

MONASH University

Business and Economics

Centre for Health Economics



The determinants of PBAC recommendations to fund drugs in Australia: an empirical analysis 1994-2004

Presented by: Anthony Harris
Centre for Health Economics, Monash University

Geoff Chin and Jing Jing Li
Centre for Health Economics, Monash University

Suzanne Hill, WHO

Emily Walkom, University of Newcastle

Funded by NHMRC project grant

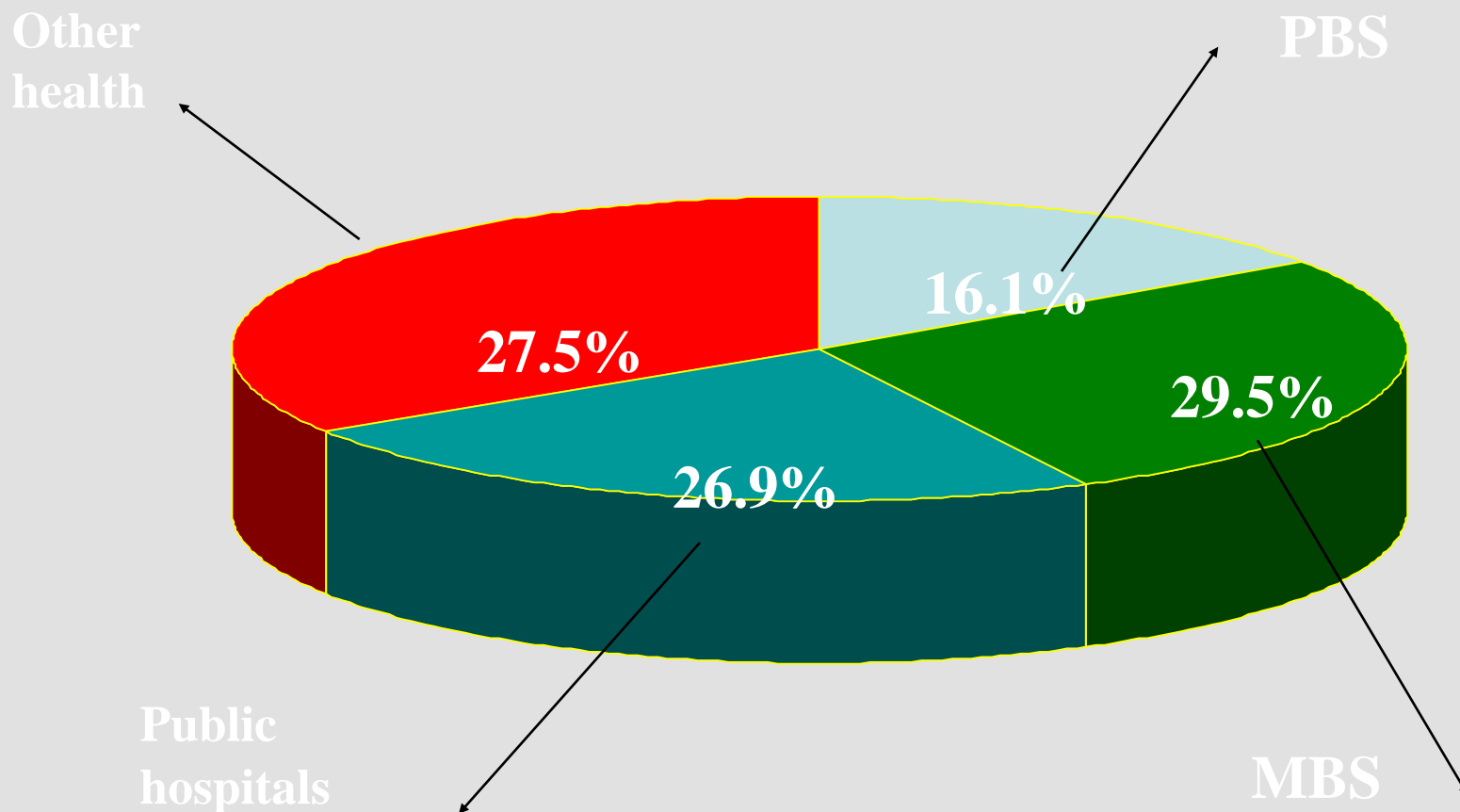
Context to pharmaceutical subsidy decisions in Australia

- **National Health Act 1953 that set up the PBAC sets framework**
 - “For the purpose of deciding whether to recommend to the Minister that a drug ... be made available as pharmaceutical benefits, the Committee shall give consideration to *the effectiveness and cost of therapy involving the use of the drug, ... by comparing the effectiveness and cost of that therapy with that of alternative therapies, whether or not involving the use of other drugs or preparations.*
 - The Minister for Health and Ageing cannot list a medicine on the PBS that has not been recommended by the PBAC.
 - Since 1954 the PBAC has considered comparative effectiveness of a drug prior to subsidy under PBS
 - Since 1992 it has also formally considered value for money
- 1947: 139 life-saving drugs at cost A\$300,000.
- 2005: >650 drugs at cost \$5.8 billion

