Australian Clinical Trials Alliance

A pilot study to prospectively estimate the health and economic return on research investment

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This report was prepared for the Australian Clinical Trials Alliance by A/Professor Haitham Tuffaha and Professor Stephen Birch, The University of Queensland.

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LIST OF ACRONYMS

Acronym	Definition
ACTA	The Australian Clinical Trials Alliance
ANZICS CTG	The Australian and New Zealand Intensive Care Society Clinical Trials Group
ARISE: Fluids	Australasian Resuscitation In Sepsis Evaluation: Fluid or vasopressors in emergency department sepsis
CTN	Clinical Trials Network
DAOH	Days Alive Out of Hospital
DCE	Discrete Choice Experiments
EVPI	Expected Value of Perfect Information
EVSI	Expected Value of Sample Information
HTA	Health Technology Assessments
ICER	Incremental Cost Effectiveness Ratio
INMB	Incremental Net Monetary Benefit
MCDA	Multiple Criteria Decision Analysis
MRFF	Medical Research Future Fund
NB	Mean Net Monetary Benefit
NHMRC	National Health and Medical Research Council
PATHS	Preliminary Assessment of Technology for Health Services
PCORI	Patient-Centered Outcomes Research Institute
QALYs	Quality-Adjusted Life-Years
RCT	Randomised Controlled Trial
REFRESH	Restricted fluid resuscitation in suspected sepsis association hypotension
ROI	Return on Investment
VOI	Value of Information

EXECUTIVE SUMMARY

Clinical trials are vital to inform policy and medical decision making; however, research funds are limited, and therefore, it is essential to ensure that the funded trials represent value for money. Assessing the economic and health impact of clinical trials prospectively (i.e., before conducting the trials) could optimise research prioritisation and funding decisions by identifying the trials with the potential to maximise the returns on research investments.

The Value of Information (VOI) framework is an analytical approach to prospectively estimate the expected return on investment of clinical trials and cohort studies. This approach considers that research is valuable as it informs decision making in two ways: First, collecting more information can reduce the chance of making suboptimal decisions (e.g., adopting an intervention that is not cost-effective) when the existing evidence is uncertain. A larger randomised control trial (RCT) can reduce uncertainty by providing more precise estimates of the parameters of interest, which in turn better informs decision making to avoid the costly consequences of suboptimal decisions. Second, research may influence the implementation of interventions (e.g., changing practice). Collecting further evidence has the potential to improve health outcomes by encouraging the implementation of the most effective and/or cost-effective intervention. These expected research benefits are scaled up by considering the population expected to benefit from research findings and the evidence durability (i.e., the time over which evidence is useful). Then, the expected value of research at the population level is compared to the expected research costs to estimate the return on investment of a research study.

This report presents the results of a pilot study where the VOI framework is applied to prospectively estimate the return on investment (ROI) of two clinical trials based on the information extracted from real-world grant applications, using no or minimal decision modelling. Two CTNs were able to provide clinical trials grant applications which were analysed in this pilot project. However, and due to UK funding constraints for one of the CTN groups, they requested that the information on their trial to be removed. This resulted in the inclusion of one clinical trial which is the Australasian Resuscitation In Sepsis Evaluation Fluid or vasopressors in emergency department sepsis (ARISE:Fluids) trial by the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG).

ARISE:Fluids is a large-scale, multi-centre, prospective trial to test the hypothesis that in patients with septic shock presenting to the emergency department, performing fluid restricted resuscitation (i.e., using less intravenous fluid) strategy with earlier introduction of vasopressors (e.g., noradrenaline) is more effective than usual care intravenous fluid with later vasopressors. The primary study outcome is the number of days alive out of hospital (DAOH) at 90 days post randomisation. The value of the ARISE:Fluids trial in reducing decision uncertainty is approximately $66 million and its expected value in improving implementation (assuming 10% uptake over ten years) is $85 million, with a total expected value of $151 million. For the clinical trial budget of $2.3 million, the expected ROI is 6465% (i.e., $64.7 in value per $1 of funding).

The prospective assessment of the ROI of clinical trials is feasible. The development of a programmable, user-friendly tool will enhance VOI analysis and help Clinical Trials Networks (CTNs) and funding organisations assess the value for money of new clinical trials to maximise expected returns of research investments.

BACKGROUND AND OBJECTIVES

THE NEED TO ASSESS THE HEALTH AND ECONOMIC IMPACT OF CLINICAL TRIALS

Clinical trials test the safety, efficacy, and cost-effectiveness of a wide range of healthcare interventions to provide the evidence needed to inform clinical and health policy decisions. Clinical trial volumes have experienced strong growth over the past decade in Australia with an annual expenditure of $1.1 billion.[1,2] However, the demand for research funding by investigators always exceeds research budgets, and therefore, research funding bodies (e.g., the National Health and Medical Research Council (NHMRC) and the Medical Research Future Fund (MRFF) must make decisions about which clinical trials to fund from a large pool of competing research proposals. Thus, investigators and Clinical Trials Networks (CTNs) are increasingly required to demonstrate the value for money of their proposed clinical trials, as research funders are more interested in evaluating research impact and the return on investment of their research budgets.

A previous study retrospectively estimated the overall health and economic impact of 25 investigator-initiated clinical trials from three CTNs.[2,3] The results of that study showed that the overall consolidated benefit-to-cost ratio for the networks was 5.8:1, or a return of $5.80 for every $1 invested. It also showed that for every $1 awarded in NHMRC grants to the 25 trials included in the analysis, a return of $51.10 was achieved.[2,3] Despite the significance of that study in demonstrating the impact of CTN led clinical trials, its results represent the return on investment across selected clinical trials that were funded and conducted between 2004 and 2015.[2,3] Thus, the estimated return on investment may not be representative of the impact of other CTNs or new clinical trials.

Assessing the economic and health impact of clinical trials prospectively (i.e., before conducting the trials) could optimise research prioritisation and funding decisions by identifying the trials with the potential to maximise the returns on research investments.[4,5] It will also help investigators and CTNs demonstrate the value for money of their proposed trials and advocate for more funding.

