Australian Clinical Trials Alliance

Assessing the impact of clinical trials: a scoping literature review

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

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GLOSSARY

Acronym	Definition
ACTA	Australian Clinical Trials Alliance
AIHS	Alberta Innovates Health Solutions
ANZICS CTG	Australian and New Zealand Intensive Care Society Clinical Trials Group
ASTN	Australasian Stroke Trials Network
BCEAweb	Web interface to the Bayesian Cost-Effectiveness Analysis
CAHS	Canadian Academy of Health Sciences
CHOICE	Comparative Health Outcomes, Policy, and Economics
CIHR	Canadian Institutes of Health Research
CTNs	Clinical Trials Networks
DALY	Disability-adjusted life years
EVPI	Expected value of perfect information
EVPPI	Expected value of perfect parameter information
EVSI	Expected value of sample information
FAIT	Hunter Medical Research Institute Framework to Assess the Impact from Translational Health Research
HTA	Health technology assessment
IMPACT	Interdisciplinary Maternal Perinatal Australasian Collaborative Trials
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
MRFF	Medical Research Future Fund
NCREN	National Centre of Research Excellence for Nursing
NHMRC	National Health and Medical Research Council
NICE	National Institute for Health and Clinical Excellence
PATHS	Preliminary assessment of technology for health services
PRISMA-ScR	Preferred reporting items for systematic reviews and meta-analyses extension for scoping reviews
QALY	Quality-adjusted life years
RANE	Rapid assessment of need for evidence
RCT	Randomised controlled trial
SAVI	Sheffield accelerated value of information
VICTOR	Value of information for cardiovascular trials and other comparative research
VOI	Value of information
WTP	Willingness to pay

SUMMARY

As pressure on health research budgets increases, Clinical Trials Networks (CTNs) are expected to evaluate their research impact and to demonstrate value for money of their clinical trials. While traditionally research impact evaluation has been conducted on completed research projects (i.e., retrospective evaluation) for accountability and quality improvement purposes, there is an increasing interest in evaluating research impact prospectively for advocacy purposes (e.g., making the case for funding a research program), and to steer research activities to optimise health, economic and broader societal benefits.

The purpose of this report is to conduct a scoping review of the literature to identify research impact frameworks and measures as well as approaches and tools that can be used in the prospective (i.e., predictive) assessment of clinical trials impact.

A scoping review of the literature was conducted of articles published in English from January 2000 to December 2020. Articles were included if they reported methods, frameworks or case studies describing how research impact and/or value for money can be prospectively evaluated. The publications were collated into three groups: 1) research impact frameworks, 2) approaches to estimate the monetary value of the impact of research, and 3) tools to estimate the monetary value of the impact of research.

From this review, twelve research impact frameworks were identified. Most of these frameworks were adapted from the Payback framework as logic models that depict the relationship between research inputs, process, output, outcome and impact. Key impact domains include advancing knowledge, building research capacity, influencing health policy, improving health and health systems, and broader societal and economic benefits. The two main analytic approaches to estimate the monetary value of the impact of research are: 1) the Preliminary Assessment of Technology for Health Services (PATHS), and 2) the Value of Information (VOI) analysis. Four web-based tools that can be freely accessed to estimate VOI measures were identified: 1) Sheffield Accelerated Value of Information (SAVI), 2) the web interface to the Bayesian Cost-Effectiveness Analysis (BCEAweb), 3) Rapid Assessment of Need for Evidence (RANE), and 4) Value of Information for Cardiovascular Trials and Other Comparative Research (VICTOR).

The application of impact frameworks in practice, to prospectively evaluate the impact of clinical trials, is limited by the intensive resources required to conduct the evaluations, and the difficulty in identifying relevant data sources for the different impact domains. Importantly, none of the identified frameworks allow the aggregation of expected benefits across impact domains in a single metric that can be compared with research costs to estimate the return on research investment. The analytical approaches to estimate the monetary value of research impact provide an objective approach to estimate and monetise research benefits to allow for return on investment assessment; however, these methods are complex and require advanced economic modelling skills. The web-based VOI tools provide user-friendly and free to use platforms to rapidly calculate VOI measures; nevertheless, their value in practice has yet to be tested in terms of acceptability, fit for purpose and practicality by end users.

Future research may focus on understanding the barriers and facilitators for the prospective evaluation of research impact of clinical trials. To facilitate impact assessments, future efforts should build on existing methods to develop more practical and fit for purpose tools to estimate the value for money of clinical trials by CTNs. There is a need to develop indicators to monitor the quality of the research impact evaluation process and the reporting of research impact assessment findings.

BACKGROUND

Health research is essential to improve health and inform decision making. Therefore, governments and research funding bodies around the world allocate considerable resources to support clinical trials and other research studies.[1,2,3] Spending on health and medical research in Australia, for example, increased from $3.7 billion in 2008 to $5.6 billion in 2018, around 80% of this funding was contributed by the Australian Government.[4]

Clinical trials, in particular, test the safety, efficacy, effectiveness and cost-effectiveness of healthcare interventions including preventive measures, diagnostic tests, treatments, and health services.[3] In Australia, Clinical Trials Networks (CTNs) have been formed to bring together clinical researchers with a common interest to identify important clinical questions and design clinical trials to answer them.[3] One of their primary functions is the collective peer review and endorsement of trial proposals to ensure that trials conducted are investigating important clinical questions, engaging consumers and other stakeholders, scientifically rigorous, and feasible to conduct. The Australian Clinical Trials Alliance (ACTA) is the national peak body supporting and representing networks of clinicians and clinical researchers conducting investigator-initiated clinical trials, Clinical Quality Registries and Clinical Trial Coordinating Centres.[5] ACTA coordinates activities to connect these clinicians and clinical researchers with governments, policymakers and consumers on issues that impact the conduct of investigator-initiated clinical trials across the Australian healthcare system.[5]

With increasing pressure on health research budgets, CTNs are required to demonstrate the value of their investigator-initiated research, as research funders are increasingly interested in evaluating research impact and the value for money of the research they fund. Research impact refers to identifiable benefits to the economy, society, public policy, health, the environment, or knowledge.[6,7,8] Research value for money (return on investment) is assessed by comparing research benefits with research costs.[8,9,10]

Research impact evaluation is used for many different, but not mutually exclusive, purposes including accountability, analysis and learning, advocacy, and allocation.[11,12] Research impact evaluation makes research funding bodies accountable for their activities. It also provides a tool to understand how and why research is effective and how it can be better supported. Importantly, evaluating research impact has a vital role in supporting advocacy for research funding as well as in steering the research process towards desired outcomes and informing research budget allocation.[11,12]

A recent study assessed the overall health and economic impact of investigator-initiated clinical trials conducted by selected CTNs and found that the benefit-to-cost ratio for the networks was 5.8:1 (i.e., a return of $5.80 for every $1 invested).[3] The study also found that for every $1 awarded in National Health and Medical Research Council (NHMRC) grants, a return of approximately $51 was achieved.[3] That study represents an important step to demonstrate the value for money of investigator initiated clinical trials in Australia. However, there are other elements of impact beyond health and economic gains that should be considered (e.g., equity, and broader societal impact). Because of the retrospective nature of the impact evaluation in that study (i.e., evaluating impact of already funded and completed trials), the results may not be informative if the objective of impact evaluation is to advocate for new research or to identify clinical trials that have the potential to maximise return on research investment. Nevertheless, conducting evaluations of clinical trials' benefits and costs may not be feasible by CTNs due to the complexity associated with these analyses. Therefore, there is a need for practical methods and tools to help CTNs and research funders prospectively assess the value for money of clinical trials, considering multiple dimensions of research impact.

