COST-EFFECTIVENESS OF PULSE OXIMETRY SCREENING FOR CRITICAL CONGENITAL HEART DEFECTS IN ONTARIO

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ABSTRACT

Background: Pulse oximetry screening (POS) for critical congenital heart defects (CCHDs) is being increasingly adopted, but sparsely populated regions in Ontario present unique challenges.

Objective: To estimate cost-effectiveness of POS for CCHD in Ontario, Canada.

Methods: A cost-effectiveness analysis using a Markov model was conducted from a healthcare payer perspective over a life-time horizon. Outcome measures, discounted 1.5%, were quality-adjusted life months (QALMs), lifetime costs, and incremental cost-effectiveness ratios (ICER) [ΔCost / ΔQALMs]. An ICER threshold of CAD$4,166.67 per QALM was used. Probabilistic sensitivity analysis was conducted within expected variable ranges.

Results: POS is expected to lead to timely diagnosis of 51 CCHD cases annually. The estimated ICER of CAD$1,110.79 was well below the threshold. Probabilistic sensitivity analysis estimated a 93% chance of POS being cost-effective.

Conclusion: Routine implementation of POS for CCHD in Ontario is expected to be cost-effective. Further validation of this model may be conducted following implementation.

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ABBREVIATIONS

AAP – American Academy of Pediatrics
AC – Ambulatory Care
ADRQL – Alzheimer's Disease Related Quality of Life
AoS – Aortic Stenosis
BORN – Better Outcomes Registry and Network
CCHD – Critical Congenital Heart Disease
CET – Cost-effectiveness threshold
CHQ – Child Health Questionannaire
CIHI – Canadian Institute for Health Information
CoA – Coarctation of Aorta
DORV – Double Outlet Right Ventricle
ECHO – Echocardiogram
EKG – Electrocardiogram
GERD – Gastroesophageal Reflux Disease
HLHS – Hypoplastic Left Heart Syndrome
ICER – incremental cost-effectiveness ratio
ICES – Institute for Clinical Evaluative Sciences
IP – Inpatient
LHIN – Local Health Integrated Network
MeSH – Medical Subject Heading
MOH – Ministry of Health
MOHLTC – Ministry of Health and Long Term Care
OCCI – Ontario Case Costing Initiative
PA+IVS – Pulmonary Atresia with Intact Ventricular Septum
PA+VSD – Pulmonary Atresia with a Ventricular Septal Defect
PedsQOL – Pediatric Quality of Life Scale
POS – Pulse Oximetry Screening
QALM – Quality-adjusted life month
QALY – Quality-adjusted life year
QOL-AD – Quality of life – Alzheimer's Disease
SD – Standard deviation
SF-36 – Short Form-36
SpO_2 – Oxygen saturation level
TACQOL – TNO-AZL Child Quality of Life
TGA (D-TGA/L-TGA) – Transposition of Great Arteries (Dextro- or Levo-)
TOF – Tetralogy of Fallot
UK – United Kingdom
USA – United States of America
WHOQOL – World Health Organization Quality of Life

1. BACKGROUND: CLINICAL PROBLEM

1.1 Critical congenital heart disease lesions and clinical impact

Congenital heart diseases are structural cardiac malformations during fetal development and occur in approximately 8-9 per 1,000 live births.(1, 2) Of these, up to 30% are considered "critical" congenital heart disease (CCHD) lesions – which are severe lesions that typically require invasive intervention (catheter-based, surgery or a combination of both) within the first months of life.(3, 4) Broadly, CCHD lesions are categorized into those that result in mixing of blood carrying deoxygenated and oxygenated hemoglobin (e.g. transposition of the great arteries, truncus arteriosus), and those that result in obstruction of flow to either the lungs and/or to the body (e.g. aortic stenosis, interrupted aortic arch). Both these groups of lesions result in suboptimal delivery of oxygen to tissues throughout the body including vital organs such as the brain. As such, these lesions are associated with significant morbidity and mortality, and are responsible for more deaths than any other type of congenital malformation.(5, 6) Early detection of CCHDs allows for interventions that minimize the duration of impaired tissue oxygenation and is therefore important in order to improve survival, minimize morbidity and improve post-surgical outcomes.(7, 8)

There is a spectrum of severity among various types of CCHD lesions. A newborn with transposition of the great arteries with an intact ventricular septum will present soon after birth with symptoms of cyanosis whereas coarctation of the aorta in a newborn may not be clinically apparent for hours or even days after delivery. There may also be differences in the severity and timing of onset of symptoms depending on the degree of abnormality within the same lesion. For example, a tetralogy of fallot with severe obstruction of blood flow to the lungs may be apparent

shortly after birth, whereas the same lesion but less severe obstruction may not become apparent for days after birth. Additionally, clinical presentation in many CCHD lesions is masked by the presence of a patent ductus arteriosus, which is a conduit between the right and left-sided circulations that is essential during fetal life. The presence of the patent ductus arteriosus allows for mixing of blood as well as flow of blood to the body in various CCHDs, and its closure – normally occurring at 24-28 hours of age – often heralds the onset of symptoms. This variability in presentation and specifically, the lack of clinical symptoms and signs in early hours of life results in the lack of detection of many cases of CCHD prior to discharge home post-delivery. It has been estimated that 20-30% of CCHDs are missed by routine physical examination.(9, 10) Cyanosis, the physical sign indicative of tissue hypoxemia and hallmark feature of mixing type CCHDs, is commonly missed on physical examination, particularly in newborns.(11) Routine antenatal ultrasound scans for fetal anatomy detect many CCHDs, but many cases still remain undetected by the time of delivery.(12, 13) Various factors have been postulated as reasons for lack of detection of all CCHD lesions by routine antenatal anatomy ultrasound, including limitations in access in certain rural areas, variability of skill of technicians and subtleties of certain CCHD lesions that preclude antenatal detection.(14) Nevertheless, CCHD lesions remaining undetected prior to discharge home remains a significant burden of illness. A recent review of data from Ontario revealed that in a 10 year period from April 2002 to March 2012, 16% of all CCHD lesions from hospital births were undetected prior to discharge home.(15)

1.2 Pulse oximetry screening for CCHD

Pulse oximetry is a simple, reliable, point-or-care technique which is now used routinely in medical practice for assessment of hypoxemia. It employs the use of spectrophotometric methodology, by illuminating the skin and measuring changes in differential light absorption of deoxygenated and oxygenated hemoglobin.(16) This yields the pulse oximetry measured hemoglobin oxygen saturation level (SpO_2), which has been found to be a reliable estimate of the measured arterial saturation of oxygen (SaO_2).(17, 18) Pulse oximeters are readily available, and are in widespread use in hospitals – emergency rooms, inpatient settings including intensive care as well as in emergency services such as ambulances. Its ubiquity and relative ease of use, along with its reliability in estimating oxygen saturation of hemoglobin, sparked interest in its use as a screening tool for detection of CCHDs.(19) As described earlier, many CCHDs that are undetected clinically do have underlying hypoxemia which is not reliably determined on clinical exam, making pulse oximetry an attractive screening tool to help reduce morbidity and mortality associated with missed CCHD. A low SpO_2 detected on pulse oximetry would trigger a detailed evaluation for the presence of CCHD, which may include an echocardiogram.

Initial studies on the use of pulse oximetry screening (POS) for detection of CCHD were conducted in the early 2000s and were seen as largely "proof of concept".(20, 21) The largest of these were by Koppel et al, a study of more than 11,000 well appearing newborns, which found a sensitivity of 60.0%, specificity of 99.95% and false positive rate of 0.009%.(21) Since that time, numerous studies have confirmed these findings,(22-25) and a systematic review of this literature published in 2011 (13 studies representing 229,421 babies) found an overall sensitivity of 76.5% for detection of CCHD, overall specificity of 99.9% with a false positive rate of 0.14%.(26) The sensitivity of the screening tool appears rather low compared to other screening tools, but is due to the fact that some CCHDs do not present with hypoxemia until closure of the

patent ductus arteriosus, which may occur at a time following the conduct of the screening test. As such, it is known and accepted that not all CCHDs will be detected by POS.(4) Nevertheless, based on the accumulating evidence on the effectiveness of POS as a screening tool for CCHD in comparison to clinical examination alone, in 2011 the United States Secretary of Health and Human Services recommended the inclusion of CCHD to the panel of conditions routinely screened for in the newborn period.(19) This view was subsequently also endorsed by the American Academy of Pediatrics (AAP).(27)

Implementation of POS for CCHD in the USA has been rapid, with 46 states and the District of Columbia incorporating this practice into routine newborn screening within 4 years of the endorsement by the AAP.(28) Many centres in the USA and UK have also published their local experience with the implementation of POS for CCHD, and have reported detecting CCHD cases that might have been missed prior to initial hospital discharge.(29-33) However, there are other common themes from these studies, namely: (a) the detection of other non-CCHD conditions among the "false-positive" cases including sepsis, respiratory illnesses, non-critical CCHDs; (b) re-affirmation that not all CCHDs will be detected by POS; and (c) feasibility of POS implementation even in centres that do not have access to immediate definitive testing with echocardiography. Some other important points were that (a) there is still variation in the list of congenital cardiac lesions that are labeled as CCHDs; and (b) there are discrepancies in the algorithm of POS testing (including cut-off values for what is considered a "positive" screen).(28) Finally, most centres in the US and UK who report on POS implementation have relatively quick access to confirmatory echocardiogram, even if it is not in the centre where baby is delivered. For instance, in the relatively sparsely populated state of Wisconsin, USA, same-day neonatal echocardiography service was available for approximately 75% of births, and for

hospitals without this service, the nearest regional centre was on average only 53 miles (85 km) away.(33) In summary, in settings where implementation of POS for CCHD has been reported, it appears to be feasible and has led to the detection of cases that would have otherwise been missed. In recent months, the Canadian Cardiovascular Society, Canadian Pediatric Cardiology Association and the Canadian Pediatric Society have all endorsed implementation of routine pulse oximetry screening for well appearing newborns.(34) However, this has not been implemented in all hospitals in Ontario, and as described in the subsequent sections, it remains unknown whether this will be a cost-effective endeavour in Ontario.

1.3 Pulse oximetry screening for CCHDs and cost-effectiveness

Unlike most other screening tests, POS is a point-of-care test that requires real-time interpretation and in cases of positive result – immediate action to provide timely diagnosis and appropriate management. While there have been various algorithms used for POS, the most commonly employed is the algorithm proposed by the AAP (**Appendix A**). This algorithm indicates that screening should be performed at >24 hours of age (or before discharge if discharge is at <24 hours) on the right hand ("pre-ductal") and either foot ("post-ductal"). If either reading is <90%, the result is considered a positive screening result. If either reading is ≥95% and the difference between the 2 readings is ≤3%, the result is considered a negative. Results outside of these 2 scenarios results in repeat testing after 1 hour for up to 2 additional tests.(28) Unless another reason for the hypoxemia is identified in the ensuing investigations following a positive screen, an echocardiogram must be performed, which may require transfer to another centre where neonatal echocardiography is available.

Due to the resource implications, particularly the lack of availability of neonatal echocardiography at all centres, as well as the burden of a potentially large number of false positive results; there have been a number of cost-effectiveness analyses of POS for CCHD.(24, 35-39) A summary of the cost-effectiveness analyses published to date is shown in **Table 1.1** below.

Table 1.1: Cost-effectiveness analyses of POS for CCHD

Author, Year	Study Characteristics	Summary of Findings
Knowles, 2005(35)	• UK-based study on cost-effectiveness of POS (ICER per diagnosis of CCHD) • Time horizon: until diagnosis of CCHD established • Perspective: National Health Service (UK)	• ICER was £4,900 per additional CCHD diagnosed • Sensitivity analysis showed 92% chance of being cost-effective at cost-effectiveness threshold of £10,000

Griebsch, 2007(36)	• UK-based study on cost-effectiveness of POS (ICER per diagnosis of CCHD) • Time horizon: until diagnosis of CCHD established • Perspective: National Health Service (UK)	• ICER was £4,894 per additional CCHD diagnosed • Deemed "likely" to be cost-effective
de-Wahl Granelli, 2009(24)	• Used model created by Griebsch et al (36) and employed Swedish-based population data • Perspective: Not specified	• ICER was estimated at £3,430 per timely diagnosis of CCHD • Estimated to be "at a minimum" cost neutral
Ewer, 2012(37)	• UK-based study on cost-effectiveness of POS (ICER per diagnosis of CCHD) • Time horizon: until diagnosis of CCHD established • Perspective: National Health Service (UK)	• ICER was £24,900 per additional diagnosis of CCHD • Deemed "likely" to be cost-effective
Roberts, 2012(38)	• UK-based study on cost-effectiveness of POS (ICER per diagnosis of CCHD) • Time horizon: until diagnosis of CCHD established • Perspective: National Health Service (UK)	• Expected to lead to timely diagnosis of 30 additional cases of CHD per 100,000 births • ICER was approximately £24,000 per additional timely diagnosis of CCHD • Sensitivity analysis showed 90% chance of being cost-effective at a cost-effectiveness threshold of £100,000
Peterson, 2013(39)	• US-based study on cost-effectiveness of POS (ICER per case identified and per life-year gained) • Time horizon: infancy (< 1 year) • Perspective: US healthcare sector	• ICER was $20,862 per case identified and $40,385 per life year gained • Sensitivity analysis indicated a 52% and 73% chance of cost-effectiveness at a threshold of <$50,000 and < $100,00 per life year gained, respectively

Abbreviations: CCHD – critical congenital heart disease; ICER – incremental cost-effectiveness ratio; POS – pulse oximetry screening

1.4 Knowledge gap on cost-effectiveness in Ontario

All of the above models suggest that screening for CCHD using pulse oximetry is likely to be cost-effective. However, there are some important considerations from these analyses. With the exception of the Swedish model by de-Wahl Granelli et al and the US analysis by Peterson et al, all others were from the UK, where the availability and distribution of clinical resources is much different than in Ontario. For instance, in the analysis by Peterson et al, they estimated that approximately 43% of infants would require transport to another facility to complete a confirmatory echocardiogram.(39) This figure is expected to be much higher in Ontario, as only 17.1% of all deliveries occur at a level 3 institution with immediate access to echocardiograms, and it is estimated that only up to 22% of level 2 hospitals have intermittent access to echocardiography and often only during regular office hours (described in **Section 4**). In the UK studies (which used similar data as identified by Knowles et al), it was estimated that the cost of transport would be £238, which is a reflection of a relatively densely populated region with relatively quick access to tertiary level care centres.(35) On the other hand, in a geographical distribution such as that of Ontario whereby densely populated regions are intermixed with remote locations that are very far from regional centres, even a relatively low percentage of deliveries in the latter regions may incur significantly more costs. Even among deliveries in the densely populated regions, the majority of babies will still require transfer to another centre where an echocardiogram can be performed. (**Appendix B** contains a description of levels of care on newborns in Ontario and the geographical based Local Health Integration Networks (LHINs) which plan, integrate and fund local health care, as it relates to POS screening for CCHD).

Another limitation of the previous studies is that the cost effectiveness models represent the time until a diagnosis is made, with the exception of the study by Peterson et al where the

time horizon spanned 1 year.(39) It may be argued that if POS is likely to be cost-effective until a diagnosis is made, it is even more likely to be cost-effectiveness over a longer time horizon. However, one factor that has not been included in previous studies is the quality of life associated with CCHDs and particularly in CCHD cases where there may be associated morbidity, which may have an impact on cost-effectiveness.

In light of the aforementioned limitations as well as in consideration of some of the unique logistical challenges towards the implementation of POS for CCHD in Ontario as described above, we conducted a cost-effectiveness analysis of the implementation of this screening program. This was a model based economic evaluation run over a life-time horizon, incorporating quality of life indicators, and conducted from the perspective of the Ontario healthcare payer. The details of the decision model and its structure are delineated in **Section 3.**

2. BACKGROUND: MEDICAL DECISION MODELS

2.1 Decision Analysis

Originally developed in the field of economics, decision analysis has been applied to the field of medicine in order to rationalize often complex medical decisions,(40) both at an individual patient level (e.g. with regards to choice of a particular treatment strategy), as well as at an institutional or policy level (e.g. implementation of routine publicly funded vaccination programs). Inherent in such complex decisions is a large degree of uncertainty as to what is the "optimal choice", which often cannot be rationalized in an unstructured approach.(40) Medical decision analysis is a structured, explicit and systematic approach to rational decision making incorporating probabilities of events occurring and the values (also known as "utilities") associated with various health states or conditions.(41)

Medical decision analysis is conceptualized in the form of a decision tree, whereby a decision is divided into two main "stems" representing the two choices, each in turn followed by a series of chance occurrences (based on probabilities of events occurring depending on the medical condition under evaluation, and outcomes of interventions that may follow). The various possible health outcomes are associated with a "utility" value. Patient utility is assigned an index value between 0 (death) and 1 (perfect health), which incorporates individuals' assessment of and value associated with a particular health state, representing the quality of life.(40) The utilities associated with various health states are multiplied by the chances of each health state occurring (based on the probabilities), the sum of which yields the expected utility resulting from each of the decision choices. The decision with the higher expected utility is regarded as the "optimal" decision.

The following example illustrates the concepts described above. In this hypothetical situation, medical "Condition X" (with a quality of life value or utility score of 0.8) has a treatment available, which cures the condition but also has the possibility (20%) of a significant side effect (associated with a quality of life value or utility score of 0.5). On the other hand, not treating the condition results in a very small possibility (5%) of death. Without a structured approach, it may not be clear which option is the most optimal approach for an individual patient. However, this can be turned into a structured rational approach by use of a decision analysis tree, as shown in **Figure 2.1** below. By convention, a decision is indicated by a square node, a round node represents a chance occurrence (based on known probabilities), and a triangular node represents the end of the decision tree, usually culminating in a particular health state.

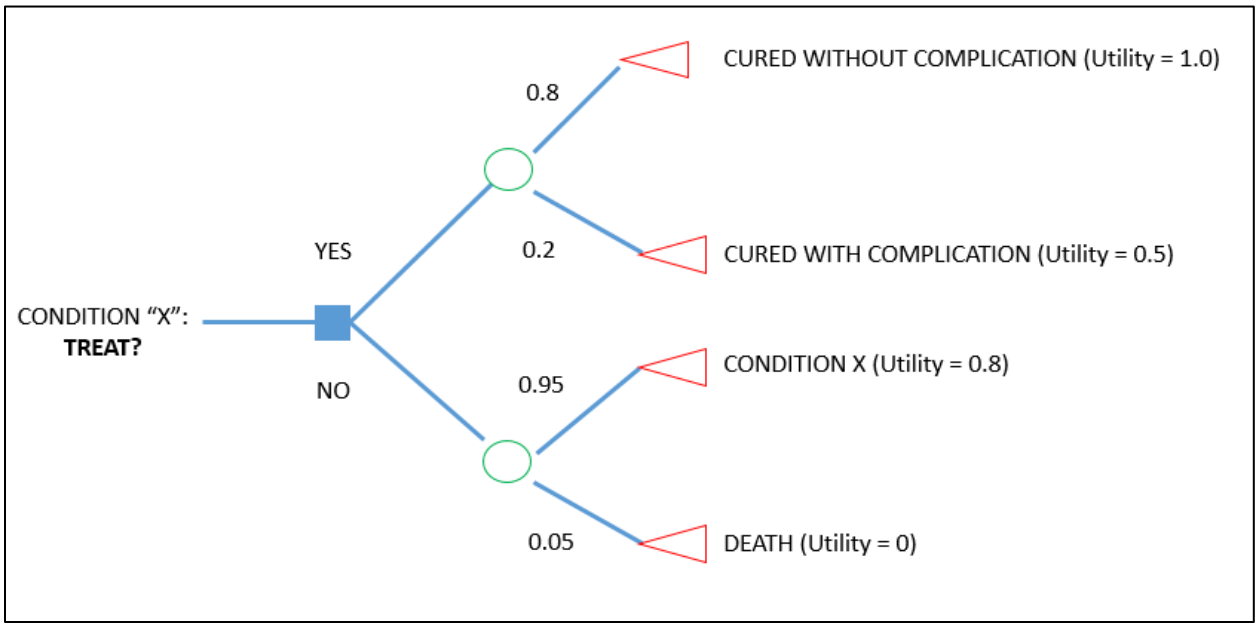

Figure 2.1: An example of a simple medical decision analysis tree regarding whether to treat a hypothetical condition X

In this above example, the expected utility of each decision option (i.e. treating vs. not treating) will be calculated by multiplying the probability of health outcome by its utility and

adding together the expected utilities of each health state resulting from each choice. For treatment, this would yield: (0.8 x 1.0) + (0.2 x 0.5) = 0.9 estimated utility. On the other hand, for no treatment, the estimated utility will be: (0.95 x 0.8) + (0.05 x 0) = 0.76. Therefore, in this example, based on the utilities assigned to each health state, treatment of condition X would be the "rational" and preferable choice, despite the possibility of a severe complication of treatment.