APPROACHES TO PROSPECTIVELY ASSESS THE VALUE FOR MONEY OF CLINICAL TRIALS

Analytic approaches have been proposed to prospectively assess the value for money of clinical trials and cohort studies.[6,7] These approaches draw largely from the economic evaluation literature in the way they identify, measure and value research benefits and costs.[8] They are based on the notion that the objective of clinical trials is to inform decision making (e.g., changing practice or adopting a new intervention), and thus, the value of generating new evidence through research is inferred from the additional benefits expected to accrue from improved decision making.[6–8] These benefits could be expressed as health outcomes (e.g., Quality-Adjusted Life-Years (QALYs) gained) and monetised using a willingness-to-pay threshold (e.g., $50,000 per QALY gained). The value for money of a clinical trial could be assessed by comparing its expected health or monetary benefits with its costs.[9,10] The two key analytical approaches are the preliminary assessment of technology for health services (PATHS), which is also known as the prospective payback of research approach, and the value of information (VOI) approach.[4,7]

A comparison of the two approaches is presented in Table 1.

Table 1: A comparison of the PATHS and the VOI approaches[7]

	PATHS	VOI
Rationale	The value of research is inferred from the benefit expected from a beneficial change in clinical practice	The value of research is inferred from the benefit expected from eliminating or reducing the uncertainty around a decision problem
Methodology	Comparison of costs and benefit associated with two hypothetical 'states of the world': with research ('factual' state) and without research ('counterfactual' state)	Comparison between the expected benefit of collecting information and the cost of acquiring this information (e.g., cost of clinical trial)
Specification of change in clinical practice following a possible outcome	Direction and magnitude of change is hypothesised, depending on each possible outcome	Perfect implementation of the optimal strategy is typically assumed, but VOI estimates could be adjusted based on expected implementation
Estimation of costs and benefit of research	Estimation of cost and benefit of research associated with different possible outcomes	Estimation of costs and benefit for different possible realisation of results in sensitivity analysis
Calculation of aggregate results	Results are calculated as the costs and benefit (e.g., net monetary benefit)	Results are calculated as the costs and benefit (e.g., net monetary benefit)
Decision rules	Positive net monetary benefit indicate that research is potentially beneficial	Positive net monetary benefit indicate that research is potentially beneficial

Abbreviations: PATHS: the preliminary assessment of technology for health services; VOI: value of information

The PATHS approach

Under the PATHS approach, the value of a clinical trial is estimated based on its projected ability to result in a beneficial change in clinical practice.[7,8,11] However, the application of this approach in practice has been extremely limited because it requires full decision analytic modelling and scenario analyses to predict the influence of the trial on practice.[7] Importantly, the PATHS approach does not assess whether there is a need for a given clinical trial by considering the level of uncertainty in the existing evidence.[4,7] The evidence required to change practice could be available and the change of practice could be achieved through better implementation of that evidence rather than investing in another clinical trial.

The VOI approach

The VOI approach considers that generating new information would reduce decision uncertainty and optimise the expected payoffs associated with a decision.[12] VOI is the most common analytic approach to assess value for money of clinical trials[7,13]; however, VOI analyses were conducted as part of Health Technology Assessments (HTA) to inform reimbursement decisions using complex decision modelling. Due to the complexity in the methods, the application of VOI to prospectively estimate the return on investment of clinical trials by CTNs and research funding organisations have been relatively limited compared to its use in HTA.[14–18] Nevertheless, recent efforts in this field of research resulted in the development of best practice guidelines and more practical methods to use VOI in estimating the value for money clinical trials and cohort studies.[19–23] Moreover, the VOI approach has been extended to incorporate the impact of clinical trials on implementation (i.e., the Value of Implementation analysis).[24] It was proposed that the VOI approach could be prospectively applied to estimate the return on investment of clinical trials based on certain information provided in research proposals for funding (i.e., grant applications) using no or minimal decision modelling.[4,5,17,25]

REPORT OBJECTIVES AND STRUCTURE

This report presents the results of a pilot study where a VOI framework is applied to prospectively estimate the return on investment (ROI) of a CTN's clinical trial.

Section 2 of the report will give an overview about the VOI framework. Section 3 presents an application of the VOI framework using a real-world grant application for a clinical trial. Section 4 recommends approaches consider value elements beyond health and economic impact, and Section 5 discusses the overall findings of the report and provides future recommendations.

VOI FRAMEWORK

The VOI framework was developed to prospectively estimate the expected return on investment of clinical trials.[12,26] It assumes that conducting a new clinical trial can provide two kinds of value[25,27] (Figure 1):

1. Resolving or reducing the uncertainty in existing evidence (e.g., by conducting a trial with a larger sample size) could eliminate or minimise the chance of making 'wrong' decisions (e.g., adopting an intervention that is not safe or effective), which could consequently optimise patient outcomes and avoid the costs associated with that suboptimal decision.
2. The generated evidence could change practice and improve patient outcomes by encouraging the implementation of the most effective and/or cost-effective intervention.

The expected value (i.e., benefits) of the new clinical trials is estimated by comparing two states: (1) a factual state in which research takes place, and (2) a counterfactual state, in which research is not conducted.[5,7,28]

