

**Lessons Learned:
Surrogates & Intermediate
Outcomes**

David L. DeMets, Ph.D.

**Department of Biostatistics
and Medical Informatics
University of Wisconsin-Madison**

Definition of Surrogate & Intermediate Outcome

- **A physiologic or biological measurement that is used instead of a clinical outcome (e.g. live longer, feel good, function better)**
- **Surrogate may be used to**
 - **Develop a new intervention**
 - **Assess biological or mechanical activity**
 - **Assess clinical efficacy**

Appeal of Surrogates/Intermediate Outcomes

- **Criticism of clinical trials**
 - Too long
 - Too large
 - Too expensive

- **May allow for studies to be**
 - Smaller
 - Shorter and faster
 - Less expensive

Response Variables

- **Cancer**
 - Death or disease recurrence
 - Tumor shrinkage

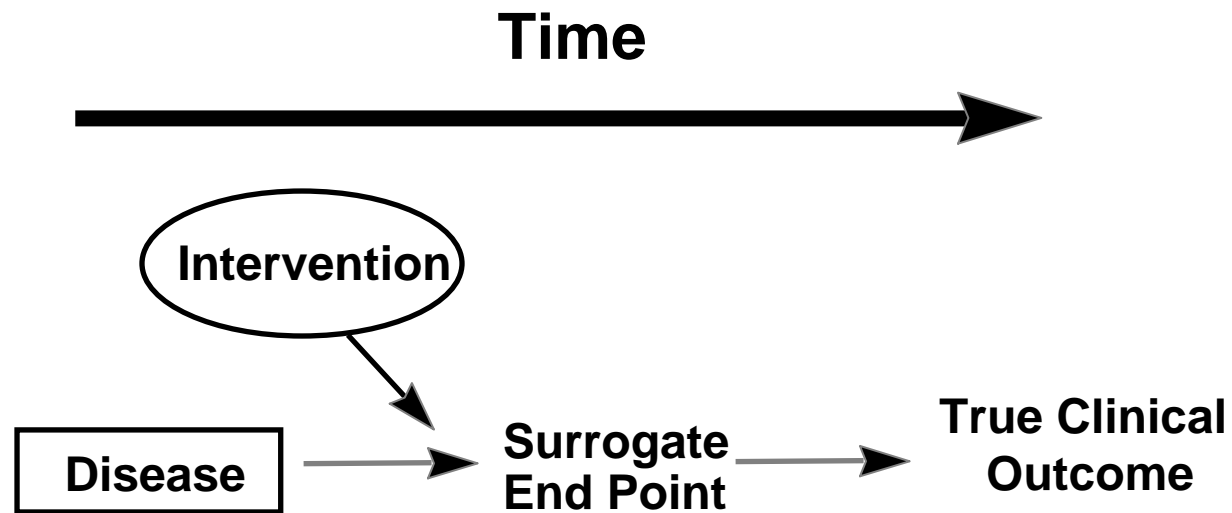
- **Cardiology**
 - Death, non fatal MI or hospitalization
 - Blood pressure, lipid levels, PVCs, cardiac output

Response Variables

- **AIDS**
 - Death or progression to AIDS
 - T4 Cells, viral load
- **Diabetes**
 - Death, visual impairment, kidney failure
 - Microaneurysms, clearance

Use of Surrogates

- **Phase I Trials**
 - **Maximum Dose/Dose Response**
- **Phase II Trials**
 - **Measures of Activity**
- **Phase III Trials**
 - **Supporting Evidence/Secondary Outcomes**
e.g., **Cholesterol Changes**
 - **Primary Outcome?**



The setting that provides the greatest potential for the surrogate endpoint to be valid. Reprinted from *Ann Intern Med* 1996; 125:605-13.

Reasons for failure of surrogate end points.