There is a growing body of literature providing information on the best measures and methods of assessing health research impact.[6,7,10,13–15] A number of research impact frameworks have been developed and implemented in different settings and jurisdictions.[6,7,10,13–15] In addition, analytical methods and tools have been proposed to estimate return on investment of clinical trials and cohort studies.[16,17] The purpose of this report is to conduct a scoping review of the literature to identify research impact frameworks and measures as well as approaches and tools that can be used in the prospective (i.e., predictive) assessment of clinical trials impact. The specific questions addressed by this scoping review are:

1) Which research impact frameworks can be used to prospectively assess the impact of clinical trials?
2) What are the approaches to estimate the monetary value of the impact of clinical trials?
3) What tools are available to estimate the monetary value of the impact of clinical trials?

The findings from this review will be instrumental in informing the development of practical tools to assess the value for money of clinical trials in Australia.

METHODS

A scoping review of the literature was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR).[18] Search terms included ("research impact" OR "payback" OR "value of information" OR "value of research" OR "return on investment") AND ("clinical trial" OR "research"). Electronic databases searched included: PubMed, CINAHL, EMBASE and CRD. In addition, grey literature and the websites of relevant organisations were searched. The search was limited to articles published in English from January 2000 to December 2020. Articles were included if they reported methods, frameworks or case studies describing how research impact and/or value for money can be prospectively evaluated. Both primary research and reviews fitting these criteria were included; however, editorials, lecture notes and protocols were excluded. Studies not focussed on medical or health research were excluded together with studies about early phase biomedical research and registries. Furthermore, studies that solely examined bibliographic impact were excluded.

Frameworks and approaches were deemed suitable for prospective impact evaluation if they allow prior determination of the potential final impact and the pathway to this goal, and incorporate metrics to measure that impact.[7,19] For the return on investment element, the methods and tools should compare research impact in monetary terms with research costs.[8–10] Relevance to clinical trials setting was decided by the presence of case studies demonstrating the application of the approach to clinical trials and/or the assessment of the experts in the research team.

The citations were screened by title and abstract before full-text articles of potentially eligible publications were retrieved for evaluation. A full-text screening identified the articles included for data extraction. Data extracted included a summary of the frameworks and approaches, what they measure and how, examples of practical applications, and existing tools to support the impact measurement in the form of return on investment. Two reviewers (Padraig Oakley and A/Professor Haitham Tuffaha) independently charted the data and discussed the results in an iterative process. Disagreements on a publication selection and data extraction were resolved by consensus and discussion with a third reviewer. The publications were collated into three groups:

1) research impact frameworks
2) approaches to estimate the monetary value of the impact of research, and
3) tools to estimate the monetary value of the impact of research.

RESULTS

The review identified 2,652 citations after excluding duplicates. Searches of reference lists and the grey literature identified a further 17 documents. The review identified 83 publications for full review including: 18 reviews and technical reports, 12 research impact frameworks, 49 for approaches to estimate the monetary value of research impact, and four for tools to estimate the monetary value of the impact of research.

