Disegno degli studi clinici

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15 pivotal R phase III registration trials, 9 biologics , 8 cancer types

	median HR	median absolute gain
PFS	.57	2.7 months
OS	.73	2.0 months

Very good / fantastic

...hmm...

Sobrero and Bruzzi , JCO 2009

The 3 problems

1. HR vs absolute delta
2. low target HR in trial design
3. target HR in trial design vs p value in trial analysis and interpretation.

INNOVATIVE DEFINITION OF MCWE COMBINING MINIMUM HR AND MINIMUM ABSOLUTE MEDIAN GAIN IN OS OR PFS "Substantial" tox

Prognosis in Control arm	OS HR		OS abs med gain	PFS HR		PFS abs med gain	alive at twice median OS relative % gain
4	0.65	AND	2.0	0.65	AND	2.0	100
6	0.75	AND	2.0	0.65	AND	3.0	100
10	0.80	AND	2.5	0.70	AND	3.5	50
12	0.80	AND	2.5	0.75	AND	3.5	50
24	0.80	AND	3.0	0.75	AND	4.0	50

PROBLEM 2. ‘ LOW PROFILE’

Typical phase III trial design in advanced cancer (PFS 6 mo)

- Delta 25% i.e. HR [illegible] 5
- Median delt[illegible] 1.8 mo
- Pow[illegible] 0
- [illegible] 800
- Cost = 100

If we get this , is this really clinically worthwhile?

