Value of Information Analysis Applications in Healthcare Interventions

Haitham Tuffaha
BPharm, MBA, MSc

School of Medicine
Griffith Health
Griffith University

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Abstract

Background

Decisions on adopting new healthcare interventions should be supported by the best available evidence on their safety, effectiveness and cost-effectiveness. Evidence is never certain and so is any decision based on that evidence. This uncertainty may lead to suboptimal decisions with costly consequences. Collecting more information may reduce uncertainty; however, there is a cost for additional research. Value of information (VOI) analysis is a systematic approach to quantify the value of research in reducing decision uncertainty. It compares the marginal research benefits and marginal costs to inform whether additional research is worthwhile. Furthermore, research studies can be designed and prioritised to optimise the net benefits from additional research. Despite its value, the use of VOI analysis in practice is limited.

Objectives

To apply VOI analysis in a group of real-world healthcare interventions to guide implementation decisions, and optimise research design and research priorities.

Methods

All analyses were conducted from the perspective of Queensland Health, the public provider of healthcare in Queensland, Australia. Four interventions were evaluated: clinically-indicated peripheral intravenous catheter replacement, tissue adhesive for securing arterial catheters, negative pressure wound therapy (NPWT) in caesarean sections, and nutritional support in preventing pressure ulcers in high-risk patients. For each intervention, an economic evaluation was performed, decision uncertainty characterised, and VOI measures calculated using Monte Carlo simulations. The benefits and costs of additional research were considered together with the costs and consequences of implementing the intervention now versus
waiting for more information. The optimal trial design is the one that maximises the expected net research benefit. Finally, the future research studies were ranked according to their expected net monetary benefits.

**Results**

All interventions were cost-effective, but with various levels of decision uncertainty. Negligible uncertainty in the clinically-indicated catheter replacement intervention suggested that current evidence is sufficient for implementation. For the tissue adhesive intervention, an additional research study before implementation is worthwhile with a four-arm trial of 220 patients in each arm, collecting data on its cost and efficacy compared to other securement devices. Additional research on NPWT before implementation is also worthwhile with a two-arm trial of 200 patients per arm, investigating the relative effectiveness of NPWT for preventing surgical site infections in caesarean section patients compared with standard dressings. Nutritional support should be implemented concurrently with a two-arm trial of 1,200 patients in each arm, evaluating the relative effectiveness of nutritional support in preventing pressure ulcers compared with standard hospital diet. Based on their expected net monetary benefits, the future studies would be ranked as: 1) NPWT (AUD 1.2 million), 2) tissue adhesive (AUD 0.3 million), and 3) nutritional support (AUD 0.1 million).

**Conclusion**

VOI analysis is a useful and practical tool to inform decisions, optimise trial design and prioritise research studies. Efforts should be focused on promoting the use of this approach and facilitating its integration into decision making frameworks.
This work has not previously been submitted for a degree or diploma in any university. To the best of my knowledge and belief, the thesis contains no material previously published or written by another person except where due reference is made in thesis itself.

Haitham W Tuffaha

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Included in this thesis are papers in Chapters 2, 4, 5, 6, 7 and 8 which are co-authored with other researchers. I designed, undertook the analysis and was the lead author on all articles. My contribution to each paper is outlined at the front of the relevant chapter. The bibliographic details and status for these papers are summarised below:

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Appropriate acknowledgments of those who contributed to the research but did not qualify as authors are included in each paper.

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Haitham W Tuffaha

(Countersigned)________________________________________(Date)___________________________________

Supervisor: Prof. Paul Scuffham
<table>
<thead>
<tr>
<th>Abbreviation</th>
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<tr>
<td>AHRQ</td>
<td>Agency for Healthcare Research and Quality</td>
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<td>ARD</td>
<td>Absolute Risk Difference</td>
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<td>AR-DRGs</td>
<td>Australian Refined Diagnosis Related Groups</td>
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<td>AS</td>
<td>Administration Set</td>
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<td>Australian Dollar</td>
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<td>AWR</td>
<td>Approve with Research</td>
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<td>BC</td>
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<td>Body Mass Index</td>
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<td>Bordered Polyurethane</td>
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<td>Bloodstream Infection</td>
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<td>CAD</td>
<td>Canadian Dollar</td>
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<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
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<tr>
<td>CEAC</td>
<td>Cost-Effectiveness Acceptability Curve</td>
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<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<tr>
<td>CLT</td>
<td>Central Limit Theorem</td>
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<tr>
<td>CRBSI</td>
<td>Catheter-Related Bloodstream Infection</td>
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<td>CS</td>
<td>Caesarean Section</td>
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<tr>
<td>DSA</td>
<td>Deterministic Sensitivity Analysis</td>
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<td>EGFR</td>
<td>Epidermal Growth Factor Receptor ()</td>
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<tr>
<td>ENBS</td>
<td>Expected Net Benefit of Sampling</td>
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<tr>
<td>EVPI</td>
<td>Expected Value of Perfect Information</td>
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<td>EVPIm</td>
<td>Expected Value of Perfect Implementation</td>
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<td>EVPPI</td>
<td>Expected Value of Perfect Parameter Information</td>
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<tr>
<td>EVSI</td>
<td>Expected Value of Sample Information</td>
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<td>GBP</td>
<td>Great Britain Pound</td>
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<td>HR</td>
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<td>Incremental Cost-Effectiveness Ratio</td>
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<td>NCREN</td>
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<td>NIHR</td>
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<td>NPUAP</td>
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<td>NPWT</td>
<td>Negative Pressure Wound Therapy</td>
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<td>NSCLC</td>
<td>Non-Small Cell Lung Cancer</td>
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<tr>
<td>OIR</td>
<td>Only in Research</td>
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<tr>
<td>PIVC</td>
<td>Peripheral Intravascular Venous Catheters</td>
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<td>PSA</td>
<td>Probabilistic Sensitivity Analysis</td>
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<td>PU</td>
<td>Pressure Ulcer</td>
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<tr>
<td>QALY</td>
<td>Quality-Adjusted Life-Year</td>
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<td>RCT</td>
<td>Randomised Controlled Trial</td>
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<td>ROI</td>
<td>Return on Investment</td>
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<td>RR</td>
<td>Relative Risk</td>
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<td>SAVI</td>
<td>Sheffield Accelerated Value of Information</td>
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<td>SD</td>
<td>Standard Deviation</td>
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<td>SPU</td>
<td>Standard Polyurethane</td>
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<td>SSD</td>
<td>Sutureless Securement Device</td>
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<td>SSI</td>
<td>Surgical Site Infection</td>
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<td>TA</td>
<td>Tissue Adhesive</td>
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<td>USD</td>
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<td>VOI</td>
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1. CHAPTER 1 INTRODUCTION

1.1 Background

With rising healthcare costs and limited budgets, decision makers should allocate scarce healthcare resources wisely to maximise benefits to their systems.[1] Therefore, economic evaluation is increasingly performed to inform decisions about the funding of new healthcare interventions and programmes. Economic evaluation involves the comparative analysis of the costs and consequences of alternative options.[2] This requires identifying, measuring, valuing and comparing all important costs and outcomes of the considered interventions.[2] Appropriate evaluation also requires comparing the new intervention with all relevant alternative options, incorporating all available relevant evidence, and reflecting the uncertainty in evidence in the findings of the evaluation.[3] This introductory chapter reviews the types of economic evaluations and their frameworks as well as uncertainty handling in these evaluations.

1.2 Types of economic evaluations

While costs identification and measurement may be similar across economic evaluations, the nature of the outcomes evaluated may differ according to the decision question and the evaluated interventions.[2] There are four types of economic evaluations: cost-minimisation analysis, cost-effectiveness analysis, cost-utility analysis and cost-benefit analysis.[2] Cost-minimisation analysis assumes that the evaluated interventions have equivalent outcomes but different costs, and accordingly, the decision can be made on the basis of the difference in total cost alone.[4] Importantly, the decision of equivalent effectiveness/efficacy should be justified and based on a high quality assessment of the interventions. Briggs and O’Brien have argued that ‘absence of evidence is not evidence of absence’, and therefore, unless a study has been specifically designed to show the equivalence
of treatments it would be inappropriate to conduct cost-minimisation analysis on the basis of an observed lack of significance in effect difference between interventions.[4] In cost-effectiveness analysis, however, the incremental costs are compared with the incremental outcomes, as measured in natural units (e.g., life-years gained, target blood pressure achieved).[2] A disadvantage of cost-effectiveness analysis is that it does not enable direct comparison of interventions treating different conditions. Furthermore, a cost-effectiveness analysis may be inappropriate when using one measure of outcome that does not account for the full range of important patient outcomes following an intervention.[2] In cost-utility-analysis, outcomes are measured as health-related preferences (e.g., utility values) and often expressed as quality-adjusted life-years (QALYs) gained. The QALY adjusts the length of time gained through an intervention by the utility value of the resulting health status.[2] Utility values range from zero (i.e., death) to one (i.e., perfect health). Cost-utility-analysis is useful when interventions have an impact on quality (i.e., morbidity) and length of life (i.e., mortality). Moreover, because cost-utility analysis uses a generic outcome measure (i.e., QALY), it allows decision makers to compare different interventions for different conditions.[2]

In cost-effectiveness and cost-utility analyses, the incremental benefits and costs are generally expressed as the incremental cost-effectiveness ratio (ICER) which is the difference in cost (i.e., ΔC) divided by the difference in health effect (ΔE) between the mutually exclusive evaluated interventions. The ICER must be compared with the decision maker’s willingness-to-pay threshold (λ); an intervention is cost-effective when the ICER is less than the willingness-to-pay threshold (i.e., ΔC/ΔE < λ). The willingness-to-pay threshold in a limited budget healthcare system represents the opportunity cost of health benefits forgone elsewhere from the investment in the new intervention.[5] An alternative approach to using
an ICER is to estimate the incremental net monetary benefit (INB), which is the increase in effect (ΔE) multiplied by the willingness-to-pay-threshold (λ), less the increase in cost (ΔC). When INB is positive (i.e. ΔE*λ – ΔC > 0), the new intervention is cost-effective.[6] An analysis that measures both the costs and outcomes in monetary units is called cost-benefit analysis.[7]

Because cost-utility analysis is a special case of cost-effectiveness analysis and as the two approaches can be expressed in terms of the net benefit, the term ‘cost-effectiveness analysis’ is often used to refer to the three types of economic evaluations.

1.3 Economic evaluation frameworks

The economic analyses described above can be conducted either alongside clinical trials (i.e., using patient-level data) or using decision analytic models.

1.3.1 Economic evaluation using patient-level data

Under this framework, all the costs and outcomes relevant to the research question are measured and then averaged across all patients in the different trial arms to obtain mean cost and mean outcome for each group.[8] All resources used by patients, such as hospital admissions, diagnostic tests, and medications are identified, measured, valued and recorded for each patient over the trial follow-up and according to the perspective of the economic evaluation. For the outcome measure of QALYs gained, patients typically complete a generic health-related quality-of-life questionnaire with pre-existing preference weights that can be attached to each health state. The preference weights for these measures are generally drawn from surveys of the general population, and so descriptive data from patients about their health states are combined with health related quality of life weights (i.e., utility values) from the general population and survival data from the trial to generate QALY profiles.[8, 9]
The costs and outcomes of the trialled interventions and the respective differences between them can be presented in several ways. Arithmetic mean cost (i.e., average cost) is a commonly used measure, although cost data are often right skewed and may not allow comparing differences in arithmetic means under the assumptions for standard statistical tests (i.e., normality and all observations are independent).[10] Nevertheless, high sample sizes guarantee near-normality of sample means as demonstrated by the central limit theorem (CLT). Additionally, nonparametric bootstrapping, an approach that randomly re-samples from the data set with replacement and re-estimates the sample means for each replicate, is often used to enable means to be compared and calculate confidence intervals.[11] Of note, both CLT and bootstrap approaches are asymptotically valid as sample sizes increase, but may not provide accurate mean estimates in small samples with highly skewed data.[12-14] Alternatively, where the data are skewed and/or heavy tailed, costs can be modelled using probability distributions (e.g., gamma or lognormal distributions).[13-15]

Using clinical trials as a vehicle for economic evaluation confers some advantages including the relatively small marginal cost associated with the economic evaluation compared to the cost of the trial, the reliable estimation of cost and outcome data, and the opportunity of working on patient-level data and performing subgroup analyses.[8, 16] However, using the results of an economic evaluation from a single trial to inform decision making has many shortcomings. A single clinical trial usually does not compare all relevant interventions for a given condition, the trial follow-up time is usually shorter than the appropriate time for the cost effectiveness, the data from a given clinical trial on a given population may not be applicable to different populations within the same country or across jurisdictions, and finally, the possible lack of relevance to the decision context.[8, 16] Thus, it is important for any informed decision making to consider all available current evidence from
different sources and not to rely solely on the data from one trial. [8, 16] A preferred way of informing decision making is to use decision-analytic models based on trial-based data coupled with full evidence synthesis. The value of the clinical trials and economic studies within this context lies in providing estimates (i.e., measurements) as a source of inputs into a decision model.[8, 16]

1.3.2 Economic evaluation using decision analytic models

A decision model provides an appropriate structure to describe the decision problem and the impact of all relevant parameters under evaluation.[17] Within this framework, all existing relevant evidence can be brought together and translated into estimates of the costs and outcomes for the evaluated interventions to inform the cost-effective option.

The first step in the development of an economic model is to specify the decision problem (i.e., research question) based on the decision maker’s requirements. Then, it is essential to identify the perspective of the analysis, the population expected to benefit and the clinical setting, the relevant treatment options available for evaluation, the time horizon, and the relevant outcome measures to define the scope (i.e., boundaries) of the model.[18] A model structure can then be developed to incorporate all these factors. In general, the simplest model structure should be chosen as long as it describes the decision problem and options, and all relevant inputs can be incorporated.[19] The common types of models include decision trees, Markov models, patient-level simulation (micro-simulation), discrete event simulation and dynamic (i.e., transmission) models.[20] For relatively simple decision problems with short time horizons, a decision tree may be appropriate. However, when the decision problem can be described as a series of health states, state transition models (e.g., Markov) are often appropriate.[20] The primary disadvantage of the Markovian assumption is that the transition probabilities do not depend on the past history of the patient; in this case,
an individual-based state-transition model (i.e., patient-level simulation) is an alternative.[20] When the disease treatment process includes interactions between individuals (e.g., infectious disease controls), the model should be able to represent and evaluate the effects of those interactions (e.g., dynamic transmission models, discrete event simulations). Nevertheless, for some decision problems, combinations of model types, hybrid models, and other modelling approaches might be appropriate.[20] Good modelling practice requires also that all structural assumptions (e.g., cycle length in a Markov model, time horizon, discount rates) should be adequately described and justified.[20]

Once the structure of the model has been established, it is necessary to identify available data to populate that model. Data inputs such as efficacy, costs and quality of life that populate a decision model should be collected systematically from the best available evidence sources. Evidence synthesis may be needed for some parameters where there are a number of sources; for example, meta-analysis is a good approach when there are a number of similar trials evaluating the effect of an intervention, or using indirect treatment comparisons when head-to-head trials are not available.[19, 21, 22] When the data on all variables required by the model have been assembled, the model is run for each intervention being evaluated in order to estimate its expected costs and outcomes. The results are typically compared in terms of ICERs or INBs.

1.4 Uncertainty in economic evaluation

Any assessment of costs and effects in economic evaluations will contain some uncertainty.[23] This uncertainty can arise from different sources such as the uncertainty in the estimates of cost and effect parameters, the possible bias and limitations in the available evidence, and the assumptions made during economic modelling (e.g., time horizon).[2] Here it is important to differentiate between uncertainty, variability and heterogeneity. Uncertainty
reflects the fact that we can never know for certain the true costs and effects mean values for a particular population, and thus, additional evidence may reduce uncertainty and provide more precise estimates.[23] Variability, on the other hand, refers to the natural variation in outcomes and costs between patients even when they have the same characteristics, and therefore, additional evidence cannot reduce variability.[23] Finally, heterogeneity refers to differences between patients who have different characteristics. To address heterogeneity, economic evaluations are conducted for predefined subgroups of patients of certain characteristics.[17, 19]

Uncertainty in the economic evaluations means that the decisions based on these evaluations are also uncertain, and therefore, it is essential to assess and present the uncertainty in the conclusions of economic evaluations.[17] The method of assessing uncertainty depends on its source and the type of the economic evaluation being performed.[23-25]

1.4.1 Handling uncertainty in economic evaluations using patient-level data

Sampling uncertainty (i.e., stochastic or first-order) arises when cost-effectiveness analyses are undertaken alongside clinical trials using patient-level costs and effects data. This uncertainty is usually reported as a confidence interval for the costs and outcomes within the same group, the difference in outcomes and costs between groups and for the ICER.[9] Nevertheless, the ICER is a ratio and ratios are difficult to work with statistically (e.g., if the denominator is zero).[11] In addition, it would be inappropriate to assume that the ICER’s sampling distribution follows a normal distribution.[11] Therefore, two approaches have been proposed to overcome these problems and allow the estimation of the ICER’s confidence limits: the Fieller’s method and non-parametric bootstrapping. Fieller’s method assumes that the cost and outcome differences follow a joint normal distribution, and the confidence
interval is calculated using an equation that incorporates the differences in costs and effects together with their respective variances and the covariance between them.[11] The bootstrap, on the other hand, re-samples from the original data to build an empirical estimate of the sampling distribution of the ICER that can be plotted on the cost-effectiveness plane as illustrated in Figure 1-1.

![Figure 1-1: Confidence ellipses and a scatter plot of bootstrap results](image)

WTP = willingness-to-pay

A further problem with the ICER is that a single negative value might represent improved outcomes and lower costs or worse outcomes and higher costs. This makes confidence intervals hard to estimate and interpret.[8, 11] A solution to this is to move from the ICER to the net benefit (i.e., estimate the INB).[8, 11] Unlike the ICER, the INB has the advantage of being a linear expression, and thus, it is more tractable and has a sampling distribution.[2, 6] Decision uncertainty for INB or ICER estimates can be presented using cost-effectiveness acceptability curves (CEACs) where the probability that the new intervention is cost-effective (i.e., INB > 0 or ICER < $\lambda$) is presented over a range of willingness-to-pay values as illustrated in Figure 1-2.[11, 26]
1.4.2 Handling uncertainty in economic models

In general, there are two types of uncertainties arising during economic modelling: parameter uncertainty (i.e., second order) and structural uncertainty; nevertheless, when models are structured around events occurring at the individual level (e.g. discrete event simulation, micro-simulation) elimination of the stochastic uncertainty (i.e., first order) is required. [17] Structural uncertainty reflects the uncertainty surrounding the structure of the model and the assumptions underpinning it including the different types of simplifications and scientific judgments that have to be made when conceptualising a model (e.g. disease pathway, discount rates). [24] The presence of structural assumptions requires their testing in sensitivity analysis; however, additional approaches have been proposed to handle structural uncertainty such as model averaging and parameterising structural uncertainty. [23, 24] Model averaging involves building alternative models with different structural assumptions, and averaging their results, weighted by some measure of their adequacy or credibility. [23, 24] Alternatively, parameterising a structure entails considering different model scenarios as either missing or uncertain parameters. [23, 24]
Parameter uncertainty, on the other hand, reflects the uncertainty and imprecision surrounding the value of the input parameters that go into the model (e.g., transition probabilities, costs, and utility values) as these are usually estimated from sampled data. To handle parameter uncertainty it is important to assess its impact on the results of the economic analysis. This can be done through the standard deterministic sensitivity analysis (DSA) or by probabilistic sensitivity analysis (PSA).[17] In DSA, each parameter in turn is set at an ‘extreme’ but plausible value (e.g., taken directly from the estimation process and its 95% confidence interval) and individually the model is re-run to measure the impact of this change on the cost effectiveness analysis. Alternatively, a threshold value for a parameter is found at which the decision changes.[23] Although DSA is easy to implement it is likely to underestimate uncertainty because, in reality, parameters will not vary in isolation. Conducting multi-way sensitivity analysis (i.e., assuming extreme possible values for a group of parameters simultaneously) is difficult to present, and where parameter correlation exists, DSA becomes impossible to interpret.[27]

In PSA, model parameters are assigned specific probability distributions to represent uncertainty in their estimation.[17, 28] The distributions chosen should follow standard statistical methods; for example, beta distributions are suitable for binomial data, gamma or log-normal for right-skewed parameters, log-normal for relative risks or hazard ratios, and logistic for odds ratios.[17] Expert opinion must be elicited on the proper distribution when there is very little information on a parameter, because either there are very few studies informing the estimation or there are no data.[17] In certain occasions, model parameters may be correlated. For example, if a regression analysis is used to estimate model parameters, the relationship between parameters can be estimated from the co-variance matrix; this enables correlations between regression coefficients to be included in PSA in the multi-variate normal
The next step in a PSA is to propagate the uncertainty through the model using a simulation technique such as Monte Carlo simulation to sample values at random from those distributions in order to evaluate simultaneously the implications of uncertainty for the economic analysis results. The outputs of the model are recorded for each set of samples from all the parameters. This process of sampling inputs and recording outputs is repeated (e.g., 10,000 times) so that the range of values that the parameters are likely to take is represented in the range of outputs.[17, 23, 28] Probabilistic models allow the effects of joint uncertainty across all the parameters of the model to be considered so that cost-effectiveness results indicate the uncertainty surrounding the adoption decision rather than the uncertainty surrounding a single input.[28] The output of this process also provides the proportion of times (i.e., the probability) that each alternative intervention is cost-effective which can be used to build a CEAC.[17, 23, 28]

1.5 Value of information analysis

The above methods for handling and presenting decision uncertainty estimate the probability of an intervention being cost-effective; however, this probability is not perfect and there is always a chance that the resulting decision is wrong. Whether or not this chance of error matters depends on its consequences.[31] There is an opportunity loss when suboptimal interventions are chosen. Furthermore, there is a cost for intervention implementation (e.g., training, equipment) that cannot be recovered if the decision is reversed; for example, if future research suggests that the intervention is not cost-effective.[32, 33] Moreover, implementing a decision may discourage future research and development efforts, and hence, potential benefits of additional research may be forgone.[33]

Decision uncertainty can be reduced with more information, but there are also costs associated with conducting additional research. Value of information (VOI) analysis has been
proposed as the preferred approach to measure the uncertainty surrounding a decision based on economic evaluation, since it combines the probability of incorrect decision making with the consequential opportunity loss.[1, 17, 34] The consequences (i.e., cost) of uncertainty estimated by VOI analysis is the expected benefit (i.e., value) of additional information.[1, 34] By comparing the expected benefits of research with its expected costs, VOI analysis informs whether the available evidence is sufficient to inform a decision or if additional research is worthwhile.[34]

Summary

Economic evaluation is increasingly performed to inform healthcare decisions. It involves the comparison of the costs and effects of alternative options and can be conducted alongside clinical trials or using economic models. There is always uncertainty in economic evaluation analyses and in the decisions they guide; and therefore, it is essential to characterise and present this uncertainty. VOI analysis is a systematic approach to measure decision uncertainty and quantify the value of additional research in reducing uncertainty. The next chapter reviews the principles and applications of VOI analysis in health care.
2. CHAPTER 2 LITERATURE REVIEW

Statement of contribution to co-authored published paper

This chapter includes a co-authored paper. The bibliographic details of the paper are:


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I contributed to the original idea of the paper, reviewed the literature and wrote the manuscript.

(Signed)____________________________________(Date)___________________________

Haitham W Tuffaha

(Countersigned)_____________________________(Date)____________________________

Corresponding author: Haitham W Tuffaha

(Countersigned)_____________________________(Date)____________________________

Supervisor: Prof. Paul Scuffham
Review

Value of information analysis in healthcare: a review of principles and applications

Abstract

Background

Economic evaluations are increasingly utilized to inform decisions in healthcare; however, decisions remain uncertain when they are not based on adequate evidence. Value of Information (VOI) analysis has been proposed as a systematic approach to measure decision uncertainty and assess whether there is sufficient evidence to support new technologies.

Scope

The objective of this paper is to review the principles and applications of VOI analysis in healthcare. Relevant databases were systematically searched to identify VOI articles. The findings from the selected articles were summarized and narratively presented.

Findings

Various VOI methods have been developed and applied to inform decision making, optimally designing research studies and setting research priorities. However, the application of this approach in healthcare remains limited due to technical and policy challenges.

Conclusion

There is a need to create more awareness about VOI analysis, simplify its current methods, and align them with the needs of decision making organizations.

Introduction

Comparative effectiveness research has been proposed as a potential avenue to identify, evaluate, and provide effective, safe, and cost-effective healthcare on the basis of informed and evidence-based decisions. When comparing alternative healthcare options, it is essential to identify and combine the best available evidence on treatment effects, health-related preferences (utilities), resource use, and costs. Nevertheless, the evidence could be absent or uncertain due to the limitations and weaknesses of the available studies. A cost-effectiveness analysis that is based on such evidence is uncertain and, thus, any decision based on this analysis will also be uncertain. Decision uncertainty is associated with risk, because making the wrong decision could lead to costly consequences for the healthcare system (e.g., adopting sub-optimal treatment). Acquiring additional information could reduce uncertainty and better inform decisions; however, there is a cost for obtaining further evidence in terms of the direct costs of conducting research and the opportunity cost of delaying the decision awaiting research results. In addition, under limited budgets, the money spent on a specific research study could be spent on healthcare or on other competing...
2.1 Abstract

Background
Economic evaluations are increasingly utilised to inform decisions in health care; however, decisions remain uncertain when they are not based on adequate evidence. Value of information (VOI) analysis has been proposed as a systematic approach to quantify the value of additional evidence to reduce decision uncertainty.

Scope
The objective of this paper is to review the principles and applications of VOI analysis in health care. Relevant databases were systematically searched to identify VOI articles. The findings from the selected articles were summarised and narratively presented.

Findings
Various VOI methods have been developed and applied to inform decision making, optimally designing research studies and setting research priorities. However, the application of this approach in health care remains limited due to technical and policy challenges.

Conclusion
There is a need to create more awareness about VOI analysis, simplify its current methods, and align them with the needs of decision making organisations.
2.2 Introduction

Comparative effectiveness research has been proposed as a potential avenue to identify, evaluate, and provide effective, safe, and cost-effective health care on the basis of informed and evidence-based decisions. When comparing alternative health care options, it is essential to identify and combine the best available evidence on treatment effects, health-related preferences (i.e., utilities), resource use, and costs. Nevertheless, the evidence could be absent or uncertain due to the limitations and weaknesses of the available studies. A cost-effectiveness analysis that is based on such evidence is uncertain, and thus, any decision based on this analysis will also be uncertain. Decision uncertainty is associated with risk because making the wrong decision could lead to costly consequences for the healthcare system (e.g., adopting suboptimal treatment). Acquiring additional information could reduce uncertainty and better inform decisions; however, there is a cost for obtaining further evidence in terms of the direct costs of conducting research and the opportunity cost of delaying the decision awaiting research results. In addition, under limited budgets, the money spent on a specific research study could be spent on health care or on other competing research proposals. Therefore, it is recommended to assess the need and value of additional research before making decisions.

Value of information (VOI) analysis has been proposed to aid decision makers decide simultaneously on the adoption of new technologies and the need for further research. Various VOI methods have been developed and successfully applied to inform whether there is sufficient evidence to support a decision on new technologies, optimally designing research studies and setting research priorities.

The majority of the published papers on VOI analysis are methodological. Even in the applied papers, the topic is often presented with complexity rendering this approach
difficult to grasp by non-specialist. Thus, there is a need to present the principles and advantages of VOI analysis to decision makers, researchers, and practitioners in a succinct but comprehensive manner. The objective of this paper is to review VOI principles and applications in health care.

2.3 Scope

The following section of this paper describes the principles of value of information analysis, and the last section reviews the applications of VOI in health care. The general approach is to identify the relevant literature to inform this review searching various databases including PubMed, Medline, CINAHL and the National Health Service Economic Evaluation Database for VOI articles published from January 2003 to January 2013. Search terms included: ‘value of information’, ‘value of perfect information’, ‘value of sampling information’, and ‘value of perfect parameter information’. These terms were searched in combination with the terms ‘decision making’, ‘trial design’ and ‘research prioritisation’. A narrative approach is used to summarise and present the principles and applications of VOI from the reviewed articles.

2.4 Principles of VOI analysis

VOI analysis provides an analytic framework to quantitatively estimate the value of acquiring additional evidence to address a decision problem. It is based on the principle that information is valuable because it reduces the expected cost of making the wrong decisions under uncertainty.[1, 33] By measuring the expected benefits of additional evidence and comparing this with the expected costs of further research, the VOI approach helps decision makers answer the following five related questions:[32, 38]

1. Is additional research required? And if yes,

2. What type of research?
3. Do the expected benefits of sampling exceed the costs?

4. What is the optimal research study design?

5. What priority should this research study take?

2.4.1 Is additional research required?

To know whether additional research is potentially worthwhile, we need to consider the expected cost of making a wrong decision (i.e., the cost of uncertainty).[23] High expected cost of uncertainty indicates a need for acquiring further information before making a decision. The expected cost of uncertainty is determined by two factors: 1) the probability that a decision is wrong, and 2) the consequences of this potentially wrong decision.[32]

To explain how the cost of uncertainty is estimated, a simplified hypothetical example is presented for two treatment interventions (A and B) modelled in a cost-effectiveness analysis. The uncertainty in the results of the cost-effectiveness analysis is characterised by presenting the expected net benefit estimates (i.e., effects measured in monetary terms minus costs) for each intervention. In this example, the model is calculated five times to reflect various possible values of the model parameters (Table 2-1). Because the expected average net benefit for intervention B ($1,200) is higher than for A ($1,000), selecting intervention B would be the preferred decision. However, this decision is imperfect as there is a 40% probability that a wrong decision is made; in two out of five scenarios treatment A is cost-effective. The consequence of this wrong decision is the opportunity loss (i.e., benefit forgone) from choosing treatment B when treatment A was the preferred intervention. This opportunity loss is calculated by taking the difference between the net benefits of the two interventions in each scenario when A was preferred. The average opportunity loss across all scenarios is the expected cost of uncertainty of the decision for adopting treatment B, which is $40 per patient in this example. Equivalently, if we knew all parameters with absolute
certainty (i.e., we have perfect information), we would choose the intervention with the maximum expected net benefit in each scenario. Averaging the maximum values across all scenarios gives the expected benefit of a decision made with perfect information, which is $1,240. The difference between the expected benefit of a decision made with perfect information and a decision made without perfect information ($1,240 - $1,200 = $40 per patient) is the expected value of perfect information (EVPI) which is also the expected cost of uncertainty.[34]

Table 2-1: Illustrative example of the expected value of perfect information

<table>
<thead>
<tr>
<th>Sampling scenario</th>
<th>Intervention A net benefit</th>
<th>Intervention B net benefit</th>
<th>Optimal choice</th>
<th>Opportunity loss</th>
<th>Maximum net benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$1,000</td>
<td>$1,400</td>
<td>B</td>
<td>$0</td>
<td>$1,400</td>
</tr>
<tr>
<td>2</td>
<td>$1,200</td>
<td>$1,100</td>
<td>A</td>
<td>$100</td>
<td>$1,200</td>
</tr>
<tr>
<td>3</td>
<td>$900</td>
<td>$1,300</td>
<td>B</td>
<td>$0</td>
<td>$1,300</td>
</tr>
<tr>
<td>4</td>
<td>$800</td>
<td>$1,200</td>
<td>B</td>
<td>$0</td>
<td>$1,200</td>
</tr>
<tr>
<td>5</td>
<td>$1,100</td>
<td>$1,000</td>
<td>A</td>
<td>$100</td>
<td>$1,100</td>
</tr>
<tr>
<td>Average</td>
<td>$1,000</td>
<td>$1,200</td>
<td></td>
<td>$40</td>
<td>$1,240</td>
</tr>
</tbody>
</table>

The EVPI calculated above is an average estimate (i.e., per patient EVPI). Multiplying per-patient EVPI by the population of patients expected to benefit from the evaluated intervention over a period of time gives the population EVPI which represents the maximum potential value (i.e., upper bound) of additional research.[32, 38] If the population EVPI appears to exceed the cost of additional research study, then this study is potentially worthwhile and further assessment is required to inform its optimal design.[32, 39] Nevertheless, it has been argued that population EVPI is neither necessary nor sufficient to
inform whether additional research is worthwhile because it is impossible to estimate the expected cost of research without knowing the specific research study design (e.g., sample size, follow-up time).[38] However, calculating population EVPI is relatively simple and considered a continuation step to uncertainty assessment in cost-effectiveness analyses. When the population EVPI approaches zero it is unlikely that the value of additional research will exceed its cost and there will be no need to undertake further VOI analyses.[40]

2.4.2 What type of research?

If further research appears potentially worthwhile based on the population EVPI, it would be useful to identify the particular aspects of a decision problem that are worth studying to resolve the uncertainty surrounding them.[39] This could be achieved by estimating the expected VOI for certain input parameters in a given economic evaluation, often referred to as the partial EVPI or the expected value of perfect parameter information (EVPPI).[23] EVPPI is defined as the difference between the expected value of a decision made with perfect information on the selected parameter(s) and the decision made based on current information.[39] EVPPI serves as a measure of the sensitivity of the economic evaluation to the uncertainty in its different input parameters.[23, 39] A parameter with a higher EVPPI is more uncertain and further research can be designed and focused to get more precise estimate of its value. Importantly, the nature of the uncertain parameter(s) would inform the type and possibly the cost of the additional research study needed (e.g. randomised controlled trial versus observational study).[23, 39]

2.4.3 Do the expected benefits of sampling exceed the costs?

When the expected benefits of additional research study in reducing decision uncertainty exceeds its total cost, then this study is worthwhile. EVPI and EVPPI measure the expected value of additional research providing perfect information to resolve uncertainty of
all parameters or specific parameters.\[34\] However, acquiring perfect information requires a very large research sample (i.e., infinite sample size) which is not practical. In reality, it is only possible to reduce uncertainty with additional information from a research study of a finite sample size.\[1\] The expected value of sample information (EVSI) estimates the expected value of reducing the uncertainty by a given research study with a specific sample size within a particular study design.\[38\] This can be calculated for all effect and cost parameters (i.e., total EVSI) or for the parameter(s) of interest (i.e., partial EVSI).\[41\] Population EVSI is calculated by multiplying the per-patient EVSI by the size of the population to whom information from the trial is valuable.\[38\]

The expected total cost of a research study includes three components: 1) fixed cost (e.g., set-up cost, salaries), 2) variable cost per patient, and 3) an opportunity cost for those patients who receive the suboptimal intervention while the study is underway.\[33\] The total cost commonly takes a societal perspective; however, this cost may also be from the perspective of the sponsor of the study. The difference between the population EVSI for a specific study design and its expected total cost is the expected net benefit of sampling (ENBS).\[38\] A positive ENBS indicates that the research study is cost-effective. Conversely, when the ENBS is negative, it would be irrational to conduct further research because the expected costs of the study exceed its expected benefits, and in this case, the decision should be based on the current evidence.\[42\] The EVSI and the ENBS are the preferred measures of VOI because they provide a sufficient condition to inform whether a specific research study is expected to be worthwhile.\[38\]

### 2.4.4 What is the optimal research study design?

The sample sizes of clinical trials are usually calculated based on type I and II error, and the minimum clinically important difference.\[43\] The VOI framework provides an
alternative to the standard hypothesis testing approach which relies on arbitrary chosen error probabilities where type I and type II error receive the same weight (e.g., 5% and 20% respectively), regardless of the consequences of making an error.[34, 44] Figure 2-1 shows the population EVSI across a number of sample sizes for a future research study. As the sample size increases and more uncertainty resolved the calculated population EVSI converges to the population EVPI (i.e., upper bound). Deducting the expected total cost from the EVSI results in the ENBS curve which, in this example, is positive for a wide range of sample sizes; however, the ENBS is at maximum when the sample size is 250 patients in each arm which represents the optimal sample size.

