameter. The value of 0.23 is chosen because the incident rate of abnormal neurologic outcome caused by surgery is 23% from Sara Lozano et al. (2004). We consider the best scenario for NeoDoppler technology is all the patients who will have neurocomplication outcomes can be diagnosis earlier from reliable data change to prevent the adverse event. For PVP, the RR is 2.38 applied to have 100% probability of test positive when a patient who has disease. If the accuracy and precision of innovation can 100% avoid type I error (false positives) and type II error (false negatives), PVP is considering as 100% true positive of a patient who has a positive result. In second condition, we combine the first best scenario with additional ciPne parameter. We assume there are no neurocomplication resulting from clinical intervention followed by guideline so the ciPne is 0 to be set.

5.14 Assumptions

(1) In our study, the intervention arm is defined as monitoring with multi-monitoring system and clinical algorithm available. The control arm is defined as no multi-monitoring system applied in intraoperation.

(2) According to Erle H. Austin III *et al*. (1997), patients' age range from less than 7 days up to more than 5 years old. In our model, we assume the patients' age are under 1 year old and the outcomes are in this age range. We also assume the control arm has the same patient characteristics as intervention arm in the decision tree model.

(3) The mortality rate in abnormal neurologic outcome is 42.8%. The mortality rate in normal neurologic outcome is 2.6%.

(4) The probabilities of parameters in the decision tree are calculated in an indirectly way. They are not the direct results from a clinical trial. We assume patients had data change from monitoring system and available treatment guidelines followed are true positive. Patients had data change from monitoring system and unavailable treatment guidelines can followed are false positives. Patients had neurologic sequelae outcome in no data change group are true negative. Patients had neurologic sequelae outcome in no data change group is false negative. By using the monitoring system, the probability of neurologic sequelae are obtain from Erle H. Austin III *et al*. (1997).

(5) There are several types of complications in surgery. We only consider neurologic complication costs, with the mean costs of $US 53,611 in the cost-effectiveness analysis. A complication implies addition 7 days at the hospital.

5.15 Model Validation

Regarding the cross validation, we constructed two decision tree models, model A and model B. Decision tree model A was built on the values of pSens, pSpec, pTP, pTN, PVP, and PVN. The results of this thesis analyzed from model A. Decision tree model B was built in a different way of estimation. The probability and input parameters in decision tree model B were directly derived from the results of paper, Erle H. Austin III et al., (1997). The values of pSens, pSpec, pTP, pTN, PVP, and PVN were not implanted into model B for analysis. We compare the results of decision tree model A with decision tree model B for validation.

6. Results

6.1 Cost-Effectiveness Analysis (CEA) for Existing Multi-monitoring System

6.1.1 Incremental Cost-Effectiveness Ratio (ICER)

In our study, we included cost components, costs related to clinical intervention and the cost of neurologic complication. The estimated total costs for three outcomes in the intervention and control groups are US$ 64,452 and US$ 71,805. In the estimated outcome survival rate, the survival rates are 0.93 and 0.88, respectively. The ICER is US$ -141,243 per life-years gained. The negative ICER is calculated from reducing costs and increasing survival rate from 88% to 93%. The survival rate is increasing 5% in the intervention arm. In the estimated outcome neurocomplication rate, the neurocomplication rate are 0.09 in the intervention arm and 0.23 in the control arm. The ICER is US$ -53,611. The negative ICER is calculated from reducing costs and neurocomplication rate from 23% to 9%. It indicates non-neurocomlication increasing 14% though the intervention. In the estimated outcome LOS, the LOS are 10.99 and 12 days, respectively. The ICER is US$ -7,245. The negative ICER is calculated from reducing costs and reducing the LOS. It is proximately 1 day less at the hospital in the intervention arm. The results refer to a cost-saving alternative combined with improved health outcomes. The results are shown in Table 5.

Table 5 Strategies, endpoints and ICERs

Strategy	Endpoint	Expected costs	Expected outcome	Incremental costs	Incremental effects	Incremental cost-effectiveness ratio (ICER)
Monitoring device	Survival rate	64,452	0.93	-7,353	0.05	-141,243
No monitoring device		71,805	0.88			
Strategy	Endpoint	Expected costs	Expected outcome	Incremental costs	Incremental effects	Incremental cost-effectiveness ratio (ICER)
Monitoring device	Neurocomplication rate	64,452	0.09	-7,353	(0.14)	-53,611
No monitoring device		71,805	0.23			
Strategy	Endpoint	Expected costs	Expected outcome	Incremental costs	Incremental effects	Incremental cost-effectiveness ratio (ICER)
Monitoring device	Length of stay	64,452	10.99	-7,353	(1.01)	-7,245

No monitoring device		71,805	12.00			

1. ICERs of intervention arm and control arm are estimated in three endpoints, survival rate, neurocomplication rate, and length of stay (LOS). Incremental cost and incremental effect are the different between two arms. ICERs are calculated from the formula.
2. Number within ( ) indicates negative value.
3. The unit of costs and ICER(s) are USD. The unit of effects for length of stay is day.

6.1.2 One-Way Sensitivity Analysis

Model sensitivity to input parameters is evaluated by one-way sensitivity analysis. The results is presented in a tornado diagram in Figure 4. It shows the ICER with survival at the outcome, was robust by changing the values of parameters by+/- 20% or 3%. For the probability of test negative (pTN), ICER is declining in the lower values of pTN. They are in a positive correlation. For other parameters, when reducing the probability value, the ICER(s) is increase in certain level(s), which is a negative correlation. Regarding the degree of changing on ICER, the value can up to US $ +/- 28,250 given +/- 20%. The cost of neurological complications (ncC) has a large impact on ICER in three estimates outcomes, which may influence the reimbursement decision as the ICER is above the willingness-to-pay US$ 50,000. Our model is more sensitive to pTP and pTN than pSens, pSpec, and pPrev parameters.

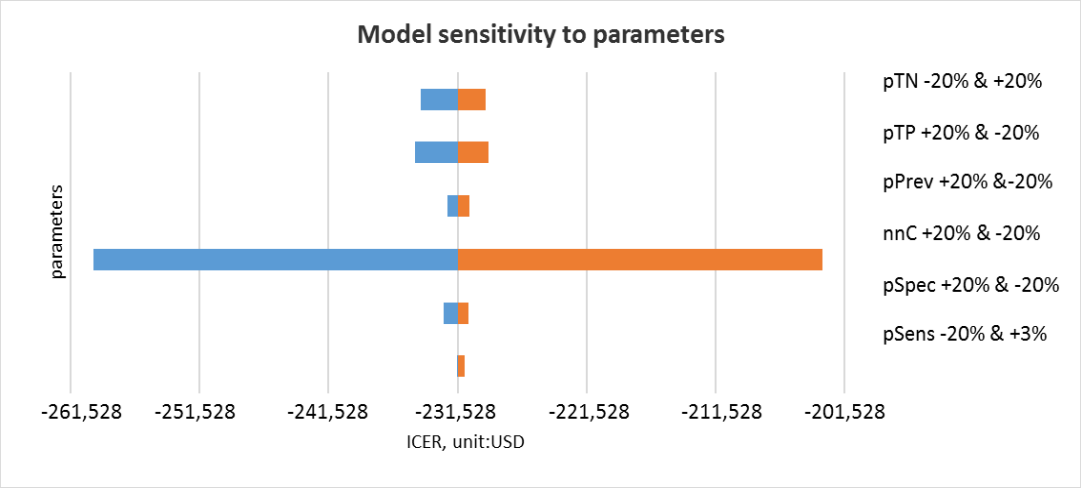


Figure 4 The variation of ICER by giving different value of probability in the selected parameters

There are two conditions given in each parameters to estimate the ICERs. The probability values of parameters, pTN, pTP, pPrev, nnC, pSpec are tested in -20% and +20%, respectively. For pSens, -20% and +3% are applied in the analysis.

* pTN: probability of test negative
* pTP: probability of test positive
* pPrev: prevalence rate
* nnC: cost of neurologic complication
* pSpec: probability of specificity (probability of test negatives and conditional on do NOT HAVE clinical guideline can follow based on the data from multi-monitoring system).

* pSens: probability of sensitivity (probability of test positives and conditional on HAVE clinical guideline can follow based on the data from multi-monitoring system).

We present the relationship between the values of specific input parameters and the ICER for the three health outcomes. Figures 5 and 6 show the ICER are decrease along the increased probability of pSens, and pSpec. In Appendix C, Figure 7 shows ICER is decrease when prevalence rate is increased. The ICER(s) do not change in the estimated outcomes (neurocomlication rate and LOS). The results of declined ICER are contributed by the decrease in costs and increase effects in parameter shown in Figures 5.1, 5.2, 6.1, 6.2, 7.1, and 7.2 in Appendix C. In the outcomes with no ICER changed, it is because the difference of costs and effects do not affect the ICER in calculation.

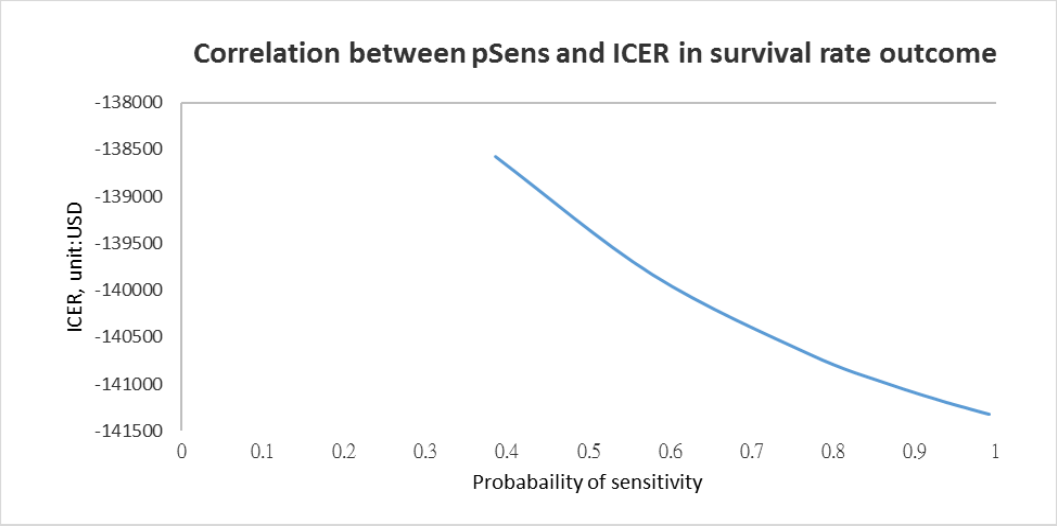


Figure 5 Probability of sensitivity and ICER in survival rate outcome

Given a series values of probability of sensitivity in x-axis corresponding to the values of ICER in y axis.

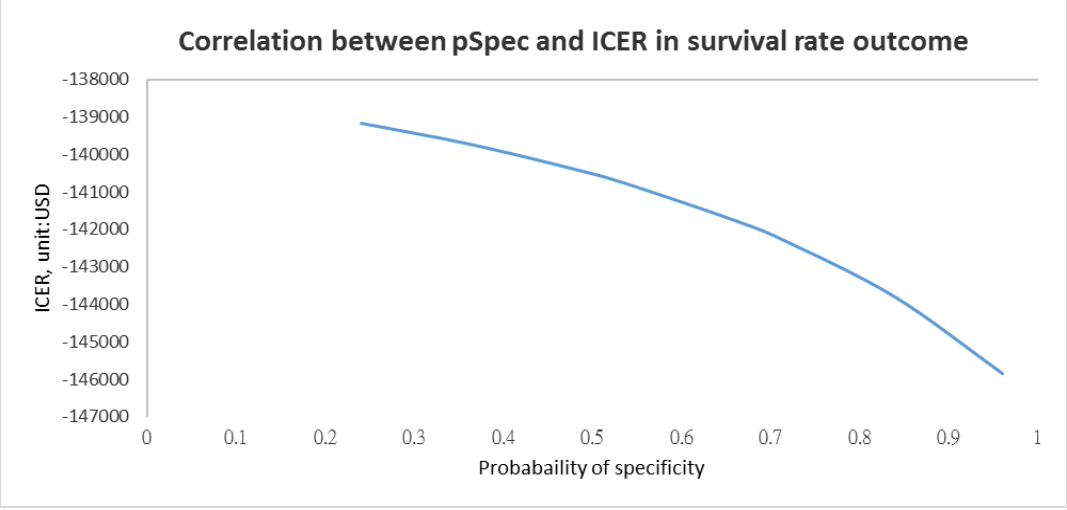


Figure 6 Probability of specificity and ICER in survival rate outcome

Given a series values of probability of specificity in x-axis corresponding to the values of ICER in y axis.

In Appendix C, Figure 8 indicates the ICER trends to decline as the probability of pTP increasing because of increasing costs and decreasing effects shown in Figures 8.1 and 8.2. On the other hand, there is a negative correlation of pTN and ICER presented in Figure 9 contributing by decreasing costs and increasing effects shown in Figures 9.1 and 9.2. The ICER(s) remains the same in the estimated outcomes (neurocomlication rate and LOS). In addition, in the survival outcome, pSens, pSpec, pPrev, pTP, and pTN parameters are influent on ICER(s) in certain degree. Especially pTP and pTN, they have opposite effect on ICER. The higher probability of test positive lower the value of ICER. The higher probability of test negative higher the value of ICER. Even we test probability of these parameters up to ± 60% changing value; they remain cost saving and dominate on effects. The ICERs change from US$-135,500 to US$-170,000 in pTP with probabilities range from 0.21 to 0.95 (-60% to + 80%) and US$-163,000 to US$-134,800 in pTN in a range from 0.09 to 0.85 (-80% to + 80%). In the pSens parameters, the ICERs vary from US$-138,500 to US$-141,300 in the probabilities 0.39 to 0.99. In the pSpec, the ICERs are from US$-139,170 to US$-145,855 at probabilities 0.24 to 0.96. Regarding the pPrev parameter, there is more cost saving as the incidence rate increase. The ICERs are from US$-137,700 to US$-143,260 in the 0.09 to 0.37 probability.

However, when nnC is increase, the ICER(s) is dramatically decrease because of decreasing costs presented in Figure 10.1. They have the same trends in three estimated outcomes, which is more cost saving. Given a series value of nnC from US$ 21,444 to US$ 85,778, the degree of changing ICER is from US$ -56,500 to US$ -226,000 in survival rate, -US$ -21,400 to US$ -85,800 in neurocomplication rate, and US$ -2898 to US$ -11,600 in LOS. The results are shown in Figures 10, 11, and 12 in Appendix C.

6.2 Cost-Effectiveness Plane (CE-Plane) for Existing Multi-Monitoring System

In deterministic analysis, the incremental cost-effective ratios (ICERs) in the three estimated outcomes are all negative values calculated from the reduced costs and increased effects in intervention arm. Figure 13 in the probabilistic modeling illustrates the incremental cost and effects pairs simulated by Monte Carlo simulation plotted in the CE-plane. In the CE-Plane of survival rate, 1000 simulations distributed among the NE, SE, and SW quadrants, in which the control located in the origin of the 2-dimensional scatterplot. It indicates the intervention arm has some uncertainty concerning whether the intervention is cost-effective. In the cost-effectiveness plane of neurocomlication rate, simulations distributed among the NE and SE quadrants shown in Figure 14. All points spread on the right of vertical axis so the uncertainty of effective is less. In the SE quadrant, the intervention arm is

dominant and cost-saving comparing with control arm. In the NE quadrant, there is a trade-off between increased costs and more effects. The decision is made by given a threshold ratio through the origin, the willingness-to-pay for health effect gained. The cost-effective only consider only if the ICERs lies below the threshold. In the cost-effectiveness plane of LOS, 1000 simulations distributed though the origin and along the NE, SE, SW and NW quadrants shown in Figure 15. The points lie in the SE and NW quadrants indicating that the intervention arm both reduces LOS and costs or increases LOS and costs comparing with control arm. The CE-plane(s) present the uncertainly of the estimated effects and costs for intervention arm versus control arm.

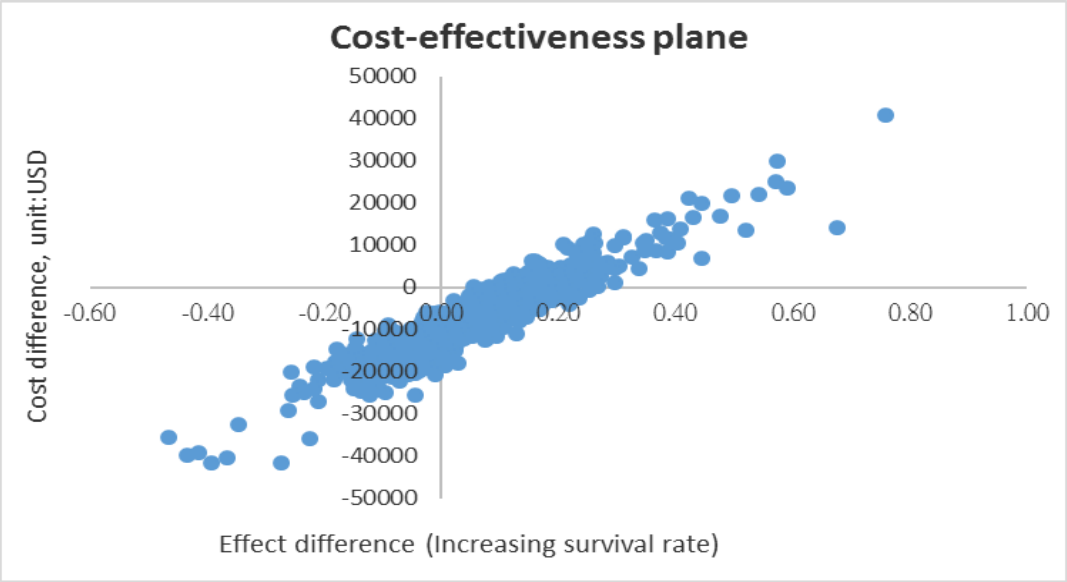


Figure 13 The Scatterplot of incremental cost-effective ratios (ICERs) in survival rate outcome

Monte Carlo 1000 simulations are distributed among the NE, SE, and SW quadrants. The trade-off decision will be made based on the threshold (willingness-to-pay) given in the NE and SW quadrants. The intervention is dominate as the dots locate in the SE quadrant.

