Matched Studies in Medical Research

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Division of Biostatistics
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What is a Matched Pairs Design?

- Data consisted of observations of treatment outcome and control outcome on subjects that are paired.
- Pairing is done in the hope that all other factors are the same within a pair.
- Comparison of treatment and controls is between like subjects.
Examples
Biological Matching

• Diabetic Retinopathy LASER
  – Patient eyes randomized to treatment or not.
  – Event time to loss of vision

• Effects of Skin Graft HLA matching on burn patients
  – Patient’s with extensive burns given grafts which are 8/8 match or mismatched HLA
  – Time to graft failure measured
Examples

Biological Examples

• Study of a surgical device to show tumor cells
  – Mice have tumor implanted in one flank
  – Mouse injected with radioactive iodine. Theory is tumor will pick up iodine have higher radioactivity count then opposite side.
  – Small pen like counter used to measure radioactive count
  – Experiment complicated by iodine absorption in thymus
Examples
Tests Based on Matched subjects

• Comparison of drug 6-MP with placebo (Freireich et al. Blood 1963)
  – Multicenter trial of 6-MP as a remission maintenance therapy for children with acute leukemia
  – At each hospital patients in remission following prednisone therapy matched on disease status and one of pair randomized to 6-MP one to placebo
  – Study measured time to relapse
Tests Based on matched subjects
Retrospective studies

- Studies using retrospective large cohort samples
- Number of treated cases is small
- Number of control cases is large
- Each treated case is matched on some key risk factors to a treated case
Test Based on matched studies
Prospective studies

• Studies require a relatively homogenous population so it is easy to find a match

• Can match on only a few characteristics
Advantages of Design

• Allows comparison of like to like patients

• Allows additional data collection on smaller cohort of patients

• Simpler to understand
Disadvantages of design
Retrospective Studies

• Don’t use all the data
  – Cases without control deleted
  – In survival outcomes some pairs with censored outcomes are deleted

• Can not examine risk factors used to match subjects

• Outcome may depend on how you matched
Disadvantages of design
Prospective Studies

• Logistics
  – Need to find match
  – What to do while waiting
  – How to randomize
  – Need similar measurement for each pair

• Dropouts
  – What to do with pair when there is a drop-out—keep as solo, drop pair, find new match
Alternatives to Matched Designs

• Regression Adjusted Analysis
• Stratified Analysis
• Propensity Score Adjusted Designs
  – Fit Logistic regression model to chance a subject got treatment
  – Predicted probability is a propensity score
  – Stratify analysis, match on propensity score, use propensity in regression to make adjustment for risk factors
Example of Matched Pair Design
Crossover Designs

• Two treatments A and B
• Patients randomized to one of two scenarios
  1. Treatment A ->washout-> Treatment B
  2. Treatment B-> washout-> Treatment A
• If there is no carryover effect (Effect of A in 1 same as effect in 2) then the crossover study is analyzed as a matched pairs using
Tests in Crossover Design

$\mu_j$—Patient effect  \quad $\tau$—Effect of Treatment A

$\lambda_A$ ($\lambda_B$)—Carryover effect of A (B) in Period 1

<table>
<thead>
<tr>
<th></th>
<th>Period 1</th>
<th>Period 2</th>
<th>Difference</th>
<th>Sum</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/B</td>
<td>$\mu_j + \tau$</td>
<td>$\mu_j + \lambda_A$</td>
<td>$\tau - \lambda_A$</td>
<td>$2\mu_j + \tau + \lambda_A$</td>
</tr>
<tr>
<td>B/A</td>
<td>$\mu_k$</td>
<td>$\mu_k + \tau + \lambda_B$</td>
<td>$\tau + \lambda_B$</td>
<td>$2\mu_k + \tau + \lambda_B$</td>
</tr>
</tbody>
</table>

• Comparison of sums in two arms tests for carryover effect—Independent two sample test

• No carryover use paired test on crossover differences

• Significant carryover effect use independent two sample test on period 1 data only
Advantages of Crossover Trials
No Carryover

• To obtain the same number of observations as a parallel design fewer patients need to be recruited
• To obtain the same power or precision as a parallel design fewer patients are needed
Disadvantages of Crossover Designs

• Dropouts
• Not reasonable for disease where the patient may deteriorate over time
• Complicated Analysis
• Period by treatment interactions
• Carryover effects
• For last two problems the data in the first period only is used
Approach 1 to Analysis of Paired Data

Data

\((X_1, Y_1), \ldots, (X_n, Y_n)\)

- Compute difference between individuals within a pair. Base tests on \(d_i = (X_i - Y_i)\). Test if the \(d_i\)'s are sampled from a population centered at zero.