2.2 Markov models

A simple decision analysis tree, as described above, has several practical limitations. One of the most important limitation is having to identify a finite time-horizon over which the model is applicable. This has limitations, as many of the health states described at the end of model may not be the "final" outcomes, and that individuals may have variable life spans. In the example of condition X above, one cannot explore condition X over time. Presumably, remaining in condition X over the years will shorten the life expectancy, but due to a set time-frame this cannot be evaluated. One option is to design a "recursive" tree, whereby condition X (with a probability of 0.05 of death each year) is run over a chance node repeatedly. However, this approach becomes impractical in complex decision trees. Another related limitation of regular decision analysis trees is the inability to change probabilities over time. What if condition X has varying probability of death (e.g. as a person ages, the probability of death increases)? Regular decision trees cannot easily incorporate such variations in probabilities over time. Finally, one of the important outcome measures in medical decision modeling is determining "quality-adjusted life spans" resulting from medical decisions or policy implementations (to be discussed in **Section 2.3**). While these can be derived in regular decision models, such outcome measures are very readily derived by employing Markov models.(42)

Also known as health state transition models, Markov models place simulated individuals or a cohort into one of a number of exhaustive and mutually exclusive health states. The model is run over time, wherein during each time cycle, a simulated individual (or a certain fraction of the cohort) in the model may "transition" from one health state to another, or remain in the same health state as in the previous cycle.(42) Cycles are run repeatedly in this model, with health state transitions occurring with each cycle, until either: (a) all simulated individuals are transitioned to the absorbing health state (usually "death"); (b) a predetermined number of cycles have run; or (c) the "incremental" utility (i.e. the utility added by running another cycle of the model) is lower than a predetermined threshold. A simple example of a Markov model is depicted in **Figure 2.2** below.

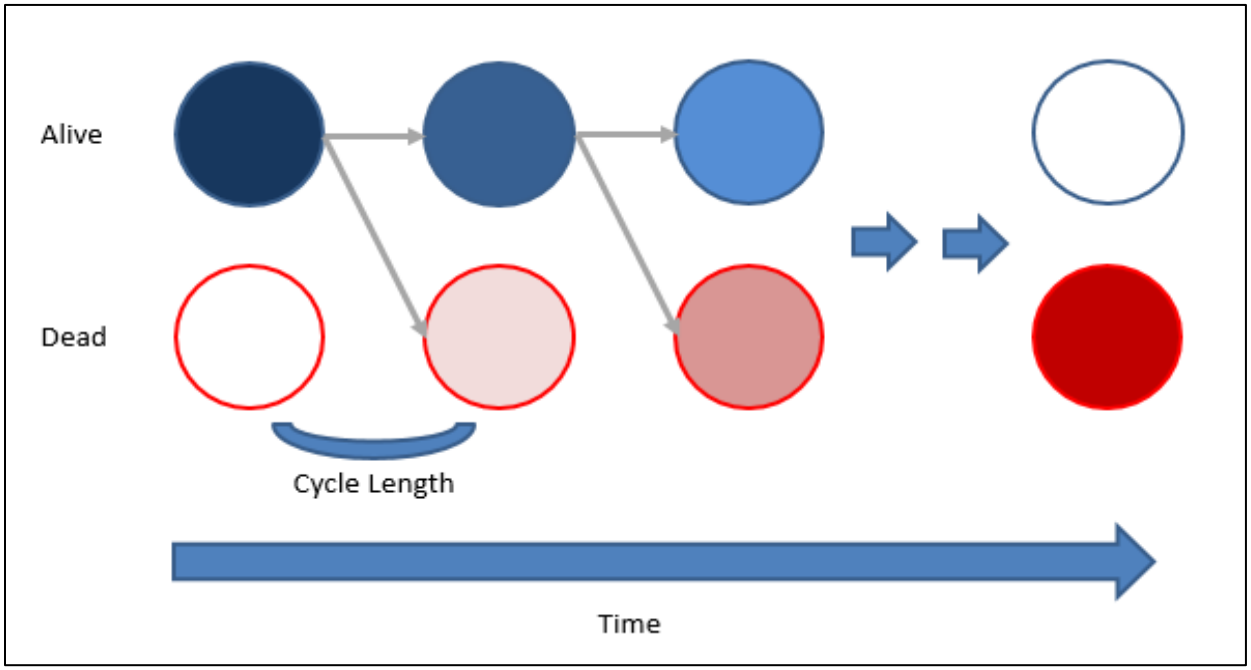

Figure 2.2: A simple Markov (health state transition) model.

In the example shown in **Figure 2.2** above, simulated individuals in the model are placed in 1 of 2 mutually exclusive health states – Alive or Dead. At time 0, all individuals are alive.

With each cycle of the model, a certain fraction of alive individuals "transition" to the death state – determined by the "transitional probability", while the remainder stay in the same health state of Alive. The transition probability can be made to vary over time if needed. A Markov model may have any number of health states, so long as they are mutually exclusive (i.e. there can be no ambiguity about which health state an individual simulated patient can belong to) and exhaustive (i.e. an individual simulated patient must be able to find a "home"). Each cycle of a Markov model yields "incremental" expected utility for each cycle – determined by the sum of the proportion of simulated individuals in each health state multiplied by the utility values associated with the respective health state during the given cycle. As will be described in the following **Section 2.3**, the cost associated with each health state may also be incorporated to yield an "incremental" total cost associated with each cycle of a Markov model.

2.3 Cost effectiveness analysis

When applying medical decision analysis at the level of an individual patient, cost may not be an important factor in most cases – particularly in settings where the cost is incurred by a third party (e.g. insurance company or public funds). This is because both the health care practitioner and the patient have the interest of the individual patient as their primary focus.(40) However, when applying medical decision analysis at the policy level – e.g. whether to implement a publically funded vaccination program for influenza – cost is of paramount importance.(43) Once it is established that a particular medical strategy is clinically effective, feasible, and does not lead to significant harm or side effects, cost becomes an important factor in determining whether widespread implementation of such a strategy is in the interest of the population as a whole (as compared to another initiative where the funds may be better suited –

or more "cost effective"). As such, cost-effectiveness analyses are an important piece of evidence that helps guide the most effective allocation of resources.

A cost-effectiveness analysis compares the relative costs and outcomes of two or more interventions or course of action (e.g. implementation of a vaccination program vs. not implementing the vaccination program, or medical treatment vs. surgical treatment for medical condition "X"). A cost-effective analysis may be performed from a healthcare payer perspective or from a societal perspective, and may be run over varying time horizons depending on the nature of the question. The effectiveness refers to the outcome being evaluated, which may incorporate quality of life indicators (in such a case the analysis is more correctly termed a cost-"utility" analysis), yielding what is known as "quality adjusted life year (QALY)" (or any other arbitrary unit of time). When one treatment or intervention is more effective with respect to the outcome at a lower cost, the decision is simple. However, the decision becomes more complex when one intervention is more effective but also costs more. To help standardize this in order to allow for comparisons with another intervention for the same condition (or whether to use the limited available resources to fund a different intervention for another medical condition entirely), the concept of incremental cost-effectiveness ratio (ICER) is used.(43) The ICER is the ratio of the "incremental" costs incurred by a certain medical intervention divided by the "incremental" QALYs achieved. In effect, this yields the how much it would cost to gain a unit of QALY (or any other unit of quality-adjusted life).

This ICER may then be compared against a pre-determine ICER "threshold", below which an intervention is deemed cost-effectiveness. This ICER threshold is also known as the "cost-effectiveness" threshold (sometimes also referred to as the "willingness to pay" threshold).(43) Any intervention ICER that falls below the cost-effectiveness threshold (CET)

threshold would be cost-effective, whereas any intervention with an ICER above the CET threshold deemed not. In Canada, an ICER threshold of $50,000 per QALY is commonly considered to be cost-effective.(44) **Figure 2.3** below illustrates the concept of ICER and CET thresholds.

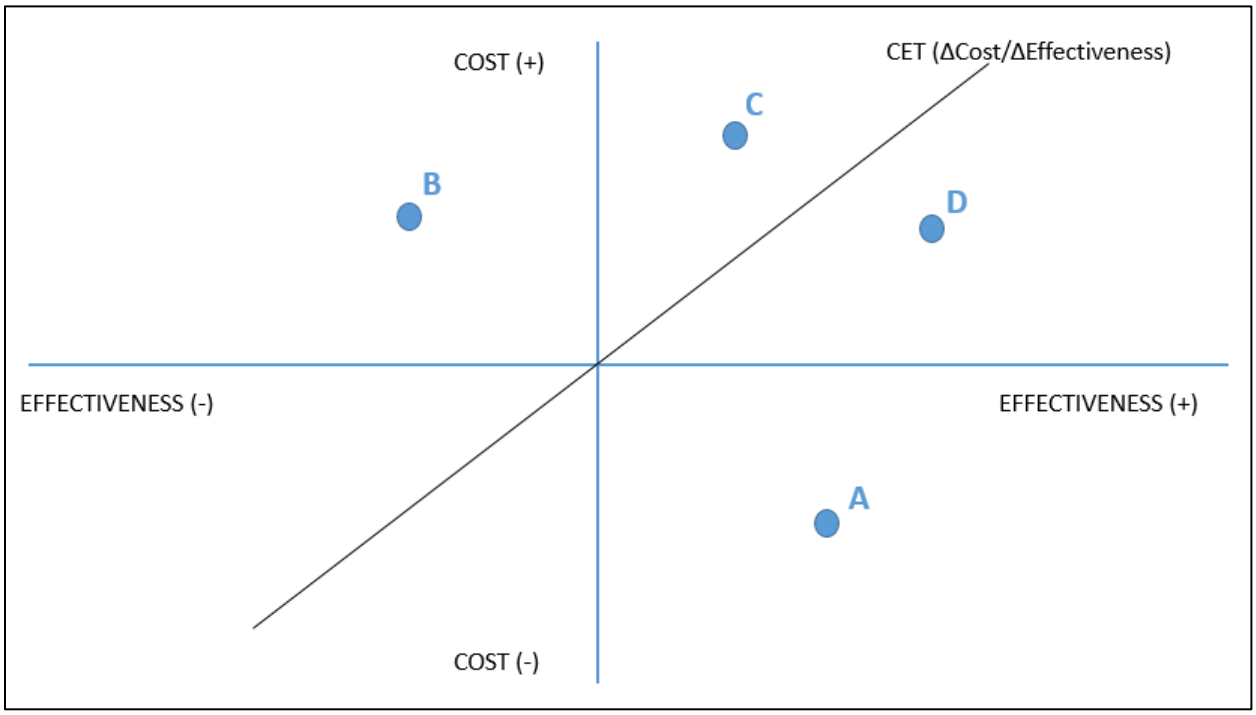

Figure 2.3: Plot of incremental cost vs. incremental effectiveness

In the hypothetical example shown above in **Figure 2.3** of various interventions, intervention A costs less and leads to more effectiveness and as such is an easy choice for implementation. Similarly, intervention B costs more and is less effective, therefore is an obvious decision to not be implemented. Interventions C and D are in the quadrant where the cost is greater but so is effectiveness. However, intervention D is below the CET (therefore would be deemed cost effective), whereas intervention C lies above the threshold and would not be considered cost-effective. Any intervention for which the incremental cost and incremental effectiveness plots "below" the CET slope is deemed to be cost-effective.

3. DECISION MODEL FOR CCHD SCREENING IN ONTARIO

The following section delineates the development of the medical decision model structure employing Markov cycles for the implementation of CCHD screening using POS in Ontario, Canada. A cost-effectiveness (utility) analysis was developed following the Canadian Agency for Drugs and Technologies in Health guidelines,(44) and using Ontario-specific data wherever possible.

3.1 The Base Case

The base case subject was a well newborn infant ~24 hours old born in Ontario. The newborn could be born at home or in hospital but must be born in the presence of a qualified attendant (midwife, family doctor, or obstetrician) capable of performing POS. Following birth, the infant had to have been asymptomatic of CCHD and not requiring any medical attention beyond routine care for the first 24 hours of life.

3.2 Diagnostic Strategies

We compared two diagnostic strategies: pulse oximetry screening and no pulse oximetry screening (**Figure 3.1**). Our perspective was that of the Ontario Ministry of Health (healthcare payer)

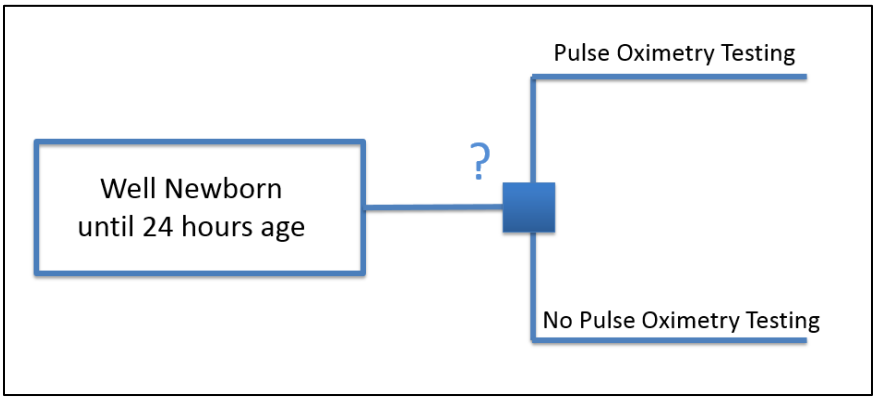

Figure 3.1: Base case and diagnostic strategies

3.3 Model Structure

TreeAge Pro software 15.2.1.0-v20150831 (TreeAge Software Inc., Williamstown, MA, USA) was used to create a Markov decision model with one-month cycles, allowing lifetime follow-up of the simulated study cohort. The following exhaustive and mutually exclusive health states were created: 1) CCHD (pre-op); 2) No CCHD (< 1 month); 3) Post-op CCHD (with morbidity); 4) Post-op CCHD (no morbidity); 5) No CCHD (> 1month), and 6) Death. At any given point in time, a simulated individual could only be in 1 of the 6 aforementioned mutually exclusive health states.

At the beginning of cycle 1, all simulated individuals could only be in either one of the following two health states: 1) CCHD (pre-op); or 2) No CCHD (< 1 month). An individual with (undiagnosed) CCHD at the time of 24 hours could have the screening performed and yield either a (true) positive result or a (false) negative result, latter being a case of missed CCHD. Similarly, an individual with No CCHD could have a (false) positive or a (true) negative result. All positive results (regardless of whether true or false) were designed to require follow-up which may or may not have included a series of transfers to a tertiary level care facility. A brief overview of this initial portion of the model schematic for both health states is as outlined in **Figure 3.2** below.

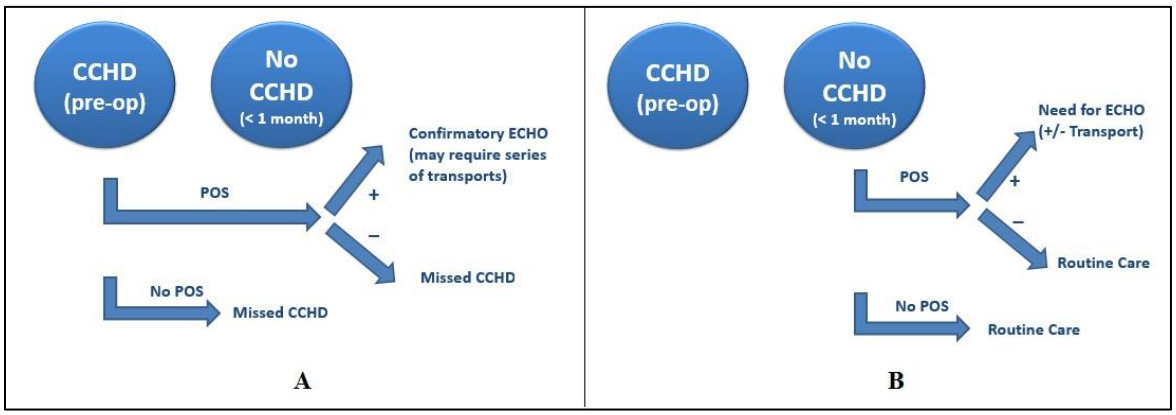

Figure 3.2: Brief overview of results from POS screening in first Markov Cycle. Panels A and B depict the diagnostic possibilities in an individual with CCHD and without CCHD, respectively

In the initial Markov cycle, the model depicted in detail the possibilities of patient location and requirement of transfers (as outlined in **Figure 3.3**), and in cases of confirmed CCHD, the possible outcomes from a CCHD surgery (**Figure 3.4**). The model also depicted the possible outcomes in the event of a missed CCHD sent home after birth hospitalization (**Figure 3.5**). In the figures below, the green circles represent a "chance" node with a certain probability associated with either arm emanating from that node being chosen (determined by the values for probabilities inputted into the model) while the red triangles represent a "terminal" node, culminating in the transition to another health state.

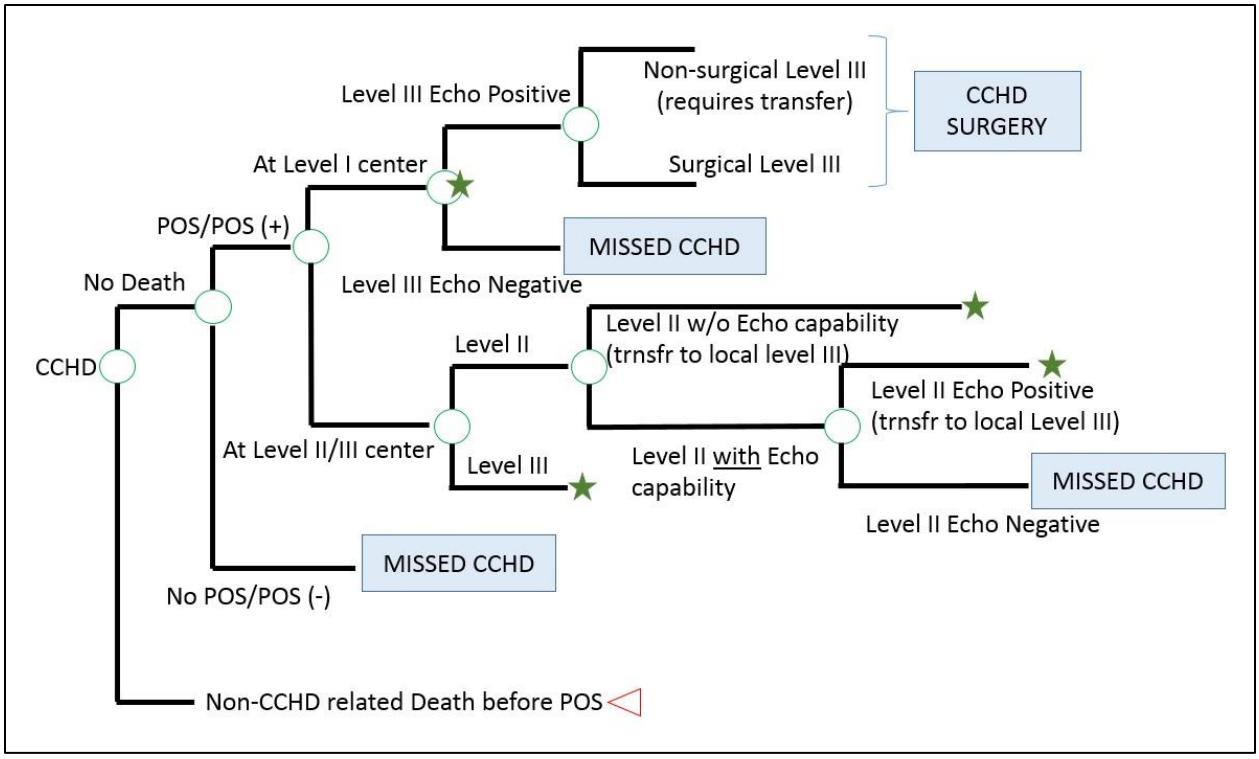

Figure 3.3: Illustration of decision tree during first Markov cycle and various possible outcomes, in a simulated individual who has CCHD

