

Enhancing the case for research funding with economic evaluation

Retrospective case study: the CRASH trial

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Rationale

- **Problem:** Can fund only proportion of research proposals
- **Solution:** Assess benefits and opportunity cost of competing alternatives on the basis of available evidence
 - Select alternatives that offer best value for money
- **Proposed toolkit:** Economic evaluation
 - Formalise relationship between evidence base and decision problem
 - Show how evidence can translate to information about overall benefits and opportunity cost
 - Current evidence
 - Evidence resulting from proposed research
 - Link research with provision of health care

Rationale

- Economic evaluation used to aid allocation of scarce resources
- Frequently used in health care to prioritise funding of interventions and programmes by the health service
- Benefits: transparency, consistency, accountability

- Same can be applied to research funding
- In fact same should be applied given relationship between research and provision of health care services
 - Benefits of research achieved if results translated into practice
 - Results of research should inform decisions about which interventions to use
 - Address decision uncertainty

Economic evaluation for HTA

- At least 3 conceptually distinct but simultaneous decisions must be made:
 - What intervention should be used in practice given the existing evidence base and the uncertainty surrounding outcomes and resource use?
 - Estimate cost-effectiveness of alternative healthcare programmes
 - Is more evidence required to reduce the consequences of making an incorrect decision about which intervention to adopt?
 - Estimate (maximum) returns to investment in further research
 - Is investment required to get decisions actually implemented into clinical practice?
 - Estimate returns to investment in implementation

How it works

- Utilise mathematical relationships to link together evidence base and describe implications for benefits and opportunity cost of alternatives
- Compare everything in same terms
- Outline what current evidence supports
- Assess cost of uncertainty
- Outline what impact additional evidence could have
- Key issue: how to communicate all this in a way that benefits users
 - Is the added value lost in translation of simply not valued by users?
 - How much expertise can be expected of users?
 - Can the results be provided in a timely manner?

Retrospective case study

- Decision problem: Should steroids be given in the treatment of acute severe brain injury?
 - Incidence of ~ 15 per 100,000 population
 - 9,000+ per year in UK
- Current (1997) practice variable
 - ~12% treated with steroids
 - What does current evidence support?
 - What is required to change practice?
- Clinical benefits of steroids uncertain
 - Is further research required?
 - If so, should research be prioritised?
 - Generic intervention demanding of public research funds

Original bid:

Made case for further research on basis of uncertain benefits

Assumed research would eliminate variation in practice and identify optimal treatment