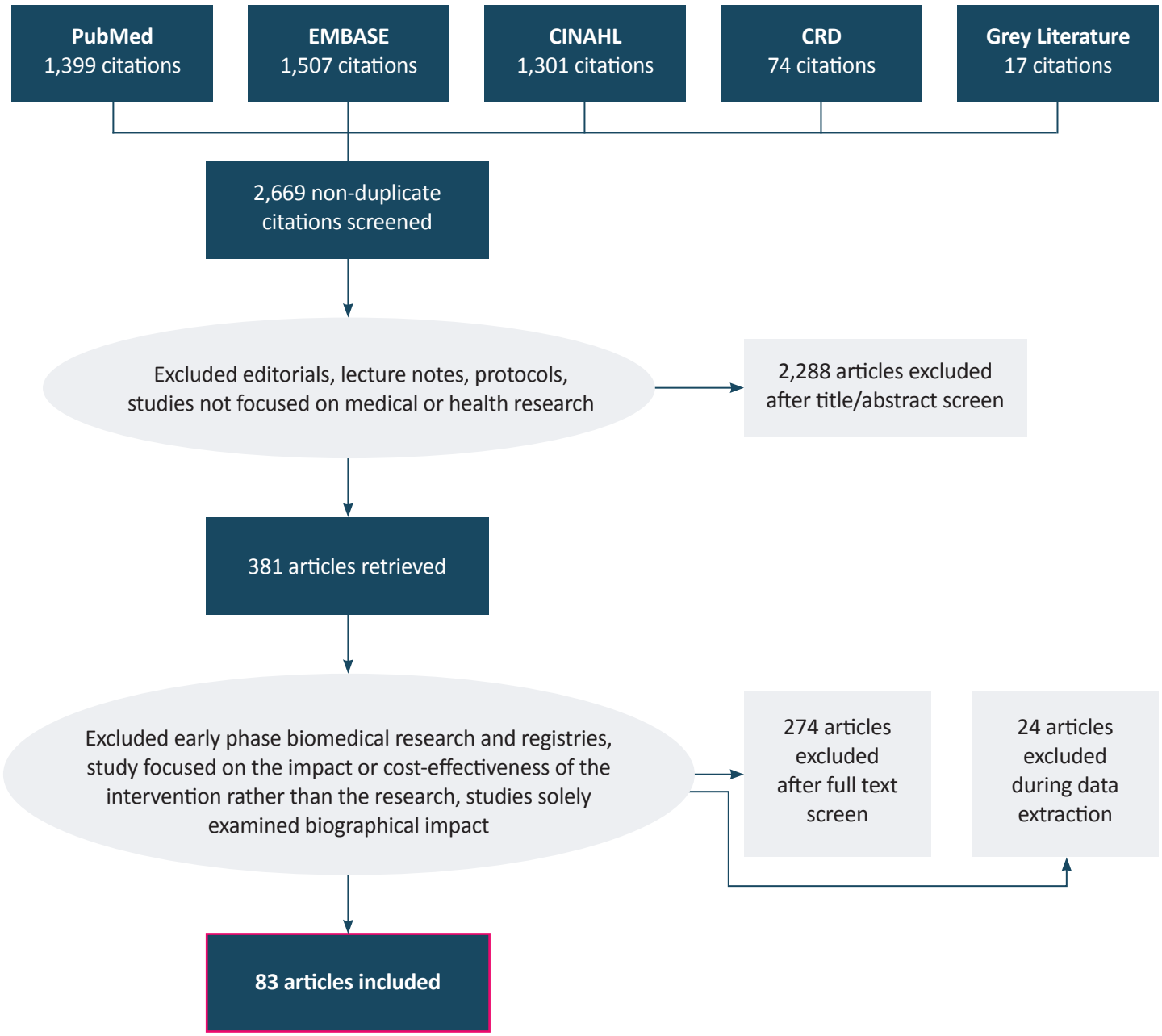

Figure 1: PRISMA flow diagram

RESEARCH IMPACT FRAMEWORKS

Twelve research impact frameworks were included in the review. Most of these frameworks were adapted from the Payback framework by Buxton and Hanney[20] as logic models that depict the relationship between research inputs, process, output, outcome and impact. The Payback framework has been widely implemented in several settings and at various levels (i.e., program of research and individual projects).[6–8,10,21] It consists of two components: 1) a logic model that depicts research stages from conceptualisation to impact, and 2) five impact categories (paybacks) including advancing knowledge, building research capacity, influencing health policy, improving health and health system, and broader societal and economic benefits.[6–8,10] Impact domains from the original Payback framework and its adapted versions are described below.

ADVANCING KNOWLEDGE

This domain refers to the generation of new knowledge and knowledge dissemination, measured in terms of research outcomes (e.g., number of publications), and knowledge transfer (e.g., the rates of article citations and adoption of research findings).

BUILDING RESEARCH CAPACITY

Refers to 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.

INFLUENCING HEALTH POLICY

This domain focuses on 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).

IMPROVING HEALTH AND HEALTH SYSTEMS

This domain captures impacts on health and healthcare systems in terms of 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.

BROADER ECONOMIC IMPACT

The broader economic impacts of health research include the economic benefits emerging from the commercialisation of research outputs, healthy workforce (i.e., reduction in working days lost), intellectual property, spillover effects (i.e., secondary benefit gained by sectors beyond health), patents, the development and sales of spinout companies, and research contracts and income from industry.

SOCIETAL IMPACT

Societal impact includes health literacy, attitudes and behaviour changes in the society, changes in the ability of patients to make informed healthcare decisions, reduce health risks, improvements in equity, inclusion, or cohesion and human rights.

OTHER CONSIDERATIONS

These include process indicators (e.g., engagement with stakeholders) and organisational performance metrics (e.g., staff recruitment and retention, business initiatives and programs developed). Other impact domains were identified for Aboriginal and Torres Strait Islander Research for the Impact Tool (e.g., Indigenous ownership and participation, and unintended research consequences).[22]

Table 1: Summary of the research impact frameworks that can be used prospectively

Framework	Description	Impact categories	Impact assessment methods
Payback Framework[20,23]	A logic model encompasses research stages from conceptualisation to impact.	■ Knowledge benefits ■ Benefits to future research and research use ■ Benefits to policy ■ Benefits to health and health systems ■ Broader economic benefits.	Mixed methods. Sources of information include literature, interviews, surveys and bibliometric databases.
Canadian Academy of Health Sciences (CAHS)[24]/Canadian Institutes of Health Research (CIHR)[25]	Adapted payback approach. Encourages context and discipline considerations.	■ Advancing knowledge ■ Research capacity building ■ Informing policy and decision making ■ Health and health sector ■ Broad socioeconomic benefits.	Mixed methods. Provides a comprehensive menu of metrics and measures.
Research Impact Framework[26]	Conceptual framework to describe the possible impacts of health research outcomes.	■ Research-related impacts ■ Policy impacts ■ Service impacts (health and intersectorial) ■ Societal impacts.	Mainly using semi-structured interviews and narrative case studies.
Alberta Innovates Health Solutions (AIHS) Impact Framework[27]	Adapted Payback and CAHS.	■ Advancing knowledge ■ Building capacity ■ Informing decision making ■ Health ■ Broad socioeconomic ■ Impact ■ Organisational performance.	Mixed methods including surveys and interviews.
Comprehensive Research Metrics Logic Mode[28]	Logic model and associated metrics focusing on environmental health research programs.	■ Improvements in human health ■ Benefits on the environment ■ Benefits to the economy.	Quantitative indicators including economic evaluations.
Health Services Research Impact Framework[29]	Building on Exchange Model, Research Impact Framework.	■ Knowledge generation and communication ■ Capacity building, training, and leadership ■ Informing policy ■ Improving health and health systems ■ Social and economic benefit impact.	Quantitative indicators including economic evaluations.
Hunter Medical Research Institute Framework to Assess the Impact from Translational Health Research (FAIT)[30]	Adapted payback approach.	■ Advancing knowledge ■ Clinical implementation ■ Community benefit ■ Policy and legislation ■ Economic benefit ■ Social return on investment.	Mixed methods including interviews and economic evaluations.

Framework	Description	Impact categories	Impact assessment methods
Institute for Translational Health Sciences Kellogg Logic Model – World Health Organization Health Services Assessment Model[31]	A logic model of research impact combined with process indicators.	■ Relevance ■ Adequacy ■ Efficiency ■ Effectiveness ■ Process ■ Impact ■ Equity ■ Sustainability.	Mixed methods, and process indicators.
Weiss Logic Model[32]	An adapted logic model focusing on research outcomes.	■ Initial outcome (awareness) ■ Intermediate outcome (implementation) ■ Long-term outcome (patient benefit).	Mixed methods including surveys, economic evaluation and interviews.
Exchange Model[33]	Measures impact through three research uptake mechanisms: 'producer push', 'user pull' and 'exchange', which depends upon strong collaboration between producers and users.	■ Process measures ■ Intermediate outcome measures ■ Final outcome measures.	Mixed methods, and process indicators.
Aboriginal and Torres Strait Islander Research for Impact Tool[22]	Focus on Aboriginal and Torres Strait Islander Research.	■ Quality and fitness for purpose ■ Indigenous ownership and participation ■ Priority setting ■ Health benefits ■ Costs ■ Unintended research consequences.	Mixed methods including surveys and interviews.