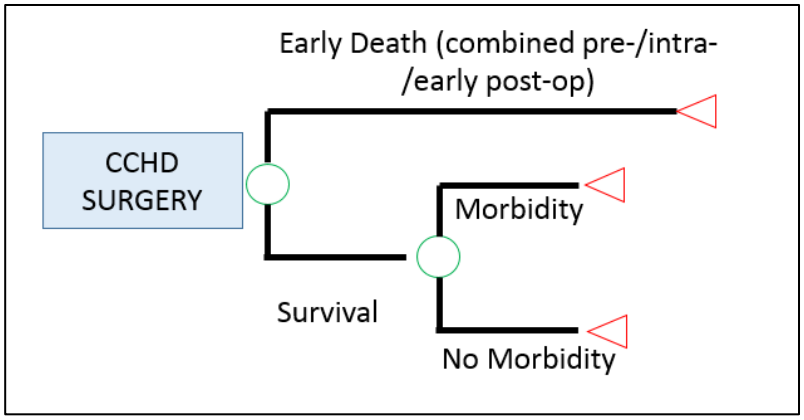

Figure 3.4: Possible outcomes of CCHD surgery incorporated into first cycle of Markov model

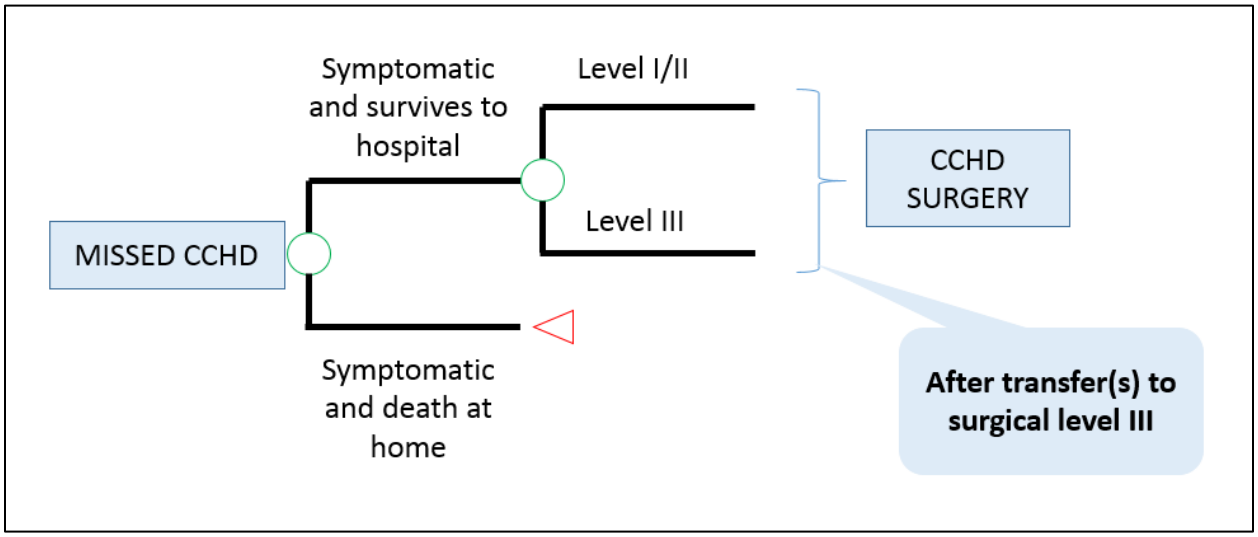

Figure 3.5: Illustration of possible outcomes after missed CCHD incorporated into first cycle of Markov decision model

The end of the first Markov cycle resulted with a simulated individual transitioning to 1 of the following remaining mutually exclusive health states: 1) Post-op CCHD (no morbidity); 2) Post-op CCHD (with morbidity); 3) No CCHD (> 1month); or 4) Death. For the purpose of this model, morbidity referred to any neurodevelopmental impairment (**Section 4**). In subsequent Markov cycles, a simulated individual could stay in the same health state, or transition to another health state. These probabilities varied over time (**Section 4**). The Markov cycles continued until all individuals transitioned to the health state of "Death" in keeping with a life-time horizon of

the model. Possible transitions amongst health states in these subsequent Markov cycles are depicted in **Figure 3.6** below.

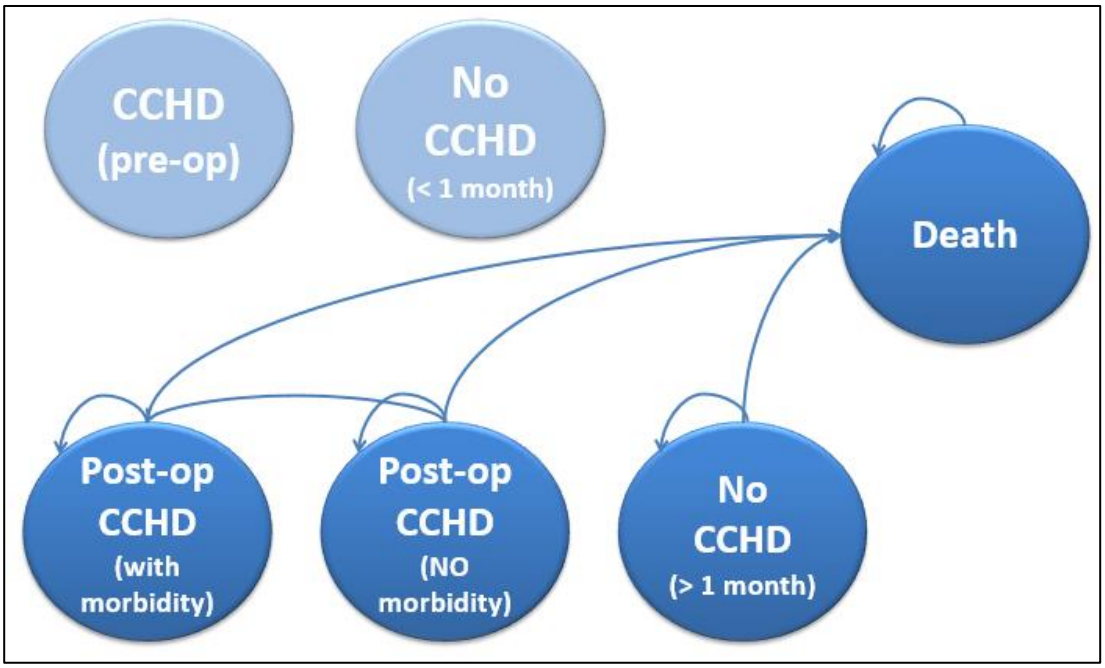

Figure 3.6: Illustration of the possible transitions (denoted by arrows) amongst the 4 health states in subsequent Markov cycles

3.4 Parameter values

Three major categories of variables were used the decision model: (a) probabilities; (b) utilities; and (c) costs. Probabilities determined the path through the decision tree that any simulated individual took during the first Markov cycle, and the transitions amongst health states in the subsequent cycles. Utilities were an indicator of the quality of life associated with being in any particular health state, as well as "transitional utilities" associated with temporary phenomenon such as transfers, having POS performed and having surgical procedures. These utility values were used to determine the expected number of "quality adjusted life months" with either diagnostic strategy (i.e. implementation of POS vs. no POS), and are described in further

detail below. Finally, costs associated with all procedures (including POS, echocardiograms), transfers, surgical procedures and being in health states were inputted to identify the comparative lifetime costs of either diagnostic strategy. Given the life-time horizon of the model, all costs were discounted 1.5% annually to adjust for inflation, as per Canadian guidelines.(44) It is also acknowledged that for utilities and costs, spillover (caregiver) effects were not considered as part of this model, and values for these variables represented the individual patient. The only exception to this was the group of utility variables designated as "DIS-utilites" associated with POS screening itself, transfer and surgery – which represented parental disutility associated with these action steps.

3.5 Outcomes

3.5.1 Quality Adjusted Life Months

The quality of life in each cycle (1 month) in a given health state was represented by a corresponding incremental utility score associated with that health state. The utilities could range from 0 (death) to 1 (perfect health/no CCHD). Each cycle of the model used the incremental utility to determine the quality adjusted life month (QALM) for that given health state. Run over a lifetime horizon, the model yielded the expected per patient QALMs with POS and per patient QALMs without POS implementation.

3.5.2 Costs

The per cycle incremental costs of being in a given health state included medical costs to the public health care system. In addition, costs of POS, transports, echocardiograms and hospitalizations were incorporated into the model. The model yielded the lifetime cost per individual with either diagnostic strategy (i.e. POS implementation vs. without POS implementation.)

3.5.3 Cost-effectiveness (utility) analysis

Incremental cost-effectiveness (utility) ratio (ICER) expressed as added cost per QALM gained with POS (versus no POS) were calculated from the above outcomes. In order to determine the value of POS from a health care perspective, a cost-effectiveness threshold of CAD$4,167 per QALM (equivalent to CAD$50,000 per QALY, a commonly used cost-effectiveness threshold)(45) was used and our ICER result was compared to this threshold. All outcomes were discounted at 1.5% annually, as mentioned previously.

3.6 Sensitivity Analyses

One-way sensitivity analyses were performed for each parameter value used in order to assess parameter uncertainty. In these analyses the model was run at various pre-specified intervals for each included variable within their plausible ranges. The model was considered robust if the overall ICER result at any of the interval values did not change from the main analysis using point estimate values for each variable. The plausible ranges for each value were derived from existing literature where available. In cases when a plausible range was not available from the literature, a Monte-Carlo simulation with beta-distributions was run using the raw numbers (events over total number) to estimate the range – this strategy was employed for probability and utility values. For cost variables without a plausible range from the literature, a 50% reduction and increase in the estimate was used to determine the lower and upper ranges, respectively. The derivation of these ranges for all variables is described in detail in **Section 4**. In addition to the one way sensitivity analysis, for select variables (either due to significant uncertainly regarding their plausible ranges, or their importance in the decision model), an analysis of extreme thresholds was run, where the range was extended to extremes and one-way sensitivity analyses were run. Finally, a probabilistic sensitivity analysis was conducted in which

multiple simulations were run where selected variables were varied simultaneously. This was used to generate an ICER scatter plot as well as a cost-effectiveness acceptability curve (**Section 5**).

3.7 Model Validity

Validity of the model generated was assessed via face validity as the extent to which the model and its assumptions and applications correspond to current science and evidence.(46) Verification of the model structure was performed by B.S., one of the thesis committee members with expertise in medical decision modeling, as well as other committee members with significant clinical experience and expertise in the areas of neonatology and neonatal cardiology. An external validation was deemed to be beyond the scope of the current study, but recognized that following implementation of POS screening – there will be adequate data available from the province to conduct this validation at a later time.

4. VARIABLES AND SEARCH STRATEGIES

4.1 Probability variables

4.1.1 Baseline Health State Probabilities

4.1.1.1 Probability of a well appearing individual at 24 hours age (base case) having CCHD

The incidence of critical congenital heart disease (CCHD) is estimated to be 0.25%.(4) A recent report from the Institute for Clinical Evaluative Sciences (ICES) reported that over a 10 year period (April 2002 to March 2012) in Ontario, 16% of patients with CCHD were missed and sent home from hospital prior to establishing the diagnosis.(15) These are the individuals with CCHD who are likely to represent the base case of a well appearing baby, and as such the **probability of CCHD in a well appearing baby was estimated to be 16% of 0.25% = 0.0004**. To estimate the range, a Monte-Carlo simulation with a beta-distribution was run (1000 samples) which yielded an estimate of 0.0001 for the 2.5th%ile and 0.0009 for the 97.5th%ile.

4.1.1.2 Probability of a well appearing individual at 24 hours age (base case) not having CCHD

An individual without CCHD at 24 hours of age was designated in this (only other) alternate health state, yielding **a point estimate probability value of 0.9996**. A Monte-Carlo simulation with beta-distribution was run (1000 samples) to estimate the range of 0.9991 to 0.9999.

4.1.2 Transitional Probabilities – Mortality

A detailed literature search was conducted on MEDLINE with the help of a reference librarian (Ms. Laura Banfield, Health Sciences Library, McMaster University) for mortality related to CCHD (**Appendix C**). There were 3,267 records identified from this search (after elimination of duplicate records). After screening titles and abstracts, 115 records were reviewed in detail for data on short-term mortality related to CCHD (within 1st month of life). For long-

term mortality rates associated with CCHD (beyond first month of life), 158 records were reviewed in detail. After eliminating Non-Western European/Non-North American studies, studies related to specific lesions/procedures, review articles, case reports (or series with < 100 patients), and studies deemed not relevant including those that did not provide raw data of mortality or survival rates, a final of 23 articles provided data for short-term mortality, whereas 18 articles provided data for long-term mortality.

4.1.2.1 Probability of Early Mortality (1st month) if individual has CCHD

From the search strategy outlined in **Appendix C**, 23 articles (47-68) were included in the analysis to determine the point estimate of the probability of early mortality with CCHD. Data from these studies (individual proportions) were meta-analyzed using a binary random effects model (Meta-Analyst Software, Brown University, USA), yielding **a probability point estimate of 0.081** (with a 95% confidence interval of 0.064 to 0.097), as shown in **Figure 4.1** below.

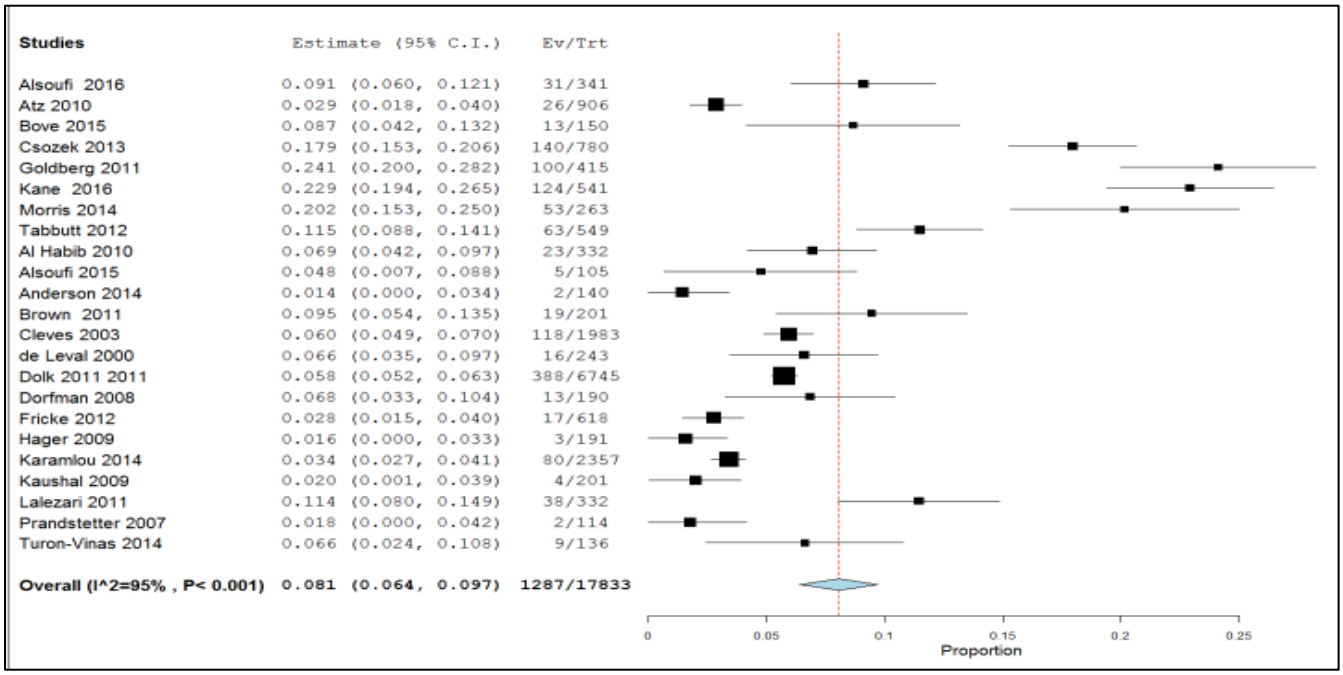

Figure 4.1: Forest plot of proportions of early mortality with CCHD

4.1.2.2 Relative Risk of Early Mortality (1st month) if CCHD is detected late

The search strategy for mortality and complications did not yield any suitable records for this variable. Therefore, the following targeted search strategy was conducted on MEDLINE on August 2, 2017: "mortality"[Title/Abstract] AND "congenital heart disease"[Title/Abstract] AND "hospitalization"[Title/Abstract] AND "late"[Title/Abstract]. This search yielded 5 articles, only 1 of which (Peterson et al. 2013)(69) was reviewed in detail (full text) after screening of titles and abstracts. In this study, the mortality rate with early detection (prior to initial hospital discharge) was 20.4% whereas it was 8.0% with late detection. This was counter to the intuitive hypothesis, and is assumed to be due to the fact that more severe lesions were probably picked up clinically prior to discharge (and not in the scope of the base case our model is targeting), while the indolent and less severe lesions were discharged home, and likely to have less impact on mortality. Additionally, since the lesions detected prior to discharge home in this study were detected clinically, rather than detected via a screening program, it is once again not generalizable to our context. Hence this data was not used in the model. Based on author consensus, it was agreed that **a point estimate relative risk of neonatal mortality of 1.2** would be used for late identification of a CCHD (with an estimated range of 1 to 2).

4.1.2.3 Probability of all-cause neonatal (1st month) mortality

This data was obtained from Statistics Canada report (70) on mortality (2011) when there were 492 neonatal deaths in Ontario out of 140,652 births, **yielding a probability of 0.0035**. Because some neonatal mortality in our model is expected to include undiagnosed CCHD cases, and also due to the relatively low burden of CCHD as a cause of mortality compared to all causes, we did not alter this number. Using a Monte-Carlo simulation with beta distribution, a 2.5% to 97.5% range of 0.0032 to 0.0038 was estimated.

4.1.2.4 Probability of a home death (1st month) if have CCHD

The following targeted search strategy was conducted on MEDLINE on August 3, 2017: "mortality"[Title/Abstract] AND "home"[Title/Abstract] AND "missed"[Title/Abstract] AND "congenital heart disease"[Title/Abstract]. This search yielded only 1 article (de-Wahl Granelli et al 2009),(24) in which study 4 out of 18 patients who were discharged with a missed CCHD died at home, **yielding a probability of 0.222**. A Monte-Carlo simulation with beta distribution resulted in an estimated range of 2.5% to 97.5% of 0.074 to 0.422, this large range reflecting the small sample size in original data and thus large degree of uncertainty around this parameter.

4.1.2.5 Probability of death per cycle if individual does not have CCHD

The probabilities (annual) of mortality for all ages from 1 to 100 were obtained from Statistics Canada – data available at: http://www.statcan.gc.ca/pub/91-209-x/2013001/article/11867/fig/desc/desc04-eng.htm (accessed on August 1, 2017). The annual probabilities of mortality were converted to monthly probabilities of mortality by the following formula:

Monthly mortality = 1 – ([1 – (Average Annual Mortality Probability)]^(1/12))

Each point estimate was then multiplied by 0.5 and 1.5 to yield an estimate of the low and high ranges, respectively. For ages 7-10 years where the average monthly mortality rate was 0, the upper range for ages 6 and 11 were used. This data is shown in **Appendix D**.

4.1.2.6 Probability of death per cycle if individual is post-CCHD repair without any morbidity

From the detailed literature search for mortality as described above, 18 articles provided data for long-term mortality rates related to CCHD.(49, 58, 62, 67, 68, 71-83) Detailed characteristics and outcome data from these studies are as shown in **Table 4.1** below.

Table 4.1: Characteristics of studies reporting on long-term mortality associated with CCHD

Author, year	Age at assessment	CCHD Lesion	Survival Rate
Alexiou 2002	10 years	TOF	155/160 (97%)
Amark 2006	10 years	PA+VSD	131/185 (71%)
Bove 2015	1 year	Various	137/150 (91.3%)
Brown 2003	8 years	AoS	449/468 (96%)
Cleves 2003	1 year	Various	1749/1865 (93.8%)
Cross 2014	1 year	HLHS	224/247 (90.7%)
Daubeney 2005	5 years	PA-IVS	107/168 (63.8%)
Dyamenahalli 2004	5 years	PA-IVS	141/210 (67%)
Fixler 2010	5 years	Various	599/1007 (59.4%)
Frike 2012	10 years	TGA	612/618 (99.1%)
Ghanayem 2012	1 year	HLHS	376/426 (88.3%)
Hirsch 2011	1 year	HLHS	231/406 (57%)
Lee 2014	18 years	CoA	158/170 (93%)
Losay 2001	15 years	TGA	1056/1200 (88%)
Oster 2013	1 year	Various	830/1007 (82.5%)
Prandstetter 2007	2 years	TGA	113/114 (99.1%)
Turon-Vinas 2014	6 years	TGA	114/126 (90.4%)
Wong 2008	15 years	TGA/DORV	202/244 (83%)

Studies that reported on probability of survival at 1 year's age were meta-analyzed together, resulting in a pooled point estimate probability of survival of 0.84 (95% CI 0.76 to 0.92), as shown in **Figure 4.2** below. This was converted to monthly probability of survival over 2-12 months of life (excluding neonatal mortality period which was already ascertained previously), by solving for X in the following equation $X^{11} = 0.84$. This yielded a monthly probability of survival of 0.984. Similar calculations were performed for the 95% CIs, yielding 0.975 to 0.992. Finally, these values were converted to monthly probabilities of mortality (by subtracting from 1) yielding final point estimates and 95% CIs over months 2-12 of: **0.016 (95% CI: 0.008 to 0.025)**.

