Role of Economic Analysis in Phase III Clinical Trials

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Overview

- CEA basics
- CEA alongside clinical trials
- Example
- Policy Context

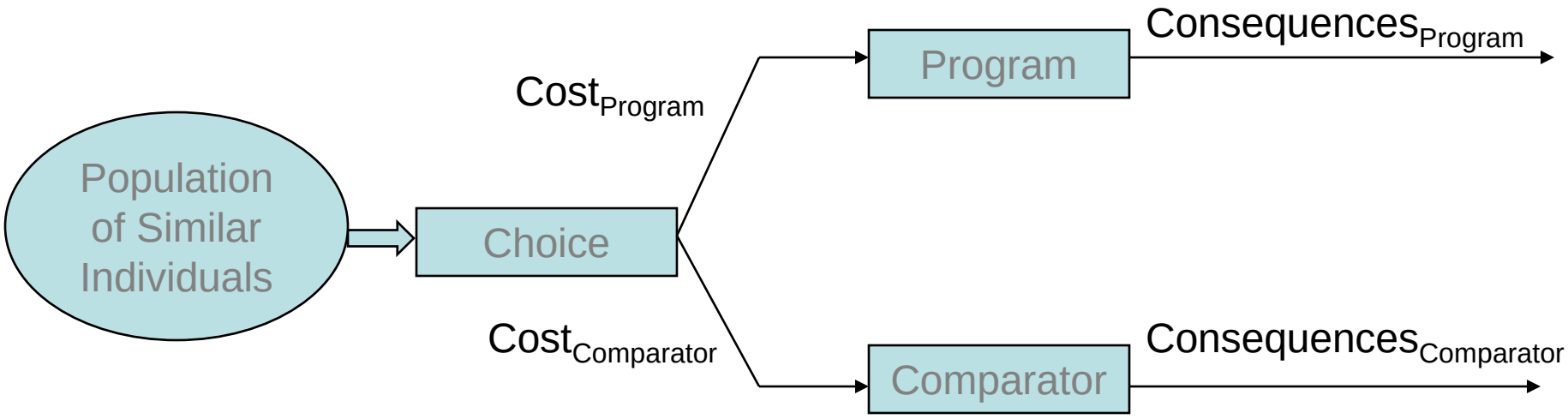
CEA Basics

Cost-Effectiveness Analysis

- Standardized methodology for comparing benefits and costs of interventions designed to improve health*
- Compare alternative treatment strategies
  - Is the new treatment strategy “cost-effective” compared to standard care?
- Provide standard metric to compare value across therapies for different diseases
  - Where should we spend limited health dollars?

*Weinstein et al. Recommendations of the Panel on Cost-effectiveness in Health and Medicine. JAMA 1996;276:1253