![Graph showing EVSI, ENBS, and Research cost against sample size per arm.](image)

EvSI = expected value of sample information; ENBS = expected net benefit of sampling

**Figure 2-1: Optimal sample size determination using value of information methods**

Beyond sample size determination, VOI analysis can optimize additional aspects of research design such as possible comparator arms and alternative follow-up periods.[38, 45] More uncertainty is expected to resolve with longer follow-up and with more comparator arms albeit with additional research costs. The preferred trial design would be the one that maximises the ENBS.[38]
2.4.5 What priority should this research study take?

Typically, decisions to fund and prioritise research proposals have been subjectively made based on the opinions, judgments and consensus among experts on a research panel evaluating the scientific merit and relevance of the proposals.[46] However, some objective approaches have been proposed and implemented to prioritise research projects such as the burden of disease and the Payback approach.[46, 47] In the burden of the disease, the higher the cost of a disease the greater the need for research, but this does not take into consideration the expected incremental costs and returns from the additional research.[38, 46] Moreover, the burden of the disease approach might undermine investment in rare diseases as it focuses the decision maker’s attention on common diseases where there is usually a high illness cost. In the payback approach, however, the benefits and costs from conducting and implementing research are evaluated and compared.[38, 46] Under this approach, a research project is worthwhile if its expected benefits outweigh its expected costs.[46] Nevertheless, the Payback requires the comparison of the costs and benefits of undertaking a predesigned research project, implicitly assuming that the proposed research has been optimally designed.[48]

VOI analysis has been proposed as an alternative quantitative approach to prioritise research studies.[38, 49] Under the VOI approach, competing research proposals are ranked according to their expected values whereby priority is given to the studies with the highest ENBS.[38] This is illustrated in a hypothetical example in Table 2-2 where five research proposals are being compared. Of note, it has been argued that the proposal with the highest ENBS may not necessarily provide the highest return on investment (i.e., ENBS divided by the expected total cost of research).[38]
Table 2-2: Prioritising alternative research proposals using the value of information approach

<table>
<thead>
<tr>
<th>Study</th>
<th>EVSI</th>
<th>Total cost</th>
<th>ENBS</th>
<th>ROI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>$5,000,000</td>
<td>$1,500,000</td>
<td>$3,500,000</td>
<td>233%</td>
</tr>
<tr>
<td>Study 2</td>
<td>$4,500,000</td>
<td>$1,250,000</td>
<td>$3,250,000</td>
<td>260%</td>
</tr>
<tr>
<td>Study 3</td>
<td>$3,000,000</td>
<td>$1,250,000</td>
<td>$1,750,000</td>
<td>140%</td>
</tr>
<tr>
<td>Study 4</td>
<td>$3,000,000</td>
<td>$1,500,000</td>
<td>$1,500,000</td>
<td>100%</td>
</tr>
<tr>
<td>Study 5</td>
<td>$2,000,000</td>
<td>$1,250,000</td>
<td>$750,000</td>
<td>60%</td>
</tr>
</tbody>
</table>

EVSI = expected value of sample information; ENBS = expected net benefit of sampling; ROI = return on investment which is the ENBS divided by the total cost.

2.5 VOI applications in health care

VOI analysis is increasingly applied in health care to inform decisions, optimise trial design and prioritise research.[38] In a systematic review on the application of VOI in health technology assessment, a total of 118 papers were identified of which 59 were applied.[31] The authors of this review observed a rapidly accumulating literature base on VOI from 1999 onwards for methodological papers and from 2005 onwards for applied papers.[31] Most of the identified applied articles estimated the EVPI and the EVPPI, indicating that the majority of the studies used the VOI approach to estimate the maximum value of additional information to assess whether further research is warranted.[31] However, limited number of applied papers reported the preferred VOI measures of EVSI (six articles) and ENBS (four articles).[31] Similar results were reported in a recent systematic review on VOI application in oncology where less than 10% of the identified articles reported the use of this approach to inform optimal trial design and research prioritisation.[50]

2.5.1 Informing decisions

The most explicit use of VOI methods to inform decisions is by the National Institute
for Health and Care Excellence (NICE) in England. Claxton et al. have developed a VOI-based framework for NICE to inform the following decision options:[32]

1. Approve based on existing information.
2. Approval with research (i.e., Approve and ask for additional research)
3. Only in research (i.e., Delay approval and ask for additional research)
4. Reject based on existing information.

Generally, an intervention may be approved if cost-effective or rejected if not cost-effective based on the available evidence if additional research is not worthwhile. When the intervention is cost-effective ‘approval with research’ would be appropriate if additional research is possible and worthwhile.[32] Conversely, if the technology is not cost-effective but additional research is worthwhile, ‘only in research’ would be the preferred option. Nevertheless, exceptions from this general rule would be appropriate depending on the presence of irrecoverable cost associated with the implementation of the new intervention (e.g., cost of training).[32] Thus, ‘only in research’ or even ‘reject based on existing information’ rather than ‘approval with research’ or ‘approve based on existing information’ may be appropriate even if the research is possible and worthwhile when there are significant irrecoverable costs.[32]

A recent study reviewed NICE technology appraisals with ‘only in research’ or ‘approval with research’ recommendations and examined the key considerations that led to those decisions.[51] In total, 29 final documents and 31 draft guidance documents included ‘only in research’ or ‘approval with research’ recommendations. Overall, 86% of final guidance included ‘only in research’ recommendations. Of these, the majority were for technologies considered to be cost ineffective (83%) with 66% of the final guidance specified the need for further evidence on relative effectiveness.[51]
From the industry perspective, any change in the price of the intervention, such as through patient access schemes or price negotiations, will affect the key assessments, and possibly leading to a different decision.[32, 52] Subsequently, once the need for additional information and the size of irrecoverable costs are recognised, the threshold price that would lead to ‘adopt based on existing evidence’ rather than ‘only in research’ will always be lower than a single value-based price based on expected cost effectiveness alone.[32] Willan and Eckermann have proposed a framework to bring together the societal and industry perspectives, allowing for trade-offs between the value and cost of research and the price of the new intervention.[53] Under this framework, if the decision maker’s threshold price exceeds the sponsor’s, then current evidence is sufficient since any price between the thresholds is acceptable to both. However, if the decision maker’s threshold price is lower than the sponsor’s, then no price is acceptable to both and the sponsor’s optimal strategy is to conduct additional research.[53]

2.5.2 Optimising trial design

The use of VOI methods in optimising trial design remains limited and most applications have been restricted to the estimation of optimal sample size, and mainly in two-arm randomised trials.[42, 54, 55] For example, Koerkamp et al. have applied VOI analysis to patient-level data from two randomised trials on intermittent claudication and magnetic resonance imaging (MRI) in acute knee trauma.[54, 56] The optimal study design for the treatment of intermittent claudication would involve a trial collecting data on the quality-adjusted life expectancy and additional admission costs for 525 patients per treatment arm.[54] For the MRI in acute knee trauma, three parameters were found responsible for most of the decision uncertainty: number of quality-adjusted life-years, cost of an overnight hospital stay, and friction costs.[56] A study in which data on these three parameters are
gathered would have an optimal sample size of 3,500 patients per arm.[56] Soares et al. showed how VOI analysis informed the optimal future trial design on negative-pressure wound therapy for severe pressure ulcers.[57] In their study, a three-arm trial with one-year follow-up and a sample size of 497 patients in each arm was estimated to be the most efficient.[57]

2.5.3 Prioritising research

In a survey prepared for the Agency for Healthcare Research and Quality (AHRQ), research prioritisation approaches for 48 research-sponsoring organisations from the United States, United Kingdom, Australia, Germany, and Canada were identified and compared.[58] The results showed that only 31 (65%) organisations utilised specific priority-setting methods. The most explicit use of VOI and other quantitative methods was by NICE, where the assessment is usually performed by a network of academic centres under the umbrella of the National Institute for Health Research (NIHR) Health Technology Assessment programme.[58] This is expected, because in the United Kingdom where research is often commissioned on a tender basis, the application of VOI methods in identifying areas of value for funding bodies may be useful. On the other side, in settings where grant applicants have more active role in defining research questions (e.g., United States and Australia), it is suggested that more emphasis be placed on application of VOI methods by applicants in showing the connection of proposed trial designs to value of research and decision making.[38]

Recently, Carlson et al. have evaluated the feasibility and outcomes of incorporating VOI analysis into a stakeholder-driven research prioritisation process within a program to prioritise comparative effectiveness research in cancer genomics.[59] The authors described how they convened an external group of stakeholders to identify three high-priority cancer
genomics tests for further research and to rank these in order of priority for conducting further research.[59] These included expression testing for platinum-based adjuvant therapy (ERCC) in resectable non–small cell lung cancer (NSCLC), epidermal growth factor receptor (EGFR) mutation testing for erlotinib maintenance therapy in advanced NSCLC and breast cancer tumour markers (BC markers) for detection of recurrence after primary breast cancer therapy.[59] The study demonstrated how providing the stakeholders with VOI estimates about the three tests resulted in participants changing their ranking of the tests from 1) ERCC, 2) EGFR, 3) BC markers to 1) ERCC, 2) BC markers, 3) EGFR.[59]

**2.5.4 Challenges for VOI application**

The wide adoption of VOI methods in health care faces technical and policy challenges. From a technical perspective, conducting VOI analyses, especially calculating the EVSI and the EVPPI in non-linear models (e.g., Markov models) , requires sophisticated computations together with advanced expertise in economic evaluation and simulation techniques;[31] nevertheless, recent years have witnessed a progressive evolution and simplification of methods as well as advanced computing tools to reduce computational challenges.[38, 60-63] Another technical challenge is that certain assumptions are necessary when estimating VOI measures. These include the population expected to benefit from the technology, the lifetime of the technology, and the level of its implementation since the value of research is reduced if the results were not fully implemented.[37, 64-66] Several papers have addressed these assumptions and provided guidance to handle the uncertainty surrounding their estimates.[37, 64-66]

For the policy aspect, the main issue is that the decisions to adopt technologies and to conduct research are usually separate.[39] Claxton et al. noted this point in their first pilot study on VOI: “The key problem seems to be the policy environment where accountability
and transparency for research prioritisation and commissioning lags behind adoption and reimbursement decisions, and where there appears to be a separate remit for reimbursement and research decisions”. [39] Furthermore, the approach is relatively new and it will be some time before its value is realised by decision makers. Therefore, there is a need to create more awareness about the value of this approach through more applied studies, particularly using EVSI and ENBS as a sufficient condition for decision making. Moreover, there is a need to align VOI methods with the needs of the decision making organisations.[31]

Conclusion

VOI analysis is a systematic framework to quantify the value of additional evidence in reducing decision uncertainty. Various VOI methods have been developed to guide decision making, optimally design research studies and set research priorities. The application of VOI analysis in health care is increasing but remains limited due to conceptual, technical and policy challenges. Therefore, there is a need for more applied studies to demonstrate the value of this approach in real-world examples. There is also a need to simplify current VOI methods and align them with the needs of different jurisdictions to facilitate its incorporation into decision making frameworks.
STUDY AIM AND OBJECTIVES

Aim
Apply value of information analysis in a group of healthcare interventions to inform implementation decisions, optimise trial designs and prioritise research studies.

Objectives
1. Evaluate the cost-effectiveness of the included interventions and characterise decision uncertainty.
2. Perform value of information analysis to answer the following questions:
   - Is additional research required? And if yes,
   - What type of research?
   - Do the expected benefits of sampling exceed the costs?
   - What is the optimal research study design?
   - What priority should this research study take?
3. CHAPTER 3 METHODS

This chapter summarises the methods used to address the overall aim and objectives of this study. The methods presented in this chapter are general; however, the detailed methods are presented in the upcoming relevant chapters. The general approach in this study is to conduct an economic evaluation, characterise decision uncertainty and estimate value of information (VOI) measures for each intervention. The first section of this chapter gives an overview about the included healthcare interventions. The second section describes the methods for the economic evaluation and uncertainty handling. The third section reviews the methods for VOI measures calculation. The last section describes how the performed analyses would inform implementation decisions, optimise trial designs and prioritise future research studies.

3.1 The healthcare interventions

The National Centre of Research Excellence in Nursing (NCREN) at Griffith University, Queensland, is Australia’s first centre of research excellence in nursing funded by the National Health and Medical Research Council (NHMRC). The purpose of the NCREN is to provide evidence for clinicians and policy makers to improve the care of hospitalised patients. The centre has established partnerships with public hospitals in Queensland such as the Gold Coast Hospital, Princess Alexandria Hospital and the Royal Brisbane and Women’s Hospital. Although some of the clinical researchers in the NCREN had an idea about economic evaluations, the concept of VOI was totally new to them. The chief investigators received a presentation about the role of VOI in quantifying the value of additional research and how comparing the expected research benefits with its expected costs would help researchers design their trials in an economic way. The involved NCREN researchers were interested in exploring how sample size calculation would differ between VOI and the
traditional approach. They also thought that demonstrating the value of their intended research to funders would be helpful for future grant applications.

The research projects under the NCREN focus on two main areas: 1) interventions to manage symptoms, and 2) interventions to promote skin integrity (Figure 3-1).

![Diagram of NCREN interventions]

**Figure 3-1: NCREN interventions**

An intervention should meet the following criteria to be included in the study: targets a wide population of patients, the evidence to support its adoption is limited, and there is an NCREN pilot study or a systematic review on its effectiveness. Although interventions promoting skin integrity in hospitalised patients (e.g., intravascular devices) can benefit a wide population of patients in Australia and beyond, there is a paucity of published evidence to support a decision on their implementation. The NCREN has been evaluating or intend to evaluate these interventions in a number of research studies. Therefore, NCREN research projects evaluating skin integrity interventions would provide a good real-world example for the application of VOI analysis. These interventions include interventions addressing intravascular devices, pressure ulcers, and wound management.
3.1.1 Interventions for intravascular devices

Intravascular devices such as peripheral intravascular venous catheters (PIVC) are commonly used in hospitalised patients to deliver parenteral medications, fluids, blood products, and nutritional supplements. Millions of catheters are used around the world as up to 70% of patients in acute care hospitals need a short PIVC.[67] The inserted catheters can cause complications in patients such as irritation of the vein (i.e., phlebitis) or catheter-related blood stream infections. Additionally, the catheter may fail to function due to obstruction or simply dislodge from its place. Prolonging the dwelling time of the inserted catheters would save healthcare resources in terms of staff time and equipment.

Two catheter related interventions are evaluated in this study: 1) clinically-indicated replacement of peripheral intravenous catheters, and 2) tissue adhesive for securing arterial catheters. The current practice in hospitals is to change peripheral venous catheters regularly every 72-96 hours, regardless of the presence of complications.[68] The safety and efficacy of replacing peripheral catheters when clinically indicated compared with regular catheter replacement have been evaluated by the NCREN in a large, multicentre, randomised controlled trial.[69] For catheter securement, there are various devices to keep the catheters inserted in their place including conventional dressings (e.g., standard polyurethane) and a novel tissue adhesive material. A pilot study was conducted to assess the feasibility of a clinical trial to compare the efficacy and cost of different devices in securing arterial catheters in the operating theatre and the intensive care unit (ICU).[70]

3.1.2 Nutritional support for the prevention of pressure ulcers

A pressure ulcer is a localised injury to the skin or underlying tissue usually over a bony prominence as a result of pressure and/or shear.[71] This complication is associated with pain, an increased risk of infection and sepsis, longer hospital stay, higher hospitalisation
costs and mortality; however, the majority of pressure ulcers cases are preventable.[71-73] Hospitalised patients who are at high risk of pressure ulcers (e.g., older patients with restricted mobility) are at increased risk of malnutrition.[74, 75] The occurrence of pressure ulcers can increase with inadequate nutritional intake because balanced nutrition is associated with better skin integrity and reduced tissue breakdown.[76-79] Standard care for pressure ulcer prevention at hospitals includes regular risk assessment, standard hospital diet, redistribution surfaces, repositioning and skin protection strategies.[76, 77] A number of randomised controlled trials have shown that nutritional support, mainly in the form of oral high protein supplements, can reduce the incidence of pressure ulcers in high-risk patients.[80-83] The NCREN had explored the feasibility of a patient-centred nutritional support intervention to improve oral intakes among patients at risk of pressure ulcer.[84]

### 3.1.3 Negative pressure wound therapy for the prevention of surgical wound infections in caesarean sections

Millions of operations are carried out annually worldwide. Depending on patient factors (e.g., age, nutritional status, immunity) and the type and site of surgery, certain complications may affect surgical wound healing. One of the well-known complications is surgical site infections (SSI) which continue to be a major source of patient morbidity and represent a substantial burden to health care worldwide.[85, 86] Negative pressure wound therapy (NPWT) is a novel technology that has been used to prevent and treat a variety of surgical wound complications. NPWT consists of a closed, sealed system that produces negative pressure (i.e., suction) to the wound surface.[85, 86] Obesity in pregnant women increases the need for caesarean section delivery.[87-89] Moreover, obese women undergoing caesarean section are at increased risk of post-operative complications including surgical site infections. There is a paucity of literature on the safety and efficacy of NPWT in preventing
SSI in high-risk patients.[90] A feasibility NCREN study evaluated the efficacy of NPWT in obese women undergoing elective caesarean section.[90]

### 3.2 Economic evaluation of the included healthcare interventions

The economic evaluations are from the perspective of the State health department, Queensland, Australia. Depending on the decision problem and the evidence required, the evaluations are performed either alongside clinical trials (i.e., using patient-level data) or economic models. The economic models are structured to represent the decision problem and were validated by the NCREN clinicians. Evidence on the costs, utility scores and clinical effectiveness is obtained from various sources, including evidence synthesis, to populate the models.

The net monetary benefit (NB) is calculated for the evaluated interventions and their comparators, which is the effect multiplied by the willingness-to-pay threshold ($\lambda$), minus the cost. The NB for an intervention $i$ informed by the set of input parameters $\theta$ is calculated as:

$$ NB = \lambda \times Effect - Cost $$

Equation 3-1

The preferred intervention would be the one with the highest expected NB, that is when the incremental net benefit (INB) between the evaluated intervention and its comparator is positive.[6] Costs and monetary benefits are expressed in Australian dollar (AUD) at 2012-2014 prices. Further, costs and effects are not discounted because the time horizons in the analyses for these acute interventions are less than one year.

For the economic evaluations using patient-level data, non-parametric bootstrapping is used to characterise the uncertainty in the INB. Probabilistic sensitivity analysis (PSA) using Monte Carlo simulation is used to characterise uncertainty in the decision models. Input parameters are assigned probability distributions. In general, beta distributions for
probabilities and utilities, gamma distributions for costs and disutilities, and lognormal distributions for relative risks (RR). Cost-effectiveness acceptability curves (CEACs) are plotted to present the probability of an intervention being cost-effective across a range of possible willingness-to-pay thresholds.

3.3 Value of information analysis

Several methods have been proposed and reported in the literature to estimate VOI measures.[34, 38, 41, 44] These methods can be broadly categorised into analytical (i.e., mathematical) methods and simulation methods. The analytical approach provides closed-form solutions (i.e., equations) allowing fast VOI measures calculation.[34, 38, 44] It is based on the assumption that the (incremental) NB is approximately normal, supported by the central limit theorem.[44] The normality assumption may be reasonable if cost and effectiveness data were collected alongside a randomised controlled trial with a large sample size; however, NB is unlikely to be normally distributed in non-linear decision models or when the sample size in the trial is small.[13] Further, it is difficult to apply this approach in multi-arm clinical trials, and there is no analytical solution to calculate partial VOI such as the expected value of sample information for the parameter(s) of interest.[91]

Simulation methods include Monte Carlo simulation and bootstrapping. The latter shares most of the limitations of the analytical approach above. Its use is restricted to analyses using patient-level data and it does not calculate partial VOI measures.[61] On the other hand, Monte Carlo simulation provides a reliable and flexible approach to calculate the full spectrum of VOI measures. In economic models, VOI estimation using Monte Carlo simulation is an extension to the PSA. Moreover, this approach can be applied to trial-based economic evaluations by turning the output of the trial into a (multivariate) normal distribution of NBs for which the algorithms of VOI analysis for model-based economic
evaluations can be applied.[54, 61] Therefore, the main approach in this study is to calculate VOI measures using Monte Carlo simulation. Nevertheless, Monte Carlo simulation may be computationally demanding especially when two-level (i.e., nested) simulation is required. Recently, methods for efficient VOI calculation have been introduced.[62, 92-95] These include methods for efficient EVPPI calculation of single parameters. Unfortunately, these do not extend to groups of parameters simultaneously.[60, 96] Further, a method based on the numerical approximation of the posterior expected net benefit, conditional on sampled data, has been proposed as an efficient approach for EVSI calculation; however, this requires significant skills and effort to write the necessary computer code.[62, 97] Recently, Strong et al. have proposed a more straightforward non-parametric regression approach for calculating multi-parameter EVPPI and EVSI directly from a PSA sample.[94, 98] To explore the usefulness of this method in calculating VOI measures, the non-parametric regression approach is applied to the economic models in this study and the results are compared with the estimates obtained using Monte Carlo simulation.

The details of the VOI analyses are presented in the following chapters. Below is the general framework for VOI measures calculation using Monte Carlo simulation.

### 3.3.1 Expected value of perfect information (EVPI)

For an economic evaluation informing a decision on a number of interventions \(i\) with unknown parameters \(\theta\), Monte Carlo simulation takes \(K\) samples from the joint distribution of \(\theta\), and generates a corresponding set of \(K\) net benefits \(\text{NB}(i, \theta^1), \ldots, \text{NB}(i, \theta^K)\), for each intervention. Averaging these values, the optimal decision with current information is to adopt the intervention with the maximum expected NB, \(\max_i E_{\theta} \text{NB}(i, \theta)\). If we have perfect information on \(\theta\), the maximised NB becomes \(\max_i \text{NB}(i, \theta)\); however, because the true value of \(\theta\) is unknown, averaging the maximised values gives the expected maximum NB.
under perfect information, \( E_\theta \max_i NB (i, \theta) \). The EVPI is the difference between the expected NB of a decision with perfect information and the decision based on current information:[1]

\[
EVPI = E_\theta \max_i NB (i, \theta) - \max_i E_\theta NB (i, \theta)
\]

Equation 3-2

EVPI calculated using Equation 3-2 is an estimate for an individual patient episode (i.e., per-patient EVPI); however, because decisions are taken at the population level, population VOI measures should be determined. The population EVPI is the per-patient estimate multiplied by the total number of patients who will benefit from additional information over the expected lifetime of the intervention.[32, 34] In general, where \((P)\) is the prevalent population, \((T)\) is the lifetime of the intervention, \((I_t)\) is the incidence in each future time period \((t)\), and \((r)\) is the discount rate. The population EVPI can be expressed as follows:[32, 34]

\[
Population\ EVPI = EVPI \cdot (P + \sum_{t=1}^{T} \frac{I_t}{(1+r)^t})
\]

Equation 3-3

Due to the acute nature of the evaluated nursing interventions, the prevalence component can be removed from Equation 3-3 to become:

\[
Population\ EVPI = EVPI \cdot \sum_{t=1}^{T} \frac{I_t}{(1+r)^t}
\]

Equation 3-4

3.3.2 Expected value of perfect parameter information (EVPPPI)

For a subset of one or more parameters where \((\theta_i)\) is the parameter of interest and \((\theta_C)\) is the complementary set of parameters, the optimal decision is that with the maximum expected NB after averaging over the distribution of \(\theta_C\), conditional on \(\theta_i\), \nax_i E_{\theta_C|\theta_i} NB(i, \theta_i, \theta_C). Again, because we do not have perfect information on \(\theta_i\) we must take the expectation with respect to \(\theta_i\) which is \(E_{\theta_i} max_i E_{\theta_C|\theta_i} NB(i, \theta_i, \theta_C)\). The
EVPPI is the difference between the expected NB with perfect information and the expected NB with current information:[39, 99]

\[
EV_{\theta_{I}} = E_{\theta_{I}} \max_{i} E(\theta_{C}|\theta_{I}) NB(i, \theta_{I}, \theta_{C}) - \max_{i} E_{\theta} NB(i, \theta) \quad Equation \ 3-5
\]

The Monte Carlo solution to the conditional term in Equation 3-5 is to run a two-level simulation. The outer-loop samples from \( \theta_{I} \) and then the inner loop samples from \( \theta_{C} \) conditional on the outer sampled value of \( \theta_{I} \). Convergence of the EVPPI estimates informed the number of inner and outer simulations.

When the model is linear (e.g., a decision tree) with no correlation between input parameters, a one-level simulation approach can be used in which we sample from \( \theta_{I} \), but keep the complementary parameters \( \theta_{C} \) fixed at their prior means:[99]

\[
EV_{\theta_{I}} = E_{\theta_{I}} \max_{i} NB(i, \theta_{I}, E(\theta_{C})) - \max_{i} E_{\theta} NB(i, \theta) \quad Equation \ 3-6
\]

Similarly to the population EVPI, population EVPPI can be calculated by multiplying the per-patient estimate by the population in Equation 3-4.

### 3.3.3 Expected value of sample information (EVSI)

For a future study with a sample size \( n \) that will provide additional information for \( \theta_{I} \), the study data can be summarised in a low dimensional summary statistic \( D \). Assuming that \( \theta_{I} \) and its complement set \( \theta_{C} \) are a priori independent, the expected optimal NB given \( D \) is found by taking the expectation over the posterior distribution of \( \theta_{I} \) given \( D \) and the prior distribution of \( \theta_{C} \), which is \( \max_{\theta_{I}, \theta_{C}} E_{\theta_{C}|\theta_{I}}(D) NB(i, \theta_{I}, \theta_{C}) \). As \( D \) is unknown, we average over the distribution of \( D \), which gives \( E_{D} \max_{i} E_{\theta_{C}|\theta_{I}}(D) NB(i, \theta_{I}, \theta_{C}) \). The EVSI is the difference between this, and the expected NB with current information:[41]

\[
EVSI_{n} = E_{D} \max_{i} E_{\theta_{C}|\theta_{I}}(D) NB(i, \theta_{I}, \theta_{C}) - \max_{i} E_{\theta} NB(i, \theta) \quad Equation \ 3-7
\]
As with EVPPI calculation, the first term in Equation 3-7 has a two-level Monte Carlo solution. The inner expectation requires a Bayes update of $\theta_I$ given data $D$, and the averaging of the NB function over this posterior distribution combined with the prior distribution of $\theta_C$. This is made assuming that the likelihood for the proposed data $D$ is conjugate with prior parameter distributions, which means that the parameters for posterior distributions can be estimated using closed forms and to scalar priors with no correlations.[41]

This nested simulation, with a potentially difficult inner loop, can be avoided if posterior mean parameter values can be calculated analytically and if the NB function takes a simple form such that we can “plug in” the posterior means directly [41].

$$EVSI_n = E_{\theta} \max_i NB(i, E(\theta_I|D), E(\theta_C)) - \max_i E_{\theta} NB(i, \theta)$$

Equation 3-8

### 3.3.4 Expected net benefit of sampling (ENBS)

Additional research is worthwhile when the expected benefits of a given research study (i.e., EVSI) exceeds its expected total cost. The total cost has two components, one financial (i.e., direct costs) and the other reflecting opportunity loss. Direct trial costs comprise the fixed costs $(C_f)$ of setting up a trial, and variable costs $(C_v)$ which is the cost per patient. Direct costs of research are obtained from the estimated research costs for relevant grant applications submitted by the NCREN team. The opportunity cost component stems from the fact that patient allocated to the standard intervention arm will not benefit from the new intervention; similarly, the eligible population that is not included in the trial will also incur opportunity cost awaiting results reporting and intervention implementation.[37, 45]

Accordingly, where $\tau$ is the time of recruitment and follow-up of the trial, $I_t$ is the incidence rate, and $(I_t(\tau))$ is the number of new eligible patients during trial recruitment and follow-up;
the total research cost for a two arm trial of \( n \) patients in each arm can be expressed as follows: [37, 45]

\[
\text{Total cost} = C_f + 2nC_v + (I_e(r) - n).\text{INB} \tag{3-9}
\]

The ENBS is the difference between the population EVSI and the total cost for a future research study:[34, 38]

\[
\text{ENBS} = \text{population EVSI}_n - \text{Total cost} \tag{3-10}
\]

### 3.4 Informing decision making, optimising trial design and prioritising research studies

The economic evaluation informs whether an intervention is cost-effective. To know if additional research is required, the EVPI is estimated. When the population EVPI appears to be too small compared with the expected research costs (e.g., when individual EVPI approaches zero), additional research would not be required, and accordingly, the decision would be to adopt or reject the intervention based on the current evidence. On the other hand, when the population EVPI is likely to exceed the costs of additional research, then further research is potentially worthwhile. In this case, the EVPPI is calculated to know the focus (i.e., the parameter(s) of interest) and type of the additional research; for instance, a randomised trial would typically be required to evaluate relative effectiveness. After that, the EVSI is calculated for the possible future study designs investigating the parameter(s) of interest. To establish a sufficient condition to decide whether additional research is worthwhile, the expected benefits of research are compared with the expected costs. When the expected direct research costs exceed the expected benefits, the research would not be cost-effective and the decision should be to adopt or reject based on the results of the cost-effectiveness analysis. When the expected research benefits exceed research costs (i.e., research is worthwhile), we need to assess whether we should delay the decision and wait for
the results of the future research (i.e., only in research (OIR)), allowing for opportunity costs of delay; or approve the intervention and undertake the research study (i.e., approve with research (AWR)), allowing for irrecoverable costs.\[33, 100\] Irrecoverable costs are the sunk costs that cannot be recovered when a decision is reversed.\[32, 101\] These include costs associated with intervention implementation (e.g., purchasing equipment, training) and an opportunity cost when the benefits of additional research are forgone because the research is less likely to take place when the intervention is implemented.\[32, 33, 100\] Delaying a decision is a preferable option if irreversible costs are greater than the opportunity costs of delay.\[32, 33, 100\] In this study, and assuming that additional research is possible with approval, OIR would be decided if the intervention is not cost-effective but additional research is worthwhile, or if the intervention is cost-effective and additional research is worthwhile but there is significant irrecoverable costs. AWR would be decided if the intervention is cost-effective, additional research is worthwhile, and the irrecoverable costs are lower than the opportunity cost of delay. Figure 3-2 illustrates decision pathways in this study.
Finally, the optimal design of a future trial would be the one that maximises the ENBS. Trial design dimensions would include sample size, number of comparators, and follow-up duration. Further, the future research studies are ranked according to their expected monetary benefits whereby the research study with the highest ENBS would be prioritised.