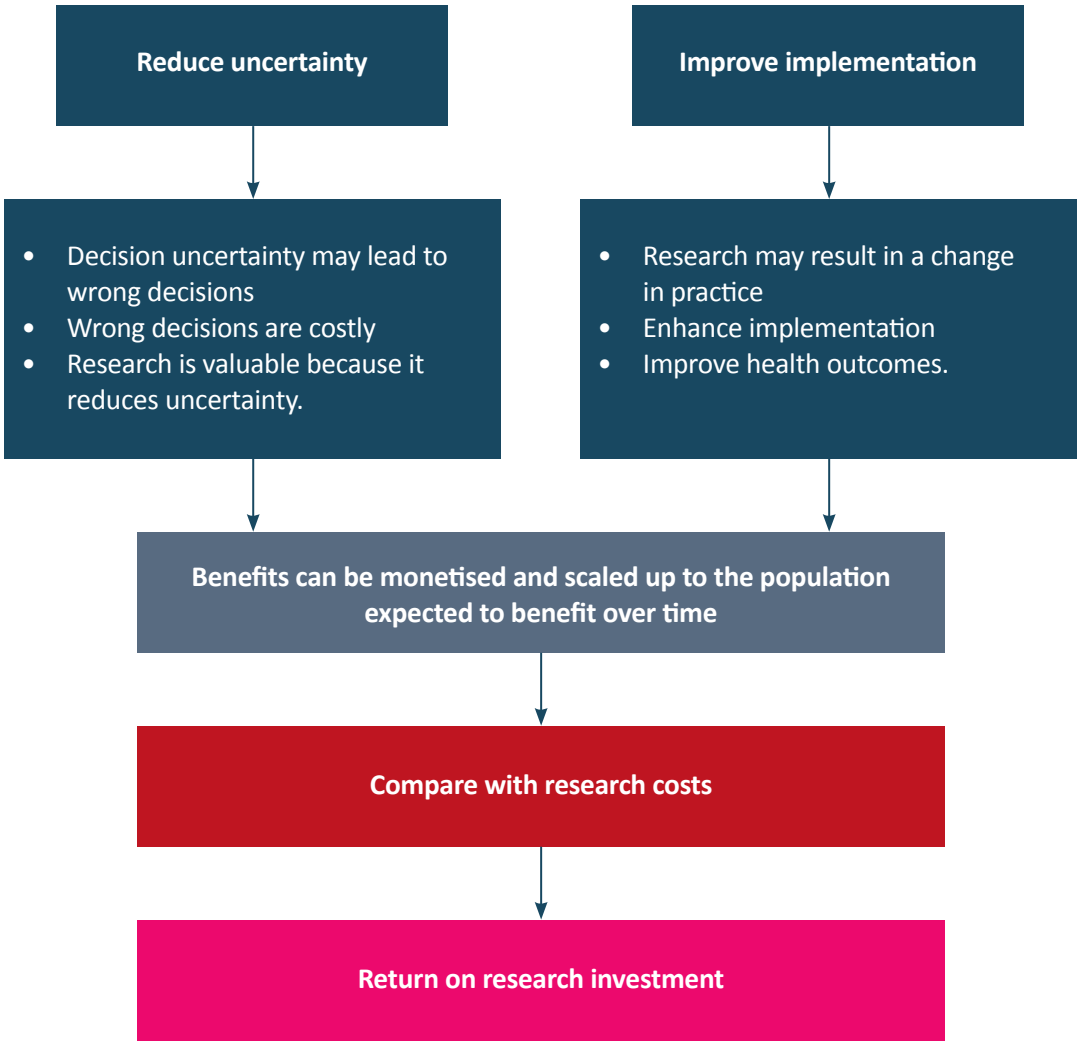

Figure 1: VOI framework

THE VALUE OF RESOLVING/REDUCING UNCERTAINTY

In assessing the value of a clinical trial in reducing decision uncertainty, the VOI approach considers the uncertainty in the available evidence (e.g., uncertainty in efficacy estimates), the consequences of this uncertainty (i.e., the implication of making a wrong decision), and the population that would be affected by the research results.

To illustrate how the value of research can be estimated using VOI analysis, let us take a hypothetical example of a new intervention to treat a given condition (Table 2). Based on what we know from the results of small trials, the new intervention appears to be more effective than the current standard of care because, on average, it delivers 21 years of survival compared with 19 years from the standard of care. However, if we are to adopt the new intervention, there is a 50% chance the decision is wrong (i.e., standard of care is the more effective option in two out of four scenarios). Due to evidence uncertainty (50% chance or error in this example) clinicians may be reluctant to adopt the new intervention as there is a clinical equipoise between the two interventions, which may warrant a future trial.

Table 2: A hypothetical example of two health interventions

Scenarios	Efficacy of standard of care	Efficacy of the new intervention	Preferred option (i.e., more effective)	Loss from selecting the less effective intervention
Scenario 1	18 years	23 years	New Intervention	0 years
Scenario 2	20 years	19 years	Standard of care	1 year
Scenario 3	17 years	22 years	New Intervention	0 years
Scenario 4	21 years	20 years	Standard of care	1 year
Average	19 years	21 years	New Intervention	0.5 years

To know whether the future trial is worthwhile conducting, we need to consider the consequences of adopting the new intervention based on the existing evidence (i.e., no new research is conducted). In this example (Table 2) the consequence of adopting the new intervention would be a loss of one year in Scenario 2 and one year in Scenario 4 because in those two scenarios the standard of care is the preferred option. Averaging these values across the four scenarios would translate into 0.5 years potentially lost per patient treated. If we conducted a new clinical trial that was large enough to resolve this uncertainty, we would maximise the expected benefit from that decision by avoiding the potential loss (0.5 years) associated with decision uncertainty. The 0.5 years is the expected value of perfect information (EVPI) of the new trial, which is the maximum expected benefit (upper-bound) of the trial from resolving decision uncertainty.[20,29] In practice, resolving uncertainty with perfect information (i.e., perfect precision) may not be achievable because of the extremely large sample size required; however, the value of the new trial in reducing (not completely resolving) uncertainty can be calculated for various sample sizes by simulating how different sample sizes could affect decision uncertainty. The expected value of a clinical trial of a specific sample size in reducing decision uncertainty is referred to as the expected value of sample information (EVSI).[14,20,23,29] Figure 2 shows the VOI measures used in practice to estimate the value for money of new clinical trials.

VOI measures can be calculated at the population level by considering the size of the population expected to be affected by the decision to adopt the new intervention over a given number of years.[20,30] If the incidence of the disease is 1,000 patients per year, then we expect the decision to affect 5,000 patients over five years. The consequence of the decision on that population is 0.5 years X 5,000, which is 2,500 years potentially lost due to uncertainty. This value represents the population EVPI. If we assign a monetary value to the life-year gained (e.g., 50,000 per life year), then the monetary benefit of the new trial is expected to be $125 million (2,500 years X $50,000/year).