Cost-Effectiveness Analysis is a Comparison of Alternatives

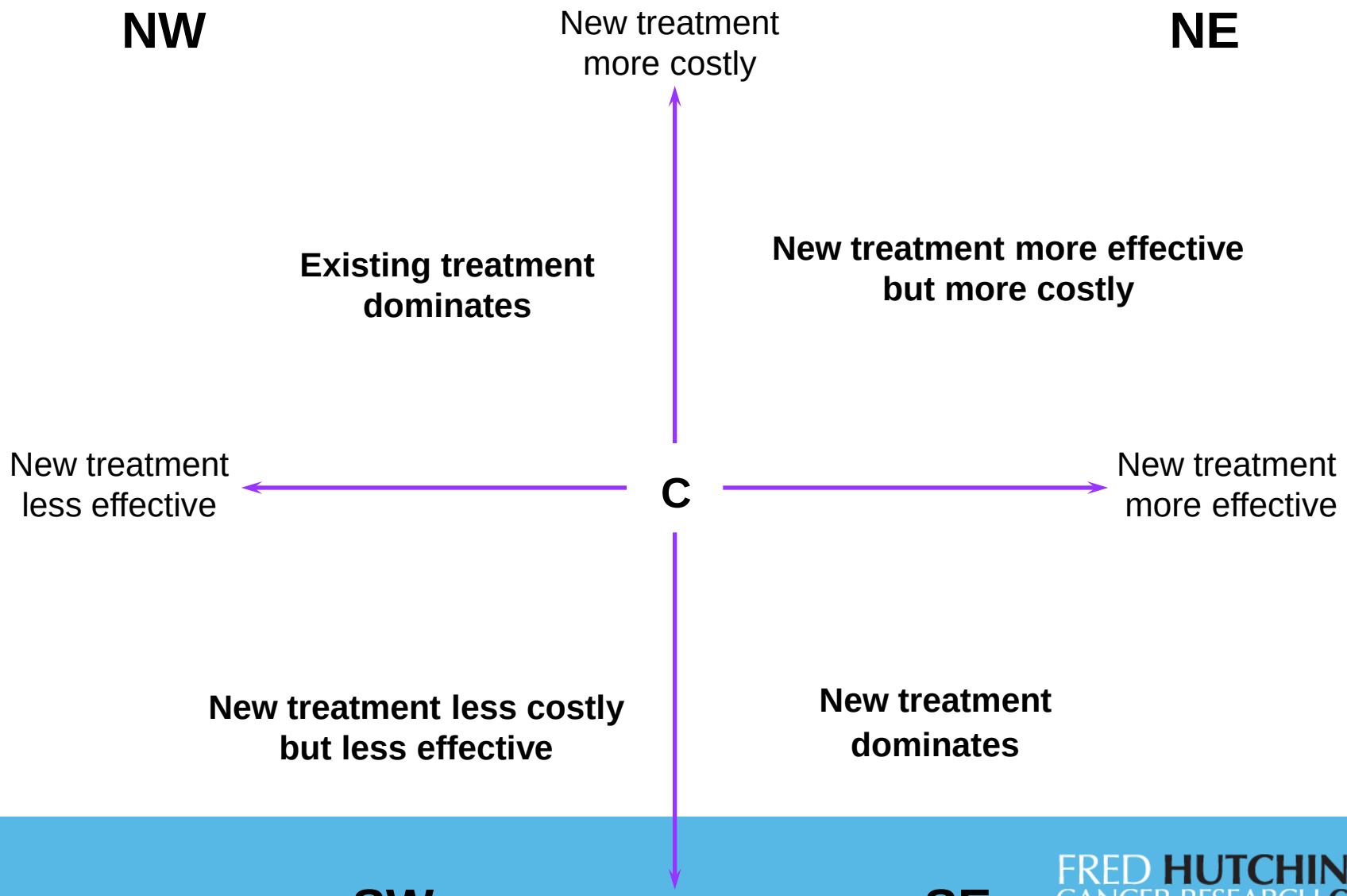


From Drummond MF et al. Methods for the Economic Evaluation Of Health Care Programmes, Oxford, 1997

Incremental Cost-Effectiveness Ratio (ICER)
Therapy *A* Vs. Therapy *B*

$$= \frac{\text{Cost (A) - Cost (B)}}{\text{Outcome (A) - Outcome (B)}}$$

THE COST-EFFECTIVENESS PLANE



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Type of Economic Analysis	*Description of Outcome*
Cost-minimization	**None** **(Least expensive way to treat a condition)**
Cost-effectiveness	**Natural effects** **(e.g. cases identified, life years gained)**
Cost-utility	**Quality adjusted life years** **(quantity of life adjusted for quality** **1 = ideal health, 0 = dead)**
Cost-benefit	**Monetary value of health and life** **(willingness to pay for health effects)**

CEA Alongside Clinical Trials

Economic Evaluation Alongside Clinical Trials: What are the Advantages?

- High internal validity of RCTs
  - RCT/CEA vs. synthetic CEA (i.e., via models)
- Efficiency
  - Lower costs of piggyback CEAs vs post hoc CEA
- Timing
  - Clinical and economic results presented together

Clinical Trial + CEA = Imperfect Marriage

- External Validity
  - clinical care which occurs in the trial is not representative of care that occurs in typical medical practice
- Study Objectives
  - Clinical trials and cost-effectiveness analyses are designed for different purposes and audiences

Methods are Standardized for CEA Alongside RCTs

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VALUE IN HEALTH

Good Research Practices for Cost-Effectiveness Analysis Alongside Clinical Trials: The ISPOR RCT-CEA Task Force Report

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ABSTRACT

Objectives: A growing number of prospective clinical trials include economic end points. Recognizing the variation in methodology and reporting of these studies, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) chartered the Task Force on Good Research Practices: Randomized Clinical Trials—Cost-Effectiveness Analysis. Its goal was to develop a guidance document for designing, conducting, and reporting cost-effectiveness analyses conducted as a part of clinical trials.

Methods: Task force cochairs were selected by the ISPOR Board of Directors. Cochairs invited panel members to agement, analysis, and reporting of results. Task force members agreed that trials should be designed to evaluate effectiveness (rather than efficacy), should include clinical outcome measures, and should obtain health resource use and health state utilities directly from study subjects. Collection of economic data should be fully integrated into the study. Analyses should be guided by an analysis plan and hypotheses. An incremental analysis should be conducted with an intention-to-treat approach. Uncertainty should be characterized. Manuscripts should adhere to established standards for reporting results of cost-effectiveness analyses.

Resourcing a Piggyback CEA*

- Consent form modifications
- Staff time
  - Design and collection
    - Health care use (e.g., insurance claims)
    - QOL surveys
  - Data entry
- Analyst time

*Not all clinical trials need a piggyback CEA!

RCT/CEA Example

SWOG 9509: PC vs VC

Untreated Patients with Stage IIIb and IV NSCLC

RANDOMIZED

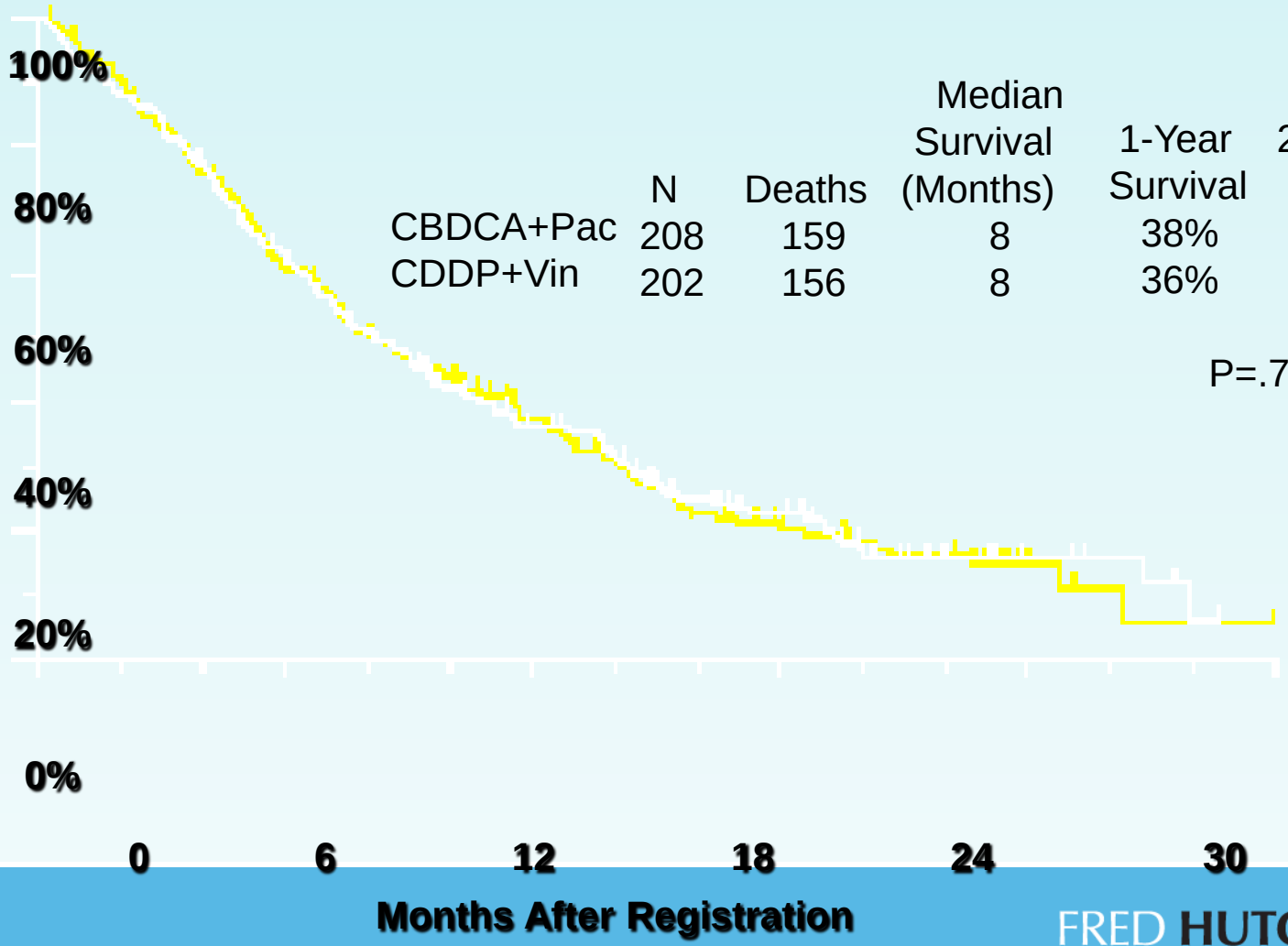
Paclitaxel 225 mg/m2
+
Carboplatin AUC 6
q 3 wks