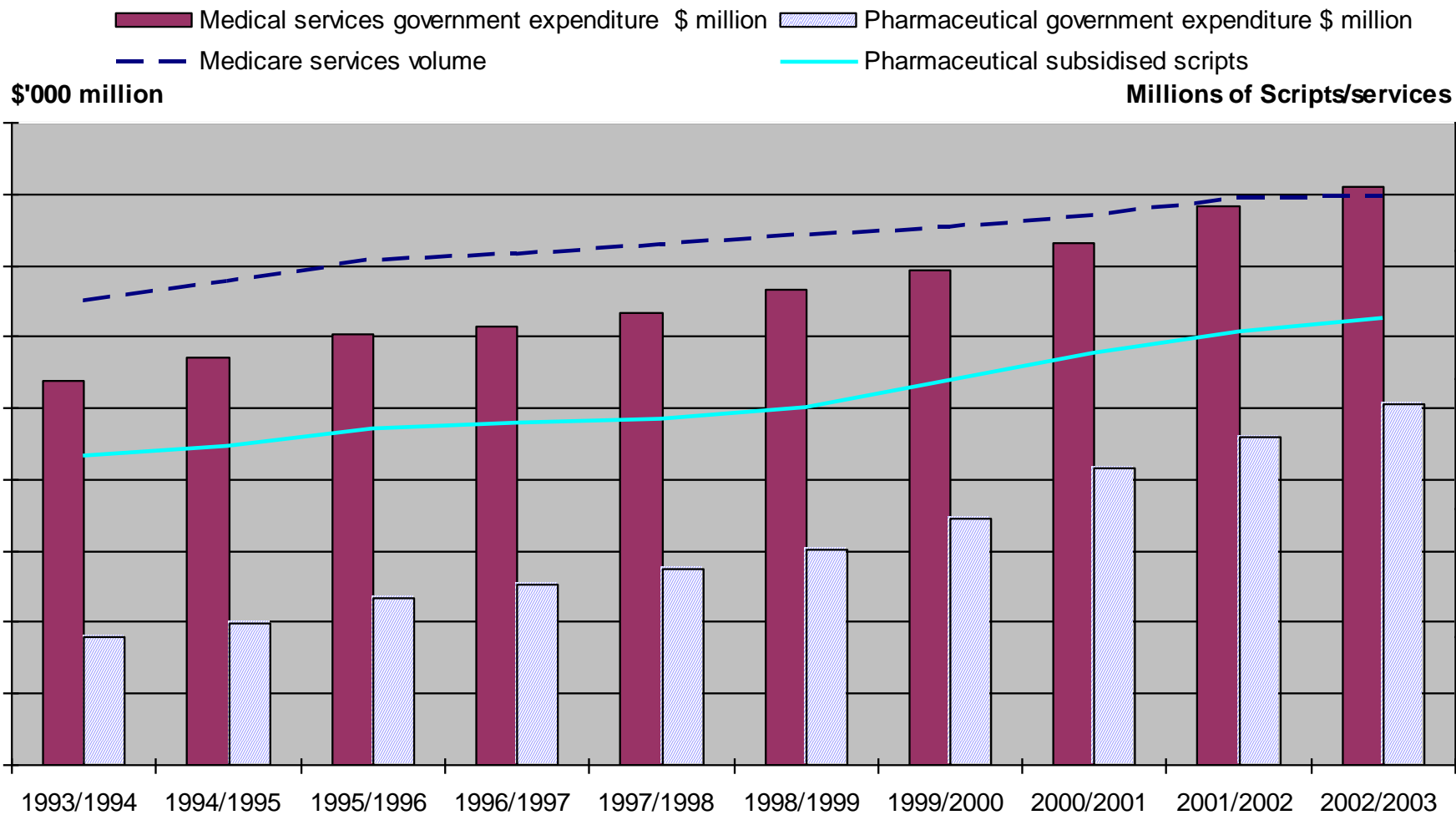
PHARMACEUTICAL EXPENDITURE

- **80% OF THE COST is DIRECTED TOWARDS CONCESSIONAL CARDHOLDERS**
- **PATIENT CONTRIBUTIONS % OF TOTAL COSTS**
 - 19.5% in 90/91,
 - 22.2% in 94/95
 - 17.0% in 01/02
 - 14.2 %in 02/03

Australian Govt Health Expenditure (\$29.7bn) 2002-2003



Government expenditure and volume of medical services and pharmaceuticals in Australia 1993/4 to 2002/3