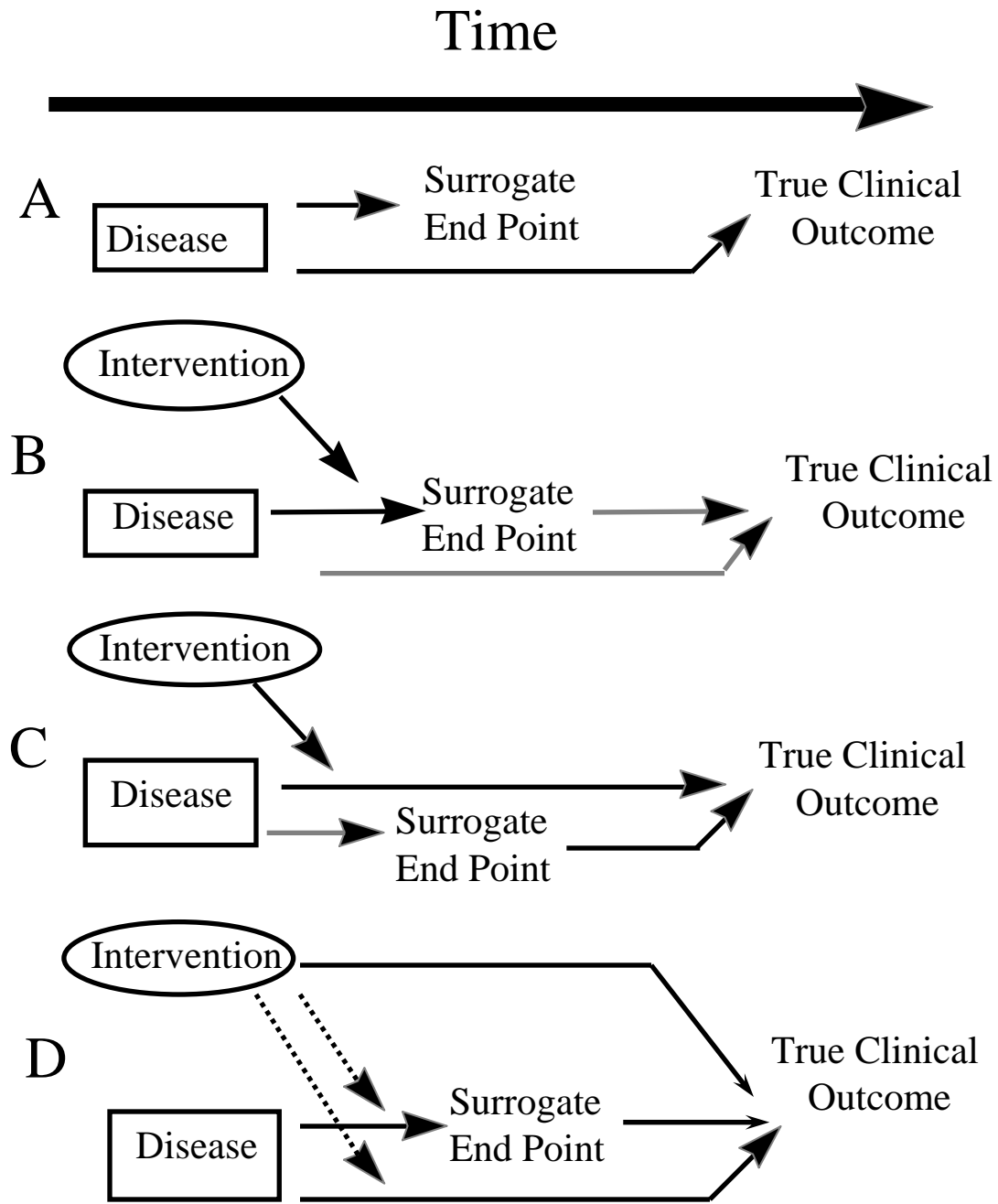
A. The surrogate is not in the causal pathway of the disease process.

B. Of several causal pathways of disease, the intervention affects only the pathway mediated through the surrogate.

C. The surrogate is not in the pathway of the intervention's effect or is insensitive to its effect.

D. The intervention has mechanisms for action independent of the disease process.

Dotted lines = mechanisms of action that might exist.



