Value of Information for CRASH

Claire McKenna, Susan Griffin, Karl Claxton

Centre for Health Economics, University of York, UK

Purpose and principles

- Demonstrate the principles of what assessments are required when considering the need for additional evidence and the priority of proposed research
- Illustrate how these assessments might be informed by quantitative analysis based on standard methods of systematic review and meta-analysis
- Distinguish between the value of additional evidence and the value of implementing the findings of existing research
- Expected value of information analysis can be used to identify the need for further research to reduce uncertainty in decision making
- Are the expected health benefits of additional evidence sufficient to regard CRASH as potentially worthwhile?
  → Should it have been prioritized over other research topics that could have been commissioned with the same resources?

CHE
Centre For Health Economics

What assessments are needed?

- Value of evidence and the value of implementation
  - Improve patient outcomes by resolving uncertainty in the existing evidence about the effectiveness of the interventions available
  - How much does the uncertainty matter?
  - Scale of the consequences of uncertainty
  - Will the findings of research be implemented into clinical practice?

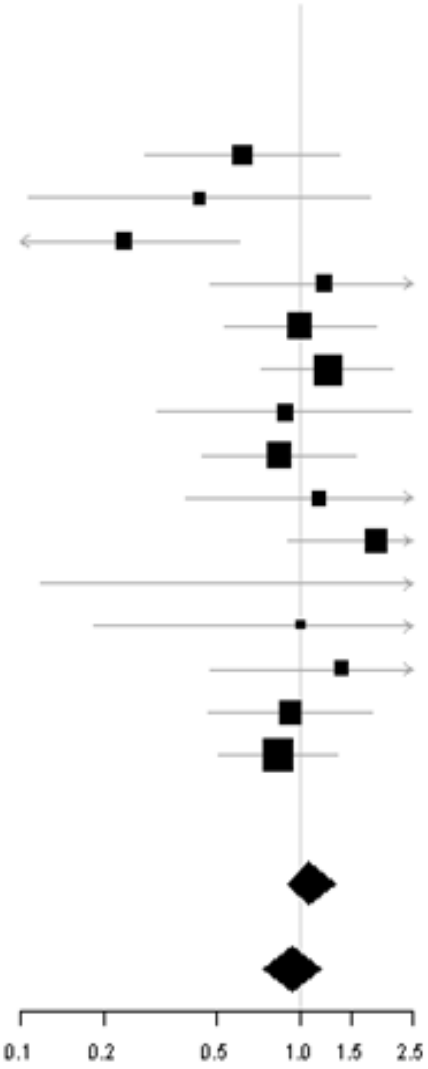
- Minimum clinical difference (MCD) in outcomes required
  - Clinical practice is unlikely to change without it (effect size)
  - Other aspects of outcome not captured in the primary endpoint
  - Significant resource, system or patient cost implications