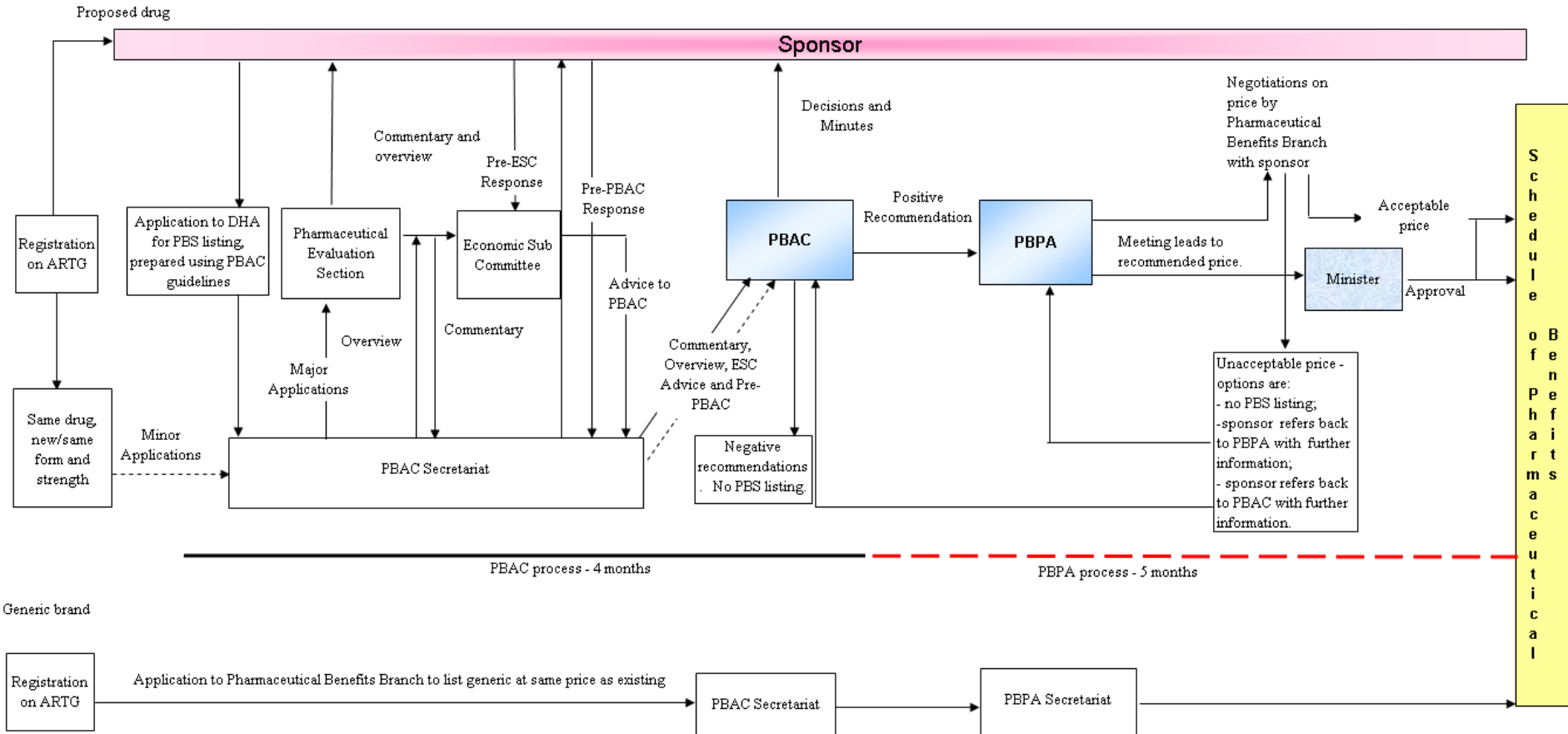
Aims of paper

- 1. To quantify the factors influential in decisions to reimburse drugs on the Pharmaceutical Benefits Scheme in Australia**
- 2. To assess the extent to which confidence in the strength of evidence on effectiveness and costs modifies the influence of cost and cost effectiveness**
- 3. Assess the relevance of other factors not in stated objective**
- 4. Focus on drugs considered on the basis of incremental cost per QALY**

Previous Australian studies on the impact of economics on decision making in drugs

- **George et al (Pharmacoeconomics 2001)** showed that PBAC in the first few years the PBAC had been influenced by economic data
- **Hill Mitchell and Henry in JAMA 2000** emphasized the intensity of the review process and shown that there is considerable uncertainty introduced by the quality of the clinical and economic evidence

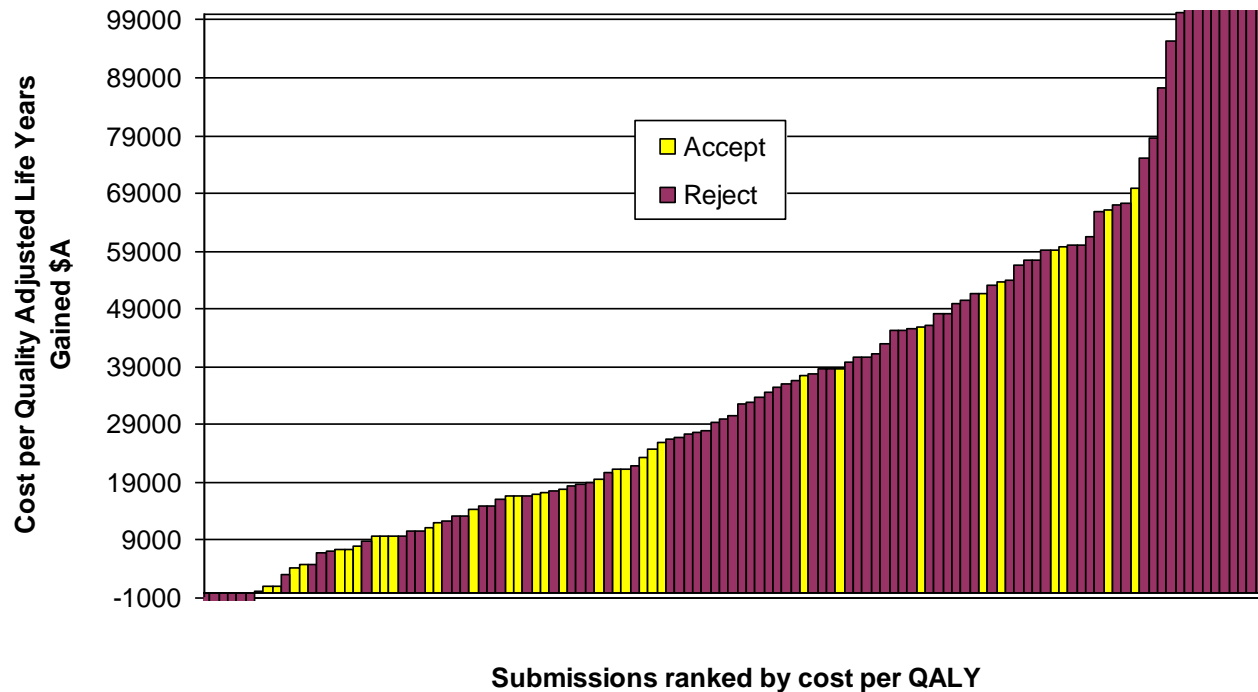
Pharmaceutical Benefits Scheme approval process in Australia



