Reciprocal Control and Other Designs for Investigating Multiple Interventions in the Same Study

Laurence Freedman
Gertner Institute for Epidemiology and Health Policy Research
COMMENTARY

Statistical Designs for Investigating Several Interventions in the Same Study: Methods for Cancer Prevention Trials

Laurence S. Freedman,* Sylvan B. Green

While the importance of prospective randomized clinical trials is widely appreciated among medical researchers and practitioners, pressure due to a shortage of funds for such projects is increasing. Trials of interventions for disease prevention often require many thousands of subjects and a follow-up period of many years. Such trials can be very costly. It is therefore desirable to explore carefully the possibilities of improving the efficiency of study designs.

There are two interventions, A and B, each having two levels (administered or not administered), then the $2 \times 2$ factorial design consists of four groups of subjects receiving (a) neither A nor B (group 1), (b) only A (group 2), (c) only B (group 3), or (d) both A and B (group 4). Usually, these four groups have equal numbers of individuals, in which case the design is "balanced," but this is not a necessary condition for the factorial design. It is necessary, however, that the various interventions can be given together, in the same doses as when given separately.
Why test multiple interventions in the same study?

1. Efficiency – potential savings of time and money
2. (Sometimes) Interest in joint effects of interventions
Available Designs for Multiple Interventions

1. Separate studies
2. Reciprocal control
3. All versus none
4. Factorial
Because our focus is on reciprocal control designs, I will discuss here only studies where the target outcome for each intervention is different.

**Examples**

- Low dose CT of the lung for screening lung cancer
- PSA for screening prostate cancer
- Low-fat diet for preventing breast cancer
- Hormone replacement therapy for preventing MI
Separate studies

- Does low dose CT reduce lung cancer mortality?
- Does PSA reduce prostate cancer mortality?

**Study 1**

- Randomize
  - Low dose CT of lung
  - No Intervention

**Study 2**

- Randomize
  - PSA
  - No Intervention
Reciprocal Control Design (Byar)

- Group 1 receives low dose CT of lung
- Group 2 receives PSA
Reciprocal Control Design (Byar)

- Does low dose CT reduce lung cancer mortality?
  Compare lung cancer mortality rates:
  Low dose CT group v PSA group

- Does PSA reduce prostate cancer mortality?
  Compare prostate cancer mortality rates:
  PSA group v Low dose CT group
Reciprocal Control Design

Assumptions for valid comparison

- Low dose CT of lung has no effect on prostate cancer mortality
- PSA has no effect on lung cancer mortality
- In particular, lung cancer mortality and prostate cancer mortality are independent risks
Reciprocal Control Design

Advantages over separate studies

- Half the number of patients needed to answer the two questions

- Avoids “no intervention” group – easier recruitment, better compliance (?)
All versus None Design

- Group 1 receives Low dose CT of lung and PSA
- Group 2 receives neither
Main interest is in the combination of Low dose CT of lung and PSA

The screening program is offered as a package and the interest is in the effect of the package on mortality from lung cancer and prostate cancer

OR

(See next slide)
All or None Design

Assumptions for valid comparison 2

We want to estimate the effect of each intervention separately:

- Low dose CT of lung has no effect on prostate cancer mortality
- PSA has no effect on lung cancer mortality
- Low dose CT of lung and PSA testing do not “interact”
All or None Design

Advantages over separate studies

- Half the number of patients needed to answer the two questions
- Can study the combined effect of the interventions
- When the two interventions form a natural combination - easier recruitment, better compliance (?)
All or None

versus

Reciprocal Control

for estimating separate effects

- Both require the assumption that neither intervention affects the other outcome.
- All or None requires the extra assumption of no interaction.
- Choice between them also rests on which design leads to easier recruitment and better compliance.
All or None (AoN) versus Reciprocal Control (RC)

<table>
<thead>
<tr>
<th>Low dose CT of lung</th>
<th>PSA</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>AoN</td>
<td>RC</td>
<td>AoN</td>
</tr>
<tr>
<td>None</td>
<td>RC</td>
<td>AoN</td>
</tr>
</tbody>
</table>
Factorial Design

- Group 1: Low dose CT of lung + PSA
- Group 2: Low dose CT of lung
- Group 3: PSA
- Group 4: No intervention
Factorial Design

Advantages and Disadvantages

✔ Allows testing of assumptions that are needed in the Reciprocal Control and All or None designs

✗ Greater complexity

✗ Recruitment and compliance may suffer
## Compliance rates

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Separate</th>
<th>All or None*</th>
<th>Reciprocal Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung X-ray</td>
<td>95%</td>
<td>91%</td>
<td>95%</td>
</tr>
<tr>
<td>No Lung X-ray</td>
<td>89%</td>
<td>89%</td>
<td>93%</td>
</tr>
<tr>
<td>PSA</td>
<td>95%</td>
<td>93%</td>
<td>95%</td>
</tr>
<tr>
<td>No PSA</td>
<td>48%</td>
<td>48%</td>
<td>60%</td>
</tr>
</tbody>
</table>

* Data from the PLCO trial

Assuming that:

For **active interventions**, All or None studies have lower compliance rates than other designs.

For **non-active interventions**, RC studies have higher compliance rates than other designs.
A hypothetical numerical example 2
Numbers required for 90% power to detect a 20% reduction in prostate or lung cancer mortality

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Separate</th>
<th>All or None</th>
<th>Reciprocal Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>99,900</td>
<td>74,000</td>
<td>41,100</td>
</tr>
<tr>
<td>Prostate</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### A hypothetical numerical example 3

#### Recruitment costs

<table>
<thead>
<tr>
<th></th>
<th>Separate</th>
<th>All or None*</th>
<th>Reciprocal Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost per participant</td>
<td>$18</td>
<td>$20</td>
<td>$16</td>
</tr>
</tbody>
</table>

Assuming that participants prefer to do one screening test over zero tests or two tests.
A hypothetical numerical example 4

**Total recruitment costs**

<table>
<thead>
<tr>
<th></th>
<th>Separate</th>
<th>All or None*</th>
<th>Reciprocal Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cost</td>
<td>$1.80m</td>
<td>$1.48m</td>
<td>$0.66m</td>
</tr>
</tbody>
</table>
Conclusions

1. Multiple intervention designs, with each intervention targeting a different health outcome have the potential to save costs, compared to conducting separate studies.

2. Careful attention needs to be paid to the assumption that each intervention does not affect the non-targeted outcome.

3. Selection of the design should be based on pilot studies evaluating recruitment and compliance.