CHE
Centre For Health Economics

Evidence before CRASH: Mortality endpoint

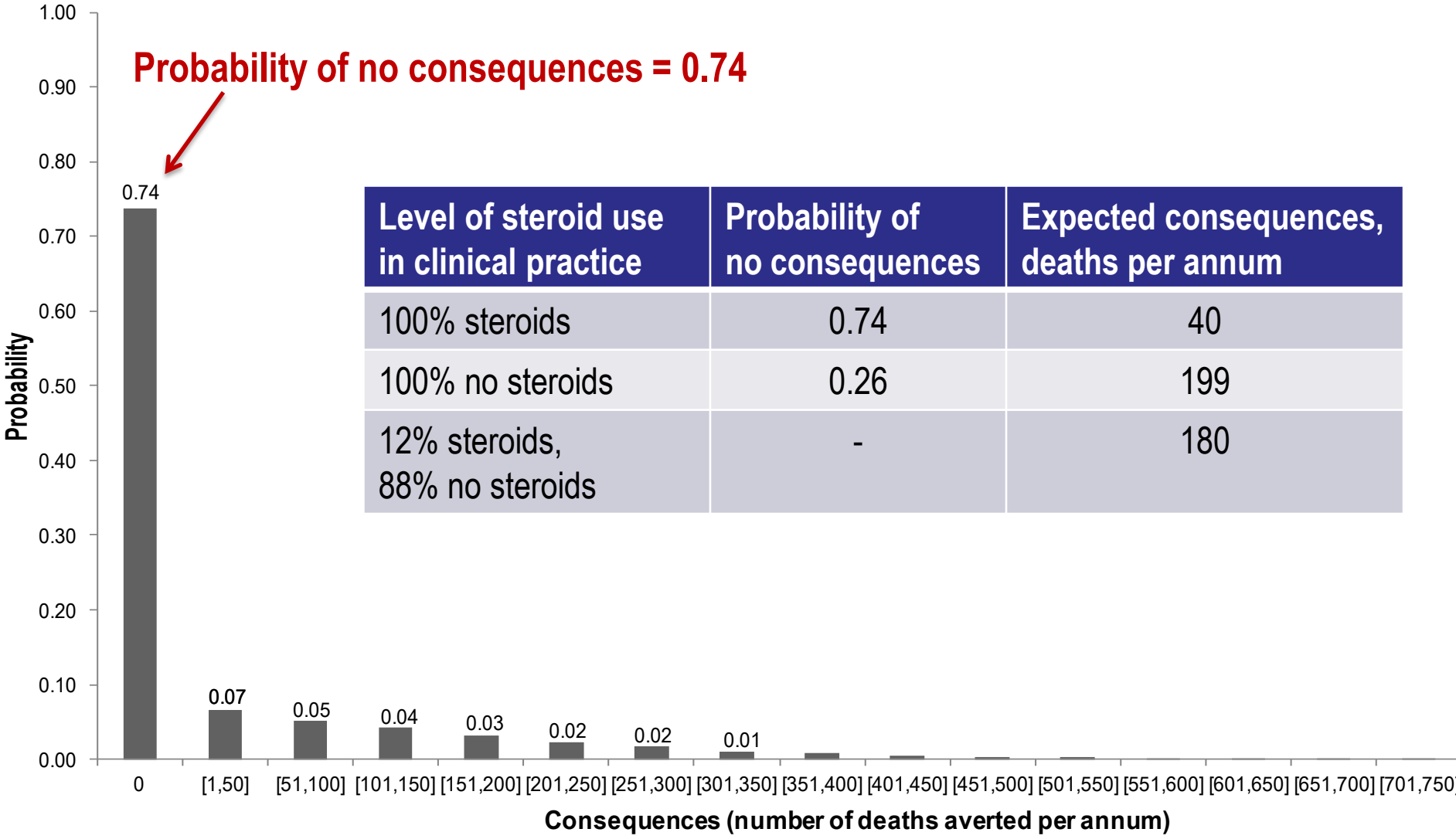
Meta-analysis of existing evidence

Study	Steroids deaths/total	Control deaths/total	OR	95%CI
Alexander 1972	16/55	22/55	0.62	(0.28 - 1.36)
Ransohoff 1972	9/17	13/18	0.43	(0.11 - 1.76)
Faupel 1976	16/67	16/28	0.24	(0.09 - 0.60)
Cooper 1979	26/49	13/27	1.22	(0.48 - 3.12)
Hernesniemi 1979	35/81	36/83	0.99	(0.54 - 1.84)
Pitts 1980	114/201	38/74	1.24	(0.73 - 2.12)
Saul 1981	8/50	9/50	0.87	(0.31 - 2.47)
Braakman 1983	44/81	47/80	0.83	(0.45 - 1.56)
Giannotta 1984	34/72	7/16	1.15	(0.39 - 3.42)
Dearden 1986	33/68	21/62	1.84	(0.91 - 3.74)
Chacon 1987	1.5/6	0.5/6	3.67	(0.12 -113.74)
Zagara 1987	4/12	4/12	1.00	(0.18 - 5.46)
Stubbs 1989	13/104	5/54	1.40	(0.47 - 4.16)
Gaab 1994	19/133	21/136	0.91	(0.47 - 1.79)
Grumme 1995	38/175	49/195	0.83	(0.51 - 1.34)
Zarate 1995	0/30	0/30		
Summary OR (fixed effect analysis)			**1.07**	**(0.89 - 1.28)**
Summary OR (random effects analysis)			**0.93**	**(0.71 - 1.18)**