* NE quadrant: Northeast quadrant
* SE quadrant: Southeast quadrant
* SW quadrant: Southwest quadrant

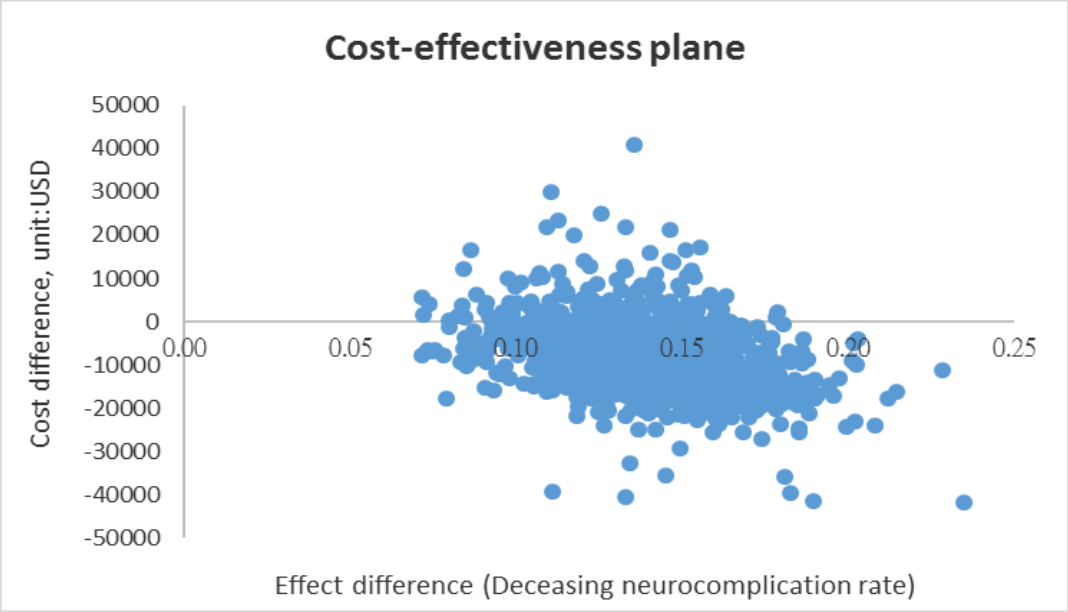


Figure 14 The Scatterplot of incremental cost-effective ratios (ICERs) in neurocomplication outcome

Monte Carlo 1000 simulations are distributed in the NE and SE quadrants. The trade-off decision will be made based on the threshold (willingness-to-pay) given in the NE quadrants. The intervention is dominate as the dots locate in the SE quadrant.

* NE quadrant: Northeast quadrant
* SE quadrant: Southeast quadrant

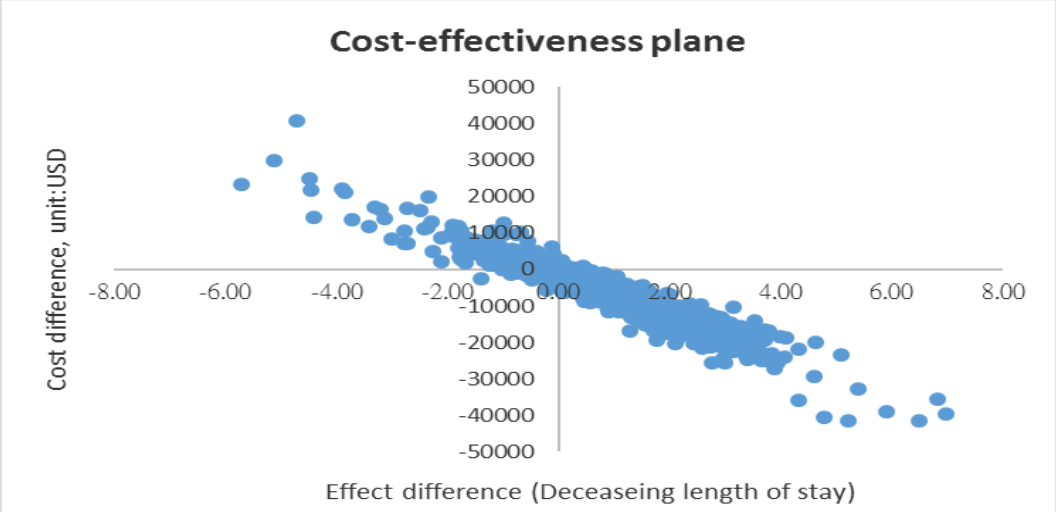


Figure 15 The Scatterplot of incremental cost-effective ratios (ICERs) in length of stay outcome

Monte Carlo 1000 simulations are distributed among the NE, SE, SW and NW quadrants. The trade-off decision will be made based on the threshold (willingness-to-pay) given in the NE and SW quadrants. The intervention is dominate as the dots locate in the SE quadrant, but not being cost-effective in the NW quadrant comparing with control arm.

* NE quadrant: Northeast quadrant
* NW quadrant: Northwest quadrant
* SE quadrant: Southeast quadrant
* SW quadrant: Southwest quadrant

6.3 EarlyHTA for NeoDoppler Technology

Starting from this section, we are moving into the second part of assessment to evaluate the possible criteria for the NeoDoppler technology to be considered cost-effective compared to the existing multiple monitoring system.

Potential Cost-Effectiveness Analysis

6.3.1 Incremental Cost-Effectiveness Ratio (ICER)

For NeoDoppler technology (innovation), there are certain conditions to be tested whether it is more cost-effective than existing multi-monitoring system (comparator). We consider the NeoDoppler technology to have higher quality of diagnosis, resulting in increased accuracy of pTP (identify those with a risk of neurological complication by the monitoring device) and PVP (successful intervention for all with the risk of a neurological complication) to increase true positive and true negative result in reducing the neurocomplication and increase the health outcomes. Therefore, in table 6, there are several scenarios tested in our decision tree model by giving a series values of pTP, PVP and ciPne parameters. The ICER(s) are calculated from incremental cost and incremental effects in each scenario in three endpoints (survival rate, neurocomplicaiotn, and length of stay) presented in table 6, 7, and table 8.

In the two cases of best scenario A and B, we assume 1) pTP is equal to 0.23, which means 23% patients undergoing surgery can be detected by NeoDoppler technology. 2) PVP is 1.00. The true positive rate in a patient who has disease and conditional on the test positive is 100%. 3) The probability of neurocomplication in clinical intervention (ciPne parameter) is 0.05 or 0.00. The probability of neurocomplication caused by surgery is 5% (scenario A) or non (scenario B). In survival rate outcome, in table 6, the ICER is -133,662 in best scenario A and -134,276 in best scenario B. The ICERs in other scenarios are from -101,762 to -160,083. In neurocomplication outcome, the ICERs are -53,611 in all scenarios in table 7. In length of stay outcome, the ICERs are -7,245 in all scenarios in table 8. It is more cost saving and effects gained in scenario B. In the results in table 6, 7, and table 8, they indicate that by increasing the accuracy it can less the cost of health service and more health outcomes gained. Later, basing on the results of incremental costs and incremental effects, we conduct headroom analysis to determine the possible maximum reimbursement price on the innovation shown in table 9 and table 10.

Table 6 ICER(s) in the values of pTP, PVP, and ciPne parameters in survival rate outcome

Scenarios	Endpoint	Parameter	Probability of Parameter	Incremental costs	Incremental effects	Incremental cost-effectiveness ratio (ICER)
Best Scenario A	Survival rate	pTP	0.23	-4,259	0.032	-133,662
		PVP	1.00			
		ciPne	** 0.05			
Best Scenario B		pTP	0.23	-4,913	0.037	-134,276
		PVP	1.00			
		ciPne	** no cases			
Scenario 1		pTP	0.50	-246	0.002	-123,079
		pTP	0.37	-1,474	0.012	-123,079
		pTP	0.24	-2702	0.022	-123,079
Scenario 2		PVP	0.44	-123	0.001	-160,083
		PVP	0.54	-737	0.005	-160,083
		PVP	0.65	-1,352	0.008	-160,083
Scenario 3		pTP	0.50	-129	0.001	-101,762
		PVP	0.40			
		pTP	0.37	-957	0.009	-109,440
		PVP	0.29			
		pTP	0.24	-2,093	0.018	-115,331
		PVP	0.19			
Scenario 4		pTP	0.50	-362	0.003	-132,984
		PVP	0.44			
		pTP	0.37	-1,990	0.015	-130,931
		PVP	0.54			
		pTP	0.24	-3,310	0.026	-128,540
		PVP	0.65			

* pTP: Probability of test positive
* PVP: Probability of predictive value positive
* ciPne: Probability of neurocomplication in clinical intervention
  **In the scenario A, the probability of neurocomplication in clinical intervention (ciPne parameter) is 0.05 (5%).
  **In the scenario B, we assume there are no any cases of neurocomplication in clinical intervention.
* Unit for costs and ICER(s) is USD
* Effect indicates survival rate. Unit is percentage

Table 7 ICER(s) in the values of pTP, PVP, and ciPne parameters in neurocomplication outcome

Scenarios	Endpoint	Parameter	Probability of Parameter	Incremental costs	Incremental effects	Incremental cost-effectiveness ratio **(ICER)
Best Scenario A	Neurocomplication	pTP	0.23	-4,259	(0.079)	-53,611
		PVP	1.00			
		ciPne	** 0.05			
Best Scenario B		pTP	0.23	-4,913	(0.092)	-53,611
		PVP	1.00			
		ciPne	** no cases			
Scenario 1		pTP	0.50	-246	(0.005)	-53,611
		pTP	0.37	-1,474	(0.027)	-53,611
		pTP	0.24	-2702	(0.050)	-53,611
Scenario 2		PVP	0.44	-123	(0.002)	-53,611
		PVP	0.54	-737	(0.014)	-53,611
		PVP	0.65	-1,352	(0.025)	-53,611
Scenario 3		pTP	0.50	-129	(0.002)	-53,611
		PVP	0.40			
		pTP	0.37	-957	(0.018)	-53,611
		PVP	0.29			
		pTP	0.24	-2,093	(0.039)	-53,611
		PVP	0.19			
Scenario 4		pTP	0.50	-362	(0.007)	-53,611
		PVP	0.44			
		pTP	0.37	-1,990	(0.037)	-53,611
		PVP	0.54			
		pTP	0.24	-3,310	(0.062)	-53,611
		PVP	0.65			

* Number within ( ) indicates negative value
* pTP: Probability of test positive
* PVP: Probability of predictive value positive
* ciPne: Probability of neurocomplication in clinical intervention
  **In the scenario A, the probability of neurocomplication in clinical intervention (ciPne parameter) is 0.05 (5%).
  **In the scenario B, we assume there are no any cases of neurocomplication in clinical intervention
* Unit for costs and ICER(s) are USD.
  **The ICER(s) are round up. The difference among the numbers are very small so the ICER(s) present the same US$-53,611 in scenarios.
* Effect indicates neurocomplication rate. Unit is percentage.

Table 8 ICER(s) in the values of pTP, PVP, and ciPne parameters in length of stay outcome

Scenarios	Endpoint	Parameter	Probability of Parameter	Incremental costs	Incremental effects	Incremental cost-effectiveness ratio **(ICER)
Best Scenario A	Length of stay	pTP	0.23	-4,259	(0.588)	-7,245
		PVP	1.00			
		ciPne	** 0.05			
Best Scenario B		pTP	0.23	-4,913	(0.678)	-7,245
		PVP	1.00			
		ciPne	** no cases			
Scenario 1		pTP	0.50	-246	(0.034)	-7,245
		pTP	0.37	-1,474	(0.203)	-7,245
		pTP	0.24	-2702	(0.373)	-7,245
Scenario 2		PVP	0.44	-123	(0.017)	-7,245
		PVP	0.54	-737	(0.102)	-7,245
		PVP	0.65	-1,352	(0.187)	-7,245
Scenario 3		pTP	0.50	-129	(0.018)	-7,245
		PVP	0.40			
		pTP	0.37	-957	(0.132)	-7,245
		PVP	0.29			
		pTP	0.24	-2,093	(0.289)	-7,245
		PVP	0.19			
Scenario 4		pTP	0.50	-362	(0.050)	-7,245
		PVP	0.44			
		pTP	0.37	-1,990	(0.275)	-7,245
		PVP	0.54			
		pTP	0.24	-3,310	(0.457)	-7,245
		PVP	0.65			

* Number within ( ) indicates negative value
* pTP: Probability of test positive
* PVP: Probability of predictive value positive
* ciPne: Probability of neurocomplication in clinical intervention
  **In the scenario A, the probability of neurocomplication in clinical intervention (ciPne parameter) is 0.05 (5%).
  **In the scenario B, we assume there are no any cases of neurocomplication in clinical intervention
* Unit for costs and ICER(s) are USD.
  **The ICER(s) are round up. The difference among the numbers are very small so the ICER(s) present the same US$-7,245 in scenarios.
* Effect indicates length of stay. Unit is day.

6.3.2 The probability of test positive and test negative in the values of sensitivity and specificity parameters

In Table 9, the effect of different values for sensitivity and specificity (0.51 to 0.99) on the probability of test positive (pTP) are reported. The results show pTP are positively correlation with sensitivity (pSens) and negatively with the specificity (pSpec). The red shaded area presents the value of pTP ≧0.49, which indicate the maximum reimbursement price (Headroom) for NeoDoppler technology.

The results in pTN are opposite of pTP. As the probability of sensitivity decreases, the value of pTN is higher. In converse, the pTN reduces when the probability of specificity increased. The value of pTN ≦0.51 marked with red shaded for comparing with the results of pTP. The pTP is lower when pSens and pSpec both have high probability but higher in pTN. The red shaded also present the available headroom (MRP) for innovative device. In Table 9, the areas without red shaded indicate the headroom (MRP) are negative numbers.

Probaability of test positive (pTP)

specificity \ sensitivity	0.99	0.96	0.93	0.9	0.87	0.84	0.81	0.78	0.75	0.72	0.69	0.66	0.63	0.6	0.57	0.54	0.51
0.99	0.24	0.23	0.22	0.21	0.21	0.20	0.19	0.19	0.18	0.17	0.17	0.16	0.15	0.15	0.14	0.13	0.13
0.96	0.26	0.25	0.24	0.24	0.23	0.22	0.22	0.21	0.20	0.20	0.19	0.18	0.18	0.17	0.16	0.16	0.15
0.93	0.28	0.27	0.27	0.26	0.25	0.25	0.24	0.23	0.23	0.22	0.21	0.21	0.20	0.19	0.19	0.18	0.17
0.9	0.30	0.30	0.29	0.28	0.28	0.27	0.26	0.26	0.25	0.24	0.24	0.23	0.22	0.22	0.21	0.20	0.19
0.87	0.33	0.32	0.31	0.31	0.30	0.29	0.29	0.28	0.27	0.27	0.26	0.25	0.25	0.24	0.23	0.22	0.22
0.84	0.35	0.34	0.34	0.33	0.32	0.32	0.31	0.30	0.30	0.29	0.28	0.28	0.27	0.26	0.25	0.25	0.24
0.81	0.37	0.37	0.36	0.35	0.35	0.34	0.33	0.33	0.32	0.31	0.31	0.30	0.29	0.28	0.28	0.27	0.26
0.78	0.40	0.39	0.38	0.38	0.37	0.36	0.36	0.35	0.34	0.34	0.33	0.32	0.31	0.31	0.30	0.29	0.29
0.75	0.42	0.41	0.41	0.40	0.39	0.39	0.38	0.37	0.37	0.36	0.35	0.34	0.34	0.33	0.32	0.32	0.31
0.72	0.44	0.44	0.43	0.42	0.42	0.41	0.40	0.40	0.39	0.38	0.37	0.37	0.36	0.35	0.35	0.34	0.33
0.69	0.47	0.46	0.45	0.45	0.44	0.43	0.43	0.42	0.41	0.40	0.40	0.39	0.38	0.38	0.37	0.36	0.36
0.66	0.49	0.48	0.48	0.47	0.46	0.46	0.45	0.44	0.43	0.43	0.42	0.41	0.41	0.40	0.39	0.39	0.38
0.63	0.51	0.51	0.50	0.49	0.49	0.48	0.47	0.46	0.46	0.45	0.44	0.44	0.43	0.42	0.42	0.41	0.40
0.6	0.54	0.53	0.52	0.52	0.51	0.50	0.49	0.49	0.48	0.47	0.47	0.46	0.45	0.45	0.44	0.43	0.43
0.57	0.56	0.55	0.55	0.54	0.53	0.52	0.52	0.51	0.50	0.50	0.49	0.48	0.48	0.47	0.46	0.46	0.45
0.54	0.58	0.58	0.57	0.56	0.55	0.55	0.54	0.53	0.53	0.52	0.51	0.51	0.50	0.49	0.49	0.48	0.47
0.51	0.61	0.60	0.59	0.58	0.58	0.57	0.56	0.56	0.55	0.54	0.54	0.53	0.52	0.52	0.51	0.50	0.49

Probaability of test negative (pTN)

specificity \ sensitivity	0.99	0.96	0.93	0.9	0.87	0.84	0.81	0.78	0.75	0.72	0.69	0.66	0.63	0.6	0.57	0.54	0.51
0.99	0.76	0.77	0.78	0.79	0.79	0.80	0.81	0.81	0.82	0.83	0.83	0.84	0.85	0.85	0.86	0.87	0.88
0.96	0.74	0.75	0.76	0.76	0.77	0.78	0.78	0.79	0.80	0.80	0.81	0.82	0.82	0.83	0.84	0.85	0.85
0.93	0.72	0.73	0.73	0.74	0.75	0.75	0.76	0.77	0.77	0.78	0.79	0.79	0.80	0.81	0.82	0.82	0.83
0.9	0.70	0.70	0.71	0.72	0.72	0.73	0.74	0.74	0.75	0.76	0.76	0.77	0.78	0.79	0.79	0.80	0.81
0.87	0.67	0.68	0.69	0.69	0.70	0.71	0.71	0.72	0.73	0.73	0.74	0.75	0.76	0.76	0.77	0.78	0.78
0.84	0.65	0.66	0.66	0.67	0.68	0.68	0.69	0.70	0.70	0.71	0.72	0.73	0.73	0.74	0.75	0.75	0.76
0.81	0.63	0.63	0.64	0.65	0.65	0.66	0.67	0.67	0.68	0.69	0.70	0.70	0.71	0.72	0.72	0.73	0.74
0.78	0.60	0.61	0.62	0.62	0.63	0.64	0.64	0.65	0.66	0.67	0.67	0.68	0.69	0.69	0.70	0.71	0.71
0.75	0.58	0.59	0.59	0.60	0.61	0.61	0.62	0.63	0.64	0.64	0.65	0.66	0.66	0.67	0.68	0.68	0.69
0.72	0.56	0.56	0.57	0.58	0.58	0.59	0.60	0.61	0.61	0.62	0.63	0.63	0.64	0.65	0.65	0.66	0.67
0.69	0.53	0.54	0.55	0.55	0.56	0.57	0.58	0.58	0.59	0.60	0.60	0.61	0.62	0.62	0.63	0.64	0.64
0.66	0.51	0.52	0.52	0.53	0.54	0.55	0.55	0.56	0.57	0.57	0.58	0.59	0.59	0.60	0.61	0.61	0.62
0.63	0.49	0.49	0.50	0.51	0.52	0.52	0.53	0.54	0.54	0.55	0.56	0.56	0.57	0.58	0.58	0.59	0.60
0.6	0.46	0.47	0.48	0.49	0.49	0.50	0.51	0.51	0.52	0.53	0.53	0.54	0.55	0.55	0.56	0.57	0.57
0.57	0.44	0.45	0.46	0.46	0.47	0.48	0.48	0.49	0.50	0.50	0.51	0.52	0.52	0.53	0.54	0.54	0.55
0.54	0.42	0.43	0.43	0.44	0.45	0.45	0.46	0.47	0.47	0.48	0.49	0.49	0.50	0.51	0.51	0.52	0.53
0.51	0.40	0.40	0.41	0.42	0.42	0.43	0.44	0.44	0.45	0.46	0.46	0.47	0.48	0.48	0.49	0.50	0.51

Table 9 Two-way sensitivity analysis on probability of test positive (pTP) and probability of test negative (pTN) respectively by giving a series values of parameters sensitivity (pSens) and specificity (pSpec). The red shaded areas are the value ≧0.49 in pTP and ≦0.51 in pTN, respectively. They indicate there are room for reimbursement on innovative device in these conditions.