The application of the identified framework for the prospective assessment of research impact is limited in practice. Graham et al illustrated how the Canadian Academy of Health Sciences (CAHS) framework can be prospectively applied during the early implementation phase of two research programs funded by the Alberta Heritage Foundation for Medical Research programs.[27] Searles et al provided an illustrative example of the Framework to Assess the Impact from Translational health research (FAIT) from an Australian perspective using a case study.[30] A number of challenges were reported for these applications including the intensive resources in terms of staff time and expertise required to evaluate research impact. Moreover, there were challenges in identifying relevant data sources, the reliance on researcher self-report, and in measuring impact elements beyond the traditional indicators (e.g., publications) such as societal and economic benefits.[27]

APPROACHES TO ESTIMATE THE MONETARY VALUE OF THE IMPACT OF RESEARCH

There has been an increasing interest in the development of approaches to estimate the monetary value of the impact of research.[10] The monetised benefits of research can be compared with research cost to estimate research return on investment.[9,34] These approaches draw largely from the economic evaluation literature in the way they identify, measure and value research benefits and costs.[8–10] Research benefits may reflect benefits to the economy from a healthy workforce or research commercialisation (e.g., patents, spin-outs) as well as benefits to the health system in terms of health gains and /or cost savings. Approaches to assess the monetary value of research, including clinical trials, can be split into two categories based on how research benefits are measured and aggregated[9,10]: 1) top-down approaches, and 2) bottom-up approaches.

TOP-DOWN APPROACH

The top-down approach, also known as the macroeconomic approach, calculates the return on research investment by estimating the total health and economic improvements over a period of time, a percentage is then applied to represent the contribution of research to these improvements.[10] Examples of this approach are the reports by Deloitte Access Economics estimating the return on investment from NHMRC and MRFF in five disease areas (cardiovascular disease, cancer, asthma, muscular dystrophy and sudden infant death syndrome).[35,36] Health gains estimation was based on projections from burden of disease studies to estimate disability-adjusted life years (DALYs) averted in the period 2033 to 2045 relative to the year 2000. It was assumed that the proportion of gains as a result of research and development was 50%, and 3.14% of these gains were attributed to Australian research using bibliometric techniques (e.g., proportion of citations from Australian studies), approximately 25% of Australian research publications were funded by NHMRC. The DALYs averted were monetised using a willingness-to-pay value of $168,166 per statistical life year. The studies also considered the value of avoiding direct health system costs (i.e., cost savings), the value of avoiding indirect costs through productivity losses avoided for the five diseases, and the value of direct commercial gains from the NHMRC-funded research and development by applying the bibliometric percentage to the value of bioscience companies that received funding from the NHMRC. They estimated that the return on investment ranged from 509% in cardiovascular research to 30% for muscular dystrophy.[35,36]

The limitations of the top-down approach, as reported in the literature[8,10], include uncertainty about the appropriate time lag between research and impact realisation as well as the attribution of health and non-health benefits to health research. Attribution becomes particularly challenging when evaluating the return on investment from a single project (e.g., a clinical trial) or a relatively small portfolio of projects compared to the return on investment from a large body of funding (e.g., NHMRC funding over a decade). Furthermore, future predictions of health and economic gains are overly reliant on historical trends in population health improvements.[8]

BOTTOM-UP APPROACH

In the bottom-up approach, benefits are built up from individual research projects, mainly evaluative research in the form of clinical trials and cohort studies, to estimate the overall value of health research programs.[10] In general, this approach is based on the notion that the objective of evaluative research is to inform decision making (e.g., adopting new interventions), and thus, the value of generating new evidence through research is inferred from the additional benefits expected to accrue from improved decision making. These benefits are typically expressed as health outcomes (e.g., Quality-Adjusted Life-Years [QALYs] gained) that can be monetised using willingness-to-pay estimates for the outcome measures (e.g., using a willingness-to-pay threshold of $50,000 per QALY gained).[10,34]

An example of this approach is the study that assessed the overall health and economic impact of investigator-initiated clinical trials conducted by the Australasian Stroke Trials Network (ASTN), the Interdisciplinary Maternal Perinatal Australasian Collaborative Trials (IMPACT) Network and the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG).[3] The study evaluated 25 high-impact clinical trials (out of 460 individual trials) across the three networks. For every $1 awarded in National Health and Medical Research Council (NHMRC) grants to the 25 trials, a return of $51.10 was achieved.[3] A similar evaluation was conducted by Johnston et al[37] who evaluated return on investment from the US National Institute of Neurological Disorders and Stroke's funding of 28 Phase III randomised controlled trials (RCTs) prior to 2000. They estimated a return on investment of 46% per year based on 10-year estimates of post-funding

QALYs from eight interventions.[37] Glover et al[38] applied the same methodology in a series of studies and reported returns ranging between 7% and 10% in improved health outcomes from publicly and charitably funded cancer, cardiovascular and musculoskeletal research in the UK[38].

The studies reported above were retrospective as they were applied to research studies that had been funded. Prospective impact evaluation, however, aims to infer the value of research by estimating the benefit that a research proposal is likely to bring about before the study is considered for funding. We identified two prospective approaches: 1) the preliminary assessment of technology for health services, and 2) the Value of Information Analysis approach.

The preliminary assessment of technology for health services (PATHS)

Under this approach, which is also known as the prospective payback approach, the value of a research program (e.g., clinical trial) can be inferred from the additional benefit that the program is expected to generate through informing a change in practice.[34,39] In estimating the additional value of a new research study, the expected benefits of two states are compared: (1) a factual state in which research takes place and informs a beneficial change in clinical practice, and (2) a counterfactual state, in which research is not conducted and clinical practice remains unchanged (i.e., the status quo).[19,34,39] The net benefits of conducting the research are determined by the difference between the outcomes and costs for the targeted populations if the research is conducted and if the research is not conducted. To represent the uncertainty in trial results, the approach considers three broad scenarios of potential trial outcomes: positive, negative and inconclusive.[34] The next step is to predict how clinical practice would change following each of the hypothesised scenarios, and the net effects of these changes estimated in terms of costs and benefits. The estimated costs and benefits are compared with those that are expected if research is not conducted and are then extrapolated to the population expected to benefit from research over a specified time horizon.[34]

The applications of the PATHS approach in practice are limited. Townsend et al applied this approach to case studies including RCTs of early surgery for small abdominal aortic aneurysms, infusion protocols for adult pre-hospital care, postnatal midwifery support, and interferon for multiple sclerosis treatment.[34] Fleurence et al[39] and Andronis et al[40] applied the PATHS approach to case studies in the context of comparing the performance of the approach with the Value of Information approach. In all these case studies, PATHS application required the development of decision analytic models to evaluate the cost-effectiveness of the interventions of interest.[39,40] Furthermore, the analyses assumed that the changes in practice were attributed to the results of the clinical trials; however, implementation in practice maybe be influenced by other factors, and thus, estimated research benefits may be overestimated. Importantly, because the PATHS approach does not assess whether there is a need for a given research program by considering the level of uncertainty in the existing evidence, it may lead to funding unnecessary research.[19,41]

Value of information analysis (VOI)