Odds ratio for death with steroids

Consequences of uncertainty in no. of deaths per annum



Level of steroid use in clinical practice	Probability of no consequences	Expected consequences, deaths per annum
100% steroids	0.74	40
100% no steroids	0.26	199
12% steroids, 88% no steroids	-	180

Primary endpoint linked to other outcomes

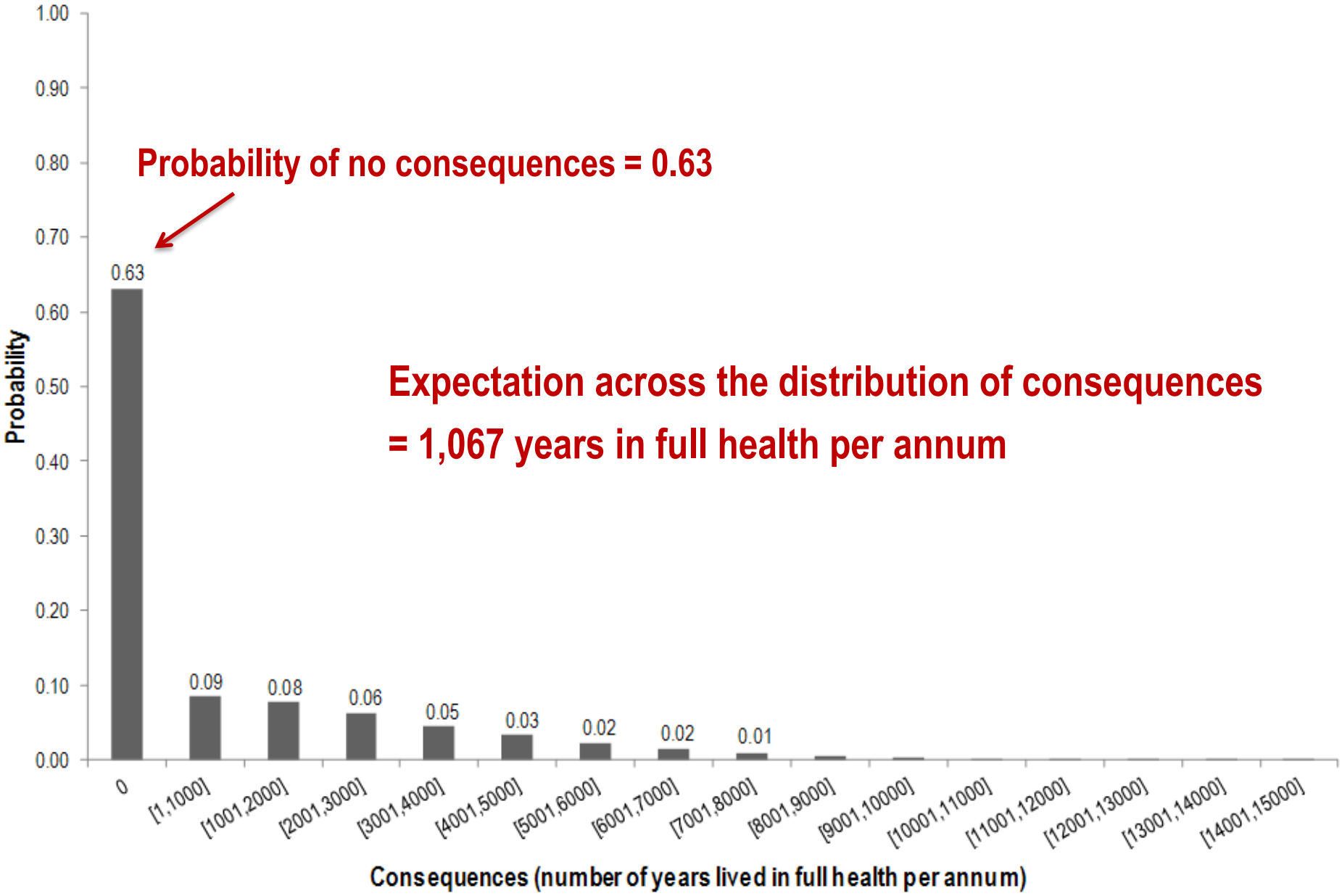
Before CRASH:

Glasgow Outcome Scale outcome	Percentage of individuals (95% CrI) by treatment	
	Steroids	No steroids
Dead	33.5 (22.8, 45.2)	35.3 (24.8, 46.9)
Vegetative	4.8 (2.8, 7.5)	3.8 (2.4, 5.9)
Severe disability	13.5 (8.3, 20.1)	10.7 (7.1, 15.8)
Moderate disability	11.6 (8.6, 14.8)	12.1 (9.2, 15.1)
Good recovery	36.5 (28.1, 44.8)	38.0 (30.1, 45.6)

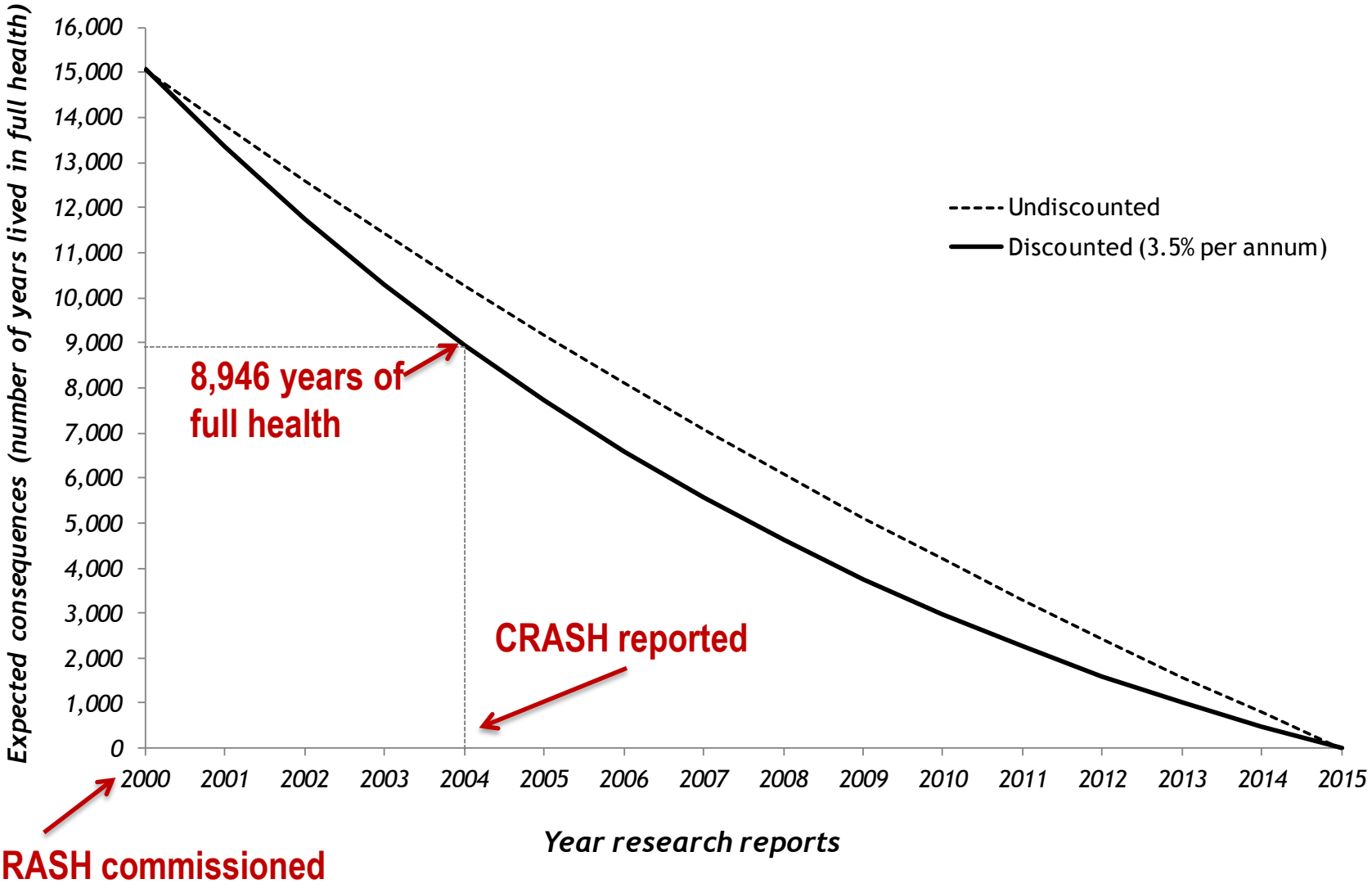
- Life expectancy given survival and estimates of quality of life associated with GOS outcomes → **Equivalent years of full health**