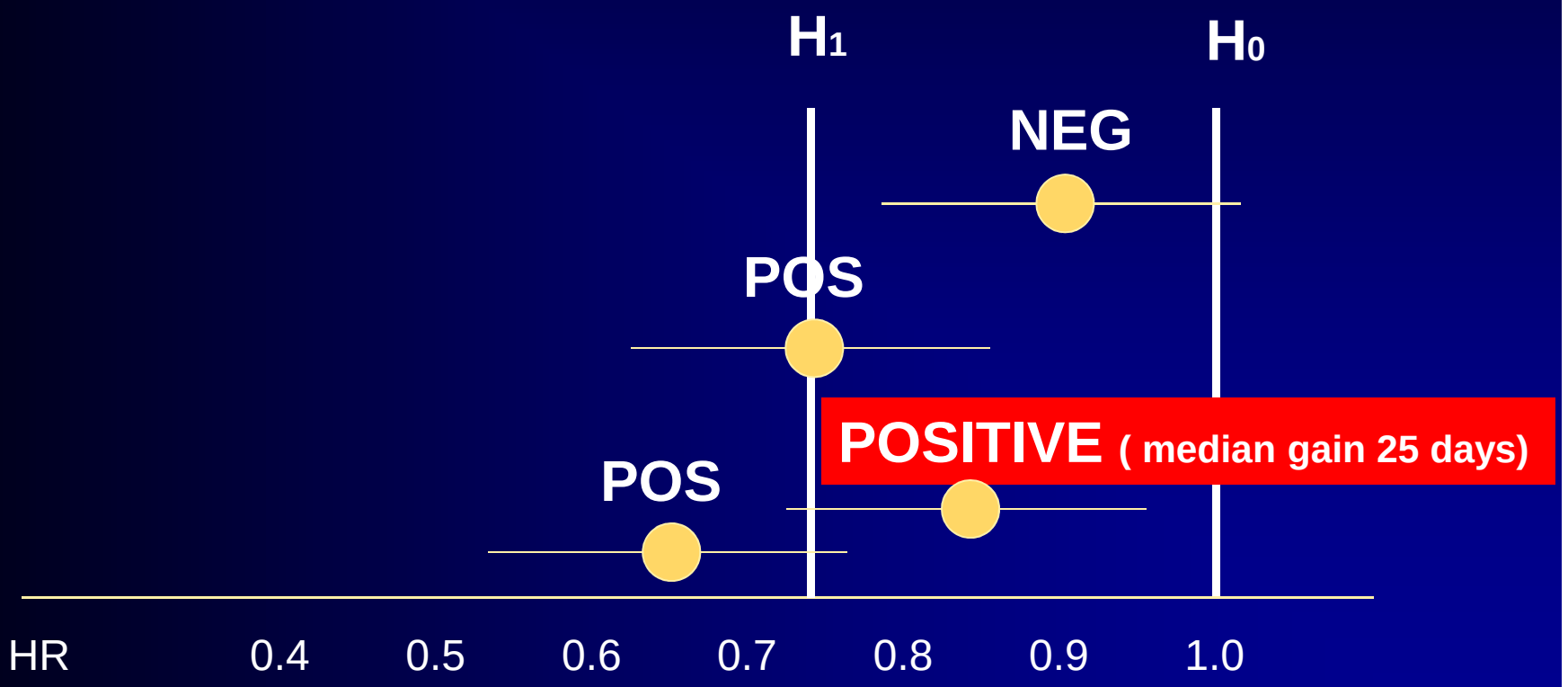
Be more corageous : raise the bar

PROBLEM 3: INCONSISTENCY



Define target delta……...target delta is ignored and...
p value becomes the focus…

Problem 3 : INCONSISTENCY



‘Statistically positive’ trials with deltas lower than those pre-specified in the protocol