In Table 10, it indicates the PVP and PVN are both have positive but different magnitude effects by pSens and pSpec parameters. PVP is more sensitive to the pSpec parameters. The estimated PVP value could vary from 0.967 to 0.376 in the range of pSpec from 0.99 to 0.51 and pSens stay in 0.99. By following one of the method of obtaining PVP is true positive rate/ (true positive rate + false positive rate), the lower PVP caused by the increasing false positive rate. The yellow shaded area presents the value of PVP ≧ 0.44, which values are consider to gain the headroom for NeoDoppler technology. The areas without yellow shad present the value of PVP < 0.44. They indicate there are no room for reimbursement on innovative device. Moreover, PVN has more sensitive by pSens than pSpec. Gaven the pSpec at 0.99, the estimated PVN decline from 0.997 to 0.871 in the range of pSens from 0.99 to 0.51. The PVN is derived by true negative rate/(true negative rate + false negative rate). Therefore, the false negative rate contribute to the decrease value of PVN. The results of two-way analysis for PVP related to the headroom study for NeoDoppler technology. We also test PVN value at 0.99 and 1 in the headroom analysis. The results shows the MRP are negative and no revenues generated because the headroom are less than unit cost per patient. The other reason is that our comparator has high value of PVN, 0.98, in our estimation. In Table 10, there is no yellow shaded area in PVN whereas indicating the available headroom for reimbursement on innovative device.

According to the results of in table 9 and table 10, PVP and PVN both are higher in high values of sensitivity and specificity. The pTP is 0.24 at sensitivity and specificity both at 0.99 probabilities, which is close to the incident rate 0.23 (pPrev). The PVP and PVN are 0.967 and 0.99 to be estimated. This present the best performance and quality of the monitoring system. Most of true positives and true negatives can be distinguished by the devices and intervene following the clinical guidelines. As the PVP is much more sensitive to pSpec than PVN, the probability declines to 0.24 at 0.51 probability in both pSens and pSpec parameters. Finally, in Table 6, 7, and Table 8, the ICER(s) indicate the potential cost-effectiveness for NeoDoppler technology given the values of pTP and PVP. The estimated values of pTP and PVP can be estimated by given numbers of sensitivity and specificity as the results shown in table 9 and table 10. Furthermore, the headroom for NeoDoppler technology in each scenario of three endpoints are calculated from the incremental costs and incremental effects from Table 6, 7, and Table 8. The predictive revenues are only presented in survival rate outcome, where willingness-to-pay could be referred. The headroom and revenues results are shown in the table 11 and table 12 at two different product unit costs, respectively.

Probability of predictive value positive (PVP)

specificity \ sensitivity	0.99	0.96	0.93	0.9	0.87	0.84	0.81	0.78	0.75	0.72	0.69	0.66	0.63	0.6	0.57	0.54	0.51
0.99	0.97	0.97	0.97	0.96	0.96	0.96	0.96	0.96	0.96	0.96	0.95	0.95	0.95	0.95	0.94	0.94	0.94
0.96	0.88	0.88	0.87	0.87	0.87	0.86	0.86	0.85	0.85	0.84	0.84	0.83	0.82	0.82	0.81	0.80	0.79
0.93	0.81	0.80	0.80	0.79	0.79	0.78	0.78	0.77	0.76	0.75	0.75	0.74	0.73	0.72	0.71	0.70	0.69
0.9	0.75	0.74	0.74	0.73	0.72	0.72	0.71	0.70	0.69	0.68	0.67	0.66	0.65	0.64	0.63	0.62	0.60
0.87	0.69	0.69	0.68	0.67	0.67	0.66	0.65	0.64	0.63	0.62	0.61	0.60	0.59	0.58	0.57	0.55	0.54
0.84	0.65	0.64	0.63	0.63	0.62	0.61	0.60	0.59	0.58	0.57	0.56	0.55	0.54	0.53	0.52	0.50	0.49
0.81	0.61	0.60	0.59	0.59	0.58	0.57	0.56	0.55	0.54	0.53	0.52	0.51	0.50	0.49	0.47	0.46	0.44
0.78	0.57	0.57	0.56	0.55	0.54	0.53	0.52	0.51	0.50	0.49	0.48	0.47	0.46	0.45	0.44	0.42	0.41
0.75	0.54	0.53	0.53	0.52	0.51	0.50	0.49	0.48	0.47	0.46	0.45	0.44	0.43	0.42	0.41	0.39	0.38
0.72	0.51	0.51	0.50	0.49	0.48	0.47	0.46	0.45	0.44	0.43	0.42	0.41	0.40	0.39	0.38	0.37	0.35
0.69	0.49	0.48	0.47	0.46	0.46	0.45	0.44	0.43	0.42	0.41	0.40	0.39	0.38	0.37	0.35	0.34	0.33
0.66	0.47	0.46	0.45	0.44	0.43	0.42	0.42	0.41	0.40	0.39	0.38	0.37	0.36	0.35	0.33	0.32	0.31
0.63	0.44	0.44	0.43	0.42	0.41	0.40	0.40	0.39	0.38	0.37	0.36	0.35	0.34	0.33	0.32	0.30	0.29
0.6	0.43	0.42	0.41	0.40	0.39	0.39	0.38	0.37	0.36	0.35	0.34	0.33	0.32	0.31	0.30	0.29	0.28
0.57	0.41	0.40	0.39	0.38	0.38	0.37	0.36	0.35	0.34	0.33	0.32	0.31	0.30	0.29	0.28	0.27	0.26
0.54	0.39	0.38	0.38	0.37	0.36	0.35	0.34	0.34	0.33	0.32	0.31	0.30	0.29	0.28	0.27	0.26	0.25
0.51	0.38	0.37	0.36	0.35	0.35	0.34	0.33	0.32	0.31	0.31	0.30	0.29	0.28	0.27	0.26	0.25	0.24

Probability of predictive value negative (PVN)

specificity \ sensitivity	0.99	0.96	0.93	0.9	0.87	0.84	0.81	0.78	0.75	0.72	0.69	0.66	0.63	0.6	0.57	0.54	0.51
0.99	1.00	0.99	0.98	0.97	0.96	0.95	0.95	0.94	0.93	0.92	0.91	0.91	0.90	0.89	0.89	0.88	0.87
0.96	1.00	0.99	0.98	0.97	0.96	0.95	0.94	0.94	0.93	0.92	0.91	0.90	0.90	0.89	0.88	0.87	0.87
0.93	1.00	0.99	0.98	0.97	0.96	0.95	0.94	0.93	0.93	0.92	0.91	0.90	0.89	0.89	0.88	0.87	0.86
0.9	1.00	0.99	0.98	0.97	0.96	0.95	0.94	0.93	0.92	0.91	0.91	0.90	0.89	0.88	0.88	0.87	0.86
0.87	1.00	0.99	0.98	0.97	0.96	0.95	0.94	0.93	0.92	0.91	0.90	0.90	0.89	0.88	0.87	0.86	0.86
0.84	1.00	0.99	0.98	0.97	0.96	0.95	0.94	0.93	0.92	0.91	0.90	0.89	0.88	0.88	0.87	0.86	0.85
0.81	1.00	0.99	0.97	0.96	0.95	0.94	0.93	0.92	0.92	0.91	0.90	0.89	0.88	0.87	0.86	0.85	0.85
0.78	1.00	0.98	0.97	0.96	0.95	0.94	0.93	0.92	0.91	0.90	0.89	0.88	0.88	0.87	0.86	0.85	0.84
0.75	1.00	0.98	0.97	0.96	0.95	0.94	0.93	0.92	0.91	0.90	0.89	0.88	0.87	0.86	0.85	0.85	0.84
0.72	1.00	0.98	0.97	0.96	0.95	0.94	0.93	0.92	0.91	0.90	0.89	0.88	0.87	0.86	0.85	0.84	0.83
0.69	1.00	0.98	0.97	0.96	0.95	0.94	0.92	0.91	0.90	0.89	0.88	0.87	0.86	0.85	0.84	0.83	0.83
0.66	1.00	0.98	0.97	0.96	0.94	0.93	0.92	0.91	0.90	0.89	0.88	0.87	0.86	0.85	0.84	0.83	0.82
0.63	1.00	0.98	0.97	0.95	0.94	0.93	0.92	0.91	0.89	0.88	0.87	0.86	0.85	0.84	0.83	0.82	0.81
0.6	1.00	0.98	0.97	0.95	0.94	0.93	0.91	0.90	0.89	0.88	0.87	0.86	0.84	0.83	0.82	0.81	0.80
0.57	0.99	0.98	0.96	0.95	0.94	0.92	0.91	0.90	0.88	0.87	0.86	0.85	0.84	0.83	0.82	0.81	0.80
0.54	0.99	0.98	0.96	0.95	0.93	0.92	0.90	0.89	0.88	0.87	0.85	0.84	0.83	0.82	0.81	0.80	0.79
0.51	0.99	0.98	0.96	0.94	0.93	0.91	0.90	0.89	0.87	0.86	0.85	0.83	0.82	0.81	0.80	0.79	0.78

Table 10 Two-way sensitivity analysis on probability of predictive value positive (PVP) and probability of predictive value negative (PVN) respectively by giving a series values of parameters sensitivity (pSens) and specificity (pSpec). The yellow shaded areas are the value of PVP ≧ 0.44. They indicate there are room for reimbursement on innovative device in these conditions.

6.4 Headroom Analysis and Value of the Revenues

In our study, there are several scenarios shown in Table 11 to estimate the Headroom for NeoDoppler technology in the assumptions made. In our estimation, the multi-monitoring system (comparator) has pTP 0.53 and PVP 0.42. Therefore, in our headroom analysis, we test what the best scenario would be for NeoDoppler technology. The best scenario is in the conditions of pTP 0.23, PVP 1, and no cases on neurologic complication as shown in Scenario B. The best scenarios for NeoDoppler technology is that the pTP is 0.23, which related to the incident rate 23%. In the best scenario B, the results of survival rate indicate the headroom (MRP) will be US$ 7,610. The predictive revenues is US$ 849,182 based on the MRP in survival rate in one year period. In neurocomplication rate, the headroom will up to US$ 10,717. In length of stay outcome, the headroom in the best scenario B is US$ 43,816 to be estimated.

In addition, there are two parameters, pTP and PVP, selected in scenario 1, 2, 3, and scenario 4, We test a series of values of one parameter or varying two parameters at the same time. In the survival rate outcome, as the result of scenarios 1 indicates the headroom increase from US$ 390 to US$ 4288 at the range of the probability of pTP from 0.50 to 0.24. The result of scenarios 2 presents the headroom increase from US$ 182 to US$ 2003 at the range of the probability of PVP from 0.44 to 0.65. The result of scenarios 3, the headroom increases from US$ 217 to US$ 3387 by giving a range of pTP from 0.5 to 0.24 and PVP from 0.4 to 0.19. The result of scenarios 4, the headroom increase from US$ 563 to US$ 5,189 by giving a range of pTP from 0.5 to 0.24 and PVP from 0.44 to 0.65. In the neurocomplication rate outcome, headroom range is from US$ 281 to US$ 7,221 among scenario 1, 2, 3, and scenario 4. For length of stay outcome, the headroom start from US$1,096 and up to US$ 29,521 among four scenarios. The predictive revenues is from US$ 10,781 (scenario 2) to US$ 575,956 ((scenario 4) based on the headroom (MRP) in survival rate in one year period. The above results are presented in Table 11. The increasing headroom calculated from the less incremental costs and more effects obtained shown in Tables 11.1, 11.2, and 11.3 in Appendix D. Furthermore, we assume the costs of good is US$ 564 per patient in Table 12. In the survival rate, the revenue turn to negative value at the pTP 0.5, PVP 0.44 and 0.46, varying both pTP and PVP at 0.5 and 0.4, 0.48 and 0.38. In the neurocomplication rate, the negative revenue are at PVP 0.44, varying both pTP and PVP at 0.5 and 0.4. There are no negative values in the length of stay outcome. The revenues gain less in three estimated outcomes shown in Tables 12.1, 12.2, and 12.3 in Appendix D.

Table 11 Headroom and revenue scenarios for NeoDoppler technology in three estimate outcomes at product unit costs US$ 97.68

Scenarios	Parameter	Probability of Parameter	(Survival Rate) Headroom	***Revenue	(Neurocomplication Rate) Headroom	(Length of Stay) Headroom
Best Scenario A	pTP	0.23	6.605	735,712	9,290	37,980
	PVP	1.00				
	ciPne	** 0.05				
Best Scenario B	pTP	0.23	7,610	849,182	10,717	43,816
	PVP	1.00				
	ciPne	** no cases				
Scenario 1	pTP	0.50	390	34,233	536	2,190
	pTP	0.37	2,339	254,237	3,215	13,143
	pTP	0.24	4,288	474,241	5,893	24,095
Scenario 2	PVP	0.44	182	10,781	286	1,096
	PVP	0.54	1,092	113,524	1,609	6,577
	PVP	0.65	2,003	216,268	2,949	12,058
Scenario 3	pTP	0.50	217	14,712	281	1,149
	PVP	0.40				
	pTP	0.37	1,574	167,932	2,089	8,539
	PVP	0.29				
	pTP	0.24	3,387	372,525	4,566	18,669
	PVP	0.19				
Scenario 4	pTP	0.50	563	53,754	790	3,232
	PVP	0.44				
	pTP	0.37	3,104	340,541	4,341	17,747
	PVP	0.54				
	pTP	0.24	5,189	575,956	7,221	29,521
	PVP	0.65				

In table 11, headroom and revenue are calculated basing on the assumption: 1) The given values of pTP, PVP, and ciPne parameters are as the same as Table 6, 7, and Table 8 in three estimated endpoints. 2) The headroom in each scenario is calculated from the results of incremental costs and incremental effects in Table 6,7 and Table 8. 3) Threshold value: US$ 50,000 2) Unit cost per patient: US$ 97.68 4) Period of time: At the first year of product launch 5) ***Revenue: The revenue is calculated and based on the headroom result of survival rate, where willingness-to-pay could be referred.

* pTP: Probability of test positive
* PVP: Probability of predictive value positive
* ciPne: Probability of neurocomplication in clinical intervention
  **In the scenario A, the probability of neurocomplication in clinical intervention (ciPne parameter) is 0.05 (5%).
  **In the scenario B, we assume there are no any cases of neurocomplication in clinical intervention
* Unit for headroom (maximum reimbursement price) is USD
* Unit for revenue is USD

Table 12 Headroom and revenue scenarios for NeoDoppler technology in three estimate outcomes at product unit costs US$ 564.00

Scenarios	Parameter	Probability of Parameter	(Survival Rate) Headroom	***Revenue	(Neurocomplication Rate) Headroom	(Length of Stay) Headroom
Best Scenario A	pTP	0.23	6,605	689,045	9,290	37,980
	PVP	1.00				
	ciPne	** 0.05				
Best Scenario B	pTP	0.23	7,610	802,515	10,717	43,816
	PVP	1.00				
	ciPne	** no cases				
Scenario 1	pTP	0.50	390	-12,434	536	2,190
	pTP	0.37	2,339	207,569	3,215	13,143
	pTP	0.24	4,288	427,573	5,893	24,095
Scenario 2	PVP	0.44	182	-35,886	268	1,096
	PVP	0.54	1,092	66,857	1,609	6,577
	PVP	0.65	2,003	169,600	2,949	12,058
Scenario 3	pTP	0.50	217	-31,955	281	1,149
	PVP	0.40				
	pTP	0.37	1,574	121,265	2,089	8,539
	PVP	0.29				
	pTP	0.24	3,387	325,857	4,566	18,669
	PVP	0.19				
Scenario 4	pTP	0.50	563	7,087	790	3,232
	PVP	0.44				
	pTP	0.37	3,104	293,874	4,341	17,747
	PVP	0.54				
	pTP	0.24	5,189	529,289	7,221	29,521
	PVP	0.65				

In table 12, headroom and revenue are calculated basing on the assumption: 1) The given values of pTP, PVP, and ciPne parameters are as the same as Table 6, 7, and Table 8 in three estimated endpoints. 2) The headroom in each scenario is calculated from the results of incremental costs and incremental effects in Table 6,7 and Table 8. 3) Threshold value: US$ 50,000 2) Unit cost per patient: US$ 564.00 4) Period of time: At the first year of product launch. 5) ***Revenue: The revenue is calculated and based on the headroom result of survival rate, where willingness-to-pay could be referred.

* pTP: Probability of test positive
* PVP: Probability of predictive value positive
* ciPne: Probability of neurocomplication in clinical intervention
  **In the scenario A, the probability of neurocomplication in clinical intervention (ciPne parameter) is 0.05 (5%).
  **In the scenario B, we assume there are no any cases of neurocomplication in clinical intervention
* Unit for headroom (maximum reimbursement price) is USD
* Unit for revenue is USD

Furthermore, we estimate the revenues correlated with headroom and units sold in two different units cost in Figure 18. First, the unit cost is set at US$ 97.68 per patient. The two-way analysis result indicates the revenues become US$ 0 approximately at negative at headroom at US$ 97.68 with system sold at 10 units. Second, the unit cost is up to US$ 564 per patient. The revenues generate from 0 at headroom US$ 564 and 10 units sold. As the production costs for Neodoppler technology per patient is from US$ 97.68 to US$ 564 range. The lowest nproduction costs per patient US$97.68 chosen, which othe best scenario of the cost estimated is.