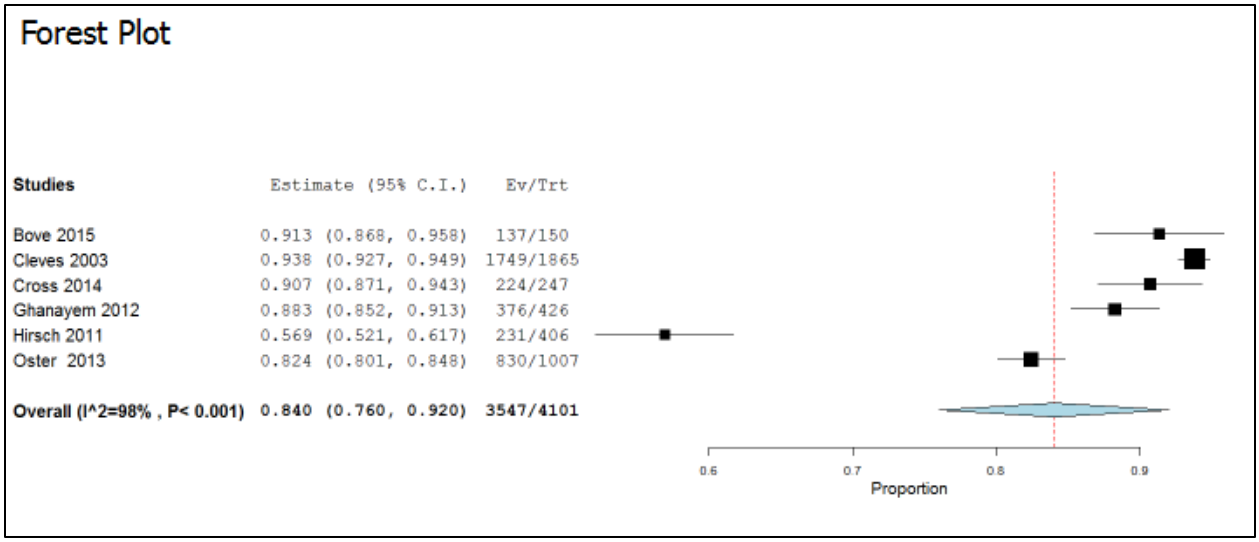

Figure 4.2: Forest plot of studies reporting on survival associated with CCHD in 1st year of life

The remaining 12 studies that reported on survival rates beyond 1 year of age were pooled separately, as shown in **Figure 4.3** below, yielding a pooled point estimate of survival of 0.842 (95% CI 0.780 to 0.905). A similar procedure described for conversion to monthly mortality as for months 2-12 was performed, assuming a constant cumulative mortality rate from age 1 to 18 years (17 years x 12 months = 204 months). A similar process as described earlier was used to derive estimates of monthly mortality rates and 95% CI, yielding transitional monthly probabilities of death of **0.00085 (95% CI 0.00049 to 0.00122)**. Although there was scarcity of data that fit the criteria for study inclusion beyond age 18 years, it was assumed that a similar rate of mortality would continue beyond 18 years' age.

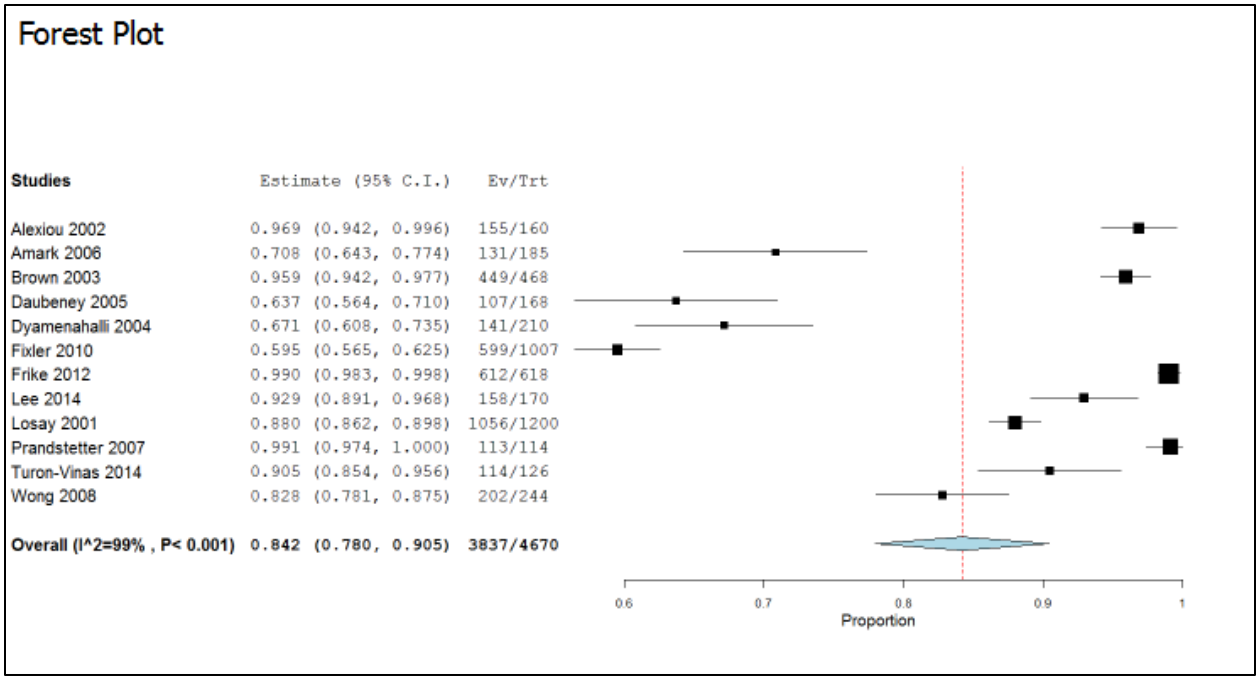

Figure 4.3: Forest plot of studies reporting on survival associated with CCHD beyond the 1st year of life

4.1.2.7 Probability of death per cycle if individual is post-CCHD repair with morbidity

No data specific to this health state transition was available from the detailed literature search. It was assumed that some individuals in the studies for mortality rates indeed had CCHD associated morbidity. As such, the same probability estimates as for the probability of death per cycle for individuals post-CCHD repair without morbidity were used for this set of transitional probabilities, although acknowledged that in reality it may be higher.

4.1.3 Transitional Probabilities - Morbidity

A detailed literature search was conducted on MEDLINE with the help of a reference librarian (Ms. Laura Banfield, Health Sciences Library, McMaster University) for morbidity related to CCHD (**Appendix E**). This search yielded 1,500 articles after exclusion of duplicates, and after initial screen of titles and abstracts, 24 articles were evaluated in detail (full text). Out of these, 7 articles met pre-defined eligibility criteria (after exclusion of studies that were Non-Western Europe/Non-North American in origin, studies that related to a very specific

lesion/procedure, case/report or series of < 100 subjects, or articles deemed not relevant). The 7 articles, their characteristics and outcomes are as listed in **Table 4.2** below.(84-90)

Table 4.2: Study characteristics and data for morbidity related to CCHD

Author, Year	Age Range	CCHD Lesion	Morbidity Evaluation	Morbidity Probability
Bellinger 2003	8 years	D-TGA	Wechsler IQ > 2SD below norm	5/155 (3%)
Bellinger 2011	16 years	D-TGA	Executive function above cut-off for clinical concern (by parental report) using BRIEF tool	32/139 (23%)
Fuller 2010	4 years	Various	Wechsler IQ > 2SD below norm	26/235 (11.1%)
Gaynor 2007	1 year	Various	Bayley MDI > 2SD below norm	17/188 (9%)
Jonas 2003	1 year	Various	Bayley MDI > 2SD below norm	6/112 (5.4%)
Neuberger 2008	1 year	Various	Bayley MDI > 2 SD below norm	2/104 (1.9%)
Wernovsky 2000	11 years	HLHS	Weshcler IQ > 2SD below norm	10/128 (7.8%)

Abbreviations: D-TGA – dextro-transposition of the great arteries; HLHS – hypoplastic left heart syndrome

4.1.3.1 Probability of Early Morbidity (1st month) if individual has CCHD

The 3 studies reporting on probabilities morbidity over the first year were meta-analyzed using Meta-Analyst software (Brown University, USA), which yielded a pooled probability estimate of 0.052 (95% CI 0.009-0.095), as shown in **Figure 4.4**. This was taken to be the probability at the 1 year mark, which was then converted to monthly probabilities by solving for X in the following equation $X^{12} = 1.052$. **This yielded a monthly probability of developing CCHD associated morbidity of 0.00423** over the first year of life. Similarly, the monthly 95% CIs for the probabilities were estimated to be 0.000747 to 0.00759. These transitional probability values were used for the first month, as well as the subsequent 11 months of life.

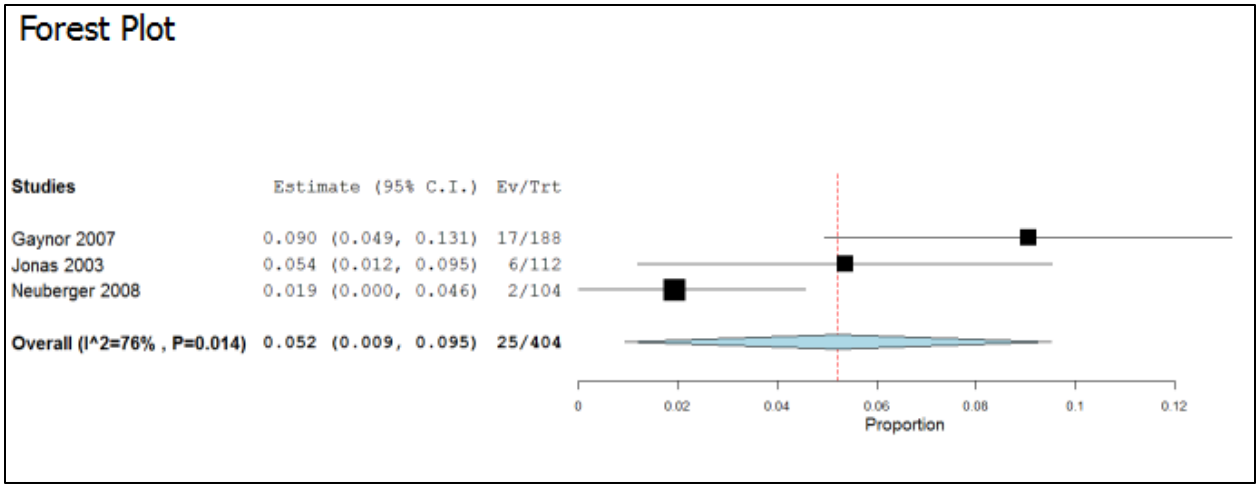

Figure 4.4: Forest plot of pooled estimate of CCHD associated morbidity at 1 year of age

4.1.3.2 Relative Risk of Early Morbidity (1st month) if CCHD is detected late

None of the articles included from the detailed search addressed increase in morbidity based on late detection of CCHD. Therefore, a targeted search on MEDLINE was conducted on September 7, 2017 using the following search terms: "morbidity"[Title/Abstract] AND "congenital heart disease"[Title/Abstract] AND "hospitalization"[Title/Abstract] AND "late"[Title/Abstract]. This search yielded 2 articles, neither of which were relevant based on review of titles and abstracts. As such, **a relative risk of 1.2** was assumed after consensus amongst authors, with an estimated range of 1 to 2.

4.1.3.3 Probability of an individual post-CCHD repair without morbidity developing CCHD-associated morbidity

The probabilities of morbidity related to CCHD from remaining 4 studies identified in **Table 4.2** above were similarly meta-analyzed to yield an overall pooled point estimate probability of 0.107 (95% CI 0.039 to 0.176), as shown in **Figure 4.5**. This probability was assumed to represent a cumulative occurrence over ages 1 year to 16 years (representing 15 x 12 = 180 months). This pooled probability was then converted to monthly probabilities by solving

the following for X: $X^{180} = 1.107$, yielding **monthly probability of CCHD associated morbidity of 0.000564**. Similar conversion of the 95% CIs yielded a range of 0.000213 to 0.000901. There probability estimates were used until age 16. After that stage no data were available. It was assumed and agreed upon by authors based on consensus that development of new morbidities after that age would be exceedingly rare, and as such, probability values of 0 were used thereafter.

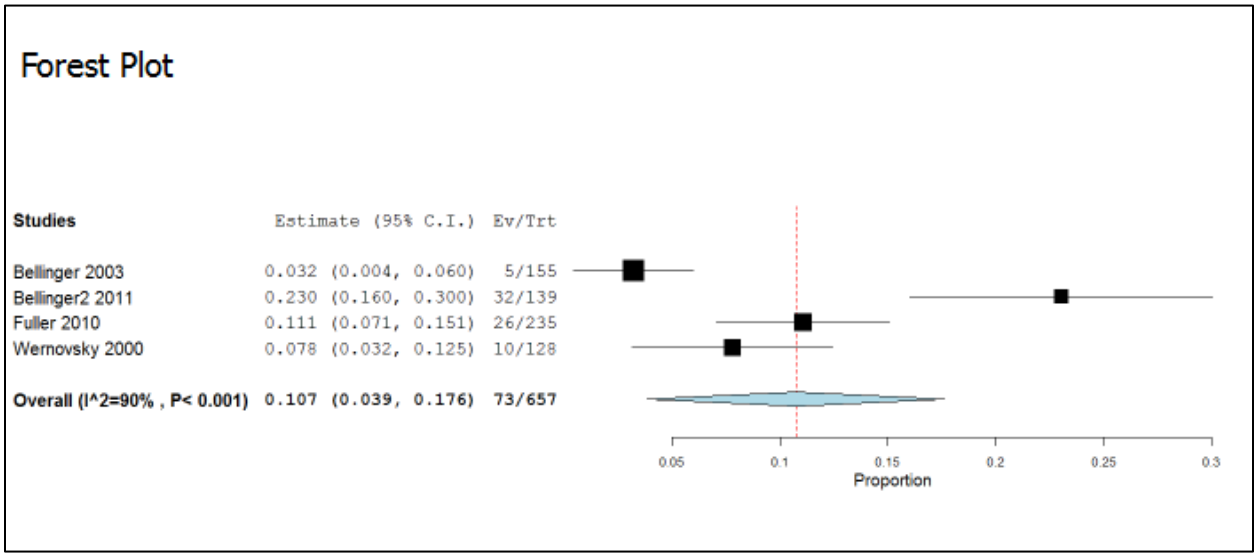

Figure 4.5: Forest plot of pooled estimate of CCHD associated morbidity at ages 1-16 years

4.1.4 Population Distribution and Levels of Care

4.1.4.1 Probability that an individual patient will deliver at a level 1 facility

A customized request was made to Better Outcomes Registry & Network (BORN) Ontario whereby all deliveries in Ontario between April 1, 2012 and March 31, 2015 categorized by level of care were provided. Out of 422,939 Ontario deliveries in this time period, 46,858 occurred at level 1 facilities, **yielding a probability of 0.111**. A Monte-Carlo simulation with beta-distribution (1000 samples) yielded a 2.5% to 97.5% range of 0.109 to 0.112.

4.1.4.2 Probability that an individual in level 2 or level 3 catchment area delivers at a level 2 facility

A customized request was made to BORN Ontario whereby all deliveries in Ontario between April 1, 2012 and March 31, 2015 categorized by level of care were provided. There were 291,492 births in level 2 facilities while there were 72,487 births at a level 3 facility, **yielding a probability of 0.801** (291,491/[291,491+72,487]). A Monte-Carlo simulation with beta-distribution yielded a 2.5% to 97.5% range of 0.800 to 0.802.

4.1.4.3 Probability that an individual patient's home hospital is a level 3 facility

A customized request was made to BORN Ontario whereby all deliveries in Ontario between April 1, 2012 and March 31, 2015 categorized by level of care were provided. There were 72,487 births at a level 3 facility, out of a total of 422,939 Ontario births, **yielding a probability of 0.171** (72,487/422,939). A Monte-Carlo simulation with beta-distribution yielded a 2.5% to 97.5% range of 0.170 to 0.172.

4.1.4.4 Probability that an individual belongs to SickKids LHIN

This data was extracted from the BORN Ontario annual reports from 2012-2013 and 2013-2014. All births in Ontario were categorized by LHIN in these reports. LHINs 5, 7, 8, 9, 12 are served completely by SickKids region, while LHINs 6 and 13 are shared with another centre; for the latter it was assumed that half the deliveries belonged to the SickKids region. After eliminating individuals with missing data, there were 276,393 births in Ontario registered in BORN, out of which 143,132 deliveries occurred in the SickKids catchment area, yielding **a probability of being born in SickKids region of 0.518**. A Monte-Carlo beta distribution simulation yielded a range of 0.516 to 0.520.

4.1.4.5 Probability that an individual patient is from the Northern region that requires air transport

It was assumed that a patient born in LHINs 13 or 14 would require air transport due to the remote nature of these locations and distance from the nearest level 3 facility. As such, from the BORN Ontario annual reports for 2012/2013 and 2013/2014, all deliveries in these 2 LHINs (15,809) were divided by the total number of births in Ontario (276,393, after eliminating births with unknown LHIN). This yielded **a probability of 0.0572**, with a 2.5% to 97.5% range of 0.0564 to 0.0581 by way of Monte-Carlo simulation using beta distribution (1000 samples).

4.1.5 Techniques and Detection Rates

4.1.5.1 Probability that a level 2 facility has pediatric echocardiography capability

For each level 3 neonatal intensive care unit, the proportion of their regional level 2 nurseries with the capability to perform pediatric echocardiograms was ascertained by way of personal communication (McMaster University: Dr. Michael Marrin, Transport Director, Neonatology; University of Ottawa: Dr. Stephanie Redpath, Transport Director, Neonatology; Western University: Dr. Henry Roukema, Transport Director, Neonatology; University of Toronto: Dr. Catalina Tomayo, Former Clinical Fellow, Pediatric Cardiology). It was estimated that 9 out of the 41 level 2 facilities have access to pediatric cardiology and echocardiogram (albeit not 24/7 coverage). This yielded **a probability of 0.22** and a Monte-Carlo simulation with beta-distribution yielded and 2.5% to 97.5% range of 0.11 to 0.34.

4.1.5.2 Probability of a false negative echocardiogram result at a level 3 facility

The following search strategy was conducted on MEDLINE on July 15, 2017: "congenital heart"[Ti] AND ("echocardiography"[All Fields] OR "echocardiogram"[All Fields]) AND ("accuracy"[All Fields] OR "sensitivity"[All Fields] OR "precision"[All Fields] OR

"miss*"[All Fields]). This search yielded 259 articles, and after screening of titles/abstracts – 3 were reviewed in detail and 2 were included.(91, 92) Combining data from these studies, it was noted that out of 147,098 cases – there were 221 missed cases, **yielding a probability of 0.0015**. The missed cases were identified by way of "sources of diagnostic error case discovery included information obtained from other tests (e.g., cardiac catheterization, magnetic resonance imaging), operative observations, subsequent echocardiographic examinations, and autopsy" in the former and "(1) results of subsequent imaging tests, consisting of either repeat echocardiograms or cardiac MRI; (2) cardiac catheterization; (3) surgery; (4) clinical follow-up; and (5) autopsy" in the latter study. A Monte-Carlo simulation with beta-distribution yielded a 2.5% to 97.5% range of 0.0013 to 0.0017.

4.1.5.3 Probability of a false negative echocardiogram result at a level 2 facility

No such data specifically for level 2 pediatric echocardiograms were available in the aforementioned literature search (which was not specific to level of care of facility). It was assumed that the false negative rate would be similar at a level 2 facility and similar values as for level 3 facilities were used in the model.

