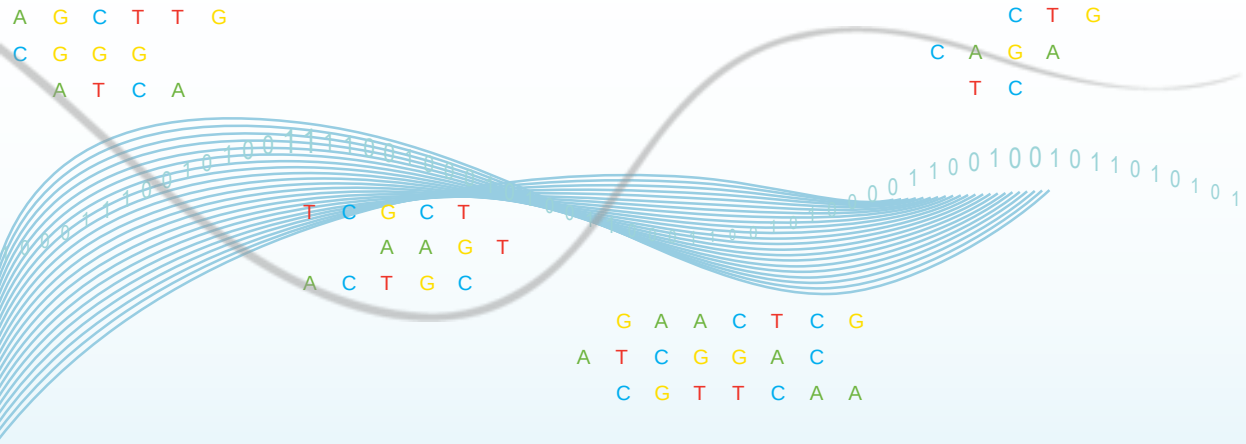
Payers Perspective: Defining Clinically Meaningful Effect for the Design and Interpretation of RCTs



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Robert S. Epstein MD MS

Chief R&D Officer, Medco

President, UBC

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- Eva Lydick PhD
  - > Retired epidemiologist

- J. Russell Teagarden, RPh, MS, PhD
  - > Medco-UBC

Evolution of Evidence

- Statistical Significance
  - > Findings not due to chance alone – $p<0.05$
  - > Sir Roland Fisher 1926*
    - – If one in twenty does not seem high enough odds, we may, if we prefer it, draw the line at one in fifty (the 2 per cent point) or one in a hundred (the 1 per cent point). Personally, the writer prefers to set a low standard of significance at the 5 per cent point, and ignore entirely all results which fail to reach this level. A scientific fact should be regarded as experimentally established only if a properly designed experiment rarely fails to give this level of significance."

Source: Fisher RA: The arrangement of field experiments. J Ministry Agriculture 1926:33;503-513.

Clinical significance

- Minimally clinically meaningful difference (Jaeschke 1989)*
  - "The smallest difference…which patients perceive as beneficial, and which would mandate, in the absence of troublesome side effects and cost, a change in the patient's management"

Source: Jaeschke R et al. Control Clin Trials 1989:10;407-415.

Clinical Significance
Distribution-based interpretations*

Measure	Definition
Effect size	Mean change/variability in stable patients
Statistical significance	Post-test $\geq$ (Pre-test + 2 SD)
Reliable change index	(Post-test – Pre-test)/$\sqrt{2}$ $(SE)^2$
1 unit of change	Change associated with 1 on an ordered set
Normative level of functioning	Test result $\geq$ Mean of normal population + 2 SD

Source: Lydick E, Epstein RS: Interpretation of quality of life changes. Q Life Res 1993;2:221-226.

Clinical Significance
Anchor-based interpretations

Measure	Example
Global ratings	Change associated with overall change
Life events	Change related to illness, job loss, etc.
Threshold effect	Change required to hit a threshold (e.g. burden, interference)
Change with time	Change associated with x years of disease
Change associated with health conditions	Change associated with being diagnosed