Revenues (unit cost:US$ 97.68)

Units sold \ Headroom	45000	42000	39000	36000	33000	30000	27000	24000	21000	18000	15000	12000	10000	9000	8000	7000	6000	5000	4000	3000	2000	1000	900	800	700	600	500	400	300	200	100	90	80	70
200	10136250	9459030	8781810	8104590	7427370	6750150	6072930	5395710	4718490	4041270	3364050	2686830	2235350	2009610	1783870	1558130	1332390	1106650	880910	655170	429430	203690	181116	158542	135968	113394	90820	68246	45672	23098	524	-1734	-3991	-6248
190	9629437	8986078	8342719	7699360	7056001	6412642	5769283	5125924	4482565	3839206	3195847	2552488	2123582	1909129	1694676	1480223	1265770	1051317	836864	622411	407958	193505	172060	150615	129169	107724	86279	64833	43388	21943	498	-1647	-3792	-5936
180	9122625	8513127	7903629	7294131	6684633	6075135	5465637	4856139	4246641	3637143	3027645	2418147	2011815	1808649	1605483	1402317	1199151	995985	792819	589653	386487	183321	163004	142688	122371	102054	81738	61421	41105	20788	471	-1560	-3592	-5624
170	8615812	8040175	7464538	6888901	6313264	5737627	5161990	4586353	4010716	3435079	2859442	2283805	1900047	1708168	1516289	1324410	1132531	940652	748773	556894	365015	173136	153948	134760	115573	96385	77197	58009	38821	19633	445	-1474	-3392	-5311
160	8109000	7567224	7025448	6483672	5941896	5400120	4858344	4316568	3774792	3233016	2691240	2149464	1788280	1607688	1427096	1246504	1065912	885320	704728	524136	343544	162952	144893	126833	108774	90715	72656	54597	36537	18478	419	-1387	-3193	-4999
150	7602187	7094272	6586357	6078442	5570527	5062612	4554697	4046782	3538867	3030952	2523037	2015122	1676512	1507207	1337902	1168597	999292	829987	660682	491377	322072	152767	135837	118906	101976	85045	68115	51184	34254	17323	393	-1300	-2993	-4686
140	7095375	6621321	6147267	5673213	5199159	4726105	4251051	3776997	3302943	2828889	2354835	1880781	1564745	1406727	1248709	1090691	932673	774655	616637	458619	300601	142583	126781	110979	95177	79376	63574	47772	31970	16168	367	-1214	-2794	-4374
130	6588562	6148369	5708176	5267983	4827790	4387597	3947404	3507211	3067018	2626825	2186632	1746439	1452977	1306246	1159515	1012784	866053	719322	572591	425860	279129	132398	117725	103052	88379	73706	59033	44360	29687	15014	340	-1127	-2594	-4062
120	6081750	5675418	5269086	4862754	4456422	4050090	3643758	3237426	2831094	2424762	2018430	1612098	1341210	1205766	1070322	934878	799434	663990	528546	393102	257658	122214	108669	95125	81581	68036	54492	40947	27403	13859	314	-1040	-2395	-3749
110	5574937	5202466	4829995	4457524	4085053	3712582	3340111	2967640	2595169	2222698	1850227	1477756	1229442	1105285	981128	856971	732814	608657	484500	360343	236186	112029	99614	87198	74782	62367	49951	37535	25119	12704	288	-954	-2195	-3437
100	5068125	4729515	4390905	4052295	3713685	3375075	3036465	2697855	2359245	2020635	1682025	1343415	1117675	1004805	891935	779065	666195	553325	440455	327585	214715	101845	90558	79271	67984	56697	45410	34123	22836	11549	262	-867	-1996	-3124
90	4561312	4256563	3951814	3647065	3342316	3037567	2732818	2428069	2123320	1818571	1513822	1209073	1005907	904324	802741	701158	599575	497992	396409	294826	193243	91660	81502	71344	61185	51027	40869	30711	20552	10394	236	-780	-1796	-2812
80	4054500	3783612	3512724	3241836	2970948	2700060	2429172	2158284	1887396	1616508	1345620	1074732	894140	803844	713548	623252	532956	442660	352364	262068	171772	81476	72446	63417	54387	45357	36328	27298	18269	9239	209	-693	-1596	-2499
70	3547687	3310660	3073633	2836606	2599579	2362552	2125525	1888498	1651471	1414444	1177417	940390	782372	703363	624354	545345	466336	387327	308318	229309	150300	71291	63391	55490	47589	39688	31787	23886	15985	8084	183	-607	-1397	-2187
60	3040875	2837709	2634543	2431377	2228211	2025045	1821879	1618713	1415547	1212381	1009215	806049	670605	602883	535161	467439	399717	331995	264273	196551	128829	61107	54335	47563	40790	34018	27246	20474	13702	6929	157	-520	-1197	-1875

Revenues (unit cost:US$ 564)

Units sold \ Headroom	45000	42000	39000	36000	33000	30000	27000	24000	21000	18000	15000	12000	10000	9000	8000	7000	6000	5000	4000	3000	2000	1000	900	800	700	600	500	400	300	200	100	90	80	70
200	10030983	9353763	8676543	7999323	7322103	6644883	5967663	5290443	4613223	3936003	3258783	2581563	2130083	1904343	1678603	1452863	1227123	1001383	775643	549903	324163	98423	75849	53275	30701	8127	-14447	-37021	-59595	-82169	-104743	-107001	-109258	-111516
190	9529434	8886075	8242716	7599357	6955998	6312639	5669280	5025921	4382562	3739203	3095844	2452485	2023579	1809126	1594673	1380220	1165767	951314	736861	522408	307955	93502	72056	50611	29166	7720	-13725	-35170	-56616	-78061	-99506	-101651	-103795	-105940
180	9027884	8418386	7808888	7199390	6589892	5980394	5370896	4761398	4151900	3542402	2932904	2323406	1917074	1713908	1510742	1307576	1104410	901244	698078	494912	291746	88580	68264	47947	27631	7314	-13003	-33319	-53636	-73952	-94269	-96301	-98332	-100364
170	8526335	7950698	7375061	6799424	6223787	5648150	5072513	4496876	3921239	3345602	2769965	2194328	1810570	1618691	1426812	1234933	1043054	851175	659296	467417	275538	83659	64471	45283	26096	6908	-12280	-31468	-50656	-69844	-89032	-90951	-92869	-94788
160	8024786	7483010	6941234	6399458	5857682	5315906	4774130	4232354	3690578	3148802	2607026	2065250	1704066	1523474	1342882	1162290	981698	801106	620514	439922	259330	78738	60679	42620	24561	6501	-11558	-29617	-47676	-65735	-83795	-85601	-87407	-89212
150	7523237	7015322	6507407	5999492	5491577	4983662	4475747	3967832	3459917	2952002	2444087	1936172	1597562	1428257	1258952	1089647	920342	751037	581732	412427	243122	73817	56886	39956	23025	6095	-10836	-27766	-44697	-61627	-78558	-80251	-81944	-83637
140	7021688	6547634	6073580	5599526	5125472	4651418	4177364	3703310	3229256	2755202	2281148	1807094	1491058	1333040	1175022	1017004	858986	700968	542950	384932	226914	68896	53094	37292	21490	5689	-10113	-25915	-41717	-57519	-73320	-74901	-76481	-78061
130	6520139	6079946	5639753	5199560	4759367	4319174	3878981	3438788	2998595	2558402	2118209	1678016	1384554	1237823	1091092	944361	797630	650899	504168	357437	210706	63975	49302	34629	19955	5282	-9391	-24064	-38737	-53410	-68083	-69550	-71018	-72485
120	6018590	5612258	5205926	4799594	4393262	3986930	3580598	3174266	2767934	2361602	1955270	1548938	1278050	1142606	1007162	871718	736274	600830	465386	329942	194498	59054	45509	31965	18420	4876	-8668	-22213	-35757	-49302	-62846	-64200	-65555	-66909
110	5517040	5144569	4772098	4399627	4027156	3654685	3282214	2909743	2537272	2164801	1792330	1419859	1171545	1047388	923231	799074	674917	550760	426603	302446	178289	54132	41717	29301	16885	4470	-7946	-20362	-32777	-45193	-57609	-58850	-60092	-61334
100	5015491	4676881	4338271	3999661	3661051	3322441	2983831	2645221	2306611	1968001	1629391	1290781	1065041	952171	839301	726431	613561	500691	387821	274951	162081	49211	37924	26637	15350	4063	-7224	-18511	-29798	-41085	-52372	-53500	-54629	-55758
90	4513942	4209193	3904444	3599695	3294946	2990197	2685448	2380699	2075950	1771201	1466452	1161703	958537	856954	755371	653788	552205	450622	349039	247456	145873	44290	34132	23974	13815	3657	-6501	-16660	-26818	-36976	-47135	-48150	-49166	-50182
80	4012393	3741505	3470617	3199729	2928841	2657953	2387065	2116177	1845289	1574401	1303513	1032625	852033	761737	671441	581145	490849	400553	310257	219961	129665	39369	30339	21310	12280	3251	-5779	-14809	-23838	-32868	-41897	-42800	-43703	-44606
70	3510844	3273817	3036790	2799763	2562736	2325709	2088682	1851655	1614628	1377601	1140574	903547	745529	666520	587511	508502	429493	350484	271475	192466	113457	34448	26547	18646	10745	2844	-5057	-12957	-20858	-28759	-36660	-37450	-38240	-39030
60	3009295	2806129	2602963	2399797	2196631	1993465	1790299	1587133	1383967	1180801	977635	774469	639025	571303	503581	435859	368137	300415	232693	164971	97249	29527	22755	15982	9210	2438	-4334	-11106	-17879	-24651	-31423	-32100	-32777	-33455

Figure 16 Two-way sensitive analysis on predicted revenues by giving a series values of headroom (MRP) and units sold at unit cost US$ 97.68 and US$ 564 respectively.

7. Ethical Issue

All data are extracted from literary review. There are no ethical concerns in our study. For future clinical trial conduction, risk-benefit analysis and ethical issues will be reviewed by Ethics Review Committees to ensure participants' rights (autonomy, non-maleficence, beneficence, and justices), safety, risk of adverse events, well-being, and individual data protection. The assessment process for trial approval should compliant with applicable transparency and disclosure regulations.

8. Discussion

Medical diagnostic and monitoring devices aim at guiding decisions regarding treatment, so options are more targeted. The methods to estimate treatment or intervention effects is to assess four parameters; sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) (Thomas Jue and Kazumi Masuda, 2013; Robert S. Bonser *et al.*, 2011). The values of sensitivity and specificity would vary with the choice of outpoint. Therefore, finding the optimized outpoint depending on the type of diseases or disorders is critical for diagnosis device developing. Clinical guidelines guide physicians during the surgery. To establish clinical guidelines based on the cutoff values of medical devices can enhance the effective therapy or intervention (Gary R. Cutter and Yuliang Liu, 2012).

Innovative technology improves patient's outcomes, and provides better health services. Accuracy and precision are the key factors of performance as a diagnosis device. Clinical effectiveness is associated with the quality of medical devices. Reliability of medical devices is determined by sensitivity and specificity. Less reproducibility and significant bias can be generate from patient's characteristic, type of surgery, and limitations of diagnosis devices. The potential risk of bias could lead to type I error (false positives) or type II error (false negatives). The robustness of results aims to optimize the treatment algorithm and reduce side effects through an innovative technology. According to previous studies, there is no significant direct evidence on applying one type of medical device in monitoring cerebral oxygenation (rSO_2) or cerebral blood flow (CBF) interoperation can improve patients' outcomes. In our study, as the results of clinical trials are not yet complete so we use the model-based analysis to estimate the short-term effects resulting from pediatric cardiac surgery. From our estimation shown in Table 3, specificity value is 0.6. It indicates there are some false negatives detected by the multi-monitoring system. Sensitivity value is 0.96 that is higher than its specificity value 0.6. It indicates there are few false positives and less than false negatives. When incident rate is 23%, the

probability of test positive (pTP) and the probability of test negative (pTN) are 53% and 47%, respectively. Therefore, there is a room for ameliorating the detecting rate of a monitoring device. Available clinical interventions based on data observed can reduce neurologic complication and mortality rate. Moreover, when side effects or complications are reduced, length of stay at the hospital will become less as the consequence of surgeries. Moreover, total costs will be reduced following by enhancing the health effects. It could be a cost-saving approach for an existing multi-monitoring system or an innovation device.

In the first part of cost-effectiveness analysis for a multi-monitoring system, survival rate is increased proximately 5% and neurologic complication declined 14% through a monitoring system with sensitivity 0.96, specificity 0.6, pTP 0.53, and PVP 0.42. In our study, sensitivity and specificity of a monitoring system are conditional with treatment guidelines can follow. Treatment algorithms are based on data observed can enhance surgical outcomes.In the deterministic analysis, negative ICER(s) shows that intervention is cost saving and dominate in three estimated outcomes. ICER in survival rate is lowest than neurocomplication rate, and LOS. Considering life expectancy, increasing the survival rate is an important value of a monitoring system. In the probabilistic analysis, CE-plane of survival rate presents that there are some simulations located in NE and SW quadrants, whereas the trade-off between costs and effects. The decision of adopting intervention bases on a threshold givens. In neurocomplication rate, it shows that intervention gains effects since all simulations spreading on the right of vertical axis but costs may tend to increase or decrease. Regarding length of stay, intervention could be dominate or dominated depending on the negative or positive effects. From the results of scatterplots, it indicates that there are certain uncertainties surrounding by intervention for being cost-effective. The choice of threshold value depends on perspectives. It could be patients and their family, health care providers, payers, or society. Measurement costs will be different among them. In our study, survival rate is relate to life expectancy. Decision makers may have higher threshold for per effect gained. As for neurocomplicaiton, it may have an impact on health related quality of life (HRQOL) in a longer-term. Thus, it could be plausible to have higher threshold and less concern about the risk of having adverse events and serious illness. Thresholds would be justifiable based on estimated outcomes. Therefore, cost-effectiveness analysis provides an information on whether intervention is reasonable efficient, questionable efficiency, or inefficient.

Uncertainties can contribute from the bias of input values of parameters (standards errors), model-based analysis, and assumptions in our study. In deterministic one-way sensitivity analysis, it indicates that neurologic complication costs (nnC parameter) has larger impact on the ICER(s) in three

endpoints. In expensive and complicate surgeries, there are more cost saving and higher negative ICER(s). nnC parameter is more sensitive to survival rate than neurocomplication rate, and length of stay in our model.

In cost-effectiveness analysis for NeoDoppler technology, the results of ICER(s) are negative numbers in three estimated endpoints. Negative ICER(s) result from less costs and more health effects gained. Available headroom (MRP) and revenues for NeoDoppler technology can be created, if innovation has higher accuracy and quality than comparator. We present several scenarios in our study. If pTP lower in NeoDoppler technology but the same PVP as comparator, it would result from higher value of specificity or lower value of sensitivity in NeoDoppler technology . In the same value of sensitivity but higher value of specificity than comparator, NeoDoppler technology is able to obtain headroom and revenues. It presents higher true negatives. If NeoDoppler technology has the same value of pTP as comparator but higher PVP, it indicates true positives moved from false positives distinguished by NeoDoppler technology. If both pTP and PVP are lower in NeoDoppler technology, it has lower sensitivity and higher specificity than comparator. Headroom obtains from increasing true negatives and decreasing false positives. If NeoDoppler technology has lower value of pTP and higher value of PVP, its specificity is higher. Then NeoDoppler technology has higher true positives and higher true negatives. Therefore, innovative technology aims to enhance accuracy and precision of diagnosis by reducing type I error (false positives) and type II error (false negatives).

Innovative technology can focus on having the same performance as exist multimodality neurologic monitoring system but less costs or better quality to generate more health benefits. In our cost-effectiveness analysis, existing multi-monitoring system is a cost saving and dominate approach. In Dean B, (2004), it indicates that the data from NIRS is more responsible for monitoring abnormalities, which is 58%. TCD is 37% in the second place. EEG is 5% only. NeoDoppler has ameliorated some boundaries and limitations of NIRS and TCD to achieve the unmet need. Innovative technology has a chance to create some advantages on enhancing patient's outcomes and efficiency of health care. Considering the role of innovation, whether it can replace the function of NIRS and/or TCD in a multi-monitoring system by giving the same or greater reliability to prevent neurologic complication. Moreover, innovative technology could have scientific spillovers on further application for other intended use in pediatric care such as preterm infant monitoring. As target population is pediatric patients, neurodevelopment will be associated with long-term health outcomes. It would reflect perceived value from societal and benefit health economics. Value-based care (VBC) can evaluate with evidence development and manage in performance-based agreements. This type of agreement is one

of reimbursement strategies to reduce the risk of uncertainty between payer and producer as a bundled payment model.

In our estimation, the performance of innovative device is the key factor of obtaining maximum reimbursement price. Improvement of accuracy and precision leads to reduce health care service costs and gain more health benefits. Threshold also can drive headroom value. Thus, the willingness-to-pay for innovation is critical. Patient-relevant endpoints, and appropriate comparator(s) have impact on reimbursement price. Payers may have concerns on the gap between clinical trial and real-world evidence (RWE) such as heterogeneity among patients. Clinical trial is a controlled setting to maximize internal validity only. Another challenge is that standard of care evolves with time and vary across countries.

Revenues are influenced by unit costs. If headroom (MRP) is equal or smaller than unit costs, there will be no revenues. Producers may consider terminating development of innovative products. If the difference between headroom and unit cost is large, it would drive higher amount of revenues when the number of items sold is set. Therefore, high quality of device, low unit costs, market launch strategy, healthcare system, and coverage environment are the key elements to sustain product's profitability.

8.1 Model Validation Results

By comparing ICER(s) in three estimated endpoints between decision tree model A and decision tree model B, the expected values are close and results are similar to each other in the cost-effectiveness analysis. ICER of survival rate in model A is US$ -141,243 and in model B is US$-136,014. As for neurocomplication rat, ICER is US$-53,611 in both model A and model B. Both models also have the same ICER(s) US$-7,245 in length of stay outcome.