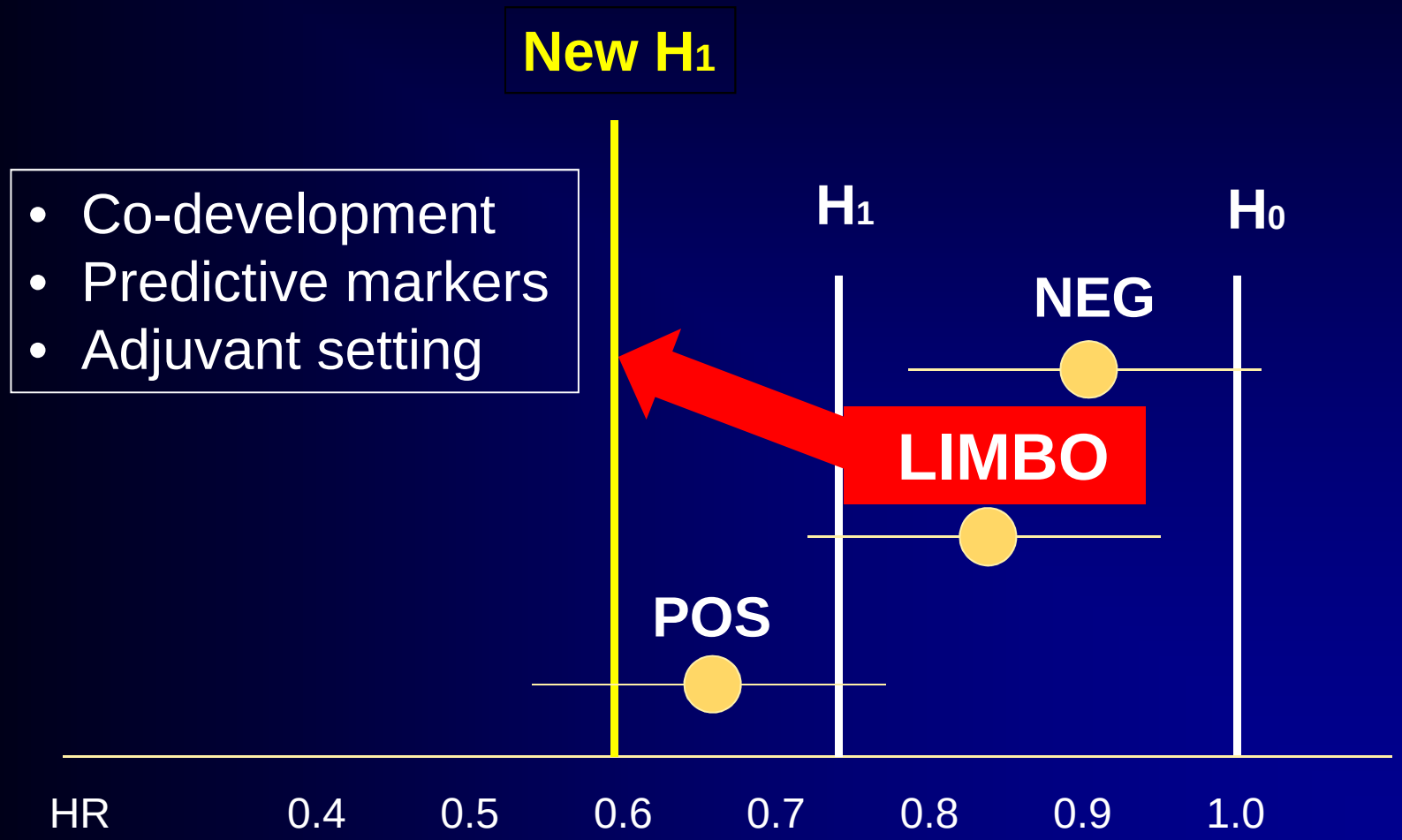
AUTHOR	DRUG	TUMOR	predefined HR	reported HR	p value
Johnstone 09	lapatinib	breast	0.64	0.71	0.019
Jonker 07	cetuximab	colon	0.74	0.77	0.001
Moore 07	erlotinib	pancreas	0.75	0.82	0.038
Llovet 08	sorafenib	liver	0.6	0.69	0.001
Escudier 07	sorafenib	renal	0.67	0.72	0.02