Payer Significance

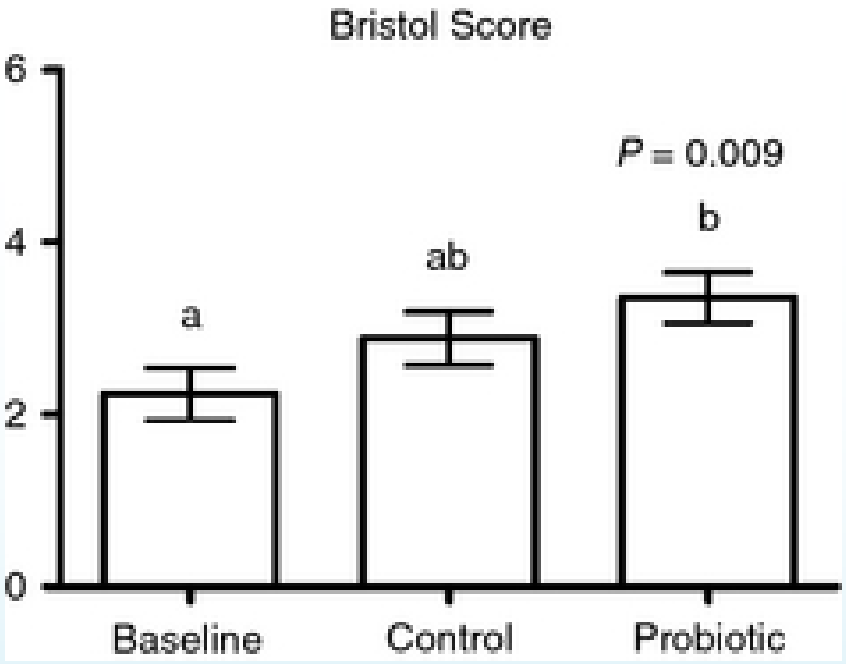
- "The smallest clinical difference which would mandate reimbursement for a particular technology" (Epstein, Teagarden 2012*)

- Particular challenges in this thinking:
  - > Multiple payer perspectives – no 'single' answer
  - > May be in conflict with either statistical or clinical significance (i.e. an additional hurdle)

Bristol Stool Chart

Type 1		Separate hard lumps, like nuts (hard to pass)
Type 2		Sausage-shaped but lumpy
Type 3		Like a sausage but with cracks on its surface
Type 4		Like a sausage or snake, smooth and soft
Type 5		Soft blobs with clear-cut edges (passed easily)
Type 6		Fluffy pieces with ragged edges, a mushy stool
Type 7		Watery, no solid pieces. **Entirely Liquid**

Randomised clinical trial: efficacy of *Lactobacillus paracasei*-enriched artichokes in the treatment of patients with functional constipation – a double-blind, controlled, crossover study



Alimentary Pharmacology & Therapeutics
pagesn/a-n/a, 8 JAN 2012 DOI: 10.1111/j.1365-2036.2011.04970.x
http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2036.2011.04970.x/full#apt4970-fig-0003

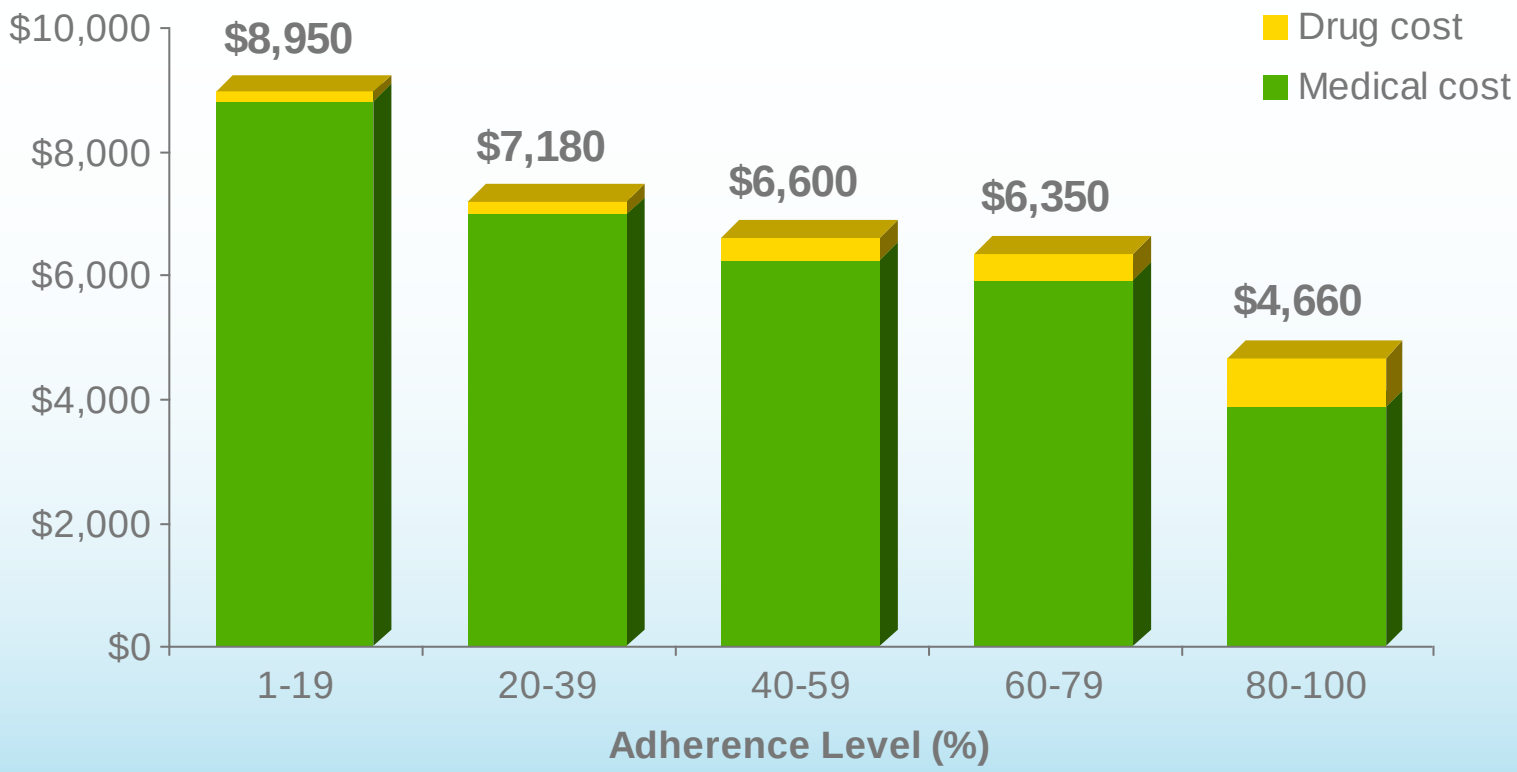
Role of Bridging Study
A form of anchor-based interpretation