8.2 Strength, Limitation, and Bias

Considering data availability and limited evidence from literature review, we need to make strong assumptions in our analysis. Costs data may not comprehensive and involve all relative perspectives, for instance, all relevant costs should be take into consideration from society perspective. We focus on large medical cost items (e.g. treatment for neurocomplication including length of stay) as direct costs. It is the only costs different between two arms. Other direct costs (e.g. informal care time) and indirect costs (e.g. costs on complications during life years gained, special education needed in adolescent, or productivity cost in the later life) as treatment costs of postoperative complications or non-

medical costs are ignored in costs identification. It may lead to underestimate and inconsistent because only effects are included in analysis. Data on surgical costs are slightly right-skewed distribution in our estimation. It could lead to bias and less precision when data are skewed. In order to deal with this problem, we obtain mean value from logarithmic transformation in a normal distribution. Regarding the mortality rate from neurologic sequelae, the data is not available from Erle H. Austin III *et al.* (1997). We calculate in an indirect way in order to obtain proportion of mortality from neurologic sequelae. This may contribute to bias on ICER(s) in our models.

In the results of one-way sensitivity analysis, neurocompliction costs has large influence on ICER (s). It creates a great uncertainty on budget impact to decision makers. On the other hand, the probabilities are patched and calculated from non-real head-to-head trial. It could lead to bias on the model-based analysis. We only estimate short-term effect in surgery and ignore long-term effect (e.g. neurodevelopment benefits). Bedsides, up-to-date clinical guidelines are not evaluated in our study that may also generate bias in our study. In overall, sources of bias and variation can contribute to different estimate values. Excepting the weakness, model-based analysis can predict potential cost-effectiveness and revenues for innovative medical devices in the early product development stage. It provides producers an information on continuing development, refining technology, or terminating the products.

9. Conclusion

As a role of innovative device, higher accuracy and available clinical guidelines based on data observed would be critical points to gain cost-effective. Its aim is to reduce neurocomplication and enhance survival rate. The better health outcomes result in earlier discharge from hospitals. Survival rate could be a major index of willingness-to-pay for payers. However, mortality is one of the consequences of neurocomplication resulting from surgery procedure. Therefore, reducing neurologic complication or severity of neurologic complication through a high quality-monitoring device can drive down mortality rate. In addition, whether the severity of neurologic complication can be prevented or reduced from surgery procedure though innovative technology, it requires further research and evidence in the future. Besides stand-alone use, innovative device could consider to work together with other diagnosis devices as a multi-monitoring system or develop a multi-function device to extend the intended for use. These can be the possible proposition of Neodoppler technology.

Reference

Sidra Kaleem Jafri, Lubaina Ehsan, Qalab Abbas, Fatima Ali, Prem Chand, and Anwar Ul Haque (2017), Frequency and Outcome of Acute Neurologic Complications after Congenital Heart Disease Surgery, *J Pediatr Neurosci* ; 12(4): 328–331.

Juilien I. E. Hoffman, and Samuel Kaplan (2002), The Incidence of Congenital Heart Disease, *Journal of the American College of Cardiology* ;Vol. 39, No. 12.

Joseph B. Clark, Mollie L. Barnes, CNIM, Akif Undar, and John L. Myers (2012), Multimodality neuromonitoring for pediatric cardiac surgery: Our approach and a critical appraisal of the available evidence, *World Journal for Pediatric and Congenital Heart Surgery*; 3(l): 87-95.

Jenkins KJ, Correa A, Feinstein JA, and Botto L, et al. (2007), Noninherited risk factors and congenital cardiovascular defects: current knowledge: a scientific statement from the Ameri-can

Heart Association Council on Cardiovascular Disease in the Young: endorsed by the American Academy of Pediatrics. *Circulation* ;115(23): 2995-3014.

Dean B Andropoulos, Stephen A. Stayer, Laura K. Diaz and Chandra Ramamoorthy (2004), Neurological Monitoring for Congenital Heart Surge, Anesthesia & Analgesla; 99:1365-75.

Sara Lozano, Emad Mossad Cerebral, Martin J. (2004) Cerebral function monitors during pediatric cardiac surgery: Can they make a difference? *Journal of Cardiothoracic and Vascular Anesthesia*; Vol 18, No 5: pp 645-656.

Harvey L. Edmonds (2005), Multimodality neuromonitoring for perioperative brain protection, *Seminars in Anesthesia, Perioperative Medicine and Pain*, 24:186-194.

National Heart, Lung, and Blood Institute, Available: https://www.nhlbi.nih.gov/health-topics/congenital-heart-defects

Erle H. Austin III, Harvey L. Edmonds Jr., Steven M. Auden,…, and Karen M. Corlett (1997), Benefit of neurophysiologic monitoring for pediatric cardiac surgery, *The journal of Thoracic and Cardiovascular Surgery*; 114; 707–717.

Sushmita Purkayastha and Farzaneh Sorond (2012), Transcranial Doppler Ultrasound: Technique and Application, *Semin Neurol.*; 32(4): 411–420.

Angelo Polito, Zaccaria Ricci, Luca Di Chiara,..., and Sergio Picardo (2006), Cerebral blood flow during cardiopulmonary bypass in pediatric cardiac surgery: the role of transcranial Doppler-a systematic review of the literature, *Cardiovasc Ultrasound*; 4: 47.

Y Durandy , M Rubatti, R Couturier (2011), Near Infrared Spectroscopy during pediatric cardiac surgery: errors and pitfalls. *Perfusion*; 26(5): 441-446.

Sigrid Dannheim Vik, Hans Torp, Turid Follestad, Ragnhild Støen, and Siri Ann Nyrnes (2019) Neo Doppler: New ultrasound technology for continous cerebral circulation monitoring in neonates. *Pediatric Research*; Vol.87, pages 95–103.

Jennifer C. Hirsch, John R. Charpie, Richard G. Ohye, and James G. Gurney (2009), Near-infrared spectroscopy-What we know and what we need to know—A systematic review of the congenital heart disease literature. *J Thorac Cardiovasc Surg*; 137(1):154-159.

Sadaf Aslam and Patricia Emmanual (2010), Formulating a researchable question: A critical step for facilitating good clinical research. *Indian J Sex Trans Dis AIDS*; 31(1): 47-50.

C. Lee Ventola (2008), Challenges in Evaluating and Standardizing Medical Devices in Health Care Facilities. *Pharmacy and therapeutics*; 33: 348-359.

G. Gregory Raab and David H. Parr (2006), From Medical Invention to Clinical Practice- The Reimbursement Challenge Facing New Device Procedures and Technology. *Journal of the American College of Radiology* ;3: 694-850.

Karen B Ekelman (1988), New Medical Devices: Invention, Development, and Use. *National academy press*; 204 pages.

Michael E. Porter (2006). Redefining Health Care.

Jacoline C. Bouvy, Claudine Sapede, and Sarah Garner (2018), Managed Entry Agreements for Pharmaceuticals in the Context of Adaptive Pathways in Europe. *Front. Pharmacol.*; 9:280.

Justin S Yu, Lauren Chin, Jennifer Oh, and Jorge Farias (2017), Performance-Based Risk-Sharing Arrangements for Pharmaceutical Products in the United States: A Systematic Review, *Jounal of Managed Care and Specialty Pharmacy*; 23(10):1028-1040.

Martin Wenzl and Suzannah Chapman (2020),Performance-based managed entry agreements for new medicines in OECD countries and EU member states: How they work and possible improvements going forward. *OECD Health Working Papers*, No. 115.

Josh J Carlson, Katharine S Gries, Kai Yeung, Sean D Sullivan, Louis P Garrison Jr. (2014), Cur rent status and trends in performance-based risk-sharing arrangements between healthcare pay-ers and medical product manufacturers. *Applied Health Economics and Health Policy*; 12: 231–238.

Patricia Vella Bonanno, Michael Ermisch,..., and Alan Haycox (2017), Adaptive Pathways: Possi ble Next Steps for Payers in Preparation for Their Potential Implementation. *Frontiers Pharmacology*; 8:497.

TylerO'NeillBSc, Rebecca Miksad, Danelle Miller, Lesley Maloney, Ani John, Carolyn Hiller, and John Hornberger (2019), ISPOR, the FDA, and the Evolving Regulatory Science of Medical Device Products. Elsevier; 22: 754-76.

Stefanos Zenios, Josh Makower, Paul Yock, Lyn Denend, Todd J. Brinton, Uday N. Kumar, and Thomas M. Krummel (2010), Biodesign: The Process of Innovating Medical Technologies. *Cambridge University Press*; 742 pages.

Hiroyuki Uchino, Kazuo Ushijima, and Yukio Ikeda (2015), Neuroanesthesia and Cerebrospinal Protection.

J. M. Murkin and M. Arango (2009), Near-infrared spectroscopy as an index of brain and tissue oxygenation. *British Journal of Anesthesia*; 103:i3-i13.

Giuseppe Filiberto Serraino and Gavin J Murphy (2017), Effects of cerebral near-infrared spectroscopy on the outcome of patients undergoing cardiac surgery: a systematic review of randomised trials. *BMJ Open*; 7(9).

Samra SK, Dy EA, Welch K, Dorje P, Zelenock GB, and Stanley JC (2000), Evaluation of a cerebral oximeter as a monitor of cerebral ischemia during carotid endarterectomy. *Anesthesiology*; 93: 964-70.

Robert S. Bonser, Domenico Pagano, and Axel Haverich (2011), Brain Protection in Cardiac Surgery.

H. Marc Watzman, C. Dean Kurth, Lisa M. Montenegro, Jonathan Rome, James M. Steven, Susan

C. Nicolson (2000), Arterial and Venous Contributions to Near-infrared Cerebral Oximetry. *Anesthesiology* ; 93(4):947-953.

Andropoulos, Dean B., MD; Stayer, Stephen A., MD; Diaz, Laura K., MD; Ramamoorthy, Chan dra, MB, BS, FFA (UK) Neurological Monitoring for Congenital Heart Surgery (2004), Anesthesia & Analgesia; 99: 1365-1375.

Suzanne Verlhac (2011), Transcranial Doppler in children. *Pediatr Radiol*; 41:S153-S165.

M. Akif Topcuoglu (2012), Transcranial Doppler ultrasound in neurovascular diseases: diagnostic and therapeutic aspects. *Journal of Neurochemistry*; 123:39-51.

Thomas Jue and Kazumi Masuda (2013), Application of Near Infrared Spectroscopy in Biomedicine. Springer; 151 pages.

Gary R. Cutter and Yuliang Liu (2012): Personalized medicine: The return of the house call?, *Neurology: Clinical Practice*.

Lucy Abel, Bethany Shinkins, Alison Smith,…, and Peter Hall (2019), Early Economic Evaluation of Diagnostic Technologies: Experiences of the NIHR Diagnostic Evidence Co-operatives, *Medical Decision Making*; 39(7): 857-866.

Maarten J IJzerman, Hendrik Koffijberg, Elisabeth Fenwick, and Murray Krahn (2017), Emerging Use of Early Health Technology Assessment in Medical Product Development: A Scoping Review of the Literature. *Pharmacoeconomics*; 35(7): 727-740.

Emma Cosh, Alan Girling, Richard Lilford, Helen McAteer, and Terry Young (2007), Investing in new medical technologies: A decision framework, *Journal of Commercial Biotechnology* 13: 263–271.

Jane W. Newburger and David C. Bellinger (2006), Brain Injury in Congenital Heart Disease, *Circulation*;113:183–185.

Juhyeok Park, Eungdo Kim, and Kwangsoo Shin (2019), Developing an Evaluation Framework for Selecting Optimal Medical Devices, *J. Open Innov. Technol. Mark.* Complex*; 5(3):64.*

Glyn D Williams and Chandra Ramamoorthy (2007), Brain monitoring and protection during pediatric cardiac surgery, *Semin Cardiothorac Vasc Anesth*;11(1): 23-33.

Catherine Jane Golics , Mohammad Khurshid Azam Basra, Andrew Yule Finlay, and Sam Salek (2013), The impact of disease on family members: a critical aspect of medical care, *The Royal Sociaty of Medicine*;106(10):399-407.

Briggs A, Claxton Kl and Sculpher M. Decision (2006), Modelling for health economic evaluation, *Oxford University Press.*

Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. (2015), Methods for the economic evaluation of health care programmes, fourth edition, *Oxford University Press*.

William C. Black (1990), The CE plane: a graphic representation of cost-effectiveness, *Med Decis Making*;10(3):212-4.

Barnett S. Kramer, John K. Gohagan, Philip C. Prorok (1999), Cancer Screening: Theory and Practice.

David Simon, John R. Boring III, H Kenneth Walker, W Dallas Hall, and J Willis Hurst (1990), Sensitivity, Specificity, and Predictive Value, *Clinical Methods: The History, Physical, and Laboratory Examinations*; 3rd edition.

Rajul Parikh, Annie Mathai,..., and Ravi Thomas (2008), Understanding and using sensitivity, specificity and predictive values, *Indian Journal of Ophthalmology*; 56(1):45-50.

Vetter, Thomas R., Schober, Patrick, and Mascha, Edward J. (2018), Diagnostic testing and deci sion-making: Beauty is not just in the eye of the beholder, *Anesthesia & Analgesia*; 127 (4): 1085-1091.

Karlijn J van Stralen, Vianda S Stel, Johannes B Reitsma, Friedo W Dekker, Carmine Zoccali, and Kitty J Jager (2009), Diagnostic methods I: sensitivity, specificity, and other measures of accuracy, *Kidney International*;75(12):1257-1263.

Holger J Schünemann, professor, Andrew D Oxman, researcher,..., and Gordon H Guyatt (2008), GRADE: Grading quality of evidence and strength of recommendations for diagnostic tests and strategies, *BMJ*;336(7653):1106-10.

Cosh, E., Girling, A., Lilford, R., Mcateer, H., and Young, T. (2007), Investing in new medical technologies: A decision framework. *Journal of Commercial Biotechnology*; 13, 263-271.

Girling, A., Lilford, R., Cole,A., H., and Young, T. (2012), Pricing of medical devices under coverage uncertainty--a modelling approach, *Health Econ*; 21, 1502-7.

Girling, A., Lilford, R., Cole,A., H., and Young, T. (2015), Headroom Approach to Device Development: Current and Future Directions, *Int J Technol Assess Health Care*; 31, 331-8.

Hartz, S. and John, J. (2008), Contribution of economic evaluation to decision making in early phases of product development: a methodological and empirical review, *Int J Technol Assess Health Care*, 24, 465-72.

Ijzerman, M. J., Koffijberg, H., Fenwick, E., and Krahn, M. (2017), Emerging Use of Early Health Technology Assessment in Medical Product Development: A Scoping Review of the Literature. *Pharmacoeconomics;* 35, 727-740.

Janneke P.C. Grutters, Tim Govers, Jorte Nijboer, Marcia Tummers, Gert Jan van der Wilt, and Maroeska M. Rovers (2019), Problems and Promises of Health Technologies: The Role of Early Health Economic Modeling. *Int J Health Policy Manag*; 8(10), 575–582.

A.M. Chapman, C.A. Taylor, and A.J. Girling (2013), Early HTA to inform medical device development decisions-The headroom method, *XIII Mediterranean Conference on Medical and Biological Engineering and Computing*; 1151-1154.

David M.Eddy, William Hollingworth, ,…, and John B.Wong (2012), Model Transparency and Validation: A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force-7, *ISPOR−SMDM Modeling Good Research Practices Task Force.*

Joyce T. Johnson, Jacob F. Wilkes,...,and Nelangi M. Pinto (2018), Admission to Dedicated Pediatric Cardiac Intensive Care Units is Associated with Decreased Resource Use in Neonatal Cardiac Surgery, *The Journal of Thoracic and Cardiovascular Surgery* ;Volume 155, Issue 6: 2606-264.

David K Stevenson, William E Benitz, and Philip Sunshine (2003), Fetal and Neonatal Brain Injury: Mechanisms, Management, and the Risks of Practice, *Cambridge University Press*.

Joseph J. Volpe (2008) Neurology of the newborn.

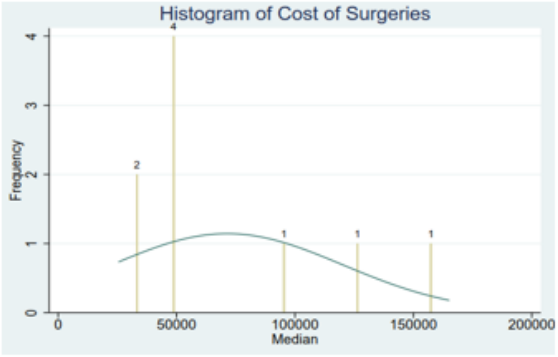
Sara K Pasquali, Xia He, ,…, and Jeffrey P Jacobs (2014), Excess costs associated with complications and prolonged length of stay after congenital heart surgery, *Thorac Surg* ;98(5) 1660-6.