- OR for death, vegetative and severely disabled combined = 1.10 (0.81, 1.53)

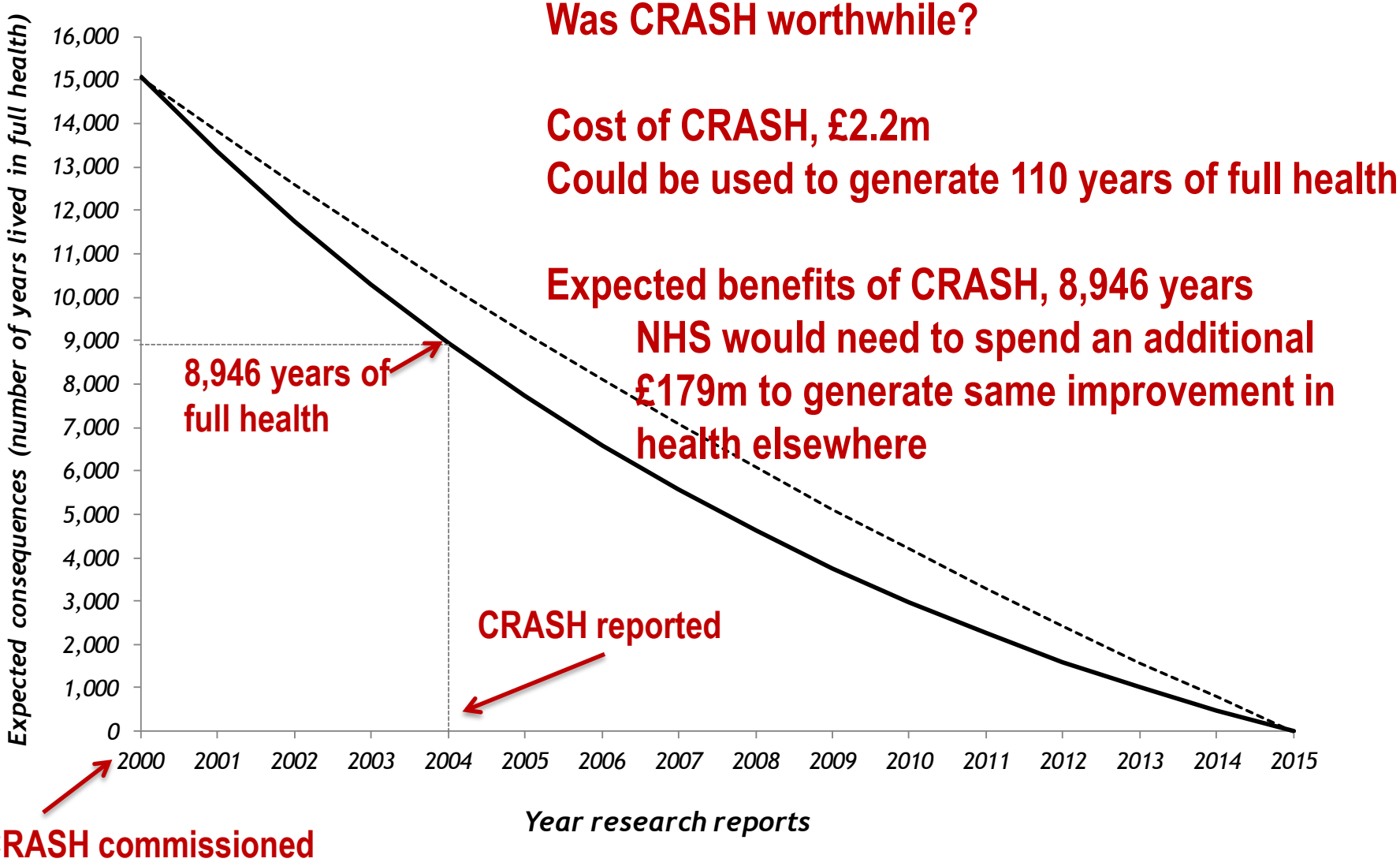
Primary endpoint linked to other outcomes



