Strategies for supporting trials of high value

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Strategies for supporting more trials of high value

- Increase recognition by govt and community of the value to clinical trials to change practice and improve outcomes
- Enhancing criteria for funding relevant clinical trials – as cost-effective use of the health care dollar
- Embedding high quality clinical research in health care with metrics for clinical trials linked to health care funding
- Further building capacity for high quality trials through relevant expertise (trials networks, coordinating centres and clinical quality registries) and through more efficient systems

Increase recognition by govt and community of the value to clinical trials

- Clinical trials can be a more cost-effective use of the health care dollar than many of the treatments we currently support
- The recognition of government AND the wider community is critical to realizing the level of investment needed to make real improvements
- Many examples presented today including economic assessment of trials and trial networks

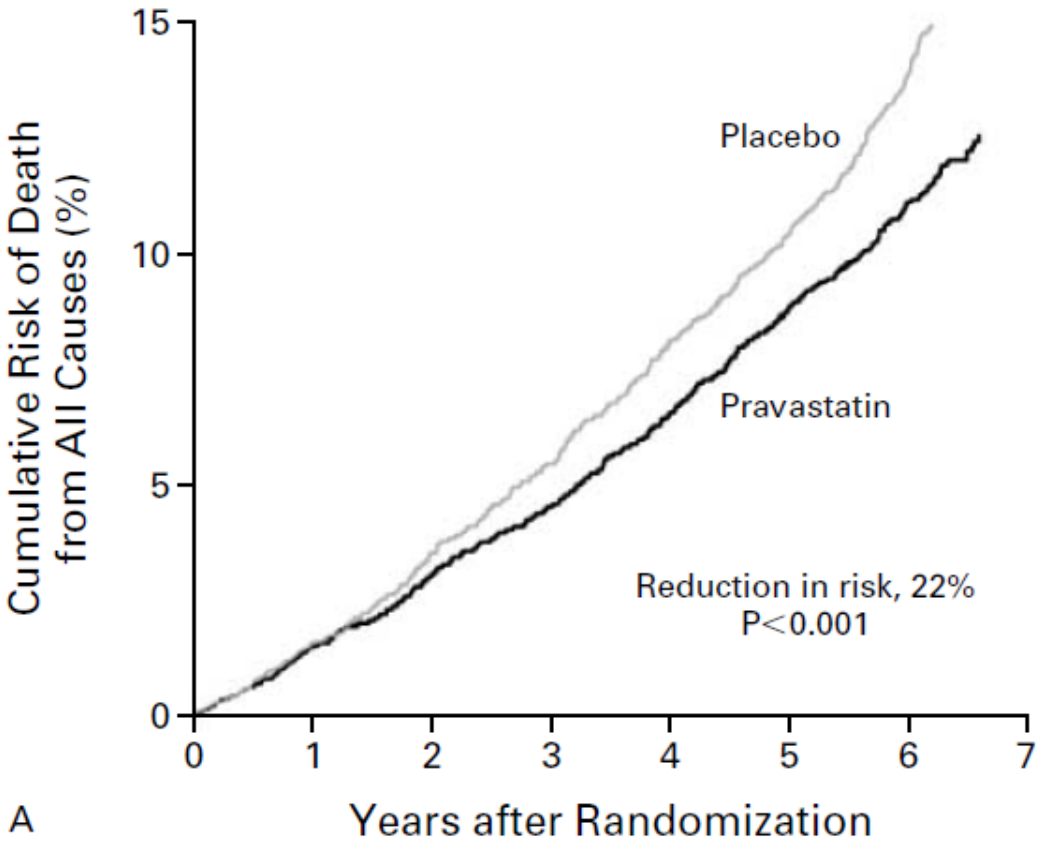
Clinical trials and practice: are they good value for money?

- Additional examples of clinical trial programs and individual clinical trials that are cost effective:
  - NIH program of neurological trials
  - LIPID trial and statins for preventing CVD events
- Examples of clinical trials that are cost saving
  - Aspirin therapy for recurrent VTE
  - Ideal trial for delayed dialysis
  - HRT in post-menopausal women

The LIPID Trial

LIPID Study Group. NEJM 1998; 339:1349-57.

