ACTA Reference Goup D
Embedding Clinical Trials

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on behalf of the Group D members

Disclosures

- Group Director of Research Epworth HealthCare
  - Soma Consulting pty ltd and advisor to Chrysalis Advisory Pty Ltd, AHRECS and Emerald Clinics
- Received funds from
  - Roche, Astra Zeneca, Pfizer, Merck Serono, Boeringher Ingelheim, Amgen, Bayer.
- Affiliations
  - Australian Clinical Trials Alliance (Founding Board member, Chair Embedding Reference group),
  - Australasian Gastrointestinal Trials Group (Scientific Advisory Committee)
  - Primary Care Collaborative Trials Group (PC4) (Chair Advisory Committee)
  - Clinical Oncology Society of Australia (Council and Board)
  - International Cancer Genome Consortium-ARGO. Co-chair Patient Participation and Engagement Committee, member Ethics and Policy Committee

Objectives

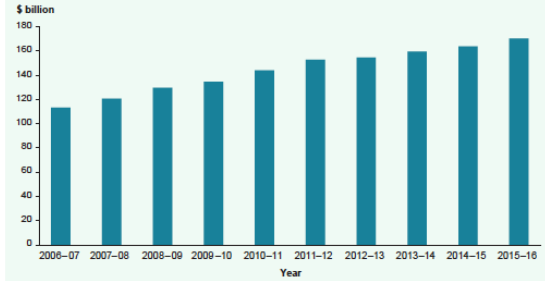
Australian Clinical Trials Alliance

- Promote the concept and definition of embedding within **'routine health care'**
- Identify the barriers and enablers to successful embedding; develop **'model of embedding'** to effectively achieve it
- Highlight exemplars of successfully embedded clinical trials in routine care, creating a **'community of practice'**
- Develop **'guidance'** for networks and health-service providers to optimise embedding of clinical trials

Australian Government
Australian Institute of Health and Welfare

Australia's health 2018

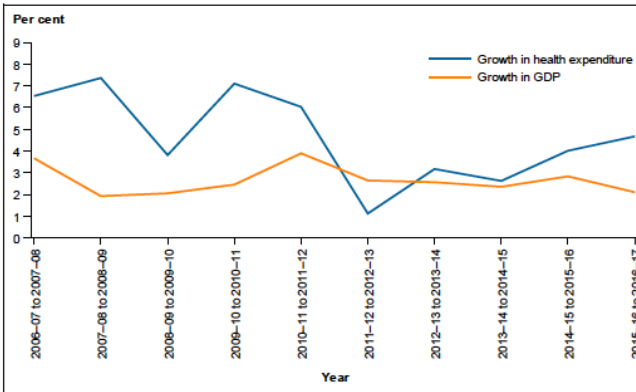
Figure 2.2.1: Total health expenditure, adjusted for inflation, 2006–07 to 2015–16



Note: Inflation-adjusted prices expressed in terms of 2015–16 prices.
Source: AIHW health expenditure database; Table S2.2.1.

AIHW

Australian Institute of Health and Welfare 2018. *Australia's health 2018*. Australia's health series no. 16. AUS 221. Canberra: AIHW.

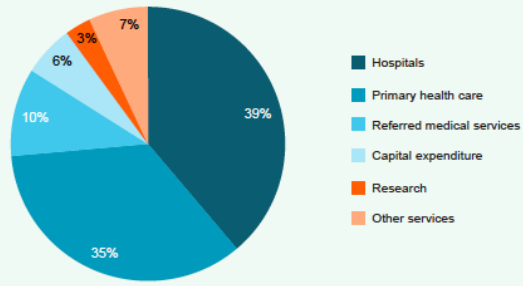


(a) Constant price health expenditure is expressed in terms of 2016–17 prices. See Appendix C for more details.

Source: Table 2.3.