The VOI approach provides an analytic framework to assess the value of research, based on the notion that generating new information would reduce decision uncertainty and optimise the expected payoffs associated with a decision.[17,42–44] The expected value of research can then be compared with its costs to inform if investing in a new research program is potentially worthwhile. The approach considers the uncertainty in the relevant available evidence (e.g., uncertainty in efficacy estimates), the consequences of this uncertainty (i.e., the cost of making a wrong decision), and the population that would benefit from the results of the intended research.[17]

There is a range of VOI measures to inform research and reimbursement decisions. The most common measure is the expected value of perfect information (EVPI), which is the value of additional information to resolve uncertainty in all decision parameters.[17] Another measure is the expected value of perfect parameter information (EVPPI), which estimates the value of resolving uncertainty in a parameter or a subset of parameters.[17] Both EVPI and EVPPI measure the maximum (i.e. upper bound) value of research, allowing for a rapid screening for the need and potential value of additional evidence. For instance, a negligible EVPI indicates that there is little value from additional research and a decision can be made based on existing evidence. However, if additional research is potentially worthwhile (i.e. EVPI is significant), the value of reducing uncertainty through collecting data in a study of a specific sample size can be estimated using the expected value of sample information (EVSI).[17,41] By comparing the expected monetary benefits and costs of research studies, VOI analysis informs whether a decision can be made based on existing evidence or if additional evidence is required and worthwhile. VOI analysis informs various types of decisions including (i) reimbursement decisions to adopt, reject, or ask for additional evidence (e.g., coverage with evidence development), (ii) efficient trial design by selecting sample sizes that maximise monetary benefits and (iii) prioritising research studies with the highest returns on research investments.[41,43]

Traditionally, VOI has been regarded as a research prioritisation tool to identify strategic research areas based on evidence uncertainty and was excluded from the research impact literature because it did not consider the impact of research on practice.[8,10] Nevertheless, extensions to the VOI approach has been proposed to include the value of implementation, which captures the net monetary benefit from implementing the findings of a research program in practice albeit under the assumptions of immediate and perfect implementation.[17,45–47] Further extensions have been introduced to relax these assumptions by considering the gradual dissemination of research findings, and estimating research benefits in improving implementation by projecting the level of change in implementation that can be attributed to research.[48–50]

The VOI approach is increasingly used to inform reimbursement decisions within the context of health technology assessment[10,45]; however, its application to estimate the value of clinical trials[50–61] and to set research priorities remains limited[55,56,62–64]. Claxton et al applied VOI in nine different interventions for the National Co-ordinating Centre for Health Technology Assessment and the National Institute for Health and Clinical Excellence (NICE).[62] Two studies from the US by Carlson et al[64] and Bennette et al[56] applied VOI to inform funding decisions in cancer clinical trials cooperative groups. Tuffaha et al[55] applied the approach to a portfolio of clinical trials under the NHMRC National Centre of Research Excellence for Nursing (NCREN).

The calculation of VOI measures typically requires conducting a cost-effectiveness analysis using decision analytic modelling, and characterisation of decision uncertainty by expressing input parameter uncertainty in terms of probability distributions.[17,65] However, CTNs and similar organisations may not have the capacity to conduct advanced decision modelling, which may affect the application of VOI approaches in practice. Recent efforts to facilitate the application of VOI include the publication of two best practice reports by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR).[17,65] Furthermore, efficient calculation methods and web-based tools have been developed to facilitate VOI calculation.[65–69]

TOOLS TO ESTIMATE THE MONETARY VALUE OF THE IMPACT OF RESEARCH

We could not identify publicly available tools that estimate the monetary value of clinical trials using the PATHS approach. We have identified four web-based tools that can be freely accessed to estimate VOI measures: 1) Sheffield Accelerated Value of Information[69], 2) the web interface to the Bayesian Cost-Effectiveness Analysis[70], 3) Rapid Assessment of Need for Evidence[71], and 4) Value of Information for Cardiovascular Trials and Other Comparative Research[72]. Table 2 summarises the features of the four web-based tools.

SHEFFIELD ACCELERATED VALUE OF INFORMATION (SAVI)

This tool was developed at the University of Sheffield's School of Health and Related Research and programmed as an R-Shiny Server application http://savi.shef.ac.uk/SAVI. It requires the development of a cost-effectiveness decision model and the results of a probabilistic sensitivity analysis, which are obtained by assigning probability distributions to input parameters and randomly sampling from those distributions.[69] In addition, the tool asks the user to provide information about their model including effectiveness and cost measures and units, the willingness-to-pay threshold, the size of the population that will be affected by the decision each year (i.e., annual prevalence), and the time horizon of the decision (i.e., number of years that the decision is relevant). SAVI estimates the EVPI and the EVPPI for single parameters and groups of parameters; however, it does not estimate the EVSI. The tool produces a report in .pdf, .html or .docx format that summarises the results of the VOI analysis in text, tables and graphs.

THE WEB INTERFACE TO THE BCEA (BAYESIAN COST-EFFECTIVENESS ANALYSIS) R PACKAGE (BCEAWEB)

This tool provides a web interface for the BCEA R package, implemented as an R-Shiny Server application (https://egon.stats.ucl.ac.uk/projects/BCEAweb). Like SAVI, it is designed to post-process the results of probabilistic decision model.[70] The user is also asked to include a plausible range of willingness-to-pay thresholds. The tool estimates EVPI and EVPPI, but does not calculate EVSI. The results are summarised in a report that includes useful graphs such as the cost-effectiveness acceptability curve, cost-effectiveness acceptability frontier, and the Info-rank plot, which is useful to assess how parameters contribute to the uncertainty in the model by ordering them in decreasing order of the ratio of the single-parameter EVPPI to the EVPI for a given willingness-to-pay threshold.

VALUE OF INFORMATION FOR CARDIOVASCULAR TRIALS AND OTHER COMPARATIVE RESEARCH (VICTOR)

VICTOR was a development based on collaborative work between The CHOICE Institute and the Department of Cardiology at the University of Washington using R-Shiny Server application (https://uwchoice.shinyapps.io/victor). The tool aims to help researchers estimate the potential value of their cardiovascular disease studies, and researchers are not expected to develop their own decision models. The tool uses a 'minimal modelling' approach in estimating VOI measures whereby expected payoffs are applied to the outcomes obtained from prior clinical trials or epidemiological studies.[72,73] These outcomes could be comprehensive (e.g., Life years gained, Quality Adjusted Life Years gained), or intermediate outcomes (e.g., stroke) that can be linked to a comprehensive outcome. Inputs include relevant demographic information about the target population such as gender, age and history of cardiovascular disease, study design elements including the number of comparators, primary and secondary endpoints, and duration of the study in years. Other information includes duration of the effect in years, discount rate, and population size. The tool also considers the effect of the results of implementation in clinical practice. The tool estimates EVPI, and EVSI expressed in terms of life years gained for different sample sizes.