**Summary**

This chapter has summarised the healthcare interventions that are evaluated in this study and the methods to achieve study objectives. The healthcare interventions include: 1)
clinically-indicated replacement of peripheral intravenous catheters; 2) tissue adhesive for securing arterial catheters; 3) NPWT in caesarean section wounds; and 4) nutritional support for preventing pressure ulcers in high-risk patients. The general approach in this study is to conduct economic evaluation, characterise decision uncertainty and estimate VOI measures. Uncertainty and characterisation and VOI measures calculation are performed mainly using Monte Carlo simulations. When additional research is required, marginal research costs and marginal benefits are compared to inform whether additional research is worthwhile and at what design. Further, future research studies are prioritised according to their expected monetary benefits.

Chapters 4 to 7 present the economic evaluations and VOI analyses performed for each of the four interventions. Chapter 8 describes the application of non-parametric regression methods in NPWT and nutritional support interventions to calculate VOI measures.
4. CHAPTER 4 CLINICALLY-INDICATED REPLACEMENT OF PERIPHERAL INTRAVENOUS CATHETERS

Statement of contribution to co-authored published paper

This chapter includes a co-authored paper. The bibliographic details of the paper are:


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I led the research project, conducted the analysis and was the lead author.

(Signed)____________________________________(Date)________________________________

Haitham W Tuffaha

(Countersigned)_____________________________(Date)____________________________

Corresponding author: Haitham W Tuffaha

(Countersigned)_____________________________(Date)____________________________

Supervisor: Prof. Paul Scuffham
Cost-Effectiveness Analysis of Clinically Indicated Versus Routine Replacement of Peripheral Intravenous Catheters

Halhah W. Tuffaha · Claire M. Rickard · Joan Webster · Nicole Marsh · Louisa Gordon · Marianne Wallis · Paul A. Scuffham

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Abstract
Background Millions of peripheral intravenous catheters are used worldwide. The current guidelines recommend routine catheter replacement every 72–96 h. This practice requires increasing healthcare resource use. The clinically indicated catheter replacement strategy is proposed as an alternative.

Objectives To assess the cost effectiveness of clinically indicated versus routine replacement of peripheral intravenous catheters.

Methods A cost-effectiveness analysis from the perspective of Queensland Health, Australia, was conducted alongside a randomized controlled trial. Adult patients with an intravenous catheter of expected use for longer than 4 days were randomly assigned to receive either clinically indicated replacement or third-round routine replacement. The primary outcome was phlebitis during catheterization or within 48 h after catheter removal. Resource use data were prospectively collected and valued (2010 prices). The incremental net monetary benefit was calculated with uncertainty characterized using bootstrap simulations. Additionally, value of information (VOI) and value of implementation analyses were performed.

Results The clinically indicated replacement strategy was associated with a cost saving per patient of AU$7.60 (95% confidence interval [CI] 4.96–10.62) and a non-significant difference in the phlebitis rate of 0.41% (95% CI 0.26 to 2.15). The incremental net monetary benefit was AU$7.60 (95% CI 4.96–10.62). The expected VOI was zero, whereas the expected value of perfect implementation of the clinically indicated replacement strategy was approximately AU$3 million over 5 years.

Conclusion The clinically indicated catheter replacement strategy is cost saving compared with routine replacement. It is recommended that healthcare organizations consider changing to a policy whereby catheters are changed only if clinically indicated.

Key Points for Decision Makers

Routine replacement of peripheral intravenous catheters does not reduce the rate of catheter-related complications compared with clinically indicated replacement (e.g. because of catheter failure).

Replacing catheters only if clinically indicated saves healthcare costs.

It is recommended that healthcare organizations change to a policy whereby peripheral intravenous catheters are replaced when clinically indicated and not routinely.
4.1 Abstract

Background

Millions of peripheral intravenous catheters are used worldwide. The current guidelines recommend routine catheter replacement every 72-96 hours. This practice requires increasing healthcare resources. The clinically-indicated catheter replacement strategy is proposed as an alternative.

Objectives

To assess the cost-effectiveness of clinically-indicated versus routine replacement of peripheral intravenous catheters.

Methods

A cost-effectiveness analysis from the perspective of Queensland Health, Australia, was conducted alongside a randomised controlled trial. Adult patients with an intravenous catheter of expected use longer than four days were randomly assigned to clinically-indicated replacement, or third daily routine replacement group. The primary outcome was phlebitis during catheterisation or within 48 hours after removal. Resource use data were prospectively collected and valued (2010 prices). The incremental net monetary benefit was calculated with uncertainty characterised using bootstrap simulations. Additionally, value of information (VOI) and value of implementation analyses were performed.

Results

The clinically-indicated replacement strategy was associated with cost saving per patient of AUD 7.60 (95%CI: 4.96 to 10.62) and a non-significant difference in phlebitis rate 0.41% (95%CI: (−1.33 to 2.15). The incremental net monetary benefit was AUD 7.60 (95%CI: 4.96 to 10.62). The expected VOI was zero, whereas the expected value of perfect implementation
of the clinically-indicated replacement strategy was approximately AUD 5 million over five years.

Conclusion

The clinically-indicated catheter replacement strategy is cost-saving compared to routine replacement. It is recommended that healthcare organisations consider changing to a policy whereby catheters are changed only if clinically indicated.
4.2 Introduction

Peripheral venous catheters are commonly used to deliver medications, fluids, blood products, and nutritional supplements intravenously. Up to 70% of patients in acute care hospitals need a short peripheral intravenous catheter; about 330 million are sold each year in the USA alone.[67] The insertion of intravenous catheters is an invasive procedure that can cause discomfort to patients and is associated with complications such as irritation of the vein (phlebitis) in (2.3%-60%) and catheter-related bloodstream infections (CRBSI) in (0.1%) of the cases.[102-104] To reduce the incidence of these adverse events in adult patients, the current guidelines from the USA Centers for Disease Control and Prevention (CDC) recommend routine intravenous catheter replacement no more frequently than every 72–96 hours.[68] This routine replacement is the current practice in most of the hospitals around the world although it subjects patients to repeated invasive procedures and increases health-care costs. [69, 105] Interestingly, recent studies have found no evidence to support the routine replacement of catheters as a measure to mitigate catheter-related complications.[105-108]

A trial by Rickard et al.[69] tested whether patients who had their peripheral intravenous catheters replaced when clinically indicated would have equivalent rates of phlebitis and other complications but reduced health care resources and costs compared to the patients who had routine catheter replacement every three days. Patients in the clinically indicated group had their intravenous catheters removed only for completion of therapy, phlebitis, infiltration, occlusion, accidental removal, or suspected infection.[69] The aim of this paper is to determine the cost-effectiveness comparing the two approaches of clinically-indicated versus routine replacement of peripheral venous catheters based on the results of the clinical trial of Rickard et al.[69], within the context of the public health system in Queensland, Australia. In addition, a value of information and value of implementation
analyses were undertaken to characterise decision uncertainty and inform if the implementation of the recommended strategy is worthwhile.

4.3 Methods

4.3.1 Clinical trial design and results

Full details of the design and results of the clinical trial have been reported elsewhere.[69] Briefly, this was a multicentre, randomised, non-blinded equivalence trial which recruited adult patients with an intravenous catheter of expected use longer than four days from three hospitals in Queensland, Australia, between 2008 and 2009. Computer-generated random assignment was to clinically-indicated replacement or third daily routine replacement. Patients in the clinically-indicated group had their intravenous catheters removed only for completion of therapy, phlebitis, infiltration, occlusion, accidental removal, or suspected infection.[69] The primary outcome was phlebitis during catheterisation or within 48 hours after removal. Primary analysis was by intention to treat. Of the 3,379 eligible patients, 3,283 were enrolled and they were all included in the analysis (1,593 clinically indicated; 1,690 routine replacement). Patients’ characteristics were comparable across the two groups. Phlebitis occurred in 114 of 1,690 (6.75%) patients in the routine replacement group and in 114 of 1593 (7.16%) patients in the clinically-indicated group, an absolute risk difference of 0.41% (95% CI; -1.33 to 2.15%).[69] Catheter-related bloodstream infections were rare in both groups at one per 3,283 (0.03%) patients; no serious adverse events related to study interventions occurred. The results of the trial are summarised in Table 4-1.

Table 4-1: Trial outcomes per group based on intention-to-treat analysis [69]

<table>
<thead>
<tr>
<th></th>
<th>Clinically indicated</th>
<th>Routine replacement</th>
<th>Risk (95% CI)</th>
<th>p value</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

50
**Primary outcome, intention-to-treat analysis**

<table>
<thead>
<tr>
<th></th>
<th>(n=1,593)</th>
<th>(n=1,690)</th>
<th>RR</th>
<th>ARD</th>
</tr>
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<tbody>
<tr>
<td>Phlebitis per patient, n (%)</td>
<td>114 (7.16%)</td>
<td>114 (6.75%)</td>
<td>1.06 (0.83 to 1.36)</td>
<td>0.64</td>
</tr>
<tr>
<td>Phlebitis/1000 intravenous catheter days (95% CI)</td>
<td>13.08 (10.68 to 13.11 (10.71 to 15.48)</td>
<td>15.48</td>
<td>15.52</td>
<td>HR 0.94 (0.73 to 1.23)</td>
</tr>
</tbody>
</table>

**Secondary outcomes, n (n per 1000 intravenous catheter days)**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>(n=1,593)</th>
<th>(n=1,690)</th>
<th>HR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any infusion failure(\text{a})</td>
<td>670 (76.9)</td>
<td>636 (73.2)</td>
<td>0.99 (0.89 to 1.11)</td>
<td>0.87</td>
</tr>
<tr>
<td>Infiltration</td>
<td>279 (32.0)</td>
<td>235 (27.0)</td>
<td>1.06 (0.89 to 1.27)</td>
<td>0.51</td>
</tr>
<tr>
<td>Occlusion</td>
<td>344 (39.5)</td>
<td>344 (39.6)</td>
<td>0.92 (0.79 to 1.07)</td>
<td>0.92</td>
</tr>
<tr>
<td>Accidental removal</td>
<td>166 (19.0)</td>
<td>159 (18.3)</td>
<td>0.98 (0.79 to 1.23)</td>
<td>0.88</td>
</tr>
<tr>
<td>CRBSI(\text{b})</td>
<td>0 (0)</td>
<td>1 (0.11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All BSI</td>
<td>4 (0.46)</td>
<td>9 (1.03)</td>
<td>0.46 (0.14 to 1.48)</td>
<td>0.19</td>
</tr>
<tr>
<td>Venous (local) infection(\text{b})</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality, n (%)(\text{c})</td>
<td>4 (&lt;1%)</td>
<td>4 (&lt;1%)</td>
<td>1.06 (0.27 to 4.23)</td>
<td>0.93</td>
</tr>
</tbody>
</table>

ARD = absolute risk difference; BSI = bloodstream infection; CRBSI = catheter-related bloodstream infection; HR = hazard ratio; IRR= incident rate ratio; RR = relative risk.

\(\text{a}\) Combined endpoint of phlebitis, infiltration, occlusion, accidental removal, and CRBSI.

\(\text{b}\) Risk and p value inestimable because of 0 incidence in one or both groups.

\(\text{c}\) In all cases, mortality was unrelated to intravenous catheter treatment.

### 4.3.2 Resource use measurement

Health care resource utilisation data were collected alongside the clinical trial for the two study groups. These resources included equipment required for insertion and removal of intravenous catheters and staff time to insert and remove catheters (Table 4-2). The equipment required for each intervention arm was valued using negotiated hospital supply contract rates (2010) from the perspective of the State health department, Queensland Health, Australia. Based on observed rates of 14.5 minutes per insertion and 4.5 minutes per removal, the staff time was valued at the fixed industrial award wages in Australia (2010).[69]
Table 4-2: Unit costs used in the study (2010 AUD)

<table>
<thead>
<tr>
<th>Resource item</th>
<th>Unit</th>
<th>Unit cost (AUD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Equipment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intravenous catheter plus AS, burette, and fluid bag</td>
<td>Per item</td>
<td>25.13</td>
</tr>
<tr>
<td>Intravenous catheter plus AS and fluid bag</td>
<td>Per item</td>
<td>21.83</td>
</tr>
<tr>
<td>Intravenous catheter plus end cap</td>
<td>Per item</td>
<td>12.73</td>
</tr>
<tr>
<td>Gauze and tape for removal</td>
<td>Per item</td>
<td>0.37</td>
</tr>
<tr>
<td><strong>Staff</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Registered nurse</td>
<td>Per hour</td>
<td>32.93</td>
</tr>
<tr>
<td>Junior medical staff</td>
<td>Per hour</td>
<td>45.96</td>
</tr>
<tr>
<td>Senior medical staff</td>
<td>Per hour</td>
<td>67.16</td>
</tr>
</tbody>
</table>

AS = administration set; AUD = Australian Dollar

4.3.3 Analysis

*Cost-effectiveness analysis*

The economic evaluation was from the perspective of Queensland Health. The net monetary benefit (NB) approach was used for the cost-effectiveness analysis.[6] The NB for each strategy was calculated by multiplying its effect outcome by the WTP threshold and subtracting cost. The strategy with the maximum mean NB would be the preferred option. The incremental net monetary benefit (INB) is the difference between the NBs of the compared strategies and it represents the net gain from the introduction of the new strategy. Because the primary outcome of the trial was phlebitis rate, which is an adverse event, the effect outcome chosen for the cost-effectiveness analysis was the rate of phlebitis avoided (i.e., 1-phlebitis rate). A willingness to pay (WTP) threshold was set at AUD 0.0 per phlebitis case avoided since the treatment of phlebitis typically consisted only of removal and replacement of the affected intravenous catheter, which was already accounted for in the cost
calculations. The 95% non-parametric confidence interval (percentile method) based on 1,000 bootstrap replications was calculated to characterise the uncertainty in the INB.\textsuperscript{[11]} The results of the bootstrap simulation are shown in a cost-effectiveness plane. In addition, a cost-effectiveness acceptability curve (CEAC) was plotted to show the probability of one of the two strategies being cost-effective across a range of possible WTP thresholds.\textsuperscript{[109]}

The clinical trial directly compared the two alternative strategies of catheter replacement and prospectively captured all relevant outcomes and costs; therefore, an economic evaluation based on the trial data alone was considered sufficient (i.e. there was no need for modelling). Because the time horizon of the analysis was one month, total costs and effect outcomes were not discounted.

\textit{Value of information analysis}

Value of information (VOI) analysis is a systematic approach to measure uncertainty surrounding the results of cost-effectiveness analyses.\textsuperscript{[23]} The analysis would usually start by calculating the expected value of perfect information (EVPI). The EVPI is the difference between the net benefit of a decision given perfect information and the net benefit of the decision based on current information.\textsuperscript{[23]} The population-EVPI would be estimated by multiplying the calculated EVPI by the number of patients expected to benefit from this intervention over a given time horizon. The population that would benefit from the cost-effective strategy in Queensland public hospitals over the coming five years (discounted at 5\%) was estimated to be approximately 680,000. This is based on the assumption that one third of the 450,000 overnight admissions per year (150,000) would need catheter placement for more than 3 days.\textsuperscript{[110]} The population-EVPI reflects the magnitude of uncertainty in the results of a cost-effectiveness analysis and represents the maximum (upper bound) value for conducting further research to resolve this uncertainty.\textsuperscript{[23]} If further research appears
potentially worthwhile based on the population-EVPI, the value of resolving uncertainty surrounding a particular parameter (e.g., cost, effect) would be estimated by calculating the expected value of perfect parameter information (EVPPI).[23] To inform the value of a proposed future trial design (e.g., sample size) that could reduce uncertainty surrounding our results, the expected value of sample information (EVSI) would be calculated.[34, 38] If the EVPI was small (approaching zero) then there would be very little uncertainty surrounding the findings of our cost-effectiveness analysis, and there would be no need to estimate the EVPPI or the EVSI. Our focus on this case should be directed to the implementation of the strategy that was expected to be cost-effective.[64]

Methods to calculate the above VOI measures are described in detail elsewhere.[33, 41, 54] In general, VOI analysis was performed using Monte Carlo simulation. Random values for the estimated NBs were sampled repeatedly (10,000 iterations) from the normal distribution of the mean NB of each intervention, based on the Central Limit Theorem.[54] Then, NB for each strategy at each iteration was calculated to identify the optimal strategy. Averaging the maximum NBs from all iterations and subtracting from this the mean NB of the preferred strategy (calculated from the cost-effectiveness analysis) would give the EVPI. Assuming that the NB was a linear function of the cost and effect parameters, the same one-level Monte Carlo simulation technique would be used to calculate the EVPPI for the parameters of interest.[54] Similarly, the EVSI for a proposed trial of a given sample size could be calculated by sampling from the updated (using Bayesian updating) distribution of the mean NB for each strategy.[41]

**Value of implementation analysis**

The expected value of perfect implementation (EVPIm) is the difference between the expected benefit of perfectly implementing the cost-effective strategy and the expected
benefit of this strategy with sub-optimal implementation:[64]

\[ EVPI_{m} = NB \text{ of preferred strategy} - (P \times NB \text{ of preferred strategy}) \]  

Equation 4-1

\( P \) is the proportion of the eligible population that is currently benefiting from the preferred strategy, which can take values between 0-1. The population-EVPI\(_m\) was calculated by multiplying the EVPI\(_m\) from the above equation by the number of Queensland Health patients that would benefit from the preferred strategy over the coming five years (i.e., 680,000). The population-EVPI\(_m\) could inform the cost-effectiveness of programs to improve the implementation of the preferred strategy.

### 4.4 Results

#### 4.4.1 Resource use

Table 4-3 summarises resource utilisation data over the study period. The clinically indicated catheter replacement group had fewer catheters inserted compared to the routine replacement group (1.7(SD1.05) versus 1.9 (SD 1.17)) with a reduction of 0.21 catheter per patient (95% CI: 0.14 to 0.29). In addition, replacing peripheral intravenous catheters only when clinically indicated was associated with a significant reduction in the staff time for the insertion and removal of catheters at 3.08 minutes (95%CI: 1.97 to 4.19) and 0.94 minutes (95%CI: 0.60 to 1.30), respectively.

<table>
<thead>
<tr>
<th>Resources</th>
<th>Routine replacement (n=1,690)</th>
<th>Clinically-indicated (n=1,593)</th>
<th>Difference</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catheters inserted</td>
<td>1.90 (1.17)</td>
<td>1.70 (1.05)</td>
<td>-0.21</td>
<td>-0.29,-0.14</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Catheter + AS + burette + fluid  98%  97%
Catheter + AS + fluid  1%  1.5%
Catheter  1%  1.5%
Catheters removed 0.90 (1.17)  0.70 (1.05) -0.21 -0.28,-0.13 <0.0001
Gauze and tape for removal  100%  100%

Staff time
Insertion time (min)  27.58 (17.01)  24.50 (15.00) -3.08 -4.19,-1.97 <0.0001
Registered Nurse  51%  47%
Junior medical staff  37%  39%
Senior medical staff  12%  14%
Removal time (min)  4.07(5.30)  3.13 (4.70) -0.94 -1.30,-0.60 <0.0001
Registered Nurse  100%  100%

AS = Administration set; SD = standard deviation

4.4.2 Cost

Cost results are reported in Table 4-4. The routine replacement group incurred equipment cost of AUD 47.80 (SD 30.00) and staff cost of AUD 21.50 (SD14.10). For the clinically-indicated replacement group, the average cost for the equipment and staff was AUD 42.50 (SD 27.00) and AUD 19.20 (SD 13.10), respectively. The clinically-indicated replacement group had lower total cost (AUD 61.70; SD 39.50) versus AUD 69.30; SD 43.50)) with a statistically significant reduction in total cost at AUD 7.60 (95%CI: 4.96 to 10.62) per patient.

Table 4-4: Cost comparison between the trial groups (2010 AUD)

<table>
<thead>
<tr>
<th></th>
<th>Routine replacement (n=1690)</th>
<th>Clinically-indicated (n=1593)</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean</td>
</tr>
<tr>
<td>Cost (AUD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Equipment cost</td>
<td>47.80 (30.00)</td>
<td>42.50 (27.00)</td>
<td>-5.30</td>
</tr>
<tr>
<td>Staff cost</td>
<td>21.50 (14.10)</td>
<td>19.20 (13.10)</td>
<td>-2.30</td>
</tr>
</tbody>
</table>
4.4.3 Cost-effectiveness analysis

At a WTP of AUD 0.0, the clinically-indicated catheter replacement strategy was associated with a higher NB compared to the routine-replacement strategy (AUD -61.70 versus AUD -69.30) indicating that the clinically-indicated replacement is the preferred strategy (Table 4-5). The INB was AUD 7.60 (95%CI: 4.96 to 10.62) in cost saving. Figure 4-1 presents the INB in AUD with 95% uncertainty interval across a range of values for the WTP. From the CEAC, the probability of the clinically-indicated replacement strategy being cost-effective was greater than 95% as long as the WTP threshold was less than AUD 350 per phlebitis case avoided (Figure 4-2).

Table 4-5: Cost-effectiveness analysis

<table>
<thead>
<tr>
<th></th>
<th>Routine replacement</th>
<th>Clinically indicated</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=1,690)</td>
<td>(n=1,593)</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>93.25% (25.10)</td>
<td>92.84% (25.80)</td>
<td>-0.41%</td>
</tr>
<tr>
<td>Phlebitis avoided</td>
<td>AUD 69.30 (43.50)</td>
<td>AUD 61.70 (39.50)</td>
<td>AUD -7.60</td>
</tr>
<tr>
<td></td>
<td>-4.96 to -10.62</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cost</td>
<td>AUD 69.30 (43.50)</td>
<td>AUD 61.70 (39.50)</td>
<td>AUD 7.60</td>
</tr>
<tr>
<td></td>
<td>4.96 to 10.62</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NB *</td>
<td>AUD -69.30 (43.50)</td>
<td>AUD -61.70 (39.50)</td>
<td>AUD 7.60</td>
</tr>
<tr>
<td></td>
<td>4.96 to 10.62</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NB = net benefit; AUD = Australian Dollar; SD = standard deviation
*Willingness to pay threshold = AUD 0.0
INB = incremental net benefit

*From 1,000 bootstraps

Figure 4-1: The INB for the clinically-indicated replacement strategy with 95% uncertainty boundaries

Figure 4-2: Cost-effectiveness acceptability curve (CEAC) and the expected value of perfect information (EVPI)
4.4.4 Value of information analysis

The VOI analysis estimated the EVPI to be AUD 0.0 per patient for the proposed WTP threshold of AUD 0.0. Because the EVPI is the upper bound for the cost of uncertainty the EVSI would be also AUD 0.0. The EVPI was found to remain around AUD 0.0 as long as the WTP threshold per phlebitis case avoided was below AUD 350 (Figure 4-2).

4.4.5 Value of implementation analysis

Assuming that the current implementation of the clinically-indicated catheter replacement is zero, the value of perfectly implementing this strategy (EVPIm) based on the results of the cost-effectiveness analysis would be the NB of the clinically-indicated replacement strategy. The population-EVPIm was estimated to be around AUD 5 million (680,000 x AUD 7.6) for Queensland public hospitals over the coming five years.

4.5 Discussion

This study presents a cost-effectiveness and VOI analysis based on a multicentre randomised controlled trial comparing the clinically-indicated versus routine replacement of intravenous peripheral venous catheters. The clinical analysis concluded that the two strategies had the same rate of phlebitis and other complications including bloodstream infections. The cost-effectiveness analysis showed that the clinically-indicated replacement strategy was associated with a significant reduction in health care resources in terms of equipment and staff time, resulting in an average cost reduction of AUD 7.6 per patient. Because patient-level data on cost and effect were available from the clinical trial, the decision was made to conduct a full cost-effectiveness analysis to estimate the joint density of cost and effect differences and present uncertainty on cost-effectiveness acceptability curve. Performing a cost-minimisation analysis based on the equivalence in effect could result in biased estimation of uncertainty surrounding the results.[111] A VOI analysis was also
undertaken measure this uncertainty and to assess whether the evidence from the clinical trial is sufficient to change the current practice.

The results of the cost-effectiveness analysis suggested that adopting the clinically indicated catheter replacement strategy would result in an INB of AUD 7.6 per patient; the probability of this strategy being cost-effective approached 100% as long as the WTP for phlebitis case avoided was below AUD 350. The EVPI was also approaching zero under this WTP threshold suggesting negligible uncertainty and minimal value for additional research. This is one example of how the VOI analysis can support new strategies when decisions on strategy adoption and the need for further research are taken simultaneously.

Because globally a high number of patients need intravenous catheters, there is significant value of implementing the findings of this study by changing the current guidelines to recommend catheters replacement only if indicated clinically. The EVPIm in Queensland public hospitals over the coming five years was approximately AUD 5 million. This benefit of implementation would amount to higher figures if this strategy was implemented worldwide. For example, of the 37 million patients admitted to hospitals each year in the USA alone, if one-third (12.5 million) needed a catheter for more than 3 days, then a change to clinically-required replacement would prevent around 2.5 million unnecessary intravenous catheter insertions and would save up to 1 million hours of staff time. The expected monetary value of perfectly implementing this strategy in the USA alone over five years would be around USD400 million in health cost savings. To implement this strategy, hospitals with routine catheter replacement practice already in place need to change current policies and develop protocols to allow regular patient assessment and subsequent catheter removal or replacement for phlebitis, other complications, or when therapy has been completed. Nevertheless, the expected cost of implementation is less likely to exceed the
benefits from adopting the proposed strategy.

This study has a number of limitations. First, the analysis was based on a single clinical trial from Australia. However, the clinical trial was multisite with a large sample size (3,283 patients), with high quality methods to eliminate selection, allocation, and detection bias, together with 100% follow-up for the primary endpoint. Furthermore, the results of this study are in line with the findings from previous smaller randomised trials and a recent systematic review.[105, 106, 108] Second, the resources measured included equipment and staff time but excluded other resources such as hospital stay. Nevertheless, patients in the two groups were well matched in their baseline characteristics including the reason of admission, and it is unlikely that the hospital stay would be prolonged due to the complications associated with the compared strategies (e.g., phlebitis). Third, measuring and valuing different resources were from the perspective of one health department, Queensland Health. However, different jurisdictions and organisations can assign local values to relevant resources in order to have more accurate estimate of the magnitude of cost savings. We would expect that the relative costs of the key resources valued in these analyses (e.g., nursing time, catheter equipment) will be similar in other jurisdictions. The other assumption made was the WTP threshold of AUD 0.0; however, the effect of varying WTP values on the findings of the cost-effectiveness analysis was clearly presented in the results section. Finally, due to the acute nature of this intervention, it was difficult to measure the effect of each strategy on the quality of life of the hospitalised patients and conduct a cost utility analysis. Patients are presumably unlikely to want routine replacement since insertion of an intravenous catheter is painful, requiring piercing of skin, tissue, and vein with a steel needle at least once, or several times for a difficult insertion.[69]

4.6 Conclusion
There was no significant difference in the rate of phlebitis or other complications between the clinically-indicated versus the routine peripheral catheter replacement strategies. Changing catheters only when clinically indicated reduces health care resources and saves costs. Health care organisations should consider changing current policies to recommend the clinically indicated replacement of peripheral intravenous catheters.
5. CHAPTER 5 TISSUE ADHESIVE FOR SECURING ARTERIAL CATHETERS

Statement of contribution to co-authored published paper

This chapter includes a co-authored paper. The bibliographic details of the paper are:


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I led the research project, conducted the analysis and was the lead author.

(Signed)_____________________________(Date)___________________________

Haitham W Tuffaha

(Countersigned)_____________________________(Date)___________________________

Corresponding author: Haitham W Tuffaha

(Countersigned)_____________________________(Date)___________________________

Supervisor: Prof. Paul Scuffham
Value of information analysis optimizing future trial design from a pilot study on catheter securement devices

Haitham W Tuffaha1,2, Heather Reynolds3,4, Louisa G Gordon1,2, Claire M Rickard3,4 and Paul A Scurrham1,2

Abstract:
Background: Value of information analysis has been proposed as an alternative to the standard hypothesis testing approach, which is based on type I and type II errors, in determining sample sizes for randomized clinical trials. However, in addition to sample size calculation, value of information analysis can optimize other aspects of research design such as possible comparator arms and alternative follow-up times, by considering trial designs that maximize the expected net benefit of research, which is the difference between the expected cost of the trial and the expected value of additional information.

Purpose: To apply value of information methods to the results of a pilot study on catheter securement devices to determine the optimal design of a future larger clinical trial.

Methods: An economic evaluation was performed using data from a multi-arm randomized controlled pilot study comparing the efficacy of four types of catheter securement devices: standard polyurethane, tissue adhesive, bordered polyurethane and sutureless securement device. Probabilistic Monte Carlo simulation was used to characterize uncertainty surrounding the study results and to calculate the expected value of additional information. To guide the optimal future trial design, the expected costs and benefits of the alternative trial designs were estimated and compared.

Results: Analysis of the value of further information indicated that a randomized controlled trial on catheter securement devices is potentially worthwhile. Among the possible designs for the future trial, a four-arm study with 220 patients/arm would provide the highest expected net benefit corresponding to 130% return-on-investment. The initially considered design of 388 patients/arm, based on hypothesis testing calculations, would provide lower net benefit with return-on-investment of 79%.

Limitations: Cost-effectiveness and value of information analyses were based on the data from a single pilot trial which might affect the accuracy of our uncertainty estimation. Another limitation was that different follow-up durations for the larger trial were not evaluated.

Conclusions: The value of information approach allows efficient trial design by maximizing the expected net benefit of additional research. This approach should be considered early in the design of randomized clinical trials.

Keywords
Value of information, trial design, cost-effectiveness, peripheral catheters

1Griffith Health Institute, Griffith University, Gold Coast, Qld, Australia
2Centre for Applied Health Economics, School of Medicine, Griffith Health Institute, Griffith University, Meadowbrook, Qld, Australia
3National Health and Medical Research Council (NHMRC) Centre for Research Excellence in Nursing Interventions for Hospitalised Patients, Centre for Health Practice Innovation, Griffith Health Institute, Griffith University, Nathan, Qld, Australia
4Department of Anaesthesiology, Royal Brisbane and Women’s Hospital, Brisbane, Qld, Australia

Corresponding author:
Haitham W Tuffaha, Centre for Applied Health Economics, School of Medicine, Griffith Health Institute, Griffith University, Meadowbrook, Qld 4131, Australia.
Email: haitham.tuffaha@griffith.edu.au
5.1 Abstract

Background

Value of information analysis has been proposed as an alternative to the standard hypothesis testing approach, which is based on type I and type II error, in determining sample sizes for randomised clinical trials. However, in addition to sample size calculation, this approach can optimise other aspects of research design such as possible comparator arms and alternative follow-up times, by considering trial designs that maximise the expected net benefit of research, which is the difference between the expected cost of the trial and the expected value of additional information.