- Pravastatin improved survival in patients with coronary heart disease and with average cholesterol levels
- Trial led directly to change in Australian guidelines and in Pharmaceutical Benefits Scheme
- Significant impact on international guidelines
- Estimated cost-effectiveness $6,300 per LY gained



Cost-effectiveness of clinical trials

- LIPID Study
  - Cost of trial / follow-up ~$40 million
  - Additional QALYS at $6300 per LY with trial impacting on treatment 10s of 1,000s
  - Cost per QALY < $7,000

Lancet 2002; 359: 1379-1387

- Return on investment for a program of controlled trials in US NIH program on neurological disorders and stroke was
  - 28 trials at a cost of $335 million
  - Additional 470,000 QALYs at a cost of $3.6 billion
  - Cost per QALY = $7,700

Lancet 2006; 367: 1319-27.

Aspirin for Preventing the Recurrence of Venous Thromboembolism

Outcome and Study	Placebo	Aspirin	Hazard Ratio (95% CI)	P Value	P Value for Heterogeneity
	no. of events/total no. of patients				
Venous thromboembolism					0.42
ASPIRE	73/411	57/411	0.74 (0.52–1.05)	0.09	
WARFASA	43/197	28/205	0.58 (0.36–0.93)	0.02	
Pooled	116/608	85/616	0.68 (0.51–0.90)	0.007	
Major vascular events					0.96
ASPIRE	88/411	62/411	0.66 (0.48–0.92)	0.01	
WARFASA	48/197	36/205	0.67 (0.43–1.03)	0.06	
Pooled	136/608	98/616	0.66 (0.51–0.86)	0.002	
Clinically relevant bleeding					0.50
ASPIRE	8/411	14/411	1.72 (0.72–4.11)	0.22	
WARFASA	4/197	4/205	0.98 (0.24–3.96)	0.97	
Pooled	12/608	18/616	1.47 (0.70–3.08)	0.31	

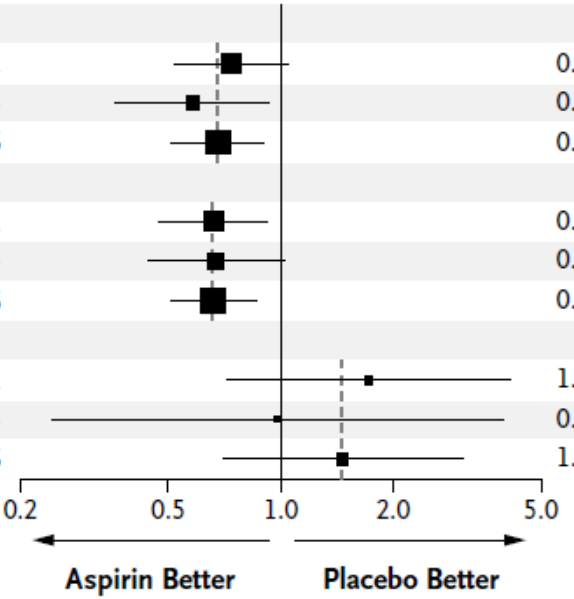


Figure 2. Hazard Ratios for Venous Thromboembolism, Major Vascular Events, and Clinically Relevant Bleeding.

Aspirin prevents about one third of recurrent thrombotic events: for every 1000 patients treated for 1 year, aspirin can be expected to prevent about 20 to 30 episodes of recurrent major thrombotic events at the cost of about 3 significant bleeding episodes.

Are these trials cost saving?

- Additional health care costs for patients having VTE ~$10,000 per case (in 2008).

- For every 1000 cases treated with aspirin per year
  - 25 fewer recurrent episodes of VTE or other major thrombotic events
  - 3 extra bleeding episodes
  - cost saving of over $200,000.

- Aspirin if used in several thousand patients worldwide with significant savings to the health care system (millions of dollars).