4.1.5.4 Probability of a false positive echocardiogram result at a level 3 facility

A MEDLINE search was conducted on July 15, 2017 using the following strategy: "congenital heart"[Ti] AND ("echocardiography"[All Fields] OR "echocardiogram"[All Fields]) AND "false positive"[All Fields]. This search yielded 43 articles; however, after review of titles/abstracts, none of them were suitable for the specific question. After discussion amongst authors, it was agreed that a **probability of 0 for a false positive echocardiogram for CCHD at a level 3 facility** would be a reasonable estimate, with a proposed range of 0 to 0.0001.

4.1.5.5 Probability of a false positive echocardiogram result at a level 2 facility

As for level 3 false positives, no data was found for level 2 false positive rates for CCHD. After extensive discussion amongst committee members, **a point estimate of 0.05** was chosen with a range of 0 to 0.1 (this was largely based on the collective anecdotal experience of committee members, most of whom are neonatologists who receive such calls from level 2 facilities).

4.1.5.6 Probability of POS occurring with MOH approval

No Ontario-specific data were available for this parameter, as POS has not yet been implemented. It was agreed upon by the authors to use **a point estimate probability of 0.98** (with an assumed range of 0.95 to 1.0) of POS occurring for any individual baby if POS for CCHD is approved by the ministry of health in Ontario.

4.1.5.7 Probability of POS occurring without MOH approval

Similarly, it was assumed that an individual patient would have **a probability of 0.05** (with an estimated range of 0 to 0.1) of receiving POS, if the screening were not to be approved by the ministry of health.

4.1.5.8 Probability of a POS screen being positive if individual has CCHD

The following targeted search was conducted on MEDLINE (July 20, 2017): ("pulse oximetry screening"[Title/Abstract]) AND ("congenital heart"[Title/Abstract] OR "cardiac disorder"[Title/Abstract]), which yielded 115 articles. After screening of titles and abstracts, the following 21 articles (listed in **Table 4.3**) were included to provide data on true positives as well as false positive results, to provide estimates of overall accuracy of POS screening.(20-24, 31, 93-104)

Table 4.3: Studies reporting on accuracy of pulse oximetry screen for CCHD

Study Name	How was a positive screen determined?	True Pos	False Pos	False Neg	True Neg	Disease N	Disease Free N
Bhola 2014	Post-ductal saturation < 95% on two readings (second reading only if necessary at least 1-2 hours later); or if < 90% at any time	4	11	0	18786	4	18797
Ewer 2011	Saturation < 95% or and pre-post gradient > 2%; followed by expedited physical exam. If abnormal → confirmed positive, if exam normal → repeat test with same criteria 1-2 hours later and if still same results → confirmed positive	18	177	6	19854	24	20031
Koppel 2003	Any SpO_2 < 95% → followed by ECHO	3	1	2	11275	5	11276
Meberg 2008	SpO_2 < 95% x 2 or after 1st if obvious clinical signs (repeated once 2-3 hours later if needed)	27	297	8	49676	35	49973
Bakr 2005	SpO_2 < 90% (1 reading) → followed by ECHO. 90 to < 94% repeated thrice → ECHO	3	2	0	5206	3	5208
Arlettaz 2006	SpO_2 < 90% → ECHO, if 90 to < 95% - repeat 4-6 hours later and if still < 95% → ECHO	12	12	0	3238	12	3250
Sendelbach 2008	< 96% → repeated after repositioning probe and warming up foot - if still < 96% → ECHO	1	24	0	15208	1	15232
Reich 2003	< 95% → repeated contra-diaphragm x 2 if between90 to 94 and if persisted → ECHO. ECHO also if single reading < 90% and if > 4% difference in contra-diaphragmatic values	0	4	0	2110	0	2114

Rosati 2005	≤ 95% at > 24 hours → ECHO	2	1	1	5288	3	5289
Richmond 2002	< 95% → clinical exam (if normal, SpO_2 repeated 1-2 hours later) if either exam or repeat SpO_2 abnormal → ECHO	8	56	1	5561	9	5617
de Wahl Granelli 2009	< 95% in both pre and postductal or > 3% gradient → repeated thrice. If < 90% any time → ECHO	19	68	10	39724	29	39792
Riede 2010	≤ 95% → repeated once 1-2 hours later → then ECHO	14	40	4	41384	18	41424
Kawalec 2006	Unknown	7	13	1	27179	8	27192
Hoke 2002	7% or more gradient, OR postductal SpO_2 < 92%	4	53	0	2819	4	2872
Kochilas 2013	If SpO_2 < 90 either site → fail; if between 90-94 or arm-foot gradient > 3: repeat → if still same → fail	1	5	0	7543	1	7548
Ruangritnamchai 2007	If SpO_2 < 95% → ECHO	3	0	0	1844	3	1844
Singh 2014	If SpO_2 < 95% in either limb, or difference > 2% between limbs → clinical exam and if normal → repeated. It still same findings or initial clinical exam abnormal → admitted to NICU for detailed assessment	9	199	6	25584	15	25783
Tautz 2010	If between 90-94% → repeat 4-6 h later and if still abnormal → ECHO. If initial < 90% → immediate ECHO	9	9	2	3344	11	3353

Turska-Kmiec 2012	If SpO_2 < 95%, repeated after 1 h → if persisted → standard protocol for suspected congenital heart disease (saturation measurement on upper extremity, hyperoxia test)	15	14	4	51665	19	51679
Zhao 2014	If any SpO_2 measurement < 90%; if between 90-94% on both separated by 4 hours (repeat measurement) or greater that 3% difference (also repeated, separated by 4 hours)	136	3446	10	117115	146	120561
Zuppa 2014	If 2 measurements < 95% (15-30 min apart) → EKG and ECHO	75	226	9	151	84	377
OVERALL		**295**	**4432**	**55**	**454403**	**350**	**458835**

Abbreviations: CCHD – critical congenital heart disease; ECHO – echocardiogram; EKG – electrocardiogram; SpO_2 – oxygen saturation

Based on the overall numbers from the studies listed in **Table 4.3**, the probability of POS being positive if an individual has CCHD was determined by dividing the true positive number (295) by total number of CCHD cases included in these studies (350) to yield **a probability of 0.843**. A Monte-Carlo simulation with beta distribution yielded a 2.5% to 97.5% range of 0.802 to 0.878.

4.1.5.9 Probability of a POS screen being positive if individual does not have CCHD

From the data in **Table 4.3** above, this probability was determined by dividing the false positives (4,432) by the number of individuals without CCHD (458,835) to **yield a probability of 0.00966**, and 2.5% to 97.5% range of 0.00940 to 0.00994.

4.1.6 Summary of all probabilities and their ranges

Table 4.4: All probability variables used in the mode with point estimates and ranges

Variable	Point estimate	Low Range	High Range
Probability of a well appearing individual at 24 hours age (base case) having CCHD*	0.0004	0.0001	0.0009
Probability of a well appearing individual at 24 hours age (base case) not having CCHD*	**0.9996**	0.9991	0.9999
Probability of a well appearing individual at 24 hours age (base case) being dead	0	0	0
Probability of a well appearing individual at 24 hours age (base case) being post-CCHD with morbidity	0	0	0
Probability of a well appearing individual at 24 hours age (base case) being post-CCHD without morbidity	0	0	0
Probability of a well appearing individual at 24 hours age (base case) being non-CCHD (> 1 month)	0	0	0
Probability of early mortality (1st month) if individual has CCHD*	**0.081**	0.064	0.097

Relative Risk of early mortality (1st month) if CCHD is detected late*†	1.2	1	2
Probability of non-CCHD related neonatal (1st month) mortality*	**0.0035**	0.0032	0.0038
Probability of a home death (1st month) if have CCHD*	**0.22**	0.074	0.422
Probability of death per cycle if individual does not have CCHD	As shown in **Appendix C**		
Probability of death per cycle if individual is post-CCHD repair without any morbidity			
Year 1	**0.016**	**0.008**	**0.025**
Subsequent years	**0.00085**	**0.00049**	**0.00122**
Probability of death per cycle if individual is post-CCHD repair with morbidity			
Year 1	**0.016**	**0.008**	**0.025**
Subsequent years	**0.00085**	**0.00049**	**0.00122**
Probability of early morbidity (1st month) if individual has CCHD*	**0.00423**	0.000747	0.00759
Relative Risk of early morbidity (1st month) if CCHD is detected late*†	1.2	1	2
Probability of an individual post-CCHD repair without morbidity developing CCHD-associated morbidity			
Year 1	**0.00423**	0.000747	0.00759
Years 2-16	**0.000564**	0.000213	0.000901
Years 17 and above	0	0	0
Probability that an individual patient will deliver at a level 1 facility*	**0.111**	0.109	0.112
Probability that an individual in level 2 or level 3 catchment area delivers at a level 2 facility*	0.801	0.800	0.802
Probability that an individual patient's home hospital is a level 3 facility*	0.171	0.170	0.172

Probability that an individual belongs to SickKids LHIN*	0.518	0.516	0.520
Probability that an individual patient is from the Northern region that requires air transport*	**0.0572**	0.0564	0.0581
Probability that a level 2 facility has pediatric echocardiography capability*	0.22	0.11	0.34
Probability of a false negative echocardiogram result at a level 3 facility*	**0.0015**	0.0013	0.0017
Probability of a false negative echocardiogram result at a level 2 facility*	**0.0015**	0.0013	0.0017
Probability of a false positive echocardiogram result at a level 3 facility†	0	0	0.0001
Probability of a false positive echocardiogram result at a level 2 facility*†	**0.05**	0	0.1
Probability of POS occurring with MOH approval*†	**0.98**	0.95	1
Probability of POS occurring without MOH approval*†	0.05	0	0.1
Probability of a POS screen being positive if individual has CCHD*	**0.843**	0.802	0.878
Probability of a POS screen being positive if individual does not have CCHD*	**0.00966**	0.00940	0.00994

Abbreviations: CCHD – critical congenital heart disease; LHIN – local health integrated network; MOH – Ministry of Health; POS – pulse oximetry screening
*Variables included in probabilistic sensitivity analysis
†Variables for which point estimate and ranges were estimated by author consensus

4.2 Utility variables

4.2.1 Utilities associated with health states

Utilities (quality of life indicator) for the following mutually exclusive health states were ascertained for use in the model.

4.2.1.1 Utility of CCHD

The utility of CCHD referred to that of the first month of life of an individual with CCHD. The search strategy, screening and determination of point estimates and ranges were the same as for "Utility of CCHD post-repair without morbidity" – as such, please refer to Section 4.2.1.3 for details.

4.2.1.2 Utility of No CCHD

The utility of a no CCHD health state was assumed to be 1, and no further formal literature search was conducted.

4.2.1.3 Utility of CCHD post repair without morbidity

This utility referred to quality of life living with CCHD following repair without any additional morbidity. Note that the same search strategy and determination of point estimates was conducted for utility for CCHD in the first month of life. A comprehensive literature search was conducted on MEDLINE with help of a reference librarian (Ms. Laura Banfield, Health Sciences Library, McMaster University). The search strategy (conducted on September 15, 2016) is shown in **Appendix F**.

The search strategy for CCHD yielded 1,451 studies, of which 82 were screened in after review of titles and abstracts. Of these, 10 studies were ultimately included.(105-114) Reasons for exclusion were (a) lack of relevance (no utility data); (b) review article (without utility data); (c) relating to a very specific (or minor CHD), surgery, therapy, assessment tool; (d) Non-English article, or non-North America/non-Western European source; (e) surgery or disease onset in adulthood (mean/median age 30 years or higher); (f) studies with repeat patients already assessed previously (whether excluded or included); (g) lack of control group/data; and (h) other miscellaneous reasons (including studies with fewer than 20 patients).

Of the 10 included studies, 3 provided data for the pediatric age range (< 16 years' age) while 5 studies provided data only for adult age range (≥ 16 years' age). Two studies provided extractable such data for both age ranges. The details of studies contributing to these two age ranges are as shown in **Tables 4.5 and 4.6** below, including age range of subjects, tool used to assess quality of life and CCHD lesions involved. Quality scores relating to mental and physical health (or closest equivalent based on tool used in study) were gathered, and general health scores – when available – were also taken.

Table 4.5: Studies contributing utility for CCHD post-repair without morbidity (age < 16 years)

					CCHD			**Control**		
Author Year	**Age Range (years)**	**Tool**	**Lesion**	**Measure**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
Culbert 2003	12-14	CHQ	TGA repair	Physical	306	93.2	11.3	354	88.8	14
				General Health	306	74.6	16.4	354	66.4	14.6
				Mental Health	306	78.7	13.8	354	72.7	16
				SUMMARY	**306**	**82.17**	**13.99**	**354**	**75.97**	**14.89**
de Koning 2008	8-15	TACQOL	TGA repaired	Motor functioning	31	27.6	4.3	2330	29.8	3.2
				Cognitive function	31	27.4	4.6	2330	28	4.1
				SUMMARY	**31**	**27.5**	**4.45**	**2330**	**28.9**	**3.68**
Frigiola 2014	4-18	PedsQOL	TOF repaired	Total	15	78.4	10.3	1399	82.3	13.1
				SUMMARY	**15**	**78.4**	**10.3**	**1399**	**82.3**	**13.1**
Idorn 2013	5-9	PedsQL	Univen-tricular lesion	Physical Health	37	75	5.5	24	97.5	1.7
				Psychosocial health	37	65	4.3	24	92.3	3.2
				SUMMARY	**34**	**70**	**4.94**	**866**	**94.9**	**2.56**
	10-15	PedsQL	Univen-tricular lesion	Physical Health	56	83	6.6	34	97	1.7

				Psychosocial health	56	80	6.3	34	92	2.9
				SUMMARY	**34**	**81.5**	**6.45**	**866**	**94.5**	**2.38**
Neal 2015	13-16	CHQ	TOF repair	Psychosocial	66	50.9	9.4	85	57.2	4.2
				Physical	66	49.4	9.5	85	55.8	4.9
				SUMMARY	**66**	**50.15**	**9.45**	**85**	**56.5**	**4.56**

Abbreviations: CHQ – child health questionnaire; PedsQL – Pediatric quality of life scale; TACQOL – TNO-AZL child quality of life; TGA – transposition of the great arteries; TOF – tetralogy of fallot

Table 4.6: Studies contributing utility for CCHD post-repair without morbidity (age ≥ 16 years)

					CCHD			**Control**		
Author Year	**Age Range (years)**	**Tool**	**Lesion**	**Measure**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
Bygstad 2012	18-60	SF-36	TOF repaired	Male Physical	55	54	5	32	58	5
				Male Mental	55	53	6	32	50	8
				SUMMARY	**55**	**53.5**	**5.52**	**32**	**54**	**6.67**
Cotts 2012	26-58	SF-36	TGA	Physical component summary	25	49.5	9.2	25	49.3	10.1
				Mental component summary	25	47.5	11.5	25	51.3	11.8
				SUMMARY	**25**	**48.5**	**10.41**	**25**	**50.3**	**10.98**
Daliento 2005	28-36	SF-36	TOF repaired	Physical	54	84.29	17.19	54	94.75	13.18
				General Health	54	67.27	20.27	54	75.78	16.14
				Mental Health	54	73.74	16.45	54	72.72	16.97
				SUMMARY	**54**	**75.1**	**18.05**	**54**	**81.08**	**15.52**
Dulfer 2014	16-25	SF-36	TOF/Single ventricle	Physical functioning	20	93.8	5.8	1742	93.1	11.8
				General health	20	72.8	10.5	1742	78.2	17.3
				Mental health	20	85.3	6.1	1742	78.7	15.2
				SUMMARY	**20**	**83.97**	**7.77**	**1742**	**83.33**	**14.94**
				Physical functioning	11	95	2.9	1742	93.1	11.8

				General health	11	65	5.8	1742	78.2	17.3
				Mental health	11	83	8.1	1742	78.7	15.2
				SUMMARY	**11**	**81**	**5.99**	**1742**	**83.33**	**14.94**
Frigiola 2014	19-57	WHOQOL	TOF repaired	Physical	34	83.9	17	866	82.6	3.4
				Psychosocial	34	75.5	13.6	866	72.8	1.7
				SUMMARY	**34**	**79.7**	**15.39**	**866**	**77.7**	**2.69**
Idorn 2013	>15	SF-36	Univen-tricular lesion	Physical component score	54	83	4.9	172	91.5	3.4
				Mental component score	54	86	7.2	172	83	5.2
				SUMMARY	**34**	**84.5**	**6.16**	**866**	**87.25**	**4.39**
Irtel 2005	16-62	RAND-36	TOF/TGA repair	TOF General health perception	35	82	19	594	76	18
				SUMMARY	**35**	**82**	**19**	**594**	**76**	**18**
				TGA General health perception	32	73	24	594	76	18
				SUMMARY	**32**	**73**	**24**	**594**	**76**	**18**

Abbreviations: SF-36 – short form-36 questionnaire; TGA – transposition of the great arteries; TOF – tetralogy of fallot; WHOQOL – world health organization quality of life scale

Where a study provided more than 1 component of utility – a "SUMMARY" utility score for that study was determined by taking the average of the individual score components. The standard deviations were combined using the following formula: $\mathrm{SD} = \sqrt{[\sum_{k=1}^{n}((\mathrm{SDk})\text{^}2)/\mathrm{n}]}$ where n is the number of individual component scores provided, to yield the standard deviation of the summary utility score for each study. Next these summary means and their standard deviations for the cases (CCHD) and controls/reference ranges from each study were meta-analyzed using the "ratio of means" technique, as described by Friedrich et al(115) to yield a composite ratio of utility values (with 95% confidence intervals) for CCHD post repair without

morbidity compared to controls (no CCHD). These values are shown in the summary **Table 4.8** below.

4.2.1.4 Utility of CCHD post repair with morbidity

For post-CCHD repair with morbidity, a targeted literature search on MEDLINE was conducted for childhood developmental disorder (representative of morbidity in post-CCHD repair) using the following search terms: ("neurodevelopmental impairment"[Title] OR "neurodevelopmental disorder"[Title] OR "developmental disorder"[Title] OR "neurological disorder"[Title] OR "neurological impairment"[Title] OR "mental retardation"[Title] OR "cognitive impairment"[Title]) AND (utility[Ti] OR quality[Ti]). The search strategy yielded 205 articles, and after initial screening based on article titles that eliminated studies that evaluated morbidity states with adult/late adult onset (n=15), studies on very specific populations where it was deemed that baseline measures of quality of life may already be low before adding on the effects of neurodevelopmental morbidity (n=52), and non-North American/non-Western European/non-Australasian studies (n=25), and studies deemed not relevant (n=94), 19 were evaluated in detail (full article). Of these 2 studies contributed utility data to adult age range,(116, 117) while 1 study contributed utility data for the pediatric age range.(118) The details of these studies are shown in **Table 4.7**.

Table 4.7: Studies contributing data towards utility of neurological morbidity

Author Year	Age Range	Condition	Tool	N	Mean	SD	N [Control]	Mean [Control]	SD [Control]
Adult Values									
Barrios 2012	70.8 years (6.2)	Mild Cognitive Impairment	QOL-AD Question-naire	50	32.1	6.9	50	35.3	4.9
				50*	27.2	6.7	50	35.6	4.9
			SUMMARY	**50**	**29.65**	**6.8**	**50**	**35.45**	**4.9**

Missotten 2008	83.72 years (7.04)	Mild cognitive impairment	ADRQL	**36**	**82.11**	**13.31**	**72**	**79.75**	**15.82**
Pediatric Values									
Srivastava 2007	2.2 years	Neurological Impairment with GERD (and fundo)	SF-36	**44**	**59.07**	**18.75**	**1000**	**71.95**	**20.34**

Abbreviations: ADQRL – alzheimer's disease related quality of life; GERD – gastroesophageal reflux disease; QOL-AD – quality of life – alzheimer's disease; SF-36 – short form-36 questionnaire
*Second 50 are "informants"

As before, the range of means meta-analysis technique described by Friedrich et al was utilized to determine the utility (and respective 95% confidence intervals) associated with neurological morbidity in both pediatric age as well as in adulthood.(115) Subsequently, these utility values were combined with the utility values for health state post-CCHD repair without morbidity (multiplying the two utilities and their respective 95% confidence intervals) to yield a composite utility for the health state of post-CCHD repair *with* morbidity. These final values are as shown in the summary **Table 4.8** below.

4.2.1.5 Utility of death

The utility of death was assumed to be 0, and no further formal literature search was conducted.