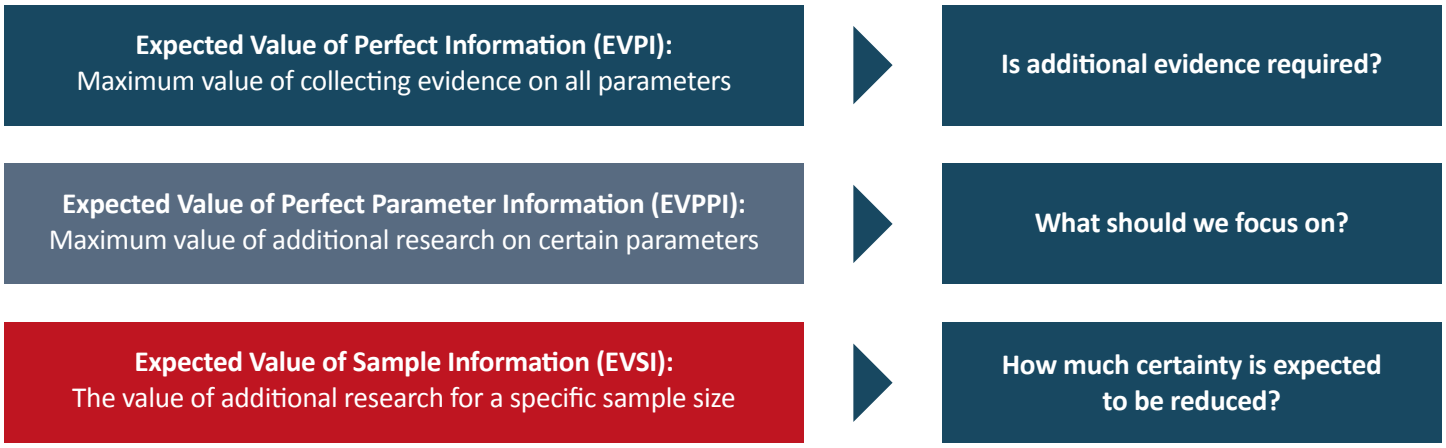

Figure 2: VOI measures

The value of the new trial in improving implementation

Assume that a larger trial was conducted, and the clinicians now were more convinced to adopt the new intervention because the new intervention is expected to improve survival by two year (21 vs 19 years). In the five years after the trial, and if only 10% of the target patients received the new intervention, that is 500 patients (10% of the 5,000 patients), then the expected monetary benefit from improved implementation would be $50 million (500 patients X 2 years gained X $50,000/year). Information about implementation levels could be obtained from historical data about the utilisation of the intervention or similar interventions and/or by eliciting this information from experts.

Methods to estimate VOI measures

VOI calculations typically require the development of a decision analytic model to: 1) assess the cost-effectiveness of the interventions evaluated, and 2) characterise decision uncertainty based on the results of the cost-effectiveness analysis.[20,30] However, rapid, and more practical approaches to estimate VOI have been proposed where no or limited modelling is required.[25,31] These approaches can be performed when the outcomes of interest (e.g., relative risk) and the uncertainty around these estimates (e.g., 95% confidence interval) are sufficiently reported in prior evidence (e.g., systematic review) to inform a decision about the benefits of alternative interventions. These outcomes could be comprehensive outcomes such as improvement in survival or quality-adjusted life-years (QALYs) gained, or intermediate outcomes (e.g., progression free survival) that could be extrapolated using epidemiological data or simplified models to estimate the final outcome.[31] The minimal modelling requires a limited number of parameters to estimate the value of research compared with the full modelling approach.[5,25,31]

APPLICATIONS OF THE VOI FRAMEWORK

THE SELECTION OF THE CLINICAL TRIALS

The Australian Clinical Trials Alliance (ACTA) identified and engaged with a number of CTNs who were interested in assessing the value for money of their clinical trials. Two CTNs were able to provide clinical trials grant applications which were analysed in this pilot project. However, and due to UK funding constraints for one of the CTN groups, they requested that the information on their trial to be removed. This resulted in the inclusion of one clinical trial proposal from one CTN, which is the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG).

THE GENERAL APPROACH

The grant proposals were reviewed to identify key information required to estimate the value for money of the clinical trials. The set of inputs required is summarised in Table 3. If the information provided in the grant proposal was not sufficient to inform the calculations, additional information was sought from other sources. The modelling approach used in the analysis was dependent on the intervention and the primary outcome in the clinical trial (i.e., a final comprehensive outcome or intermediate). No modelling would be required in the case of an intervention in the acute care setting when the final outcome is expected to be realised during the clinical trial duration. However, minimal modelling was applied to extrapolate the intermediate outcomes of a chronic intervention over the lifetimes of the patients.

Table 3: Summary of the information required to calculate VOI[5]

Domains	Inputs	Clarifying statements
Value of resolving uncertainty	Primary outcome(s) of the new trial	The primary outcome in the research proposal (e.g., survival, quality of life, event avoided)
	Existing evidence	The source of current evidence (e.g., meta-analysis, clinical study, or expert opinion)
	Effectiveness of the comparator/control	The effectiveness of the comparator (e.g., baseline probability or mean estimate of the outcome), with standard error or confidence interval
	Relative effectiveness of the intervention	The relative effectiveness of the intervention (e.g., relative risk or absolute difference), with standard error or confidence interval
	Costs or resources utilised of the comparator	The expected costs/resources utilised (e.g., staff time, equipment, tests)
	Costs or resources utilised of the intervention	The expected costs/resources utilised (e.g., staff time, equipment, tests)
Value of improved implementation	Current level of implementation/uptake	The current level of implementation/uptake based on existing evidence
	Expected level of implementation/uptake	The expected level of implementation/uptake with the new evidence
Population benefiting from research findings	Annual incidence	Incidence of the condition being researched
	Prevalence	Prevalence of the condition being researched
	Durability of information	Time in years over which the findings from the new research is useful
Other inputs	Time to report research results	Time in years for research results to report
	Direct research costs	Research study budget including fixed and variable costs (i.e., cost/participant)

AUSTRALASIAN RESUSCITATION IN SEPSIS EVALUATION FLUID OR VASOPRESSORS IN EMERGENCY DEPARTMENT SEPSIS (ARISE:FLUIDS) TRIAL

Summary

Sepsis is an overwhelming host response to infection. Although rare (incidence of 1 in 3,000) sepsis has a significant impact on the individuals affected and the healthcare system.[32] International guidelines recommend large volumes of intravenous fluids (2–3 L in a typical adult) followed by medications to support the blood pressure (vasopressors) for the early resuscitation of septic shock.[33] Emerging evidence of harm associated with intravenous fluids has resulted in clinical uncertainty and substantial variation in practice. However, there is no high-quality evidence to guide early resuscitation practices in the emergency department.[32]