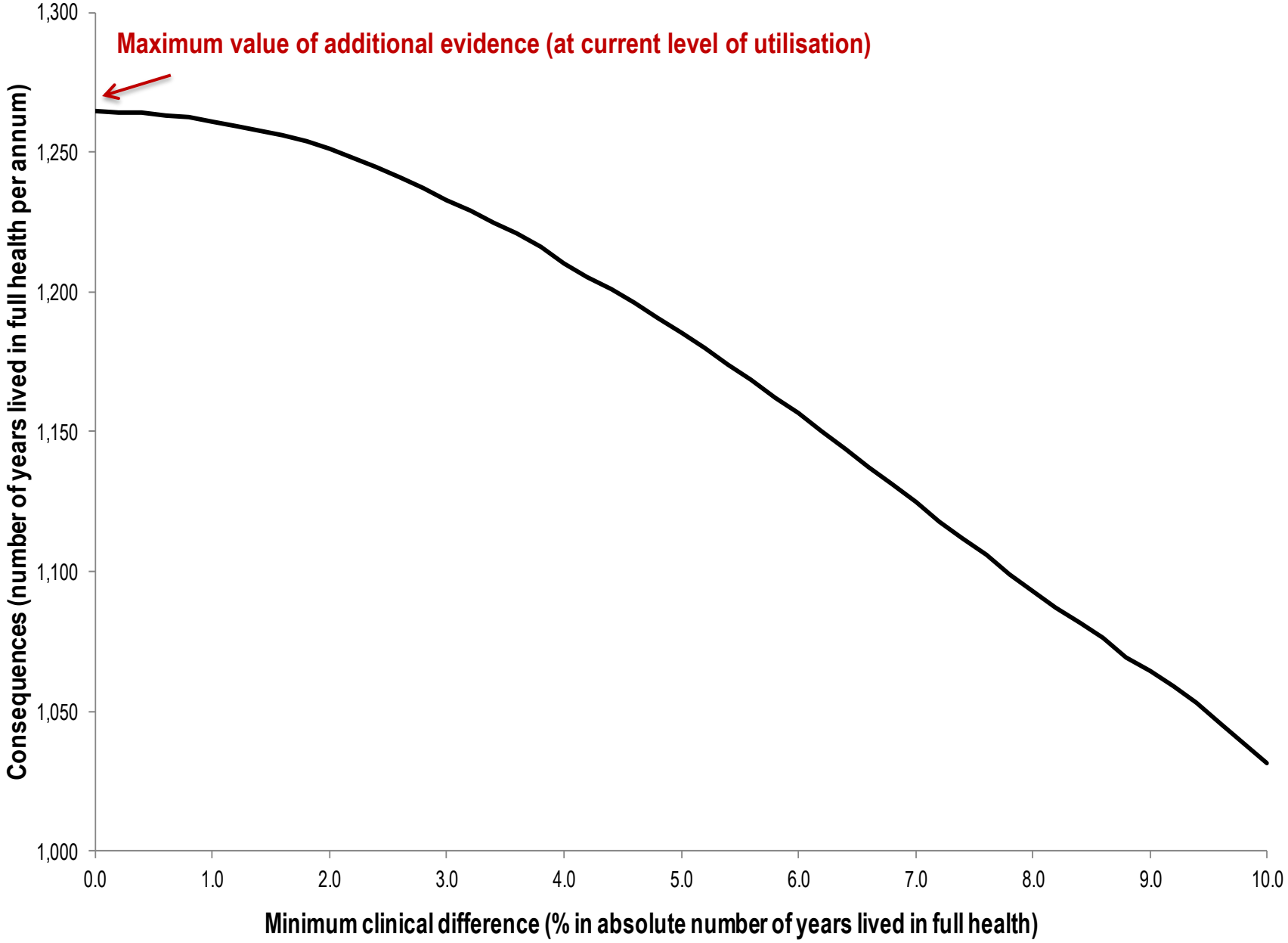
Value of additional evidence



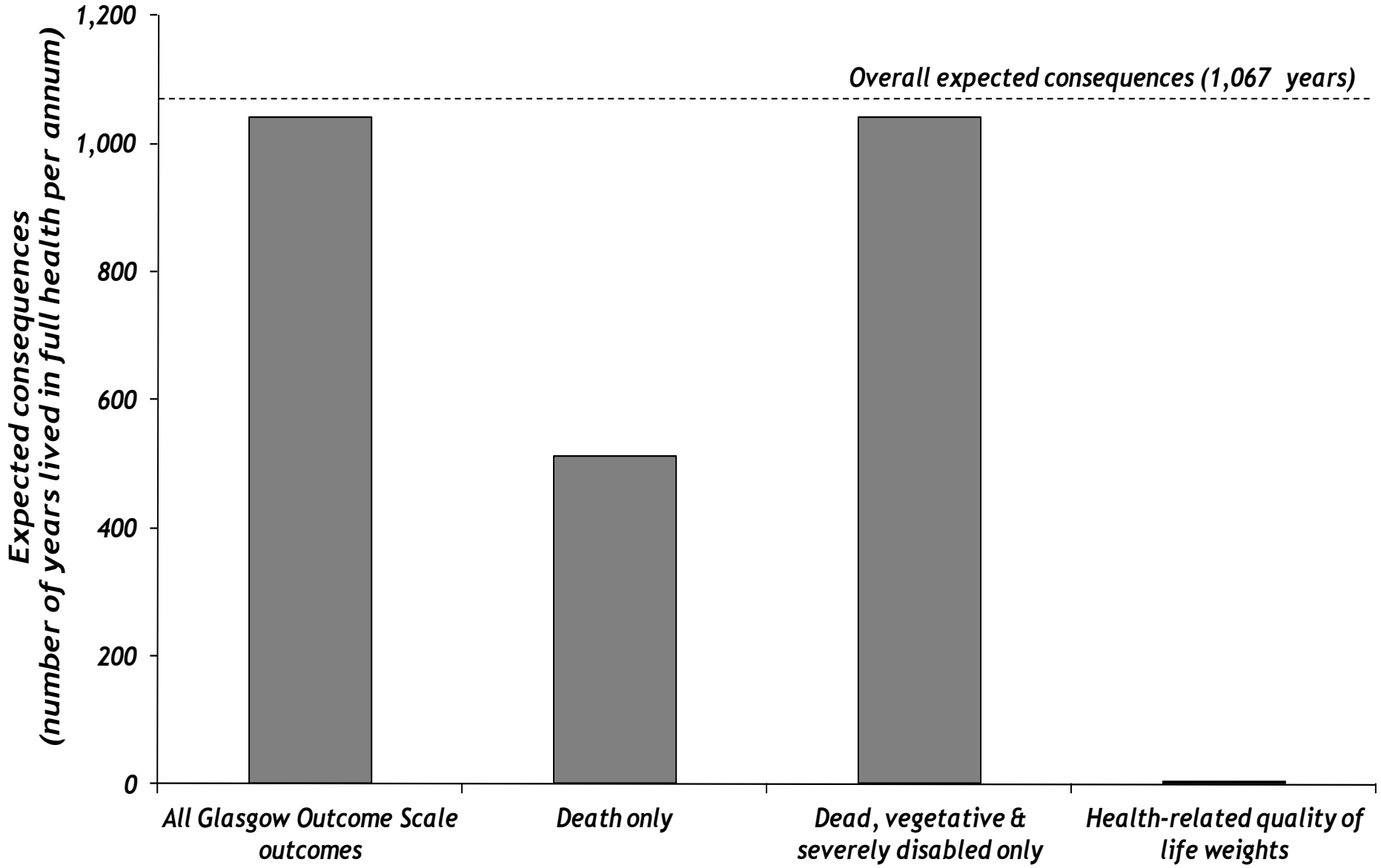
Value of additional evidence



Minimum clinical difference in outcomes



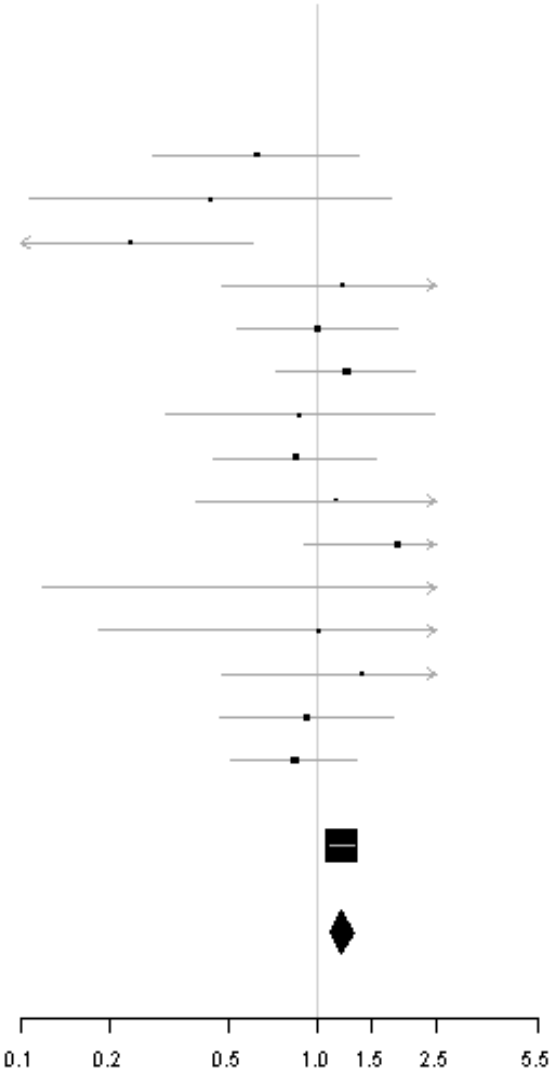
Informing research design



Impact of commissioned research: CRASH

Meta-analysis of existing evidence

Study	Steroids deaths/total	Control deaths/total	OR	95%CI
Alexander 1972	16/55	22/55	0.62	(0.28 - 1.36)
Ransohoff 1972	9/17	13/18	0.43	(0.11 - 1.76)
Faupel 1976	16/67	16/28	0.24	(0.09 - 0.60)
Cooper 1979	26/49	13/27	1.22	(0.48 - 3.12)
Hernesniemi 1979	35/81	36/83	0.99	(0.54 - 1.84)
Pitts 1980	114/201	38/74	1.24	(0.73 - 2.12)
Saul 1981	8/50	9/50	0.87	(0.31 - 2.47)