Vinorelbine 25 mg/m2
+
Cisplatin 100 mg/m2
q 4 wks

Economic Analysis Alongside SWOG 9509

- Research question:
  - Estimate the cost-effectiveness of vinorelbine + platinum vs. paclitaxel + carboplatin for patients with advanced non-small cell lung cancer

SWOG 9509: PC vs VC
Overall Survival



	N	Deaths	Median Survival (Months)	1-Year Survival	2-Year
CBDCA+Pac	208	159	8	38%	15%
CDDP+Vin	202	156	8	36%	16%

P=.73

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SWOG 9509: PC vs VC

Quality of Life Analysis at 25 weeks

	VC N = 30	PC N = 36
Improved	**37%**	**28%**
Stable	**23%**	**33%**
Declined	**40%**	**39%**
p=NS		

Lifetime Average Costs

	Cis + Vinorelbine (N=186)	*Carbo + Paclitaxel (N=187)*
Medical Procedures*	$ 2,637	$ 3,161
Blood Products	$ 166	$ 182
Supportive Care Medications	$4,804	$ 4,339
Prot Chemo Deliv*	$2,199	$1,007
Prot Chemo Drug*	$5,069	$16,732
Non-Protocol Therapy	$8,372	$7,037
Medical Care Days/Visits	$ 9,964	$11,062
Total*	**$33,209**	**$43,522**

* = Significant difference

How to Identify Cancer Clinical Trials for Piggyback CEA Studies?

- General issues
  - Disease burden
  - Cost of therapies (new and established)
  - Downstream impact on costs and outcomes
  - Likelihood of clinical impact of a positive study

- Value of Information analysis holds promise as a way to identify studies that warrant funding

Estimated Value of Information Provided by the National Emphysema Treatment Trial*

TABLE 3. EVI Results for LVRS at WTP Thresholds of $50,000 and $100,000 per QALY Assuming 1250 Subjects per Arm in the NETT (Millions of Dollars)

Parameter	WTP = $50,000/ QALY	WTP = $100,000/ QALY
Incremental cost-effectiveness ratio (ICER)	0.31	0.31
Expected value of perfect information	46	670
Expected value of sample information	41	660
Expected net benefit of sampling	−19	600
Probability of change in decision	0.04	0.24

*Multicenter NHLBI-sponsored RCT of lung volume reduction surgery (LVRS) for persons with severe emphysema. Included a piggyback CEA.