- Correlates clinical difference (or change) with total direct and indirect medical care costs

- Defines the ‘minimal change’ clinically that would be associated with meaningful cost difference

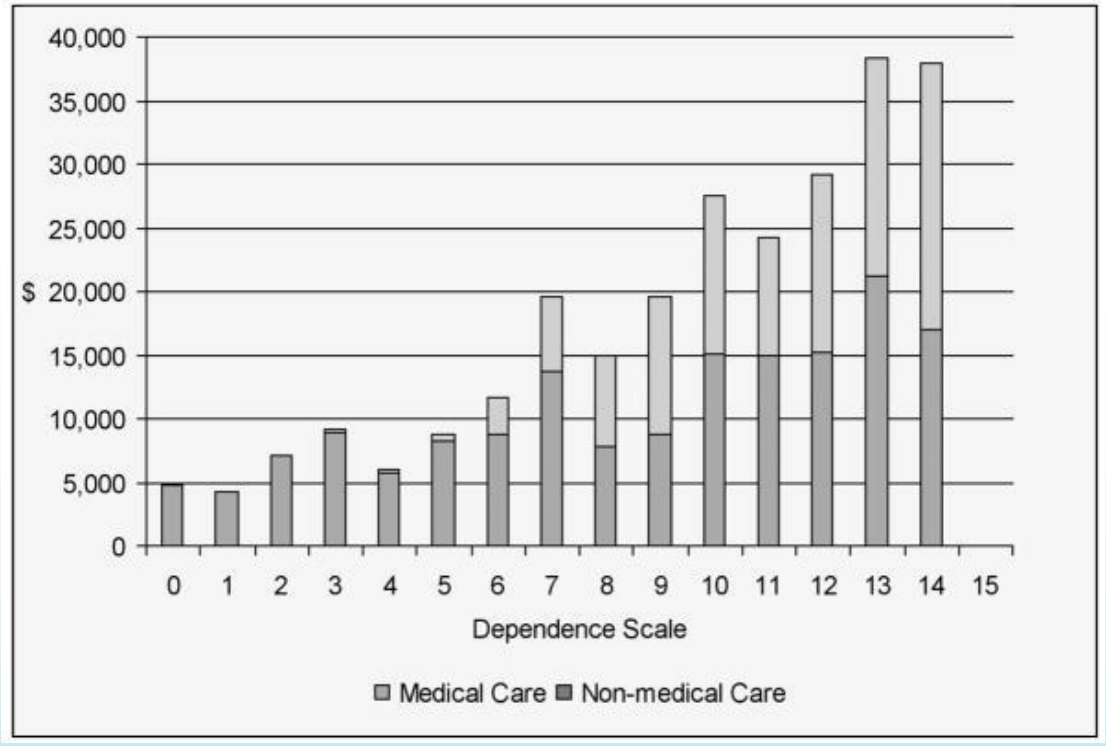
Example: Relating compliance to healthcare costs