Figure 2.1: Annual growth rates of health expenditure and GDP, constant prices[(a)], 2006–07 to 2016–17

Figure 2.2.6: Proportion of total health expenditure, by broad area of expenditure, 2015–16

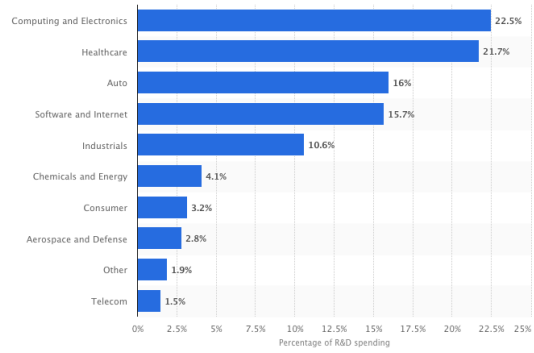


Sources: AIHW health expenditure database; Table S2.2.6.

Society › Economy › Percentage of global R&D spending 2018, by industry

PREMIUM

Percentage of global research and development spending in 2018, by industry



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DESCRIPTION SOURCE MORE INFORMATION

by Erin Duffin,
last edited Apr 29, 2019

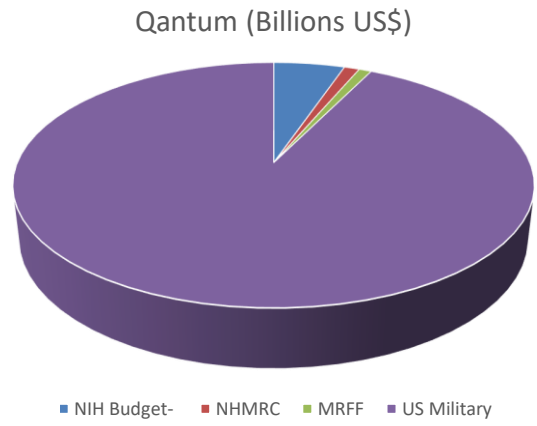
This statistic shows the percentage of global research and development spending in 2018, by industry. In 2018, about 2.8 percent of global research and development spending was made by the aerospace and defense industry. Lockheed Martin's expenditure on research and development in 2017, for example, stood at 1.2 billion U.S. dollars.

Additional information on research and development in the healthcare industry

What is the investment?

Australian Clinical Trials Alliance

- NIH Budget- US$39.2 Billion ($130 per capita)
- NHMRC AUD$830 million ($38 per capita)
- MRFF $1 Billion ($45 per capita)
- US Military US$693 Billion ($2310 per capita)



Definition of Embedding

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*

International Scan

'The clinical research enterprise is not producing the evidence decision makers arguably need in a timely and cost effective manner, research currently involves the use of labor-intensive parallel systems that are separate from clinical care'

Weinfurt et al: BMC Medical Research Methodology

The consequence

Inadequate evidence to guide care

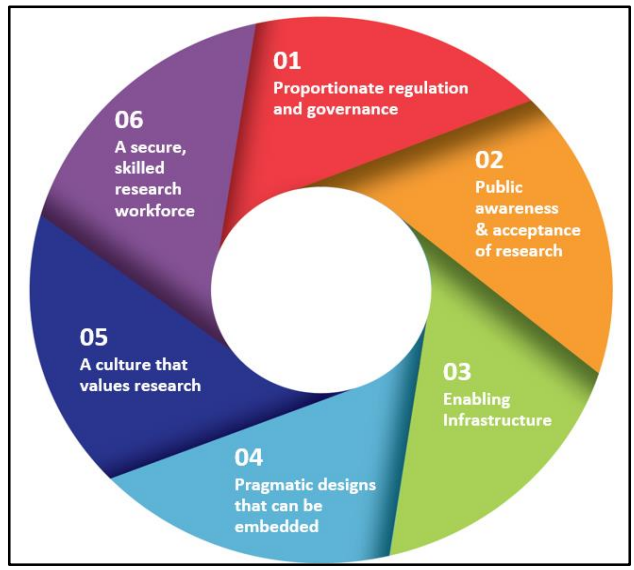
International Scan

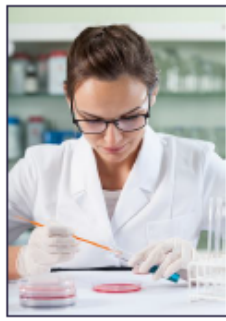
- A Learning Healthcare System (LHS) is gaining traction as a way to achieve the best possible patient outcomes at reasonable cost.
- Traditional ethics and governance frameworks apply poorly to pragmatic trials. Continuous improvement and research form a continuum that should be better valued as a core responsibility of delivering safe and effective healthcare.
- Changing the culture of the health service is seen as one of the biggest challenges.
  - All stakeholders should value clinical trials as part of an LHS and be able to convey their importance with patients and the public.