Purpose

To apply value of information methods to the results of a pilot study on catheter securement devices to determine the optimal design of a future larger clinical trial.

Methods

An economic evaluation was performed using data from a multi-arm randomised controlled pilot study comparing the efficacy of four types of catheter securement devices: standard polyurethane, tissue adhesive, bordered polyurethane and sutureless securement device. Probabilistic Monte Carlo simulation was used to characterise uncertainty surrounding the study results and to calculate the expected value of additional information. To guide the optimal future trial design, the expected costs and benefits of the alternative trial designs were estimated and compared.

Results

The analysis of the value of further information indicated that a randomised controlled trial on catheter securement devices is worthwhile. Among the possible designs for the future trial,
a four-arm study with 220 patients per arm would provide the highest expected net benefit corresponding to 130% return-on-investment. The initially considered design of 388 patients per arm, based on hypothesis testing calculations, would provide lower net benefit with a return-on-investment of 79%.

**Limitations**

Cost-effectiveness and value of information analyses were based on the data from a single pilot trial which might affect the accuracy of our uncertainty estimation.

**Conclusion**

Value of information analysis allows efficient trial design by maximising the expected net benefit of additional research. This approach should be considered early in the design of randomised clinical trials.
5.2 Introduction

Peripheral venous and arterial catheters are widely used around the world. Up to 70% of patients in acute care hospitals need a peripheral catheter; about 330 million are sold each year in the United States alone.[67] Effective securement of peripheral catheters to the skin is necessary to ensure that the device does not dislodge and move out of its place.[113] Additionally, adequate catheter securement minimises the chance for common catheter related complications such as catheter site irritation, catheter occlusion and catheter-related bloodstream infections.[113, 114] Despite the use of dressings to secure catheters, up to 92% of catheters still fail.[69, 113] Catheter failure requires removal and reinsertion of a new device, which consumes health care resources in terms of equipment and staff time, and causes discomfort to patients. Because most failures are likely to be preventable with effective catheter securement, there is a need to improve current catheter securement techniques. Unfortunately, this topic has received little research attention and there is a paucity of evidence to support practice improvement.[113, 115] A pilot study was conducted to assess the feasibility of a clinical trial to compare the efficacy of different devices in securing peripheral arterial catheters in the operating theatre and the intensive care unit (ICU). Typically, and based on the results of a pilot study, a larger clinical trial will be designed to more definitively answer the research question.

The sample sizes of clinical trials are usually calculated based on type I and type II error, and the minimum clinically important difference. The smallest sample size to identify the minimum clinically important difference is usually most economical due to the costs of running large clinical trials. However, an alternative to calculating sample size based on hypothesis testing is the value of information (VOI) approach. This is based on the notion that errors are costly and information is valuable since it reduces the risk of making wrong
decisions. VOI analysis estimates the expected benefits (i.e., value) of reducing this uncertainty with additional research, and subsequently informs optimal future trial design.[34, 38, 44] Based on this approach, if the expected benefit of an intended clinical trial outweighs its expected cost, then this study is worthwhile. Beyond sample size determination, VOI analysis can optimise additional aspects of research design such as possible comparator arms and alternative follow-up periods, by considering trial designs that optimise the expected benefits of research.[38, 45] In recent years, the application of the VOI analytic framework in healthcare interventions has grown; however, a limited number of applied papers have reported the use of this approach in informing optimal trial design.[31, 57, 116] Most applications of VOI analysis have been restricted to the estimation of optimal sample size, and the majority were in two-arm randomised trials.[42, 54, 55]

The aim of this paper is to apply VOI analysis to the results of a pilot study to determine the optimal trial design of a larger clinical trial on arterial catheter securement devices, from the perspective of the State health department, Queensland Health, Australia.

5.3 Material and methods

The general approach to achieve the aim of this paper was to conduct an economic evaluation to compare different types of arterial catheter securement devices, using the results from the pilot study. After that, probabilistic Monte Carlo simulation was performed to characterise uncertainty surrounding the analysis results and to calculate relevant VOI measures. To guide the optimal trial design, the expected costs and benefits of the alternative trial designs were estimated and compared.

5.3.1 The pilot study

A single centre, four-arm randomised controlled, non-blinded pilot study was conducted from November 2012 to February 2013, in Queensland, Australia. The included
subjects were adult surgical patients admitted post-operatively to the ICU and had a peripheral arterial catheter inserted. The study was approved by the health authority and the University Human Research Ethics Committees (Trial ID: ACTRN12611000769987). A centralised web-based randomisation service allocated patients in a 1:1:1:1 ratio to the control product of standard polyurethane dressing, or to the experimental arms of tissue adhesive, bordered polyurethane dressing or a sutureless securement device. The primary endpoint was catheter failure defined as any early removal of the catheter due to dislodgement, occlusion, phlebitis, local infection or catheter-related blood stream infection. Additionally, health care resource utilisation data were collected alongside the clinical trial. Resources captured included the equipment and staff time required for insertion and removal of arterial catheters and both initial and any replacement dressings required while in the ICU. Data were analysed by intention-to-treat analysis. A total of 123 participants were randomised and all received the allocated intervention. There were no differences in demographic or clinical risk factors between groups at enrolment. Catheter failure was lowest in the tissue adhesive group (2/32, 6.3%) and highest in standard polyurethane (6/30, 20%), with sutureless securement device (5/31, 16.1%) and bordered polyurethane (4/30, 13.3%) in the mid-range, but these differences were not statistically significant (p=0.43). Based on p value of 0.05, 95% power and at least 10% absolute reduction in catheter failure from the control value, the projected sample size for a larger four-arm clinical trial was estimated at 388 patients in each arm.

5.3.2 Economic evaluation

A decision tree was used to describe the research question (Figure 5-1). Clinical outcomes and cost data collected from the pilot study were used to populate the decision tree. Because the primary outcome of the trial was catheter failure probability, which is an adverse event, the effect outcome chosen for this cost-effectiveness analysis was the probability of
catheter success (i.e., 1- failure probability). Resources collected alongside the clinical trial were valued from the perspective of the State health department, Queensland Health, Australia, at 2012 prices and wages. Due to the acute nature of the evaluated interventions, it was difficult to measure the effect of each dressing on the quality of life of the hospitalised patients and conduct a cost utility analysis. The net monetary benefit approach was used for the cost-effectiveness analysis; the net benefit is the difference between the clinical effect valued at a given willingness-to-pay threshold and cost.[6] Considering the implications of catheter failure in terms of staff time and equipment, the willingness-to-pay threshold was set at AUD100 per catheter success. The net benefit was estimated for the four catheter securing devices, the preferred option would be the one with the maximum average net benefit.[6]

Figure 5-1: A decision tree based on the clinical trial

To characterise the uncertainty in the cost-effectiveness analysis, cost and effect parameters were characterised by probability distributions (Table 5-1). For this analysis, the probability of a catheter being successful was assigned a beta distribution. Thus, Success~

BPU = bordered polyurethane; SD = standard deviation; SPU = standard polyurethane; SSD = sutureless securement device; TA = tissue adhesive
1= successful catheter; 0= failed catheter
Beta \((a_0, b_0)\); where \(a_0\) is the number of successful catheters and \(b_0\) is the number of failed catheters in the initial clinical trial of sample size \(n_0\), for each intervention. Conditional on the outcome being 1 or 0 (i.e. successful or failed catheter), cost of success \(\text{Cost}_S\) and cost of failure \(\text{Cost}_F\) were assigned lognormal distributions; thus, the natural log of the cost is approximately normally distributed:

\[
\log(\text{Cost}_S) \sim \text{Normal}(V_S, \tau_{S(n_0)}^2) \\
\log(\text{Cost}_F) \sim \text{Normal}(V_F, \tau_{F(n_0)}^2)
\]

Where \(V_S\) and \(V_F\) are the respective mean log costs for success and failure, and \(\tau_{S(n_0)}\) and \(\tau_{F(n_0)}\) are the standard deviations of the log costs of success and failure in the initial trial. The mean intervention cost is a weighted average of the means of the lognormal distributions of success and failure costs.\[13\]

\[
\text{Cost} = \text{Success probability} \times \exp(V_S + 1/2\tau_{S(n_0)}^2) + (1 - \text{Success probability}) \times \exp(V_F + 1/2\tau_{F(n_0)}^2)
\]

Equation 5-1

**Table 5-1: Parameters used in the value of information analysis**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Efficacy parameters</th>
<th>Distribution</th>
<th>Cost parameters</th>
<th>Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPU</td>
<td>Catheter success probability</td>
<td>Beta (24,6)</td>
<td>Cost of catheter success</td>
<td>Lognormal (4.1,0.01)</td>
</tr>
<tr>
<td></td>
<td>Catheter failure probability</td>
<td>1- Success probability</td>
<td>Cost of catheter Failure</td>
<td>Lognormal (4.9,0.01)</td>
</tr>
<tr>
<td>BPU</td>
<td>Catheter success probability</td>
<td>Beta (26,4)</td>
<td>Cost of catheter success</td>
<td>Lognormal (4.2,0.02)</td>
</tr>
<tr>
<td></td>
<td>Catheter failure</td>
<td>1- Success</td>
<td>Cost of catheter</td>
<td>Lognormal</td>
</tr>
</tbody>
</table>
SSP

<table>
<thead>
<tr>
<th>Probability</th>
<th>Probability</th>
<th>Failure</th>
<th>Cost of catheter success</th>
<th>Cost of catheter failure</th>
<th>Lognormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catheter success</td>
<td>Beta (26,5)</td>
<td>Cost of catheter</td>
<td>Lognormal</td>
<td>(4.2,0.02)</td>
<td></td>
</tr>
<tr>
<td>probability</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catheter failure</td>
<td>1- Success</td>
<td>Cost of catheter</td>
<td>Lognormal</td>
<td>(4.9,0.01)</td>
<td></td>
</tr>
<tr>
<td>probability</td>
<td>probability</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TA</td>
<td>Catheter success</td>
<td>Cost of catheter</td>
<td>Lognormal</td>
<td>(4.3,0.01)</td>
<td></td>
</tr>
<tr>
<td>probability</td>
<td>Beta (30,2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catheter failure</td>
<td>1- Success</td>
<td>Cost of catheter</td>
<td>Lognormal</td>
<td>(4.9,0.01)</td>
<td></td>
</tr>
<tr>
<td>probability</td>
<td>probability</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BPU = bordered polyurethane; SD = standard deviation; SPU = standard polyurethane; SSD = sutureless securement device; TA = tissue adhesive

5.3.3 VOI analysis

Three measures of VOI were calculated: 1) the expected value of perfect information, 2) the expected value of sample information, and 3) the expected net benefit of sampling.

The first step in VOI analysis was to calculate the expected value of perfect information, this measure represents the value of the total uncertainty surrounding a research results.[23] In other words, the expected value of perfect information is the maximum value expected to be gained from resolving uncertainty by conducting additional research, hypothetically with infinity sample size.[34] This is the first hurdle before deciding whether additional research is worthwhile. If the expected value of perfect information was small then there would be low value for additional research. Conversely, if the expected value of perfect information is high, then the next step is to calculate the expected value of sample information to determine the value of information from additional trial with a specific sample size.[34] Finally, the expected net benefit of sampling is the difference between the expected value of sample information and the total cost of the intended trial for that sample size. The
total cost of a future trial should include fixed costs (e.g. salaries), variable costs (i.e., per patient recruited), and opportunity costs (i.e., benefits forgone) incurred by patients who receive the inferior intervention while the trial is performed.[38, 41] Because the intervention is acute and the recruitment of patients who require arterial catheters should not take long time, it was assumed that the future trial would report results in one year. The total cost for a future study was estimated to be AUD 120,000 of fixed costs and AUD 150 per patient in variable cost. To decide on the optimal future trial design in terms of the number of arms and optimal sample size, the expected value of sample information and the expected net benefit of sampling were calculated for the alternative possible designs (i.e., two-arm, three-arm, four-arm) across distinct sample sizes. The optimal trial design would be the design with the maximum expected net benefit of sampling.[34, 44]

Methods to calculate VOI measures are described in detail elsewhere.[33, 41, 62, 63] In general, VOI analysis was a continuation of the above probabilistic sensitivity analysis and included the steps below:[41, 63]

1. Sampling repeatedly (10,000 iterations) random values from the effect and cost parametric distributions.
2. Calculating the overall average net benefit for each intervention to determine the intervention with the highest net benefit (i.e., the preferred intervention).
3. Calculating the net benefit for each intervention at each simulation (i.e., iteration) to identify the intervention with the maximum net benefit at that iteration.
4. Averaging the maximum net benefits from all iterations (Step3) and subtracting from this the net benefit of the preferred intervention (Step2) would give the per-patient expected value of perfect information.
The expected value of sample information for a future study of $n$ sample size per arm was calculated using the following algorithm assuming the net benefit is linear on effect and cost parameters [41]:

1. Sampling effect and cost parameter values from their prior probability distributions

   \[
   \text{Success}_{\text{prior}} \sim \text{Beta} (a_0, b_0) \\
   \log (\text{Cost}_{\text{Sprior}}) \sim \text{Normal} (V_S, \tau_{S(n_0)}^2) \\
   \log (\text{Cost}_{\text{Fprior}}) \sim \text{Normal} (V_F, \tau_{F(n_0)}^2)
   \]

2. Sampling from the predictive distribution of the sufficient statistics arising from the new study size $n$, given the sampled value in step 1.

   \[
   \text{Success}_{\text{predicted}} \sim \text{Binomial} (\text{Success}_{\text{prior}}, n) \\
   \log (\text{Cost}_{\text{Spredicted}}) \sim \text{Normal} (\log (\text{Cost}_{\text{Sprior}}), \tau_{S(n)}^2) \\
   \log (\text{Cost}_{\text{Fpredicted}}) \sim \text{Normal} (\log (\text{Cost}_{\text{Fprior}}), \tau_{F(n)}^2)
   \]

3. Combining prior and predicted data to estimate the posterior expectations for the cost and effect parameters for each intervention.[41]

   \[
   \text{Success}_{\text{posterior}} = \frac{(a_0 + \text{Success}_{\text{predicted}})}{(n+n_0)} \quad \text{Equation 5-2}
   \]

   \[
   \text{Cost}_{\text{Sposterior}} = \exp \left( (\log (\text{Cost}_{\text{Sprior}})*n_0 + \log (\text{Cost}_{\text{Spredicted}})*n / (n_0+n)) + 1/2 \right. \\
   \left. \tau_{S(n+n_0)^2} \right) \quad \text{Equation 5-3}
   \]

   \[
   \text{Cost}_{\text{Fposterior}} = \exp \left( (\log (\text{Cost}_{\text{Fprior}})*n_0 + \log (\text{Cost}_{\text{Fpredicted}})*n / (n_0+n)) + 1/2 \right. \\
   \left. \tau_{F(n+n_0)^2} \right) \quad \text{Equation 5-4}
   \]

The posterior expected cost of the intervention ($\text{Cost}_{\text{posterior}}$) as a function of the posterior expectations for the cost and effect parameters can be expressed as,

\[
\text{Cost}_{\text{posterior}} = \text{Success}_{\text{posterior}} \times \text{Cost}_{\text{Sposterior}} + (1 - \text{Success}_{\text{posterior}}) \times \text{Cost}_{\text{Fposterior}}
\quad \text{Equation 5-5}
\]
4. Calculating the posterior net benefit for each intervention, using the posterior expectations above.

5. Identifying the intervention that has the expected maximum posterior net benefit.

6. Repeating Steps 1-5 (10,000 times) and averaging the posterior net benefits from Step 5.

7. The per-patient expected value of sample information for a new study with \( n \) sample size per arm is the difference between the average net benefit in Step 6 and the net benefit of the preferred intervention calculated in Step 2 of the expected value of perfect information algorithm.

The VOI measures estimated from these simulations are for the individual patient; however, to calculate VOI at the population level, the per-individual measures were multiplied by the number of patients expected to benefit from the evaluated devices over a given time period. The expected population for the State of Queensland was estimated at 125,000 ICU patients over the coming five years.

5.4 Results

5.4.1 Cost-effectiveness analysis

Clinical outcomes and costs for the four catheter securement devices are summarised in Table 5-2. At a willingness-to-pay threshold of AUD 100 per catheter success, the average net benefit was the highest for tissue adhesive (AUD 14.1) indicating that tissue adhesive was the preferred intervention. The probability of tissue adhesive being the dressing with the highest net benefit was 35%; however, the effect of varying willingness-to-pay threshold on this probability was shown in the cost effectiveness acceptability curve in Figure 5-2.
Table 5-2: Cost-effectiveness analysis results

<table>
<thead>
<tr>
<th>Device</th>
<th>Success Mean (SD)</th>
<th>Cost Mean (SD)</th>
<th>NB(^a) Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPU (n=32)</td>
<td>0.80 (0.40)</td>
<td>AUD 74.4 (28.1)</td>
<td>AUD 5.6 (68.0)</td>
</tr>
<tr>
<td>BPU (n=30)</td>
<td>0.87 (0.34)</td>
<td>AUD 75.1 (26.4)</td>
<td>AUD 13.5 (59.2)</td>
</tr>
<tr>
<td>SSD (n=31)</td>
<td>0.83 (0.37)</td>
<td>AUD 79.0 (27.4)</td>
<td>AUD 5.3 (63.5)</td>
</tr>
<tr>
<td>TA  (n= 30)</td>
<td>0.93 (0.25)</td>
<td>AUD 80.1 (16.3)</td>
<td>AUD 14.1 (39.2)</td>
</tr>
</tbody>
</table>

AUD = Australian dollar; NB = Net benefit; SD = standard deviation; BPU = bordered polyurethane; SD = standard deviation; SPU = standard polyurethane; SSD = sutureless securement device; TA = tissue adhesive

\(^a\)Willingness-to-pay per catheter success = AUD 100

Figure 5-2: The probability of an intervention being cost-effective under different willingness-to-pay thresholds per catheter success

5.4.2 VOI analysis

The expected value of perfect information from the pilot study was AUD 6.8 per patient at the willingness-to-pay threshold of AUD 100 per catheter success, this amounted to a population expected value of perfect information of AUD 850,000 (125,000 patients x AUD
6.8). Such value indicated high level of uncertainty in the pilot study results, suggesting that additional research might be potentially worthwhile. As the sample size increased and more uncertainty resolved the calculated expected value of sample information converged to the expected value of perfect information (Figure 5-3). The highest expected value of sample information was associated with the four-arm trial design followed by the three-arm designs of (standard polyurethane, bordered polyurethane and tissue adhesive) and (standard polyurethane, bordered polyurethane, and sutureless securement device); however, the three-arm design of (standard polyurethane, sutureless securement device, and tissue adhesive) provided lower expected value of sample information compared to the two-arm trial (standard polyurethane, bordered polyurethane). Subtracting the associated total research cost from the four designs with the highest expected value of sample information values generated the expected net benefit of sampling curves (Figure 5-4).

![Figure 5-3: Expected value of sample information for the alternative future trial designs](image)

**Figure 5-3: Expected value of sample information for the alternative future trial designs**
The expected net benefit of sampling was positive, that is the expected research benefits exceeded expected costs, for sample sizes from 50 to 980 in each arm for all future trial designs. However, the expected net benefit of sampling was the highest in the four-arm design with 220 patients in each arm with AUD $325,324 at a total cost of AUD $250,000, providing a return-on-investment of 130%; however, the return-on-investment for the three-arm design (standard polyurethane, bordered polyurethane and tissue adhesive) was the highest with 132% although it had lower expected net benefit of sampling compared to the four-arm design (Table 5-3). Finally, the expected net benefit of sampling from the initially calculated sample size of 388 patients per arm was AUD $282,200 at a cost of AUD $357,800, providing a return-on-investment of 79%.

Figure 5-4: Expected net benefit of sampling for the alternative future trial designs
Table 5-3: Calculated value of information measures for the alternative trial designs

<table>
<thead>
<tr>
<th>Design</th>
<th>EVSI (AUD)</th>
<th>Total cost (AUD)</th>
<th>ENBS (AUD)</th>
<th>ROI</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPU,BPU,SSD,TA</td>
<td>575,324</td>
<td>250,000</td>
<td>325,324</td>
<td>130%</td>
</tr>
<tr>
<td>SPU,BPU,TA</td>
<td>510,645</td>
<td>220,000</td>
<td>290,645</td>
<td>132%</td>
</tr>
<tr>
<td>SPU,BPU,SSD</td>
<td>474,650</td>
<td>220,000</td>
<td>255,650</td>
<td>116%</td>
</tr>
<tr>
<td>SPU,BPU</td>
<td>429,255</td>
<td>190,000</td>
<td>239,255</td>
<td>126%</td>
</tr>
<tr>
<td>SPU,SSD,TA</td>
<td>370,314</td>
<td>220,000</td>
<td>150,314</td>
<td>68%</td>
</tr>
<tr>
<td>SPU,TA</td>
<td>315,583</td>
<td>190,000</td>
<td>125,583</td>
<td>66%</td>
</tr>
<tr>
<td>SPU,SSD</td>
<td>224,990</td>
<td>190,000</td>
<td>34,990</td>
<td>18%</td>
</tr>
</tbody>
</table>

EVSI = expected value of sample information; ENBS = expected net benefit of sampling; BPU = bordered polyurethane; AUD = Australian dollar; SD = standard deviation; SPU = standard polyurethane; SSD = sutureless securement device; TA = tissue adhesive; ROI = return on investment.

In a sensitivity analysis, the optimal design remained with four arms and a sample size of 220-250 per arm when the life time of the technology was increased to 10 years, and a sample size between 190-220 per arm when the willingness-to-pay varied between AUD 50 to AUD 400 for catheter success.

5.5 Discussion

This paper presents an application of VOI analysis to inform the optimal trial design for a clinical trial based on the results of a pilot study on arterial catheter securement devices. The pilot study showed that newer devices such as tissue adhesive and bordered polyurethane were more effective than the conventional standard polyurethane dressing. However, when considering the costs of the evaluated devices, the tissue adhesive appeared to be more cost-effective compared to the other options. This finding was not certain because the probability of tissue adhesive being cost-effectiveness was only 35%. Applying VOI methods to the
results of the pilot study indicated that the value of this uncertainty is sufficient to justify further research.

VOI analysis compared alternative future trial designs and suggested the optimal design that maximises research benefits in terms of the number of arms and sample size; the four-arm trial design with 220 patients provided the highest expected net benefit of sampling. In addition, calculating the expected net benefit of sampling and return-on-investment enabled a quantitative prioritisation of the proposed designs.[38] Interestingly, the design with the highest expected net benefit of sampling may not necessarily provide the highest return-on-investment, which was obvious from the expected net benefit of sampling and the return-on-investment for the four-arm design and the three-arm design (standard polyurethane, bordered polyurethane and tissue adhesive). Because the objective of health care systems is to maximise health benefits, research proposals should be prioritised based on their expected net benefits.[34, 38] The return-on-investment is a useful indicator to compare the efficiency (i.e., how favourable the investment gains are compared to cost) of the competing research proposals, particularly when two or more proposals provide the same net benefit.

Another important feature of this analysis was that the VOI-based sample size (i.e., 220 patients per arm) was more economical than the sample size initially calculated based on type I and II error, and the smallest clinically significant difference. It has been argued that the VOI framework can provide an alternative to the standard hypothesis testing approach which relies on arbitrary chosen error probabilities where type I and type II error receive the same weight (e.g., 5% and 20% respectively) regardless of the consequences of making an error.[34, 44] In optimising trial design, the VOI approach takes several factors into consideration. Such factors include the relative benefits and costs of the evaluated
interventions, the life-time of the intervention, the population expected to benefit from research findings, the trial follow-up time, level of intervention implementation, and the associated research costs. Selecting the appropriate values for the above mentioned factors is challenging and has been explored in several recent papers on VOI analysis informing multi-stage trial design, between-study variation, imperfect research implementation, and optimal trial design across jurisdictions.[66, 117-119]

In this paper, the calculated VOI measures were mainly driven by the level of uncertainty from the pilot study, the expected population in the State of Queensland that would benefit from the evaluated interventions over a given time period and the willingness-to-pay threshold per catheter success. However, a sensitivity analysis was performed to explore the effect of varying the willingness-to-pay threshold and the time horizon of the technology on our VOI estimates. Another issue is that the opportunity cost incurred by the patients not benefiting from the intervention during the trial period was negligible; the difference in the net benefit between the tissue adhesive and the second best alternative was less than one dollar per patient. Thus, avoiding this opportunity cost by adopting the tissue adhesive intervention and undertaking additional research instead of delaying implementation and awaiting the results of the future trial would not significantly alter the results of this analysis. Furthermore, delaying adoption would be a reasonable decision given the difficulty of reversing implementation if the results of the larger trial showed that tissue adhesive is not the preferred intervention.

A limitation of our work is that the cost-effectiveness and VOI analyses were based on the data from a single pilot study; therefore, it is possible that we have not accurately estimated decision uncertainty.[54, 120] Moreover, the design and conduct of pilot studies is not as rigorous as large randomised controlled trials which may result in biased results.[120]
Ideally, different sources of information should be sought to inform the analyses; however, the evidence in the field of catheter devices is scarce and we could not identify relevant studies despite an extensive systematic search of literature. In addition, the experience of clinicians with the novel tissue adhesive material is limited, and thus, expert opinion may not be helpful. Furthermore, we had to make certain assumptions regarding parameter distributions. Given the small sample size in the multi-arm pilot study, we preferred to model patient-level data instead of using bootstrapping or sampling from an assumed normally distributed net benefit.[13] We also assumed that the pilot study population was the same as the population that would be included in the full trial, and also the same as the population that we would make treatment decisions for. Another limitation of this analysis is that different follow-up durations were not evaluated in informing the optimal trial design; due to the acute nature of the interventions it was assumed that the outcomes would be readily available after the end of the proposed trial (i.e., one year). With chronic diseases for example, longer follow-up period provides more information to resolve uncertainty; however, this comes with increased research costs.

Unfortunately, despite the benefits of VOI methods, the application of this approach in informing optimal trial design remains limited for two main reasons.[42, 54, 55, 121, 122] First, it is commonly believed that estimating VOI measures, particularly the expected value of sample information, is computationally challenging.[31] Nevertheless, in recent years there has been a progressive evolution and simplification of VOI methods.[43, 60, 62, 96, 120, 123] For instance, closed form solutions (i.e. equations) are available to enable simpler calculation of VOI measures including the expected value of sample information.[38, 43, 44] Second, optimising research designs using VOI methods is relatively new; therefore, there is
a need to create more awareness about the usefulness of this approach among researchers and research organisations using applied real-world examples.

In conclusion, the results in this paper indicated that a larger clinical trial on catheter securement devices is worthwhile. Based on the VOI analysis, a future trial design of four arms with 220 patients in each arm is more economical than a design with the sample size calculated by hypothesis testing. The VOI approach should be considered early in the design of costly large clinical trials.
6. CHAPTER 6 NEGATIVE PRESSURE WOUND THERAPY IN CAESAREAN SECTION WOUNDS

Statement of contribution to co-authored published paper

This chapter includes a co-authored paper. The bibliographic details of the paper are:


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I led the research project, conducted the analysis and was the lead author.

(Signed)________________________________________(Date)________________________

Haitham W Tuffaha

(Countersigned)_____________________________(Date)____________________________

Corresponding author: Haitham W Tuffaha

(Countersigned)_____________________________(Date)____________________________

Supervisor: Prof. Paul Scuffham
Cost-utility analysis of negative pressure wound therapy in high-risk cesarean section wounds

Haitham W. Tuffaha, BPharm, MSc, MBA, a, b, c,*, Brigid M. Gillespie, PhD, a, c Wendy Chaboyer, PhD, a, c, Louise G. Gordon, PhD, a, b and Paul A. Scuffham, PhD, a, b

a Griffith Health Institute, Griffith University, Gold Coast, Queensland, Australia
b Centre for Applied Health Economics, School of Medicine, Griffith University, Meadbrook, Queensland, Australia
c NHMRC Centre of Research Excellence in Nursing Interventions for Hospitalised Patients, Research Centre for Health Practice Innovation, Griffith University, Gold Coast, Queensland, Australia

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ABSTRACT
Background: Obese women undergoing cesarean section are at increased risk of postoperative infection. There is growing interest in negative pressure wound therapy (NPWT) to prevent closed surgical incision complications including surgical site infection; however, the evidence on the effectiveness and cost-effectiveness of this technology is limited. The objective of this study was to evaluate the cost-effectiveness of NPWT compared with that of standard dressing in preventing surgical site infection in obese women undergoing elective cesarean section based on current evidence and to estimate the value and optimal design of additional research to study this technology.

Methods: The analysis was from the perspective of Queensland Health, Australia, using a decision model. Parameters were obtained from the published literature, a pilot clinical trial, and expert opinion. Monte Carlo simulation was performed to calculate the net monetary benefit, characterize decision uncertainty, and estimate the value of additional research. Comparing the expected monetary benefits and costs of alternative trial sample sizes informed the optimal future study design.

Results: The incremental net monetary benefit of NPWT was Australian dollars 70, indicating that NPWT is cost-effective compared with that of standard dressing. The probability of NPWT being cost-effective was 95%. The estimated value of additional research to resolve decision uncertainty would be Australian dollars 2.7 million. The optimal sample size of a future trial investigating the relative effectiveness of NPWT would be 200 patients per arm.

Conclusions: Based on the current evidence, NPWT is cost-effective; however, there is high uncertainty surrounding the decision to adopt this technology. Additional research is worthwhile before implementation.

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1. Introduction

The increasing prevalence of obesity in women of childbearing age is a major health problem. Studies from the United States, England, and Australia reported around 25% of women of childbearing age are obese with a body mass index (BMI) of ≥30 kg/m² [1–4]. Maternal obesity poses serious complications during and after pregnancy to both the affected mothers and
6.1 Abstract

Background

Obese women undergoing caesarean section (CS) are at increased risk of post-operative infection. There is growing interest in negative pressure wound therapy (NPWT) to prevent closed surgical incision complications including surgical site infection (SSI); however, the evidence on the effectiveness and cost-effectiveness of this technology is limited. The objective of this study was to evaluate the cost-effectiveness of NPWT compared with standard dressing in preventing SSI in obese women undergoing elective CS based on current evidence, and to estimate the value and optimal design of additional research to study this technology.

Methods

The analysis was from the perspective of Queensland Health, Australia, using a decision model. Parameters were obtained from the published literature, a pilot clinical trial, and expert opinion. Monte Carlo simulation was performed to calculate the net monetary benefit, characterise decision uncertainty and estimate the value of additional research. Comparing the expected monetary benefits and costs of alternative trial sample sizes informed the optimal future study design.