Synthesis of pre-CRASH evidence

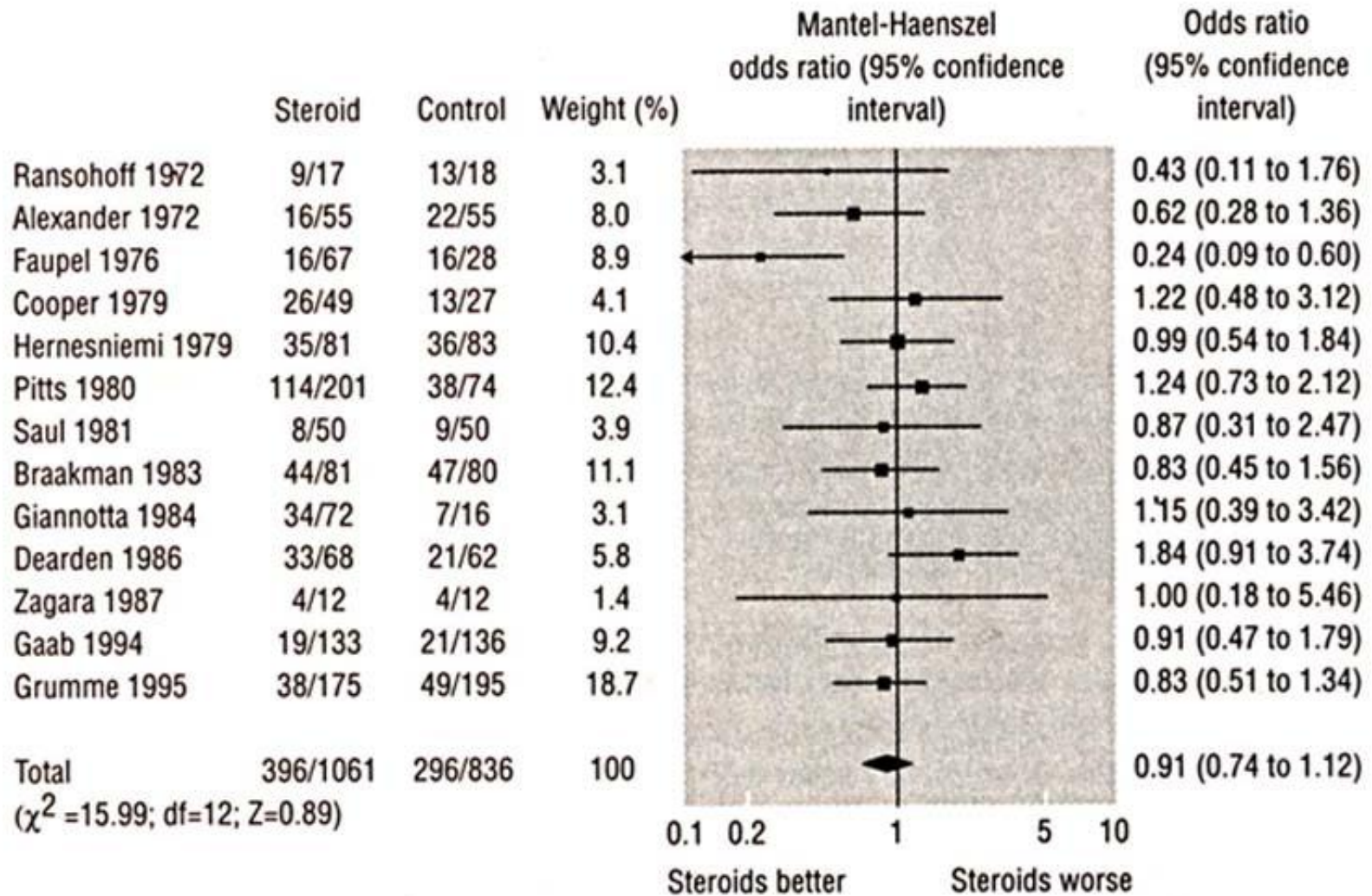


Fig 1 Summary odds ratio for death at end of study **OR death = 0.91 (0.74 to 1.12)**

Case study - CRASH

Evidence

Disease burden of all head injury:
Affected, # Deaths, # Disabled

Variable corticosteroid use in
current practice

Meta-analysis: 2% reduction in risk of
death from 39% to 37% (CI -6% to +2%)

International trial with 15% baseline risk
of death, 43% risk of disability

Case for support

2% reduction in risk of death from 15% to 13% would prevent 10,000
deaths and 10,000 disability per 500,000 treated for significant head injury

Power calculation indicates sample size of 20,000

Value of evidence

Identify cheap, practicable intervention to prevent death and disability
OR
Protect 1,000s from unnecessary treatment

Establish network for future studies

Case study - CRASH

- Huge numbers of lives lost and disability as a result of brain injury
- Uncertain potential for corticosteroids to prevent death and disability

OR death	Prob of occurrence	Relative # deaths per 100	UK deaths over 5yrs:		Best treatment choice	Cost of uncertainty in # of deaths by incorrect treatment choice:	
			Steroids	No steroids		Steroids	No steroids
0.730	10%	-7	13,681	16,849	Steroids	0	3,168
0.819	15%	-4	14,582	16,600	Steroids	0	2,018
0.887	25%	-3	15,078	16,299	Steroids	0	1,221
0.961	25%	-1	15,572	15,973	Steroids	0	401
1.038	15%	+1	16,028	15,646	No steroids	382	0
1.159	10%	+3	16,673	15,185	No steroids	1,488	0

- Existing evidence seemingly inconclusive
 - In terms of statistical significance
 - In making a persuasive case for or against use of steroids
 - Reason behind variable use of steroids to treat brain injury?