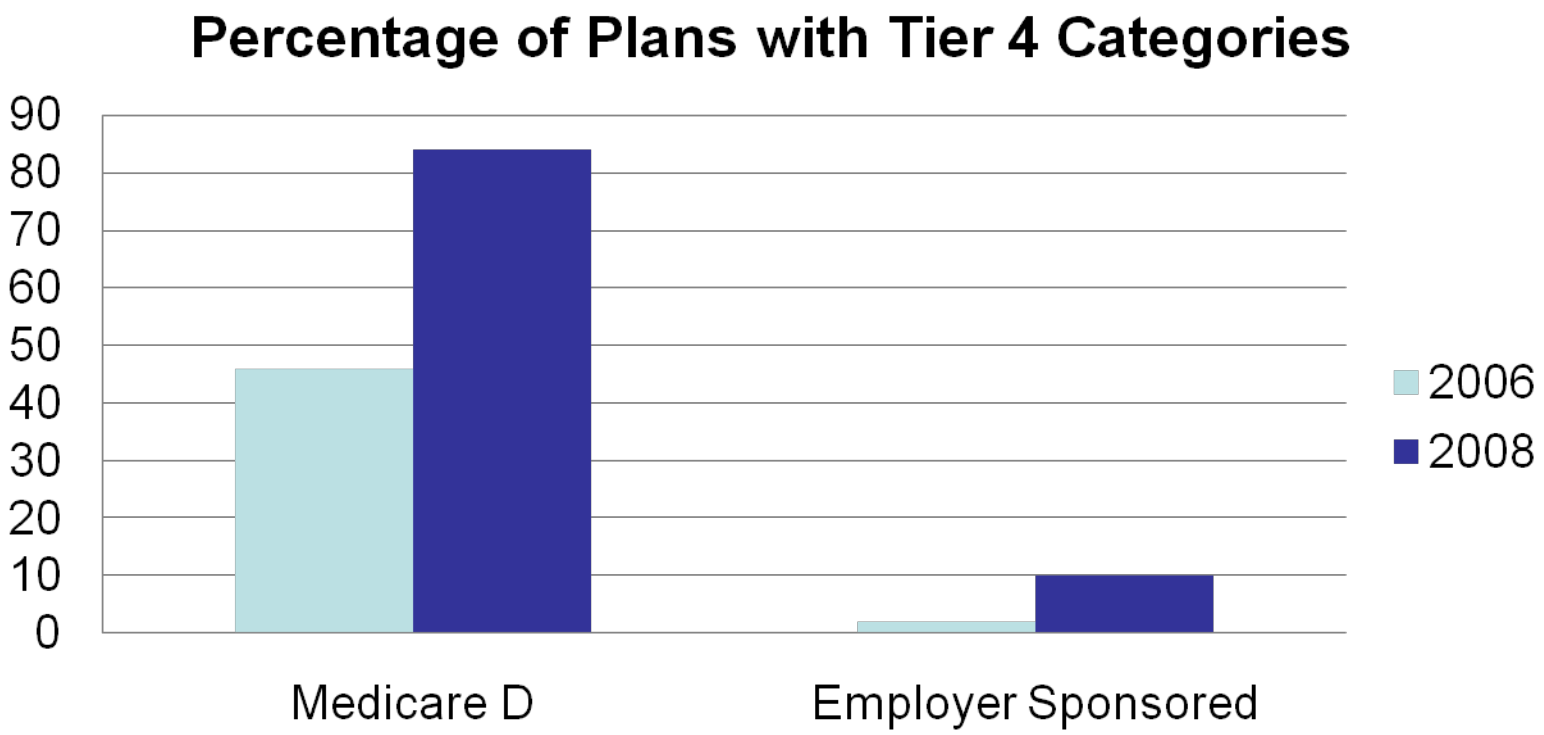
Source: Medical Care 2008;46:542

Policy Context

Oncology Spending

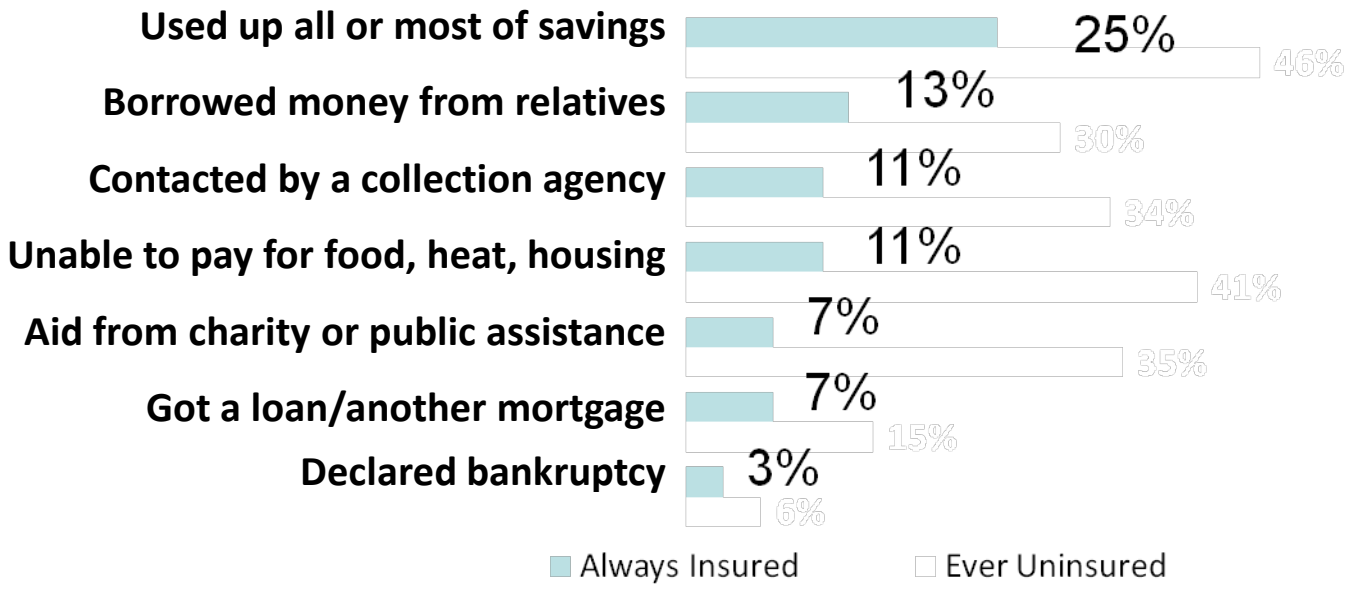
- Oncology spending is rising >15% percent annually, faster than total health care spending
- Much of the cost increase in oncology is driven by three factors
  - Replacement of less expensive with more expensive treatments
  - More aggressive use of treatment and treatment combinations
  - Prolongation of the period of treatment
- Cost is becoming an increasingly intrusive concern for patients, providers, and payers alike