modified from Ocana A. JNCI,2011

The solutions: raising the bar above the minimum clinically worthwhile effect

- Maintaining today's statistical thinking
  - Change H_1: Shoot at larger, clinically worthwhile effect

Proposal maintaining today's classical stat thinking: raise the bar, change H_1



- Co-development
- Predictive markers
- Adjuvant setting

The pros of raising the bar

1. POP agents off market → credibility / uniformity
2. Smaller trials → reduced costs, more rapid clinical devel.
3. Trials on selected patients→ selective approval

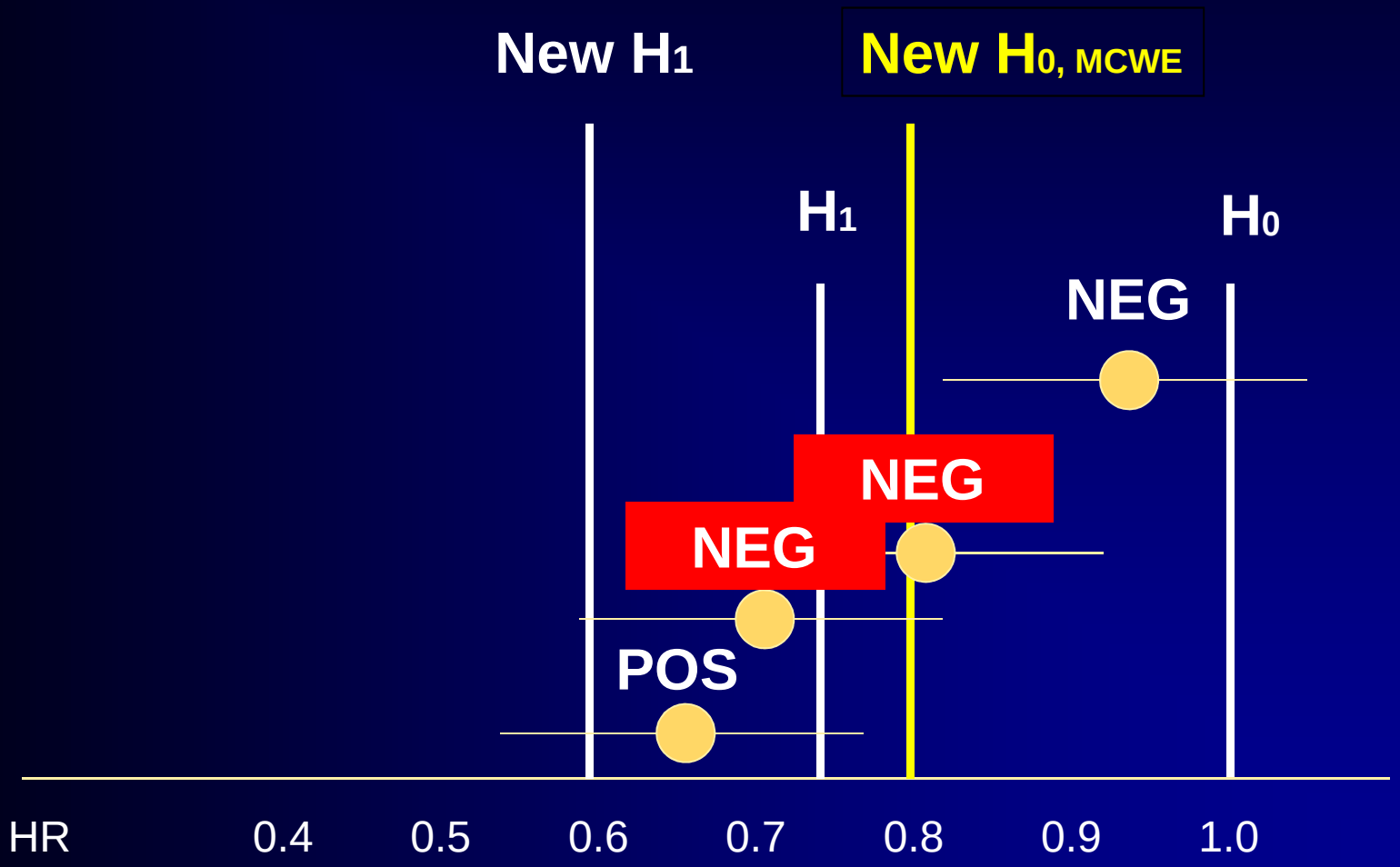
The contras of raising the bar

1. Increased statistical uncertainty
2. Missing cumulative effect of incrementalists
3. Cost and devel. time vs RISK → fewer agents
4. Less funding to clinical and translational research

