National Cancer Institute

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

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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

Statistical Designs for Investigating Several Interventions in the Same Study: Methods for Cancer Prevention Trials. *JNCI 82(11):910-914 (1990)*

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
  - Sharing of resources; potential savings
- Improved recruitment and retention
  - 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

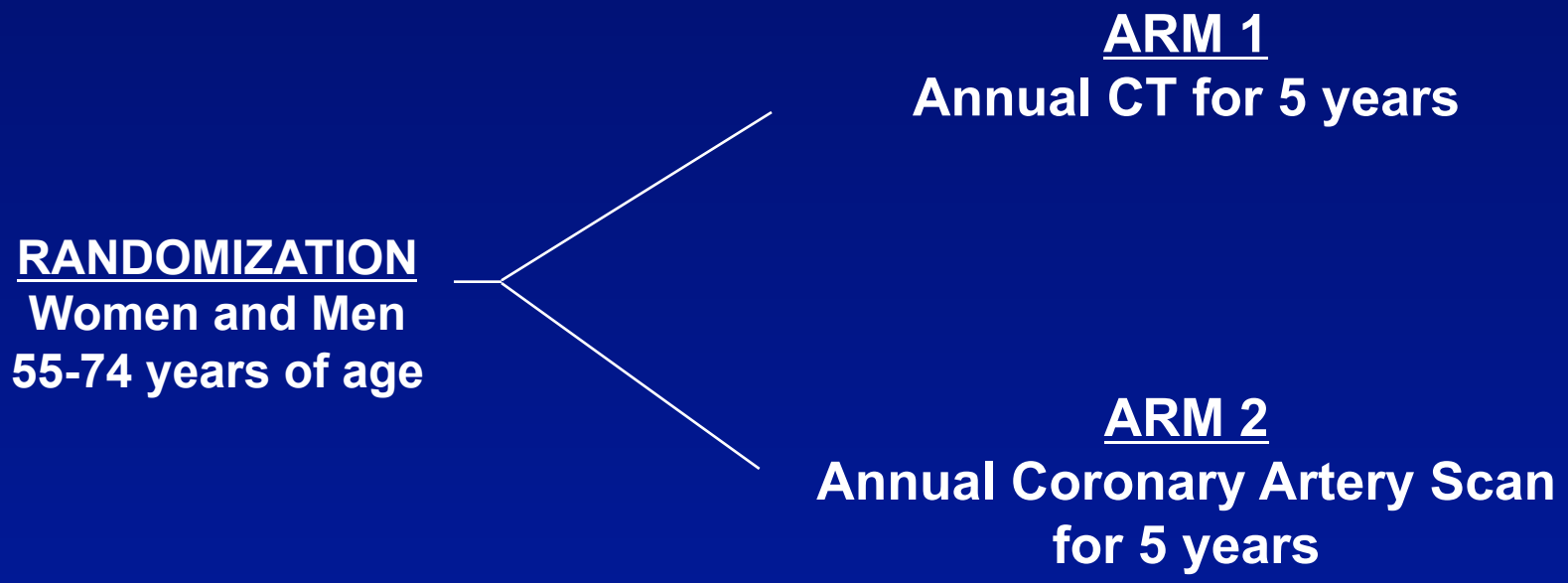
Hypothetical NIH Trial

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



[10-year follow-up from entry]

Sample Size - AVERAGE Mortality Risk Population
Pancreatic cancer rate 36/100K/yr, MI rate 95/100K/yr

Pancreatic Cancer Mortality	MI Mortality	Pancreatic Cancer	MI
% Reduction	% Reduction	Number	Number
10	10	1,108,000	419,945
	15		181,508
	20		99,064
	30		41,238
20	10	261,420	419,945
	15		181,508
	20		99,064
	30		41,238
30	10	**108,824**	419,945
	15		181,508
	20		**99,064**
	30		41,238

NCI Division of Cancer Prevention 2013

Sample Size - HIGH Mortality Risk Population
Pancreatic cancer rate 52/100K/yr, MI rate 160/100K/yr

Pancreatic Cancer Mortality	MI Mortality	Pancreatic Cancer	MI
% Reduction	% Reduction	Number	Number
10	15	767,206	107,770
	20		58,819
	30		24,485
20	15	180,983	107,770
	20		58,819
	30		24,485
30	15	**75,339**	107,770
	20		**58,819**
	30		24,485

China Cancer Screening Trial

Lung Cancer

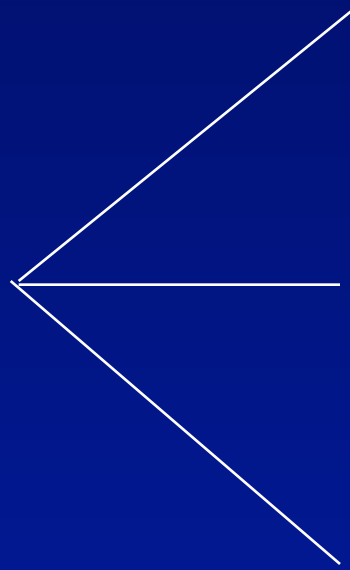
- Q1. Does annual or biennial CT reduce lung cancer mortality?
- Q2. Does annual CT reduce lung cancer mortality compared to biennial CT?

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

China Screening Trial Design

Hybrid reciprocal control and comparative effectiveness design

- **Endpoints – Lung cancer, colon cancer deaths**
- **Parameters**
  - **Type I error .05 (two-sided)**
  - **Power .9**
  - **10-year follow-up from entry**

Sample Size - HIGH Mortality Risk Population
Lung cancer rate 458/100K/yr, Colon cancer rate 55/100K/yr

Lung Cancer Mortality	Colon Cancer Mortality	Lung Cancer	Colon Cancer
% Reduction	% Reduction	Number	Number
10	20	87,106	171,111
	25		106,182
	30		71,230
20	20	20,548	171,111
	25		106,182
	30		71,230

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