

VIEWPOINT

Embedding clinical trials within routine health-care delivery: Challenges and opportunities

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The COVID-19 pandemic provides a pertinent reminder of the imperative to generate timely reliable clinical evidence. Delivery of optimal paediatric care is predicated on the availability of comprehensive, high quality, clinical evidence in a relevant population. However, over 80% of current clinical guidelines and bedside decisions are not based on direct high-level evidence. Integration of research activities into routine clinical care is paramount to address this shortfall. Active engagement of patients, families and hospital administrations is required to reframe integrated clinical trials as a tenet of quality health-care delivery. Current research funding in health care is 1–2 orders of magnitude below that of other industries. At an institutional level, investment in research should be prioritised with enhanced funding and supportive policies. Thoughtful integration of trials into routine bedside care will enable pragmatic research outcomes, tangible returns on financial investments and improved decision-making for patients in the medium- to long-term.

Current medical guidelines rely on a highly variable evidence base, from high-quality clinical trials to expert opinion. Currently, only 18% of Australian clinical guidelines addressing the top-10 causes of mortality are based on level I (or equivalent) evidence.¹ This shortfall must be addressed to optimise clinical outcomes for patients, with the benefit of economic and health-care system efficiencies.

There is a significant cost associated with poor quality evidence in health care. US data suggest that one third to one half of health-care costs are wasted expenditures,² and this is likely replicated in other geographies. A large driver of waste is variation in care due to differences in clinical judgement and practice, often leading to over-treatment or mistreatment of common conditions. This is frequently exacerbated by an inadequate evidence base. Notably, when randomised controlled trials (RCTs) are conducted to analyse commonly held practices, the results are often surprising.^{3–5} A key example of this is the finding that intensive monitoring of blood sugar levels in critically ill adults leads to increased mortality.⁴ High-quality evidence enables clinical decision-making to be more firmly guided by reliable and applicable data rather than individual experience, which may vary widely. Hence, improved clinical trials data encourages consistency in clinical practice and translates into direct benefits for patients as a result of research investments.

The Australian Commission on Safety and Quality in Health Care in July 2017 reviewed the economic impact of 24 late phase comparative effectiveness research trials conducted over the preceding decade.⁶ This review demonstrated a net health system

benefit of AUD 1.6 billion (Fig. 1). The benefit to cost ratio was between 6:1 and 51:1, assuming that two thirds of the findings were implemented into clinical practice, thus representing an enormous economic return on research investment.⁶ At a pragmatic level, there remains a gap in the implementation of high-quality evidence into clinical practice, which may be at least partially addressed through clinician engagement and cultural emphasis on the importance of evidence-based practice within health care. Equally, there is recognition that variations in host and pathogen epidemiology may impact the applicability of research results across different settings.

The traditional siloing of research from clinical management has led to systems that downplay the value of pragmatic bedside research to optimising clinical care. Opportunities abound to generate improved outcomes and enhanced efficiencies through systematically integrating clinical and research functions under a single umbrella.

Barriers to Embedded Research

Despite the obvious clinical and economic benefits of embedded clinical trials, there remain significant barriers to the establishment and conduct of clinical trials in the health-care environment.

Clinical trials are hindered by extensive bureaucratic and regulatory hurdles, which can slow the process beyond the window of utility, and carry burdensome costs. Such financial constraints often result in studies being underpowered to demonstrate convincing outcomes with indeterminate results stemming from budget-limited study sizes.