Results

The incremental net monetary benefit of NPWT was AUD 70, indicating that NPWT is cost-effective compared with standard dressing. The probability of NPWT being cost-effective was 65%. The estimated value of additional research to resolve decision uncertainty would be AUD 2.7 million. The optimal sample size of a future trial investigating the relative effectiveness of NPWT would be 200 patients per arm.
Conclusions

Based on the current evidence, NPWT is cost-effective; however, there is high uncertainty surrounding the decision to adopt this technology. Additional research is worthwhile before implementation.
6.2 Introduction

The increasing prevalence of obesity in women of childbearing age is a major health problem. Studies from the United States, England and Australia reported around 25% of women of childbearing age are obese with a body mass index (BMI) of $\geq 30$ kg/m$^2$.\[124-127\] Maternal obesity poses serious complications during and after pregnancy to both the affected mothers and their babies, including gestational diabetes, hypertensive disorders of pregnancy, and stillbirth.\[128\] Obesity also increases the need for caesarean delivery with the risk of a caesarean section (CS) being two to three times higher among obese compared with pregnant women of normal weight.\[87-89\] Obese women undergoing CS are at increased risk of complications particularly post-operative infection.\[128, 129\] In a meta-analysis of six studies, the pooled odds ratio for obese CS women having an infection was three times higher compared with non-overweight women.\[128\] A common post-operative complication is surgical site infection (SSI), which occurs after surgery in the area of the body where the surgery took place.\[130\] Controlling SSI is a health care quality indicator because it results in significant morbidity, reduced quality of life, occasional death and increased costs.\[131-133\] One case of SSI may be cost up to USD 30,000, depending on its severity (2014 price).\[132, 134, 135\] Despite the advances in infection control practices, ventilation systems in the operating rooms, sterilisation methods, surgical technique, pre-operative antimicrobial prophylaxis and wound dressings, SSI remain common in obese women undergoing CS with an estimated incidence between 16-30%.\[131, 136, 137\]

Since its introduction two decades ago, negative pressure wound therapy (NPWT) has been used to promote the healing of acute and chronic wounds as well as skin grafts.\[86, 138, 139\] It is based on a closed sealed system that applies negative pressure to the wound surface resulting in increased blood circulation, decreased oedema, enhanced granulation tissue
formation, and reduced bacterial colonisation.[86, 140] There is growing interest in extending the use of NPWT to closed surgical incision to prevent wound complications including SSI.[86, 140] Unfortunately, the available evidence on the effectiveness and cost-effectiveness of NPWT in surgical incisions is limited.[141] This is expected in surgical practice, where innovations in technologies and equipment often outpace supporting evidence. Recent systematic reviews have identified three small randomised controlled trials (RCTs) that investigated the incidence of SSI in NPWT compared with standard wound dressing.[140, 141] Those trials showed a reduction in SSI with NPWT although all trials reported that the reductions were not statistically significant.[141-144] None of the trials involved patients undergoing CS.

Given the cost of NPWT can reach AUD 100 a day, it is essential to evaluate the cost-effectiveness of this technology before its wide implementation. Nevertheless, with the limitations in the available evidence, the results of a cost-effectiveness analysis may not be certain enough to inform a decision. Clearly, conducting additional research would reduce this uncertainty and better inform decisions. But, there is a cost associated with obtaining further evidence in terms of the direct costs of conducting clinical trials and the opportunity cost of delaying the implementation of an effective intervention awaiting research results. An analytical approach known as value of information analysis has been developed and utilised in healthcare interventions to inform whether the available evidence is sufficient to support a decision on a given technology or if additional research is worthwhile.[31, 145] It is based on the principle that information is valuable because it reduces the uncertainty in the available evidence and subsequently the potential cost of making wrong decisions based on uncertain evidence.[31, 145] Furthermore, value of information analysis has been proposed as an alternative to the standard hypothesis testing approach, which is based on type I and type II
error, and the minimum clinically important difference, in determining sample sizes for RCTs.[34, 44, 146] Under this approach, researchers consider the sample sizes that maximise the expected net benefit of research, which is the difference between the expected monetary benefit of a given trial design and its expected cost.[44, 146]

The aim of this study was to conduct a cost-utility analysis of NPWT in preventing SSI in obese women undergoing CS compared with standard dressing based on currently available evidence, and to perform a value of information analysis to estimate the value and optimal sample size of a larger RCT to support this technology.

6.3 Methods

The approach to achieve the study aim was to: 1) conduct a cost-utility analysis of NPWT compared with standard dressing using a decision analytic model and; 2) perform Monte Carlo simulation to characterise decision uncertainty and estimate the expected value of additional research.

6.3.1 Cost-effectiveness analysis

The cost-effectiveness analysis was from the perspective of the State department of health in Queensland, Australia, using a decision model. The model was probabilistic with prior distributions assigned to input parameters. We used Monte Carlo simulation to sample from the input distributions to estimate the expected costs and effects associated with each intervention.[28] In general, beta distributions were assigned to probabilities and utilities, gamma distributions to costs and disutilities, and lognormal distributions to relative risks. For this analysis, the efficacy outcome was quality-adjusted life-years (QALYs) gained. The net monetary benefit was calculated, which is the efficacy multiplied by the willingness-to-pay threshold for additional unit of effect outcome, minus the cost.[6]
We set the willingness-to-pay threshold at AUD 50,000 per QALY.[147] The intervention expected to be cost-effective would be the one with the highest expected monetary net benefit. Costs and net benefits were presented in Australian dollars (AUD). The time horizon of the model was six months to allow for sufficient time to capture and treat post CS complications. Costs and effects were not discounted because the model timeline was less than one year. The output of the simulation was used to characterise decision uncertainty presented as the probability that each treatment has the highest expected net monetary benefit.

**The decision model**

To describe the clinical problem, we constructed a decision tree (Figure 6-1) in TreeAge Pro 2013 (TreeAge Software Inc, Williamstown, MA) to show the outcomes of a hypothetical group of obese women (i.e., BMI $\geq 30$ kg/m$^2$ before pregnancy) with an average age of 32 years who underwent elective CS. The two groups would receive the same antibiotic prophylaxis prior to surgery and would be operated using the same technique and under the same setting. At the completion of skin closure, NPWT would be applied to one group and the other group would receive standard dressing (i.e., hydrocolloid). The modelled patients may develop SSI which could be either superficial or deep/organ. To simplify the model, deep and organ SSI were combined as deep/organ SSI. Superficial SSI occurs within 30 days after the operation and only involves skin and subcutaneous tissue of the incision.[10] Deep SSI occurs within 30 or 90 days after the operation and involves deep soft tissues of the incision (e.g., fascial and muscle layers),[10] whereas organ SSI involves any part of the anatomy (e.g., organs and spaces) other than the incision which was opened or manipulated during an operation.[10] Patients could die or survive depending on the type of the SSI developed. Death from other causes (e.g., age-related death or death from surgery) was not included because the probability of death in this young group of patients undergoing such
procedure is minimal.[35]

Parameters for use in the model

Parameters were obtained from a systematic review of literature (Table 6-1). Expert opinion was sought when a parameter value could not be found in the published articles. Furthermore, to ensure that all relevant evidence was included in the model, data from a recent pilot study conducted by our group was included and combined with already available evidence. The details of the pilot trial are published elsewhere.[90] In brief, that trial assessed the effect of NPWT on SSI in obese women undergoing elective CS in addition to the feasibility of conducting a definitive trial. Ninety-two obese women undergoing elective CS from July, 2012 to April, 2014 were randomised in theatre (i.e., at the completion of skin closure) via a central web based system using a parallel 1:1 process to either NPWT (PICO®)
or standard dressing (Comfeel Plus®). In total, 27.9% of the control group and 22.7% of the intervention group had a SSI with a relative risk (RR) of 0.81 (95% CI 0.39; 1.68).[90] Based on the pilot study, a larger RCT to test the superiority of NPWT in reducing SSI incidence appeared feasible, with an estimated sample size of 400 patients per arm with over 90% power.[90]

Table 6-1: Model input parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Distribution</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Probabilities</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSI with standard dressing</td>
<td>24%</td>
<td>Beta</td>
<td>Johnson et al., Opoien et al., Ahmed et al. and Alanis et al.[131, 136, 137, 148].</td>
</tr>
<tr>
<td>Relative risk of SSI with NPWT</td>
<td>72%</td>
<td>Log-normal</td>
<td>Pilot trial and Masden et al. [90, 143]</td>
</tr>
<tr>
<td>Deep/organ SSI</td>
<td>20%</td>
<td>Beta</td>
<td>Wilson et al. and Henman et al.[133, 149]</td>
</tr>
<tr>
<td>Death from superficial SSI</td>
<td>4%</td>
<td>Beta</td>
<td>Astagneau et al. and Kirkland et al.[150, 151]</td>
</tr>
<tr>
<td>Death from deep/organ SSI</td>
<td>9%</td>
<td>Beta</td>
<td>Astagneau et al. and Kirkland et al.[150, 151]</td>
</tr>
<tr>
<td><strong>Utilities</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Utility with no SSI</td>
<td>0.91</td>
<td>Beta</td>
<td>Clemens et al. [152]</td>
</tr>
<tr>
<td>Disutility from superficial SSI</td>
<td>0.2</td>
<td>Gamma</td>
<td>Lipsky et al.[153]</td>
</tr>
<tr>
<td>Disutility from deep SSI</td>
<td>0.4</td>
<td>Gamma</td>
<td>Lipsky et al.[153]</td>
</tr>
<tr>
<td>Utility of death</td>
<td>0</td>
<td>Fixed</td>
<td>Assumed</td>
</tr>
<tr>
<td><strong>Costs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPWT</td>
<td>AUD 175</td>
<td>Fixed</td>
<td>Market price</td>
</tr>
<tr>
<td>Standard dressing</td>
<td>AUD 7.5</td>
<td>Fixed</td>
<td>Market price</td>
</tr>
<tr>
<td>Superficial SSI treatment</td>
<td>AUD 250</td>
<td>Gamma</td>
<td>Graves et al.[154]</td>
</tr>
</tbody>
</table>
Deep/organ SSI treatment | AUD 10,000 | Gamma ($\alpha=4$, $\beta=0.0004$) | AR-DRGs[155]
---|---|---|---
Application time (hour) | NPWT | 0.15 | Gamma ($\alpha=9$, $\beta=60$) | Expert estimate
Application time (hour) | dressing | 0.05 | Gamma ($\alpha=40$, $\beta=40$) | Expert estimate

SSI = surgical site infection; NPWT = negative pressure wound; AR-DRGs = Australian Refined Diagnosis Related Groups.

**Probabilities**

Baseline risk of SSI in the group receiving standard dressing was set at 24%, estimated from the incidence of SSI control arm in the pilot trial combined with four observational studies reporting SSI in obese women undergoing CS.[131, 136, 137, 148].

No RCTs comparing NPWT with standard dressing in CS were identified. One RCT by Masden *et al.* reported the relative effectiveness of NPWT in reducing SSI in 81 high-risk patients (i.e., BMI>30 and comorbidities) undergoing a range of procedures including abdominal surgeries; 6.8% of the NPWT group and 13.5% of the standard dressing group developed wound infection with a RR of 0.50 (95% CI 0.13; 1.95).[143] Other trials identified were an RCT by Howell *et al.* on NPWT in knee surgery that was terminated early due to blister formation,[142] and an RCT by Stannard *et al.* investigating NPWT in 249 patients with lower-extremity trauma fractures.[144] In that RCT, around 10% of wounds in the NPWT group had infection compared with 20% in the standard dressing group at a RR of 0.52 (95% CI 0.28; 0.96).[144] It was not appropriate to combine the results from Stannard *et al.* with Masden *et al.* because the analysis in the former was per wound and not per patient. Further, patient characteristics and wound types in the two studies were heterogeneous. Given the scarcity in the available evidence and in order not to overestimate uncertainty in the relative effectiveness parameter by relying on the pilot study results alone, the RR from the
pilot study was collated with the RR from Masden et al. This was achieved by undertaking a Bayesian approach under which the RR from Masden et al. (i.e., prior information) was updated with the RR from the pilot trial resulting in an updated (i.e., posterior) RR of 0.73 (0.39-1.32).[156] The effect of RR estimation on the results of the cost-effectiveness and value of information analyses was explored in sensitivity analysis.

The probability for deep/organ SSI was estimated at 19% from Wilson et al. and Henman et al.[133, 149] The probability of death from deep/organ SSI was set at 0.07 and for superficial SSI at 0.02, from Astagneau et al. and Kirkland et al.[150, 151]

**Costs**

The cost of NPWT was set at AUD 175 for the price of a disposable (one-application) device (PICO®). The cost of standard dressing was AUD 7.5 for the hydrocolloid dressing (Comfeel Plus®). The cost of treating superficial SSI was obtained from Graves et al. and was set at AUD250;[154] this includes the cost of a general practitioner visit, seven days of oral antibiotic, and the cost of test/swab. For the cost of deep/organ SSI, this was obtained from the 2009-2010 Australian Refined Diagnosis Related Groups (AR-DRGs), item T61 (postoperative & post-trauma infection) at AUD 10,000.[155] This includes the cost of hospitalisation, tests/swabs and intravenous antibiotics for seven to fourteen days.[155] The estimated staff time was ten minutes to apply the NPWT and two minutes for the standard dressing at an average wage of AUD 33 per hour.[40] Costs obtained in other price years were converted to 2014 Australian dollars using the CCEMG-EPPI-Centre Cost Converter web-based tool.[157]

**Utilities**

The utilities in the model were based on EQ-5D-3L scores, anchored between 0.0 for death and 1.0 for best possible health. Utility weights were based on the preferences of the
Australian population. The utility scores for the women undergoing CS and discharged with no complications was set at 0.9 from Clemens et al.[152] For the women who developed SSI, the disutility for superficial and deep/organ SSI was set at 0.2 and 0.4, respectively from Lipsky et al.[153] The assumption was that the disutility will take place over one week for superficial SSI and two weeks for deep/organ SSI.

### 6.3.2 Value of information analysis

The detailed algorithms for value of information calculation are described in the literature [41, 63] and are presented in Appendix 1. Briefly, the first measure to calculate was the expected value of perfect information. This is the value of the additional information that would resolve all uncertainty surrounding all input parameters; therefore, it is the maximum (i.e., upper bound) value for conducting further research to resolve this uncertainty.[156] The expected value of perfect information is the difference between the expected net monetary benefit of a decision with perfect information and the decision made based on current information.[1]

To estimate the expected value of perfect information, 10,000 Monte Carlo iterations were randomly sampled from the prior parameter distributions of all parameters to identify the intervention with the highest expected mean net monetary benefit based on current information (i.e., the cost-effective intervention). Then the intervention with the highest net monetary benefit at each iteration was identified and the identified values were averaged to calculate the expected maximum net monetary benefit (i.e. net monetary benefit with perfect information). If the expected value of perfect information exceeds the expected cost of future research, the next step would be to calculate the value of information to resolve the uncertainty in the parameter(s) of interest which is the expected value of perfect parameter information.[39, 99] Since our model (i.e., the decision tree) is linear and assuming no
correlation between input parameters since they were obtained from various sources, the same one-level Monte Carlo simulation technique described above was used to calculate the expected value of perfect parameter information; the sampling would be only from the distribution of the parameter(s) of interest whereas the other parameters were fixed at their prior means.[99]

To estimate the value of a future clinical trial with a given sample size \( n \) that could reduce uncertainty surrounding the parameter of interest, the expected value of sample information was estimated by calculating the difference between the expected value of a decision made after collecting data on the parameter of interest and the expected net benefit with current information.[41] Conceivably, the data collected from additional research is not known at this stage but could be predicted by simulation. Given the linearity of the model, calculating the expected value of sample information required the same one level Monte Carlo simulation. However, the sampling would be from the posterior distribution of the parameter(s) of interest obtained using Bayesian updating.[41]

The value of information measures described above are per-patient estimates; however, it is necessary to estimate the value of information for the population of patients expected to benefit from the research outcomes. This was calculated by multiplying the per-patient estimates by the estimated number of patients expected to benefit from NPWT over a certain time period. Obese women undergoing CS in Queensland represent 20% of the 20,000 CS performed every year in that state.[155, 158] Accordingly, we estimated the expected number of obese women undergoing CS over ten years (with 5% discounting) to be around 35,000.

To determine the optimal sample size of a future trial, the population-expected value of sample information and the expected total cost were estimated for a range of possible trial
sample sizes. The difference between the expected monetary benefit of research and the total cost of a particular study design is the expected net benefit of sampling.[34, 38] The total cost of a future trial design included fixed costs (e.g., set-up cost, salaries), variable costs per patient, and the opportunity costs expected to be incurred by patients who would receive the inferior intervention during the trial.[38, 41] We based our estimates for the cost of a future trial design on a research grant application for an RCT on NPWT in four institutions with a recruitment rate of 200 patients per site each year (Table 6-2). The estimated fixed project cost was AUD 125,000 per year for project management and data analysis, plus an annual cost of AUD 100,000 per site for recruitment and data collection. The cost per patient was set at AUD 250. If the expected net benefit of sampling is negative, additional research would not be cost-effective because the expected costs of the study would exceed its expected benefits. Conversely, a positive expected net benefit of sampling indicates that future research would be worthwhile. The optimal sample size is determined when the ENBS reaches a maximum.[45, 121]

Table 6-2: Research cost breakdown

<table>
<thead>
<tr>
<th>Item</th>
<th>Cost (AUD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fixed costs</strong></td>
<td></td>
</tr>
<tr>
<td>Data management/year</td>
<td>30,000</td>
</tr>
<tr>
<td>Project management/year</td>
<td>85,000</td>
</tr>
<tr>
<td>Office supplies/year</td>
<td>10,000</td>
</tr>
<tr>
<td>Field expenses (i.e., site visits and monitoring)/site/year</td>
<td>15,000</td>
</tr>
<tr>
<td>Recruitment and data collection salaries/site/year</td>
<td>70,000</td>
</tr>
<tr>
<td>Blinded outcome assessor/site/year</td>
<td>15,000</td>
</tr>
<tr>
<td><strong>Variable cost (i.e., per patient)</strong></td>
<td></td>
</tr>
<tr>
<td>Equipment</td>
<td>200</td>
</tr>
<tr>
<td>Randomisation services</td>
<td>50</td>
</tr>
</tbody>
</table>

AUD = Australian dollar
6.4 Results

6.4.1 Cost-effectiveness analysis

Compared with standard dressing, NPWT resulted in an average additional cost of AUD 30 (AUD 600 versus AUD 570) and additional 0.002 QALYs (Table 6-3). At a willingness-to-pay threshold of AUD 50,000 per QALY, the incremental net monetary benefit was AUD 70, indicating that NPWT is cost-effective. The probability of NPWT being cost-effective was 65%. Figure 6-2 shows the probability of NPWT being cost-effective over a range of willingness-to-pay thresholds.

Table 6-3: Cost-effectiveness analysis results

<table>
<thead>
<tr>
<th></th>
<th>Standard dressing</th>
<th>NPWT</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost (AUD)</td>
<td>570</td>
<td>600</td>
<td>30</td>
</tr>
<tr>
<td>Effect (QALY)</td>
<td>0.446</td>
<td>0.448</td>
<td>0.002</td>
</tr>
<tr>
<td>Net monetary benefit$^a$ (AUD)</td>
<td>21,730</td>
<td>21,800</td>
<td>70</td>
</tr>
</tbody>
</table>

QALY = quality-adjusted life-year; NPWT = negative pressure wound therapy; AUD = Australian dollar

$^a$ For a willingness-to-pay threshold of AUD 50,000 per QALY

AUD = Australian dollar

Figure 6-2: The probability of each intervention being cost-effective over a range of willingness-to-pay thresholds
6.4.2 Value of information analysis

The expected value of perfect information for the decision of adopting NPWT is AUD 76 per-patient which is AUD 2.7 million (AUD 76 x 35,000) for the population expected to benefit from this technology over the coming ten years. The parameter with the highest expected value of information was the RR of SSI with NPWT at AUD 75 per patient and population value of AUD 2.6 million. The value of a future RCT exploring the relative effectiveness of NPWT over a range of sample sizes per arm is depicted in Figure 6-3. As the sample size increases more uncertainty is expected to resolve and the value of additional research increases. Comparing the expected monetary benefits and costs of the suggested sample sizes, the optimal sample size would be 200 patients in each arm with an expected net benefit of sampling of AUD 1.2 million at a total cost of AUD 900,000 (Table 6-4). The expected return on investment (i.e., net benefit/cost ratio) would be 133% (AUD 1.2million/AUD 900,000). The initial design with 400 patients per arm would provide a return on investment of 66% (AUD 935/AUD 1.4million).

In a sensitivity analysis, increasing the price of NPWT, varying willingness-to-pay threshold, extending the time-line of the technology or estimating the RR based on the pilot trial alone, resulted in an estimated optimal sample sizes between 200-300 patients in each arm (Table 6-5). On the other hand, with reduced NPWT price and shorter technology lifetime the estimated sample sizes ranged between100-200 patients in each arm.
**Figure 6-3:** The expected value of information and expected cost across future trial sample sizes

**Table 6-4: Expected cost, benefits and return on investment for future trial design**

<table>
<thead>
<tr>
<th>Sample size/arm</th>
<th>EVSI</th>
<th>Research sites no.</th>
<th>Trial duration (years)</th>
<th>Total trial cost (AUD)</th>
<th>ENBS (AUD)</th>
<th>ROI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>1,645,000</td>
<td>4</td>
<td>1.25</td>
<td>656,250</td>
<td>988,750</td>
<td>151%</td>
</tr>
<tr>
<td>200</td>
<td>2,114,000</td>
<td>4</td>
<td>1.50</td>
<td>907,500</td>
<td>1,206,500</td>
<td>133%</td>
</tr>
<tr>
<td>300</td>
<td>2,275,000</td>
<td>4</td>
<td>1.75</td>
<td>1,158,750</td>
<td>1,116,250</td>
<td>96%</td>
</tr>
<tr>
<td>400</td>
<td>2,345,000</td>
<td>4</td>
<td>2.00</td>
<td>1,410,000</td>
<td>935,000</td>
<td>66%</td>
</tr>
<tr>
<td>500</td>
<td>2,380,000</td>
<td>4</td>
<td>2.25</td>
<td>1,661,250</td>
<td>718,750</td>
<td>43%</td>
</tr>
<tr>
<td>600</td>
<td>2,415,000</td>
<td>4</td>
<td>2.50</td>
<td>1,912,500</td>
<td>502,500</td>
<td>26%</td>
</tr>
<tr>
<td>700</td>
<td>2,432,500</td>
<td>4</td>
<td>2.75</td>
<td>2,163,750</td>
<td>268,750</td>
<td>12%</td>
</tr>
<tr>
<td>800</td>
<td>2,448,250</td>
<td>4</td>
<td>3.00</td>
<td>2,415,000</td>
<td>33,250</td>
<td>1%</td>
</tr>
</tbody>
</table>

EVSI = expected value of sample information; ENBS = expected net benefit of sampling
Table 6-5: Sensitivity analysis of assumptions effect on the cost-effectiveness and value of additional analyses results

<table>
<thead>
<tr>
<th>Assumption</th>
<th>Estimate</th>
<th>Incremental net benefit</th>
<th>Value of information</th>
<th>Optimal sample size/arm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NPWT Price</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>AUD 175</td>
<td>AUD 70</td>
<td>AUD 2.7 million</td>
<td>200</td>
</tr>
<tr>
<td>25% increase</td>
<td>AUD 220</td>
<td>AUD 30</td>
<td>AUD 3.2 million</td>
<td>250</td>
</tr>
<tr>
<td>25% reduction</td>
<td>AUD 130</td>
<td>AUD 125</td>
<td>AUD 2.0 million</td>
<td>150</td>
</tr>
<tr>
<td><strong>Willingness-to-pay threshold/QALY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>AUD 50,000</td>
<td>AUD70</td>
<td>AUD 2.7 million</td>
<td>200</td>
</tr>
<tr>
<td>50% increase</td>
<td>AUD 75,000</td>
<td>AUD125</td>
<td>AUD 2.8 million</td>
<td>250</td>
</tr>
<tr>
<td>50% reduction</td>
<td>AUD 25,000</td>
<td>AUD30</td>
<td>AUD 2.7 million</td>
<td>200</td>
</tr>
<tr>
<td><strong>Relative risk</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (Msden et al. and Pilot trial)[90, 143]</td>
<td>0.73</td>
<td>AUD70</td>
<td>AUD 2.7 million</td>
<td>200</td>
</tr>
<tr>
<td>Masden et al.[143] alone</td>
<td>0.5</td>
<td>AUD 200</td>
<td>AUD 3.2 million</td>
<td>250</td>
</tr>
<tr>
<td>Pilot trial alone[90]</td>
<td>0.81</td>
<td>AUD -35</td>
<td>AUD 3.8 million</td>
<td>300</td>
</tr>
<tr>
<td><strong>Technology life-time</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>10 years</td>
<td>AUD 70</td>
<td>AUD 2.7 million</td>
<td>200</td>
</tr>
<tr>
<td>50% increase</td>
<td>15 years</td>
<td>AUD 70</td>
<td>AUD 3.4 million</td>
<td>300</td>
</tr>
<tr>
<td>50% reduction</td>
<td>5 years</td>
<td>AUD 70</td>
<td>AUD 1.6 million</td>
<td>100</td>
</tr>
</tbody>
</table>

EVS = expected value of sample information; ENBS = expected net benefit of sampling; AUD = Australian dollar; ROI = return on investment

*a Based on recruitment rate of 200 patients/site/per year and additional one year for data analysis

*b Total trial cost = fixed + variable costs + opportunity cost

*c ENBS = the difference between EVSI and total trial cost

*d ROI = ENBS/total cost

AUD = Australian dollar; QALY = quality-adjusted life-year; NPWT = negative pressure wound therapy
6.5 Discussion

The use of NPWT in closed surgical wounds to enhance healing by primary intention and to prevent wound complications is a new field of application for this technology. This paper presents a cost-effectiveness analysis of NPWT in preventing SSI in obese women undergoing CS. Based on the current evidence; NPWT appears to be cost-effective compared with standard dressing with an expected incremental net monetary benefit of AUD 70. Nevertheless, the probability of NPWT being cost-effective is only 65%, indicating high decision uncertainty and thus high chance of error in a decision based on this cost-effectiveness analysis. Given the relatively high cost of NPWT and the high uncertainty in the cost-effectiveness results, it would be reasonable to conduct additional research before implementing this technology. The expected value of information to resolve the uncertainty in the available evidence would be around AUD 2.7 million, suggesting that additional research is potentially worthwhile.

Our results demonstrate how value of information analysis can provide an alternative to the standard hypothesis testing approach which relies on arbitrary chosen error probabilities where type I and type II error receive the same weight (e.g., 5% and 20% respectively), regardless of the consequences of making an error.[44] Our analysis estimates the optimal sample size for a future trial investigating the relative effectiveness of NPWT compared to standard dressing in reducing SSI. By calculating the expected monetary benefit (i.e., the expected reduction in uncertainty) of additional sampling and the expected cost of conducting this future trial, the sample size with the highest expected net benefit would be 200 patients in each arm. This sample size is lower than the sample size of 400 patients in each arm initially calculated based on hypothesis testing and this smaller sample size would be more economical providing higher return on investment (133% versus 66%). In addition to
sample size calculation, value of information analysis can optimise other aspects of trial design such as the follow-up duration.[42, 146] Obviously, more uncertainty is expected to resolve with longer follow-up albeit with additional research costs. Accordingly, the preferred design would be the one that optimises the expected research monetary benefits compared to the expected costs.[38] Our results suggest that a follow-up duration of one and a half year for this future trial would optimise the expected research benefit. The same principle can be extended to quantitatively prioritise research. Under the value of information framework, competing research proposals within a limited budget could be ranked according to their expected net benefits.[38]

In optimising trial design, value of information analysis considers a number of factors such as the relative effectiveness and costs of the evaluated technologies, the decision maker’s willingness-to-pay for the additional effectiveness, the probability and consequences of making a suboptimal decision, the population expected to benefit from research findings, and the total cost associated with the intended research.[45] The total cost of research includes the direct cost of research in terms of fixed and variable costs as well as the opportunity cost from delaying the implementation of the technology awaiting the conclusion of the future trial.[42, 145] In our analysis, the expected benefit of research was positive despite this opportunity cost indicating the the benefits of additional research would exceed the benefits of immediate full implementation. Further, a decision to implement NPWT before collecting more information might be risky since it would require the purchase and stocking of NPWT devices. It would be difficult to recover these costs if the results from the future trial do not favour NPWT and we want to reverse the decision.

To our knowledge, there is no published cost-effectiveness analysis of NPWT in preventing wound complications in closed surgical incisions.[141] There is; however, a
limited number of published studies evaluating the cost-effectiveness of NPWT in the management of chronic and open wounds.[121, 159-161] The lack of robust clinical evidence (i.e., large RCTs) on NPWT may explain the rarity of relevant economic evaluations. Nevertheless, this should not pose a problem because when evidence is scarce, information could be sought from various sources such as pilot trials, observational studies and expert opinion.[121] Ideally, this should be also accompanied by an appropriate value of information analysis to inform whether that evidence is sufficient to guide decisions or if additional research is required. For instance, Soares et al. conducted cost-effectiveness and value of information analyses on NPWT in patients with severe pressure ulcers.[121] They demonstrated how combining information from the existing evidence with a pilot trial and elicited expert views resulted in a better informed decision compared to using a single source of evidence when information is scarce. Moreover, they used value of information analysis to optimise future trial design.[121] In this paper, we populated our model with the best available evidence in the literature combined with the results of our pilot trial and expert opinion when necessary.

As expected for any economic evaluation, the results of our cost-effectiveness analysis are dependent on the assumptions made for the model structure and input parameters. We used hydrocolloid dressing, which is the standard of care for this procedure in Australia, as the comparator in our analysis; however, there are other types of surgical dressings in clinical practice at various prices. Further, our model focused on SSI as an outcome and did not include other outcomes such as healing rate or other wound complications. However, the model did not include healing as an outcome because, unlike chronic wounds, most clean incision wounds will completely heal in a relatively short time.[86] Additionally, compared with other wound complications expected with CS (e.g., seroma), SSIs are more associated
with mortality, morbidity and cost. In addition, our model was probabilistic and Monte Carlo sampling allowed for simultaneous characterisation of uncertainty in all model parameters. Finally, we tested the effect of various assumptions made to the value of information analysis on the results. In the sensitivity analysis presented, the optimal sample size remained between 100-300 patients in most of the scenarios.

6.6 Conclusion

Based on the best available evidence, NPWT appears cost-effective compared to standard dressing in preventing SSI in obese women undergoing CS. But, there is high uncertainty surrounding a decision to adopt this technology. Further research to explore the relative effective of NPWT in this population would be worthwhile before implementation.
7. CHAPTER 7 NUTRITIONAL SUPPORT FOR PREVENTING PRESSURE ULCERS IN HIGH-RISK PATIENTS

Statement of contribution to co-authored published paper

This chapter includes a co-authored paper. The bibliographic details of the paper are:


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I led the research project, conducted the analysis and significantly contributed to the writing and revision of the manuscript.

(Signed)____________________________________(Date)____________________________________

Haitham W Tuffaha

(Countersigned)_____________________________(Date)____________________________

Corresponding author: Haitham W Tuffaha

(Countersigned)_____________________________(Date)____________________________

Supervisor: Prof. Paul Scuffham
Cost-Effectiveness and Value of Information Analysis of Nutritional Support for Preventing Pressure Ulcers in High-risk Patients: Implement Now, Research Later

Haitham W. Tuffaha · Shelley Roberts · Wendy Chaboyer · Louisa G. Gordon · Paul A. Scuffham

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Abstract
Background Pressure ulcers are a major cause of mortality, morbidity, and increased healthcare cost. Nutritional support may reduce the incidence of pressure ulcers in hospitalised patients who are at risk of pressure ulcer and malnutrition.

Objectives To evaluate the cost-effectiveness of nutritional support in preventing pressure ulcers in high-risk hospitalised patients, and to assess the value of further research to inform the decision to implement this intervention using value of information analysis (VOI).

Methods The analysis was from the perspective of Queensland Health, Australia using a decision model with evidence derived from a systematic review and meta-analysis. Resources were valued using 2014 prices and the time horizon of the analysis was one year. Monte Carlo simulation was used to estimate net monetary benefits (NB) and to calculate VOI measures.

Results Compared with standard hospital diet, nutritional support was cost saving at AUS425 per patient, and more effective with an average 0.005 quality-adjusted life years (QALY) gained. At a willingness-to-pay of AUS50,000 per QALY, the incremental NB was AUS675 per patient, with a probability of 87% that nutritional support is cost-effective. The expected value of perfect information was AUS5 million and the expected value of perfect parameter information was highest for the relative risk of developing a pressure ulcer at AUS2.5 million. For a future trial investigating the relative effectiveness of the interventions, the expected net benefit of research would be maximised at AUS100,000 with 1,200 patients in each arm if nutritional support was perfectly implemented. The opportunity cost of withholding the decision to implement the intervention until the results of the future study are available would be AUS14 million.