The grant application proposed a large-scale, multi-centre (rural and metropolitan), prospective, randomised, clinical trial to test the hypothesis that in patients with septic shock presenting to the emergency department, performing fluid restricted resuscitation (i.e., using less intravenous fluid) strategy with earlier introduction of vasopressors (e.g., noradrenaline) is more effective than usual care intravenous fluid with later vasopressors.[32]

The primary study outcome is the number of days alive out of hospital (DAOH) at 90 days post-randomisation. Based on the Restricted Fluid Resuscitation in Suspected Sepsis Associated Hypotension (REFRESH) pilot study and the ARISE trial[34,35], the investigators anticipate a mean DAOH90 of 65 days at baseline. Assuming a clinically important increase of 7 days to 72 days in the restricted fluid arm, a sample size of 960 would be required.[32,35,36]

The approach

The information extracted from the grant proposal is summarised in Table 4. This is an intervention in the acute setting and the outcomes are short-term that will take place over one year. Furthermore, and based on the results of the ARISE and the REFRESH pilot the restricted fluid intervention is expected to reduce the volume of intravenous fluids used, which has negligible cost impact, with no difference in vasopressors use or the patient quality of life compared with the standard intravenous fluids.[35] As such there is no need to model the longer-term effects and costs of the intervention.

Table 4: Summary of the information extracted from the ARISE: Fluids grant application

Domains	Inputs	Clarifying statements	Information
Value of resolving uncertainty	Primary outcome(s) of the new trial	The primary outcome in the research proposal (e.g., survival, quality of life, event avoided)	DAOH90
	Existing evidence	The source of current evidence (e.g., Meta-analysis, clinical study or expert opinion)	REFRESH, pilot study, ARISE
	Effectiveness of the comparator/control	The effectiveness of the comparator (e.g., baseline probability or mean estimate of the outcome), with standard error or confidence interval	Baseline 65 days
	Relative effectiveness of the intervention	The relative effectiveness of the intervention (e.g., relative risk or absolute difference), with standard error or confidence interval	7 days (CI: -7 - 14)
	Costs or resources utilised of the comparator	The expected costs/resources utilised (e.g., staff time, equipment, tests)	usual care intravenous fluid with later vasopressors
	Costs or resources utilised of the intervention	The expected costs/resources utilised (e.g., staff time, equipment, tests)	30% reduction in intravenous fluids
Value of improved implementation	Current level of implementation/uptake	The current level of implementation/uptake based on existing evidence	Perfect implementation assumed (international guidelines)
	Expected level of implementation/uptake	The expected level of implementation/uptake with the new evidence	NA
Population benefiting from research findings	Annual incidence	Incidence of the condition being researched	1/3,000 (8,000/year)
	Prevalence	Prevalence of the condition being researched	NA
	Durability of information	Time in years over which the findings from the new research is useful	NA
Other inputs	Time to report research results	Time in years for research results to report	Five years
	Direct research costs	Research study budget including fixed and variable costs (i.e., cost/participant)	MRFF $2,335,540.20

Results

Value of reduced uncertainty

There is uncertainty in the existing evidence about the relative efficacy of the restricted fluids intervention, which can be characterised by taking random samples from the distribution of the relative effect size.[25] In this example, there is a 16% chance the intervention does not improve health outcomes (i.e., increase DAOHs compared with the standard of care). The health consequences of this uncertainty are estimated to be 0.55 DAOHs per patient. At an incidence of 8000 septic shock patients per year in Australia, and assuming that the decision will be affecting the population over 10 years from the trial completion (80,000 patients), the consequences discounted at an annual rate of 5% is approximately 35,000 DAOHs lost due to existing evidence uncertainty. If a hospital day is expected to cost around $1,900 for sepsis management[32,37], then the expected value of the new trial in reducing decision uncertainty is $1,045 per patient (0.55 X $1,900) which is $66 million (35,000 DAOHs X $1,900) at the population level. For a clinical trial budget of $2.3 million (i.e., ($66 million -$2.3 million)/$2.3 million), this represents an ROI of 2,770% (i.e., $27.7 in value per $1 of funding).

Value of improved implementation

If the results of the ARISE:Fluids trial confirmed the hypothesised increase of seven DAOHs, there would be benefits from changing practice to the use of a restricted fluid protocol to manage septic shock. With an average of seven DAOHs gained per patient, and assuming 10% implementation took place (i.e., change in practice), if only 10% of eligible patients (i.e., 80,000 patients) received the new approach over 10 years, approximately 45,000 DAOHs (discounted at 5% annual rate) will be gained. The uptake rate of 10% was not provided in the grant ARISE:Fluids grant application, but was chosen based on the uptake rate of similar interventions in previous reports [38]. The estimated cost of these DAOHs gained is $85 million (i.e., 45,000 X $1,900). This represents an ROI of 3600% (i.e., ($85 million -$2.3 million)/$2.3 million), which is $36 in value per $1 of funding.

The total expected value of the ARISE:Fluids trial is $151 million (i.e., $66 million + $85 million). For a budget of $2.3 million, the total expected ROI of the trial is 6465% (i.e., $64.7 in value per $1 of funding).

Sensitivity analysis

The results of the VOI analysis were tested in a sensitivity analysis by varying the key assumptions in the calculations as summarised in Table 5.

Table 5: Sensitivity analysis of the ARISE:Fluids VOI estimates

Scenario	Results
Base case analysis	
Expected value of reduced uncertainty	$66 million
Expected value of improved implementation	$85 million
Total expected value of research	$151 million
Expected return on investment	6,465%
Cost of hospital day is $1,000 (base case is $1,900)	
Expected value of reduced uncertainty	$36 million
Expected value of improved implementation	$45 million
Total expected value of research	$81 million
Expected return on investment	3,400%
Improvement of implementation due to research 5% (base case 10%)	
Expected value of reduced uncertainty	$38 million
Expected value of improved implementation	$48 million
Expected value of research	$86 million
Expected return on investment	3,640%

The ROI ranged from 3,400% to 6,465%. The results of the sensitivity analyses showed that the VOI estimates are sensitive to the assumptions made, particularly the cost of hospitalisation and the uptake rate. The expected value of improved implementation would increase with higher uptake rates.