Tier 4 Insurance Among Medicare Part D and Commercial Insurance Plans



Tier 4 plans typically have a 20-33% coinsurance rate

Consequences of Financial Costs of Cancer



Source: Kaiser Family Foundation, 2006

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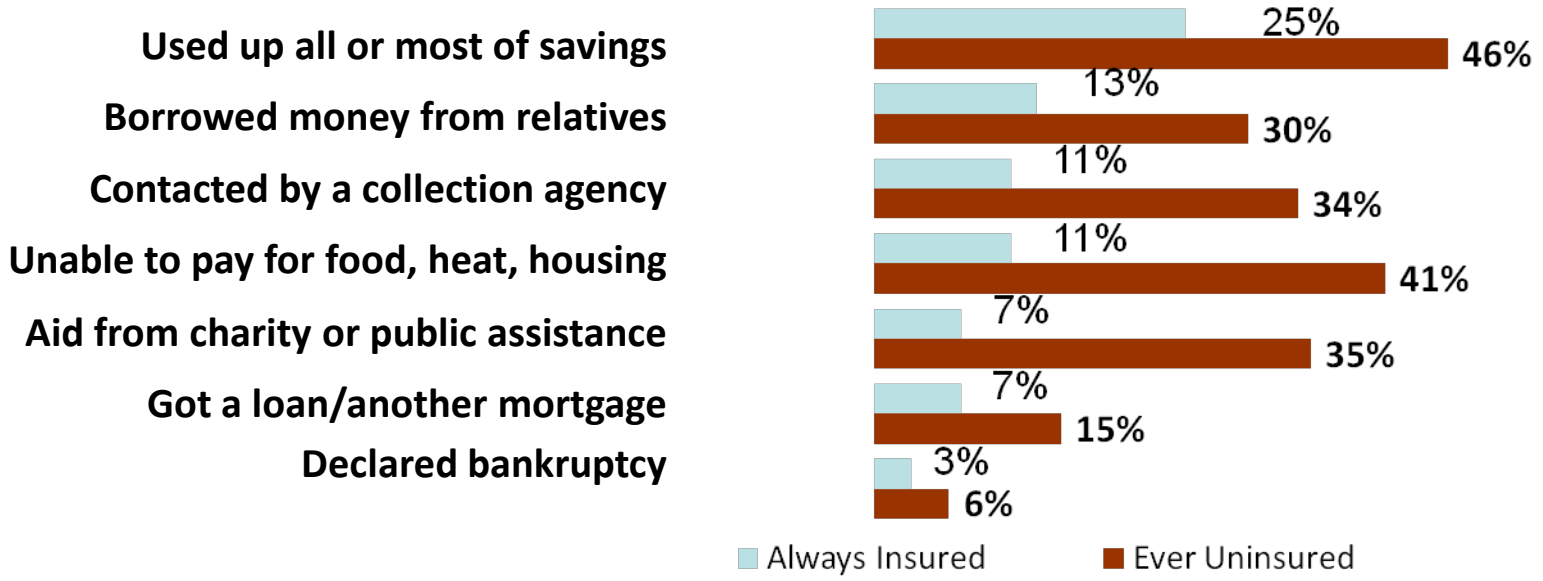

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Economic Evaluation Alongside Clinical Trials: Why Should They be Done?

- "If costs per enrollee in Medicare and Medicaid continued to grow at the same rate…federal spending on those two programs alone would increase from about 5% of GDP today to about 20% by 2050 — roughly the share of the economy now accounted for by the entire federal budget"

- "Relatively little rigorous evidence is available about which treatments work best for which patients or whether the benefits of more expensive therapies warrant their additional costs"

  – Peter Orszag, NEJM 2007;357:1885

Cost-Effectiveness Fallacies

- Cost ≠ cost-effectiveness
  - A costly cancer treatment can be highly cost-effective
  - An inexpensive cancer treatment can have poor cost-effectiveness

- Cost-effective ≠ inexpensive
  - Adopting a new cost-effective cancer treatment often increases overall health care spending

Cost-Effectiveness
Cancer Prevention and Control

Indication	Intervention	Comparator	Cost/QALY
Clinically node-negative breast cancer	Intra-operative touch imprint cytology	Standard post-operative sentinel lymph node survey	Cost-saving
ER+ breast cancer, (-) lymph nodes	Surgery + AC	Surgery alone	$12,000
Cervical cancer prevention, age 25	HPV vaccine	No vaccine	$20,000
ER+ breast cancer age 64	Anastrozole	Tamoxifen	$87,000
Local stage prostate cancer, age 75	Radiation	Watchful waiting	$220,000
Hodgkin's disease Stage III-IV complete remission	Annual computed tomography x 5 yrs	No computed tomography	$9.6 million

https://research.tufts-nemc.org/cear/Default.aspx

National Institute for Health and Clinical Excellence (NICE)

- Implemented in the United Kingdom in 1999
- A Special Authority within the National Health Service (NHS)
- Remit is to consider '*clinical and cost-effectiveness*'
  - Eliminate ineffective treatments
  - Concentrate the available budget on the cost-effective treatments
  - Ensure all patients have equal access to cost-effective care

NHS

National Institute for Health and Clinical Excellence

Tel: 0845 003 7782
www.nice.org.uk
Ref : 2009/039

PRESS RELEASE

NICE guidance recommends lenalidomide for multiple myeloma

The National Institute for Health and Clinical Excellence (NICE) has today (18 June) published final guidance on the use of lenalidomide for multiple myeloma in people who have received at least one prior therapy.

The new NICE guidance recommends lenalidomide in combination with dexamethasone as a treatment option for people with multiple myeloma who have received two or more prior therapies. The cost of the drug beyond 26 cycles (each of 28 days; normally a period of 2 years) will be met by the manufacturer, Celgene.