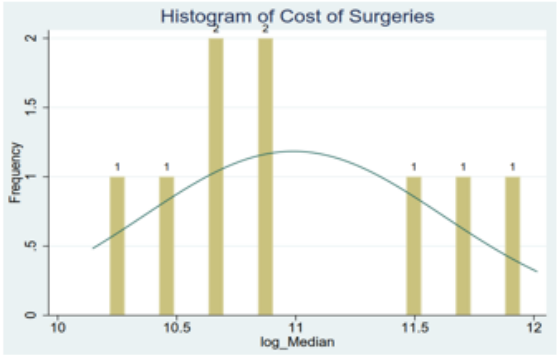
Appendix A Parameters, abbreviation, values, and sources

Parameter	Description	Value of Probability	Source
pPrev	Probability of prevalence of neurocomplication caused by surgery practice	0.23	Sara Lozno and Emad Mossad, 2004
pSens	Probability that multi-monitoring result will be positive among patients and follow treatment guidelines	0.96	Calculated data from Austin et al, 1998
pSpec	Probability that multi-monitoring result will be negative among patients and follow treatment guidelines	0.60	Calculated data from Austin et al, 1999
pTP	Probability of test positive	0.53	Calculated data from Austin et al, 2000 ; Sara Lozno and Emad Mossad, 2004
pTN	Probability of test negative	0.47	Calculated data from Austin et al, 2000 ; Sara Lozno and Emad Mossad, 2004
PVP	Predictive value positive	0.42	Calculated data from Austin et al, 2000 ; Sara Lozno and Emad Mossad, 2004
PVN	Predictive value negative	0.98	Calculated data from Austin et al, 2000 ; Sara Lozno and Emad Mossad, 2004
ciPne	Probability of neurocomplication in clinical intervention	0.05	Calculated data from Austin et al, 2002
ciPnne	Probability of non neurocomplication in clinical intervention	0.95	Calculated data from Austin et al, 2003
nciPne	Probability of neurocomplication in non-clinical intervention	0.26	Calculated data from Austin et al, 2004
nciPnne	Probability of non neurocomplication in non-clinical intervention	0.74	Calculated data from Austin et al, 2005
ndcPne	Probability of neurocomplication in non-noteworthy data change	0.07	Calculated data from Austin et al, 2006
ndcPnne	Probability of non neurocomplication in non-noteworthy data change	0.93	Calculated data from Austin et al, 2007
cinePs	Probability of survival in neurocomplication in clinical intervention	0.57	Calculated data from Austin et al, 2000 ; Sara Lozno and Emad Mossad, 2004
cinePd	Probability of die in neurocomplication in clinical intervention	0.43	Calculated data from Austin et al, 2000 ; Sara Lozno and Emad Mossad, 2004
cinnePs	Probability of survival in non neurocomplication in clinical intervention	0.96	Calculated data from Austin et al, 2000 ; Sara Lozno and Emad Mossad, 2004
cinnePd	Probability of die in non neurocomplication in clinical intervention	0.04	Calculated data from Austin et al, 2000 ; Sara Lozno and Emad Mossad, 2004

ncinePs	Probability of survival in neurocomplication in non-clinical intervention	0.57	Calculated data from Austin et al, 2000 ; Sara Lozno and Emad Mossad, 2004
ncinePd	Probability of die in neurocomplication in non-clinical intervention	0.43	Calculated data from Austin et al, 2000 ; Sara Lozno and Emad Mossad, 2004
ncinnePs	Probability of survival in non neurocomplication in non-clinical intervention	0.97	Calculated data from Austin et al, 2000 ; Sara Lozno and Emad Mossad, 2004
ncinnePd	Probability of die in non neurocomplication in non-clinical intervention	0.03	Calculated data from Austin et al, 2000 ; Sara Lozno and Emad Mossad, 2004
ndcnePs	Probability of survival in neurocomplication in non -noteworthy data change	0.57	Calculated data from Austin et al, 2000 ; Sara Lozno and Emad Mossad, 2004
ndcnePd	Probability of die in neurocomplication in non-noteworthy data change	0.43	Calculated data from Austin et al, 2000 ; Sara Lozno and Emad Mossad, 2004
ndcnnePs	Probability of survival in non neurocomplication in non-noteworthy data change	0.97	Calculated data from Austin et al, 2000 ; Sara Lozno and Emad Mossad, 2004
ndcnnePd	Probability of die in non neurocomplication in non-noteworthy data change	0.03	Calculated data from Austin et al, 2000 ; Sara Lozno and Emad Mossad, 2004
CPne	Probability of neurocomplication in control group	0.23	Sara Lozno and Emad Mossad, 2004
CPnne	Probability of non neurocomplication in control group	0.77	Sara Lozno and Emad Mossad, 2004
CnePs	Probability of survival in neurocomplication in control group	0.57	Sara Lozno and Emad Mossad, 2004
CnePd	Probability of die in neurocomplicationin control group	0.43	Sara Lozno and Emad Mossad, 2004
CnnePs	Probability of survival in non neurocomplication in control group	0.97	Sara Lozno and Emad Mossad, 2004
CnnePd	Probability of die in non neurocomplication in control group	0.03	Sara Lozno and Emad Mossad, 2004
opC	Costs of operation	59474.00	Calculated data from Sara K. Pasquali, 2014
ncC	Costs of neurologic complication (adjusted excess cost)	53611.00	Calculated data from Sara K. Pasquali, 2014
ncLOS	Length of stay at the hospital in neurologic complication	17.70	Sara Lozno and Emad Mossad, 2004
nncLOS	Length of stay at the hospital in non-neurologic complication	10.30	Sara Lozno and Emad Mossad, 2004

Appendix B






```
. mean log_Median

Mean estimation                 Number of obs    =          9
```

	Mean	Std. Err.	[95% Conf.	Interval]
log_Median	10.99033	.2098502	10.50641	11.47424

$e^{\ln(x)} = 2.71828^{(10.99033)} = 59474$

Appendix C

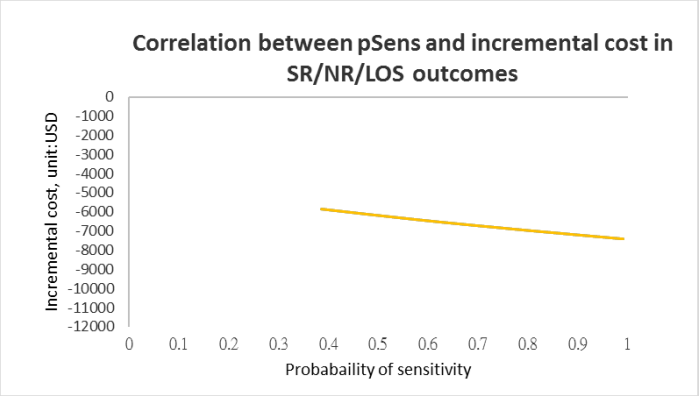


Figure 5.1 Probability of sensitivity and incremental cost in outcomes

Given a series values of probability of sensitivity in x axis corresponding to the values of incremental costs in y axis. The result shows the same trend as yellow line in three outcomes.

* SR: survival rate
* NR: euro-complication rate
* LOS: length of stay

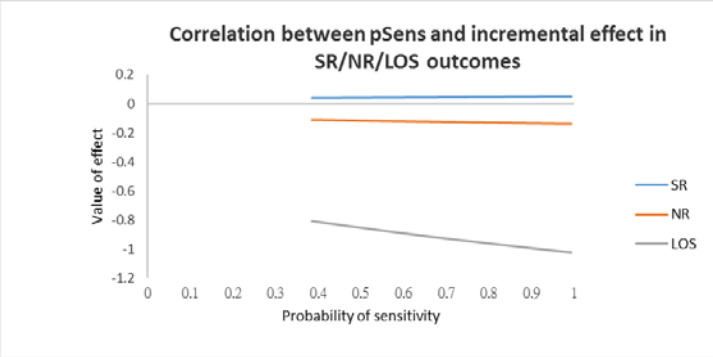


Figure 5.2 Probability of sensitivity and incremental effect in outcomes

Given a series values of probability of sensitivity in x axis corresponding to the values of incremental effect in y axis. The blue line is the trend in survival rate. The red line and grey line indicate euro-complication rate and length of stay, respectively.

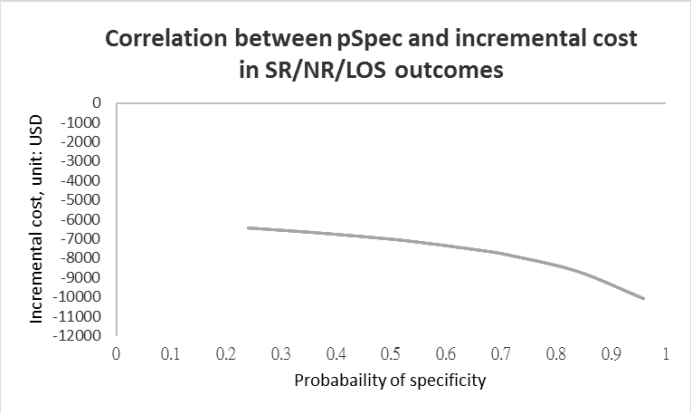


Figure 6.1 Probability of specificity and incremental cost in outcomes

Given a series values of probability of specificity in x axis corresponding to the values of incremental cost in y axis. The result shows the same trend as brown line in three outcomes.

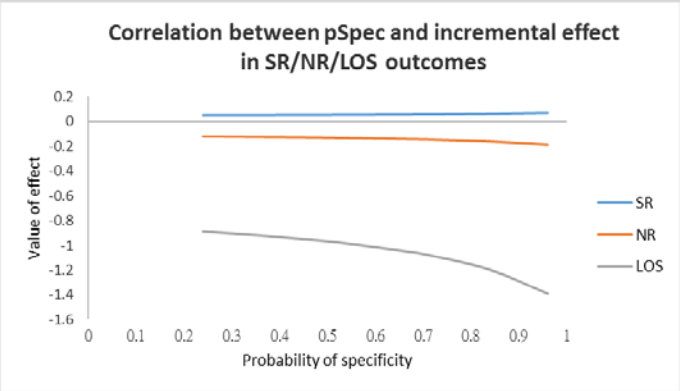


Figure 6.2 Probability of specificity and incremental effect in outcomes

Given a series values of probability of specificity in x axis corresponding to the values of incremental effect in y axis. The blue line is the trend in survival rate. The red line and grey line indicate euro-complication rate and length of stay, respectively.

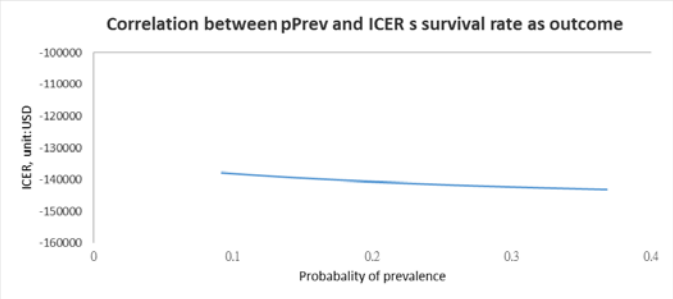


Figure 7 Prevalence rate and ICER in survival rate outcome

Given a series values of probability of prevalence in x axis corresponding to the values of ICER in y axis.

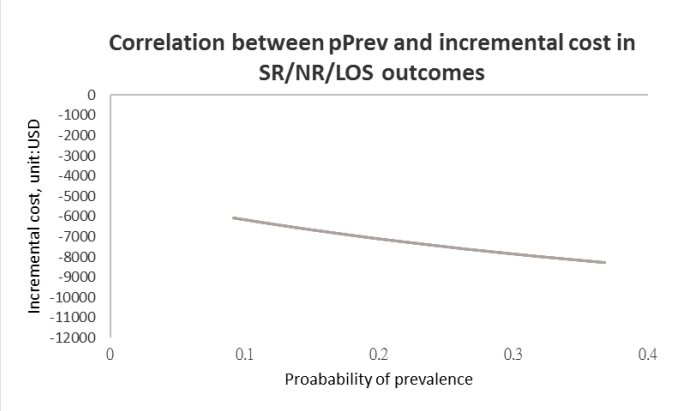


Figure 7.1 Prevalence rate and incremental cost in outcomes

Given a series values of prevalence rate in x axis corresponding to the values of incremental cost in y axis. The result shows the same trend as brown line in three outcomes.

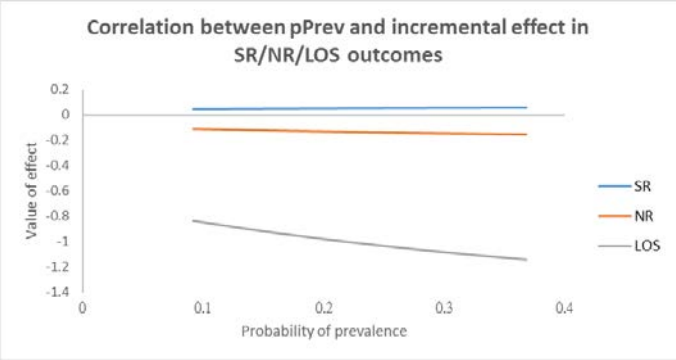


Figure 7.2 Prevalence rate and incremental effect in outcomes

Given a series values of prevalence rate in x axis corresponding to the values of incremental effect in y axis. The blue line is the trend in survival rate. The red line and grey line indicate neurocomplication rate and length of stay, respectively.

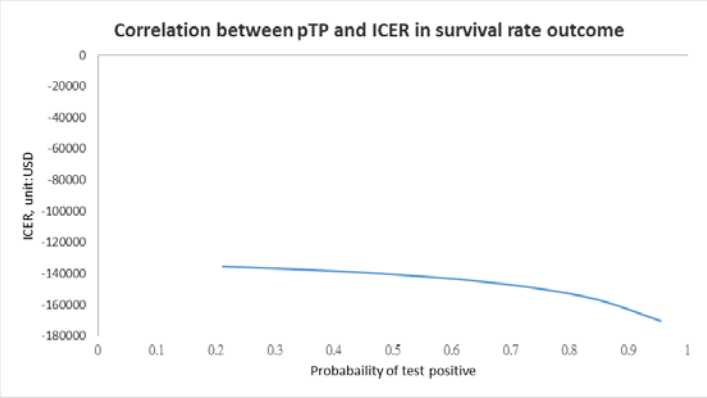


Figure 8 Probability of test positive and ICER in survival rate outcome

Given series values of probability of test positive in x-axis corresponding to the values of ICER in y-axis.

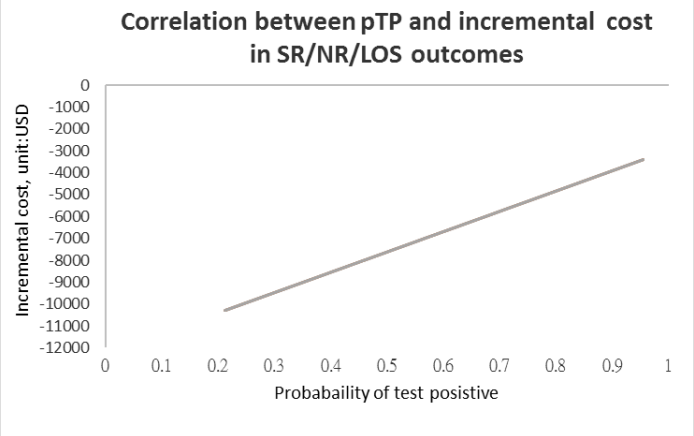


Figure 8.1 Probability of test positive and incremental cost in outcomes

Given a series values of probability of specificity in x axis corresponding to the values of incremental costs in y-axis. The result shows the same trend as brown line in three outcomes.

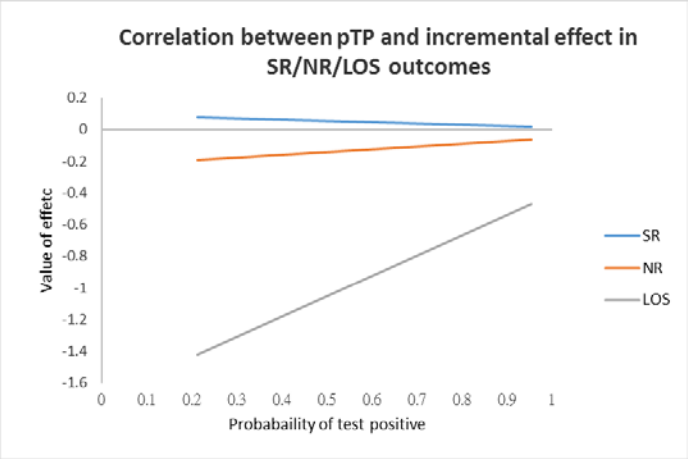


Figure 8.2 Probability of test positive and incremental effect in outcomes

Given a series values of probability of test positive in x axis corresponding to the values of incremental effect in y axis. The blue line is the trend in survival rate. The red line and grey line indicate neurocomplication rate and length of stay, respectively.

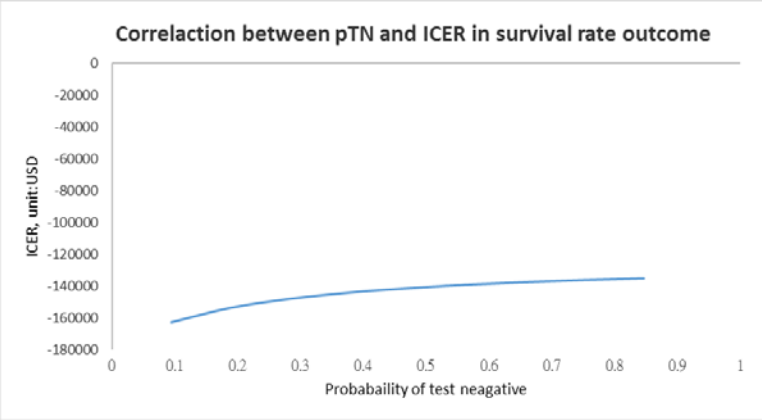


Figure 9 Probability of test negative and ICER in survival rate outcome

Given a series values of probability of test negative in x axis corresponding to the values of ICER in y axis

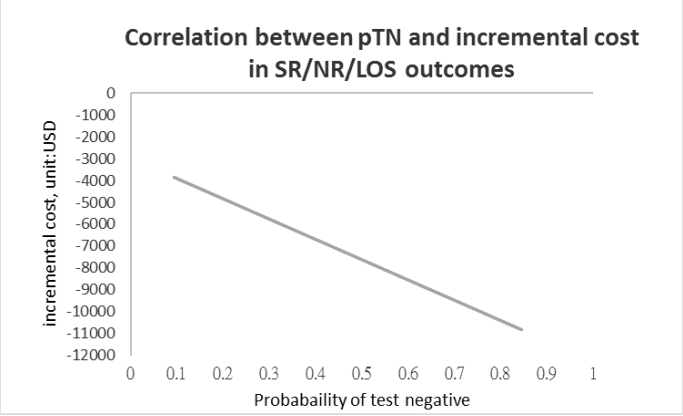


Figure 9.1 Probability of test negative and incremental cost in outcomes

Given a series values of test negative in x-axis corresponding to the values of incremental cost in y-axis. The result shows the same trend as brown line in three outcomes.

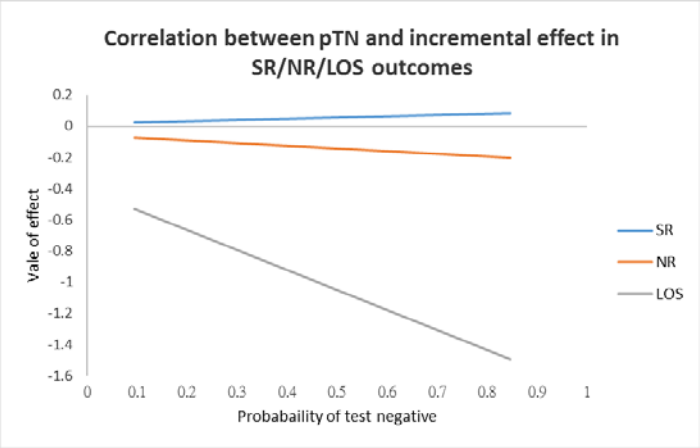


Figure 9.2 Probability of test negative and incremental effect in outcomes

Given a series values of probability of test negative in x axis corresponding to the values of incremental effect in y axis. The blue line is the trend in survival rate. The red line and grey line indicate neurocomplication rate and length of stay, respectively.