Concerns About Surrogates

- 1. Relationship between surrogate and true endpoint may not be causal, but coincidental to a third factor**
- 2. Other unfavorable effects of the drug**
- 3. Effect on surrogate may correlate with one clinical endpoint, but not others**

Intermediate/Surrogate Outcomes

- **Reliance on intermediate outcome might lead to incorrect conclusion about benefit or harm**
- **Consider a few examples**

Nocturnal Oxygen Therapy Trial (NOTT)

- **Hypothesis**

- Is continuous oxygen therapy better than nocturnal oxygen therapy in chronic obstructive lung disease patients?
 - Surrogates
 - Survival

- **Design**

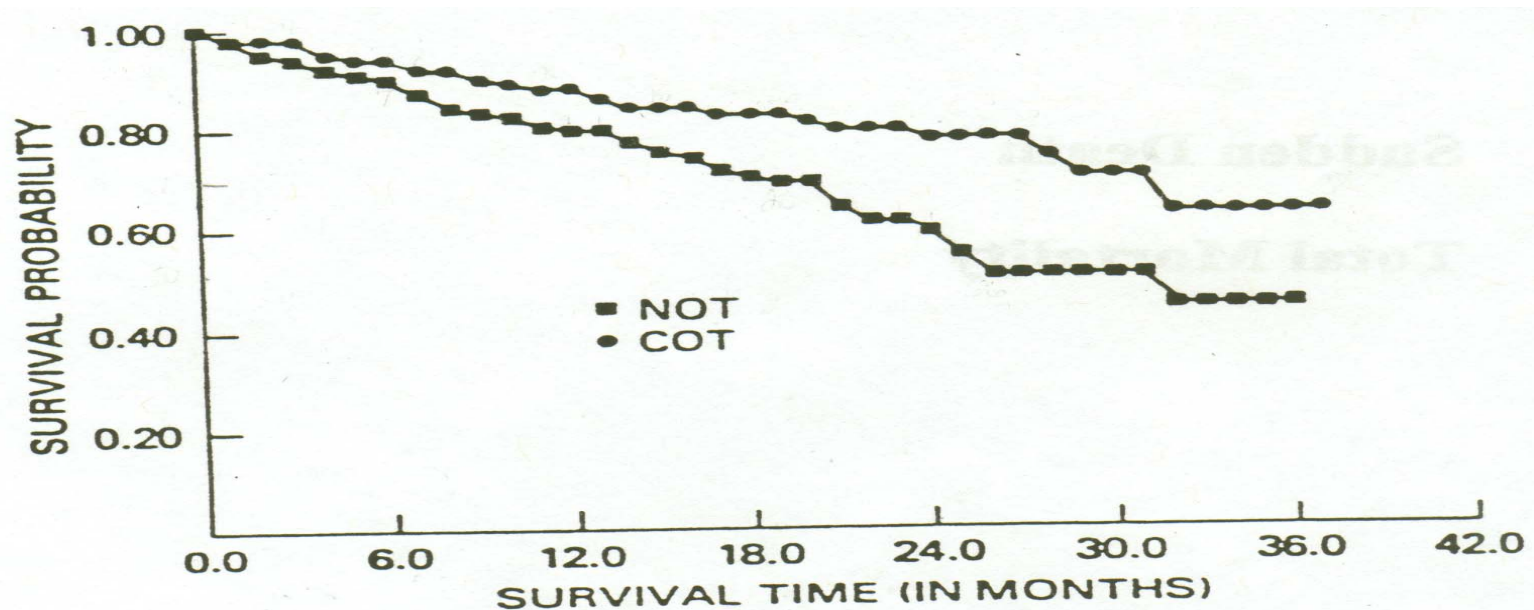
- 203 patients
- Two-sided 0.05 Type I error
- Powered for several intermediate outcomes
- Randomized, multicenter

Possible NOTT Surrogates

- **PaO₂**
- **Hematocrit**
- **FEV₁ % Predicted**
- **FVC % Predicted**
- **Maximum Workload**
- **Heart Rate**
- **Mean Pulmonary Artery Pressure**
- **Cardiac Index**
- **Pulmonary Vascular Resistance**
- **Neuropsychiatric Impairment**
- **Quality of Life**

The Nocturnal Oxygen Therapy Trial

NOTT Survival Experience for 102 Patients on Nocturnal Oxygen (NOT) and 101 Patients on Continuous Oxygen Therapy (COT)



Cardiac Arrhythmias

- **Cardiac arrhythmias associated with sudden death**
- **Class of drugs developed to suppress arrhythmias**
- **Drugs approved for high risk patients**
- **“Off-label” use increased**