International Scan

- Wider access to research design and trial coordination services is necessary to support an LHS and to avoid the potential for missed opportunities or wasteful research practice.
- The lack of interoperable digital infrastructure makes it difficult to conduct rapid-pace trials of sufficient size to support decisions in an LHS.
- The lack of clarity around privacy and the use of health data impedes the move to an LHS.

ELEMENTS TO SUPPORT THE EMBEDDING OF CLINICAL TRIALS





CHANGING CULTURE: RECOMMENDATIONS FROM THE UK ACADEMY OF MEDICAL SCIENCE:

- *The core role of health research in the delivery and improvement of the NHS should be more widely communicated to healthcare staff at all levels.*
- *Heath research should be formally and irreversibly embedded into NHS leadership and governance processes by the following: the use of appropriate metrics and incentives; training the NHS workforce to ensure it can support health research; and ensuring that within each Trust there is an executive director with specific responsibilities to promote health research'.*

Survey of Research Directors

Australian Clinical Trials Alliance

- Common barriers and enablers of embedding often experienced at an institution or service level
- **38% (14/37)** completed consultation;
  - Public & Private Health Service Directors / Executives
  - NSW, VIC, QLD, WA
- **93%** of organisations have dedicated research strategy
  - **54%** state organisation fulfils strategic intent fully
- Number of dedicated research units within organisation;
  - **54%** 4-10 research units
  - **31%** 10+ research units

Conclusions

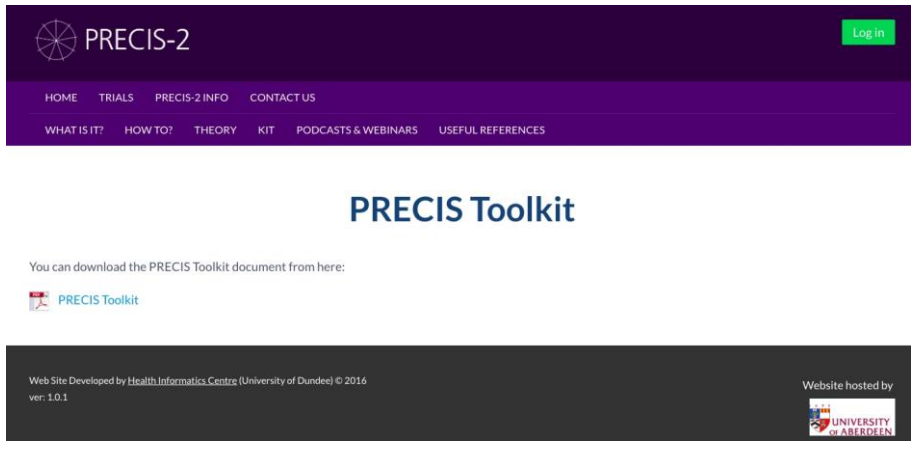
- For major healthcare institutions, embedding research activity within routine clinical care is considered **strategically important and essential for improving health care outcomes for patients.**
- **Research culture and lack of resources** (e.g. funding and infrastructure) were identified as the principal barriers affecting more effective and efficient integration of research into clinical care.
- **Operationalising research within healthcare institutions is perceived as complex** by personnel tasked with integrating activity alongside routine clinical care, often described as resource intensive and challenging to implement.
- Many healthcare institutions value research and **provide a range of services to support** and develop research activity.
- **Digital health infrastructure was recognised as one of the most challenging barriers** and at the same time provides the **greatest opportunity to integrate research into healthcare**.
- **Increasing research awareness** within healthcare institutions and amongst health consumers was considered central to improving integration.