OTHER CONSIDERATIONS BEYOND HEALTH AND ECONOMIC IMPACTS

The VOI framework presented in this report allowed the calculation of the value of clinical trials in terms of the expected health and economic benefits of resolving evidence uncertainty as well as improving implementation in practice. These elements of value are aligned with some of the measures commonly used to assess research impact including knowledge gain, influencing health policy, improving health and health systems and wider economic benefits (Table 6).[39,40] Nevertheless, there are other domains of impact such as building research capacity (e.g., building, training, and leadership in research) as well as societal impact (e.g., equity and inclusion) that are important to consider.

Table 6: Summary of research impact domains addressed by the VOI framework

Impact domain	Description	How the domain is addressed by the VOI framework
Advancing knowledge[39–41]	The generation of new knowledge and knowledge dissemination.	By identifying knowledge gaps in existing evidence and estimating the value of additional research in providing new information.
Building research capacity[39–41]	Capacity building, training, and leadership in research. These can be measured by the number of new researchers trained (PhD students and research fellows), grants obtained, academic collaborations and networks, and data sharing.	Not addressed.
Influencing health policy[39–41]	The interactions between researchers and policymakers to influence policy and practice, measured by the type and nature of the policy impact (e.g., influencing guidelines, changing clinical practice) and its level (e.g., institutional, national, international).	By characterising decision uncertainty and the evidence required to reduce this uncertainty. It informs if the existing evidence is sufficient to guide decision making or if additional research is required.
Improving health and health systems[39–41]	Improving quality of care provided (e.g., evidence-based care), health outcomes (e.g., improved survival, improved quality of life), safety (e.g., reduction in adverse drug events and hospitalisations), efficiency (e.g., cost containment and effectiveness), and health workforce development.	By estimating the value of implementation of the cost-effective interventions in practice
Economic impact[8,42]		Partially addressed by estimating the economic benefits from health gains. Could be addressed by taking a societal perspective to the economic evaluation.
Societal impact[8,42]	Improvements in equity, inclusion, or cohesion and human rights	Not addressed

The challenge in this case is how to incorporate the health and economic benefits with other impact domains. A similar challenge arises when the estimated health and economic impacts of the clinical trial are used to inform research prioritisation alongside other criteria. For example, The Australian Clinical Trials Alliance Research Prioritisation Framework[43] identifies four major criteria to assess the merit of a clinical trial including: 1) relevance (e.g., alignment with organisational goals, equity, knowledge gaps), 2) appropriateness (e.g., scientific rigour), 3) significance (e.g., impact, capacity building, innovation), and 4) feasibility (e.g., team capability and research environment).

There are two possible approaches to include other considerations in the assessment of the value for money of clinical trials:

1. A disaggregated approach: the additional considerations (e.g., equity) are presented alongside the results of the health and economic impacts assessment (i.e., ROI) as an additional lens to inform decision making. This could be demonstrated using the health equity impact plane (Figure 3) where the vertical access represents the health and economic impacts of the clinical trial, and the horizontal axis represents its impact on equity.[44] Trials with a positive impact on health and equity will be preferred (prioritised) whereas those with negative impact on health and equity will be abandoned.