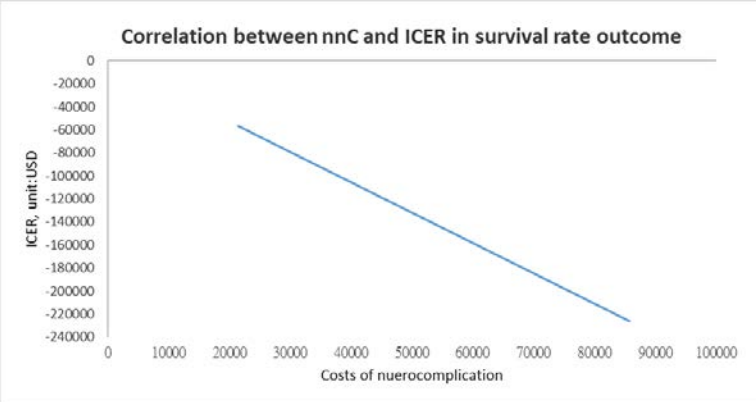


Figure 10 Cost of neurologic complication and ICER in survival rate outcome

Given a series numbers of cost of neurologic complication in x-axis corresponding to the values of ICER in y-axis.

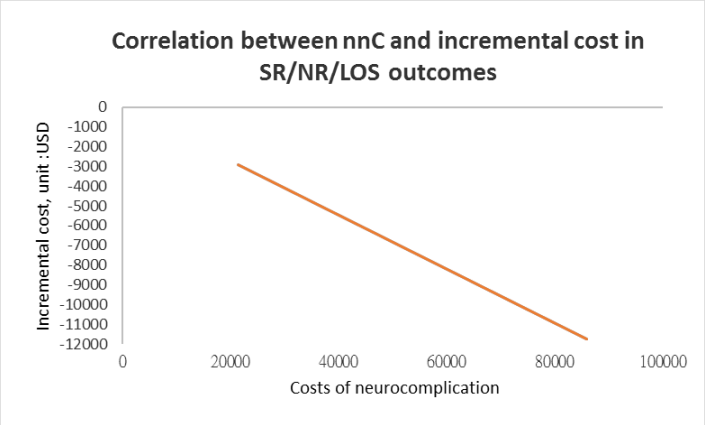


Figure 10.1 Cost of neurologic complication and incremental cost in outcomes

Given a series values of cost of neurologic complication in x axis corresponding to the values of incremental costs in y-axis. The result shows the same trend as orange line in three outcomes.

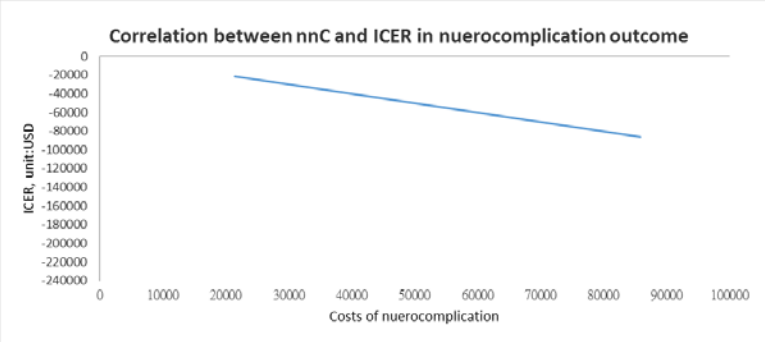


Figure 11 Cost of neurologic complication and ICER in nuerocomplication outcome

Given a series numbers of cost of neurologic complication in x-axis corresponding to the values of ICER in y-axis.

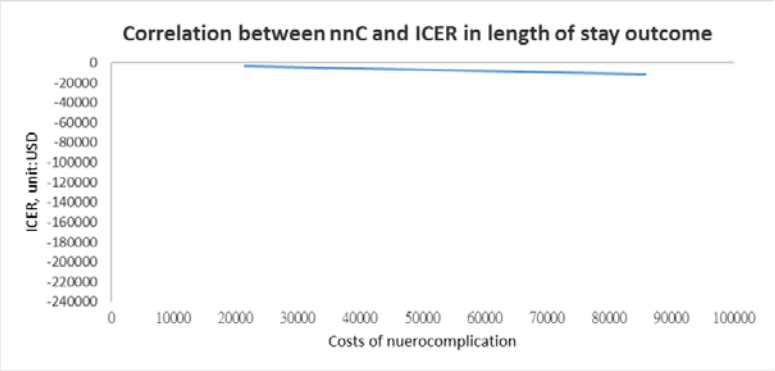


Figure 12 Cost of neurologic complication and ICER in length of stay outcome

Given a series numbers of cost of neurologic complication in x-axis corresponding to the values of ICER in y-axis.

Appendix D

Table 11.1 Headroom and revenue scenarios for NeoDoppler technology in survival rate outcome at product unit costs US$ 97.68.

Headroom and Revenu Scenarios for NeoDoppler (Estimate outcome: survival rate)					*Data and estimated values from results*		
Assumption	**Value**						
Threshold (unit:USD)	50000						
Unit cost per patient (unit:USD)	**97.68**						
	Parameter	**Pobability of parameter**	**Headroom**	**Revenues**	**ICER**	**Cost-saving of healthcare service**	**Incremental effect**
	pTP	0.50	390	34,233	-123,079	-246	0.002
	pTP	0.48	780	78,234	-123,079	-491	0.004
	pTP	0.45	1,170	122,235	-123,079	-737	0.006
	pTP	0.42	1,559	166,235	-123,079	-982	0.008
	pTP	0.40	1,949	210,236	-123,079	-1,228	0.010
Scenario 1	pTP	0.37	2,339	254,237	-123,079	-1,474	0.012
	pTP	0.34	2,729	298,238	-123,079	-1,719	0.014
	pTP	0.32	3,119	342,238	-123,079	-1,965	0.016
	pTP	0.29	3,509	386,239	-123,079	-2,210	0.018
	pTP	0.26	3,898	430,240	-123,079	-2,456	0.020
	pTP	0.24	4,288	474,241	-123,079	-2,702	0.022
	Parameter	**Pobability of parameter**	**Headroom**	**Revenues**	**ICER**	**Cost-saving of healthcare service**	**Incremental effect**
	PVP	0.44	182	10,781	-160,083	-123	0.001
	PVP	0.46	364	31,330	-160,083	-246	0.002
	PVP	0.48	546	51,878	-160,083	-369	0.002
	PVP	0.50	728	72,427	-160,083	-492	0.003
	PVP	0.52	910	92,976	-160,083	-615	0.004
Scenario 2	PVP	0.54	1,092	113,524	-160,083	-737	0.005
	PVP	0.56	1,274	134,073	-160,083	-860	0.005
	PVP	0.59	1,456	154,622	-160,083	-983	0.006
	PVP	0.61	1,639	175,170	-160,083	-1,106	0.007
	PVP	0.63	1,821	195,719	-160,083	-1,229	0.008
	PVP	0.65	2,003	216,268	-160,083	-1,352	0.008
	Parameter	**Pobability of parameter**	**Headroom**	**Revenues**	**ICER**	**Cost-saving of healthcare service**	**Incremental effect**
	pTP	0.50	217	14,712	-101,762	-129	0.001
	PVP	0.40					
	pTP	0.48	452	41,246	-103,479	-270	0.003
	PVP	0.38					
	pTP	0.45	705	69,836	-105,097	-423	0.004
	PVP	0.36					
	pTP	0.42	977	100,480	-106,625	-589	0.006
	PVP	0.33					
	pTP	0.40	1,266	133,179	-108,070	-767	0.007
	PVP	0.31					
Scenario 3	pTP	0.37	1,574	167,932	-109,440	-957	0.009
	PVP	0.29					
	pTP	0.34	1,900	204,741	-110,739	-1,160	0.010
	PVP	0.27					
	pTP	0.32	2,245	243,605	-111,973	-1,375	0.012
	PVP	0.25					
	pTP	0.29	2,607	284,523	-113,147	-1,602	0.014
	PVP	0.23					
	pTP	0.26	2,988	327,497	-114,265	-1,842	0.016
	PVP	0.21					
	pTP	0.24	3,387	372,525	-115,331	-2,093	0.018
	PVP	0.19					
	Parameter	**Pobability of parameter**	**Headroom**	**Revenues**	**ICER**	**Cost-saving of healthcare service**	**Incremental effect**
	pTP	0.50	563	53,754	-132,984	-362	0.003
	PVP	0.44					
	pTP	0.48	1,107	115,221	-132,597	-712	0.005
	PVP	0.46					
	pTP	0.45	1,634	174,634	-132,199	-1,050	0.008
	PVP	0.48					
	pTP	0.42	2,142	231,991	-131,788	-1,376	0.010
	PVP	0.50					
	pTP	0.40	2,632	287,294	-131,366	-1,689	0.013
	PVP	0.52					
Scenario 4	pTP	0.37	3,104	340,541	-130,931	-1,990	0.015
	PVP	0.54					
	pTP	0.34	3,557	391,734	-130,482	-2,278	0.017
	PVP	0.56					
	pTP	0.32	3,993	440,872	-130,019	-2,555	0.020
	PVP	0.59					
	pTP	0.29	4,410	487,955	-129,542	-2,819	0.022
	PVP	0.61					
	pTP	0.26	4,809	532,983	-129,049	-3,071	0.024
	PVP	0.63					
	pTP	0.24	5,189	575,956	-128,540	-3,310	0.026
	PVP	0.65					
Bset Scenarios for NeoDoppler							
	Parameter	**Pobability of parameter**	**Headroom**	**Revenues**	**ICER**	**Cost-saving of healthcare service**	**Incremental effect**
	pTP	0.23	6,605	735,712	-133,662	-4,259	0.032
	PVP	1.00					
	pTP	0.23			-134,276	-4,913	0.037
	PVP	1.00	7,610	849,182			
	Neurocomplication in CI	0.00					

Table 12.1 Headroom and revenue scenarios for NeoDoppler technology in survival rate outcome at product unit costs US$ 564.00.

Headroom and Revenu Scenarios for NeoDoppler (Estimate outcome: survival rate)					*Data and estimated values from results*		
Assumption	**Value**						
Threshold (unit:USD)	50000						
Unit cost per patient (unit:USD)	**564.00**						
	Parameter	**Pobability of parameter**	**Headroom**	**Revenues**	**ICER**	**Cost-saving of healthcare service**	**Incremental effect**
	pTP	0.50	390	-12,434	-123,079	-246	0.002
	pTP	0.48	780	31,566	-123,079	-491	0.004
	pTP	0.45	1,170	75,567	-123,079	-737	0.006
	pTP	0.42	1,559	119,568	-123,079	-982	0.008
	pTP	0.40	1,949	163,569	-123,079	-1,228	0.010
Scenario 1	pTP	0.37	2,339	207,569	-123,079	-1,474	0.012
	pTP	0.34	2,729	251,570	-123,079	-1,719	0.014
	pTP	0.32	3,119	295,571	-123,079	-1,965	0.016
	pTP	0.29	3,509	339,572	-123,079	-2,210	0.018
	pTP	0.26	3,898	383,572	-123,079	-2,456	0.020
	pTP	0.24	4,288	427,573	-123,079	-2,702	0.022
	Parameter	**Pobability of parameter**	**Headroom**	**Revenues**	**ICER**	**Cost-saving of healthcare service**	**Incremental effect**
	PVP	0.44	182	-35,886	-160,083	-123	0.001
	PVP	0.46	364	-15,338	-160,083	-246	0.002
	PVP	0.48	546	5,211	-160,083	-369	0.002
	PVP	0.50	728	25,760	-160,083	-492	0.003
	PVP	0.52	910	46,308	-160,083	-615	0.004
Scenario 2	PVP	0.54	1,092	66,857	-160,083	-737	0.005
	PVP	0.56	1,274	87,406	-160,083	-860	0.005
	PVP	0.59	1,456	107,954	-160,083	-983	0.006
	PVP	0.61	1,639	128,503	-160,083	-1,106	0.007
	PVP	0.63	1,821	149,052	-160,083	-1,229	0.008
	PVP	0.65	2,003	169,600	-160,083	-1,352	0.008
	Parameter	**Pobability of parameter**	**Headroom**	**Revenues**	**ICER**	**Cost-saving of healthcare service**	**Incremental effect**
	pTP	0.50	217	-31,955	-101,762	-129	0.001
	PVP	0.40					
	pTP	0.48	452	-5,421	-103,479	-270	0.003
	PVP	0.38					
	pTP	0.45	705	23,168	-105,097	-423	0.004
	PVP	0.36					
	pTP	0.42	977	53,812	-106,625	-589	0.006
	PVP	0.33					
	pTP	0.40	1,266	86,511	-108,070	-767	0.007
	PVP	0.31					
Scenario 3	pTP	0.37	1,574	121,265	-109,440	-957	0.009
	PVP	0.29					
	pTP	0.34	1,900	158,074	-110,739	-1,160	0.010
	PVP	0.27					
	pTP	0.32	2,245	196,937	-111,973	-1,375	0.012
	PVP	0.25					
	pTP	0.29	2,607	237,856	-113,147	-1,602	0.014
	PVP	0.23					
	pTP	0.26	2,988	280,829	-114,265	-1,842	0.016
	PVP	0.21					
	pTP	0.24	3,387	325,857	-115,331	-2,093	0.018
	PVP	0.19					
	Parameter	**Pobability of parameter**	**Headroom**	**Revenues**	**ICER**	**Cost-saving of healthcare service**	**Incremental effect**
	pTP	0.50	563	7,087	-132,984	-362	0.003
	PVP	0.44					
	pTP	0.48	1,107	68,554	-132,597	-712	0.005
	PVP	0.46					
	pTP	0.45	1,634	127,966	-132,199	-1,050	0.008
	PVP	0.48					
	pTP	0.42	2,142	185,324	-131,788	-1,376	0.010
	PVP	0.50					
	pTP	0.40	2,632	240,626	-131,366	-1,689	0.013
	PVP	0.52					
Scenario 4	pTP	0.37	3,104	293,874	-130,931	-1,990	0.015
	PVP	0.54					
	pTP	0.34	3,557	345,067	-130,482	-2,278	0.017
	PVP	0.56					
	pTP	0.32	3,993	394,205	-130,019	-2,555	0.020
	PVP	0.59					
	pTP	0.29	4,410	441,288	-129,542	-2,819	0.022
	PVP	0.61					
	pTP	0.26	4,809	486,316	-129,049	-3,071	0.024
	PVP	0.63					
	pTP	0.24	5,189	529,289	-128,540	-3,310	0.026
	PVP	0.65					
Bset Scenarios for NeoDoppler							
	Parameter	**Pobability of parameter**	**Headroom**	**Revenues**	**ICER**	**Cost-saving of healthcare service**	**Incremental effect**
	pTP	0.23	6,605	689,045	-133,662	-4,259	0.032
	PVP	1.00					
	pTP	0.23			-134,276	-4,913	0.037
	PVP	1.00	7,610	802,515			
	Neurocomplication in CI	0.00					

Table 11.2 Headroom and revenue scenarios for NeoDoppler technology in neurocomplication outcome at product unit costs US$ 97.68.

Headroom and Revenu Scenarios for NeoDoppler (Estimate outcome: neurocomplication rate)					*Data and estimated values from results*		
Assumption	**Value**						
Threshold (unit:USD)	50000						
Unit cost per patient (unit:USD)	**97.68**				* ( ) inducate nagetive value		
	Parameter	**Pobability of parameter**	**Headroom**	**Revenues**	**ICER**	**Cost-saving of healthcare service**	**Incremental effect**
	pTP	0.50	536	50,704	-53,611	-246	(0.005)
	pTP	0.48	1,072	111,176	-53,611	-491	(0.009)
	pTP	0.45	1,607	171,647	-53,611	-737	(0.014)
	pTP	0.42	2,143	232,119	-53,611	-982	(0.018)
	pTP	0.40	2,679	292,591	-53,611	-1,228	(0.023)
Scenario 1	pTP	0.37	3,215	353,062	-53,611	-1,474	(0.027)
	pTP	0.34	3,750	413,534	-53,611	-1,719	(0.032)
	pTP	0.32	4,286	474,006	-53,611	-1,965	(0.037)
	pTP	0.29	4,822	534,477	-53,611	-2,210	(0.041)
	pTP	0.26	5,358	594,949	-53,611	-2,456	(0.046)
	pTP	0.24	5,893	655,421	-53,611	-2,702	(0.050)
	Parameter	**Pobability of parameter**	**Headroom**	**Revenues**	**ICER**	**Cost-saving of healthcare service**	**Incremental effect**
	PVP	0.44	268	20,494	-53,611	-123	(0.002)
	PVP	0.46	536	50,755	-53,611	-246	(0.005)
	PVP	0.48	804	81,017	-53,611	-369	(0.007)
	PVP	0.50	1,072	111,278	-53,611	-492	(0.009)
	PVP	0.52	1,341	141,540	-53,611	-615	(0.011)
Scenario 2	PVP	0.54	1,609	171,801	-53,611	-737	(0.014)
	PVP	0.56	1,877	202,063	-53,611	-860	(0.016)
	PVP	0.59	2,145	232,324	-53,611	-983	(0.018)
	PVP	0.61	2,413	262,585	-53,611	-1,106	(0.021)
	PVP	0.63	2,681	292,847	-53,611	-1,229	(0.023)
	PVP	0.65	2,949	323,108	-53,611	-1,352	(0.025)
	Parameter	**Pobability of parameter**	**Headroom**	**Revenues**	**ICER**	**Cost-saving of healthcare service**	**Incremental effect**
	pTP	0.50	281	21,956	-53,611	-129	(0.002)
	PVP	0.40					
	pTP	0.48	589	56,705	-53,611	-270	(0.005)
	PVP	0.38					
	pTP	0.45	924	94,481	-53,611	-423	(0.008)
	PVP	0.36					
	pTP	0.42	1,285	135,282	-53,611	-589	(0.011)
	PVP	0.33					
	pTP	0.40	1,673	179,110	-53,611	-767	(0.014)
	PVP	0.31					
Scenario 3	pTP	0.37	2,089	225,964	-53,611	-957	(0.018)
	PVP	0.29					
	pTP	0.34	2,530	275,844	-53,611	-1,160	(0.022)
	PVP	0.27					
	pTP	0.32	2,999	328,751	-53,611	-1,375	(0.026)
	PVP	0.25					
	pTP	0.29	3,495	384,683	-53,611	-1,602	(0.030)
	PVP	0.23					
	pTP	0.26	4,017	443,642	-53,611	-1,842	(0.034)
	PVP	0.21					
	pTP	0.24	4,566	505,626	-53,611	-2,093	(0.039)
	PVP	0.19					
	Parameter	**Pobability of parameter**	**Headroom**	**Revenues**	**ICER**	**Cost-saving of healthcare service**	**Incremental effect**
	pTP	0.50	790	79,452	-53,611	-362	(0.007)
	PVP	0.44					
	pTP	0.48	1,554	165,646	-53,611	-712	(0.013)
	PVP	0.46					
	pTP	0.45	2,291	248,814	-53,611	-1,050	(0.020)
	PVP	0.48					
	pTP	0.42	3,001	328,956	-53,611	-1,376	(0.026)
	PVP	0.50					
	pTP	0.40	3,684	406,071	-53,611	-1,689	(0.032)
	PVP	0.52					
Scenario 4	pTP	0.37	4,341	480,160	-53,611	-1,990	(0.037)
	PVP	0.54					
	pTP	0.34	4,970	551,224	-53,611	-2,278	(0.043)
	PVP	0.56					
	pTP	0.32	5,573	619,261	-53,611	-2,555	(0.048)
	PVP	0.59					
	pTP	0.29	6,149	684,272	-53,611	-2,819	(0.053)
	PVP	0.61					
	pTP	0.26	6,698	746,256	-53,611	-3,071	(0.057)
	PVP	0.63					
	pTP	0.24	7,221	805,215	-53,611	-3,310	(0.062)
	PVP	0.65					
Bset Scenarios for NeoDoppler							
	Parameter	**Pobability of parameter**	**Headroom**	**Revenues**	**ICER**	**Cost-saving of healthcare service**	**Incremental effect**
	pTP	0.23	9,290	1,038,752	-53,611	-4,259	(0.079)
	PVP	1.00					
	pTP	0.23			-53,611	-4,913	(0.092)
	PVP	1.00	10,717	1,199,854			
	Neurocomplication in CI	0.00					

Table 12.2 Headroom and revenue scenarios for NeoDoppler technology in neurocomplication outcome at product unit costs US$ 564.00.