Lack of engagement from patients remains an obstacle to effective research delivery. Oncology as a sub-specialty has succeeded in fostering a culture where patients do not feel they are receiving best-practice care unless they are enrolled in a trial. In other areas of medicine, patients typically begin from a standpoint of

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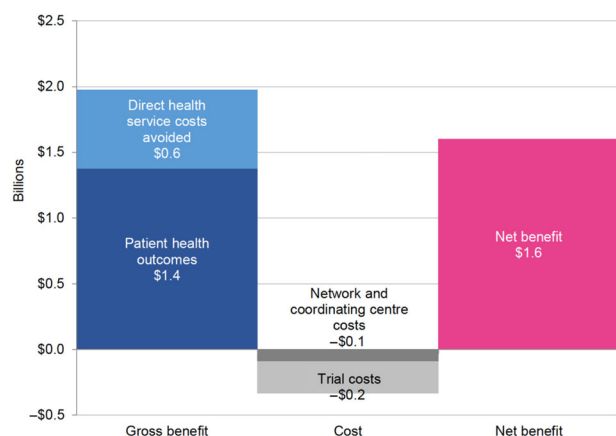


Fig 1 Health system costs and benefits from 10 year summation (2004–2014) of late phase comparative effectiveness trials in Australia.⁶

suspicion towards clinical trials, representing a cultural barrier to research implementation.

Since RCTs are expensive, slow and difficult, there are more clinical questions than trials can answer, resulting in untested interventions flowing over into clinical practice. When such over-flowing treatments are either harmful, ineffective or expensive, patients, clinicians and the health-care system will all be compromised. This issue also exacerbates a culture where integrated clinical trials are undervalued as a tool to drive clinical decision-making.

Strategies for Embedding Research

Embedding is the process of integrating research activities into routine patient care to facilitate the appropriate, timely and efficient generation and implementation of the best available evidence. The purpose of embedding is to make clinical trials easier, cheaper and faster, thus optimising the trial's relevance without compromising on quality.

To facilitate effective embedding of clinical research, trials need to adopt an appropriate design, regulatory approval processes must be streamlined and proportionate, ready access to appropriate data support must be available, and the community and health-care systems should embrace research as a critical integrated element of care.

While clinical care and research have previously functioned as silos, we know that both functions intersect on the same patients. Optimal systems require breaking down these barriers to improve efficiency of staff and resources. Research contributions can and should be part of the position description of all clinical staff and appropriate support provided by employers.

Embedding trials into clinical practice requires enhanced levels of pragmatics. Embedded trials require 'buy-in' by frontline staff who will also recruit and implement the trial. The enrolment criteria must be simple, randomisation quick and easy, and trial processes automated to the greatest extent possible. The primary end-point must be clear, well-defined and important to both clinicians and patients. Secondary end-points should include clinically relevant outcomes only. Overly complex data collection or

systems should be avoided as these will deter clinicians and participants. Critically, involving frontline clinicians and even patients in study design – from formulating research hypotheses and identifying clinically important outcomes through to the analysis and dissemination of research findings – is a key factor in achieving engagement from these key stakeholders. Such engagement will also yield downstream benefits in terms of ease of clinical implementation of the research outcomes.

The Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG) has had substantial success with embedded trials, including the SAFE trial which enrolled 7000 patients across Australia and New Zealand.⁷ After trial completion, registrars were still trying to prescribe 'SAFE fluid', demonstrating the level of acceptance and integration of this trial into their daily practice.

The most pragmatic approach to comparative effectiveness research is an RCT of two or more options where both are in widespread use, both are believed to be equally safe and effective and there is equipoise as to the efficacy of one versus the other. Platform trials (5–10-fold more efficient) or cluster cross-over trials (10–20-fold more efficient) may boost trial efficiency.^{8,9}

Normalising the clinical research process for patients is critical, including an emphasis on the principles of equipoise and of randomisation to a treatment that would be commonplace outside of the trial environment. This approach allays many of the participants' concerns when faced with the clinical trials consent process.

The ethics around consent are important in clinical trials research, and proportionate regulation should have a role. The latest revision of the Australian Government's National Statement on Ethical Conduct in Human Research suggests that the Human Research and Ethics Committee can play a role in assessing the risk of participation within the therapeutic context that would apply outside of a particular trial; opt-out consent may be considered in some contexts.¹⁰

At an organisational level, research must be highly valued as a key element of patient care. Research that has potential for impact should be prioritised in clinical environments. Governance and policy frameworks should facilitate research through accepting research risk alongside clinical risk.