Data

- **There were 858 major submissions to the PBAC between Feb 1994 and Dec 2004.**
- **There were 182 (21%) major submissions that calculate either a cost per QALY or cost life year gained (50% of which 2001-2004)**
- **Of all major submissions Feb 1994 to Dec 2003 37% were recommended by the PBAC to be listed on PBS at the price proposed. Of those with a cost per QALY or LYG 31%**

PBAC recommendations of list at price proposed 1994-2004 Cost per QALY



Influences beyond cost effectiveness: confidence in estimates

- **Evidence of differential effectiveness**
 1. Size of difference in effect
 2. Strength of evidence
 - i. Precision of effect;
 - ii. Level of evidence;
 - iii. Quality of evidence (bias)
 3. Relevance of evidence (population and comparator)
- **Modeling of costs and effects beyond experimental evidence**
 1. Relevance of model structure
 2. Measurement and extrapolation of outcomes beyond experimental evidence
 3. Measurement and extrapolation costs beyond experimental evidence
 4. Precision of net benefits

Other potential modifying influences on decision making

- **Severity of condition**
 - Life threatening
- **Availability of alternative therapies**
- **Cost to patient**
- **Cost to government**
 - Impact on budget
 - Financial risk

Statistical modeling the decision to fund

- **Test the a priori hypothesis that probability of “ a recommendation that a drug be listed on the PBS at the price proposed” determined by *the PBAC view of***
 - Incremental cost per QALY
 - Average utility gain of patients
 - Annual predicted cost to government
 - Highest cost per QALY in sensitivity analysis
 - Severity of condition:
 - > Life threatening illness or not (expected survival <5 years); or
 - > (QALY baseline commentary or HoDAR utility baseline scores)
 - Availability of effective alternatives last line treatment with placebo as accepted comparator
 - **Confidence in clinical claim – strength of evidence**
 - > **Clinical significance, precision, level, quality, relevance**
 - **Confidence in economic claim**
 - > **Model validity, outcome measurement, cost measurement**
 - Resubmission
- **Using probit regression of P.recommend list on these exogenous variables**

Data extraction process

- **Double data extraction on the variables in the statistical model by two teams of experienced evaluators**
- **Primary data - PBAC minutes**
 - Secondary data from Economics Sub-committee advice to PBAC
 - If not definitive then last from Pharmaceutical Evaluation Section Commentary on the submission
- **Consensus achieved on values of items**

Categories of confidence – clinical

Criterion	Items	Levels
Clinical		
Size of effect	1	2 (1= clinically meaningful 0= not)
Precision of effect	0.05<p>0.05	2 (1=sig. 0=not sig.)
Level of evidence	1	3 (3= head to head RCT;2= indirect RCT; 1 =non randomised)
Quality of evidence	<u>12</u>	3 (3=high; 2=moderate; 1=low)
Relevance of evidence	2 comparator & population	2 (1=relevant 0= not)

Categories of confidence –Economic

Economic		
Criterion	Items	Levels
Model validity	1	3 (1=plausible, 2=non critical, 3= critical flaws)
Final health outcome measured accurately	1	3 (1=plausible, 2=non critical, 3= critical flaws)
Cost accuracy	1	3 (1=plausible, 2=non critical, 3= critical flaws)
ICER precision	1	Highest value

12-item Quality of evidence

1	All relevant studies included? Selection bias	Yes/No
2	Randomisation (concealment)	Yes/No/NA
3	Blinding (patients, investigators, assessors)	Yes/No/NA
4	Patient follow-up (ITT), drop-outs properly accounted	Yes/No
5	Baseline characteristics well balanced	Yes/No/NA
6	Dosage regimen appropriate	Yes/No
7	Duration of follow-up sufficient	Yes/No
8	Sample size adequate	Yes/No
9	Acceptable (surrogate/composite) outcomes	Yes/No
10	Method of analysis appropriate	Yes/No
11	Subgroup analysis appropriate	Yes/No/NA
12	Re-analysis of data (post hoc) appropriate	Yes/No/NA
	OVERALL QUALITY	High/Moderate/Low



Rule

For an overall quality index to be rated
“high”:

Item

- | | | | |
|---|---------------|-------------------------------------|------------|
| 2 | Randomisation | <input checked="" type="checkbox"/> | <u>and</u> |
| 3 | Blinding | <input checked="" type="checkbox"/> | <u>and</u> |
| 4 | Follow-up | <input checked="" type="checkbox"/> | |

Results of probit model of factors influencing PBAC recommended listing at price 1994-2004 full model cost per QALY n=103

	Mean	Marginal effect	p
Recommended at price	0.29		[.20,.38]
ICER \$'0,000	4.64	-0.05	(0.00)
Cost to PBS \$m	17.28	-0.01	(0.02)
Clinically significant	0.50	0.44	(0.00)
Precision of effect	0.75	-0.12	(0.22)
Level of evidence	2.79	0.05	(0.46)
Quality of studies	2.39	0.04	(0.53)
Relevance of evidence	0.56	0.13	(0.09)
Life threatening	0.17	0.37	(0.01)
Model validity	1.58	0.02	(0.72)
Modelled outcome	1.61	0.09	(0.08)
Modelled cost	2.19	-0.09	(0.08)
Last line	0.33	-0.05	(0.59)
Highest ICER \$'0000	19.45	0.00	(0.05)
Resubmission	0.63	0.25	(0.00)
Resubmission x Effectiveness	0.33	-0.17	(0.06)
Effectiveness x Life threatening	0.12	-0.22	(0.01)