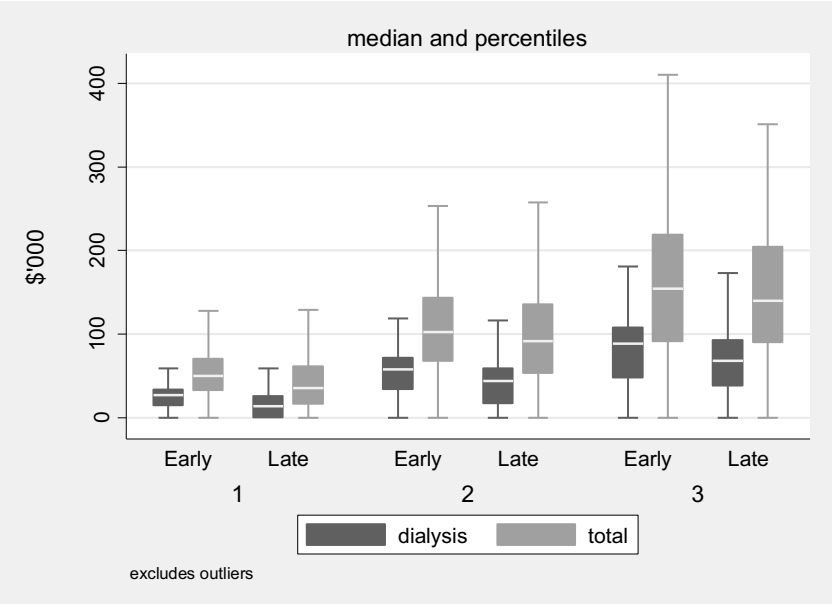
- In this context the cost of the ASPIRE trial itself ($4.5 M) is likely to have been recouped within 1 to 2 years.

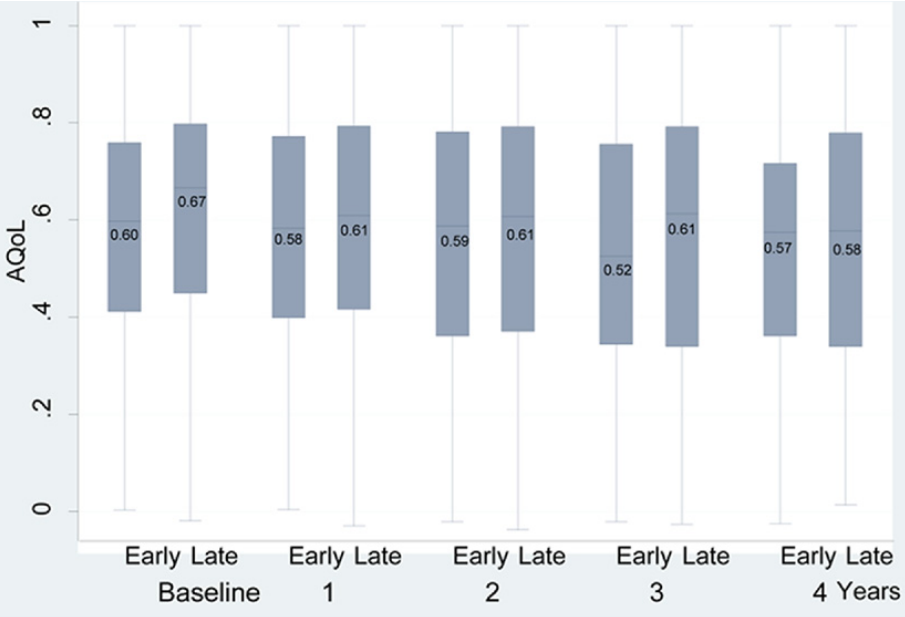
Early vs Delayed Dialysis in CKD

Within-trial cost-effectiveness: IDEAL

Costs: Additional $18,715 pp with early start (95%CI $3,162 to $43,021)

Outcomes: Additional 0.09 QALYs with late start group n/s (95% CI, -0.12 to 0.31)





Am J Kidney Dis 2011;57(5):711-15

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Economic benefit of the trial

