Role and Potential of Surrogate Outcomes

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Surrogate Response Variables

- Laboratory measurement used as alternative or substitute for desired or ideal clinically relevant response (i.e., live longer or feel better)

- Advantages
  - Smaller sample size
  - Shorter follow-up
  - Easier
  - Cheaper
Validity of Surrogate Outcome Measures

- Surrogate must be predictive of clinical outcome
- All effects of intervention on clinical outcome must be captured by the surrogate
- Implies that biological mechanism and pathway of action is known
Surrogate Response Variables

• Requirements (Prentice, 1989)
  \( T = \) True clinical endpoint
  \( S = \) Surrogate
  \( Z = \) Treatment

• \( H_0: \ P(T|Z) = P(T |S,Z) \ P(S|Z) = P(S) \)

• Sufficient Conditions
  1. \( S \) fully captures effect of \( Z \) on \( T \)
     \( P(T|S,Z) = P(T|S) \)
  2. \( S \) is informative about \( T \)
     \( P(T|S) = P(T) \)
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, drug, device, procedure or nutritional intervention

3. Effect on surrogate may correlate with one clinical endpoint, but not others
Surrogates Can Be Useful

- Phase I Trials
  - Maximum Dose

- Phase II Trials
  - Measures of Activity
  - Dose response

- Phase III Trials
  - Supporting Evidence/Secondary Outcomes
    e.g., Cholesterol Changes
Surrogates To Evaluate New Frontiers?

Genomics

Diagnostic Trials  Prevention Trials  Gene Therapy Trials  Drug Development

(Speed Up Process)

Selected Targets  Selected Patients

Francis Collins (3/2001)
Reliance on “surrogates” can be problematic

- Many examples where use of surrogates as a primary outcome has been misleading
- Includes variety of diseases
- If a surrogate is validated for one member of a class, it is valid for
  - Other members of the same class?
  - Another class?
Problematic Surrogate Use

- Lower cholesterol without evidence of survival benefit
- Increase bone density without evidence of decreased fractures in osteoporosis
- Increase cardiac function in CHF without improving survival
- Decrease rates of arrhythmias without evidence of improving survival
- Lower blood sugar without evidence about diabetic complications or survival
NOTT
(Nocturnal Oxygen Therapy Trial)

• Hypothesis
Is continuous oxygen therapy better than nocturnal oxygen therapy in chronic obstructive lung disease patients?
  – Surrogates, Neurological, Quality of Life
  – Survival?

• Design
  – 203 Patients
  – Two-sided 0.05 Type I error
  – Randomized
  – Multicenter
  – Sequential data monitoring
Possible NOTT Surrogates

P_{\text{aO}_2}  
Hematocrit  
FEV_1 \% Predicted  
FVC \% Predicted  
Maximum Workload  
Heart Rate  
Mean Pulmonary Artery Pressure  
Cardiac Index  
Pulmonary Vascular Resistance
The Nocturnal Oxygen Therapy Trial

NOTT Survival Experience for 102 Patients on Nocturnal Oxygen (NOT) and 101 Patients on Continuous Oxygen Therapy (COT)
CAST
(Cardiac Arrhythmia Suppression Trial)

- Arrhythmias are associated with sudden death
- Drugs developed to suppress arrhythmias
- Hypothesis: Does suppression of arrhythmia following an MI reduce incidence of:
  1. Sudden Death
  2. Total Mortality
Cardiac Arrhythmia Suppression Trial (CAST)

- Randomized Double Blind
- Three Drug Arms vs. Placebo
- Multicenter Study
- Group Sequential Data Monitoring
- One Sided boundary (0.025 Type I Error) for Benefit
- Advisory One Sided boundary (0.025) for Harm
CAST
Early Termination in 2 Drug Arms

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<tr>
<th></th>
<th>Drugs</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>Sudden Death</td>
<td>33</td>
<td>9</td>
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<tr>
<td>Total Mortality</td>
<td>56</td>
<td>22</td>
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PROMISE
(Packer et al. NEJM, 1991)

• Rationale
  – Patients with advanced (Class IV) congestive heart failure have 40% one year mortality
  – Milrinone enhances cardiac contractility
  – Milrinone improved cardiac output, exercise tolerance, and symptoms

• Hypothesis
  Does milrinone increase survival in severe (Class III or IV) CHF patients?
PROMISE Design

- Randomized multicenter double-blind, placebo-control trial
- Patients with Class III or IV congestive heart failure for 3 months
- Two-sided 5% significance level, 90% power for 25% reduction in mortality
- 1088 patients entered
- Milrinone (10 mg/4 times per day) vs. matched placebo
- Standard therapy of digoxin, diuretics, and a converting enzyme inhibitor
PROMISE Mortality Results

Figure 1. Kaplan-Meier Analysis Showing Cumulative Rates of Survival in Patients with Chronic Heart Failure Treated with Milrinone or Placebo.