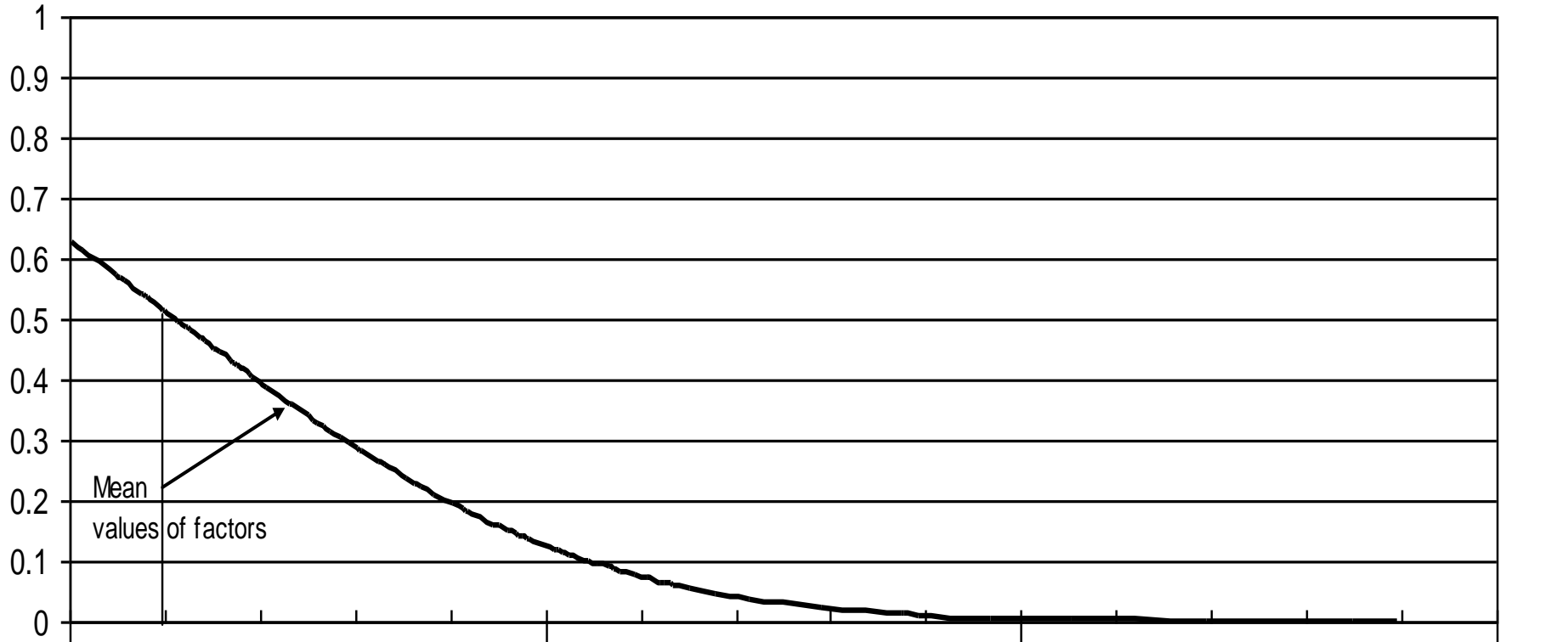
(*) dF/dx is for discrete change of dummy variable from 0 to 1; P> |z| correspond to the test of the underlying coefficient being 0; Robust CI with clustering on drug name

Probit model for decision to list

Sensitivity Pr(+ Yes)	64.52%
Specificity Pr(- no)	86.49%
Positive predictive value Pr(Yes +)	66.67%
Negative predictive value Pr(no -)	85.33%

Prob. of PBAC recommendation by incremental cost per QALY by severity of condition and confidence in the evidence