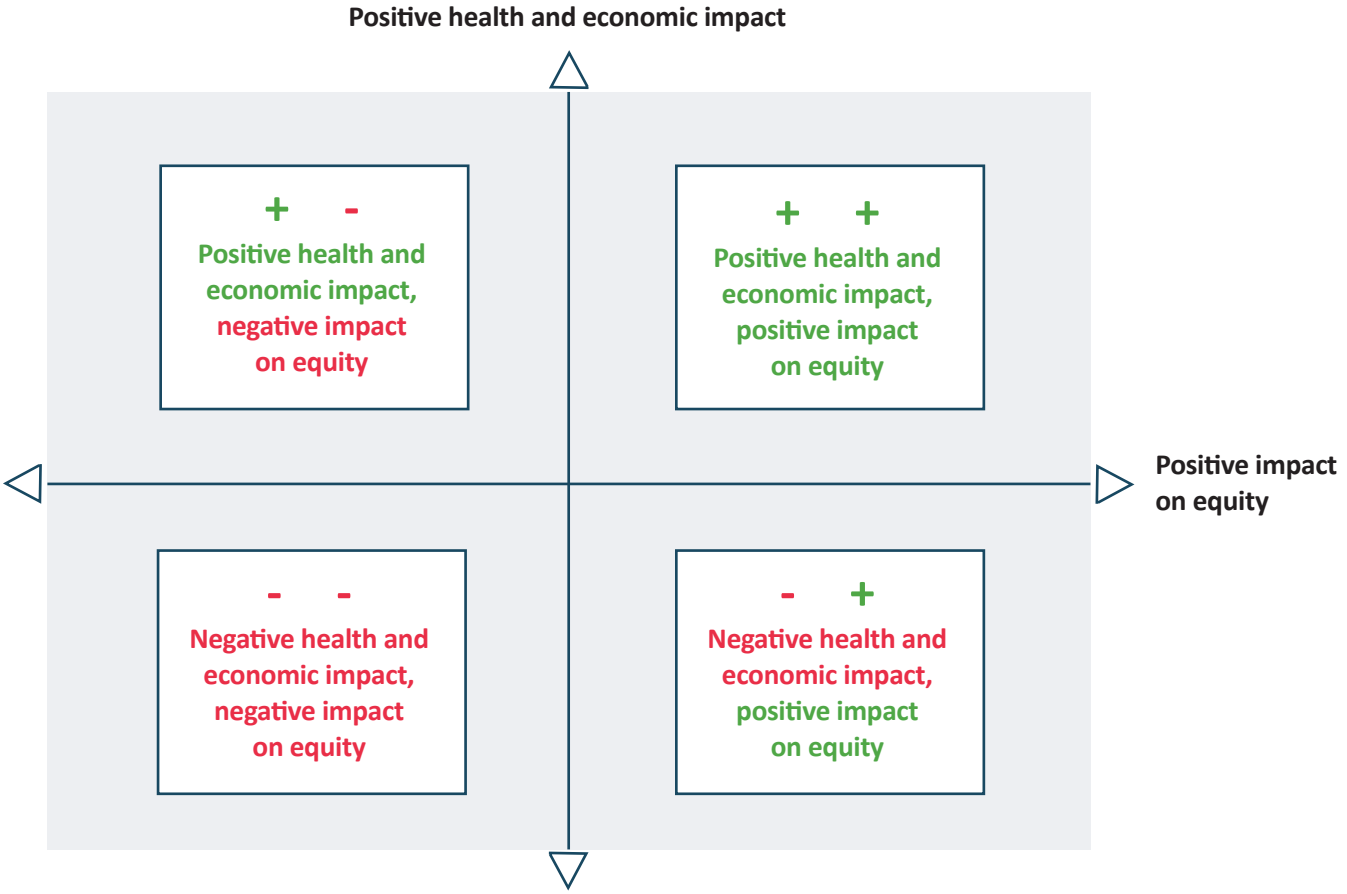

Figure 3: Health impact equity plane

In the situations where there is a positive impact on either health and economics or equity and a negative impact on the other, the trade-offs between equity and health and economic impact should be assessed. The assessment of these trade-offs could be achieved using certain equity weights for health and economic benefits that apply to certain populations (i.e., different weights for different populations) or using an equity parameter that quantifies the degree of concern for the impact on equity versus the health and economic impact.

2. An aggregated approach: a formal process such as multiple criteria decision analysis (MCDA) can be used to aggregate the research health and economic impact with other considerations (e.g., equity).[45] Conducting an MCDA involves selecting the criteria (i.e., attributes) that will be used to assess the clinical trial, scoring the criteria (e.g., on a Likert scale from 1 to 5), weighting the criteria and calculating aggregate scores.[45] Each criterion is assigned a weight based on stakeholders' preferences and trade-offs between criteria. Weighting indicates that some criteria are considered more important than others and will have more influence over the final ranking of a topic or proposal (e.g., 40% for scientific quality, 30% for significance, and 20% for feasibility).[43] The total score calculated (as a weighted average) across the criteria and their weights can be compared with the cost of research to estimate a cost to score ratio. Ideally, this approach requires the criteria weights to be determined using methods that consider the trade-offs between the criteria such as Discrete Choice Experiments (DCE). Of note, ACTA Research Prioritisation Group have conducted a DCE 1000minds software to derive the weights of the four criteria included in ACTA's Research Prioritisation Framework (i.e., relevance, appropriateness, significance, and feasibility), based on the preferences and trade-offs made by consumers, researchers and funders using.[43] 1000minds is a user-friendly software that is freely available through ACTA to help CTNs design and conduct research prioritisation projects using MCDA.[46]

DISCUSSION

KEY FINDINGS

This report presents the results of piloting the VOI framework to prospectively assess the return on investment of clinical trials. The expected value of the trials stemmed from the expected value in reducing decision uncertainty and improving implementation in practice by encouraging the implementation of the cost-effective interventions. The VOI approach considered the uncertainty in the available evidence (i.e., uncertainty in efficacy estimates), the consequences of this uncertainty (i.e., the implication of making a wrong decision), and the population that would be affected by the research results (i.e., population size). The value of the ARISE:Fluids trial in reducing decision uncertainty is $66 million and its expected value in improving implementation is $85 million, with a total expected value of $151. For the clinical trial budget of 2.3 million, the expected ROI is 6,465% (i.e., $1 funding to return $64 in value).

This pilot study is one of the very first studies in Australia that applies the VOI framework to prospectively assess the return on investment of a real-world clinical trial grant application from a CTN. The approach has been applied to assess the value for money of an RCT to study how a nurse-led intervention can improve psychosocial adjustment and quality of life in men with advanced prostate cancer.[5] The expected net benefit of that trial was estimated to be around $30 million with a return on the $1.1 million budget at 2,370% (i.e., $1 of funding to return $22.7 in value). The approach has been recently applied in the rural research setting to assess the value for money of an RCT to embed a telehealth intervention within primary healthcare for reducing diet-related CVD risk in adults living in rural and remote regions.[28] Using decision modelling, the study estimated the value of the RCT to be $60 million, with a return on the $1.03 million budget at 5800% (i.e., $1 of funding to return $58 in value).

An important feature of this pilot project is the estimation of the value of future research with minimal or no modelling, using information provided in the grant applications.[5] This information includes: the primary outcome(s), a description of existing evidence including type (e.g. pilot study, meta-analysis, or expert opinion), the effectiveness of the comparator (e.g. baseline risk), the relative effectiveness of the intervention (e.g. relative risk, risk difference), the estimated costs of the intervention and comparator, the uncertainty around effectiveness and cost estimates (e.g. standard error or confidence interval), the willingness-to-pay for an additional unit of effectiveness (e.g. per QALY gained or event avoided), and the sample size and follow-up duration of the new clinical trial. With this efficient approach, six weeks were required to review the provided proposals, extract all necessary information, validate the sources of the provided information, supplement the information with external sources, conduct the analyses and report the results.

LIMITATIONS

The VOI approach using minimal modelling has some limitations, specifically, the availability of the data required to conduct the analyses, establishing a link between the intermediate and final outcomes, and using an appropriate willingness-to-pay threshold for a unit of improvement in a clinical outcome. To overcome these limitations, certain assumptions must be made which might introduce biases to the results. For example, we used a conservative assumption of 10% implementation of the interventions included in our evaluation, which was the uptake rate used in a previous report to evaluate the ROI of investigator-initiated clinical trials [38]. To reduce the risk of bias, the assumptions used should be clear and well-justified. Furthermore, sensitivity analyses should be conducted to explore the impact of varying these assumptions on the ROI estimates.

It is worth mentioning that the ROI estimates reported were based on the expected health benefits of the included clinical trials. There is, however, other aspects of impact that could be considered beyond the narrow health gains. These, as discussed in Section 4, include the societal benefits (e.g., equity and inclusion) as well as the wider economic benefits emerging from the spillover effects (i.e., secondary benefit gained by sectors beyond health), commercialisation of research outputs, healthy workforce, intellectual property, and patents. Nevertheless, estimating the net monetary benefits beyond health gains for the individual clinical trials is challenging due to the difficulty in obtaining reliable data to allow the estimation of these benefits and to attribute these benefits to the individual clinical trials. As such, most of available studies used a macroeconomic top-down approach to calculate ROI by estimating the total economic improvements over a period of time in a jurisdiction (e.g., using gross domestic product), a percentage is then applied to represent the contribution of research to these improvements. For example, one study estimated the net monetary gains of medical research conducted in Australia from 1990 to 2004 to be $78 billion, with $26 billion attributed to the wider economic gains from a larger and more productive population and from commercialisation of medical research.[47]

USE IN PRACTICE

Using the approach described in this report to estimate the expected health and economic benefits of clinical trials could help researchers demonstrate the value for money of their investigator-initiated research programs. It could also help funders assess the value for money of funding applications they receive. The ROI estimates could be considered alongside other important criteria funding organisations use to assess research proposals such as feasibility, team capability and scientific quality.