National Institute for Health and Clinical Excellence

Tel: 0845 003 7782
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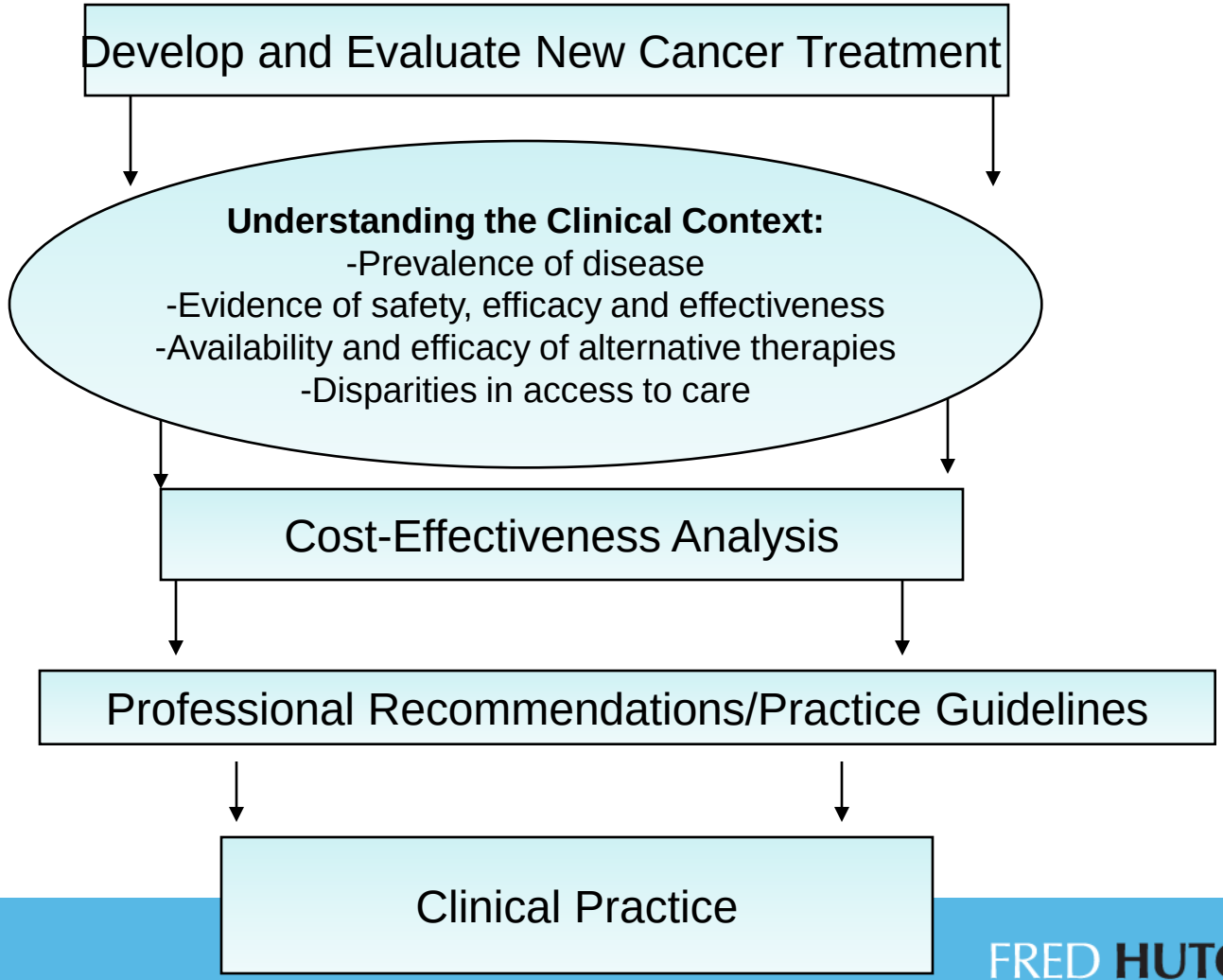
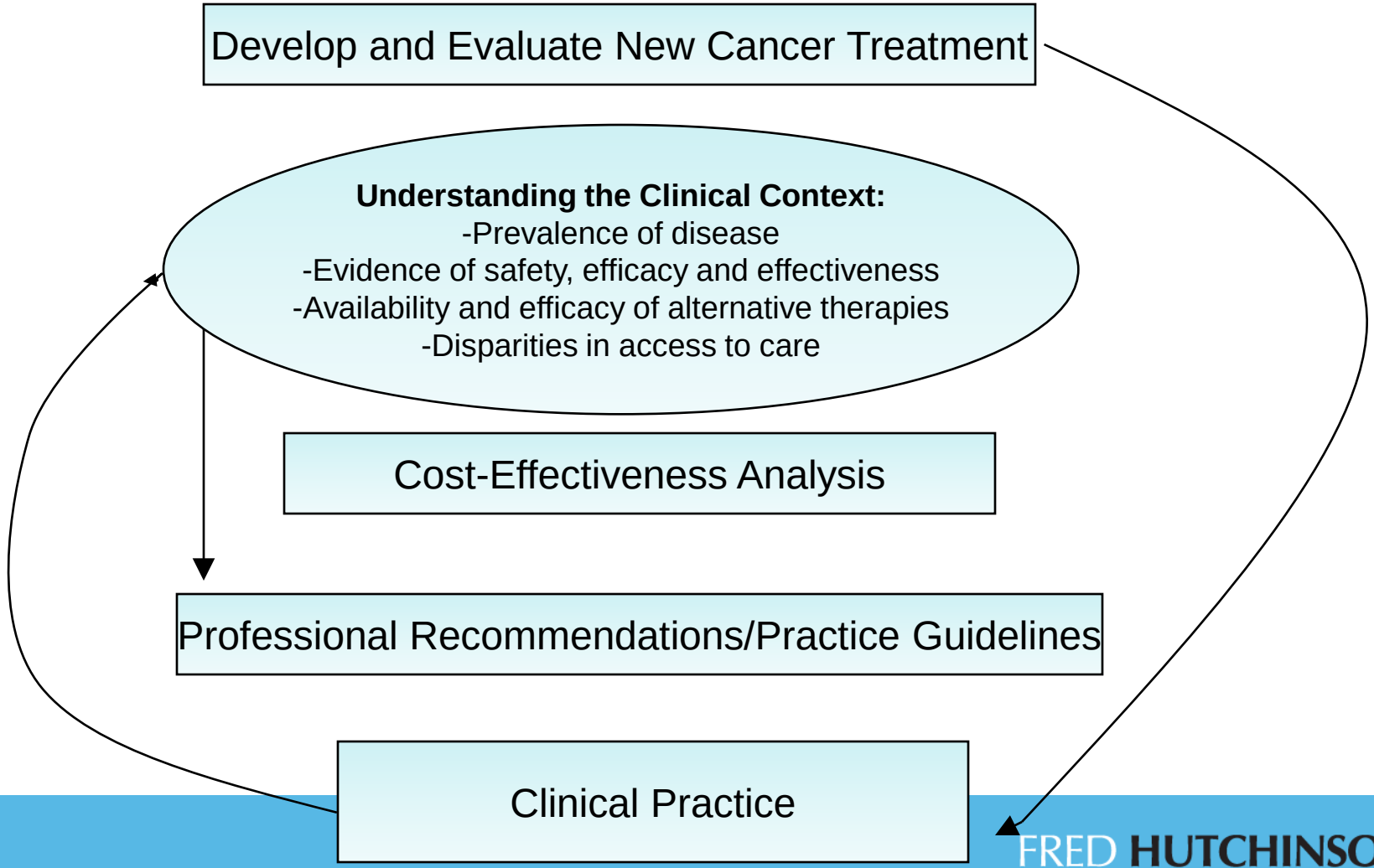
Ideal Role of Cost-Effectiveness In Cancer Care