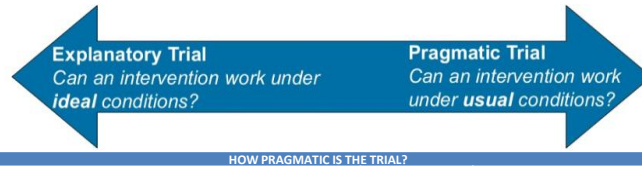
IDENTIFICATION OF AUSTRALIAN TRIALS THAT ARE EMBEDDED

- Identify groups that have successfully embedded trials within the health system to help others interested in designing trials that can be embedded into the health system

Characteristics of pragmatic trials

- Compare two or more options for the prevention, diagnosis, treatment or management of a disease or symptoms
- Address critical clinical choices faced by patients, caregivers, clinicians and systems
- Are conducted in routine clinical settings
- Attempt to minimise disruption to routine clinical workflows In the case of a platform trial - evaluate what works best, for whom, under what circumstances





HOW PRAGMATIC IS THE TRIAL?							
Question	Score						Rationale
1. Eligibility –to what extent are the participants in the trial similar to those who would receive this intervention if it was part of usual care? For example, score 5 for very pragmatic criteria essentially identical to those in usual care; score 1 for a very explanatory approach with lots of exclusions (e.g. those who don't comply, respond to treatment, or are not at high risk for primary outcome, are children or elderly), or uses many selection tests not used in usual care	1	2	3	4	5		5
1. Recruitment - how much extra effort is made to recruit participants over and above what that would be used in the usual care setting to engage with patients? For example, score 5 for very pragmatic recruitment through usual appointments or clinic; score 1 for a very explanatory approach with targeted invitation letters, advertising in newspapers, radio plus incentives and other routes that would not be used in usual care	1	2	3	4	5		3 (targeted letters, adverts)
1. Setting – how different is the setting of the trial and the usual care setting? For example, score 5 for a very pragmatic choice using identical settings to usual care; score 1, for a very explanatory approach with only a single centre, or only specialised trial or academic centres	1	2	3	4	5		5

Trials of Participating Groups

SHORT NAME	FULL NAME	REGISTRATION REFERENCE
TARGET	Energy-Dense versus Routine Enteral Nutrition in the Critically Ill	NCT02306746
ASPREE	Effect of Aspirin on All-Cause Mortality in the Healthy Elderly	NCT01038583
TRANSFUSE	Age of Red Cells for Transfusion and Outcomes in Critically Ill Adults	NCT01638416
ADRENAL	Adjunctive Glucocorticoid Therapy in Patients with Septic Shock	NCT01448109

The Augmented Versus Routine Approach to Giving Energy Trial (TARGET)

Principal Investigator(s): Professor Sandra Peake (The TARGET Investigators and the ANZICS Clinical Trials Group)

DOI: https://www.nejm.org/doi/full/10.1056/NEJMoa1811687

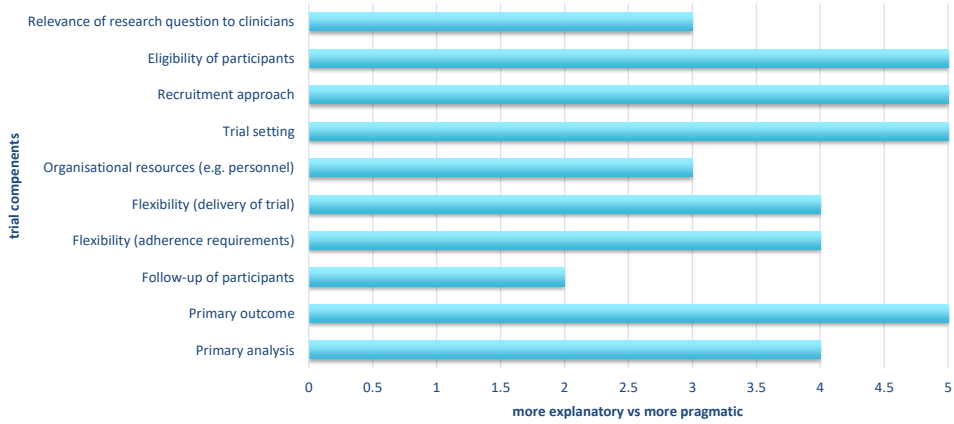
NCT01448109

Conclusions

In patients undergoing mechanical ventilation, the rate of survival at 90 days associated with the use of an energy-dense formulation for enteral delivery of nutrition was not higher than that with routine enteral nutrition.