RAPID ASSESSMENT OF NEED FOR EVIDENCE (RANE)

RANE was developed at the Centre for Health Economics, University of York and programmed using R-Shiny (https://shiny.york.ac.uk/rane). The purpose of this tool is to calculate the value of research proposals to inform research funding and prioritisation decisions. RANE does not require full economic modelling. Instead, it requires a point estimate of intervention effectiveness on a primary outcome measure (e.g., relative effectiveness measure) and an associated measure of uncertainty (e.g., confidence interval) around that estimate, which can come from a systematic review and meta-analysis, expert elicitation, meta-epidemiological evidence, or a combination of these sources.[42] Depending on the type of primary outcome, other inputs include treatment and disease related costs, health states, health utility associated with the health state and time horizon.

To capture the value of research in improving implementation in practice, the tool requires information about the baseline uptake rates of both the intervention and the comparator. Additionally, the tool requires information about the intended research study in terms of its type (e.g., randomised control trial, pilot study), the expected duration of the study, the time over which the generated evidence would be available and useful, disease incidence, the cost of the study to the funder, and the discount rate. RANE, in its current version, does not estimate EVSI and thus the research value estimated by the tool represents the upper bound of conducting research, which is still useful to rapidly screen and exclude proposals with low expected value.

Table 2: Summary of the four VOI web-based tools

VOI tool	Main purpose	Full decision-analytic model required	Key inputs	VOI measures
SAVI	General assessment of VOI measures, focus on HTA	Yes	Probabilistic analysis results, effectiveness and cost measures and units, WTP, population size and time horizon.	EVPI, EVPPI
RANE	Rapid assessment of the value of research proposals	No	Type of research, research duration and cost, type of primary endpoint and the level of uncertainty around that endpoint, WTP, population size and time horizon, uptake rate of interventions.	EVPI
BCEAweb	General assessment of VOI measures	Yes	Probabilistic analysis results, effectiveness and cost measures and units, WTP, population size and time horizon.	EVPI, EVPPI
VICTOR	Assessment of the value of research proposals in cardiovascular studies	No	Demographic information, primary and secondary endpoints, duration of the study and sample size, treatment duration and utilisation rate, and population size.	EVPI, EVSI

Abbreviations: HTA: health technology assessment; EVPI: expected value of perfect information; EVPPI: expected value of perfect parameter information; EVSI: expected value of sample information; VOI: value of information; WTP: willingness-to-pay threshold.

DISCUSSION

This review identified frameworks and measures that have the potential to be used prospectively to predict the impact of clinical trials, as well as approaches to estimate the monetary value of research impact and the practical tools to support those methods.

Research impact frameworks that are based on logic models provide a systematic approach to evaluate research impact by linking research inputs and processes, to outputs, outcomes and impacts.[6–8,10] The logic models utilised are intuitive and can be potentially used to prospectively evaluate the impact of clinical trials by CTNs. However, measuring research impact comprehensively using these frameworks is a resource intensive and complex task that requires various types of methods, and often a combination of methods (e.g., mixed methods).[6] One of the key challenges when applying the frameworks prospectively is to predict long-term research benefits that are difficult to capture due to the time lag between research and impact realisation (e.g., health and economic gains).[8,10] Whilst modelling might help estimate downstream health and economic benefits, other benefits to society maybe difficult to estimate ex ante.[8,10] Surveys and interviews have been used in impact assessments to elicit expert opinions about certain research benefits, however, these assessments may be inaccurate and subjective. Another limitation in many of the frameworks was the absence of process indicators that are important to monitor the quality and the research impact assessment process, and to facilitate the translation of research results into impact.[74,75] Finally, although value for money and potential cost savings can be captured by some of the frameworks, none of the identified frameworks allow the aggregation of expected benefits in one single metric that can be compared with research cost to estimate the return on research investment.

Approaches to estimate the monetary value of the impact of research may provide a solution to the aggregation problem by monetising research benefits (i.e., using the dollar value as a common metric).[8,10] The PATHS and VOI approaches have been successfully applied to prospectively estimate the return on investment of clinical trials in different settings.[39,40] Nevertheless, these analytical approaches require conducting decision analytic modelling which is resource consuming and beyond the capacity of many CTNs. Furthermore, as part of any economic evaluation, assumptions have to be made in estimating the return on research investment including willingness-to-pay per unit outcome and the size of the population. Importantly, these analytical approaches focus mainly on health and economic gains and may not capture all impact domains especially for the benefits that are difficult to monetise (e.g., societal benefits, equity).[76] Here, it is important to define what is meant by 'value' and for whom to identify the impact elements that should be included and the way these elements should be measured and valued. Of note, the VOI approach, with its extensions to include the value of improved implementation in practice, considers important domains of research impact such as knowledge gain (e.g., by considering existing evidence), possible impact on policy (e.g., by considering cost effectiveness and decision uncertainty), and health gains (e.g., by considering benefits from implementation in practice). In addition, the VOI approach is supported by best practice guidelines[17,65] and online practical tools to allow value of research calculations without the need for decision analytic modelling[71,72].

The four VOI tools reviewed provide user friendly and free to use web-based platforms to rapidly calculate VOI measures.[69–72] However, despite the highlighted advantages of the tools, some considerations should be addressed to improve their utilisation in practice. The tools are based on rigorous methodologies; however, their value in practice has yet to be tested in terms of acceptability, fit for purpose and practicality by end users. This is of particular concern to funding bodies that have large numbers of health technology assessment (HTA) submissions or research proposals to assess within a short time. One possibility is to prioritise which proposals would require VOI analysis based on certain criteria (e.g., when a large budget is required).[1,19] Moreover, there are other decision criteria that are considered together with value for money of an intervention or a research study. These may include equity, feasibility, relevance to organisational strategic goals and benefits beyond health gains.[1,77–79] It would be of interest to study the impact of these considerations on VOI estimates and to develop approaches to aggregate multiple elements of research benefits.[77,80]

LIMITATIONS

A systematic review was not possible because of the broad nature of the topic, and therefore, a scoping review provides an overview of available evidence about frameworks, methods and tools for impact evaluation of clinical trials. The search was limited in terms of databases and language; furthermore, several publications were identified in the grey literature (e.g., reports, web-based tools). The scoping review presented has focused on research impact evaluation of clinical trials from the perspective of CTNs in Australia; however, most of the issues addressed in this review are relevant to clinical trials groups in other jurisdictions. We have only reviewed web-based tools for VOI calculations since they are easily and freely accessible and require no programming skills; however, we note there are some spreadsheet-based tools that have been developed for tutorial purposes.[81]

FUTURE DIRECTIONS

Future research may focus on understanding the barriers and facilitators for the prospective evaluation of research impact in practice. To facilitate impact assessments, future research should focus on building on existing methods to develop more practical and fit for purpose tools to estimate the value for money of clinical trials by CTNs. Efforts should also focus on how to aggregate health gains with other impact domains in one monetary metric to estimate the return on research investment. A number of approaches have been proposed in the literature such as multiple-criteria decision analysis whereby clinical trial proposals are scored based on certain criteria that are assigned weights reflecting stakeholders' preferences.[1,82] Early and effective engagement with stakeholders including consumers, researchers and funders would ensure that the tool meets the needs and expectations of end users in terms of its purpose, data availability and the skill mix required to use the tools.[83] Effective communication of the value of analytical approaches such as VOI and continuous capacity building within the organisations involved in research impact assessment will enhance the utilisation of these approaches and the tools in practice. Workshops, courses and tutorials may be warranted to build the skills required to perform prospective evaluations of clinical trials impact using practical tools. Finally, there is a need to develop indicators to monitor the quality of the research impact assessment process and the reporting of research impact assessment findings.