Headroom and Revenu Scenarios for NeoDoppler (Estimate outcome: neurocomplication rate)					*Data and estimated values from results*		
Assumption	**Value**						
Threshold (unit:USD)	50000						
Unit cost per patient (unit:USD)	**564.00**				* ( ) inducate nagetive value		
	Parameter	**Pobability of parameter**	**Headroom**	**Revenues**	**ICER**	**Cost-saving of healthcare service**	**Incremental effect**
	pTP	0.50	536	4,037	-53,611	-246	(0.005)
	pTP	0.48	1,072	64,508	-53,611	-491	(0.009)
	pTP	0.45	1,607	124,980	-53,611	-737	(0.014)
	pTP	0.42	2,143	185,452	-53,611	-982	(0.018)
	pTP	0.40	2,679	245,923	-53,611	-1,228	(0.023)
Scenario 1	pTP	0.37	3,215	306,395	-53,611	-1,474	(0.027)
	pTP	0.34	3,750	366,867	-53,611	-1,719	(0.032)
	pTP	0.32	4,286	427,338	-53,611	-1,965	(0.037)
	pTP	0.29	4,822	487,810	-53,611	-2,210	(0.041)
	pTP	0.26	5,358	548,282	-53,611	-2,456	(0.046)
	pTP	0.24	5,893	608,753	-53,611	-2,702	(0.050)
	Parameter	**Pobability of parameter**	**Headroom**	**Revenues**	**ICER**	**Cost-saving of healthcare service**	**Incremental effect**
	PVP	0.44	268	-26,174	-53,611	-123	(0.002)
	PVP	0.46	536	4,088	-53,611	-246	(0.005)
	PVP	0.48	804	34,349	-53,611	-369	(0.007)
	PVP	0.50	1,072	64,611	-53,611	-492	(0.009)
	PVP	0.52	1,341	94,872	-53,611	-615	(0.011)
Scenario 2	PVP	0.54	1,609	125,134	-53,611	-737	(0.014)
	PVP	0.56	1,877	155,395	-53,611	-860	(0.016)
	PVP	0.59	2,145	185,657	-53,611	-983	(0.018)
	PVP	0.61	2,413	215,918	-53,611	-1,106	(0.021)
	PVP	0.63	2,681	246,180	-53,611	-1,229	(0.023)
	PVP	0.65	2,949	276,441	-53,611	-1,352	(0.025)
	Parameter	**Pobability of parameter**	**Headroom**	**Revenues**	**ICER**	**Cost-saving of healthcare service**	**Incremental effect**
	pTP	0.50	281	-24,712	-53,611	-129	(0.002)
	PVP	0.40					
	pTP	0.48	589	10,038	-53,611	-270	(0.005)
	PVP	0.38					
	pTP	0.45	924	47,813	-53,611	-423	(0.008)
	PVP	0.36					
	pTP	0.42	1,285	88,615	-53,611	-589	(0.011)
	PVP	0.33					
	pTP	0.40	1,673	132,443	-53,611	-767	(0.014)
	PVP	0.31					
Scenario 3	pTP	0.37	2,089	179,297	-53,611	-957	(0.018)
	PVP	0.29					
	pTP	0.34	2,530	229,177	-53,611	-1,160	(0.022)
	PVP	0.27					
	pTP	0.32	2,999	282,083	-53,611	-1,375	(0.026)
	PVP	0.25					
	pTP	0.29	3,495	338,016	-53,611	-1,602	(0.030)
	PVP	0.23					
	pTP	0.26	4,017	396,974	-53,611	-1,842	(0.034)
	PVP	0.21					
	pTP	0.24	4,566	458,959	-53,611	-2,093	(0.039)
	PVP	0.19					
	Parameter	**Pobability of parameter**	**Headroom**	**Revenues**	**ICER**	**Cost-saving of healthcare service**	**Incremental effect**
	pTP	0.50	790	32,785	-53,611	-362	(0.007)
	PVP	0.44					
	pTP	0.48	1,554	118,979	-53,611	-712	(0.013)
	PVP	0.46					
	pTP	0.45	2,291	202,147	-53,611	-1,050	(0.020)
	PVP	0.48					
	pTP	0.42	3,001	282,288	-53,611	-1,376	(0.026)
	PVP	0.50					
	pTP	0.40	3,684	359,404	-53,611	-1,689	(0.032)
	PVP	0.52					
Scenario 4	pTP	0.37	4,341	433,493	-53,611	-1,990	(0.037)
	PVP	0.54					
	pTP	0.34	4,970	504,556	-53,611	-2,278	(0.043)
	PVP	0.56					
	pTP	0.32	5,573	572,593	-53,611	-2,555	(0.048)
	PVP	0.59					
	pTP	0.29	6,149	637,604	-53,611	-2,819	(0.053)
	PVP	0.61					
	pTP	0.26	6,698	699,589	-53,611	-3,071	(0.057)
	PVP	0.63					
	pTP	0.24	7,221	758,547	-53,611	-3,310	(0.062)
	PVP	0.65					
Bset Scenarios for NeoDoppler							
	Parameter	**Pobability of parameter**	**Headroom**	**Revenues**	**ICER**	**Cost-saving of healthcare service**	**Incremental effect**
	pTP	0.23	9,290	992,085	-53,611	-4,259	(0.079)
	PVP	1.00					
	pTP	0.23			-53,611	-4,913	(0.092)
	PVP	1.00	10,717	1,153,187			
	Neurocomplication in CI	0.00					

Table 11.3 Headroom and revenue scenarios for NeoDoppler technology in length of stay outcome at product unit costs US$ 97.68.

Headroom and Revenu Scenarios for NeoDoppler (Estimate outcome: Length of stay)					*Data and estimated values from results*		
Assumption	**Value**						
Threshold (unit:USD)	50000						
Unit cost per patient (unit:USD)	**97.68**				* ( ) inducate nagetive value		
	Parameter	**Pobability of parameter**	**Headroom**	**Revenues**	**ICER**	**Cost-saving of healthcare service**	**Incremental effect**
	pTP	0.50	2,190	237,469	-7,245	-246	(0.034)
	pTP	0.48	4,381	484,706	-7,245	-491	(0.068)
	pTP	0.45	6,571	731,943	-7,245	-737	(0.102)
	pTP	0.42	8,762	979,180	-7,245	-982	(0.136)
	pTP	0.40	10,952	1,226,417	-7,245	-1,228	(0.170)
Scenario 1	pTP	0.37	13,143	1,473,654	-7,245	-1,474	(0.203)
	pTP	0.34	15,333	1,720,891	-7,245	-1,719	(0.237)
	pTP	0.32	17,524	1,968,127	-7,245	-1,965	(0.271)
	pTP	0.29	19,714	2,215,364	-7,245	-2,210	(0.305)
	pTP	0.26	21,905	2,462,601	-7,245	-2,456	(0.339)
	pTP	0.24	24,095	2,709,838	-7,245	-2,702	(0.373)
	Parameter	**Pobability of parameter**	**Headroom**	**Revenues**	**ICER**	**Cost-saving of healthcare service**	**Incremental effect**
	PVP	0.44	1,096	113,956	-7,245	-123	(0.017)
	PVP	0.46	2,192	237,679	-7,245	-246	(0.034)
	PVP	0.48	3,288	361,402	-7,245	-369	(0.051)
	PVP	0.50	4,385	485,125	-7,245	-492	(0.068)
	PVP	0.52	5,481	608,848	-7,245	-615	(0.085)
Scenario 2	PVP	0.54	6,577	732,572	-7,245	-737	(0.102)
	PVP	0.56	7,673	856,295	-7,245	-860	(0.119)
	PVP	0.59	8,769	980,018	-7,245	-983	(0.136)
	PVP	0.61	9,865	1,103,741	-7,245	-1,106	(0.153)
	PVP	0.63	10,962	1,227,464	-7,245	-1,229	(0.170)
	PVP	0.65	12,058	1,351,188	-7,245	-1,352	(0.187)
	Parameter	**Pobability of parameter**	**Headroom**	**Revenues**	**ICER**	**Cost-saving of healthcare service**	**Incremental effect**
	pTP	0.50	1,149	119,932	-7,245	-129	(0.018)
	PVP	0.40					
	pTP	0.48	2,408	262,004	-7,245	-270	(0.037)
	PVP	0.38					
	pTP	0.45	3,776	416,449	-7,245	-423	(0.058)
	PVP	0.36					
	pTP	0.42	5,254	583,266	-7,245	-589	(0.081)
	PVP	0.33					
	pTP	0.40	6,842	762,455	-7,245	-767	(0.106)
	PVP	0.31					
Scenario 3	pTP	0.37	8,539	954,016	-7,245	-957	(0.132)
	PVP	0.29					
	pTP	0.34	10,346	1,157,950	-7,245	-1,160	(0.160)
	PVP	0.27					
	pTP	0.32	12,262	1,374,256	-7,245	-1,375	(0.190)
	PVP	0.25					
	pTP	0.29	14,288	1,602,934	-7,245	-1,602	(0.221)
	PVP	0.23					
	pTP	0.26	16,424	1,843,985	-7,245	-1,842	(0.254)
	PVP	0.21					
	pTP	0.24	18,669	2,097,408	-7,245	-2,093	(0.289)
	PVP	0.19					
	Parameter	**Pobability of parameter**	**Headroom**	**Revenues**	**ICER**	**Cost-saving of healthcare service**	**Incremental effect**
	pTP	0.50	3,232	355,006	-7,245	-362	(0.050)
	PVP	0.44					
	pTP	0.48	6,354	707,408	-7,245	-712	(0.098)
	PVP	0.46					
	pTP	0.45	9,367	1,047,437	-7,245	-1,050	(0.145)
	PVP	0.48					
	pTP	0.42	12,270	1,375,094	-7,245	-1,376	(0.190)
	PVP	0.50					
	pTP	0.40	15,063	1,690,379	-7,245	-1,689	(0.233)
	PVP	0.52					
Scenario 4	pTP	0.37	17,747	1,993,291	-7,245	-1,990	(0.275)
	PVP	0.54					
	pTP	0.34	20,321	2,283,831	-7,245	-2,278	(0.315)
	PVP	0.56					
	pTP	0.32	22,785	2,561,999	-7,245	-2,555	(0.353)
	PVP	0.59					
	pTP	0.29	25,140	2,827,794	-7,245	-2,819	(0.389)
	PVP	0.61					
	pTP	0.26	27,385	3,081,217	-7,245	-3,071	(0.424)
	PVP	0.63					
	pTP	0.24	29,521	3,322,268	-7,245	-3,310	(0.457)
	PVP	0.65					
Bset Scenarios for NeoDoppler							
	Parameter	**Pobability of parameter**	**Headroom**	**Revenues**	**ICER**	**Cost-saving of healthcare service**	**Incremental effect**
	pTP	0.23	37,980	4,277,080	-7,245	-4,259	(0.588)
	PVP	1.00					
	pTP	0.23			-7,245	-4,913	(0.678)
	PVP	1.00	43,816	4,935,741			
	Neurocomplication in CI	0.00					

Table 12.3 Headroom and revenue scenarios for NeoDoppler technology in length of stay outcome at product unit costs US$ 564.00.

Headroom and Revenu Scenarios for NeoDoppler (Estimate outcome: Length of stay)					*Data and estimated values from results*		
Assumption	**Value**						
Threshold (unit:USD)	50000						
Unit cost per patient (unit:USD)	**564.00**				* ( ) inducate nagetive value		
	Parameter	**Pobability of parameter**	**Headroom**	**Revenues**	**ICER**	**Cost-saving of healthcare service**	**Incremental effect**
	pTP	0.50	2,190	190,802	-7,245	-246	(0.034)
	pTP	0.48	4,381	438,039	-7,245	-491	(0.068)
	pTP	0.45	6,571	685,276	-7,245	-737	(0.102)
	pTP	0.42	8,762	932,512	-7,245	-982	(0.136)
	pTP	0.40	10,952	1,179,749	-7,245	-1,228	(0.170)
Scenario 1	pTP	0.37	13,143	1,426,986	-7,245	-1,474	(0.203)
	pTP	0.34	15,333	1,674,223	-7,245	-1,719	(0.237)
	pTP	0.32	17,524	1,921,460	-7,245	-1,965	(0.271)
	pTP	0.29	19,714	2,168,697	-7,245	-2,210	(0.305)
	pTP	0.26	21,905	2,415,934	-7,245	-2,456	(0.339)
	pTP	0.24	24,095	2,663,171	-7,245	-2,702	(0.373)
	Parameter	**Pobability of parameter**	**Headroom**	**Revenues**	**ICER**	**Cost-saving of healthcare service**	**Incremental effect**
	PVP	0.44	1,096	67,288	-7,245	-123	(0.017)
	PVP	0.46	2,192	191,011	-7,245	-246	(0.034)
	PVP	0.48	3,288	314,735	-7,245	-369	(0.051)
	PVP	0.50	4,385	438,458	-7,245	-492	(0.068)
	PVP	0.52	5,481	562,181	-7,245	-615	(0.085)
Scenario 2	PVP	0.54	6,577	685,904	-7,245	-737	(0.102)
	PVP	0.56	7,673	809,627	-7,245	-860	(0.119)
	PVP	0.59	8,769	933,351	-7,245	-983	(0.136)
	PVP	0.61	9,865	1,057,074	-7,245	-1,106	(0.153)
	PVP	0.63	10,962	1,180,797	-7,245	-1,229	(0.170)
	PVP	0.65	12,058	1,304,520	-7,245	-1,352	(0.187)
	Parameter	**Pobability of parameter**	**Headroom**	**Revenues**	**ICER**	**Cost-saving of healthcare service**	**Incremental effect**
	pTP	0.50	1,149	73,265	-7,245	-129	(0.018)
	PVP	0.40					
	pTP	0.48	2,408	215,337	-7,245	-270	(0.037)
	PVP	0.38					
	pTP	0.45	3,776	369,781	-7,245	-423	(0.058)
	PVP	0.36					
	pTP	0.42	5,254	536,598	-7,245	-589	(0.081)
	PVP	0.33					
	pTP	0.40	6,842	715,787	-7,245	-767	(0.106)
	PVP	0.31					
Scenario 3	pTP	0.37	8,539	907,349	-7,245	-957	(0.132)
	PVP	0.29					
	pTP	0.34	10,346	1,111,283	-7,245	-1,160	(0.160)
	PVP	0.27					
	pTP	0.32	12,262	1,327,589	-7,245	-1,375	(0.190)
	PVP	0.25					
	pTP	0.29	14,288	1,556,267	-7,245	-1,602	(0.221)
	PVP	0.23					
	pTP	0.26	16,424	1,797,318	-7,245	-1,842	(0.254)
	PVP	0.21					
	pTP	0.24	18,669	2,050,741	-7,245	-2,093	(0.289)
	PVP	0.19					
	Parameter	**Pobability of parameter**	**Headroom**	**Revenues**	**ICER**	**Cost-saving of healthcare service**	**Incremental effect**
	pTP	0.50	3,232	308,339	-7,245	-362	(0.050)
	PVP	0.44					
	pTP	0.48	6,354	660,741	-7,245	-712	(0.098)
	PVP	0.46					
	pTP	0.45	9,367	1,000,770	-7,245	-1,050	(0.145)
	PVP	0.48					
	pTP	0.42	12,270	1,328,427	-7,245	-1,376	(0.190)
	PVP	0.50					
	pTP	0.40	15,063	1,643,711	-7,245	-1,689	(0.233)
	PVP	0.52					
Scenario 4	pTP	0.37	17,747	1,946,624	-7,245	-1,990	(0.275)
	PVP	0.54					
	pTP	0.34	20,321	2,237,164	-7,245	-2,278	(0.315)
	PVP	0.56					
	pTP	0.32	22,785	2,515,331	-7,245	-2,555	(0.353)
	PVP	0.59					
	pTP	0.29	25,140	2,781,127	-7,245	-2,819	(0.389)
	PVP	0.61					
	pTP	0.26	27,385	3,034,550	-7,245	-3,071	(0.424)
	PVP	0.63					
	pTP	0.24	29,521	3,275,600	-7,245	-3,310	(0.457)
	PVP	0.65					
Bset Scenarios for NeoDoppler							
	Parameter	**Pobability of parameter**	**Headroom**	**Revenues**	**ICER**	**Cost-saving of healthcare service**	**Incremental effect**
	pTP	0.23	37,980	4,230,412	-7,245	-4,259	(0.588)
	PVP	1.00					
	pTP	0.23	43,816	4,889,073	-7,245	-4,913	(0.678)
	PVP	1.00					
	Neurocomplication in CI	0.00					

Annex

Declaration in lieu of oath

With this declaration, the student confirms having written the thesis him or herself without any outside help. Others' thoughts and ideas are clearly marked as such and the master thesis has not been handed in during the course of another program and has not yet been published. Each master's thesis needs to contain such a declaration and has to be signed by the student in person. An electronic signature cannot be accepted. Exact formulation of this declaration:

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SIGNATURE	
Chang Jui Pin 30/10/2020	30/10-20
date and signature of student	date and signature of supervisor