4.2.2 Summary table of utilities of health states

Table 4.8: Utilities associated with health states used in the model

Health State	Utility estimate	Minimum	Maximum
CCHD (1st month)*	0.875	0.869	0.881
No CCHD	1	1	1
Death	0	0	0
Post CCHD repair no morbidity			
< 16 years	0.875	0.869	0.881
≥ 16 years	0.983	0.975	0.991
Post CCHD repair with morbidity			

< 16 years	0.821	0.782	0.862
≥ 16 years	0.918	0.887	0.950

Abbreviations: CCHD – critical congenital heart disease
*Variable(s) included in probabilistic sensitivity analysis

4.2.3 Utilities unrelated to health states

In the model, 3 transitional "DIS-utilities" were included. These were (a) Disutility related to performing pulse oximetry screening; (b) Disutility related to transfer of patient to higher care level facility (e.g. if POS is positive); and (c) Disutility related to conduct of surgery for CCHD. These largely reflected "spillover" effect into the parents as well as their perception of the inconvenience/discomfort associated with the aforementioned interventions and their impact on the quality of life.

4.2.3.1 Disutility of having POS performed

The following search strategy was conducted on MEDLINE on July 15, 2017: ("utility"[Ti] OR "disutility"[Ti] OR "dis-utility"[Ti]) AND ("screening"[Ti] OR "pulse oximetry screening"[Ti] OR "oximetry screening"[Ti] OR "screen"[Ti]) AND "infant, newborn"[MeSH Terms]. The search strategy yielded 33 articles, and upon screening of titles (and abstracts when deemed needed) – **none** of the studies were relevant for inclusion. Given the lack of adequate data, a consensus was reached amongst authors to assume this transitional Disutility value to be -0.005 (with a range of -0.0075 and -0.0025).

4.2.3.2 Disutility of transfer (due to positive screen or for definitive surgical repair)

The following search strategy was conducted on MEDLINE on July 15, 2017: ("utility"[Ti] OR "disutility"[Ti] OR "dis-utility"[Ti]) AND ("transport"[Ti] OR "transfer"[Ti]) AND "infant, newborn"[MeSH Terms]. The search strategy yielded 2 articles, **neither** of which were relevant for inclusion. Given the lack of adequate data, a consensus was reached amongst

authors to assume this transitional Disutility value to be -0.05 (with a range of -0.075 and -0.025).

4.2.3.3 Disutility of having surgery

The following search strategy was conducted on MEDLINE on July 15, 2017: ("utility"[Ti] OR "disutility"[Ti] OR "dis-utility"[Ti]) AND ("surgery"[Ti] OR "surgical"[Ti] OR "operative"[Ti] OR "operation"[Ti]) AND ("infant, newborn"[MeSH Terms] OR "infant"[MeSH Terms]). The search strategy yielded 25 articles, and upon screening of titles (and abstracts when deemed needed) – **none** of the studies were relevant for inclusion. Given the lack of adequate data, a consensus was reached amongst authors to assume this transitional Disutility value to be 0, as no parent would conceivably relay a lower quality of state related directly to the conduct of a potentially life-saving surgery.

4.2.4 Summary of utilities unrelated to health states

The following **Table 4.9** summarizes the point estimates and ranges of Disutilities used in the model. The point estimates were used for the base case while the ranges were used to conduct individual one-way sensitivity analyses for each variable, where applicable.

Table 4.9: Estimates of Disutilities and ranges

Model Variable	Point Estimate	Minimum	Maximum
Disutility of POS*†	-0.005	-0.0075	-0.0025
Disutility of transfer*†	-0.05	-0.075	-0.025
Disutility of CCHD surgery†	0	0	0

Abbreviations: CCHD – critical congenital heart disease; POS – pulse oximetry screening

*Variable(s) included in probabilistic sensitivity analysis
†Variable(s) for which point estimates and ranges were estimated based on author consensus

4.3 Cost variables

4.3.1 Cost of health states

The following sections describe how the monthly costs for all the health states included in the model were obtained.

4.3.1.1 Cost of CCHD

The monthly cost of having CCHD in the first Markov cycle (i.e. the first month of life) was obtained from the Canadian Institute for Health Information's Financial Standards and Information department through a customized request. The acute typical inpatient **cost in the first month of life was $5,548.20**. No standard deviations were available, and therefore this cost was multiplied by 0.5 and 1.5 respectively, to yield the lower and upper limits of the estimates of the cost range.

4.3.1.2 Cost of no CCHD

This health state represents those individuals without CCHD. This monthly cost was obtained from the Canadian Institute for Health Information's National Health Expenditure Database: https://www.cihi.ca/en/national-health-expenditure-trends. For Ontario, the annual health expenditure was $6,144.45 yielding **a monthly cost of $512.03**. No standard deviations were available for the per capita health expenditure, therefore the final monthly cost was multiplies by 0.5 and 1.5 to estimate the lower and upper limits of the cost range, respectively.

4.3.1.3 Cost of CCHD post repair without morbidity

This health state represents individuals with CCHD who survived surgery and did not develop any long term morbidity. Ontario's Ministry of Health and Long Term Care (MOHLTC)

Ontario Case Costing Initiative (OCCI) tool (available at: https://hsim.health.gov.on.ca/hdbportal/) was used to determine annual average costs for case mix group labeled "Congenital Cardiac Disorder" for fiscal year 2010/2011 for *both* inpatient and ambulatory costs, with their respective standard deviations. Each of these costs was in turn provided by 3 age groups, as shown in the **Table 4.10** below.

Table 4.10: Inpatient and ambulatory costs for congenital cardiac disorders from OCCI

Age group (years)	IP Cost	IP Cost SD	AC Cost	AC Cost SD	Total Cost	Total Cost SD	Monthly Total Cost	Monthly Total Cost SD
0-17	6732	3486	908	1728	7640	2751.20	**636.67**	**229.27**
18-69	4184	2691	460	234	4644	1910	**387**	**159.17**
70+	4259	1015	n/a	n/a	4259	1015	**354.92**	**84.58**

Abbreviations: AC – ambulatory care; IP – inpatient; OCCI – Ontario Case Costing Initiative; SD – standard deviation

The total cost was determined by adding the inpatient and ambulatory costs and the total cost standard deviation was obtained by the following formula: Total Cost SD = $\sqrt{[((\text{IP Cost SD})^2 + (\text{AC Cost SD})^2)/2]}$. The total cost and the standard deviation were both divided by 12 to yield the monthly cost and monthly standard deviation, as shown in the Table. Finally, the monthly standard deviations were multiplied by two then subtracted from and added to the monthly cost to estimate the lower and upper limits of the cost ranges for each age group.

4.3.1.4 Cost of CCHD post repair with morbidity

This health state represents those individuals who have had CCHD repaired and are living with associated morbidity. For the purposes of this model, as described earlier, morbidity was limited to neurological morbidity and for the purposes of this cost estimate, Childhood/Adolescent Development Disorder (Case Mix Group 709) as defined by Canadian Institute for Health Information was used. Data was obtained through a customized request for

inpatient, day surgery and emergency visits related to this condition through the Financial Standards and Information Department of CIHI, yielding total monthly costs per individual in age groups similar to ones described above. These costs were added to the monthly costs of CCHD health state without morbidity to yield total monthly health costs. No standard deviations were available, and ranges were estimated by multiplying the point estimates for each age group by 0.5 and 1.5, as described above.

4.3.1.5 Cost of Death

The cost associated with this health state was assumed to be 0; no specific searches for cost estimates were conducted in this regard.

4.3.2 Summary table of costs of health states

The final point estimates and ranges of the costs of the aforementioned health states are as shown in **Table 4.11** below. The point estimates were used in the Markov model and the ranges were used to conduct individual one-way sensitivity analyses.

Table 4.11: Estimates of costs and ranges for health states used in Markov model

Health State	Monthly Cost Estimate ($)	Estimated Minimum ($)	Estimated Maximum ($)
CCHD (1st month)*	5,548.20	2,774.10	8,322.30
No CCHD*	512.03	256.02	768.06
CCHD post repair (no morbidity)			
0-17 years	636.67	178.13	1095.2
18-69 years	387	68.67	705.33
70 years and above	354.92	185.75	524.08
CCHD post-repair (with morbidity)			
0-17 years	1,716.70	858.35	2,575.06
18-69 years	1,301.60	650.80	1,952.39

70 years and above	1,363.71	681.86	2,045.57
Death	0	0	0

Abbreviations: CCHD – critical congenital heart disease
*Variable(s) used in probabilistic sensitivity analysis

4.3.3 Costs unrelated to health states

4.3.3.1 Cost of pulse oximetry screening

The cost of each time a screening is performed was estimated by the cost of the disposable components of measuring oxygen saturation. It was assumed that the saturation checks will occur simultaneously in upper and lower limbs. The cost of nursing time was not factored in due to the short time it takes to conduct the screening. The cost of disposable components of each saturation measurement was obtained from the Administrative coordinator at McMaster Children's Hospital (representing the Clinical Manager at the time, Ms. Lynda Aliberti – personal communication date April 10, 2017). The **final cost of each screening was estimated to be $34.00** ($17.00 per disposable unit x 2). The range was obtained by multiplying the estimate by 0.5 and 1.5 to obtain lower and upper limits.

4.3.3.2 Cost of performing echocardiogram

The cost of echocardiogram was obtained via personal communication by two independent sources (Ms. Amuna Yacob – Administrative Assistant, Division of Neonatology, University of Toronto – data obtained from Ms. Julie Alyssandratos-Amatuzio, Billing Clerk for the Department of Pediatrics, communication date March 22, 2017; as well as Dr. Tapas Mondal, Pediatric Cardiologist, McMaster Children's Hospital, personal communication date: April 4, 2017). The cost included technical/technician cost per echocardiogram ($117.60) as well as billing costs ($96.20) yielding a **total cost per echocardiogram of $213.80**. Range was estimated by multiplying the point estimate by 0.5 and 1.5.

4.3.3.3 Cost of surgery

The cost of performing surgery for CCHD was obtained through the MOHLTC's OCCI (available at: https://hsim.health.gov.on.ca/hdbportal/). A manual search for all procedures among inpatients in Ontario for fiscal year 2010/2011 was conducted and *any* procedure related to the repair of a critical congenital heart disease was selected. This yielded **a total cost of $28,940 per surgery** (with a minimum cost of $3,369 and a maximum cost of $126,904, which were used for the range of costs).

4.3.3.4 Cost of Transfer

The cost of land transport was estimated from local data at McMaster Children's Hospital (Hamilton, Ontario). The total budget for transport ($1,383,856) was divided by the number of transports (438 for 2015/2016 fiscal year) to yield an **average cost per land transport of $3,163** – which was then multiplied by 0.5 and 1.5 to yield the range of costs. All transports were assumed to be land transports for the purposes of this calculation due to the rarity of air transports at this centre (< 10 per year, personal communication Dr. Michael Marrin, Neonatologist, Neonatal Transport Director, McMaster Children's Hospital, communication date: September 5, 2017). In addition, the cost at McMaster was assumed to be representative of all land transports across the province.

Air transport costs were an estimate based on personal communication with Dr. Michael Castaldo, Neonatal Transport Director at British Columbia Children's Hospital – a centre where there is a heavy reliance on air transports, communication date: August 4, 2017). The average **cost per air transport was estimated to be $15,000** (with an estimated range of $10,000 to $20,000 per air transport).

4.3.4 Summary of costs unrelated to health states

The following **Table 4.12** summarizes all costs (and respective ranges) unrelated to health states that were used in the model.

Table 4.12: Estimates of costs and ranges unrelated to health states used in model

Model Variable	Cost Estimate ($)	Estimated Minimum ($)	Estimated Maximum ($)
Cost of Pulse Oximetry Screening*	34	17	51
Cost of Echocardiogram*	213.80	106.90	320.70
Cost of Surgery for CCHD*	28,940	3,369	126,904
Cost of Transport			
Land Transport*	3,163	1,582	4,745
Air Transport*†	15,000	10,000	20,000

Abbreviations: CCHD – critical congenital heart disease; POS – pulse oximetry screening
*Variable(s) included in probabilistic sensitivity analysis
†Variable(s) for which point estimates and ranges were estimated based on author consensus

5. RESULTS OF DECISION MODEL

5.1 Base case analysis

In our base case of a well appearing newborn, performing POS at 24 hours of life as a screening measure to detect CCHD was superior to a no screening strategy. There are approximately 150,000 births province-wide annually (Canadian Institute for Health Information; https://www.cihi.ca/en). Based on incidence of missed CCHD of 0.0004 and probability of POS detecting 0.843 of all CCHDs, it is estimated that an additional 51 cases of CCHD will be detected in a timely fashion annually (150,000 x 0.0004 x 0.843) with implementation of routine POS. As shown in **Table 5.1**, the incremental cost of performing POS was $27.27 per patient ($284,002.58 – $283,975.31), with a gain of 0.02455 quality adjusted life months (QALMs) per patient (554.52592 – 554.50137). Based on an estimated 150,000 births per year in the province, this would lead to a gain of 3,682 QALMs (150,000 x 0.02455) or 307 quality adjusted life years (QALYs). The incremental cost and QALMs yielded an **estimated incremental cost-effectiveness ratio (ICER) of $1,110.79 [Δ Cost / Δ QALMs]**. This was below the aforementioned a priori cost-effectiveness threshold of $4,166.67 per QALM.

Table 5.1: Cost and Adjusted Life Months with/without POS implementation

Strategy	**Cost***	**Quality-Adjusted Life Months***
Pulse Oximetry Screening	284,002.58	554.52592
No Pulse Oximetry Screening	283,975.31	554.50137

*Accounting for a "discounting rate" of 1.5%

Similar analysis as above without discounting yielded results as shown in **Table 5.2**, leading to an estimated incremental cost of CAD$48.50 per patient, with incremental gain in

QALM of 0.06642, for an ICER of $730.20 per QALM gained. Rest of results, however, will continue to incorporate a 1.5% discount rate.

Table 5.2: Cost and Adjusted Life Months with/without POS implementation (no discounting)

Strategy	**Cost**	**Quality-Adjusted Life Months**
Pulse Oximetry Screening	491909.99	960.57231
No Pulse Oximetry Screening	491861.49	960.50589

5.2 One-way sensitivity analyses

These analyses were conducted for all variables included in the model over their respective ranges. As described previously in **Section 3**, for variables that varied over time, these analyses were conducted by running the decision model for the lower range as well as the higher range values for each variable at a time. The model was not sensitive to any variable in one-way sensitivity analyses, i.e. the the implementation of POS was superior to no POS implementation for all variables across their plausible reference ranges.

5.3 Threshold analyses

Due to the importance and/or uncertainly around the point estimates/ranges, certain variables were tested for threshold values even outside the estimated plausible ranges based on group consensus amongst the committee members. These variables are indicated in **Table 5.3** below, and the thresholds (where identified) above or below which POS implementation is no longer expected to be cost effective for these variables are indicated, along with the Base Case values and original plausible estimated ranges. All probability variables were tested between values of 0 and 1, while the ranges tested for cost variables are indicated in footnote of **Table 5.3**.

Table 5.3: Determination of threshold values for a limited set of variables

Variable	Base Case Value	Lower Range	Higher Range	Threshold Value*
Probability that an individual patient is from the Northern region that requires air transport	0.0572	0.0564	0.0581	n/a
Probability that a level 2 facility has pediatric echocardiography capability	0.22	0.11	0.34	n/a
Probability of a false negative echocardiogram result at a level 2 facility	0.0015	0.0013	0.0017	n/a
Probability of a POS screen being positive if individual has CCHD	0.843	0.802	0.878	**<0.232**
Probability of a POS screen being positive if individual does not have CCHD	0.00966	0.00940	0.00994	**>0.118**
Probability home death with CCHD in 1st month	0.22	0.074	0.422	**<0.035**
Probability of CCHD	0.0004	0.0001	0.0009	**<0.00009**
Cost of echocardiogram†	213.80	106.90	320.70	n/a
Air Transport‡	15,000	10,000	20,000	n/a

*Variables with n/a did not have any threshold above or below which implementation of POS would no longer be cost effective.
†Tested from CAD$0 to CAD$10,000
‡Tested from CAD$0 to CAD$100,000

It was predicted that province-wide implementation of POS would not be cost-effective under the following conditions: (a) POS detects < 23.2% of CCHD lesions (well below the plausible lower limit of 80.2%); (b) POS is (falsely) positive if an individual does not have CCHD > 11.8% of the time (well above the estimated higher range of 0.994%; (c) if the probability of death at home in case of a missed CCHD is <3.5%, below the estimated lower

range value of 7.4%; or (d) incidence of CCHD in base case is less than 0.00009 (just below the estimated lower limit of 0.0001, but well below the point estimate value of 0.0004).

5.4 Probabilistic sensitivity analysis

As described previously in **Section 3**, in a probabilistic sensitivity analysis, multiple simulations of the decision model are run with a value for each variable chosen at random from within the prescribed range. Ten thousand simulations for the model were run as part of this probabilistic sensitivity analysis; most variables from the model were included in this analysis, and are indicated in **Section 4**. Time-varying variables (already found not to have impact model output in one-way sensitivity analyses) were not included. It was found that at the predetermined cost-effectiveness threshold of $4,166.67, implementation of POS would be cost effective 92.3% of the time. **Figure 5.1** below shows the incremental cost-effectiveness scatter plot. Each blue dot represents the incremental cost and incremental effectiveness (QALM) from each simulation, and all simulation values "below" the line of cost-effectiveness threshold are deemed to be cost-effectiveness, where the ones above the threshold line represent simulations where ICER for POS implementation was above the pre-determined threshold value.

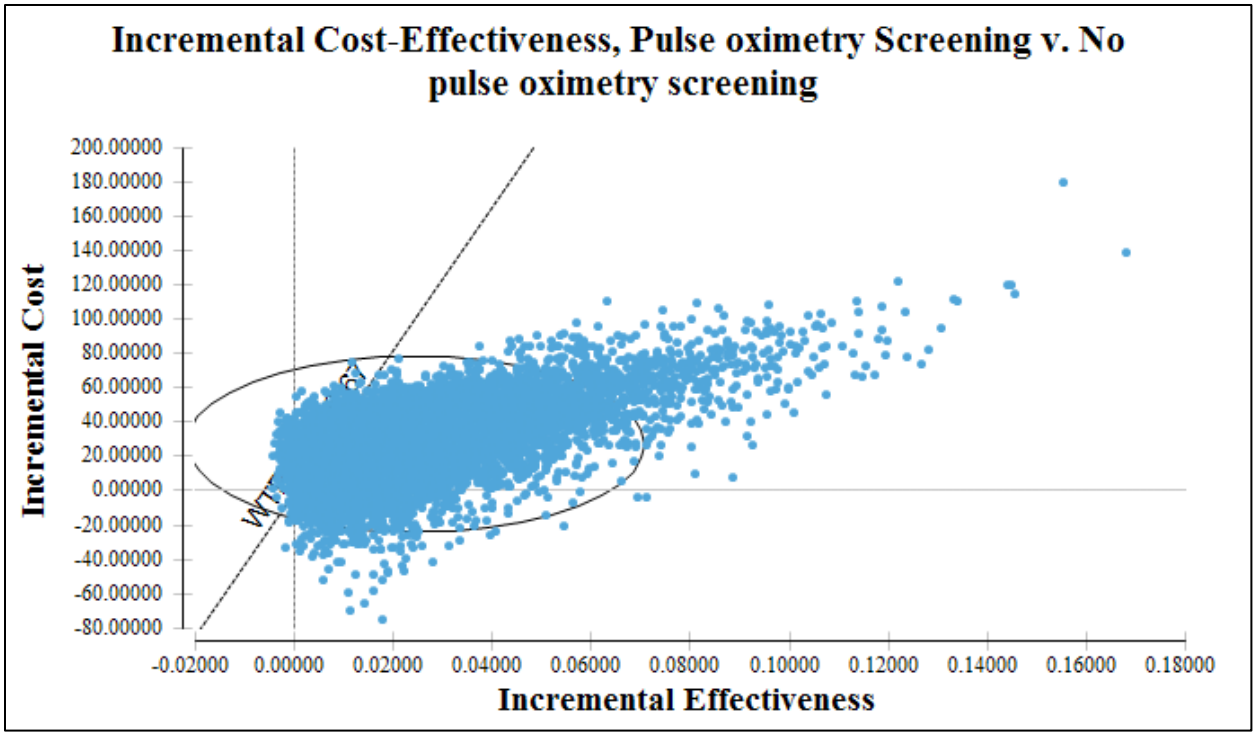

Figure 5.1: Cost-effectiveness scatter plot

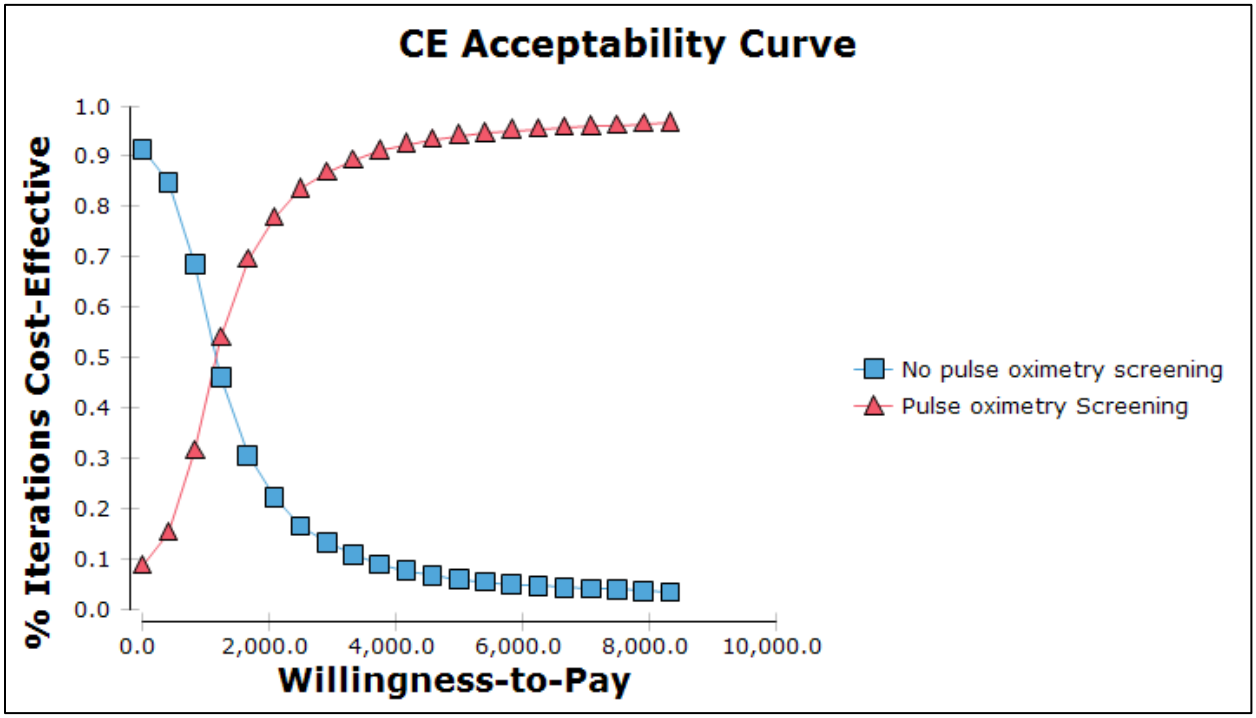

Figure 5.2: Cost effectiveness acceptability at various cost-effectiveness (or "willingness to pay") thresholds