Actual Role of Cost-Effectiveness in Cancer Care



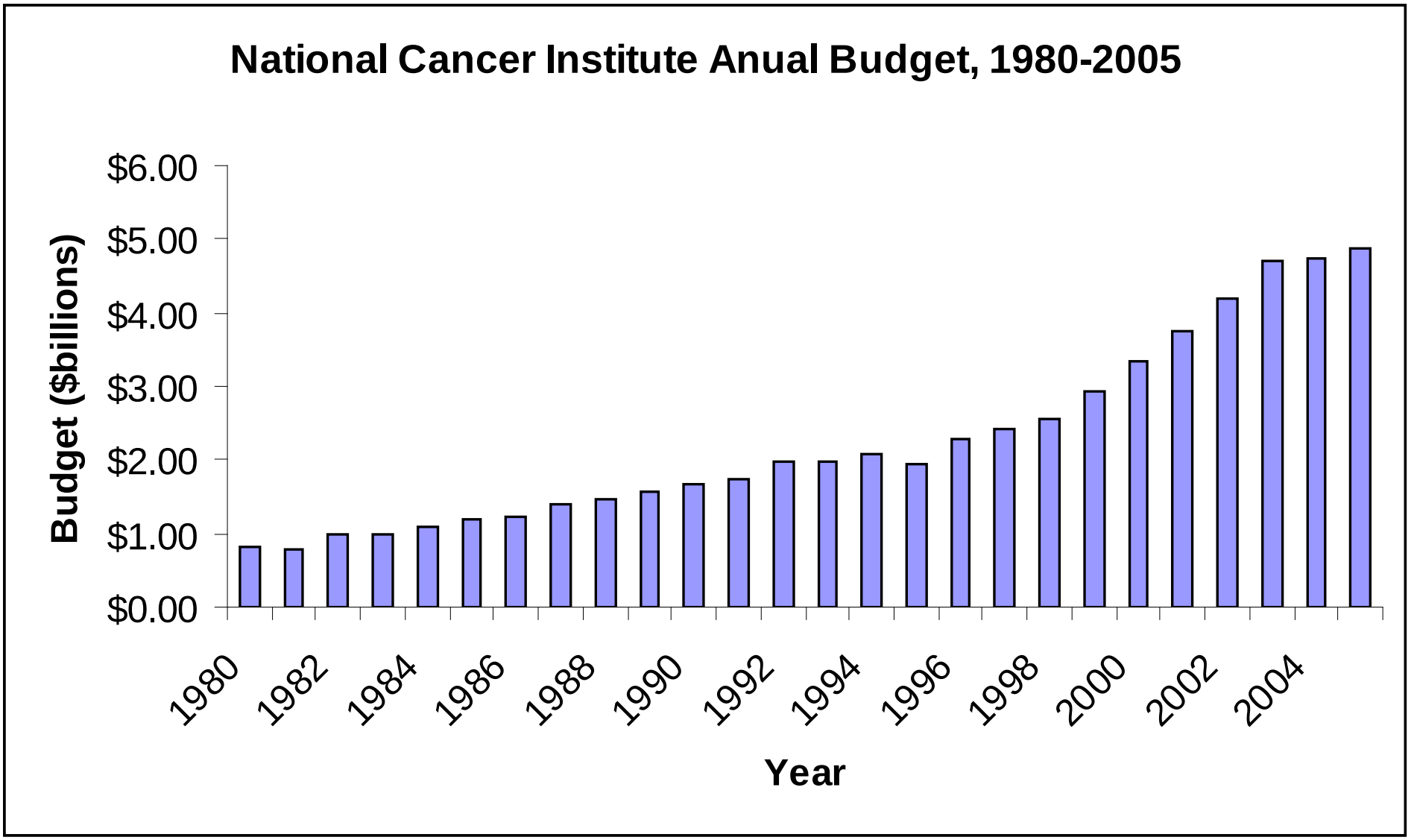
Questions?