Research investment in health care in Australia is grossly underfunded compared to almost any other industry. Public good clinical trials, generally funded by NHMRC or philanthropic organisations, comprise under AUD 150 million per year, or 0.1% of annual health-care turnover, compared to research and development investment in other industries of up to 20% annual turnover (Fig. 2).^{11,12} Health-care systems – from individual hospitals to the federal Health Department – can and should fund increased research activity, and will reap the rewards in improved outcomes for patients, with economic returns as a valuable add-on benefit.

Lessons from COVID-19 Pandemic

The emergence of the coronavirus disease 2019 (COVID-19) pandemic in December 2019 has highlighted the critical importance of real-time evidence to inform clinical and public health questions. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative coronavirus, was a novel human

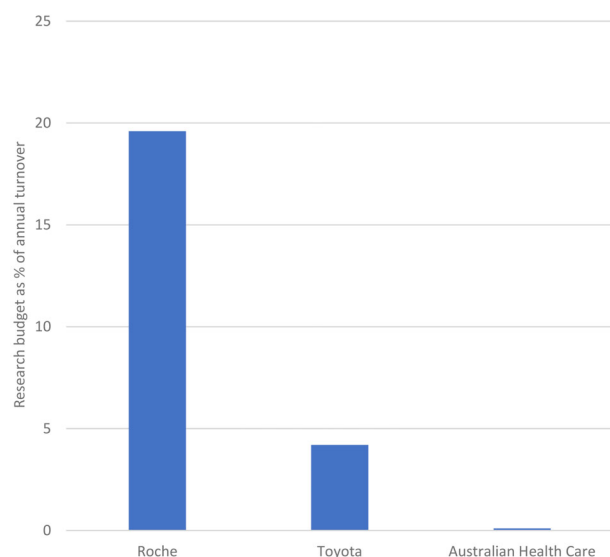


Fig 2 Allocated budget for research and development as percentage of annual turnover.^{11,12}

pathogen and hence understanding of its transmission dynamics, pathogenesis, and management was completely undeveloped at the time of emergence of the pandemic. Disease severity was highly variable but, in a fully susceptible population, transmission rates were high (R_0 estimated between 2 and 3)¹³ and mortality in older age groups up to 15%.¹⁴ There was no effective anti-viral treatment and no vaccine. Clinical equipoise was undeniable and the populace demanded trials to improve our understanding of this pathogen and its optimal management.

Embedded clinical trials were fast-tracked locally and internationally, growing from 19 registered RCTs in Australia and New Zealand in April 2020 to 127 by September 2020.¹⁵ Responsiveness of regulatory bodies in approving trials for implementation was required. Such a critical health emergency starkly highlighted the importance of adaptive clinical trials to enable optimal care delivery to the population at this key juncture and into the future.

Opportunities in Paediatrics

Quality clinical trials data are scarce in paediatrics across the spectrum of disease.¹⁶ Children are often excluded from broader clinical trials due to safety considerations, differences in pharmacokinetics and pharmacodynamics, and perceived or actual differences in pathophysiology. As such, data are frequently extrapolated from adult trials with variable validity in children. With such a paucity of data, the imperative for pragmatic, efficient, embedded research is all the more pressing. Through engagement with clinicians and families, adaptive trial design and cooperation across multiple centres, high-quality evidence can be obtained to inform clinical decision-making in paediatric populations. The principles of prioritisation and integration of research are highly relevant and important to health-care practice in the paediatric environment.

Conclusions

There is an immense unmet need for high-quality evidence in medicine, with better evidence leading to better health outcomes. Increased financial commitment and integration of research into clinical care will enable the generation of pragmatic, timely evidence alongside delivery of care. Traditional clinical trials can be slow, expensive and difficult to run, but commitment from hospitals and health-care systems can ensure prioritisation and integration of research. Improvements in medium- to long-term health outcomes and enhanced health-care efficiency will be the positive rewards of this adaptive approach.

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