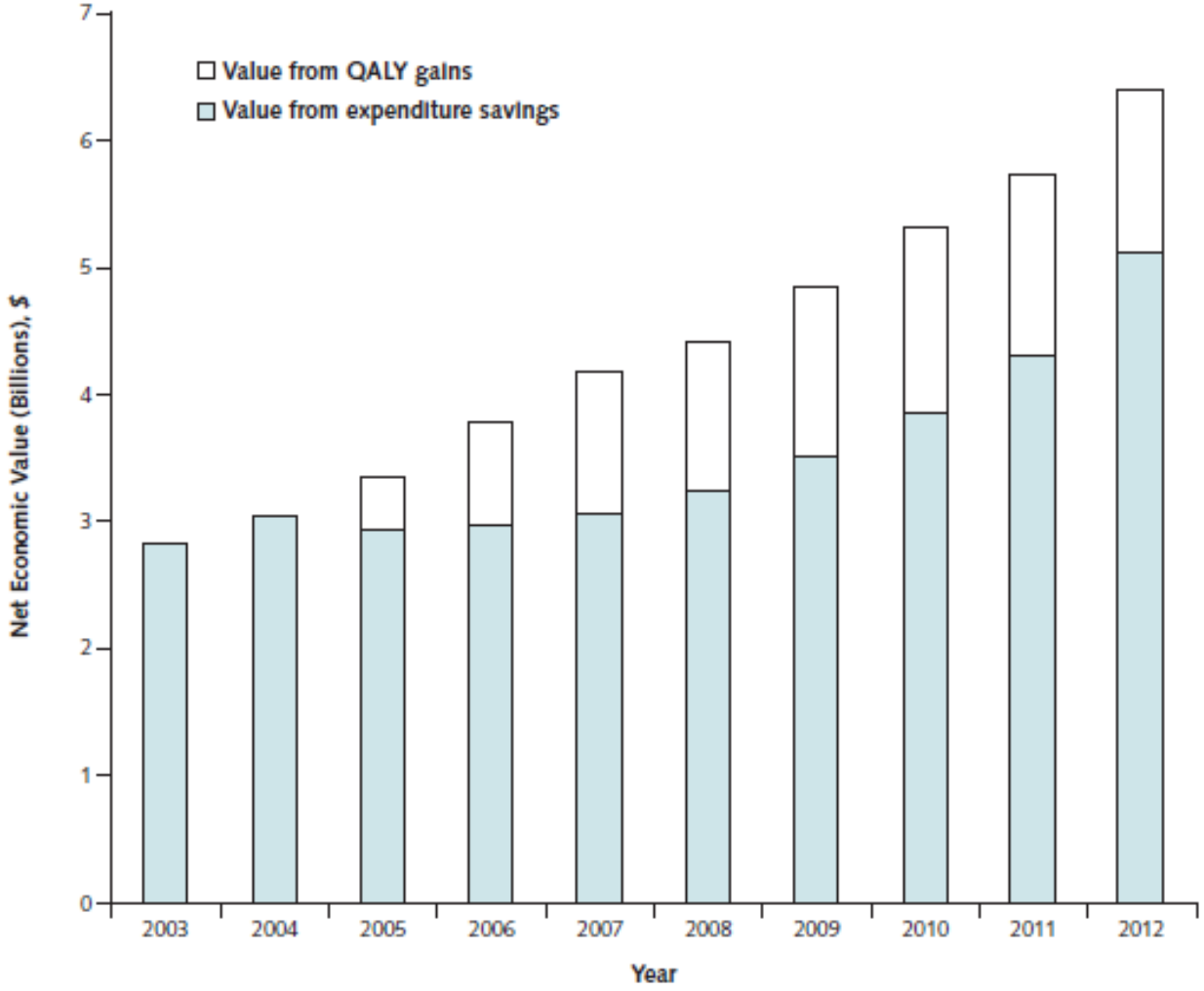
- Cost of IDEAL trial AU$8M
- Outcomes:
  - Cost savings through delayed start dialysis
  - AU$18,715 per patient x 1500 new patients / year
  - If change in practice only applied to 50% of new patients = savings >AU$14M in one year
  - Additional quality adjusted life year (QALY) gains

Economic return from the Women's Health Initiative (E+P) RCT

- One of NIH's most expensive trials
  - (US$260 million in 2012 dollars)
- Hypothesis - combined hormone therapy ↓ coronary heart disease, ↓ osteoporosis
- 2002 – Trial stopped: Main findings
  - ↑ coronary heart disease, stroke, pul. embolism
  - ↑ breast cancer risk
  - ↓ colorectal cancer & fractures

JAMA 2002;288:321-333

Net economic return – cost savings and QALY gains



Results: 4.3 M fewer cHT users; 126,000 few breast cancer cases; 76,000 fewer CHD cases, 263,000 more fractures; 145,000 more QALYs.