Probability

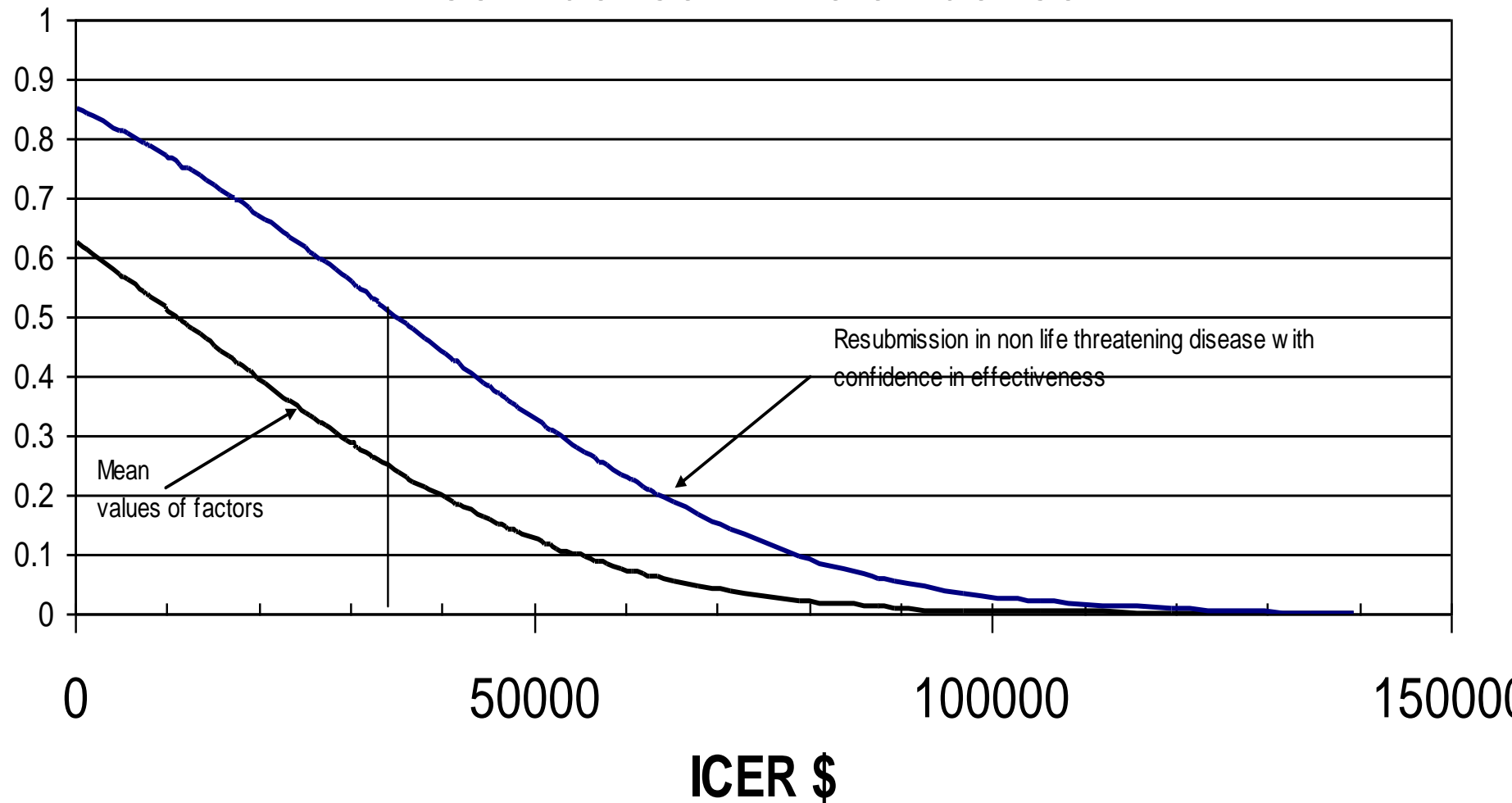


0 50000 100000 150000

ICER \$

Prob. of PBAC recommendation by incremental cost per QALY by severity of condition and confidence in the evidence