Cardiac Arrhythmia Suppression Trial

Hypothesis

Does suppression of arrhythmia following an MI reduce incidence of:

- 1. Sudden death**
- 2. Total mortality**

Cardiac Arrhythmia Suppression Trial

- **Three Drug Arms vs. Placebo**
- **Double blind placebo control**
- **One Sided (0.025 Type I Error) for Benefit**
- **Advisory One Sided (0.025) for Harm**
- **Sequential monitoring plan**

Cardiac Arrhythmia Suppression Trial

Early Termination in Two Drug Arms

	Drugs	Placebo
Sudden Death	33	9
Total Mortality	56	22

Chronic Heart Failure

- **A major problem in heart disease**
- **Increased mortality, decreased quality of life**
- **Drugs developed to improve cardiac function**
- **Not known if survival or quality of life improved**

PROFILE

(Prospective Randomized Flosequinan Longevity Evaluation)

- Flosequinan is primarily a vasodilator
- Approved for CHF
 - improved exercise tolerance
 - reduced symptoms
 - slight adverse mortality
- PROFILE Design
 - randomized double blind multicenter
 - Mortality outcome
 - placebo vs. 75 mg vs. 100 mg
 - Class III or IV CHF

PROFILE Results

Flosequinan Dose

Total	75 mg	100 mg	Combined
Flosequinan Mortality	40/206 (19.4%)	201/964 (20.9%)	241/1170 (20.6%)
Placebo Mortality	43/238 (18.1%)	138/937 (14.7%)	181/1175 (15.4%)
Relative Risk	1.05	1.48	1.39
P-value	.83	.0004	.0009

SURROGATES

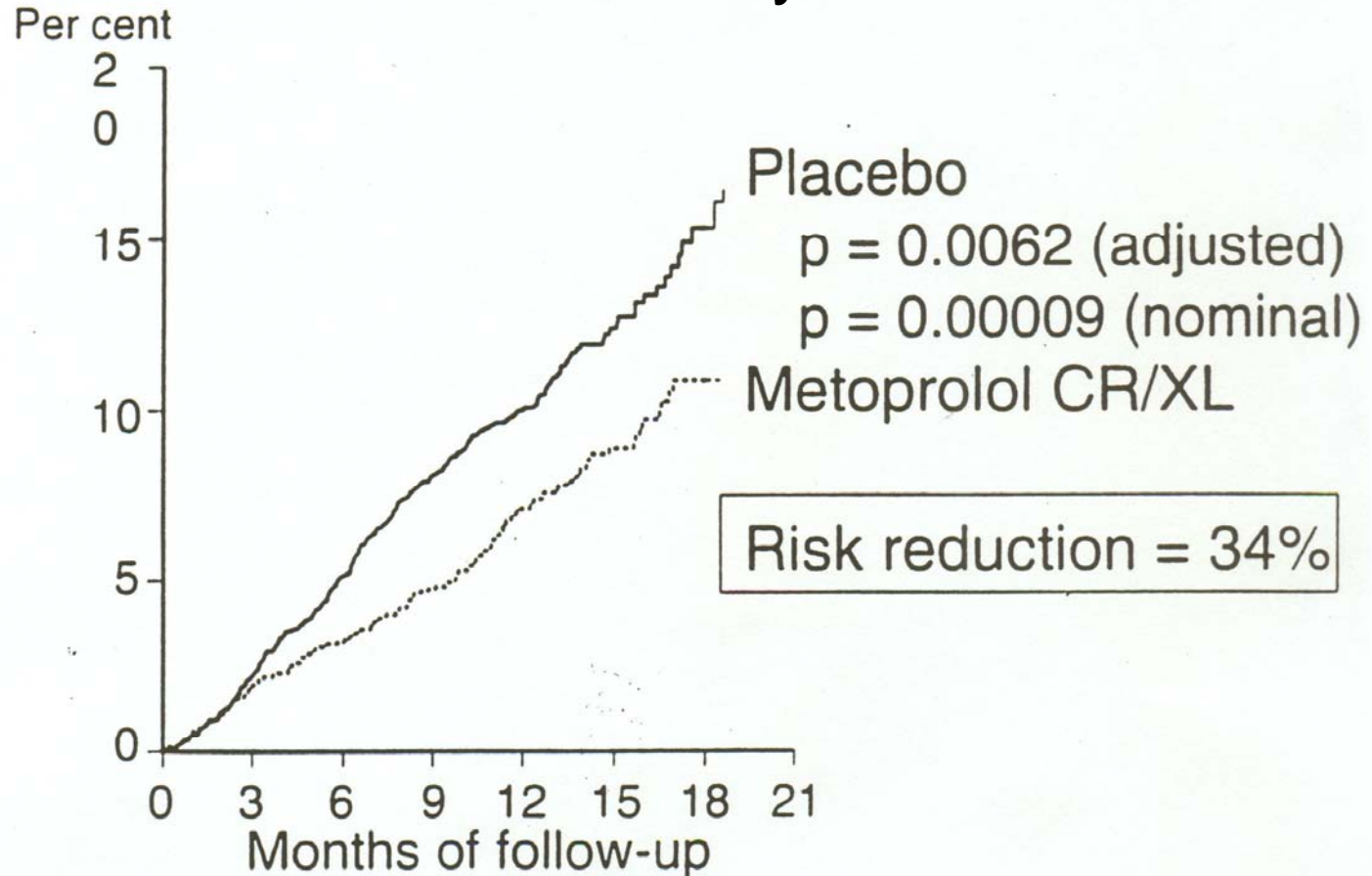
- **Can delay use of effective treatments**
- **Example: Beta blockers in congestive heart failure; betablockers known to**
 - **lower blood pressure**
 - **slow heart rate**
- **Beta blocker drugs not used for heart failure for a decade or more**

