The Reciprocal Control Design for Trials in the Early Detection and Prevention of Disease: Clinical Considerations

Society for Clinical Trials Annual Meeting
Boston, MA
May 20, 2013

Barry Kramer, M.D., M.P.H.
Director
Division of Cancer Prevention
National Cancer Institute
Disclosure/Disclaimer

• No financial conflicts

• Opinions are mine, not official positions of the Federal Government or the National Institutes of Health
Prevention & Screening Studies: The Challenge

- Large numbers of participants followed for many years
- Consequent expenditure of substantial resources
- Environment of shrinking budgets and limited resources
- Interest in exploring new, more efficient approaches to prevention studies
Study Designs for Multiple Questions

- Requires “a broad view of research and a fertile imagination”
  - Be alert to opportunities to add research questions outside of their area of study
  - Consider collaborative funding sources

Laurence S. Freedman and Sylvan B. Green
Reciprocal Control Design

- Participants in each study arm receive an intervention for a particular disease, but also serve as controls for a different intervention and disease in the other arm.
Reciprocal Control Design

- Distinct from the single intervention, multiple endpoint design
- Optimal if each intervention is distinct, independent
- Outcome risks in the arms should be similar to provide comparable sample sizes
- Could include more than two arms; e.g., for multiple intervention frequencies
Prevention vs. Early Detection

- Preventive interventions may have unknown but plausible interactions with both diseases
  - Invalidates the key assumption of the reciprocal control design
  - Factorial design may be best in a prevention setting

- Focus in this talk is on early detection (screening)
Potential Benefits of the Reciprocal Control Design

• Increased efficiency
  o Sharing of resources; potential savings

• Improved recruitment and retention
  o All participants receive some intervention – encourages enrollment

• Opportunities for smaller NIH institutes and other funding agencies with limited resources
NIH Trans-Institute Discussions

- Consider potential inter-Institute trials
- Review USPSTF “I” screening recommendations (“I” = Insufficient evidence)
- Consider appropriate “pairing” of diseases, interventions, risk groups
USPSTF “I” Screening Recommendations

- Bladder cancer, oral cancer, pancreatic cancer
- Coronary heart disease
- Diabetes
- Kidney disease
- Thyroid disease
- Osteoporosis
- Dementia, Alzheimer’s disease
- Glaucoma, visual acuity in older adults

NCI Division of Cancer Prevention 2013
Hypothetical NIH Trial

Q1. Does screening with CT reduce pancreatic cancer mortality?
Q2. Does screening with coronary artery scan reduce MI mortality?

- Endpoints – Pancreatic cancer death, MI death
- Parameters
  - Type I error .05 (two-sided)
  - Power .9
Hypothetical NIH Trial Protocol

RANDOMIZATION
Women and Men
55-74 years of age

ARM 1
Annual CT for 5 years

ARM 2
Annual Coronary Artery Scan for 5 years

[10-year follow-up from entry]
## Sample Size - AVERAGE Mortality Risk Population
Pancreatic cancer rate 36/100K/yr, MI rate 95/100K/yr

<table>
<thead>
<tr>
<th>% Reduction</th>
<th>% Reduction</th>
<th>Pancreatic Cancer</th>
<th>MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>10</td>
<td>1,108,000</td>
<td>419,945</td>
</tr>
<tr>
<td>15</td>
<td></td>
<td></td>
<td>181,508</td>
</tr>
<tr>
<td>20</td>
<td></td>
<td></td>
<td>99,064</td>
</tr>
<tr>
<td>30</td>
<td></td>
<td></td>
<td>41,238</td>
</tr>
<tr>
<td>20</td>
<td>10</td>
<td>261,420</td>
<td>419,945</td>
</tr>
<tr>
<td>15</td>
<td></td>
<td></td>
<td>181,508</td>
</tr>
<tr>
<td>20</td>
<td></td>
<td></td>
<td>99,064</td>
</tr>
<tr>
<td>30</td>
<td></td>
<td></td>
<td>41,238</td>
</tr>
<tr>
<td>30</td>
<td>10</td>
<td>108,824</td>
<td>419,945</td>
</tr>
<tr>
<td>15</td>
<td></td>
<td></td>
<td>181,508</td>
</tr>
<tr>
<td>20</td>
<td></td>
<td></td>
<td>99,064</td>
</tr>
<tr>
<td>30</td>
<td></td>
<td></td>
<td>41,238</td>
</tr>
</tbody>
</table>