Probability

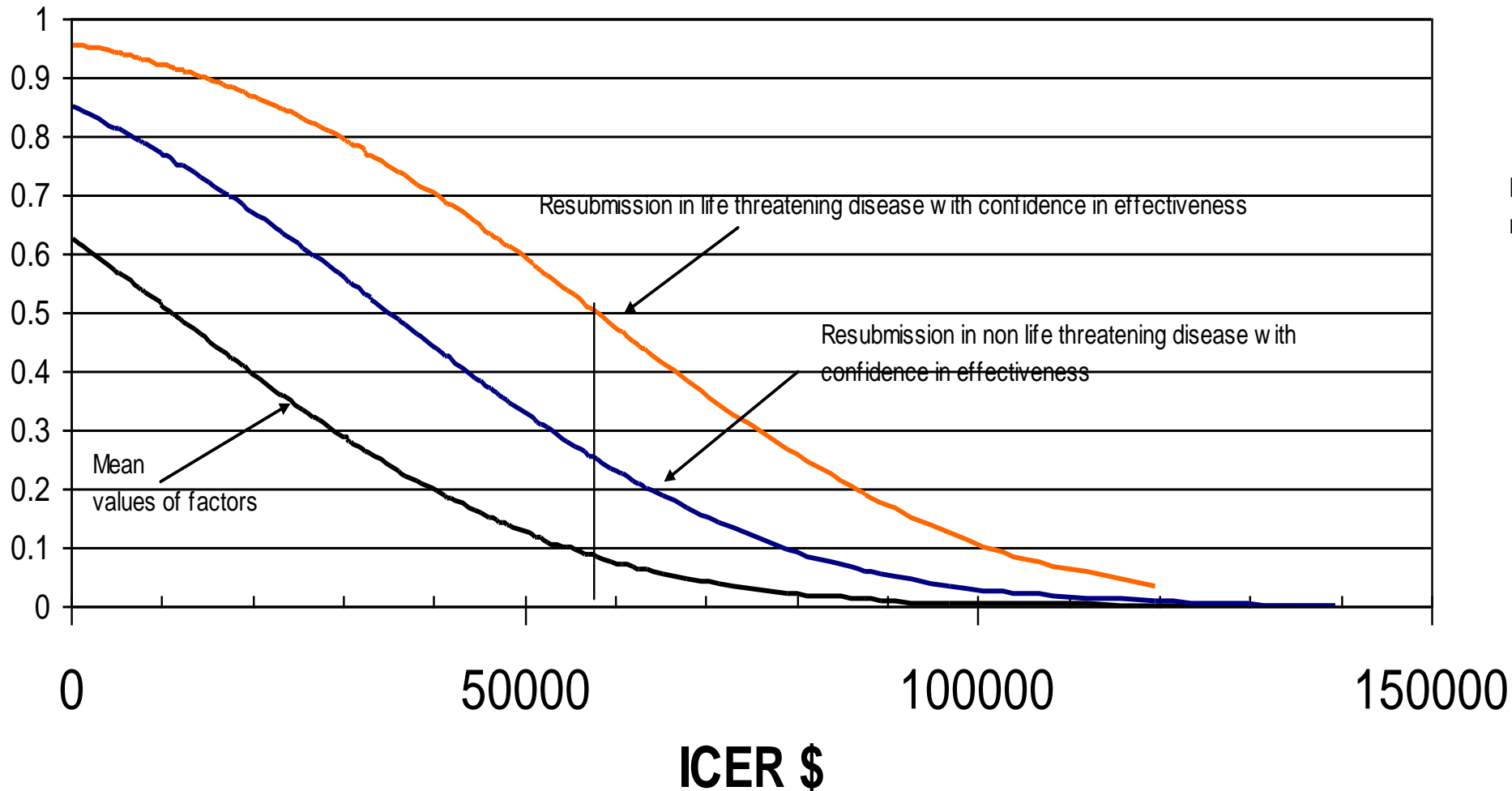


Mean values of factors

Resubmission in non life threatening disease with confidence in effectiveness

Prob. of PBAC recommendation by incremental cost per QALY by severity of condition and confidence in the evidence

Probability



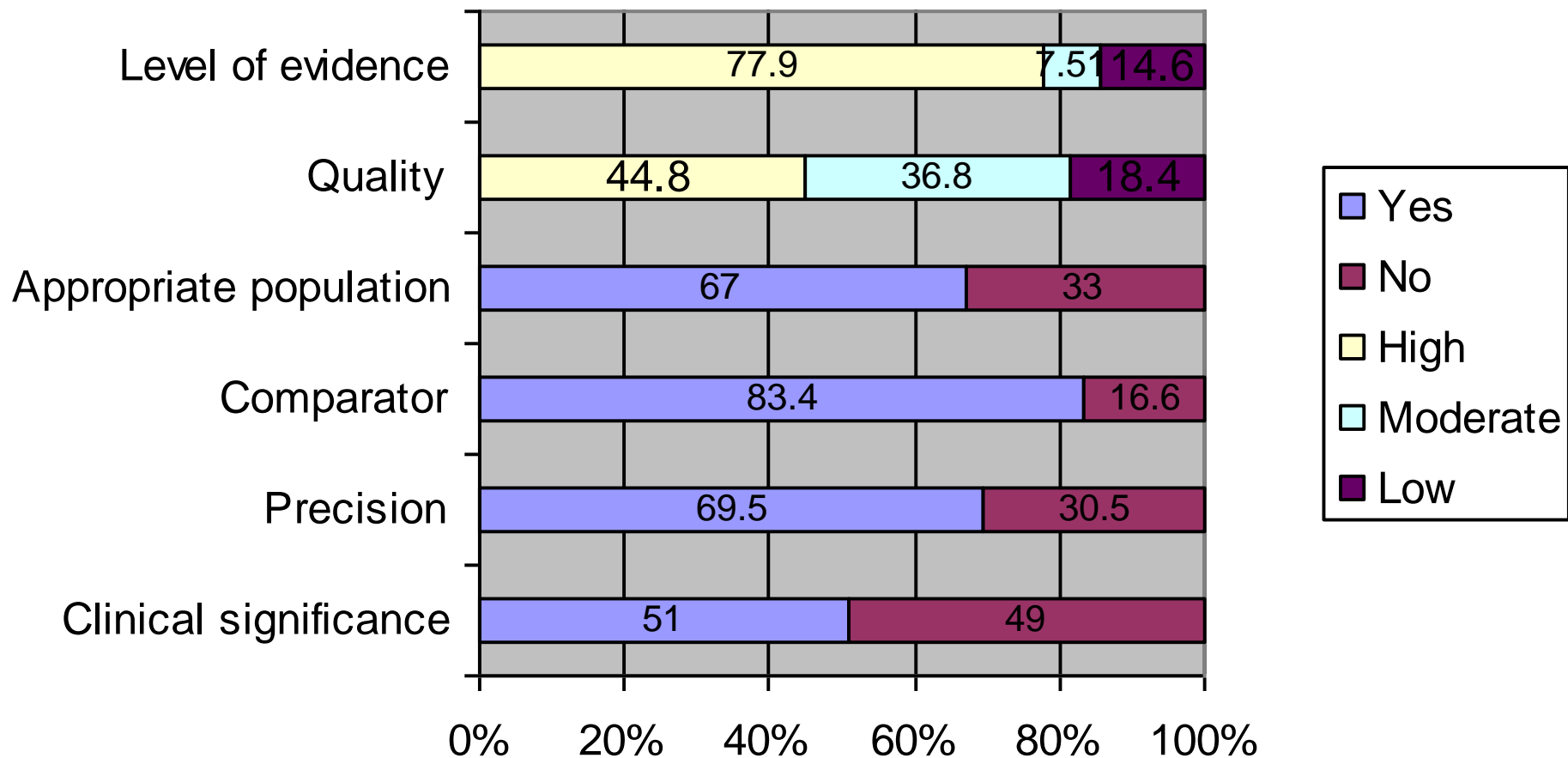
Conclusions

- **Cost effectiveness is a significant factor in decisions**
- **Cost to government is also significant**
- **The credibility and relevance of the clinical effectiveness evidence**
 - Uncertainty is more than just precision on ICER but might be structural (not easily resolved by Monte Carlo techniques)
- **Similar results for submissions with cost per life year gained**
- **Other aspects of evidence (quality of studies) do not appear to be significant**
 - not that the PBAC thinks them unimportant - there may be selection or co- linearity effects
- **Model less significant factor**
 - Possible co- linearity with clinical effectiveness for validity;
 - Timing?
- **Severity of the underlying condition as measured by threat to life can be decisive**
 - Formal rule of rescue factor introduced in 2002 although rarely used
 - Availability of (effective) alternatives not significant (or interaction)
- **Resubmissions are more likely to be recommended *ceteris paribus***
 - *Either the committee is persuaded by the weight of evidence, or they are overwhelmed by the weight?*