From this probabilistic sensitivity analysis, a cost-effectiveness acceptability curve was generated, as shown in **Figure 5.2** above. As mentioned above, at a cost-effectiveness threshold of $4166.67, POS implementation was estimated to be cost effectiveness in 92.3% of the simulations, whereas if the cost-effectiveness threshold were doubled to $8,333.34, it is estimated that POS implementation has a 96.6% chance of being cost-effective. The acceptability curve also indicated that POS implementation is more likely to be cost-effective than lack of implementation (i.e. > 50% chance) at a cost-effectiveness threshold value as low as $1,175.

5.5 Model validation

The model developed for the clinical problem underwent face validity by the authors including neonatologists with expertise in neonatal cardiology as well as an expert in medical decision modeling. Furthermore, the model – when run without any discounting – yielded QALM values of approximately 960.57231and 960.50589 (in POS and No POS arms, respectively) – equivalent to 80 years of life, which is in keeping with current Canadian life expectancy values, lending further credence to the validity of the model as structured.

6. DISCUSSION

6.1 Summary of Results

A province-wide implementation of POS for CCHD in Ontario appears to be a cost-effective endeavour. Implementation of POS is expected to be associated with detection of an additional 51 cases of CCHD that would've been otherwise missed, with an ICER of CAD$1,110.79 per QALM gained (below the predetermined cost-effectiveness threshold of CAD$4,166.67 per QALM). POS implementation was noted to have a 92.3% chance of being cost-effective at a cost-effectiveness threshold of CAD$4,166.67 per QALM, whereas at a threshold of CAD$8,333.34 per QALM – it was estimated to have a 96.6% chance of being cost-effective. These results are similar to those previously reported in the literature.(24, 35-39)

6.2 Interpretation of findings

The findings of this model are consistent with what might be considered in the context of biological plausibility. Patients with delayed diagnosis of a given CCHD lesion are more likely to experience hemodynamic compromise, resulting in prolonged decreased oxygen supply to tissues in vital organs including the brain. They are more likely to not survive, as well as have a higher chance of morbidity.(8) This results in increased health care costs, as well as lower quality of life. Our model's primary aim was to determine whether the implementation of POS is cost-effective. The actual change in incremental cost between the two diagnostic strategy (i.e. implementation of POS vs. no implementation) was $27.27 (the additional dollar spending per individual) while the gain in QALMs was 0.02455 per individual, equivalent to an estimated addition of 307 QALYs over lifetime with each year of conducting POS. It is important to note that all values were discounted by 1.5% per year, as both values of cost and QALMs are deemed to have a higher value in the present than in the future.(44)

We employed a Markov modeling technique to determine the cost-effectiveness of POS over a life-time horizon. The advantage of this technique was that it allowed for transitional probabilities to vary over time, more accurately reflecting a life-time natural history of CCHD. Simulated individuals were allowed to transition among health states with each monthly cycle, which allowed for a realistic expression of the natural course as well as care pathways. The first cycle of the model was designed in great detail to be representative of the actual sequence of events from the time of a positive screen to the confirmation of diagnosis and surgical repair, as well as a detailed depiction of plausible events if a CCHD were to be missed despite screening. As such, the model was very representative of the likely clinical scenario that will take place following implementation of such a program.

6.3 Assumptions in the model

A number of assumptions were made in the model structure itself, as well as with respect to values and ranges assigned to many variables due to lack of available data, all of which will be described in this section.

a) It was assumed that a simulated individual with CCHD and a positive POS would remain stable and asymptomatic until confirmation of diagnosis by echocardiogram. This was a reasonable assumption given the model was constructed to ensure a confirmatory echocardiogram is performed after only a single transfer.
b) It was also assumed that all CCHDs (whether they were identified or missed, and regardless of what specific lesion it was) would receive surgery upon confirmation in the first Markov cycle. This was assumed for simplicity, but it is recognized that not only can some conditions have a delay in the first surgery, but that some conditions require a series of surgeries.(119) However to build all possible permutations of timings of

surgeries, or categorizing by specific lesion type, would add a significant level of complexity to this model without any conceivable difference in the model outcome.

c) Another important assumption was that morbidity related to CCHD repair consists of neurological impairment. However, there may be many other forms of morbidity including cardiorespiratory compromise, and other issues that may impact on the quality of life including scarring from surgeries, need for pacemakers, missed school and time from work among many others.(120-122) While it is recognized that limiting to neurological impairment as morbidity may be an oversimplification of an otherwise complex array of morbidities that impact quality of life, it is acknowledged that presence of other CCHD-related morbidities amongst the survivors may decrease the quality of life further, and as such our model may be overestimating the benefit of implementation of POS.

d) Another assumption related to the issue of morbidity was that anyone that developed CCHD-associated morbidity would have that over their lifetime. This was felt to be a reasonable assumption given that we limited the scope of morbidity to that of neurodevelopmental impairment, which are generally chronic conditions.(123)

e) It was assumed that health care expenditure in an individual without CCHD would be constant throughout their life, whereas in reality the costs are expected to change over lifetime.

f) We assumed that all babies delivered in LHINs 13 and 14 (representing Northern Ontario, **Appendix B**) – whether born at a level 1 or level 2 facility – would require air transport to the nearest level 3 centre if they screened positive on POS. This is a

reasonable assumption given the sparse population distribution over a significant land mass in this part of Ontario.

g) The point estimates for a number of variables (and as a result, their ranges) were estimated due to a lack of relevant data. These have been indicated previously in **Section 4**, but are listed here once again. For all these variables, the range was selected to be reasonably wide and all these variables underwent one-way sensitivity analyses to detect the threshold (if present) above or below which the model result was no longer robust.

    a. Relative risk of neonatal mortality with late detection was assumed to be 1.2 (with an assigned range of 1-2)
    b. Similarly, the relative risk of neonatal morbidity with late detection was assumed to be 1.2 (with an assigned ranged of 1-2)
    c. Transitional monthly mortality rates among the group of individuals with CCHD remains constant during adolescence and beyond
    d. Transitional monthly mortality rates are same for CCHD individuals with and without CCHD-associated morbidity
    e. Transitional rates of development of CCHD-associated morbidity would be constant for the first year then again between ages 2-16, and that no new morbidity would arise after that age
    f. Probability of false negative results of an echocardiogram at a level 2 facility was assumed to be the same as that of a level 3 institution
    g. Probability of false positive results at a level 3 institution was assumed to be 0, while that at a level 2 facility was assumed to be 0.05

h. Probability of POS occurring in event of province-wide implementation was assumed to be 0.98 (range 0.95 to 1.0) whereas the probability was assumed to 0.05 (range 0 to 0.1) without province-wide implementation
i. Disutility associated with the conduct of POS was assumed to be -0.005 (range -0.0075 to -0.0025), and transfer assumed to be -0.05 (range -0.075 to -0.025) while disutility with conduct of CCHD surgery was assumed to be 0, as no parent would conceivably have any objections to a potentially life-saving surgery
j. Cost of air transport was estimated based on personal communication with the transport director at BC children's hospital and assumed to be $15,000 (with an estimated range of $10,000 to $20,000.

6.4 Sensitivity analyses and interpretation

On one-way sensitivity analyses limited to the estimated plausible range for each variable, model was not sensitive to any of the included variables.

However, in addition to the aforementioned sensitivity analyses, analyses of extreme values (beyond the predetermined range) was performed for certain key variables, in particular variables for which there was low confidence in the range and/or variables of importance for the model. These variables have been listed earlier in **Table 5.3**. It was found that if probability of POS screen being positive in individuals with CCHD is < 23.2% then the implementation would no longer be cost-effective, which relates to increased costs yet diminishing benefit from POS. In addition, false positive rate > 11.8% was a threshold above which POS would not be cost-effective, which intuitively also is understandable as far too many infants would require transport and evaluation. However, this model did not take into account the fact that many cases of false positive results are later identified to have some other non-cardiac etiology such as

transient tachypnea of the newborn or sepsis.(4, 24) In any case, both of these thresholds were *far* beyond the expected range for these variables. It was also estimated that POS implementation would not be cost effective if the probability of death at home with missed CCHD was less than 3.5%, and also if the incidence of CCHD in a well appearing newborn that has not been antenatally or postnatally detected fell below a threshold of 0.00009 (0.009%), indicating that the burden of illness in such an event would be far too low for POS to remain cost-effective. Importantly, there was no threshold for air transport (checked up to an upper range of CAD$100,000), which likely relates to the fact that air transport will be utilized in both decision arms, and is expected to serve a relatively small fraction of the population.

The above analyses vary only 1 variable at a time, while the probabilistic sensitivity analysis varied multiple variables at once, run over 10,000 simulations of the model. At the cost-effectiveness threshold of CAD$4,166.67 per QALM – it was estimated that POS had a 92.3% probability of being cost-effective, while the chances increased to 96.6% if the cost-effectiveness threshold was doubled. This analysis represents a more "wholesome" sensitivity analysis, as all variables placed in the model may in reality be different that those used for "base-case" analysis. The results of the probabilistic sensitivity analysis, depicted as chances of cost-effectiveness, are also more meaningful for the audience. Finally, the probabilistic analysis also allowed for determination of the cost-effectiveness threshold below which it was less likely than not that POS would be cost-effective (CAD$1,175).

6.5 Comparison to previous studies

A number of studies have previously assessed the cost-effectiveness of POS implementation. Most such studies have been done in the UK,(35-38) but also in the US and Sweden.(24, 39) Previous studies have evaluated a very limited time horizon, with all being until

the point of diagnosis of CCHD, with the exception of the study by Peterson et al, which employed a one year time horizon.(39) The ICER values for these studies varied from as low as £3,430 to as high as £24,900 per additional case of CCHD diagnosed. The reason for the wide variability in the costs certainly relate to the nature of the models created and the variables put in, but all suggested that POS was likely to be cost-effective. The study by Peterson et al determined the ICER to be $40,385 per life year gained (which converts to $3,365.42 per month gained in US dollars). It should be noted that, unlike our model, none of the aforementioned studies employed utilities to account for morbidities that may be associated with CCHD and its outcomes (i.e. the various possible health states) – and as such do not present the costs for quality-adjusted life units gained and therefore, cannot truly evaluate cost-effectiveness. In addition, our study provides a life-time horizon which provides a clear sense of total lifetime costs and quality adjusted life units to be gained by the implementation of POS, after accounting for a discount rate of 1.5% per year. In addition, the model structure of the aforementioned studies was rather simple, which did not take into account the various possible pathways to the ultimate diagnosis of CCHD following a positive screen. Finally, we employed a Markov model to enable a more realistic modeling of a lifetime time horizon. Despite these differences from our study, the aforementioned studies affirmed the cost-effectiveness of POS, and our study was consistent with this in the Canadian context employing a lifetime horizon and associated utilities of various health states.

6.6 Strengths and weaknesses

6.6.1 Model Framework

The most important strength of the model is the detailed framework (outlined in **Figures 3.3, 3.4 and 3.5**) that represents a realistic pathway from screening to diagnosis to outcomes in

the first Markov cycle. Another important strength is the employment of time varying variables that allow the values to change over time for the transitional probabilities. This is close to the realistic progression through life following CCHD. The limitations of the model framework itself relate largely to the assumptions made, and have been previously discussed in **Section 6.3**. Another important limitation is the decreasing confidence in the point estimates of many variables the farther out the time horizon gets, due to lack of available data. Additionally, evaluating a life-time span, particularly when accounting for an annual discount rate, may contribute to diluting the incremental gain in QALMs. Finally, no spillover (caregiver) effects were considered as it relates to the utility and cost variables (with a few exceptions indicated previously), although this makes our analysis conservative (i.e. if including spillover effects, it would have been expected that the ICER would be lower still).

6.6.2 Variables and Data

The variables entered into the model underwent a comprehensive, targeted search from the literature where appropriate, and Canadian specific databases included BORN, CIHI and OCCI. Canadian and Ontario specific data were used for most of the model variables, and as such the model output truly reflects the Canadian context. However, for many variables no data were available and the point estimates for the base case as well as the ranges for some values were estimated based on author consensus. Additionally, for some variables only the point estimate was available. For probabilities and utilities for which this was the case, the range was estimated using the raw data and performing a Monte Carlo simulation with beta-distribution to derive an estimate of the range. For cost variables, when no range was available from the literature, 50% below and above the point estimate were used as the range. Lack of available data and/or ranges for certain variables does inject a degree of uncertainty around the base case

ICER. However, these values and their ranges were estimated based on group consensus. Finally, it is important to acknowledge the significant clinical and statistical heterogeneity of many of the meta-analyses, largely due to differences in study design, CCHD lesion being studied, population and time-frame of follow-up. However, we employed a random effects model when meta-analyzing recognizing the degree of heterogeneity, and recognize the limitations in the resultant point estimates for many of these variables. This placed additional importance to the sensitivity analyses conducted utilizing the ranges derived from these meta-analyses, recognizing the tremendous heterogeneity in the types of lesions and clinical course that patients with CCHD are expected to experience.

6.6.3 Analyses

Multiple sensitivity analyses were conducted, which is an important strength of the model. One-way sensitivity analyses were conducted for each variable in the model, including time-varying variables. For select variables extreme threshold analyses were conducted. Finally, probabilistic sensitivity analysis was conducted with most variables. As such, despite the limitations of lack of data for point estimates and/or available ranges, these sensitivity analyses have largely shown the model to be robust.

6.7 Clinical and policy implications

The likelihood of POS being cost-effective, along with its safe and non-invasive method, make it a suitable screening tool for the early diagnosis of CCHD, a condition with clear benefit from being diagnosed early. These criteria constitute the tenets of the Wilson and Jungner screening criteria.(124) Our model also shows that despite many cases being detected antenatally and postnatally prior to 24 hours of age, POS still remains cost-effective despite the relative rarity of otherwise "missed CCHD". In order to maximize the effectiveness of POS, it would be

prudent for policy makers to create standardized guidelines for POS including recommended measurements techniques and standard procedures for follow-up (e.g. the appropriate LHIN for transport and the recommended method of transportation, including contingency recommendations if a baby becomes symptomatic prior to diagnostic confirmation). These procedures would minimize the cost to the health care system by minimizing the effect of ambiguity in steps that need to be taken and would maximize the effect of POS. Close collaboration between the various centres will be required for effective implementation of such a screening program. With the advent of telemedicine technology, it is conceivable that many infants with positive POS screens will have confirmatory echocardiograms performed remotely. Although our model does not account for the costs associated with the investment required in implementation of such technology, it is reasonable to infer than this will render POS implementation even more cost-effective than our model suggests.

6.8 Conclusions and next steps

In conclusion, POS implementation in Ontario is likely to be a cost-effective endeavour, with an estimated ICER of CAD$1,110.79 per QALM gained. Despite the creation of a realistic model framework, the limitations in available data mean that the robustness of this analysis could be enhanced by incorporating more local data. This would serve to confirm the findings on the model, and may present a more realistic estimate of incremental costs and quality-adjusted life units gained. This could be performed by incorporating data following implementation of POS into the current model structure. However, gathering such data – especially when considering the life-time horizon of the model – may be both resource and time intensive, and may not be justified given the high level of probability of cost-effectiveness based on our model. Nevertheless, it will remain important to be mindful of the thresholds for variables presented at

which POS is no longer estimated to be cost-effective, and monitoring of these values over time will be important following to ensure POS remains a cost-effective endeavour.

7. REFERENCES

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APPENDICES

Appendix A: Algorithm for Pulse Oximetry Screening proposed by the American Academy of Pediatrics(4)

Appendix B: Levels of newborn care in Ontario and geographical distribution in Local Health Integration Networks

The provincial council for maternal and child health (PCMCH) in Ontario has assigned a designation (and thereby the appropriate resources) to all hospitals that provide maternal and newborn care. The levels of care are fully delineated at their website as follows: http://www.pcmch.on.ca/health-care-providers/maternity-care/pcmch-strategies-and-initiatives/loc/. A brief summary of the capabilities of each level of care (as it relates to caring for a patient with suspected CCHD) is summarized in **Table B.1** below.

Table B.1: Summary of hospital capabilities by levels of neonatal care designated by PCMCH

Level 1	• Evaluation and postnatal care of healthy newborn infants who are predominantly cared for in a mother-baby dyad model (rooming-in) • Resuscitation and stabilization of ill infants before transfer to an appropriate care facility • No echocardiographic capability
Level 2	• Moderately ill newborns with problems expected to resolve within a week or who are convalescing after intensive care • No echocardiographic capability officially, although some centres may have this available on an intermittent basis
Level 3	• Care of acutely unwell infants as well as extremely preterm neonates including mechanical ventilation support for as long as required • Timely access to a comprehensive range of subspecialty consultants, including pediatric echocardiography • Note: Only the Hospital for Sick Children (SickKids) has access to cardiovascular surgery for CCHD in the province

In addition, delivery of healthcare in Ontario is distributed according to Local Health Integration Networks (LHINs). Each LHIN constitutes a number of hospitals with varying levels of neonatal care, and each LHIN, or certain hospitals within a LHIN, are supported by one of the

five “level 3” centre clusters in Ontario (Toronto has three level 3 hospitals, but for the purpose of this discussion are considered one cluster), which includes dedicated transport teams who would be responsible for moving such babies from the community level 1 or level 2 hospitals to the nearest level 3 institution. A map of the LHINs in Ontario is shown below in **Figure B.1**.