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APPENDIX A: SEARCH STRATEGY

PubMed

#1

(((((("value of information") OR ("value of research")) OR ("return on investment")) OR ("research impact")) OR ("payback"))

#2

("clinical trial") OR ("research")

#3

#1 AND #2 Filters: Full text, Humans, English, from 2000/1/1–2020/11/30

EMBASE

#1

('value of information' OR 'value of research' OR 'return on investment' OR 'research impact' OR 'payback') AND ('clinical trial' OR 'research')

#2

("clinical trial") OR ("research")

#3

#1 AND #2 Filters: Article or Review, Humans, from 2000/1/1–2020/11/30

CINAHL

#1

(((((("value of information") OR ("value of research")) OR ("return on investment")) OR ("research impact")) OR ("payback"))

#2

("clinical trial") OR ("research")

#3

#1 AND #2 Filters: from 2000/1/1–2020/11/30

CRD

#1

(((((("value of information") OR ("value of research")) OR ("return on investment")) OR ("research impact")) OR ("payback"))

#2

("clinical trial") OR ("research")

#3

#1 AND #2 Filters: from 2000/1/1–2020/11/30

APPENDIX B: SUMMARY OF STUDIES INCLUDED

Table B1: Summary of studies included in research impact frameworks

Author(s)	Year	Country of origin	Framework	Key findings
Buxton and Hanney[20]	1996	UK	Payback Framework	Payback framework consists of two components: 1) a logic model that depicts research stages from conceptualisation to impact, and 2) five impact categories (paybacks) including advancing knowledge, building research capacity, influencing health policy, improving health and health system, and broader societal and economic benefits.
Hanney et al[23]	2000	UK	Payback Framework	
Canadian Academy of Health Sciences[24]	2009	Canada	CAHS	CAHS framework adapted the combined logic model and impacts approach of the “payback model”, into a "systems approach" to capture impacts. It was designed to be used as a roadmap to track health-research impacts in five main categories: 1) advancing knowledge, 2) building capacity, 3) informing decision-making, 4) health impacts, and 5) broad socioeconomic impacts.
Canadian Institutes of Health Research[25]	2005	Canada	CIHR	
Kuruvilla et al[26]	2006	UK	Research Impact Framework	The Research Impact Framework provides a useful set of descriptive categories including: 1) research-related impacts, 2) policy impacts, 3) service impacts and 4) societal impacts to help researchers identify and describe the impact of their work.
Graham et al[27]	2012	Canada	Alberta Innovates Health Solutions (AIHS) Impact Framework	AIHS developed and implemented an impact framework based on a model published by the CAHS. The five main categories identified by AIHS were: 1) advancing knowledge, 2) building capacity, 3) informing decision-making, 4) health impacts, and 5) broad socioeconomic impacts.
Engel-Cox et al[28]	2008	USA	Comprehensive Research Metrics Logic Model	The conceptual logic model for research metrics that focuses on NIEHS-funded research programs to measure the contribution of environmental health research to improvements in human health, the environment, and the economy.
Buykx et al[29]	2012	Australia	Health Services Research Impact Framework	The Health Services Research Impact Framework builds upon previously published frameworks, such as Exchange Model and Research Impact Framework, for reporting the use of research. It emphasises both the broad area(s) in which impact has been made and also identifies whether that impact follows ‘producer push’ dissemination or ‘producer pull’ uptake.
Searles et al[30]	2016	Australia	Hunter Medical Research Institute Framework to Assess the Impact from Translational Health Research (FAIT)	FAIT is a mixed methods approach to encourage and measure research translation and research impact. A module for performance monitoring and feedback with the goal of encouraging research translation is embedded within FAIT model.

Author(s)	Year	Country of origin	Framework	Key findings
Scott et al[31]	2014	USA	Institute for Translational Health Sciences Kellogg Logic Model – World Health Organization Health Services Assessment Model	The Kellogg Model proceeds from resources and inputs, to activities, outputs, outcomes, and impacts. The WHO approach adds focus on eight evaluative focal points: 1) relevance, 2) adequacy, 3) efficiency, 4) effectiveness, 5) process, 6) impact, 7) equity, and 8) sustainability.
Weiss[32]	2007	USA	Weiss Logic Model	The logic model can help identify some near-term outcomes that can serve as leading indicators of long-term success. It helps in measuring three outcomes: 1) awareness, 2) implementation, and 3) patient benefit – these can provide a real sense of the clinical return on an investment in medical research.
Lavis et al[33]	2003	Canada	Exchange Model	The model measures impact through three research uptake mechanisms: 1) producer push, 2) user pull and 3) exchange, which depends upon strong collaboration between producers and users. These measures can be in turn categorised according to process, intermediate outcomes, and outcomes.
Tsey et al[22]	2016	Australia	Aboriginal and Torres Strait Islander Research for Impact Tool	The tool focused on Aboriginal and Torres Strait Islander Research in the contexts of fiscal constraints and increased competition for funding.

Abbreviations: CAHS: Canadian Academy of Health Sciences; CIHR: Canadian Institutes of Health research; AIHS: Alberta Innovates Health Solutions; NIEHS: National Institute of Environmental Health Sciences; FAIT: Framework to Assess the Impact from Translational Health Research.