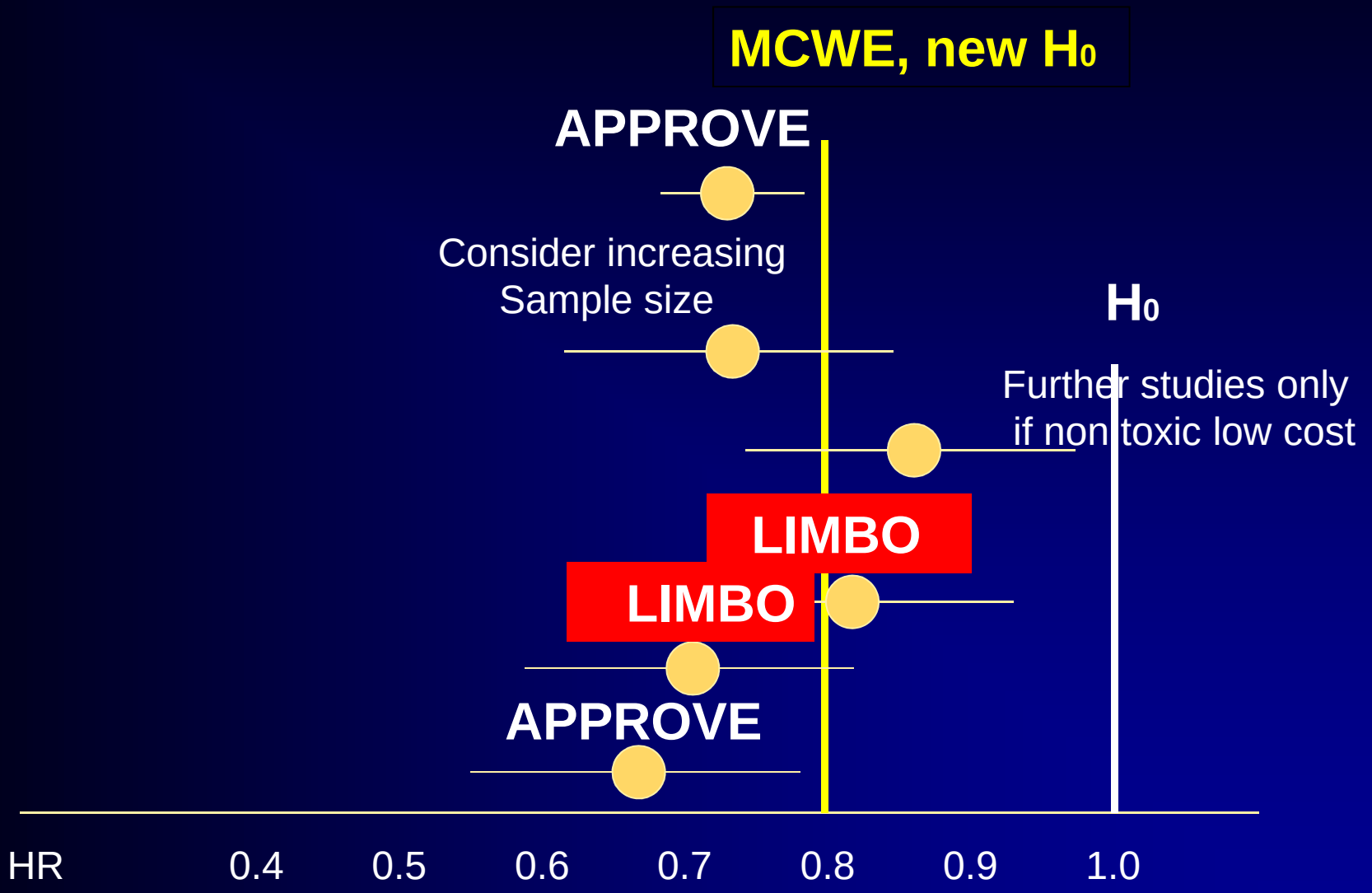
The solutions: the two ways of raising the bar above the minimum clinically worthwhile effect

- Maintaining today's statistical thinking
  - Change H_1: Shoot at larger, clinically worthwhile effect
- Changing today's statistical thinking
  - Change H_0: shoot at rejecting anything inferior to a minimum clinically worthwhile effect

Proposal changing today's classical statistical thinking: change H_0



The limbo level



Pros and cons of changing H_0

PROS	CONS
• Forces to reason in terms of relevance, not stat. significance	• Identification of MCWE difficult
• Statistical uncertainty not increased	• Size of trials (if effect close to MCWE)
• Promotes adaptive designs	

CONCLUSIONS

1. Raise the bar (H_1 or H_0) shooting at deltas larger than MCWE

2. Consistency:design vs analysis-interpretation → less emphasis on p values, more on HR AND absolute gains.

size of benefit in phase III clinical trials on advanced solid tumors

Clinically worthwhile (efficiency)
Relevant (efficacy-effectiveness)
Convincing (beyond technical consensus)

Vs

Statistically significant

Size of benefit (target delta) : a compromise

1. plausible to achieve
2. worthwhile if achieved

Target delta: HR

- **0.5** means doubling of the benefit vs control
  4→8 months

fantastic

- **0.66** means 50% increment of the benefit vs con
  4→6 months

very good

- **0.80** means 25% increment of the benefit vs control
  4→5 months

hmm…

PROBLEM 1: ABSOLUTE GAIN

Increase in median OS for different HR as a function of prognosis