A framework was developed to facilitate the incorporation of value of research assessment into existing processes to prioritise and fund research in Australia.[5] To enhance value of research assessment, that framework suggests that applicants provide the key inputs required for VOI calculation in their grant applications, and that these inputs can be verified by the experts on the panels reviewing those applications. Furthermore, that framework suggests that only shortlisted applications will be evaluated for value for money, which will reduce the burden of this vital step (Figure 4). The assessment of the ROI of the shortlisted applications could be outsourced (i.e., commissioned) or could be conducted within the funding organisations if they have the skills and capacity.

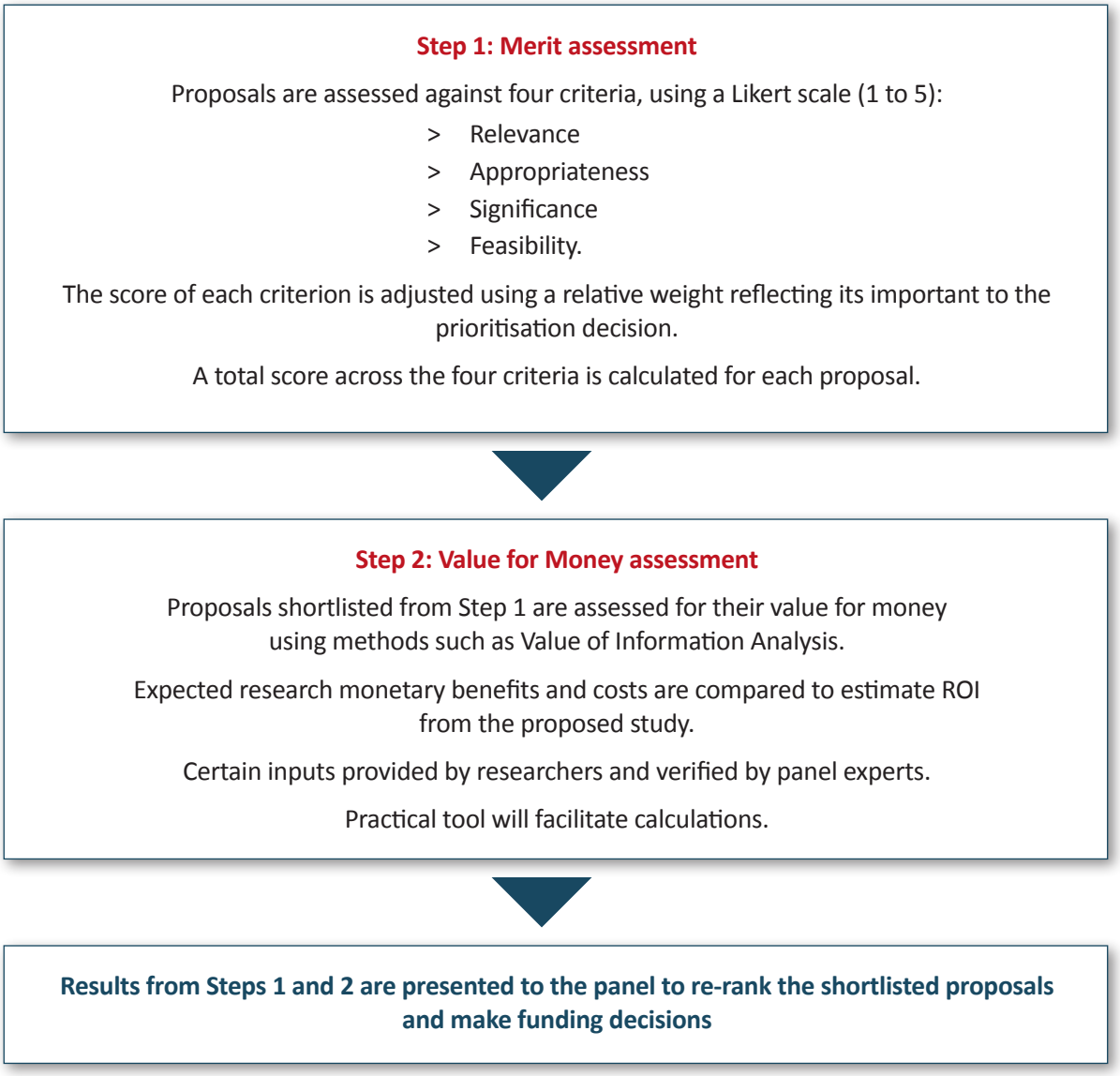

Figure 4: Framework for prioritising research proposals for funding[5]

To promote application of the VOI framework in practice, user-friendly programmable tools could be developed to help CTN investigators and research funders assess the value for money of the proposed clinical trials. Most CTNs do not have the resources to conduct complex decision analytic modelling. Likewise, a research funding organisation may not have the capacity to conduct complex analyses especially when they consider a large volume of competing grant applications. Two web-based tools are now available to estimate the value of clinical trials: Rapid Assessment of Need for Evidence (RANE), and the Value of Information for Cardiovascular Trials and Other Comparative Research (VICTOR).[18,21] However, these tools focus on the health impact of the clinical trials and do not consider the cost-effectiveness of the interventions being evaluated. This is because the two tools were developed for the US setting (e.g., for Patient-Centered Outcomes Research Institute (PCORI)) where the cost-effectiveness of new interventions is not routinely considered compared with the Australian health system.[18,21] Therefore, there is a need to develop a web-based tool that meets the needs and expectations of the CTNs and research funding organisations in Australia. That tool should be flexible to incorporate other elements beyond health and economic impact such as equity and broader societal benefits. The tool will provide a common interface between funders, researchers and consumers, which will improve transparency and acceptability of the outcomes.

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