Beta-Blockers in Heart Failure

- **Then four trials**
 - 1) Metoprolol in MERIT [*JAMA* 283(10):1295-1302, 2000]
 - 2) Bisoprolol in CIBIS-II [*Lancet* 353: 9-13, 1999]
 - 3) Carvedilol in COPERNICUS [*New Engl J Med* 334(22):1651-58, 2001]
 - 4) Bucindolol in BEST [*Am J Cardiol* 1995;75:1220-3]
- **Class II-IV heart failure, low ejection fraction patients**
- **Demonstrated beneficial effects**

MERIT

Total Mortality



Data unblinded by ISaC

The MERIT-HF Study Group. ACC, March 1999

Intermediate/Surrogate Outcomes

- **Reliance on an intermediate outcome might lead to concluding harm when in fact intervention is beneficial**

Diabetes

- **Diabetes affects several organ systems (heart, kidney, eyes)**
- **Long duration causes visual impairment (diabetic retinopathy)**
- **Clinical Outcome**
 - **Blindness**
 - **Severe visual loss**
- **Surrogate**
 - **Microaneurysm (retinal small vessel deformity filled with blood)**

DCCT

(Diabetes Complication and Control Trial)

(*NEJM*, 1994)

- Hypothesis
Does tight control of glucose reduce visual impairment compared to normal control?
- Design
 - **Tight control achieved by intense monitoring of an insulin pump**
 - **Randomized multicenter trial**
 - **1441 diabetic patients**
 - **Followed for average of 6 years**

DCCT

(Diabetes Complication and Control Trial)

- **Results**

- **Early trends for microaneurysm were in negative direction, could perhaps have led to termination if the primary outcome**
- **Longer term follow-up showed definite reduction in visual impairment**
- **Trial terminated early for benefit**

Concluding Remarks on Surrogates

- **Surrogates play an important role in the development of Phase I, II, and pilot Phase III studies**
- **Treatments may affect more than one mechanism**
- **“Surrogates” do not reliably predict treatment on clinical outcome**
- **Problems seen in many disease areas**
- **Continued success in a given field is not even guaranteed**

References

- **Prentice RL: Surrogate endpoints in clinical trials: Definition and operational criteria. *Statistics in Medicine* 8:431-440, 1989**
- **Temple RJ: A regulatory authority's opinion about surrogate endpoints. In: "Clinical Measurement in Drug Evaluation" (Ed. WS Nimmo, GT Tucker). John Wiley & Sons Ltd., 1996.**
- **Fleming TR and DeMets DL: Surrogate endpoints in clinical trials: Are we being misled? *Annals of Int Med* 125(7):605-613, 1996**