Total Healthcare Cost per Patient per Year



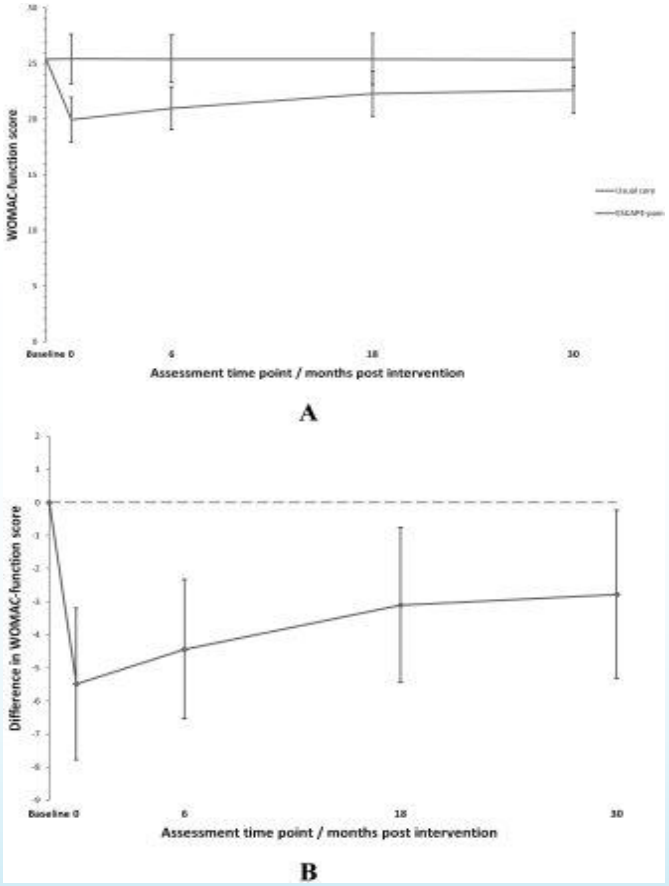
Source: Sokol, MC, McGuigan, KA, Verbugge, RR, Epstein, RS. Impact of Medication Adherence on Hospitalization Risk and Healthcare Cost. *Medical Care* 2005; 43: 521-530.

Example: Alzheimer's Disease Dependence Scale Relate Dependence Scale to Costs



Source: Zhu CW, Leibman C et al: Bridging from clinical endpoints to estimates of treatment value for external decision makers. J Nutr Health Aging 2009;13(3):256-259.

Long-term outcomes and costs of an integrated rehabilitation program for chronic knee pain: A pragmatic, cluster randomized, controlled trial



Arthritis Care & Research Volume 64, Issue 2, pages 238-247, 25 JAN 2012 DOI: 10.1002/acr.20642
http://onlinelibrary.wiley.com/doi/10.1002/acr.20642/full#fig2

Chronic Knee Pain – Impact of Rehab Program

	Difference from Usual Care	95% Confidence Interval
Total health and social costs	£1177	£-3609, £ 313
Total costs after 'trimming' outlier	£-24	£ -506, £ 413
Total costs after imputing missing data	£ -1118	£ -2566, £ -221

Source: Hurley MV, Walsh NE et al: Long-term outcomes and costs of an integrated rehabilitation program for chronic knee pain: a pragmatic, cluster randomized, controlled trial. Arth Care Res 2012;64(2):238-247.

Annual Healthcare Costs by MMSE disease-severity

Author (Year)	Country	Type	Mild		Mod.		Severe
Jonsson (2003)	Scand.	Total	**26-30** 60,730 SEK	**21-25** 93,959	**15-20** 184,081	**10-14** 226,876	**<10** 374,962
Wolsten-holme (1998)	UK	Direct	**>20** 8312 Pounds		**15-20** 11,643	**10-14** 15,681	
Lopez-Pousa (2001)	Spain	Total	**20-30** 5040 Euro		**11-19** 7704		**<11** 13,788

Source: Mauskopf J, Racketa J, Sherrill: Alzheimer's disease: the strength of association of Costs with different measures of disease severity. J Nutr Health Aging 2010:14(8):655-663.

Should studies be powered to detect economic outcomes?

- Favor
  - > What payers want to see
  - > Randomization handles baseline differences
  - > Goes beyond relating clinical outcome to economic value epidemiologically or in modeling
- Against
  - > Too much variability in costing – huge sample sizes
  - > Too many protocol mandated visits, etc. to tease out differences
  - > Setting is not ‘real world’ anyway

Using the ‘bridges’

- Before study initiated – examine statistical power to detect “X” difference in clinical measure – and model what economic savings would translate into.
  - > Challenge – is it enough?? And to whom??

- After study completion - economic models can be constructed
  - > “X” change in clinical measure = “y” change in expected dollars.
  - > Can be input into:
    - – Cost minimization models
    - – Cost benefit models
    - – Cost effectiveness models (cost/LYS)
    - – Cost utility (cost/QALY)

Conclusion

- Evolution of evidence
  - > Statistical
  - > Clinical
  - > Payer
- All about ‘what’s enough’ to create value?
- Goes beyond mechanism, pathway or other assumptions about ‘unmet needs’