= Net benefit $37.1 billion

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Choosing clinical trials which will be value for money

- Clinical trials can be shown to be value for money after completion
- But how to prioritise and select planned clinical trials for funding?

Criteria for NHMRC Research Projects

- ***Scientific Quality (50%)***
  - clarity of hypotheses and objectives,
  - strengths and weaknesses of the experimental design and
  - feasibility.
- ***Significance and/or Innovation (25%)***
  - potential to increase knowledge about human health, disease diagnoses, or biology of agents that affect human health,
  - the application of new ideas, procedures or technologies to important topics that will impact human health.
- ***Relevant team quality and capability (25%)***
  - national and international standing of the applicants based on research output (publication record, addresses, altered clinical or research practice
  - Track record is considered in relation to opportunity

Criteria for selecting trials of high value for funding

- Well designed trials of high quality
- Potential to impact on future practice & policy
- Likelihood of success based on team track record and feasibility

These criteria will still require expert review to ensure most important and likely succesful clinical trials are supported

- Good return on investment – expected value of information

Needs a more formal assessment

Value of information analysis

- Evidence from economic evaluations is used to make reimbursement decisions

- There is often a degree of uncertainty around treatment effects, resource use and costs, and quality of life

- Value of information analysis – the maximum that the health system would be willing to pay for additional information, to reduce the uncertainty (and avoid making the wrong decision)

Sculpher M, Claxton K. Establishing the cost-effectiveness of new pharmaceuticals under conditions of uncertainty--when is there sufficient evidence? *Value Health* 2005;**8**(4)**:**433-46.

Value of information analysis

- Rather than considering one trial result considers a range of possible results (based on prior information)
- Can use decision analytic / health economic modelling
- Considers potential impact on practice in terms of extent of uptake and time horizon

Challenges in assumptions made but this process can make these more explicit for decision makers in weighing up value of investing in specific trial

Strategies / Areas for funding trials

- Investigator-initiated trials in high value priority areas
- Consumer and practitioner relevant questions (eg: James Lind Alliance)
- Commissioned studies– govt / funder directed questions
- Govt – Industry funded questions

Specific examples

- Extending evidence base to other populations
- Standard of care studies where there are major variation in practice or practice-evidence gaps
- Evaluating lesser use of expensive therapies (can be can be cheaper than funding the therapy)

Strategies within MRFF and health system

- Support for capacity to undertake high quality clinical trials - clinical trial networks and coordinating centres
- Use of quality clinical registers to identify important priority questions and provide a platform for more efficient trials
- Funding of specific clinical trials tied linked to the health care dollar (see earlier criteria)
- Quality clinical trial metrics embedded in health care system and linked to funding of health care (eg hospital budgets)

Metrics for embedding clinical research in health care (some easy / some hard to measure)

- Participation in clinical research: Numbers (%) of patients in trials / clinical research
- Number and type of clinical trials undertaken
- Timeliness and efficiency of clinical trials research
- Quality of research
  - Type of research design (eg: controlled or not; clinical vs surrogate outcomes)
  - Quality of trial conduct and data
- Impact of research on changing practice and policy in health sector

Metrics for embedding clinical research in health care (cont'd)

- Culture of embedded research in health care
  - Generic consent for research participation
  - Amount of protected time for research
  - Incorporation of research in clinical activities eg MDTs
  - Use of research to inform health policy

- High quality clinical audit activities particularly
  - Clinical quality registry activity
  - Comparative effectiveness studies to define / extend evidence

More timely and efficient clinical trials

- Reduced barriers for timely trials from initiation to completions (ethics, governance, contracts, organisations)
- Monitoring and feedback of trials metrics at site and national levels (including use of trial registers)
- Only requiring marginal costs to be funded (above costs of usual care)

Conclusions

- Keep promoting the value proposition of embedding clinical trials in health care
- Build and maintain capacity in clinical trials workforce and quality clinical registries
- Significantly improve systems for highly efficient trials – of benefit to investigator-initiated and industry sponsored trials
- Incorporate metrics / performance indicators in funding models of health care
- Fund high quality trials linked to expected value of information