Conclusions Nutritional support is cost-effective in preventing pressure ulcers in high-risk hospitalised patients compared with standard diet. Future research to reduce decision uncertainty is worthwhile; however, given the opportunity losses associated with delaying the implementation, “implement and research” is the approach recommended for this intervention.
7.1 Abstract

Background

Pressure ulcers are a major cause of mortality, morbidity, and increased healthcare cost. Nutritional support may reduce the incidence of pressure ulcers in hospitalised patients who are at risk of pressure ulcer and malnutrition.

Objectives

To evaluate the cost-effectiveness of nutritional support for preventing pressure ulcers in high-risk hospitalised patients, and to assess the value of further research to inform the decision to implement this intervention using value of information analysis (VOI).

Methods

The analysis was from the perspective of Queensland Health, Australia using a decision model with evidence derived from a systematic review and meta-analysis. Resources were valued using 2014 prices and the time horizon of the analysis was one year. Monte Carlo simulation was used to estimate net monetary benefits (NB) and to calculate VOI measures.

Results

Compared with standard hospital diet, nutritional support was cost saving at AUD 425 per patient, and slightly more effective with an average 0.005 quality-adjusted life-years (QALY) gained. At a willingness-to-pay of AUD 50,000 per QALY, the incremental NB was AUD 675 per patient, with a probability of 87% that nutritional support is cost-effective. The expected value of perfect information was AUD 5.5 million and the expected value of perfect parameter information was highest for the relative risk of developing a pressure ulcer at AUD 2.5 million. For a future trial investigating the relative effectiveness of the interventions, the expected net benefit of research would be maximised at AUD 100,000 with 1,200 patients in
each arm if nutritional support was perfectly implemented. The opportunity cost of withholding the decision to implement the intervention until the results of the future study are available would be AUD 14 million.

Conclusions

Nutritional support is cost-effective in preventing pressure ulcers in high-risk hospitalised patients compared with standard diet. Future research to reduce decision uncertainty is worthwhile; however, given the opportunity losses associated with delaying the implementation, ‘implement with research’ is the approach recommended for this intervention.
7.2 Introduction

A pressure ulcer is an area of localised injury to the skin caused by pressure, friction or a combination of both.[77] Pressure ulcers are a common healthcare problem in hospitals with a reported prevalence ranging from 4% to 38%.[76, 77, 162-164] The cost of treating pressure ulcers is substantially high because it requires specialised wound care and prolonged hospitalisation. Hospital-acquired pressure ulcers cost between USD500 to USD70,000 per patient and up to USD11 billion (2009 price) every year in the United States alone.[165] The total cost of pressure ulcer care to the National Health Service in the United Kingdom was estimated between GBP1.4 billion and GBP2.1 billion (2011 price), annually.[166] One study reported 398,432 bed days lost from pressure ulcers each year in Australia at an opportunity cost of AUD 285 million (2001 price).[167] Given the burden of this complication, it is recommended that healthcare systems identify patients at risk and implement effective interventions to prevent pressure ulcers.[76, 77, 79] Prevention interventions include frequent patient repositioning, support surfaces, skin care, and nutritional assessment and supplements if required.[76, 77, 79]

Hospitalised patients at high risk of pressure ulcers including older patients with restricted mobility are also at increased risk of malnutrition.[74, 75] Due to its effect on skin integrity and ability to repair, malnutrition is an established risk factor for pressure ulcers, resulting in a two-fold chance of developing an injury in hospitalised patients.[74] The efficacy of nutritional support in preventing pressure ulcers was explored in a number of randomised controlled trials (RCTs) comparing patients who received nutritional supplements in addition to hospital standard diet to those who received only the standard hospital diet.[80-83] The RCTs have shown that nutritional support tends to reduce the incidence of pressure ulcers compared with standard hospital diet in high-risk patients; however, these studies have
limitations in terms of their small sample sizes and high risk of bias (e.g., inadequate allocation concealment or blinding).

Current clinical practice guidelines recommend comprehensive nutritional assessment and nutritional support for patients at high risk of pressure ulcers and malnutrition.[76, 77, 79] However, providing nutritional support is associated with cost incurred for the nutrients as well as the staff time for patient assessment and preparing and administering of supplements. Therefore, before health systems can implement this intervention, there is a need to assess its cost-effectiveness. Nevertheless, due to the limitations of the available studies, a cost-effectiveness analysis that is based on such evidence is uncertain and so is any decision based on this analysis. Accordingly, it is essential to assess the need for additional information before making a decision on the implementation of this intervention. Acquiring additional information could reduce uncertainty and better inform the decision; however, there is a cost for obtaining further evidence including the cost of conducting research and the opportunity cost of delaying the decision awaiting research results.[23, 37] Value of information analysis provides an analytic framework to measure the value of acquiring further information and informs whether the available evidence is sufficient to support a decision on a given intervention or if additional research study is worthwhile.[38, 145]

The aim of this study was to evaluate the cost-effectiveness of nutritional support in preventing pressure ulcers in high-risk hospitalised patients, and to assess the value for further research to support this intervention using value of information analysis.

### 7.3 Methods

The general approach to achieve the aim of this study was to 1) conduct a cost-effectiveness analysis to estimate the expected monetary benefit of nutritional support in preventing pressure ulcers compared with standard care; and 2) conduct value of information
analysis to measure decision uncertainty and calculate the expected benefit of additional research.

### 7.3.1 Cost-effectiveness analysis

The cost-effectiveness analysis was performed from the perspective of the State department of health in Queensland, Australia, using a decision model. Our model was probabilistic; Monte Carlo simulation was used to propagate the prior distributions assigned to model inputs and estimate the expected costs and outcomes associated with each intervention.[28] Effects were expressed in terms of quality-adjusted life-years (QALYs). We calculated the net monetary benefit (NB), which is the effect multiplied by the willingness-to-pay threshold ($\lambda$), minus the cost.[6] The willingness-to-pay threshold for this analysis was AUD 50,000 per QALY.[147] The NB for an intervention $i$ informed by the set of input parameters $\theta$ was calculated as:

$$NB (i, \theta) = \lambda* \text{Effect} (i, \theta) - \text{Cost} (i, \theta)$$  \hspace{1cm} Equation 7-1

The intervention expected to be cost-effective would be the one with the highest expected NB. Costs and NBs were presented in Australian dollars (AUD); AUD 1 = 0.90 USD (2014 price). We did not discount costs and effects because the time horizon of the analysis was one year. The output of the simulation was used to characterise decision uncertainty presented as the probability that each treatment has the highest expected NB.

We constructed a health state transition Markov model in TreeAge Pro 2013 (TreeAge Software Inc, Williamstown, MA) to represent the flow of a cohort of hospitalised patients at high risk of pressure ulcers and malnutrition (Figure 7-1).
Figure 7-1: The decision model
The patient cohort had an average age of 70 years. Patients were considered at high risk for pressure ulcer if they had restricted mobility (i.e., require assistance to mobilise). Patients who were at risk of malnourishment based on their Subjective Global Assessment tool were included in the study.[168] The Subjective Global Assessment is a reliable and validated nutrition assessment tool which uses clinical judgment to aggregate components of nutrition-focused medical history and physical examination.[168]

We set the cycle length to one day and the model duration to one year in order to capture the changes in pressure ulcer status based on daily assessment and to allow for sufficient time for injury healing. Standard care included pressure ulcer prevention strategies such as redistribution surfaces, repositioning, skin protection strategies, together with standard hospital diet.[76, 77] The intervention group received, in addition to the standard care, nutritional support comprising patient education, nutrition goal setting and the consumption of an additional 1,000-2,000 kilojoules of energy per day.[169, 170] The additional kilojoules equates to approximately 2-3 nutritious snacks or commercial oral high protein supplements per day.[170]

The model included the following health states: 1) hospitalised with intact skin, 2) hospitalised with a closed (i.e., grade 1) wound, 3) hospitalised with an open (grade 2-4) wound, 4) ambulatory wound management, 5) discharged, and 6) dead. The National Pressure Ulcer Advisory Panel (NPUAP) defines grade 1 as superficial erythema without skin breakdown, grade 2 as partial-thickness loss of dermis presenting as a shallow open ulcer, grade 3 as full-thickness tissue loss but with no bone, tendon, or muscle exposure, and grade 4 as full-thickness tissue loss with exposed bone, tendon, or muscle.[77] Patients start the model as newly hospitalised individuals with intact skin and receive either the standard pressure ulcer prevention care or the standard care with nutritional support. Patients would
either die of any cause, be discharged, or remain hospitalised where they could develop a closed wound. Patients with a closed wound would either die of any cause, be discharged, or remain in the hospital where their injury could heal, deteriorate to an open wound, or remain the same. Open-wound patients who are alive could be discharged to be treated in the ambulatory setting or continue to stay in the hospital where their wound would either heal or remain the same. Patients who developed a pressure ulcer of any grade would receive the appropriate treatment (e.g., wound dressing, surgery, and/or pain management) as well as pressure ulcer prevention strategies to avoid further skin injury.

Data inputs and sources

Transition probabilities

We obtained mortality, pressure ulcer development and healing rates from a systematic review of relevant literature. We assumed these rates constant over time and used the following equation to convert rates to probabilities: probability = 1−e−rate × time. Further, probabilities in various durations were converted to daily probabilities. Considering the preventive nature of the intervention, the two groups were assumed to have the same transition probabilities except for the probability of developing pressure ulcers. For the evidence on the relative effectiveness of nutritional support, we systematically searched electronic databases including PubMed, Cochrane and CINAHL for RCTs published in English at any time that evaluated nutritional support in comparison to standard hospital diet in preventing pressure ulcers. The search terms included: pressure sore, pressure ulcer, bed sore, nutrition, supplement, feeding, nutrients, protein, amino acid, arginine and zinc. Studies were eligible for inclusion in the systematic review if: 1) the subjects were hospitalised adults at risk of pressure ulcers and malnutrition, 2) the intervention comprised oral nutritional supplements, and 3) pressure ulcer incidence was reported as an outcome (Figure 7-2).
We identified five RCTs (Table 7-1) looking at the incidence of pressure ulcers with oral nutritional support.[80-83, 171] We performed a random-effects meta-analysis of the identified studies as summarised in Figure 7-3. The identified studies were small and nutritional support did not show a statistically significant effect; however, in the pooled analyses, those receiving nutritional support had significantly reduced incidence of pressure ulcers with a relative risk (RR) of 0.83 (CI: 0.71 to 0.96) compared with standard care. The meta-analysis results indicated the studies were homogenous ($I^2= 0\%$). We obtained the probability of developing a pressure ulcer with standard care from the incidence of pressure ulcer in the controlled arms of the studies included in our meta-analysis.
Table 7-1: Summary of the identified randomised controlled trials on nutritional support in the prevention of pressure ulcers

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Control</th>
<th>Outcome</th>
<th>PU grading</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bourdel-Marchasson</td>
<td>Older people, critically ill</td>
<td>Standard diet plus oral</td>
<td>Standard diet</td>
<td>Incidence of PU</td>
<td>Yes</td>
<td>2 weeks</td>
</tr>
<tr>
<td>et al.[82]</td>
<td></td>
<td>supplements</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delmi et al.[80]</td>
<td>Older people, with hip fractures</td>
<td>Standard diet plus oral</td>
<td>Standard diet</td>
<td>Incidence of PU</td>
<td>Not reported</td>
<td>2-4 weeks</td>
</tr>
<tr>
<td>Ek et al.[81]</td>
<td>Long-term medical care residents</td>
<td>Standard diet plus oral</td>
<td>Standard hospital diet</td>
<td>Incidence of PU</td>
<td>Not reported</td>
<td>9 weeks</td>
</tr>
<tr>
<td>Houwing et al.[83]</td>
<td>Older people, with hip fracture</td>
<td>Standard diet plus oral</td>
<td>Standard hospital diet</td>
<td>Incidence of PU, mortality</td>
<td>Yes</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Olofsson et al.[171]</td>
<td>Femoral, neck fracture patients</td>
<td>Standard diet plus high oral protein drinks</td>
<td>Normal post-operation time in care hospital</td>
<td>Incidence of PU,</td>
<td>Not reported</td>
<td>16 weeks</td>
</tr>
</tbody>
</table>

PU = pressure ulcer; NPUAP = National Pressure Ulcer Advisory Panel
Utilities

The utilities for the health states in the model were based on EuroQoL 5D (EQ-5D) scores, anchored between 0.0 for death and 1.0 for best possible health. Utility weights were based on the preferences of the Australian population. The background utility value for non-hospitalised patients between 65-74 years of age (i.e., the health state of being discharged with intact skin) was 0.82, from Clemens et al. (EQ-5D-3L).[152] The utility scores of hospitalised patients in the same age group and with intact skin was 0.66, from an Australian study by Hawthorne et al.[172] The reduction in quality of life (i.e., disutility) from pressure ulcers was 0.29 based on the study by Essex et al.[173]

Costs

Costs included those for hospitalisations, pressure ulcer prevention, and pressure ulcer treatment. Costs in other currencies and price years were converted to 2014 Australian dollars.
using the CCEMG-EPPI-Centre Cost Converter web-based tool.[157] The tool adjusts the original estimate of cost from the original price year to a target price year (using a Gross Domestic Product (GDP) deflator index) and converts the price-year adjusted cost estimate from the original currency to a target currency, using conversion rates based on Purchasing Power Parities for GDP.[157]

Hospitalisation cost was for a public hospital bed in Queensland, Australia, at AUD 950 per patient day (2014 price).[110] The cost of pressure ulcer prevention was AUD 90 (USD55; 2010 price) per day, from Padula et al.[165] The cost of nutritional support at AUD 17 per day based on the study by Banks et al. which estimated the staff time to provide nutritional support at 0.40 hours per day, which is AUD 13 for AUD 32/hour registered nurse (2013 wages), and the cost for the additional nutritional supplements at AUD 4 per day (2013 price).[170] The cost of treating pressure ulcers was from the study by Dealey et al.[166] The daily cost of treating closed pressure ulcer was AUD 103 (GBP43;2011 price) and the weighted average daily cost for open wound management was AUD 226 (GBP94; 2011 price), including the cost of treating wound infection and any necessary surgery.[166] The cost of treating pressure ulcer was assumed to be the same for the inpatient and ambulatory settings. Table 7-2 summarises model input parameters with their distributions and sources.

Table 7-2: Model estimates and sources

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Distribution</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Transition estimates and probabilities</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average length of stay</td>
<td>21 days</td>
<td>Gamma (α=110,β=5)</td>
<td>The average length of stay in the trials included in the Author’s meta-analysis [80-83, 171]</td>
</tr>
<tr>
<td>Excess length of stay from PU</td>
<td>8 days</td>
<td>Gamma (α=4,β=0.5)</td>
<td>Allman et al.[174]</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-------</td>
<td>------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Hospital mortality</td>
<td>0.07</td>
<td>Uniform (0.05-0.10)</td>
<td>Scott et al.[175]</td>
</tr>
<tr>
<td>Background mortality</td>
<td>0.0008</td>
<td>Fixed</td>
<td>Australian Bureau of Statistics</td>
</tr>
<tr>
<td>RR of mortality from PU</td>
<td>1.5</td>
<td>Lognormal (0.42,0.25)</td>
<td>Isaia et al.[176]</td>
</tr>
<tr>
<td>Probability of developing PU with standard care</td>
<td>0.35</td>
<td>Beta (α=254,β=479)</td>
<td>Authors’ meta-analysis of nutritional support in preventing PU (control arm)</td>
</tr>
<tr>
<td>RR of PU with nutritional support</td>
<td>0.83</td>
<td>Lognormal (-0.185,0.077)</td>
<td>Authors’ meta-analysis of nutritional support in preventing PU (Figure 2)</td>
</tr>
<tr>
<td>Probability closed wound heals</td>
<td>0.35</td>
<td>Beta (α=100,β=195)</td>
<td>Bourdel-Marchasson et al.[82]</td>
</tr>
<tr>
<td>Probability closed wound worsens to open wound</td>
<td>0.24</td>
<td>Beta (α=71,β=224)</td>
<td>Bourdel-Marchasson et al.[82]</td>
</tr>
<tr>
<td>Probability open wound heals</td>
<td>0.12</td>
<td>Beta (α=688,β=938)</td>
<td>Brandies et al.[177]</td>
</tr>
</tbody>
</table>

**Utilities**

- Utility for hospitalisation with intact skin | 0.52  | Beta (α=323,β=299) | Hawthorne et al.[172] |
- Utility discharged with intact skin | 0.82  | Beta (α=1210,β=266) | Clemens et al.[152] |
- Disutility from PU | 0.29  | Gamma (α=2.1,β=7.25) | Essex et al.[173] |
- Utility of death | 0     | Fixed | Assumed |
Daily costs

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Cost (AUD)</th>
<th>Distribution</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalisation</td>
<td>950</td>
<td>Gamma (α=10,β=0.01)</td>
<td>Australian Hospital Statistics [110]</td>
</tr>
<tr>
<td>High risk prevention</td>
<td>90</td>
<td>Gamma (α=4,β=0.04)</td>
<td>Padula et al. [165]</td>
</tr>
<tr>
<td>Oral nutritional support</td>
<td>17</td>
<td>Gamma (α=4,β=0.2)</td>
<td>Banks et al. [170]</td>
</tr>
<tr>
<td>Closed wound treatment</td>
<td>103</td>
<td>Gamma (α=3.9,β=0.04)</td>
<td>Dealey et al. [166]</td>
</tr>
<tr>
<td>Open wound treatment</td>
<td>226</td>
<td>Gamma (α=4,β=0.02)</td>
<td>Dealey et al. [166]</td>
</tr>
</tbody>
</table>

AUD = Australian dollar; PU = pressure ulcer; RR = relative risk

*Probabilities in three weeks, converted in the model to daily probabilities using the equation:
\[1 - \exp \left( \ln \left(1 - \text{probability}\right)/21\right)\]

### 7.3.2 Value of information analysis

Methods to calculate value of information measures are described in detail elsewhere.[41, 99, 178] Briefly, we started the analysis by calculating the expected value of perfect information (EVPI). We randomly sampled (10,000 iterations) from the prior parameter distributions to calculate the intervention with the highest expected average NB (i.e., NB with current information). Then we identified the intervention with the highest NB at each iterations and averaged these NBs to calculate the expected maximum NB (i.e. NB with perfect information). The EVPI per-patient is the difference between the expected NB of a decision with perfect information and the decision made based on current information (Equation 7-2).[1]

\[\text{EVPI} = \text{Expected}_0 \text{ Maximum}_i \text{ NB} (i, \theta) - \text{Maximum}_i \text{ Expected}_0 \text{ NB} (i, \theta) \quad \text{Equation 7-2}\]

We calculated population-EVPI by multiplying the per-patient EVPI by the number of patients expected to benefit from this intervention over a given time period. We estimated the population that would benefit from the cost-effective strategy in Queensland public hospitals over the coming 10 years after discounting to be approximately 150,000. This was based on the assumption that 18% of the 200,000 patients, older than 60 years, hospitalised each year...
would have restricted mobility, [110, 179] and 50% of those would be malnourished or at risk of malnourishment.[74] The population-EVPI represents the maximum (i.e., upper bound) value for conducting further research to resolve uncertainty.[23]

If further research appeared potentially worthwhile based on the population-EVPI, we would estimate the value of resolving uncertainty surrounding a particular parameter (e.g., relative effectiveness, cost) by calculating the expected value of perfect parameter information (EVPPI).[23] The EVPPI for the parameter (or set of parameters) of interest \( \theta_i \) is the difference between the expected NB with perfect information on these parameters, conditional on the complementary set of other parameters \( \theta_C \), and the expected NB with current information (Equation 7-3).[39, 99]

\[
EVPPI_{\theta_i} = \text{Expected}_{\theta_i} \text{ maximum}_i \text{ Expected}_{(\theta_C|\theta_i)} NB(i, \theta_1, \theta_C) - \text{maximum}_i \text{ Expected}_\theta NB(i, \theta) \tag{Equation 7-3}
\]

To estimate the expected NB with perfect information on the parameter(s) of interest, we performed two nested Monte Carlo simulation procedures with 1,000 simulations in each loop. We found this number of simulations sufficient for the estimates to converge (i.e., reach a plateau).[99]

To calculate the value of a future research study with a given sample size \( n \) that could reduce uncertainty surrounding the parameter(s) of interest; we calculated the expected value of sample information (EVSI).[34, 38] EVSI is the difference between the expected value of a decision made after collecting data \( D \) on the parameter(s) of interest and the expected NB with current information (Equation 7-4).[41]

\[
EVSI_n = \text{Expected}_D \text{ maximum}_i \text{ Expected}_{\theta_C(\theta_1|D)} NB(i, \theta_1, \theta_C) - \text{maximum}_i \text{ Expected}_\theta NB(i, \theta) \tag{Equation 7-4}
\]
In calculating EVSI, we used Bayesian methods to update prior information using the available data (e.g., the meta-analysis of nutritional support RCTs) to generate the posterior distributions. We assumed the prior distribution and data were conjugate distributions, and thus, the posterior distribution was known in closed form.\cite{41, 57} Similar to the EVPPI, we conducted a two-level Monte Carlo simulation with 1,000 iterations in each of the inner and outer loops.\cite{41} Appendix 2 provides detailed algorithm for our approach to calculate the above value of information estimates using Monte Carlo simulation.

We calculated the population-EVSI by multiplying the per-patient EVSI by the size of the population to whom information from the trial would be valuable, as described above for the EVPI. To choose between alternative trial designs, the costs as well as the benefits of the additional research need to be considered. The difference between the expected benefit of research (i.e., population-EVSI) and the total cost of a particular study design is the expected net benefit of sampling (ENBS).\cite{34, 38} The total cost of a future trial design should include fixed costs (e.g., set-up cost, salaries), variable costs per patient, and the opportunity costs expected to be incurred by patients who would receive the inferior intervention during the trial.\cite{38, 41} For this analysis, we estimated a fixed cost of AUD 150,000 and a variable cost of AUD 300 per patient for a future trial on pressure ulcer prevention with nutritional support, based on a previous research grant application. Further, we tested the cost assumptions in a sensitivity analysis.

The optimal future study design is determined when the ENBS reaches a maximum. If the ENBS is negative, it would be irrational to conduct further research because the expected costs of the study would exceed its expected benefits, and in this case, the current available evidence would be sufficient to accept or reject the intervention.\cite{32, 145} Conversely, a positive ENBS indicates that future research would be worthwhile. The decision in this case
would be to adopt the intervention and ask for further research or delay the adoption and await results of the future study. We calculated and presented the expected benefits from the two scenarios.

7.4 Results

7.4.1 Cost-effectiveness analysis

The mean cost per patient for the nutritional support group was AUD 33,687. This was lower by AUD 425 per patient compared with AUD 34,112 for the standard care strategy (Table 7-3). Compared with the mean QALYs of standard care (0.690), nutritional support mean QALYs were 0.695 resulting in an additional average QALY of 0.005 for nutritional support. At a willingness-to-pay threshold of AUD 50,000 per QALY, the incremental NB was AUD 675, indicating that the nutritional support was cost-effective. The probability of nutritional support being cost-effective was 87%. Figure 7-4 shows the probability of nutritional support being cost-effective over a range of willingness-to-pay thresholds.

Table 7-3: Results of the cost-effectiveness analysis

<table>
<thead>
<tr>
<th></th>
<th>Nutritional support</th>
<th>Standard care</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost</td>
<td>AUD 33,687</td>
<td>AUD 34,112</td>
<td>- AUD 425</td>
</tr>
<tr>
<td>Effect</td>
<td>0.695 QALY</td>
<td>0.690 QALY</td>
<td>0.005 QALY</td>
</tr>
<tr>
<td>Net benefita</td>
<td>AUD 1,063</td>
<td>AUD 388</td>
<td>AUD 675</td>
</tr>
</tbody>
</table>

QALY= quality-adjusted life-year; PU= pressure ulcer; AUD = Australian dollar

*a For a willingness-to-pay threshold of AUD 50,000 per QALY
EVPI = expected value of perfect information

Figure 7-4: Probability nutrition support is cost-effective and the expected value of perfect information versus willingness-to-pay threshold

7.4.2 Value of information analysis

The EVPI for the choice between the nutritional support and standard care was AUD 33 per-patient and AUD 5 million for the population expected to benefit from the full implementation of nutritional support in Queensland public hospitals over 10 years. The EVPI across a range of willingness-to-pay thresholds per QALY is presented in Figure 7-4. Because this value is likely to exceed the cost of additional research, a further study to reduce uncertainty is potentially worthwhile. The EVPPI was highest for the relative risk of pressure ulcers with nutritional support at a population value of approximately AUD 2.5 million (Table 7-4). This indicates that a future RCT should be conducted to explore the relative
effectiveness of nutritional support to standard care. Withholding implementation decision until the results of the future study are out would result in negative ENBS (Figure 7-5A). This is because the expected total costs (including the opportunity cost of NB forgone with the delay) would exceed the expected research benefit. The expected opportunity cost for one-year delay in implementation, assuming that the duration of the future trial was one year only, would be around AUD 14 million. Conversely, we show here that implementing the nutritional support intervention and conducting a future study results in a positive ENBS maximised with a sample size of 1,200 in each arm at AUD 100,000; from an EVSI of AUD 970,000 at a total cost of AUD 870,000 (Figure 7-5B). This represents a return on investment of 11% (AUD 100,000/ AUD 870,000). In a sensitivity analysis, the ENBS ranged from being negative (i.e., research is not cost-effective) to AUD 300,000 (n=1,400) for the respective willingness-to-pay of AUD 70,000 and AUD 30,000 per QALY. Similarly, the ENBS was negative with higher estimates of research cost and around AUD 400,000 (n=1,500) with lower research cost estimates (Figure 7-6).

Table 7-4: Estimates of the value of additional information to resolve uncertainty

<table>
<thead>
<tr>
<th></th>
<th>Per-patient value</th>
<th>Population valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVPI</td>
<td>AUD 33</td>
<td>AUD 4,950,000</td>
</tr>
<tr>
<td>EVPPI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR of PU with nutritional support</td>
<td>AUD 17</td>
<td>AUD 2,555,000</td>
</tr>
<tr>
<td>Transition probabilities</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Utilities</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Costs</td>
<td>AUD 5</td>
<td>AUD 750,000</td>
</tr>
<tr>
<td>Nutritional support</td>
<td>AUD 1.8</td>
<td>AUD 270,000</td>
</tr>
</tbody>
</table>
Standard PU prevention  
Hospitalisation  
PU treatment  

AUD = Australian dollar; EVPI = expected value of perfect information; EVPPI = expected value of perfect parameter information; RR = relative risk; PU = pressure ulcer

* Population estimated at 150,000 over ten years

Figure 7-5: The expected net benefit of sampling with “delay implementation and research” (A) compared with “implement and research” (B)
WTP = Willingness-to-pay

**Figure 7-6:** The expected net benefit of sampling explored with various willingness-to-pay thresholds (A) and research costs (B)

### 7.5 Discussion

Our study showed that nutritional support would be cost-effective in preventing pressure ulcers in high-risk hospital patients, with an expected NB of AUD 675 per patient. Implementing this intervention at a national level would result in substantial healthcare gains. For an estimated hospitalised high-risk population of 150,000 over the coming ten years,[110] we calculate the NB for the State department of health in Queensland, with full implementation of the intervention, to be around AUD 100 million (AUD 675 x 150,000).
Our analysis was conservative in its assumptions, and therefore, the expected NBs could be greater. For instance, we assumed that the two groups have the same rate of wound healing; however, individual small studies showed a trend towards improved pressure ulcer healing with nutritional supplements when compared to standard diet.[169, 180]

In general, our findings of favourable cost-effectiveness agree with those by Banks et al. which found that implementing nutritional support for at-risk patients in Queensland public hospitals would avoid 2,900 cases of pressure ulcer every year, avoid 12,400 bed days attributed to pressure ulcers and produce AUD 5.4 million (2003 price) saved in opportunity costs.[170] Nevertheless, that study did not estimate the incremental utility of nutritional support, which possibly underestimated the overall benefits of the intervention. In contrast, a Canadian study on the cost-effectiveness of oral nutritional support in preventing pressure ulcers in long-term care residents showed that nutritional support was not cost-effective, with an incremental cost of CAD731 (2010 price) and 0.0001 QALYs gained.[181] Probably, nutritional support was not cost saving in that study because there was no cost savings from avoiding excess length of stay in the hospital among long-term care residents. Further, that study used local data (i.e., Resident Assessment Instrument–Minimum Data Set) and not EQ-5D scores, and did not include excess mortality from pressure ulcers.[181]

Considering the uncertainty in the results of our analysis, the probability that nutritional support is cost-effective was 87%; however, the value of further information to resolve this uncertainty was high (AUD 5 million), indicating that further research would be potentially worthwhile. The highest uncertainty was for RR from the meta-analysis valued at AUD 2.5 million, supporting the need for a future RCT comparing the relative effectiveness of nutritional support and standard care. There was no heterogeneity in the pooled studies and assuming the decision population is exchangeable with the populations in the meta-analysis,
we used the estimates from the meta-analysis to inform the prior for EVSI calculation.[41] The ENBS was optimised with a sample size of 1,200 patients in each arm of the future study that should be conducted with the implementation of the nutritional support intervention. This is because the opportunity cost from the benefits forgone would be greater than the expected benefits of additional research if implementation was delayed awaiting further evidence. Furthermore, nutritional support is recommended by international clinical practice guidelines to augment but not to replace the current standard pressure ulcer prevention strategies:[76, 77, 79] and therefore, there would not be significant implementation costs (e.g., training,) or opportunity costs that could not be recovered if the decision to implement this intervention was reversed in the future based on the additional research.[32, 45] A future study is ethical and feasible with the decision to implement nutritional support. Our group has conducted a feasibility study of nutritional intervention on patients at risk of pressure ulcers in the hospital setting, using three feasibility criteria around recruitment, intervention delivery and retention. Recruitment and retention rates were 82% and 88%, respectively.[84]

Our recommendations are in line with the decision frameworks developed by Claxton and colleagues and by Eckermann and Willan.[32, 33] Generally, when the technology is cost-effective ‘approval with research’ would be appropriate if additional research is possible and worthwhile.[32, 101] On the other hand, if the technology is not cost-effective but additional research is worthwhile, ‘only in research’ would be the preferred option. Nevertheless, exceptions from this general rule would be appropriate depending on the presence of irrecoverable cost associated with the implementation of the new intervention (e.g., cost of training).[32] Thus, ‘only in research’ or even ‘reject based on existing information’ rather than ‘approval with research’ or ‘approve based on existing information’ may be appropriate even if research is possible when there are significant irrecoverable
implementation costs.\[32\] It is also important to note that even when the future research is expected to be worthwhile given the positive ENBS value, under a fixed research budget it is essential to consider the opportunity cost of displacing other more valuable research proposals (i.e., with higher ENBS).

Our study has a number of limitations. The risk of bias in the trials included in the meta-analysis was high due to unclear details of allocation concealment and lack of blinding.\[80-83, 171\] This bias may result in overestimated treatment effect. The proposed methods to handle such bias in meta-analyses include restricting the analysis to the trials with low risk of bias or to use all available trials but with down-weighting and adjusting the evidence from studies at risk of bias.\[182\] Bias-adjustment uses information from statistical analysis of meta-epidemiological data or from expert opinion elicitation to inform the prior distributions used for adjustment.\[182\] We did not adjust for bias because all included trials had high risk of bias and it was difficult to estimate accurate prior bias distributions with the limited available evidence. Another limitation is that in the absence of national data on pressure ulcer incidence, healing rate, mortality, cost estimates and disutility associated with pressure ulcer, we obtained these inputs from the published literature and some assumptions were also necessary. However, we referred to studies from Western Europe and North America where pressure ulcer management and its associated costs are relatively comparable to the Australian setting. Additionally, we used a single disutility value for all pressure ulcer grades; however, this will not affect the results given that this parameter is not a major driver of the model. A limitation in our value of information analysis was that we assumed that the parameters were not correlated as they were obtained from different sources. We also assumed full intervention implementation when we calculated value of information estimates. In practice, there are barriers for complete intervention implementation (e.g., staff resistance)
and this imperfect uptake would undermine the benefits of the intervention and the expected benefits of any relevant future research.[66]

In conclusion, investing in nutritional support as an intervention to prevent pressure ulcers in high-risk hospitalised patients is cost-effective with substantial expected health gains. Additional research to reduce decision uncertainty is worthwhile; however, the opportunity cost of delaying implementation exceeds the expected gains from further research. Therefore, nutritional support should be implemented with research.
8. CHAPTER 8 EFFICIENT VALUE OF INFORMATION CALCULATION USING NON-PARAMETERIC REGRESSION METHODS

Statement of contribution to co-authored published paper

This chapter includes a co-authored paper. The bibliographic details of the paper are:


I conducted the analyses and significantly contributed to the writing and revision of the manuscript.