What economic evaluation adds

- Health outcomes not fully captured by single clinical endpoint of mortality
 - Consider quality of life/morbidity in survivors
- Resources required to provide steroids could have been used to provide alternative treatments
 - Opportunity cost (benefit) of additional (released) resources
- Characterise decision uncertainty
 - \neq uncertainty in mortality benefit
 - Identify drivers of decision uncertainty
 - Characterise benefits of research in terms of expected health outcomes from decision to use steroids

Evidence synthesis of pre-CRASH trials

- 16 trials report mortality endpoint at end of follow-up
- 7 trials report Glasgow Outcome Scale (GOS) outcomes:
(1) dead, (2) vegetative, (3) severe disability, (4) moderate disability, (5) good recovery
- 2 additional trials report dead, vegetative and severe disability combined

Employing a Bayesian random effects meta-analysis:

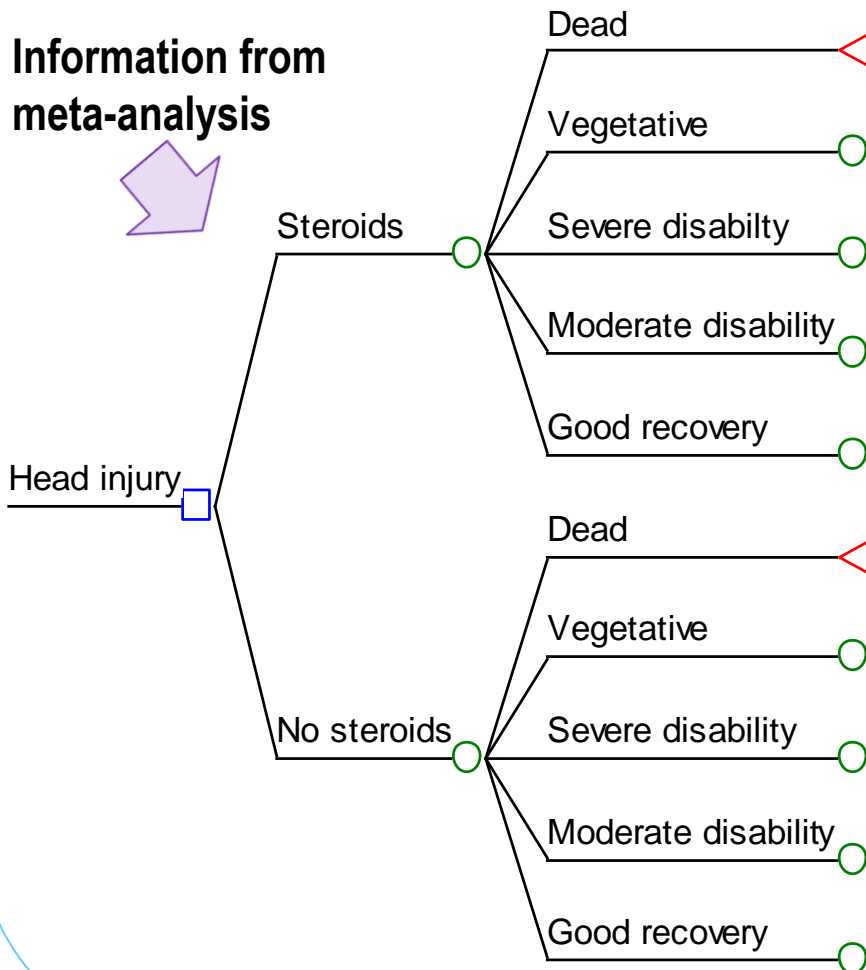
Reported in BMJ (1997)*

OR dead	0.93 (0.71, 1.19)	0.91 (0.74, 1.12)
OR dead, veg, severe	1.06 (0.81, 1.38)	
OR dead, veg, severe, moderate	0.95 (0.70, 1.31)	0.90 (0.72, 1.11)

*** 2 trials not picked up (dated 1980s) , fixed effects model**

Economic evaluation

Information from meta-analysis



Translate clinical outcomes to overall impact on patient health using additional evidence on LE and QoL

Assess health service resource implications of clinical outcomes using additional evidence on costs

Results:
Information on size of patient population and variation in clinical practice used to compare actual and potential total costs and benefits

Combined impact of uncertainty in all evidence

Added value: health impact

- Partial characterisation of impact on health and cost of uncertainty
 - Focus on odds ratio for death

Outcome	Proportion of patients		LE (yrs)	HRQoL	QALYs	Cost of rehab	Annual care costs
	Steroids	No steroids					
Dead	0.335	0.353	0	0.00	0.00	£0	£0
Vegetative	0.048	0.038	7	0.08	0.56	£0	£45,450
Sev disabled	0.135	0.107	15	0.26	3.24	£108,874	£45,450
Mod disabled	0.116	0.121	22	0.63	10.51	£19,575	£7,472
Recovered	0.365	0.380	25	0.85	15.39	£19,575	£0