Mortality was 28 percent higher in the milrinone group than in the placebo group (P = 0.038). The numbers of patients at risk are shown at the bottom of the figure.
Vesnarinone: Trial I
(Temple, 1995)

- An inotrope and vasodilator
- A 60 mg dose had no effect on exercise tolerance or symptoms
- A 120 mg dose increases exercise tolerance and reduces symptoms
- 120 mg arm stopped early with increased mortality (6 vs. 16, $p < .01$)
- 60 mg arm continued

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<th></th>
<th>Plbo</th>
<th>60 mg</th>
<th>P</th>
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<tbody>
<tr>
<td>Mortality</td>
<td>33/238</td>
<td>13/239</td>
<td>.002</td>
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<tr>
<td>Morality &amp; Morbidity</td>
<td>50/238</td>
<td>26/239</td>
<td>.003</td>
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Trial II: VEST
(NEJM, 1998)

• Vesnarinone vs. Placebo
• 60mg vs. 30 mg vs. placebo
• NYHA Class III/IV CHF patients
• LVEF less than 30%
• 3833 patients randomized
• Primary Outcome: All cause mortality
• Secondary Outcome
  – Mortality plus CHF hospitalization
  – Quality of Life
VEST

Proportion of Patients Surviving

Time to Event (days)

- Placebo
- 30 mg of vesnarinone
- 60 mg of vesnarinone

NEJM, 1998
AIDS Clinical Trials

- Clinical Outcomes
  - Death
  - Progression to AIDS
  - Progression to ARC

- Surrogate Outcome
  - CD4 Cell Count?
CPCRA #002
(Community Program for Clinical Research in AIDS)

- Comparative trial of ddI vs. ddC
- HIV infected patients; AZT intolerant
- Randomized open label
- 467 patients
- Primary outcome
  Time to AIDS or death
- Secondary
  Changes in CD4 cell count
## Results

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<tr>
<th></th>
<th>ddl</th>
<th>ddC</th>
<th>p</th>
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<tbody>
<tr>
<td><strong>Death</strong></td>
<td>100 (43%)</td>
<td>88 (35%)</td>
<td>0.070</td>
</tr>
<tr>
<td>RR = 0.76</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Progression to AIDS or death</strong></td>
<td>157 (93%)</td>
<td>152 (88%)</td>
<td>0.930</td>
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<tr>
<td><strong>Change in CD4 cell count at 2 months</strong></td>
<td>20 cells</td>
<td></td>
<td>0.009</td>
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• Diabetes affects several organ systems (heart, kidney, eyes)
• Long duration causes visual impairment (diabetic retinopathy)
• Clinical Outcome
  – Blindness
  – Severe visual loss
• Surrogate
  – Micro-aneurysm (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
  – Longer term follow-up showed definite reduction in visual impairment and need for laser surgery
Osteoporosis
(Riggs et al. *NEJM*, 1990)

- Bone loss in postmenopausal women leads to increase risk of fracture
- Sodium Fluoride stimulates bone formation and increases bone mass (double)
- Hypothesis: Will fluoride treatment decrease rate of vertebral fractures?
- Design
  - Randomized, double-blind, placebo-controlled
  - 202 post menopausal women randomized
  - All received calcium supplementation
Osteoporosis Fluoride Trial Results

• Fluoride increased bone density by
  – 35% (p=0.0002) in spine
  – 12% (p=0.0002) in femoral neck

• Vertebral fractures higher on Fluoride
  (F 163, P 136, p<0.05)

• Non-vertebral fractures higher on Fluoride
  (72 vs 24; p = 0.01)

• Fluoride concluded not effective as a treatment for post-menopausal osteoporosis
Concluding Remarks on Surrogates

- Surrogates play an important role in Phase I, II, and Pilot Phase III studies.
- Results for Phase III very mixed
- Treatments may affect more than one mechanism.
- "Surrogates" do not reliably predict treatment effect on clinical outcome.
- Success for one drug in a class does not guarantee success for the next drug in same class
- Success in one class does not guarantee the next
- Reliance on "surrogates" should be minimized.