Reference and Backup Slides

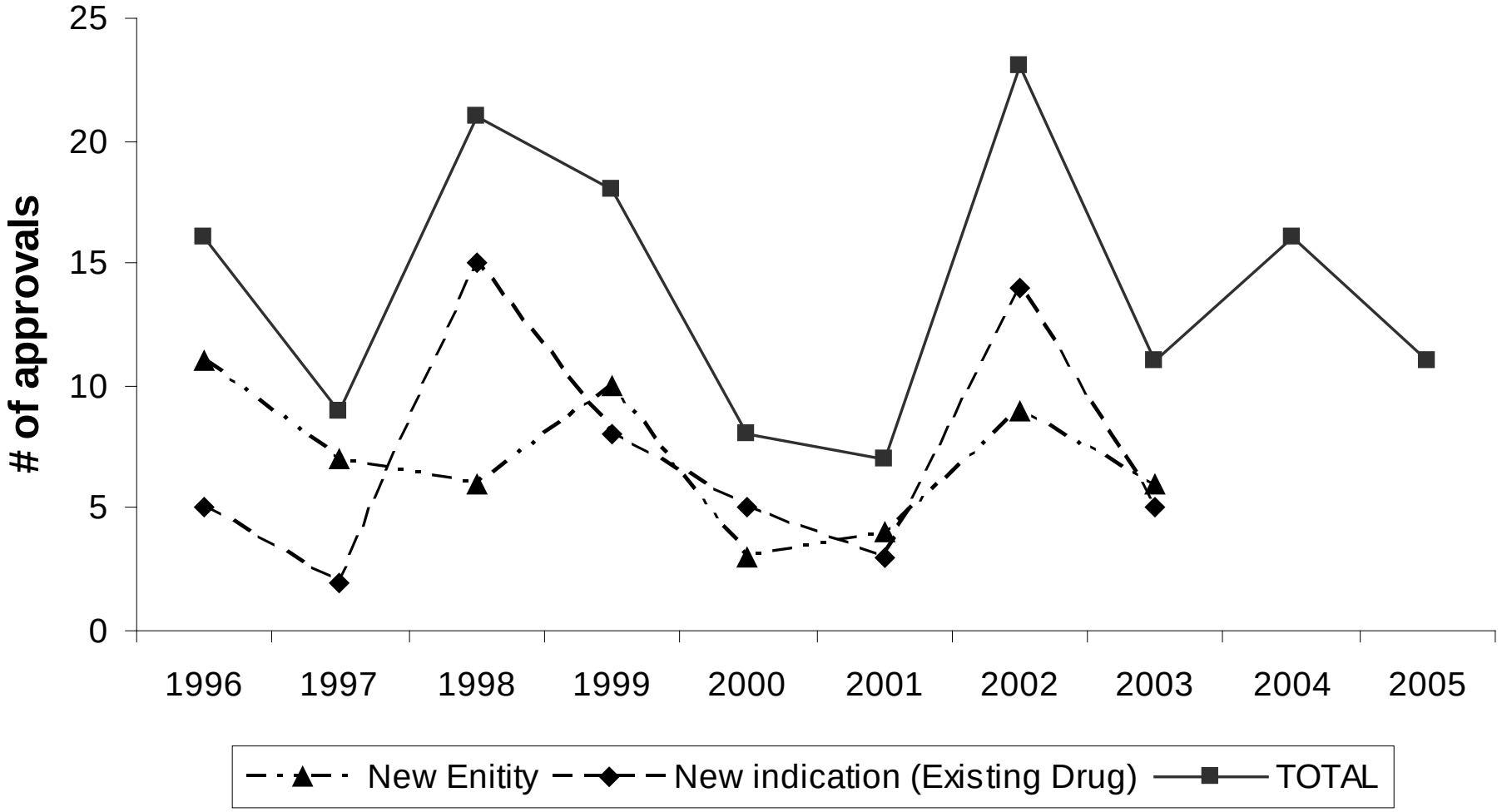
Other examples when NICE was able to use CEA in pricing negotiations

Year	Country	Disease area	Product(s)	Manufacturer	Payer	Agreement
2007	UK	Multiple myeloma	Velcade	Johnson and Johnson	NHS	J & J agreed to reimburse the NHS in either cash or product for patients who do not respond (Response measure: 50% decrease in serum M protein) after 4 cycles of treatment with Velcade. Responding patients receive additional 4 cycles.
2008	UK	Colorectal cancer	Erbitux	Merck	Primary care trust	Rebate direct to primary care trust on the cost of any vials of Cetuximab used for patients who do not achieve a pre-agreed clinical outcome ('nonresponders') at up to 6 weeks (up to an agreed maximum of 3200 milligrams).
2008	UK	NSCLC	Erlotinib	Roche	Primary care trust (UK)	Roche will rebate the cost of erlotinib for NSCLC treatment to achieve drug acquisition cost parity compared to docetaxel for an average patient duration.
2008	UK	Mesothelioma and NSCLC	Pemetrexed	Ely Lilly	Primary care trust (UK)	Discounted price for drug after certain preagreed level of expenditure at full price has been reached.
2009	UK	Kidney cancer	Sutent	Pfizer	NHS	Pfizer agreed to provide a 5% discount on the unit price of Sutent and cover the cost of the first 6 weeks of treatment

Question:
Will Cost-effectiveness Analysis Shut off the Cancer Treatment Pipeline?


National Cancer Institute Anual Budget, 1980-2005
Budget ($billions)
$6.00
$5.00
$4.00
$3.00
$2.00
$1.00
$0.00
1980
1982
1984
1986
1988
1990
1992
1994
1996
1998
2000
2002
2004
Year

FDA approvals for new cancer drug treatments,1996-2005



Recent NICE Controversy

- In August 2008, NICE published its Appraisal Consultative Document on four new drugs for treating advanced renal carcinoma (*bevacizumab,sorafenib,sunitinib,temsirolimus*).
- It recommended that none of the four drugs should be used in the NHS on the grounds that they were not cost-effective.
- Oncologists and patient organizations were outraged, since these drugs are widely used in many other countries and offer benefit to patients for whom no other effective treatments are available.
- NICE has responded with a national survey to determine if the population wants higher thresholds for treatments at the end of life