- Omit QALE and health cost of devoting resources to steroids
 - Assume £20,000 spent on providing healthcare produces 1 QALY
- Existing evidence supports range of outcomes with steroids
 - -0.10 (-0.91 to 0.65) additional QALYs
 - £10,000 (-£40,000 to £62,000) additional resources

Added value: cost of uncertainty

- £10,000 additional resources for steroids could be used to provide alternative healthcare
 - Opportunity cost of 0.5 QALYs

OR DVS	Prob given current evidence	Relative QALYs	Net benefits in QALYs (£,000s):		Best choice	Cost of uncertainty QALYs (£,000s):	
			Steroids	No steroids		Steroids	No steroids
0.831	10%	+0.7	1.96 (39.2)	1.51 (30.2)	S	0	0.45 (9.0)
0.936	15%	+0.3	1.43 (28.6)	1.71 (34.2)	No S	0.28 (5.6)	0
1.023	25%	-0.0	1.08 (21.6)	1.87 (37.4)	No S	0.79 (15.8)	0
1.128	25%	-0.3	0.64 (12.8)	2.09 (41.8)	No S	1.45 (29.0)	0
1.257	15%	-0.7	0.04 (0.8)	2.26 (45.2)	No S	2.22 (44.4)	0
1.485	10%	-1.1	-1.07 (-21.4)	2.47 (49.4)	No S	3.54 (70.8)	0

Added value: Value of research

- What is the cost of uncertainty?
 - Probability that wrong decision is made on current evidence = 15%
 - If decision is wrong, average loss of 0.19 QALYs per each of the 9,000 patients treated each year in the UK
 - Over 5 yrs equivalent to 3,400 QALYs (£68 million)
- What evidence could reduce the cost of uncertainty?
 - Examine contribution of each component to overall uncertainty
 - treatment effect on number left dead, vegetative or severe is key
 - Further research on number of deaths insufficient as decision uncertainty relates to quality adjusted life expectancy health costs of survivors
- How much evidence is required?

How much evidence?

- Benefits of research
 - Reduction in probability of wrong decision and consequences
- Fixed cost of research, opportunity cost of research
 - Enrolment in trial changes probability of receiving steroids from 0.12 to 0.5
 - Each additional patient receiving steroids expected to experience worse health and divert resources from other activities
- Assessing value of CRASH proposal (20,000 patients) indicates that value was expected to exceed cost
 - BUT assumes that results translate to zero variation in steroid use
 - How large a trial is required to change practice?
 - Would other means to change practice represent better value for money?
 - How capture benefit of network for future trials?

Benefits to users

- **Timeliness**
 - Minimal additional searching and data requirements for CRASH
 - Additional data relevant to research proposal regardless of method used
 - Other case studies could be more complex
 - Potential to make use of existing economic evaluations (e.g. NICE)
- **Interpretation of results**
 - Many potential users very uncomfortable with
 - Opportunity cost of resources
 - Net benefits
- **Expertise of users**
 - Awareness of CEA increasing among service providers
 - Driven by usage (NICE)
 - Not yet popular with research funders