20/22/2019

Q1: How pragmatic is the trial?



Q2. Protocol: Study Specific Procedures

SPIRIT Criteria	Yes	No	NA
Inclusion and exclusion criteria for participants	√		
If applicable, eligibility criteria for study centres and individuals who will perform the interventions (e.g. Surgeons, psychotherapists)		√	
Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	√		
If applicable, criteria for discontinuing or modifying allocated interventions for a given trial participant (e.g. Drug dose change in response to harms, participant request, or improving/worsening disease)		√	
Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (e.g. Drug tablet return, laboratory tests)		√	
Relevant concomitant care and interventions that are permitted or prohibited during the trial		√	
Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants	√		
Strategies for achieving adequate participant enrolment to reach target sample size		√	
Recruitment Methods: Mechanism of implementing the allocation sequence (e.g. Central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	√		
Recruitment Methods: Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	√		
If applicable, blinding (masking) who will be blinded after assignment to interventions (e.g. Trial participants, care providers, outcome assessors, data analysts)	√		
If applicable, If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	√		
Who will obtain informed consent or assent from potential trial participants or authorised surrogates	√		
If applicable, plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies			√

Key Themes

Australian Clinical Trials Alliance

- **Divergence from standard care**
- A commonality of all four exemplar embedded trials was their minimal divergence from usual care. This affected buy-in from routine staff in the health settings of trial activities, and was considered a significant enabler of trial success.

Ethics and consent

- Another key point of discussion was the ethics and consent processes used in embedded trials. Respondents found that there is a need for clarity and consensus from the research community on ethics processes when trial interventions minimally deviate from standard care, and wanted the ethics process for pragmatic trials to be uniformly applied.

Benefit to clinical staff

- “[It allowed clinical staff] to get a little bit of mastery over that aspect of clinical trials that will allow them to grow and maybe deliver more complicated interventions in the future.” – Respondent from the TRANSFUSE trial.

ENABLERS

- The most prevalent enablers were simple interventions that minimally deviated from routine care, dedicated research staff, provision of training for clinical staff, and feasibility checks prior to the trial.
- Other enablers included stakeholder engagement, funding, infrastructure and technology that supported easy randomisation.

Conclusions

- **Simple interventions**
- **Minimal interference to routine care**
- **'Making it easy': Training, tools, and instruction manuals**
- **Importance of dedicated research staff**
- **Pre-trial feasibility checks, analysis and planning**
- **Stakeholder engagement**
- **Funding**
- **Infrastructure and technology**

Strategic context

- Informed by increasing recognition that consumers are integral stakeholders in the development of evidence to improve healthcare
- Through a strong alignment with our clinical services, the opportunity presents to leverage our strengths in healthcare delivery to innovate and translate new evidence into practice
- Understanding that a learning healthcare organisation seamlessly embeds continuous improvement and innovation in the healthcare delivery process, with new knowledge of the delivery experience captured through research
- Growth in medical research has amplified the opportunity to positively impact patient experience and create a new era of innovative research at Epworth

Strategic principles

Patients and Community first	Authentic partnering with consumers to enhance their experience; improve safety and quality of care; and achieve better outcomes.
Visible and accountable leadership	Strong supportive leadership to inspire and empower our people in their commitment and accountability to achieve our goals.
A focus on the future	Forward thinking in the design of meaningful, evidence based and sustainable programs to meet the emerging needs and expectations of our patients and community.
One High Performance Epworth	We are one integrated organisation, learning from each other to optimise performance and realise efficiencies.

Australian Clinical Trials Alliance

QUESTIONS