Table B2: Summary of the studies included in approaches to estimate the monetary value of the impact of research

Author(s)	Year	Country of origin	Key findings
Raftery et al[10]	2016	UK	Research funders can benefit from continuing to monitor and evaluate the impacts of the studies they fund. They should also review the contribution of case studies and expand work on linking trials to meta-analyses and to guidelines.
Deloitte Access Economics[35]	2012	Australia	The report examined NHMRC research investment across five specific disease categories over an extended time horizon (2012–2022) and found that every dollar spent on additional NHMRC R&D resulted in seven cents returned in health expenditure savings in the future, along with other benefits that together bring returns to investment greater than 2:1.
Deloitte Access Economics[36]	2011	Australia	The projected net benefits from NHMRC health R&D performed between 2000 and 2010 is estimated to be around $4.39 billion for CVD, $1.96 billion for cancer, $0.7 million for SIDS, $35.5 million for asthma, and -$8.4 million for MD.
Greenhalgh et al[8]	2016	UK	The study concluded that: (1) different approaches to impact assessment are appropriate in different circumstances; (2) the most robust and sophisticated approaches are labour-intensive and not always feasible or affordable; (3) whilst most metrics tend to capture direct and proximate impacts, more indirect and diffuse elements of the research-impact link can and should be measured; and (4) research on research impact is a rapidly developing field with new methodologies on the horizon.
Townsend et al[34]	2003	UK	PATHS model assesses the cost-effectiveness of the research and may be useful to enhance the research design, endpoints relevant to implementation, analytical methods and dissemination.
The Australian Commission on Safety and Quality in Health Care[3]	2017	Australia	The study retrospectively evaluated 25 high-impact clinical trials across three networks found that the benefit-to-cost ratio for the networks was 5.8:1 (i.e., a return of $5.80 for every $1 invested). The study also found that for every $1 awarded in NHMRC grants, a return of approximately $51 was achieved.
Johnston et al[37]	2006	USA	The study evaluated return on investment from the US National Institute of Neurological Disorders and Stroke's funding of 28 Phase III RCTs prior to 2000 and found that the yearly return on investment was 46%.
Glover et al[38]	2018	UK	The reported returns arising from health gains to the United Kingdom for MSD, CVD and cancer research were estimated to be 7%, 9% and 10%, respectively.
Fleurence[39]	2007	UK	The study applied PATHS model to estimate the expected net benefits of conducting four clinical trials and found that the Record Trial and the Vitamin D and Calcium Trial would be cost-effective.
Andronis[19]	2015	UK	Estimates of the potential value of research are neither requested nor taken into account in research funding decisions, despite the fact that analytic approaches to provide such estimates are available.
Andronis et al[40]	2016	UK	Compared with VOI, PPoR is less complex but requires more assumptions. Although the approaches are not free from limitations, they can provide useful input for research funding decisions.
Tuffaha et al[41]	2014	Australia	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.

Author(s)	Year	Country of origin	Key findings
Fenwick et al[17]	2020	ISPOR	The report describes the process of VOI analysis, providing a top-level description of the methods and steps involved in undertaking and interpreting the results of such an analysis, from conceptualising the decision problem to developing the decision model, parameterising the model, running the probabilistic analysis, calculating the value of information (perfect, partial perfect, and sample), and determining the worth of research (expected net benefit of sampling).
Claxton et al[42]	2015	UK	Standard meta-analysis could be routinely reported and would provide quantitative assessments of the health benefits of further research and of implementing the findings of existing research.
Chilcott et al[43]	2003	UK	Use of overall expected value of perfect information should be encouraged in modelling studies seeking to inform prioritisation and planning of health technology assessments.
Willan et al[44]	2012	Canada	VOI methods provide a decision-analytic alternative to the standard hypothesis testing approach for assessing the evidence provided by cost-effectiveness studies and for determining sample sizes for RCTs.
Steuten et al[45]	2013	Netherlands	EVSI is the preferred method of VOI to inform decision making regarding specific future studies, but real-life applications of EVSI remain scarce.
Hoomans et al[46]	2009	UK	The research aims to demonstrate the use and practicality of this analytic framework by applying it prospectively alongside technology appraisal to inform the NICE about the allocation of health-care resources for mHRPC.
Fenwick et al[47]	2008	UK	Key factors that influence the EVPI and EVPIM are the maximum acceptable cost-effectiveness ratio, the level of uncertainty surrounding the adoption decision, the expected net benefits associated with the technologies, the current level of implementation, and the size of the eligible population.
Tuffaha et al[55]	2016	Australia	The study evaluated four clinical interventions from the perspective of Queensland Health, Australia and found that the net monetary benefits associated with NPWT was AU$1.2 million, tissue adhesive for securing catheters was AU$0.3 million and nutritional support for preventing ulcer was AU$0.1 million.
Bennette et al[56]	2016	USA	The study developed an efficient and customised process to calculate the expected VOI of cancer clinical trials that is feasible for use in decision making and acceptable to investigators.
Claxton et al[62]	2004	UK	The pilot study showed that, even with very short timelines, it is possible to undertake VOI that can feed into the priority-setting process that has been developed for the HTA programme.
Tappenden et al[63]	2004	UK	The study developed methods for performing EVPI analysis in computationally expensive models and reported on the developments on the health economics of interferon-beta and glatiramer acetate in the management of MS using this methodological framework.
Carlson et al[64]	2013	USA	The study developed decision-analytic models and calculate upper-bound VOI estimates for three previously selected genomic tests. The upper-bound VOI for ERCC1 was $2.2 and $2.8 billion in stage I and stage II disease, respectively; $2.1 billion for breast cancer markers; and $33 million for EGFR.
Rothery et al[65]	2020	ISPOR	This report from the ISPOR VOI Task Force describes methods for computing 4 VOI measures: 1) the expected value of perfect information, 2) expected value of partial perfect information, 3) expected value of sample information, and 4) expected net benefit of sampling.

Author(s)	Year	Country of origin	Key findings
Kunst et al[66]	2020	ConVOI	The report provides practical guidance and recommendations to help inform the choice between the four efficient EVSI estimation methods, more specifically: (1) a step-by-step guide to the methods' use, (2) the expertise and skills required to implement the methods, and (3) method recommendations based on the features of decision-analytic problems.
Jalal et al[67]	2018	USA	The study proposes a general GA approach to estimate EVSI that addresses some of the challenges associated with traditional EVSI calculations, especially when complex Bayesian updating of the prior uncertainties is required and when the prior evidence suggests that these uncertainties are correlated.
Strong et al[69]	2014	UK	The research paper describes a novel nonparametric regression-based method for estimating partial EVPI that requires only the probabilistic sensitivity analysis sample.
Strong et al[68]	2015	UK	The study presents a method for calculating per-patient EVSI that avoids the nested two-level scheme, requiring only the single set of sampled model inputs and corresponding model outputs (i.e., net benefits) that is generated in a standard probability sensitivity analysis. The method is based on a nonparametric regression of the net benefits on data samples that are generated conditional on the sampled input parameters in the PSA and follows closely the nonparametric regression method for computing partial EVPI described in Strong et al. (2014).

Abbreviations: R&D: Research and Development; CVD: cardiovascular disease; SIDS; Sudden infant death syndrome; MD: muscular dystrophy; RCT: randomised controlled trial; MSD: musculoskeletal disease; PATHS: Preliminary Assessment of Technology for Health Services; VOI: value of information; PPoR: prospective payback of research; EVSI: expected value of sample information; mHRPC: metastatic hormone-refractory prostate cancer; EVPI: expected value of perfect information; EVPIM: expected value of perfect implementation; NPWT: Negative Pressure Wound Therapy; HTA: health technology assessment; MS: multiple sclerosis; EGFR: epidermal growth factor receptor; GA: Gaussian approximation; PSA: probability sensitivity analysis.

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