(Signed)____________________________________(Date)___________________________

Haitham W Tuffaha

(Countersigned)_____________________________(Date)____________________________

Corresponding author: Haitham W Tuffaha

(Countersigned)_____________________________(Date)____________________________

Supervisor: Prof. Paul Scuffham
8.1 Abstract
Value of information (VOI) analysis provides an analytical framework to assess whether obtaining additional evidence is worthwhile to reduce decision uncertainty. The reporting of VOI measures, particularly, the expected value of perfect parameter information (EVPPI) and the expected value of sample information (EVSI), is limited because of the computational burden associated with typical two-level Monte Carlo-based solution. Recently, a non-parametric regression approach has been proposed that allows the estimation of multi-parameter EVPPI and EVSI directly from a probabilistic sensitivity analysis sample. We used the regression approach to calculate EVPPI and EVSI in two models, and compared the results with the estimates obtained via standard Monte Carlo simulation. VOI values from the two approaches were very close; however, the regression method was faster. We conclude that the non-parametric regression-based approach provides an efficient and easy-to-implement alternative for EVPPI and EVSI calculation in economic models.
8.2 Introduction

Decision models are commonly used to evaluate the cost-effectiveness of health interventions. They are populated with input parameters estimated from various sources; however, the true values of these parameters are not certain which may result in uncertain decisions.[23] The preferred approach to characterise decision uncertainty is to conduct probabilistic sensitivity analysis (PSA).[17] An additional necessary step is to know whether a decision can be made based on current evidence or if additional research is worthwhile. This can be informed using value of information (VOI) analysis.[1] Measures of VOI include (1) the expected value of perfect information (EVPI), which is the maximum value of additional information to resolve all uncertainty in the parameters; (2) the expected value of perfect parameter information (EVPPI), which is the value of resolving uncertainty in a given parameter or set of parameters; and (3) the expected value of sample information (EVSI), which estimates the value of reducing decision uncertainty from a study of a specific sample size.[34]

EVPI calculation is straightforward; however, although this measure is necessary, it is not sufficient to inform decisions because it represents the upper-bound of additional research.[1] Therefore, it is important to know the parameters that further research should focus on from the EVPPI, and the value of a given trial design from EVSI calculation.[39] Unfortunately, the reporting of EVSI and EVPPI remains limited because of the computational burden of the calculation using two-level Monte Carlo simulation.[31, 183] When the model is linear or the incremental net benefit is approximately normally distributed, one-level Monte Carlo simulation or analytical equations can be used.[41, 44, 184] Nevertheless, models are rarely linear and normality assumptions are not guaranteed. Two-level sampling is time consuming, especially with complex models. Furthermore, it is often
difficult to determine the number of simulations in each level to ensure adequate precision and avoid the upward bias that results from the maximisation step over sampled quantities.[185] Finally, the presence of parameter correlation or non-conjugacy between prior parameter distributions and proposed data likelihoods makes EVSI calculation difficult.[41]

Methods for efficient EVPPI calculation of single parameters have been developed. These show promise, but do not extend to groups of parameters simultaneously.[60, 96] A method based on the numerical approximation of the posterior expected net benefit, conditional on sampled data, has been proposed as an efficient approach for EVSI calculation; however, it requires significant skills and effort to write the necessary computer code.[62, 97] Recently, Strong et al. have proposed a more straightforward non-parametric regression approach for calculating multi-parameter EVPPI and EVSI directly from a PSA sample.[94, 98] The method has the advantage in that the model does not need to be run as part of the EVPPI or EVSI algorithm. Nevertheless, there is a need to demonstrate the value of this method in real-world cases and to compare its performance with the standard approach of Monte Carlo simulation.

In this paper we apply the non-parametric regression method to calculate the EVPPI and the EVSI in two decision models for two healthcare interventions. In addition, we compare the results and computation time with the estimates obtained using Monte Carlo simulation. The paper is structured as follows. In the next section, we present methods for VOI analysis using Monte Carlo simulation versus the non-parametric regression approach. In the third section, we describe the application of the two approaches in two decision models and compare their performance. In the last section, we discuss the implications of our work and provide practical remarks.
8.3 From Monte Carlo simulation to non-parametric regression

8.3.1 EVPI calculation

Assume that we have a model informing a decision on a number of interventions \((i)\). The model predicts \(NB(i, \theta)\), which is the net benefit of \(i\) with unknown parameters \((\theta)\). A PSA takes \(K\) samples from the joint distribution of \(\theta\), and generates a corresponding set of \(K\) net benefits \((NB(i, \theta_1), \ldots, NB(i, \theta^K))\), for each intervention. Averaging these values, the optimal decision with current information is to adopt the intervention that produces the maximum expected NB, \(\max_i E_\theta NB(i, \theta)\). With perfect information on \(\theta\), the maximised NB is \(max_i NB(i, \theta)\); however, because the true value of \(\theta\) is unknown, averaging the maximised values gives the expected maximum NB under perfect information, \(E_\theta max_i NB(i, \theta)\). The EVPI is the difference between the expected NB of a decision with perfect information and the decision based on current information:[1]

\[
EVPI = E_\theta max_i NB(i, \theta) - max_i E_\theta NB(i, \theta) \quad \text{Equation 8-1}
\]

8.3.2 EVPPI calculation

We denote the parameter set of interest \(\theta_I\), and the complementary set \(\theta_C\). With perfect information on \(\theta_I\) the optimal decision would be that with the maximum expected NB after averaging over the distribution of \(\theta_C\), conditional on \(\theta_I\), \(max_i E_{(\theta_C|\theta_I)} NB(i, \theta_I, \theta_C)\). However, we do not have perfect information on \(\theta_I\) so we must take the expectation with respect to \(\theta_I\) which gives us \(E_{\theta_I} max_i E_{(\theta_C|\theta_I)} NB(i, \theta_I, \theta_C)\). The EVPPI is the difference between the expected NB with perfect information and the expected NB with current information:[39, 99]

\[
EVPPI_{\theta_I} = E_{\theta_I} max_i E_{(\theta_C|\theta_I)} NB(i, \theta_I, \theta_C) - max_i E_\theta NB(i, \theta) \quad \text{Equation 8-2}
\]
The Monte Carlo solution to the conditional term in Equation 8-2 is to run a two-level simulation. The outer-loop samples from \( \theta_i \) and then in the inner loop we sample from \( \theta_C \) conditional on the outer sampled value of \( \theta_i \). When the model is linear with no correlation between input parameters, a one-level simulation scheme can be used in which we sample from \( \theta_i \), but keep the complementary parameters \( \theta_C \) fixed at their prior means.[99]

Under the regression methods that operate on a single PSA sample of size \( K \), the NB for a model run \( k \) is considered as the sum of the conditional expectation required and a mean zero error term \( \varepsilon \) [94], which gives us

\[
\text{NB} \left( i, \theta^k \right) = E(\theta_C | \theta^k_i) \text{NB}(i, \theta^k_i, \theta_C) + \varepsilon^k \tag{Equation 8-3}
\]

The expectation in Equation 8-3 takes a different value for each \( \theta^k_i \) and can be thought of as a function of \( \theta_i \). Counter-intuitively, the expectation is not a function of \( \theta_C \), since \( \theta_C \) has been integrated out. This unknown function can be denoted as \( g(i, \theta_i) \).[94] Thus the \( k^{th} \) model run can be expressed as:

\[
\text{NB} \left( i, \theta^k \right) = g(i, \theta^k_i) + \varepsilon^k \tag{Equation 8-4}
\]

The model outputs from the PSA can be used to estimate \( g(i, \theta^k_i) \) for each intervention via non-parametric regression. We denote the model fitted values (i.e. estimates of \( g(i, \theta^k_i) \)) as \( \hat{g}(i, \theta) \). Given \( \hat{g}(i, \theta) \) we can estimate EVPPI via:

\[
\text{EVPPI}_{\theta_i} \approx \frac{1}{K} \sum_{k=1}^{K} \max_i \hat{g}(i, \theta^k_i) - \max_i \frac{1}{K} \sum_{k=1}^{K} \hat{g}(i, \theta^k_i) \tag{Equation 8-5}
\]

Note that we use \( \hat{g}(i, \theta^k_i) \) rather than \( \text{NB}(i, \theta^k) \) in the second term in the right hand side of Equation 8-5 to exploit the positive correlation between the two terms and hence increase precision.[94]
8.3.3 EVSI calculation

We wish to estimate the expected value of a future study with a sample size, \( n \), that is informative for \( \theta_i \). The study data can be summarised in a low dimensional summary statistic that we denote \( D \). The expected optimal NB given \( D \) is found by taking the expectation over the posterior distribution of \( \theta_i \) given \( D \), and the prior distribution of \( \theta_C \), i.e.

\[
\max E_{\theta_C(\theta_i|D)} NB(i, \theta_i, \theta_C).
\]

As \( D \) is unknown, we average over the distribution of \( D \), which gives

\[
E_D \max_i E_{\theta_C(\theta_i|D)} NB(i, \theta_i, \theta_C).
\]

The EVSI is the difference between this, and the expected value of a decision made now:[41]

\[
EVSI = E_D \max_i E_{\theta_C(\theta_i|D)} NB(i, \theta_i, \theta_C) - \max_i E_{\theta} NB(i, \theta) \quad \text{Equation 8-6}
\]

As with the computation of EVPPI via two-level Monte Carlo, the first term in Equation 8-3 also has a two-level Monte Carlo solution. The inner expectation requires a Bayes update of \( \theta_i \) given data \( D \), and the averaging of the NB function over this posterior distribution combined with the prior distribution of \( \theta_C \). This nested simulation, with a potentially difficult inner loop, can be avoided if posterior mean parameter values can be calculated analytically and if the NB function takes a simple form such that we can “plug in” the posterior means directly.[41]

Under the regression-based method, consider sampling a parameter value \( \theta_i^k \) and a random data sample \( D^k \) conditional on \( \theta_i^k \). The observed NB (\( i, \theta^k \)) can be expressed as a sum of the conditional expectation we require, and a mean-zero error term:[98]

\[
NB(i, \theta^k) = E_{\theta_C(\theta_i|D^k)} NB(i, \theta_i, \theta_C) + \epsilon^k \quad \text{Equation 8-7}
\]

The expectation in Equation 8-7 can be thought of as an unknown function of \( D \), denoted \( g(i, D) \).  

140
\[
\text{NB} \left( i, \theta^k \right) = g(i, D^k) + \varepsilon^k
\]  

Equation 8-8

In terms of the choice of summary statistic \( D \), we would choose \( D \) to be a sample estimator for \( \theta_i \).\textsuperscript{98} If we wish to update more than one parameter (i.e. if \( \theta_i \) is a vector) then we would expect \( D \) also to be a vector of summary statistics.

We proceed by generating the PSA \( (\theta_1^1, \ldots, \theta_K^K) \), and then for each sampled value of \( \theta_i^k \) we generate a sample of data \( D^k \) from \( p(D \mid \theta^k) \). We fit a non-parametric regression of \( \text{NB} \) \((i, \theta^k_i)\) on \( D^k \) and extract the fitted values, which are estimates of \( g(i, D^k) \). We denote these estimates \( \hat{g}(i, D^k) \) and then estimate EVSI via:\textsuperscript{98}

\[
\text{EVSI} \cong \frac{1}{K} \sum_{k=1}^{K} \max_i \hat{g}(i, D^k) - \max_i \frac{1}{K} \sum_{k=1}^{K} \hat{g}(i, D^k)
\]  

Equation 8-9

By choosing \( \hat{g}(i, D^k) \) instead of \( \text{NB} (i, \theta^k) \) in the second term in the right hand side of (10) we exploit the positive correlation between the two terms and increase precision \textsuperscript{98}. The algorithm for EVPPI and EVSI calculation using the non-parametric approach is summarised in Box1.

**Box1: EVPPI and EVSI calculation algorithm using non-parametric regression**

**EVPPI**

1. Sample from the distribution of the parameter(s) of interest \( \theta_i \).
2. Fit regression models, regress \( \text{NB} (i, \theta^k) \) from PSA on \( \theta_i^k \) for each intervention.
3. Extract regression model fitted values for each intervention.

**EVSI**

5. Generate data and calculate summary statistic \( D^k \) conditional on each sample \( \theta_i^k \) in the PSA.
6. Fit regression models, regress \( \text{NB} (i, \theta^k) \) from PSA on \( D^k \) for each intervention.
7. Extract regression model fitted values for each intervention.
8. Calculate EVSI via Equation 9

EVPPI = expected value of perfect parameter information; EVSI = expected value of sample information; PSA = probabilistic sensitivity analysis.

### 8.4 Practical application in two models

Full details of the two models and analyses can be found elsewhere.[40, 186] Briefly, the first one is a decision tree for the cost-effectiveness of negative pressure wound therapy (NPWT) in preventing surgical site infections in caesarean sections compared to hydrocolloid dressing.[186] The second is a Markov model of six health states on the cost-effectiveness of nutritional support in preventing pressure ulcers compared with standard diet.[187] Input parameters were assigned probability distributions: beta distributions for probabilities and utilities, gamma for costs and disutilities, and lognormal for relative risks (RR). PSA was performed using Monte Carlo simulation (10,000 iterations) to characterise decision uncertainty. At a willingness-to-pay threshold of AUD 50,000 per quality-adjusted life-years, the incremental NB of NPWT was AUD 70 with 65% probability being cost-effective and AUD 675 for nutritional support with 85% probability being cost-effective.[40, 186]

The EVPI was AUD 76 and AUD 33 per patient for NPWT and nutritional support, respectively.[40, 186] Given the linearity of the NPWT model, one-level simulation (10,000 iterations) was used to calculate the EVPPI and EVSI. The parameter with the highest EVPPI was the RR of surgical site infection at AUD 75. The EVSI for a future study investigating this parameter was AUD 63 for an optimal sample size of 200 patients.[186] Two-level Monte Carlo simulation (1,000 iterations each) was used to calculate the EVPPI in the nutritional support model. The parameter with the highest EVPPI was the RR of pressure
ulcer at AUD 17. The EVSI of a study evaluating this parameter, using two-level simulation (1,000 iterations each), was AUD 6 for an optimal sample size of 1,200 patients.[40]

We repeated EVPPI and EVSI calculations for the two models using regression methods in R software, from the PSA sample of each model and following the algorithm in Box 1. For the RR parameters, we calculated the summary statistics by generating a sample data of the probability of the event in the intervention group ($P_i^k$) from a Binomial ($P_i^k$, $n$) and for the control group ($P_c^k$) from a Binomial ($P_c^k$, $n$); thus, $D^k = \log (P_i^k / P_c^k)$. The EVPPI for the RR in the NPWT model was AUD 74 and AUD 17 for the RR in the nutritional support model. The EVSI at a sample size of 200 was AUD 6 for NPWT and AUD 61 at a sample size of 1,200 for nutritional support (Table 8-1). Figure 8-1 illustrates the EVSI curves from the two models.

### Table 8-1: A comparison of value of information measures calculation using Monte Carlo simulation and non-parametric regression

<table>
<thead>
<tr>
<th>Intervention</th>
<th>EVPPI in AUD (SE)</th>
<th>Approximate computation time</th>
<th>EVSI in AUD (SE)</th>
<th>Approximate computation time</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monte Carlo simulation</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPWT RR site infection</td>
<td>74.8 (1.6)</td>
<td>1 minute</td>
<td>63.0 (1.3)</td>
<td>1 minute</td>
</tr>
<tr>
<td>Other parameters</td>
<td>3.0 (0.3)</td>
<td>1 minute</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nutritional support RR pressure ulcer</td>
<td>17.4 (2.2)</td>
<td>4 hours</td>
<td>6.4 (0.7)</td>
<td>8 hours</td>
</tr>
<tr>
<td>Other parameters</td>
<td>8.9 (1.7)</td>
<td>4 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Non-parametric regression</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPWT RR site infection</td>
<td>74.3 (0.6)</td>
<td>1 minute</td>
<td>61.2 (0.8)</td>
<td>1 minute</td>
</tr>
<tr>
<td>Other parameters</td>
<td>5.8 (1.4)</td>
<td>1 minute</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nutritional support RR pressure ulcer</td>
<td>17.2 (1.0)</td>
<td>1 minute</td>
<td>6.3 (0.8)</td>
<td>1 minute</td>
</tr>
<tr>
<td>Other parameters</td>
<td>9.4 (1.0)</td>
<td>1 minute</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Two-level Monte Carlo of 1,000 iterations each in the nutritional support model, and single level simulation of 10,000 iterations in the NPWT model.

<sup>b</sup>From a probabilistic sensitivity sample of 10,000 iterations.

<sup>c</sup>For a sample size of 200 patients in the NPWT model and 1,200 patients in the nutritional support model.

AUD = Australian dollar; NPWT = negative pressure wound therapy; EVPI = expected value of perfect information; EVPPI = expected value of perfect parameter information; EVSI = expected value of sample information; RR = relative risk; SE = standard error.
EVSI = Expected value of sample information; MS = Monte Carlo simulation

Figure 8-1: EVSI curves for the nutritional support model (A) and NPWT model (B)

8.5 Discussion

We calculated EVPPI and EVSI estimates for two decision models using non-parametric regression, and compared the results with previous calculations using Monte Carlo simulation. The estimates from the two methods were close; however, VOI computation
using regression was faster, particularly in the Markov model. From 10,000-iteration PSA, EVPPI and EVSI estimates were calculated in one step for a single parameter and for a group of parameters. The regression approach eliminated the need for two-level simulation in the Markov model. Further, we avoided the Bayesian updating step for EVSI calculation. This step becomes critical when the priors and posteriors are not conjugate to each other. In this situation, the time consuming approach of Markov Chain Monte Carlo simulation would be necessary.

One of the perceived obstacles for a wider application of VOI methods is the complexity of computation and the long time required to estimate certain measures such as EVPPI and EVSI. The non-parametric regression method used in this paper represents a significant contribution to resolve computational burden. Requiring only the PSA sample, the regression method provides a flexible approach to calculate VOI measures for models built in any software and of any complexity. The approach does not require knowledge of the statistics language R, or sophisticated programming ability. Although the R code is provided, the Sheffield Accelerated Value of Information (SAVI) online tool provides a free platform for VOI calculation.[188] It only requires that the PSA files be uploaded before VOI measures can be calculated and presented. It is worth mentioning that another efficient approach has been recently proposed by Jalal and Kuntz for EVSI calculation from a PSA sample.[189] In their method, they use linear regression metamodeling with the assumption that the incremental NB is normally distributed.[189] Unfortunately, the normality assumption makes it difficult to generalise the approach to non-linear models.[190] However, it would be interesting to see how the two regression approaches compare with models of various types and complexities.

Our work has some limitations. In our analysis, we did not examine the impact of
increasing the number of inner and outer iterations in Monte Carlo simulations and the number of the PSA samples on the results. Moreover, the two reported models were relatively simple, with the assumptions of conjugacy and no parameter correlation. Therefore, it would be useful to compare the two approaches using more complex models such as those using microsimulation, or models with non-conjugate priors (e.g., Weibull distribution) or with correlated parameters.

In conclusion, the non-parametric regression based approach provides an efficient, flexible and easy-to-implement alternative for EVPPI and EVSI calculation in economic models. The approach should resolve the complexity associated with VOI measures calculation and facilitate the incorporation of VOI analysis in decision frameworks.
CHAPTER 9 STUDY RESULTS AND DISCUSSION

This chapter summarises the study results and discusses the work performed in this study. The first section reiterates the study scope and objectives. The second section summarises the key results. The third section shows how the study questions have been addressed. The final section discusses the study findings, implications, limitations and future directions.

9.1 Study scope and objectives

The aim of this study was to apply value of information (VOI) analysis in a group of healthcare interventions to inform implementation decisions, optimise trial design and prioritise research. Four interventions under the National Centre of Research Excellence in Nursing (NCREN) were included: 1) clinically-indicated replacement of peripheral intravenous catheters; 2) tissue adhesive for securing arterial catheters; 3) negative pressure wound therapy (NPWT) in caesarean sections; and 4) nutritional support for preventing pressure ulcers in high-risk patients. The general approach in this study was to conduct economic evaluation, characterise decision uncertainty, and perform VOI analysis for each intervention to answer the following five related questions:[32, 38]

1. Is additional research required? And if yes,
2. What type of research?
3. Do the expected benefits of sampling exceed the costs?
4. What is the optimal research study design?
5. What priority should this research study take?

9.2 Cost-effectiveness and VOI analyses results

The incremental net benefit (INB) of the clinically-indicated catheter replacement intervention was AUD 7.60 suggesting that it was the preferred option compared with routine
catheter replacement.[40] The probability of this intervention being cost-effective was almost 100% and the expected value of perfect information (EVPI) was approximately AUD 0.00.[40] For the tissue adhesive for securing arterial catheters, the intervention had the highest net monetary benefit at AUD 14.10 compared with other devices, indicating that it was the preferred device.[146] The probability of tissue adhesive being cost-effective was 35%. The estimated population EVPI was AUD 850,000.[146] NPWT was cost-effective compared with standard dressing with an INB of AUD 70.00.[191] The probability of NPWT being cost-effective was 65%, and the population EVPI was AUD 2.70 million.[191] Nutritional support was cost-effective compared with standard hospital diet with an INB of AUD 675.00.[187] The probability of this intervention being cost-effectives was 87% and the population EVPI was AUD 5.50 million.[187] Table 9-1 summarises the results of the cost-effectiveness and VOI analyses for the four interventions.

Table 9-1: Cost-effectiveness and value of information analyses results

<table>
<thead>
<tr>
<th>Intervention</th>
<th>INB AUD</th>
<th>% cost-effective</th>
<th>EVPI AUD</th>
<th>EVPPI AUD</th>
<th>EVSI AUD</th>
<th>Total cost AUD</th>
<th>ENBS AUD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically-indicated Catheter replacement</td>
<td>7.6</td>
<td>100%</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Tissue adhesive</td>
<td>14.1</td>
<td>35%</td>
<td>850,000</td>
<td>573,324</td>
<td>250,000</td>
<td>325,324</td>
<td></td>
</tr>
<tr>
<td>NPWT in CS</td>
<td>70</td>
<td>65%</td>
<td>2,700,000</td>
<td>2,600,000</td>
<td>900,000</td>
<td>1,200,000</td>
<td></td>
</tr>
<tr>
<td>Nutritional support in PU</td>
<td>675</td>
<td>87%</td>
<td>5,500,000</td>
<td>2,500,000</td>
<td>870,000</td>
<td>100,000</td>
<td></td>
</tr>
</tbody>
</table>

AUD = Australian dollar; INB = incremental net benefit; EVPI =expected value of perfect information; EVPPI = expected value of perfect parameter information; EVSI = expected value of sample information; ENBS = expected net benefit of sampling; NPWT = negative pressure wound therapy; CS = caesarean section; PU = pressure ulcer.

* For the parameter with the highest value (i.e., relative risk)

* For a sample size of 220 patients in tissue adhesive, 200 patients in the NPWT and 1,200 patients in the nutritional support study.

EVPI calculations for each intervention were straightforward and took only seconds of computational time. For the linear models of the tissue adhesive intervention and NPWT, the EVSI calculation took around one minute for each possible sample size. For the nutritional...
support intervention Markov model, where expected value of perfect parameter information (EVPPI) and expected value of sample information (EVSI) calculations required two-level Monte Carlo simulation, each EVPPI estimate took around four hours and each EVSI estimate took approximately eight hours. Using non-parametric regression in nutritional support and NPWT interventions gave very close results compared with Monte Carlo simulation, but computation time was much shorter with approximately one minute for each EVPPI and EVSI estimate.

9.3 Answering the five related questions to inform implementation and research decisions

9.3.1 Is additional research required?

For the clinically indicated catheter replacement intervention, an EVPI with approximately zero value indicated that additional research is not worthwhile, and therefore, the decision should be to implement the intervention based on the available evidence. Conversely, the population EVPI values for the other interventions suggested that additional research is likely worthwhile. The calculated EVPI estimates were sensitive to the probability of an intervention being cost-effective, the willingness-to-pay (WTP) threshold, and the population expected to benefit from the intervention. The sensitivity analyses, confirmed that EVPI was negligible for the clinically catheter replacement and remained above AUD 300,000 for the rest of the interventions.

9.3.2 What type of research?

For the tissue adhesive intervention, VOI measures were calculated for both cost and effect parameters from the pilot study. This intervention is novel and data on its efficacy is scarce; further, the resources required to insert, change, or remove catheters need to be measured and valued to have accurate cost estimation. Thus, the future study should collect data on both costs and effects. For the NPWT, the parameter with the highest population
EVPPI was the relative risk (RR) of surgical site infection at AUD 2.6 million.[191] This suggested that the additional research should be a randomised controlled trial (RCT) comparing the relative effectiveness of NPWT with standard dressing in preventing surgical site infections in high-risk caesarean section patients. For the nutritional support intervention, the parameter with the highest EVPPI was the RR of pressure ulcer at AUD 2.5 million.[187] This indicated that a future RCT should study the relative effectiveness of nutritional support in preventing pressure ulcers compared with standard hospital diet in high-risk patients.

9.3.3 Do the expected benefits of sampling exceed the costs?

For the tissue adhesive intervention, the expected net benefit of sampling (ENBS) was positive for a future study with a sample size ranging from 50 to 980 patients per arm for all possible designs (i.e., two- to four-arm trial designs).[146] There was insignificant opportunity cost for delaying implementation, but there are potential irrecoverable costs for the introduction of the adhesive material into the healthcare system (e.g., cost of purchase, changing guidelines); and therefore, additional research before implementation is worthwhile. The decision in this case would be ‘only in research’ (OIR). In the NPWT intervention, the ENBS remained positive, even with the opportunity cost of delaying implementation, across a range of possible sample sizes from 50 to 800 patients in each arm.[191] This suggested that the expected benefits of additional research would exceed the expected benefits of implementation. Moreover, there would be a high irrecoverable cost from purchasing and stocking NPWT devices because it is less likely for them to be used in other indications. Thus, additional research before implementation is worthwhile and the decision should be OIR. On the other hand, withholding the implementation of nutritional support intervention until the results of the future study are known would result in a negative ENBS. Nevertheless, implementing the intervention concurrently with research would result in a positive ENBS for
a range of sample sizes between 900 to 2000 patients per arm.[187] There is minimal irrecoverable cost associated with the possible reversal of implementation decision based on the findings of the future study because there are no implementation expenses (e.g., training or equipment).[187] Further, the intervention is intended to support standard hospital diet, and therefore, there are no benefits forgone by replacing the standard intervention.[187] Thus, the decision should be ‘approve with research’ (AWR).

9.3.4 What is the optimal research study design?

For a future trial collecting data on the effects and costs of tissue adhesive compared with other catheter securement devices, the ENBS would be maximised at AUD 325,324 in the four-arm design with 220 patients in each arm, for one year of follow-up at a total cost of AUD 250,000.[146] This would provide a return on investment (ROI) (i.e., net benefit to cost ratio) of 130%.[146] The ENBS from the initially calculated sample size of 388 patients per arm was AUD 282,200, providing an ROI of 79%.[146] For the future trial on NPWT, the optimal design would have a sample size of 200 patients in each arm and a follow-up duration of one and a half year. This design would give a maximum ENBS of AUD 1.2 million at a total cost of AUD 900,000 resulting in a 133% ROI.[191] The initial design with 400 patients per arm would provide an ROI of 66%.[191] In the future trial studying the relative effectiveness of nutritional support in preventing pressure ulcers, the ENBS would be maximised at AUD 100,000 with 1,200 patients in each arm; providing an 11% ROI.[187]

9.3.5 What priority should this research study take?

The future research studies can be ranked based on their ENBS estimates. Among the three interventions where future research is worthwhile, the ENBS would be the highest for the NPWT at AUD 1.2 million, followed by tissue adhesive with AUD 325,324, and nutritional support with AUD 100,000. The same ranking would be kept if the future studies
were ranked according to their ROI with 133% for the NPWT, 130% for tissue adhesive, and 11% for the nutritional support intervention.

9.4 Discussion

This study has applied VOI methods in a group of different real-world healthcare interventions for hospitalised patients. This is the first study to apply VOI to a portfolio of interventions to inform decisions on additional research, optimal study design and research prioritisation using the sufficient condition of EVSI and ENBS estimation. The expected research benefits and costs from specific study designs were considered rather than restricting the analysis to the upper bound values of additional research (i.e., EVPI and EVPPI). The evaluated interventions appeared to be cost-effective, but there was uncertainty in their adoption decisions and this uncertainty varied across the interventions. VOI analysis guided the decision on whether to adopt an intervention based on current evidence or if additional research to reduce uncertainty is required. Further, VOI analysis informed the direction of research and the most efficient designs of those additional studies. Further, the prioritisation of the future studies was set based on their ENBS values.

9.4.1 Interventions selection

The evaluated interventions were nursing interventions for hospitalised patients under the NCREN. There was limited evidence about the effectiveness and cost-effectiveness of these interventions to guide their implementation in public hospitals in Queensland. The application of VOI in a group of NCREN projects would be ideal to advise researchers about the value and optimal design of their intended research, and to demonstrate the value and practicality of VOI methods. An important element in this study was to involve the NCREN staff. The clinical research team suggested the interventions to be evaluated, shared the results of their pilot studies and systematic reviews, provided clinical advice, validated the
constructed models, and participated in the communication of findings through publications and oral presentations. Although some of the clinical researchers had an idea about economic evaluations, the concept of VOI was foreign to them. They were interested in exploring how sample size calculation would differ between VOI and the traditional frequentist approach. They also thought that quantifying the value of research might support future grant applications.

9.4.2 Cost-effectiveness analysis and source of evidence

The evaluated interventions had different levels of evidence to support a decision on their adoption. Ideally, all relevant current evidence to guide cost-effectiveness analysis should be sought from various sources such as published research studies, reports, pilot trials and expert opinion. Nevertheless, economic evaluations alongside clinical trials remain attractive due to its high internal validity, particularly when that trial is the best available evidence to answer the decision problem.[54]

In this study, the analyses of the clinically-indicated catheter replacement and tissue adhesive for catheter securement were based on patient-level data. Although, the analysis of the clinically-indicated catheter replacement strategy was performed alongside a single clinical trial, that trial was multisite with a large sample size (around 3,000 patients) collecting data on both effectiveness and resource use. For the tissue adhesive intervention, the evidence in the field of catheter devices is scarce and relevant studies could not be identified despite an extensive systematic search of the literature. Ideally, expert opinion should have been elicited in this case; however, the investigated material (i.e., tissue adhesive) is a new introduction to catheter securement techniques and the experience of clinicians with this approach is limited; and therefore, it was difficult to obtain a reliable expert opinion on its effectiveness. For the NPWT and nutritional support interventions, the
economic evaluations were based on analytic modelling with parameter information gathered systematically from various sources together with evidence synthesis.

The WTP threshold was set at $50,000 per QALY gained in the two cost-utility analyses of NPWT and nutritional support, which is an acceptable WTP per QALY in Australia.[147] For the clinically-indicated peripheral intravenous catheter replacement and tissue adhesive interventions, WTP thresholds per effectiveness unit were proposed. This is because the two interventions are acute in nature and take place over few days, which makes it difficult to measure any change in health-related quality of life. Notwithstanding, the choice of WTP thresholds was not arbitrary. The WTP threshold of $0 for phlebitis case avoided and $100 for arterial catheter saved were suggested by the research team to reflect the opportunity cost of health benefits forgone elsewhere from adopting the new interventions. Further, the impact of varying WTP values on the results was explored and clearly presented.