Care required in language

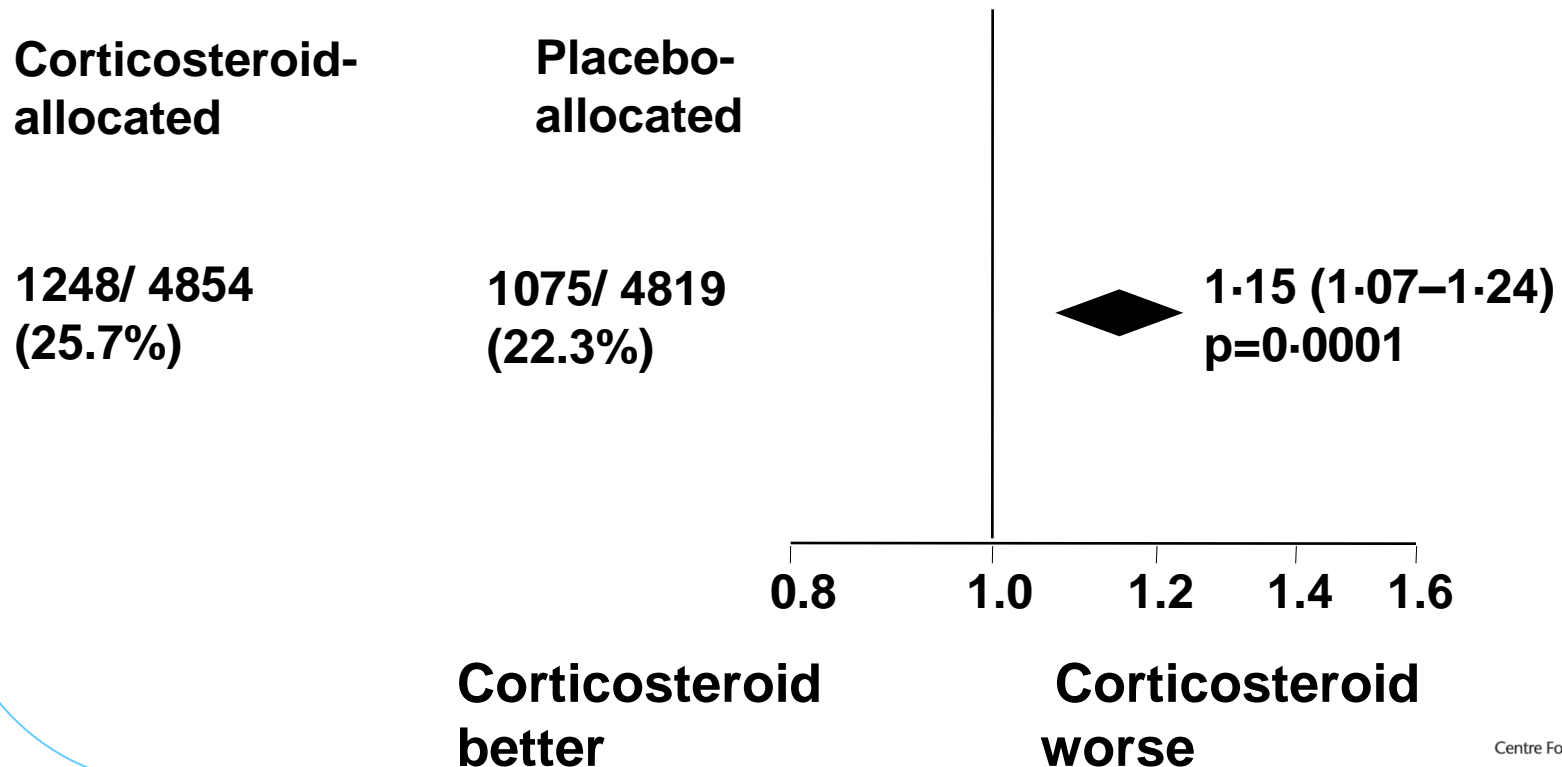
Conclusions

- Case study based on trial which was successfully funded given informal demonstration of its need
- Formal methods led to same conclusion about need for research
 - Fuller characterisation of impact on overall health
 - Different conclusion about support for steroids in current evidence
 - Added value in terms of directing research to most valuable outcome
- Many proposals put forward that are unsuccessful
- Formal methods provide means to quantify benefits of all research in same terms of overall health
 - Demonstrate that proposal addresses key uncertainty
 - Prioritise research funding to studies offering greatest improvement in health
 - Could characterise cost of changing practice with large trial

Post script: CRASH results

- Trial stopped early: analysis after recruiting 10,000 patients indicated that steroids were harmful

Relative risk death at 6 months (95% CI)



Actual cost of uncertainty/variation in practice

A CRASH landing in severe head injury

THE LANCET

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“The administration of corticosteroids to brain-injured patients has seemingly caused more than 10 000 deaths during the 1980s and earlier.”

Retrospective approach

- Case study initiated to see whether formal methods would give the 'right answer'
- Potential users comforted that value of CRASH predicted/confirmed by formal approach
 - VOI accords with their own judgement/priors
 - BUT added value of applying formal methods only if relative ranking of research proposals differs between informal and formal approach
- CRASH produced unexpected results
 - Reduction in cost of uncertainty achieved \neq predicted value
- Cannot judge any method by whether it predicts actual results of trial