NCI Division of Cancer Prevention 2013
Sample Size - HIGH Mortality Risk Population
Pancreatic cancer rate 52/100K/yr, MI rate 160/100K/yr

<table>
<thead>
<tr>
<th>Pancreatic Cancer Mortality</th>
<th>MI Mortality</th>
<th>Pancreatic Cancer Number</th>
<th>MI Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>10% Reduction</td>
<td>15% Reduction</td>
<td>767,206</td>
<td>107,770</td>
</tr>
<tr>
<td>20%</td>
<td></td>
<td>58,819</td>
<td></td>
</tr>
<tr>
<td>30%</td>
<td></td>
<td>24,485</td>
<td></td>
</tr>
<tr>
<td>20% Reduction</td>
<td>15% Reduction</td>
<td>180,983</td>
<td>107,770</td>
</tr>
<tr>
<td>20%</td>
<td></td>
<td>58,819</td>
<td></td>
</tr>
<tr>
<td>30%</td>
<td></td>
<td>24,485</td>
<td></td>
</tr>
<tr>
<td>30% Reduction</td>
<td>15% Reduction</td>
<td>75,339</td>
<td>107,770</td>
</tr>
<tr>
<td>20%</td>
<td></td>
<td>58,819</td>
<td></td>
</tr>
<tr>
<td>30%</td>
<td></td>
<td>24,485</td>
<td></td>
</tr>
</tbody>
</table>
China Cancer Screening Trial

Lung Cancer
• Q1. Does annual or biennial CT reduce lung cancer mortality?
• Q2. Does annual CT reduce lung cancer mortality compared to biennial CT?

Colon Cancer
• Q3. Does Flex Sig reduce colon cancer mortality compared to FIT?
• Q4. Does Colonoscopy reduce colon cancer mortality compared to FIT?
• Q5. Does Colonoscopy reduce colon cancer mortality compared to Flex Sig?
China Trial Protocol

RANDOMIZATION
Women and Men 55-74 years of age

ARM 1
Annual CT Scan for 5 years
Flex Sig at entry and year 5

ARM 2
Biennial CT Scan
Colonoscopy at entry

ARM 3
Annual FIT for 5 years

NCI Division of Cancer Prevention 2013
China Screening Trial Design

Hybrid reciprocal control and comparative effectiveness design

• Endpoints – Lung cancer, colon cancer deaths
• Parameters
  o Type I error .05 (two-sided)
  o Power .9
  o 10-year follow-up from entry
Sample Size - HIGH Mortality Risk Population
Lung cancer rate 458/100K/yr, Colon cancer rate 55/100K/yr

<table>
<thead>
<tr>
<th>Lung Cancer Mortality</th>
<th>Colon Cancer Mortality</th>
<th>Lung Cancer</th>
<th>Colon Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Reduction</td>
<td>% Reduction</td>
<td>Number</td>
<td>Number</td>
</tr>
<tr>
<td>10</td>
<td>20</td>
<td>87,106</td>
<td>171,111</td>
</tr>
<tr>
<td>25</td>
<td></td>
<td>106,182</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td></td>
<td>71,230</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>20</td>
<td>20,548</td>
<td>171,111</td>
</tr>
<tr>
<td>25</td>
<td></td>
<td>106,182</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td></td>
<td>71,230</td>
<td></td>
</tr>
</tbody>
</table>
Challenges of Reciprocal Control Trials

- Design issues (e.g., difficulty in matching risk groups for candidate diseases)
- Funding and review mechanisms
- Unanticipated outcomes and harms
- Analytic issues (e.g., any effect of interactions?)
- Possibility of competing risk bias
Conclusions

• Launching large prevention and screening trials is becoming more difficult
• Investigators and funding agencies need to think beyond traditional study designs
• More efficient study designs are needed
• Reciprocal control design (RCD) is a promising option
• Before RCD trial initiation, consideration of potential pitfalls is necessary