**9.4.3 VOI analysis and computation**

All measures of VOI were calculated in this study. Typically, the first VOI measure to be calculated is EVPI as the upper bound for additional research value. If EVPI seems to exceed the expected costs of a research study, then additional research is likely worthwhile and the other measures of VOI would be calculated.[1] Nevertheless, it is difficult to determine how high this value should be without knowing the expected cost of research, which depends on the study design. Therefore, EVPI is not sufficient to inform if additional research is worthwhile whereas EVSI and ENBS calculation establish a sufficient condition by considering marginal costs and marginal benefits of sampling.[1] Some health economists have even argued that EVPI is neither necessary nor sufficient to inform a decision on the need for additional research.[38]

Monte Carlo simulation is the standard approach for VOI measures calculation and it
was the main method used in this study. This approach is flexible and can be used in economic models and alongside clinical trials. One of the perceived challenges for a wider VOI application is the computational burden of VOI measures; however, the calculation of VOI measures was not the biggest challenge in this study. In fact, the most demanding tasks were performing the cost-effectiveness analyses and characterising decision uncertainty. The total time to perform economic evaluation and VOI analysis for each of the presented case studies took 3-4 months, which demonstrates the practicality of the approach to timely inform research decisions.

EVPI calculation was straightforward after characterising the extent of uncertainty. One level Monte Carlo simulation to calculate EVSI and EVPPI in the linear models took seconds. Even in the Markov model for the nutritional support intervention, which required the use of two-level Monte Carlo simulation, the computation time was four hours for EVPPI and around eight hours for each EVSI sample size estimate. This faster-than-expected computation in this study can be attributed to a number of factors: first, the model structures were relatively simple; however, each model was a good representation of the decision problem which was validated by expert clinicians. Second, EVSI calculation assumed conjugacy between prior parameter distributions and proposed data likelihoods; thus, the parameters for posterior distributions could be readily calculated using closed forms. Third, the analyses in the modelled evaluations were conducted under the assumption that there were no correlations between parameters, and hence, the available algorithms for EVSI calculation were directly applied. Fourth, the calculation was using modern computers and software that tend to perform faster than the older computers used a decade or two ago when VOI was first introduced. This being said, with more complex models such as those with patient-level simulation, or when conjugacy between priors and likelihood is not established, or when there
is correlation between input parameters, the more computationally demanding simulation approach of Markov Chain Monte Carlo becomes necessary.[41]

Simpler methods for VOI calculation are available. Analytical solutions calculate VOI measures based on the assumption that the INB is approximately normal, supported by the central limit theorem.[44] The analytical approach is fast and does not suffer from Monte Carlo error which is inherent in simulation. The normality assumption is reasonable if cost and effectiveness data were collected alongside a randomised controlled trial with a large sample size.[12] In this study for instance, the INB from the large RCT on the clinically-indicated catheter replacement was assumed normal. Nevertheless, the INB is unlikely to be normally distributed in non-linear decision models or when the sample size in the trial is small (i.e., less than 50). [13] Further, analytical solutions cannot be applied to multi-arm clinical trials and there is no such solutions to calculate partial EVSI (i.e., EVSI for a given parameter or set of parameters).[91]

Recently, methods for efficient EVPPI calculation have been developed; however, these methods are for single parameters and do not extend to EVPPI calculations for a group of parameters.[60, 96] Strong et al. (2014 & 2015) have proposed a non-parametric regression approach for calculating multi-parameter EVPPI and EVSI directly from a probabilistic sensitivity analysis (PSA) sample.[94, 98] Their method allows the efficient calculation of the two VOI measures regardless of model complexity or conjugacy and correlation assumptions. This present study reported the first applied use of this method by repeating VOI calculation for the pressure ulcer and NPWT interventions. The results were close to the estimates calculated using the standard Monte Carlo simulation approach, but the calculation time was much shorter. Although more applied research is required to demonstrate the accuracy and speed of this method in calculating VOI measures in more
complex models, the non-parametric method provides a fast, flexible, and easy to implement approach that should eliminate the computation burden of EVSI and EVPPI. The Sheffield Accelerated Value of Information (SAVI) online tool provides a free platform for VOI calculation using the non-parametric regression method.[188]

### 9.4.4 Informing decision making

This study highlighted the value of considering implementation and research decisions simultaneously using VOI and options analysis. While VOI analysis estimates the value of collecting more information, real options analysis estimates the value of waiting for this information before decisions are adopted.[100] This framework considers the trade-off between the benefits and costs of additional research (i.e., VOI analysis) together with the costs and consequences of acting now against waiting for more information (i.e., real options analysis).[100] Keeping options open to change a decision is a reasonable approach for risky decisions with irreversible costs. The framework takes a number of factors into consideration including the possibility and expected duration of additional research, the expected opportunity cost of delaying the implementation until the research results become available, and irrecoverable costs spent on training, equipment, and the opportunity loss when early adoption prevents conducting worthy research.[100, 101]

The clinically-indicated catheter replacement intervention is cost-effective but the value of additional research is negligible; thus, the decision in this case should be to approve the intervention based on the current evidence. The tissue adhesive and NPWT interventions are cost-effective, but additional research is possible and worthwhile and the opportunity cost of implementation delay is relatively small. Moreover, there are irrecoverable costs from purchasing the devices which may not be recovered if the decision is reversed in the future. Therefore, the decision in these two interventions should be to wait for the information from
the future studies (i.e., OIR). For the nutritional support strategy, it is cost-effective but additional research is required; however, the research would not be worthwhile if the adoption was delayed because of the high opportunity cost and the insignificant irrecoverable costs. There will be a higher benefit to the system if this intervention is implemented while the future study is underway; therefore, the decision in this case should be AWR. The advantage of AWR decisions is allowing the health system to benefit from a new intervention at the early stages of its development when the evidence is scarce or immature, given that the expected benefits offset the opportunity costs of delay and irreversible implementation costs. The downside of such decisions, however, is that there will be little incentive for conducting additional research when the intervention is implemented.[32]

It is worth mentioning that the decisions informed by this framework are dynamic and may be reconsidered with new information or with change in costs. For instance, OIR decision in the NPWT case may be changed to AWR or even ‘approve’ if the additional research proved the intervention more effective or if the price of the device went down. Similarly, the AWR decision in the nutritional support intervention may be changed to OIR or even ‘reject’ if the intervention was found to be less effective.

9.4.5 Optimising study design

When additional research appears worthwhile, EVPPI can inform the focus (i.e., which aspects of the research) and subsequently the type of the additional research.[39] In this study, the RR of surgical site infection and the RR for pressure ulcer were the parameters with the highest EVPPI in the NPWT and nutritional support interventions, respectively. For instance, the EVPPI of the RR of nutritional support in preventing pressure ulcer ($75) approached the EVPI ($76), indicating that this parameter is driving the results. Therefore, the future studies should be RCTs to evaluate the relative effectiveness of the two
interventions compared with standard care. Of course, more information can be collected on additional parameters in the future trials (e.g., resources use and costs) resulting in higher research value; nevertheless, the study was conservative to calculate only the EVSI for the RR parameters. Importantly, the EVPPI gives us information about the value of reducing uncertainty in the decision making that cannot be evaluated using one-way sensitivity analysis or analysis of covariance. The latter summarises the contribution of a parameter to the variance of the output of the analysis (e.g., INB) but it is not directly related to decision uncertainty.[192] The agreement between these uncertainty methods in ranking parameters according to their influence is low in non-linear models and in those with correlated inputs.[192]

The sample sizes calculated by VOI analysis were smaller and had higher ROI compared with the sample sizes calculated using the traditional approach. VOI analysis provides an alternative and economic approach to the traditional method of sample size calculation based on type I and II error and the smallest clinically significant difference.[34, 44] There is a notion that the 5% significance and 80% power are arbitrarily chosen and these values often take the same values across clinical trials, regardless of the outcomes of making an error.[44] The approach in this study was to report and compare both the sample size calculated by the traditional approach, when available, and the sample size calculated by VOI. This was useful when presenting VOI to researchers who were trained to calculate sample sizes based on error type and effect size. The clinical research team intend to use VOI calculated sample sizes to guide interim analysis time points. Moreover, VOI can be repeated in interim analyses to assess the actual reduction in initial uncertainty and the need to stop or to continue the research studies.

By comparing expected marginal research costs and marginal benefits, broader
research design aspects are informed by VOI analysis such as the number of study arms (i.e., relevant alternatives), allocation of sample between the arms, follow-up duration, and research sequence.\cite{43, 45} Expectedly, the more patients and study arms and the longer the follow-up time the more uncertainty is reduced, but this comes with additional cost. The optimal trial design is the one that maximises ENBS over these design dimensions.\cite{45} For example, VOI analysis suggested that a four-arm trial design would be optimal for the tissue adhesive intervention.\cite{146} For the NPWT, VOI analysis indicated that the optimal trial follow-up duration would be 1.5 years.\cite{191} Importantly, VOI in this intervention informed logistic aspects such as the number of research sites. Based on the estimated recruitment rate for the NPWT study, four research study sites (i.e., hospitals) was found to be optimal as it reduces the follow-up time and consequently the opportunity cost for patients receiving the sub-optimal intervention during the study.\cite{191}

Two research dimensions were not explored in this study, patient allocation to trial arms and sequential study designs. It was assumed that the number of patients in each trial arm will be equal; however, this may not necessarily be the case. The optimal allocation should be based on the number of patients in each arm that maximises the ENBS.\cite{193} The other dimension of research design is when more than one study is conducted at the same time or sequentially to collect data on different parameters related to the same decision problem. If trials are conducted and reported at the same time, the ENBS is not simply the sum of the ENBS’s for each individual trial design but the ENBS that is maximised by a given portfolio of the trial designs.\cite{193} On the other hand, when we have a series of studies, the VOI from one study should be estimated conditional on the additional information already obtained from the previous study.\cite{193, 194}
9.4.6 Research prioritisation

Under limited research resources, it is vital to prioritise research projects according to their ability to provide the best value for money. In this regard, research prioritisation needs to move from the subjective approach of evaluating research merits (e.g., panel of experts) towards objective quantitative methods that measure the value of research. Adding this economic perspective allows for a transparent and efficient allocation of scarce resources to generate information that is useful for decision making. In this study, VOI analysis was used to prioritise research across the four interventions. The results showed that it is not worthwhile to invest in further research on catheter replacement. Researching NPWT would deliver the highest monetary benefit (ENBS = AUD 1.2 million) followed by tissue adhesive (ENBS = AUD 325,324) and nutritional support (ENBS = AUD 100,000). Of note, each of the evaluated interventions was funded or applied for funding by a grant allocated to that particular project, and thus, there was no actual competition on a limited pool of research funds. Nevertheless, VOI was considered useful by the NCREN research team to support additional grant applications and to better allocate other resources (e.g., research staff).

There are two published papers on the use of VOI analysis to prioritise research studies for different interventions. The first paper was by Claxton et al. (2005) which applied VOI in nine different interventions from two studies for the National Co-ordinating Centre for Health Technology Assessment and the National Institute for Health and Clinical Excellence (NICE).[39] That study used EVPI and EVPPI to inform if additional research is required, for which aspects, subgroups, and endpoints.[39] The second paper was a study by Carlson et al. (2003) on incorporating VOI into a stakeholder-driven research prioritisation process of cancer genomics research.[59] That study demonstrated how providing the stakeholders with EVPI estimates resulted in participants changing their ranking of the future research
Both studies relied on the maximum value of additional research (i.e., EVPI, EVPPI), but did not compare the expected benefits and costs of the suggested future trial designs (i.e., EVSI and ENBS) to establish the sufficient condition for decision making, which may lead to a sub-optimal study ranking. For instance, if the future studies in this study were ranked according to their EVPI’s, the research with the highest priority would be on nutritional support (EVPI = AUD 5.5 million) followed by NPWT (EVPI = AUD 2.7 million) and tissue adhesive (EVPI = AUD 850,000), which is totally different from the ranking based on EVSI and ENBS estimation.

There are other approaches to prioritise research such as the burden of the disease and the Payback approach.[195] The burden of the disease is based on the principle that the higher the cost of a disease the greater the need for research.[49] However, this approach does not consider the marginal benefits and costs of research; a research on a disease with high burden may not be cost-effective. Further, the approach may direct resources to a group of extensively researched diseases at the expense of conditions with smaller number of patients (e.g., rare diseases) where research is most needed. The Payback approach compares the expected value of research with its expected cost.[53] In this approach, the net benefit of research is the difference between the expected health gains and costs for the targeted populations with and without conducting the intended research.[46, 49] Additionally, the population expected to benefit from the evaluated intervention and the level of its uptake are estimated.(7) While there is a strong similarity between the Payback and VOI approach regarding the need to conduct cost-effectiveness evaluations and making assumptions about the targeted population and intervention implementation, there is a major difference between the two approaches. VOI analysis follows a systematic approach starting from evaluating the cost-effectiveness of alternative interventions, followed by eliminating the need for research.
when there is low uncertainty, then informing the parameters of interest and the optimal trial
design before a comparison is made across research proposals for the selected interventions
and subgroup of patients.[46, 49] In the Payback approach, the design for a particular trial on
a given intervention is assumed optimal and the approach is used to estimate if this research is
cost-effective. Therefore, VOI is better suited to inform strategic funding decisions on which
research projects to commission, whereas the two approaches may be useful to inform the
cost-effectiveness of a proposed trial.[46, 49]

9.4.7 Study limitations

Similar to other VOI studies, our study has a number of limitations that arise from the
assumptions made during the analysis. The estimated VOI measures may be affected by the
structural assumptions in the cost-effectiveness analysis such as the model structure, WTP
thresholds and cycle length. While sensitivity analyses were performed to present the effect
of varying WTP on decision uncertainty, no attempt was made to handle structural
uncertainty because, according to the involved clinicians, the model structures were the best
representation of the investigated decision problems. Nevertheless, recent approaches have
been developed to deal with structural uncertainty such as model averaging, where the results
of multiple model structures are weighed and averaged, or parameterising this structural
uncertainty through elicitation of priors from experts.[24, 196]

The measures calculated from Monte Carlo simulation are per-patient values; however, it is essential to estimate the value of research for the population expected to benefit from the implementation of the preferred intervention over a certain time horizon.[34]

Although it is possible to obtain data on the prevalence and incidence of a condition from published reports and studies, it remains challenging to determine the time horizon over which an intervention is expected to be used as well as its uptake rate. Because the evaluated
interventions were for acute conditions, the future populations were calculated from the estimated incidences obtained from published reports. The time horizon was set between 5-10 years depending on the technology and as advised by the clinicians in the team; however, the impact of the time horizon on VOI estimates was presented in sensitivity analyses.

In the absence of robust information on the expected implementation of the interventions, perfect implementation was assumed. This could have overestimated EVSI estimates because the expected benefit of research is lower with reduced implementation.[38] In practice, perfect implementation is impossible due to uptake barriers (e.g., resistance to change, training needs). A framework for value of implementation analysis has been developed by Fenwick et al. to inform separately (i.e., there is no relationship between information and implementation) but simultaneously the EVPI and the expected value of perfect implementation.(29) Additionally, it was assumed that the patients to benefit from each intervention were homogenous as they represent defined subgroups (e.g., patients at high risk of pressure ulcers); and therefore, no attempt was made to explore heterogeneity. Individualised (i.e., personalised) care is an emerging area of research to maximise health outcomes based on patient characteristics. Frameworks motivated by VOI principles have been developed to estimate the value of heterogeneity and individualised care.[197, 198]

Correlation between effect and cost parameters was addressed in the clinically-indicated catheter replacement and tissue adhesive interventions because the two analyses were performed using patient-level data. However, an assumption was made that there is no correlation between parameters in the economic models for NPWT and nutritional support interventions. For the NPWT decision tree, the model can reasonably be assumed to be linear; and therefore, correlation may not have a significant impact on the results.[32] For the Markov model of nutritional support intervention, the parameter correlation was not deemed
an issue because input parameters were obtained from different sources. Nevertheless, when all available evidence is systematically identified and/or synthesised to populate decision models, there is a good chance that input parameters may be correlated.[27] The significance of parameter correlation in decision models has been previously recognised by a number of studies reporting the impact of correlation on the outcomes of the economic models and decision uncertainty.[27, 29] Parameter correlation by itself may sometimes have only a moderate effect on the expected costs and benefits, for example when the variance is small or the non-linearity is minor, but its effect on uncertainty of these outputs and on the expected value of further research can be substantial in more complex models.[29]

The limitations above in terms of estimated time horizons for the technologies, dealing with non-linear models, parameter correlation, and structural uncertainty have been addressed in the literature as methodological challenges for VOI applications, though they may not always have a significant impact on the results.[31, 65] Nevertheless, given the complexity introduced when handling these assumptions, it is important to assess their potential impact on VOI findings before undertaking any further intensive analysis. Importantly, such added complexity would be a new barrier for decision makers to understand and adopt VOI methods. Finally, it is important to emphasise that VOI quantifies statistical uncertainty for the input parameters in a decision model; however, it does not account for uncertainty of unknown information (i.e., epistemic uncertainty) for parameters not included in the economic evaluation.[31] All efforts were made in this study to clearly and realistically model the decision problems using the best available evidence and including all relevant parameters.

9.4.8 Future directions

Despite the usefulness of VOI methods, the application of this approach is limited in
practice. The commonly perceived barrier for a wider VOI adoption has been the complexity of the calculations required to estimate VOI measures; however, the recent introduction of simpler and more efficient methods may go some way to resolving this issue.\[93, 94\] Additionally, it is not always necessary to calculate all VOI measures if the EVPI value is low. The other reported factor for the limited application of VOI is that the decisions to adopt interventions and to conduct research are usually separate. Claxton et al. noted this in their first pilot study on VOI application: “The key problem seems to be the policy environment where accountability and transparency for research prioritisation and commissioning lags behind adoption and reimbursement decisions, and where there appears to be a separate remit for reimbursement and research decisions”.\[39\] This is true, but the main reason for not deciding simultaneously on both reimbursement and research may be that decision making organisations are not aware of the value of this approach and/or they do not believe in its usefulness and/or practicality. Therefore, it is necessary to increase the awareness about the value of this approach among stakeholders and improve their understanding of VOI principles using effective and clear communication. It is also important to understand the needs and expectations of stakeholders as well as their concerns about the approach. Additionally, there is a need to explore new areas of application for VOI analysis to meet additional needs for researchers and decision makers.

To improve awareness and understanding amongst stakeholders, publications, especially in clinical journals, applying VOI may demonstrate the value of this approach to a larger base of clinicians and researchers. Further, more health economists and analysts need to be trained on handling decision uncertainty and using VOI methods through university courses, professional workshops, and tutorials. Incorporating these methods into statistical and modelling software packages will encourage analysts to report VOI measures with their
economic evaluations. Importantly, developing guidelines for VOI analysis, for example by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), would establish good practice standards and ensure high levels of quality and transparency in the analysis.

It is essential to understand the needs, expectations and concerns of the different stakeholders. Researchers may consider VOI a barrier to limit their access to research funding; however, evaluating the cost-effectiveness of the interventions and the value of additional research would help researchers and institutions make early stop-go decisions about their research projects and make better use of their limited resources. In this regard, VOI analysis can be an essential component of feasibility and pilot studies. Expectedly, many researchers would find it difficult to accept a new method for sample size calculation which is different from the traditional use of the frequentist hypothesis-testing approach. VOI analysis can support, but not necessarily replace, the current approach by helping researchers economically calculate sample sizes and explore additional aspects of research design such as the optimum follow-up duration and allocation of participants in trial arms. Moreover, VOI analysis can be used to support grant applications by demonstrating to the funders that the intended study is value for money.

From a public research funding organisations’ perspective, VOI analysis promotes a transparent, quantitative and objective approach to allocate limited budgets for research studies that are expected to have high information value and implementation benefits. This does not mean that VOI should immediately replace the current expert panel approach especially when there are specified criteria to evaluate research proposals. Actually, VOI can complement the current qualitative approach by providing a quantitative dimension providing an important broader perspective.
For decision makers, VOI may appear as a complex academic exercise. They may also be sceptical about the robustness of the findings of VOI with the associated predictive modelling and assumptions. Nevertheless, incorporating this approach into decision frameworks is intuitive if it is introduced as a decision support tool to reduce the chance and costly consequences of sub-optimal decisions. Many decision making organisations embrace evidence based approaches in making decisions using cost-effectiveness analysis; furthermore, handling and presenting uncertainty is already embedded in the current decision frameworks in many jurisdictions. Therefore, there is no reason why an additional necessary step to evaluate the consequences (i.e., opportunity losses) of uncertainty should not be considered to optimise decision making. Ideally, links could be established between the reimbursement and research decisions whereby research is commissioned and funded based on decision making needs.[39] Of note, the VOI approach may be criticised for placing lower value on research intended for rare diseases with low prevalence, which may raise equity concerns. However, VOI depends on both the size of the population affected by a condition and the uncertainty in evidence.[199] Because the uncertainty in evidence is often high in rare conditions, VOI may be high enough to justify further research. Further, unlike the traditional hypothesis testing approach, VOI supports smaller sample sizes at lower research cost when the uncertainty is high, which makes additional research worthwhile even if the intervention does not appear to be cost-effective.[199]

From an industry’s perspective, industry may also consider VOI a barrier for reimbursement and market access. Nevertheless, VOI can sometimes support market access under AWR schemes which allow the early adoption of promising interventions while further research is underway to provide more information. Further, VOI can inform the ‘research and development’ decision, that is, to continue to investigate in a given product or not.[39]
Clearly, the expected benefit from the industry perspective is the expected profits, which is different from the societal benefits from the public organisations perspective. Even if the future product or service does not appear to be cost-effective but the uncertainty is high, the product may become cost-effective with additional research. Further, the price could be reviewed to make the product cost-effective and to reduce uncertainty.[32, 53]

It would be interesting to compare the performance of VOI analysis with the current methods of research design and prioritisation. Further, developing frameworks linking value of research (i.e., VOI) with value of implementation and/or value of heterogeneity and individualised care would be useful. It will be also interesting to explore how VOI principles can be used to prioritise other forms of research such as conducting and updating systematic reviews and meta-analyses (e.g., Cochrane reviews).

9.4.9 Conclusion

This study demonstrated the usefulness and practicality of applying VOI analysis in a healthcare interventions. VOI analysis informed implementation decisions, enhanced trial designs and prioritised future research studies in a group of real-world interventions by considering the marginal costs and marginal benefits of sampling. The study used various methods of VOI calculation and showed that methodological and computational issues that are often perceived with this approach should not be the biggest challenge for its wider application. There is now a range of simplified methods to enable efficient VOI calculation alongside clinical trials and in economic models of different levels of complexity. Efforts should be focused on promoting the use of VOI methods and facilitating their incorporation into decision making frameworks.
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Appendices

Appendix 1

The net monetary benefit (NB) NB for an intervention \(i\) informed by the set of input parameters \(\theta\) was calculated as:

\[
NB (i, \theta) = \lambda \* \text{Effect} (i, \theta) - \text{Cost} (i, \theta)
\]  

1. **Expected value of perfect information (EVPI)**

The EVPI is the difference between the expected NB of a decision with perfect information and the decision made based on current information.[1]

\[
EVPI = E_{\theta} \text{Max}_i NB (i, \theta) - \text{Max}_i E_{\theta} NB (i, \theta)
\]  

1. Assigned probability distributions to the input parameters in the mode as summarised in Table 2 in the main text.

2. Sampled random values \(k\) times (e.g. \(k = 10,000\)) from the distributions described above for each intervention.

3. Calculated the mean NB for each intervention across all simulations, and identified the preferred baseline decision, that is, the intervention with the maximum expected mean NB (\(max_i E_{\theta} NB (i, \theta)\)).

4. Calculated the NB for each intervention and identified the optimal intervention at each simulation.

5. Averaged the NBs from the identified optimal interventions in Step 4 (\(E_{\theta} max_i NB (i, \theta)\)).

6. EVPI per-patient is the difference between the average NBs in steps 5 and 3.

2. **Expected value of perfect parameter information (EVPPI)**

Because the model used was linear and assuming no correlation between input parameters, the same one-level Monte Carlo simulation technique described above was used to calculate
the EVPPI; the sampling would be only from the distribution of the parameter(s) of interest $\theta_I$ whereas the other parameters $\theta_C$ were fixed at their prior means.[99]

\[
EVPI_{\theta_I} = E_{\theta_I} \max_i NB(i, \theta_I, E(\theta_C)) - \max_i E_{\theta} NB(i, \theta) \tag{3}
\]

Steps 1-3 as in EVPI algorithm detailed above, then:

4. Sample $\theta_I$ once from its prior distribution (one-level simulation).

5. Fix $\theta_I$ at their sampled values, and fix the remaining uncertain parameters $\theta_C$ at their prior mean value.

6. Calculating the average NB of each intervention given these parameter values.

7. Identify the intervention that has the highest estimated expected NB given the sampled value for the parameters of interest ($\theta_{Ik}$).

8. Repeat steps 4-7 $k$ times (e.g., $k = 10,000$) and calculate the average NB of the preferred interventions identified in Step 7.

9. EVPPI is the difference between the average NBs in Steps 8 and 3.

3. Expected value of sample information (EVSI)

EVSI is the difference between the expected value of a decision made after collecting data $(D)$ on the parameter of interest and the expected NB with current information.[41]

\[
EVSI_n = E_D \max_i NB(i, E(\theta_I|D), E(\theta_C)) - \max_i E_{\theta} NB(i, \theta_I, \theta_C) \tag{4}
\]

Given the linearity of the model, calculating the EVSI required the same one level Monte Carlo sampling; however, the sampling would be from the posterior distribution of the parameter of interest obtained using Bayesian updating.[41] To estimate the EVSI for the relative risk (RR) of NPWT compared to standard dressing, we assumed that parameters $\theta_{NP}$ and $\theta_{SD}$ represent the probability of SSI with NPWT and standard dressing, respectively. We followed the algorithm adapted from the algorithm reported in Ades et al., [41]

Steps 0-3 as in EVPI algorithm above, then:
4. Simulated the variety of possible results of proposed data collection:

4.1 Drew a sample from the prior distribution of the RR. The logRR ~ Normal \((\mu_0, \tau_0)\)
where \(\mu_0\) is logRR in the meta-analysis and \(\tau_0\) is its variance.

4.2 Drew a sample baseline parameter \(\theta_{SD}\) from its prior distribution: \(\theta_{SD}\) ~ beta \((a, b)\)
where \(a\) is the number of patients who developed SSI and \(b\) is the number of patients who did not develop SSI from the combined data of the pilot trial and Masden et al.

4.3 Transformed back to obtain an implied prior for \(\theta_{NP}\): \(\theta_{NP} = \theta_{SD} \exp(\text{logRR})\)

5. 5.1 Drew a sample sufficient statistic \(D\), in this case a Binomial numerator, for each arm in the future trial with size \(n\), assuming equal size arms:

\[ r_{SD} \sim \text{Binomial}(\theta_{SD}, n) \text{ and } r_{NP} \sim \text{Binomial}(\theta_{NP}, n) \]

5.2 Converted the sufficient statistics to a mean and variance using the normal approximation:
\[ \mu_D = \log \left[ \frac{r_{NP}n}{r_{SD}n} \right], \]
\[ \tau_D = \left[ \frac{(n - r_{SD})/(r_{SD}n) + (n - r_{NP})/(r_{NP}n)}{1} \right]^{-1} \]

6. Updated the prior with the new simulated data to obtain parameters of the posterior distribution:
\[ \logRR \big| D \sim \text{Normal}\left((\mu_0^*\tau_0 + \mu_D, \tau_D)/(\tau_0 + \tau_D), \tau_0 + \tau_D\right) \]

7. Because the model is linear, we sampled from the expected value of the updated distribution in 6 and the mean values for \(\theta_C\) and identified the intervention with the highest expected NB.

8. Repeated steps 4-7 for 10,000 times and calculate the average NB of the preferred interventions identified in Step 7.

9. The EVSI is the difference between the average NBs in Steps 8 and 3.
Appendix 2

Expected value of perfect information (EVPI) algorithm:[99]

1. Assigned probability distributions to the input parameters in the mode as summarised in Table 1 in the main text.
2. Sampled random values $k$ times (e.g. $k = 10,000$) from the distributions described above for each intervention.
3. Calculated the mean NB for each intervention across all simulations, and identified the preferred baseline decision, that is, the intervention with the maximum expected mean NB ($\max_i E_\theta NB(i, \theta)$).
4. Calculated the NB for each intervention and identified the optimal intervention at each simulation.
5. Averaged the NBs from the identified optimal interventions in Step 4 ($E_\theta \max_i NB(i, \theta)$).
6. EVPI per-patient is the difference between the average NBs in steps 5 and 3.

Expected value of perfect parameter information (EVPPI) algorithm:[99]

Steps 1-3 as in EVPI algorithm detailed above, then:

4. Sampled $\theta_1$ once from its joint prior distribution (outer-level simulation).
5. Fixed $\theta_1$ at their sampled values $\theta_{h_k}$ and simulate the other remaining uncertain parameters $\theta_{c_{jk}}$ (e.g., $j = 1000$ times), allowing them to vary according to their conditional probability distribution on $\theta_1$ at its sampled value $\theta_{h_k}$ (inner-level simulation).
6. Calculated the conditional expected NB of each intervention by evaluating the NB at each $(\theta_{c_{jk}}, \theta_{h_k})$ and averaging ($E(\theta_{c|\theta_1}|i, i, \theta_{c})$).
7. Identified the intervention that has the highest estimated expected NB given the sampled value for the parameters of interest ($\theta_i$) from step 6.

8. Repeated steps 4-7 $k$ times (e.g., $k = 1000$) and calculate the average NB of the preferred interventions identified in step 7 ($E_{\theta_i \text{max}} \ E(\theta_i|\theta_C)NB(i, \theta_I, \theta_C)$)

9. EVPPI is the difference between the average NBs in Steps 8 and 3.

**Expected value of sample information (EVSI):** [41]

To estimate the EVSI for the relative risk (RR) of pressure ulcer with nutritional support (NS) compared to standard care (SC), we assumed that parameters $\theta_{NS}$ and $\theta_{SC}$ represent the probability of pressure ulcers with nutritional support and standard care, respectively. We followed the algorithm adapted from the algorithm reported in Ades 2004.[41]

Steps 0-3 as in EVPI algorithm above, then:

4. Simulated the variety of possible results of proposed data collection:

   4.1 Drew a sample from the prior distribution of the RR. The logRR $\sim$ Normal ($\mu_0$, $\tau_0$) where $\mu_0$ is logRR in the meta-analysis and $\tau_0$ is its variance.

   4.2 Drew a sample baseline parameter $\theta_{SC}$ from its prior distribution: $\theta_{SC} \sim$ beta ($a$, $b$) where $a$ is the number of patients who developed pressure ulcers and $b$ is the number of patients who did not develop pressure ulcers in the control arm of the meta-analysis.

   4.3 Transformed back to obtain an implied prior for $\theta_{NS}$: $\theta_{NS} = \theta_{SC} \exp(\log RR)$

5. 5.1 Drew a sample sufficient statistic $D$, in this case a Binominal numerator, for each arm in the future trial with size $n$, assuming equal size arms:

   $r_{SC} \sim \text{Binomial}(\theta_{SC}, n)$ and $r_{NS} \sim \text{Binomial}(\theta_{NS}, n)$

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5.2 Converted the sufficient statistics to a mean and variance using the normal approximation:

\[ \mu_D = \log \left[ \frac{r_{NS} \cdot n}{r_{SC} \cdot n} \right], \]
\[ \tau_D = \left[ \frac{(n - r_{SC})/r_{SC} \cdot n} + (n - r_{NS})/r_{NS} \cdot n \right]^{-1} \]

6. Updated the prior with the new simulated data to obtain parameters of the posterior distribution:

\[ \log RR \mid D \sim \text{Normal}((\mu_0 \cdot \tau_0 + \mu_D, \tau_D)/(\tau_0 + \tau_D), \tau_0 + \tau_D) \]

To allow EVSI calculation using TreeAge software, steps 4-6 were performed using Microsoft Excel and repeated 1,000 times generating a ‘coda’ of updated distributions (outer loop). This coda was then transferred to TreeAge for sampling:

7. Carried out a nested Monte Carlo simulation (inner loop) drawing 1,000 samples from each posterior distribution of the parameters \( \log RR \mid D \) in the Excel coda and from the prior distributions of \( \theta_c \), and identified the intervention that has the highest estimated expected NB.

8. Calculated the average NB of the preferred interventions identified in Step 7.

9. The EVSI is the difference between the average NBs in Steps 8 and 3.