Figure B.1: Geographical depiction of distribution of LHINs in Ontario

Appendix C: Literature search strategy on MEDLINE for mortality related to CCHD

1. aortic coarctation/ or ebstein anomaly/ or hypoplastic left heart syndrome/ or "tetralogy of fallot"/ or "transposition of great vessels"/ or double outlet right ventricle/ or tricuspid atresia/ or "trilogy of fallot"/
2. Pulmonary Atresia/
3. Aortic Valve Stenosis/
4. Pulmonary Valve Stenosis/
5. exp pulmonary valve stenosis/
6. Truncus Arteriosus, Persistent/ or Truncus Arteriosus/
7. (truncus arteriosus or transposition of the great arteries or transposition of great arteries or transposition of the great vessels or transposition of great vessels or (tetralogy adj2 fallot*) or (tricuspid adj2 atresia*) or Absent Right Atrioventricular Connection or (pulmonary adj2 atresia*) or (aortic adj2 stenos?s) or (aort* adj2 coarctation*) or (pulmon* adj2 stenos?s) or (hypoplastic adj2 heart syndrom*) or heart hypoplasia syndrom* or Taussig-Bing Anomal* or taussig bing anomal* or double outlet right ventricle or double-outlet right ventricle or (ebstein* adj1 (anomal* or malformation*))).ti,ab,kf.
8. total anomalous pulmonary venous drain*.ti,ab,kf.
9. total anomalous pulmonary venous drain*.mp.
10. total anomalous pulmonary venous return*.ti,ab,kf.
11. aortic arch atresia*.ti,ab,kf.
12. aortic arch atresia*.mp.
13. (aort* adj2 atresia*).ti,ab,kf.
14. or/1-13
15. (critical congenital heart adj1 (disease* or defect*)).ti,ab,kf.
16. (cyanotic congenital heart adj1 (disease* or defect*)).ti,ab,kf.
17. (critical heart adj1 (disease* or defect*)).ti,ab,kf.
18. (cyanotic heart adj1 (disease* or defect*)).ti,ab,kf.
19. or/15-18
20. 14 or 19
21. exp Infant, Newborn/
22. (neonate* or neo nate* or newborn*).ti,ab,kf.
23. 21 or 22
24. 20 and 23
25. exp Mortality/
26. mortalit*.ti,ab,kf.
27. death*.ti,ab,kf.
28. 25 or 26 or 27
29. fetal mortality/ or infant mortality/ or mortality, premature/ or perinatal mortality/
30. ((f?etal or newborn* or neonat* or perinatal) adj2 (death* or mortalit*)).ti,ab,kf.
31. 29 or 30
32. morbidity/ or incidence/ or prevalence/
33. morbidit*.ti,ab,kf.
34. (incidence or prevalence).ti,ab,kf.
35. or/32-34

36. 28 or 35
37. 31 or 35
38. 24 and ((28 and 23) or 31)
39. 14 and 28
40. 20 and 28
41. Survival Rate/
42. 14 and 41
43. exp Human Development/
44. exp intellectual disability/ or exp psychomotor disorders/
45. Motor Disorders/
46. exp Neurodevelopmental Disorders/
47. Cerebral Palsy/
48. 43 or 44 or 45 or 46 or 47
49. 20 and 48
50. 20 and 47
51. 20 and 48
52. 20 and 46
53. (burden adj1 (illness* or disease*)).ti,ab,kf.
54. 53 and 20

Appendix D: Monthly mortality probabilities with estimated ranges (Adapted from Statistics Canada data)

Age (years)	Males	Females	Average	Monthly Average	Low Range	High Range
Statistics Canada Data			Derived Data			
0	0.0052	0.00449	0.004855	0.000405486	0.000202743	0.00060823
1	0.0003	0.00021	0.000255	2.12525E-05	1.06262E-05	3.18787E-05
2	0.0002	0.00016	0.00019	1.58347E-05	7.91736E-06	2.37521E-05
3	0.0002	0.00013	0.00015	1.25009E-05	6.25043E-06	1.87513E-05
4	0.0001	0.0001	0.000115	9.58384E-06	4.79192E-06	1.43758E-05
5	0.0001	0	0.000055	4.58345E-06	2.29172E-06	6.87517E-06
6	0.0001	0	0.00005	4.16676E-06	2.08338E-06	6.25014E-06
7	0	0	0	0	0	0
8	0	0	0	0	0	0
9	0	0	0	0	0	0
10	0	0	0	0	0	0
11	0.0001	0	0.00005	4.16676E-06	2.08338E-06	6.25014E-06
12	0.0001	0	0.00006	5.00014E-06	2.50007E-06	7.50021E-06
13	0.0002	0.00011	0.00013	1.0834E-05	5.41699E-06	1.6251E-05
14	0.0002	0.00014	0.00017	1.41678E-05	7.08389E-06	2.12517E-05
15	0.0003	0.00018	0.00023	1.91687E-05	9.58434E-06	2.8753E-05
16	0.0004	0.00022	0.000305	2.54202E-05	1.27101E-05	3.81303E-05
17	0.0005	0.00026	0.000385	3.2089E-05	1.60445E-05	4.81335E-05
18	0.0006	0.00028	0.000435	3.62572E-05	1.81286E-05	5.43858E-05
19	0.0007	0.00029	0.000475	3.9592E-05	1.9796E-05	5.93879E-05
20	0.0007	0.0003	0.000505	4.20931E-05	2.10465E-05	6.31396E-05
21	0.0008	0.0003	0.000525	4.37605E-05	2.18803E-05	6.56408E-05
22	0.0008	0.00031	0.000535	4.45943E-05	2.22971E-05	6.68914E-05
23	0.0008	0.00031	0.000535	4.45943E-05	2.22971E-05	6.68914E-05
24	0.0007	0.0003	0.00052	4.33437E-05	2.16718E-05	6.50155E-05
25	0.0007	0.0003	0.000505	4.20931E-05	2.10465E-05	6.31396E-05
26	0.0007	0.0003	0.0005	4.16762E-05	2.08381E-05	6.25143E-05
27	0.0007	0.00031	0.0005	4.16762E-05	2.08381E-05	6.25143E-05
28	0.0007	0.00032	0.00051	4.25099E-05	2.1255E-05	6.37649E-05
29	0.0007	0.00034	0.000525	4.37605E-05	2.18803E-05	6.56408E-05
30	0.0007	0.00037	0.000555	4.62618E-05	2.31309E-05	6.93927E-05
31	0.0008	0.0004	0.00059	4.918E-05	2.459E-05	7.377E-05
32	0.0008	0.00043	0.000625	5.20983E-05	2.60491E-05	7.81474E-05
33	0.0009	0.00047	0.000665	5.54336E-05	2.77168E-05	8.31503E-05

34	0.0009	0.00051	0.00071	5.91859E-05	2.9593E-05	8.87789E-05
35	0.001	0.00056	0.00076	6.33554E-05	3.16777E-05	9.50331E-05
36	0.001	0.0006	0.00081	6.75251E-05	3.37625E-05	0.000101288
37	0.0011	0.00066	0.00087	7.25289E-05	3.62645E-05	0.000108793
38	0.0012	0.00071	0.00093	7.75331E-05	3.87665E-05	0.0001163
39	0.0012	0.00077	0.001	8.33716E-05	4.16858E-05	0.000125057
40	0.0013	0.00084	0.00108	9.00446E-05	4.50223E-05	0.000135067
41	0.0014	0.00092	0.00117	9.75523E-05	4.87762E-05	0.000146328
42	0.0015	0.001	0.001265	0.000105478	5.27389E-05	0.000158217
43	0.0017	0.00109	0.00137	0.000114238	5.71192E-05	0.000171358
44	0.0018	0.00118	0.001485	0.000123834	6.19172E-05	0.000185751
45	0.0019	0.00129	0.001615	0.000134683	6.73415E-05	0.000202025
46	0.0021	0.0014	0.001755	0.000146368	7.31839E-05	0.000219552
47	0.0023	0.00153	0.00191	0.000159306	7.96531E-05	0.000238959
48	0.0025	0.00166	0.002085	0.000173916	8.69581E-05	0.000260874
49	0.0028	0.00181	0.00228	0.000190199	9.50994E-05	0.000285298
50	0.003	0.00197	0.00249	0.000207737	0.000103869	0.000311606
51	0.0033	0.00215	0.00273	0.000227785	0.000113893	0.000341678
52	0.0036	0.00235	0.002995	0.000249927	0.000124963	0.00037489
53	0.004	0.00257	0.00329	0.000274581	0.00013729	0.000411871
54	0.0044	0.0028	0.003605	0.000300914	0.000150457	0.000451371
55	0.0048	0.00307	0.003955	0.000330182	0.000165091	0.000495273
56	0.0053	0.00336	0.004345	0.000362806	0.000181403	0.00054421
57	0.0059	0.00368	0.00477	0.000398372	0.000199186	0.000597558
58	0.0065	0.00403	0.00524	0.000437719	0.000218859	0.000656578
59	0.0071	0.00442	0.005755	0.000480853	0.000240427	0.00072128
60	0.0078	0.00485	0.006325	0.000528618	0.000264309	0.000792926
61	0.0086	0.00533	0.00696	0.000581858	0.000290929	0.000872788
62	0.0095	0.00586	0.007655	0.000640166	0.000320083	0.000960249
63	0.0104	0.00645	0.008425	0.000704809	0.000352405	0.001057214
64	0.0115	0.0071	0.009275	0.000776222	0.000388111	0.001164333
65	0.0126	0.00782	0.01021	0.000854841	0.000427421	0.001282262
66	0.0139	0.00862	0.011245	0.000941948	0.000470974	0.001412922
67	0.0153	0.00951	0.012395	0.001038832	0.000519416	0.001558247
68	0.0168	0.01051	0.013665	0.001145945	0.000572973	0.001718918
69	0.0185	0.01161	0.015065	0.001264169	0.000632085	0.001896254
70	0.0204	0.01284	0.01662	0.001395664	0.000697832	0.002093495
71	0.0225	0.0142	0.018335	0.001540909	0.000770455	0.002311364
72	0.0248	0.01573	0.02024	0.001702519	0.000851259	0.002553778

73	0.0273	0.01743	0.022345	0.001881431	0.000940715	0.002822146
74	0.03	0.01934	0.02469	0.002081157	0.001040579	0.003121736
75	0.0331	0.02146	0.02728	0.002302263	0.001151132	0.003453395
76	0.0365	0.02384	0.030155	0.002548332	0.001274166	0.003822498
77	0.0402	0.02649	0.03334	0.002821715	0.001410858	0.004232573
78	0.0443	0.02947	0.036885	0.003126972	0.001563486	0.004690458
79	0.0488	0.0328	0.040815	0.003466587	0.001733293	0.00519988
80	0.0538	0.03654	0.045185	0.003845726	0.001922863	0.005768589
81	0.0594	0.04074	0.050045	0.004269249	0.002134625	0.006403874
82	0.0654	0.04545	0.05544	0.004741728	0.002370864	0.007112592
83	0.0722	0.05074	0.061445	0.005270547	0.002635273	0.00790582
84	0.0796	0.05669	0.06813	0.005862909	0.002931454	0.008794363
85	0.0878	0.06338	0.07557	0.00652677	0.003263385	0.009790155
86	0.0968	0.07091	0.083855	0.007271817	0.003635909	0.010907726
87	0.1068	0.0794	0.09309	0.00810961	0.004054805	0.012164415
88	0.1178	0.08897	0.103385	0.009052834	0.004526417	0.013579251
89	0.13	0.09977	0.11487	0.010116873	0.005058436	0.015175309
90	0.1434	0.11196	0.127685	0.011319174	0.005659587	0.016978761
91	0.1579	0.12542	0.14168	0.012650821	0.006325411	0.018976232
92	0.1733	0.13991	0.156585	0.014091124	0.007045562	0.021136685
93	0.1893	0.15541	0.17236	0.015641137	0.007820568	0.023461705
94	0.206	0.1719	0.18897	0.017302744	0.008651372	0.025954116
95	0.2184	0.18849	0.20344	0.018775897	0.009387948	0.028163845
96	0.2354	0.20653	0.220945	0.020591182	0.010295591	0.030886773
97	0.2529	0.22549	0.239195	0.022523977	0.011261988	0.033785965
98	0.2709	0.24526	0.25809	0.024570389	0.012285194	0.036855583
99	0.2893	0.26571	0.27752	0.026725184	0.013362592	0.040087777
100	0.308	0.28671	0.297365	0.028981551	0.014490775	0.043472326

Appendix E: Detailed search strategy for mortality and complications related to CCHD

1. aortic coarctation/ or ebstein anomaly/ or hypoplastic left heart syndrome/ or "tetralogy of fallot"/ or "transposition of great vessels"/ or double outlet right ventricle/ or tricuspid atresia/ or "trilogy of fallot"/
2. Pulmonary Atresia/
3. Aortic Valve Stenosis/
4. Pulmonary Valve Stenosis/
5. exp pulmonary valve stenosis/
6. Truncus Arteriosus, Persistent/ or Truncus Arteriosus/
7. (truncus arteriosus or transposition of the great arteries or transposition of great arteries or transposition of the great vessels or transposition of great vessels or (tetralogy adj2 fallot*) or (tricuspid adj2 atresia*) or Absent Right Atrioventricular Connection or (pulmonary adj2 atresia*) or (aortic adj2 stenos?s) or (aort* adj2 coarctation*) or (pulmon* adj2 stenos?s) or (hypoplastic adj2 heart syndrom*) or heart hypoplasia syndrom* or Taussig-Bing Anomal* or taussig bing anomal* or double outlet right ventricle or double-outlet right ventricle or (ebstein* adj1 (anomal* or malformation*))).ti,ab,kf.
8. total anomalous pulmonary venous drain*.ti,ab,kf.
9. total anomalous pulmonary venous drain*.mp.
10. total anomalous pulmonary venous return*.ti,ab,kf.
11. aortic arch atresia*.ti,ab,kf.
12. aortic arch atresia*.mp.
13. (aort* adj2 atresia*).ti,ab,kf.
14. or/1-13
15. (critical congenital heart adj1 (disease* or defect*)).ti,ab,kf.
16. (cyanotic congenital heart adj1 (disease* or defect*)).ti,ab,kf.
17. (critical heart adj1 (disease* or defect*)).ti,ab,kf.
18. (cyanotic heart adj1 (disease* or defect*)).ti,ab,kf.
19. or/15-18
20. 14 or 19
21. obstetric labor, premature/ or premature birth/
22. infant, premature/ or infant, extremely premature/
23. infant, low birth weight/ or infant, small for gestational age/ or infant, very low birth weight/ or infant, extremely low birth weight/
24. ((prematur* or preterm*) adj2 (labo?r or infant* or newborn* or bab* or birth* or born)).ti,ab,kf.
25. (low adj1 (birthweight* or birth weight*)).ti,ab,kf.
26. (preemie* or premie*).ti,ab,kf.
27. or/21-26 [preterm birth and low birth weight]
28. multiple birth offspring/ or quadruplets/ or quintuplets/ or triplets/ or twins/ or twins, dizygotic/ or twins, monozygotic/

29. pregnancy, multiple/ or pregnancy, quadruplet/ or pregnancy, quintuplet/ or pregnancy, triplet/ or pregnancy, twin/ or superfetation/
30. ((birth or pregnan* or born) adj2 (twin* or triplets or quadruplets or quintuplet* or multiple*)).ti,ab,kf.
31. or/28-30 [multiples]
32. human development/ or adolescent development/ or child development/ or language development/ or child language/ or crying/
33. intellectual disability/ or auditory perceptual disorders/
34. exp Mental Disorders/
35. 20 and 34
36. (infant* or neonate*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
37. 35 and 36
38. exp neurocognitive disorders/ or exp neurodevelopmental disorders/
39. growth disorders/ or fetal growth retardation/
40. exp Infant, Premature, Diseases/
41. child development disorders, pervasive/ or asperger syndrome/ or autism spectrum disorder/ or autistic disorder/
42. exp hearing disorders/ or exp vision disorders/
43. cognition disorders/ or mild cognitive impairment/
44. Cerebral Palsy/
45. mental disorders/ or neurocognitive disorders/ or neurodevelopmental disorders/
46. neurodevelopmental disorders/ or communication disorders/ or developmental disabilities/ or intellectual disability/ or learning disorders/ or motor skills disorders/
47. (vision or hearing disorders).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
48. 46 and 47 [scope of neurodevelopmental disorders]
49. Breast Neoplasms/ and utility.mp.
50. Health Status Indicators/ and "Quality of Life"/
51. 20 and 50
52. Oximetry/
53. pulse oximetry screening.ti,ab,kf.
54. exp "Sensitivity and Specificity"/
55. 53 and 54
56. remove duplicates from 55 [POS and Sensitivity]
57. echocardiography/ or echocardiography, doppler/ or echocardiography, doppler, color/ or echocardiography, doppler, pulsed/ or echocardiography, three-dimensional/
58. 54 and 57

59. Infant, Newborn/
60. (newborn* or neonate* or neo nate*).ti,ab,kf.
61. 59 or 60
62. 58 and 61
63. diagnostic errors/ or false negative reactions/ or false positive reactions/
64. (54 or 63) and 57
65. 61 and 64
66. remove duplicates from 65
67. 66 and 20
68. remove duplicates from 67 [ECHO CCHD Infant Sens and Spec]

Appendix F: Detailed search strategy for utility related to CCHD

1. disutilit*.ti,ab,kf.
2. standard gamble*.ti,ab,kf.
3. time tradeoff.ti,ab,kf.
4. time trade off*.ti,ab,kf.
5. tto.ti,ab,kf.
6. (hui or hui1 or hui2 or hui3).ti,ab,kf.
7. (eq or euroquol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab,kf.
8. (utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease* or score* or weight*)).ti,ab,kf.
9. (burden* adj3 (illness* or disease*)).ti,ab,kf.
10. "Quality of Life"/
11. (quality adj2 life).ti,ab,kf.
12. value*.ti.
13. (quality adjusted or daily adjusted or QALY or DALY).ti.
14. health stat* value*.ti,ab,kf.
15. (patient* adj2 (perspective* or perce*)).ti,ab,kf.
16. Decision Support Techniques/
17. gamble*.ti,ab,kf.
18. prospect theory.ti,ab,kf.
19. preference score*.ti,ab,kf.
20. preference elicitation*.ti,ab,kf.
21. (elicit* adj2 preference*).ti,ab,kf.
22. health state.ti,ab,kf.
23. feeling thermomet*.ti,ab,kf.
24. best-worst scal*.ti,ab,kf.
25. best worst.ti,ab,kf.
26. probability tradeoff*.ti,ab,kf.
27. probability trade off*.ti,ab,kf.
28. preference based.ti,ab,kf.
29. multiattribute*.ti,ab,kf.

30. multi attribute*.ti,ab,kf.
31. (euroq?l5d or eq5d or sf6d or sf 6d or hui or 15d).ti,ab,kf.
32. (sf36 or sf 36 or sf12 or sf 12 or hrqol or qol).ti,ab,kf.
33. or/1-32
34. aortic coarctation/ or ebstein anomaly/ or hypoplastic left heart syndrome/ or "tetralogy of fallot"/ or "transposition of great vessels"/ or double outlet right ventricle/ or tricuspid atresia/ or "trilogy of fallot"/
35. Pulmonary Atresia/
36. Aortic Valve Stenosis/
37. Pulmonary Valve Stenosis/
38. exp pulmonary valve stenosis/
39. Truncus Arteriosus, Persistent/ or Truncus Arteriosus/
40. (truncus arteriosus or transposition of the great arteries or transposition of great arteries or transposition of the great vessels or transposition of great vessels or (tetralogy adj2 fallot*) or (tricuspid adj2 atresia*) or Absent Right Atrioventricular Connection or (pulmonary adj2 atresia*) or (aortic adj2 stenos?s) or (aort* adj2 coarctation*) or (pulmon* adj2 stenos?s) or (hypoplastic adj2 heart syndrom*) or heart hypoplasia syndrom* or Taussig-Bing Anomal* or taussig bing anomal* or double outlet right ventricle or double-outlet right ventricle or (ebstein* adj1 (anomal* or malformation*))).ti,ab,kf.
41. total anomalous pulmonary venous drain*.ti,ab,kf.
42. total anomalous pulmonary venous drain*.mp.
43. total anomalous pulmonary venous return*.ti,ab,kf.
44. aortic arch atresia*.ti,ab,kf.
45. aortic arch atresia*.mp.
46. (aort* adj2 atresia*).ti,ab,kf.
47. or/34-46
48. (critical congenital heart adj1 (disease* or defect*)).ti,ab,kf.
49. (cyanotic congenital heart adj1 (disease* or defect*)).ti,ab,kf.
50. (critical heart adj1 (disease* or defect*)).ti,ab,kf.
51. (cyanotic heart adj1 (disease* or defect*)).ti,ab,kf.
52. or/48-51
53. 47 or 52

54. 33 and 53
55. remove duplicates from 54