Braakman 1983	44/81	47/80	0.83	(0.45 - 1.56)
Giannotta 1984	34/72	7/16	1.15	(0.39 - 3.42)
Dearden 1986	33/68	21/62	1.84	(0.91 - 3.74)
Chacon 1987	1.5/6	0.5/6	3.67	(0.12 -113.74)
Zagara 1987	4/12	4/12	1.00	(0.18 - 5.46)
Stubbs 1989	13/104	5/54	1.40	(0.47 - 4.16)
Gaab 1994	19/133	21/136	0.91	(0.47 - 1.79)
Grumme 1995	38/175	49/195	0.83	(0.51 - 1.34)
Zarate 1995	0/30	0/30		
CRASH 2005	1248/4854	1075/4819	1.21	(1.10 - 1.32)
Summary OR			**1.21**	**(1.10 - 1.33)**



Odds ratio for death with steroids

Impact of commissioned research: CRASH

- Steroids should not be used in clinical practice
  - The likelihood that steroids improves mortality is effectively zero (<0.0001)
  - The likelihood that steroids improves survival and quality of life is almost zero (probability of 0.005)

- There are no expected benefits of acquiring additional evidence
  - Value of evidence is a maximum of 3.2 years of full health per annum for the population

Discussion

- Sample size for CRASH
  - Use expected value of sample information
  - Was CRASH too big?
  - Does a trial need to be big to persuade change in clinical practice?
    - implementation conditional on a statistically significant result

- Interpretation and synthesis of evidence
  - Implications for expected value of information
  - Relationship between existing evidence and the new trial

  Trial designed for a particular clinical setting