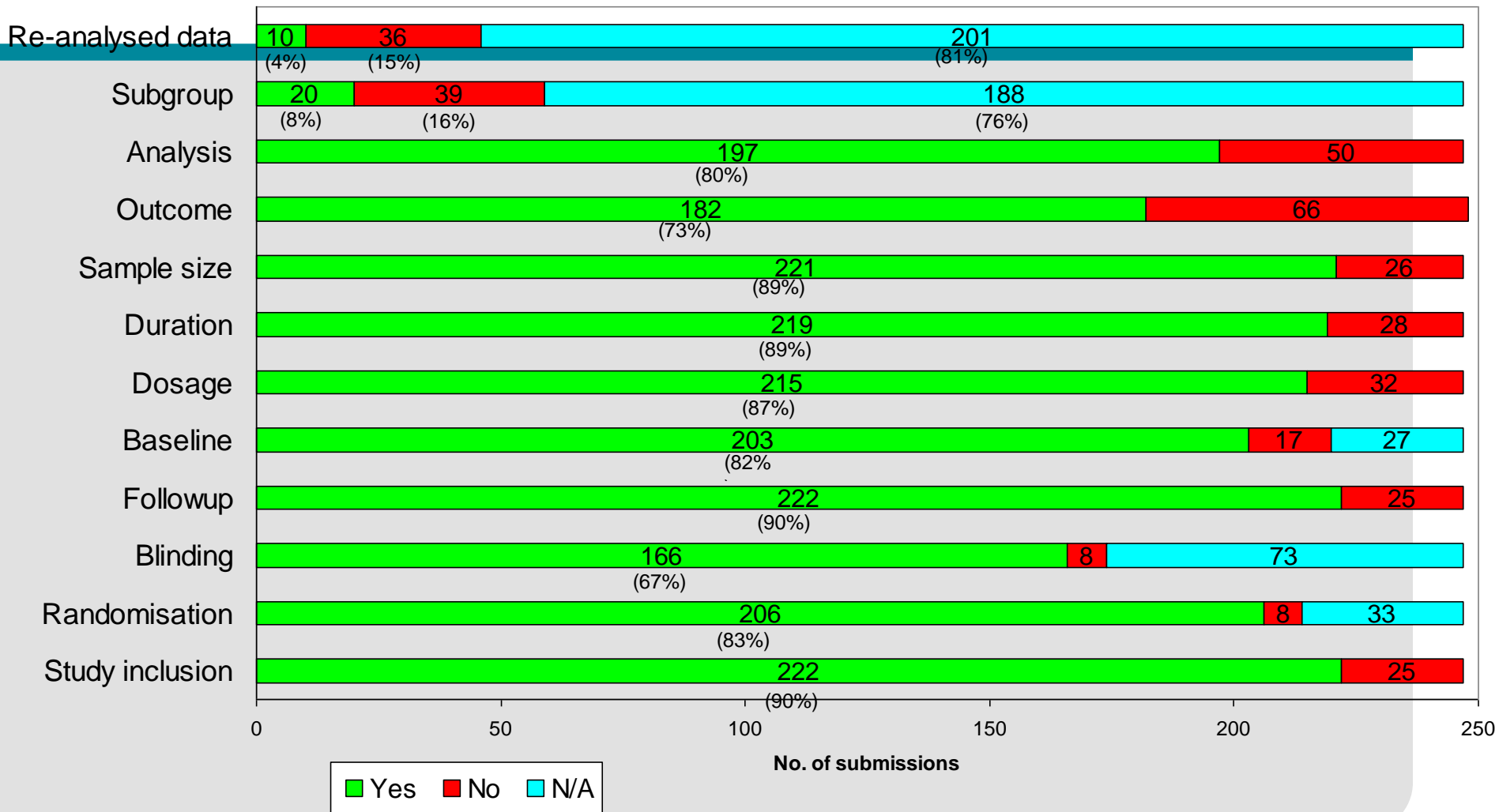
Cost per life year gained

<i>DECISION TO LIST COST PER LIFE YEAR GAINED N=105</i>	<i>MEAN VALUE LYG</i>	<i>DY/DX P[Y=1 X=1] LESS P[Y=1 X=0]</i>	<i>ROBUST 95% CI</i>
<i>ICER \$'0000</i>	<i>10.33</i>	<i>-0.016</i>	<i>(-0.031 - 0.001)</i>
<i>COST TO PBS PER YEAR \$ '000,000</i>	<i>15.324</i>	<i>0.003</i>	<i>(-0.001 0.007)</i>
<i>CLINICALLY SIGNIFICANT EFFECT</i>	<i>.552</i>	<i>0.372</i>	<i>(0.205 0.540)**</i>
<i>LIFE THREATENING</i>	<i>.448</i>		

Strength and quality of clinical evidence in cost per QALY or cost LYG submissions 1994-2004



12-item Quality Checklist (1994-2004)



List of items with most quality problems (ratio of no:yes)

1. Randomisation *(LEAST problems)*
 2. Blinding
 3. Baseline comparability
 4. Follow-up & study inclusion
 5. Sample size
 6. Trial duration
 7. Dosage
 8. Method of analysis
 9. Outcome (eg surrogate, composite)
 10. Subgroup
 11. Reanalysed data *(MOST problems)*
- 