- Examples of tests for continuous data
  - Paired t-test
  - Sign test
  - Sign Rank Test
  - McNemar’s test
Approach 2 to Analysis of Paired Data

Data

\((X_1, Y_1), \ldots, (X_n, Y_n)\)

- \(X\) has mean \(\mu_X (M_X)\)
- Variance \(\sigma_X^2\)
- \(Y\) has mean \(\mu_Y (M_Y)\)
- Variance \(\sigma_Y^2\)
- \(\text{Cov}(X, Y) = \sigma_{xy}\)

- Test based on \((M_X - M_Y)\)
- Variance of \((M_X - M_Y) = \text{Var}[M_X] + \text{Var}[M_Y] - 2 \text{Cov}[M_X, M_X]\)
- Test Statistic

\[
T = \frac{(M_X - M_Y)}{(S_X^2/n + S_Y^2/n - 2*S_{xy}/n)}
\]
Two Approaches with Normal Data

• \((M_X - M_Y) = \text{average values of the } d\text{'s in approach 1}\)
• \(\text{Var}[M_X - M_Y] = \text{Variance of } d\text{'s in approach 1}\)
• Two tests give same result
• Note when \(S_{xy} = 0\) the T test is not the usual two sample t-test in textbooks since that assumes equal variances
## Affect of Incorrect Use of Unpaired t-test

- Paired samples of size 20
- Data Bivariate Normal (1,1), $\sigma_x = \sigma_y = 1$, Correlation $\rho$, 100,000 samples

<table>
<thead>
<tr>
<th>$\rho$</th>
<th>Unpaired</th>
<th>Paired</th>
<th>$\rho$</th>
<th>Unpaired</th>
<th>Paired</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.9</td>
<td>0.157</td>
<td>0.048</td>
<td>0.9</td>
<td>0.000</td>
<td>0.049</td>
</tr>
<tr>
<td>0.8</td>
<td>0.145</td>
<td>0.051</td>
<td>0.8</td>
<td>0.000</td>
<td>0.049</td>
</tr>
<tr>
<td>0.7</td>
<td>0.133</td>
<td>0.050</td>
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<td>0.001</td>
<td>0.050</td>
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<tr>
<td>0.6</td>
<td>0.120</td>
<td>0.050</td>
<td>0.6</td>
<td>0.004</td>
<td>0.050</td>
</tr>
<tr>
<td>0.5</td>
<td>0.108</td>
<td>0.051</td>
<td>0.5</td>
<td>0.007</td>
<td>0.049</td>
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<tr>
<td>0.4</td>
<td>0.096</td>
<td>0.050</td>
<td>0.4</td>
<td>0.013</td>
<td>0.050</td>
</tr>
<tr>
<td>0.3</td>
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<td>0.051</td>
<td>0.3</td>
<td>0.021</td>
<td>0.051</td>
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<tr>
<td>0.2</td>
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<td>0.050</td>
<td>0.2</td>
<td>0.030</td>
<td>0.051</td>
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<tr>
<td>0.1</td>
<td>0.061</td>
<td>0.049</td>
<td>0.1</td>
<td>0.039</td>
<td>0.050</td>
</tr>
<tr>
<td>0</td>
<td>0.051</td>
<td>0.050</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Comparison of Number of Patients needed—Paired vs. parallel design

• Assume testing mean difference = 0 versus mean difference = Δ
• Two sided test with 5% type one error
• Data normal with standard deviations of 1
• Either use paired t-test for paired data test or an unpaired t-test with assumed equal variances for the parallel design
• Values from Proc Power in SAS
## Comparison of Sample Sizes Needed

<table>
<thead>
<tr>
<th>Difference in Means = 0.5</th>
<th>Difference in Means = 1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Paired Design---Number of Pairs</strong></td>
<td><strong>Paired Design---Number of Pairs</strong></td>
</tr>
<tr>
<td><strong>rho</strong></td>
<td><strong>80% power</strong></td>
</tr>
<tr>
<td>-.5</td>
<td>97</td>
</tr>
<tr>
<td>-.3</td>
<td>84</td>
</tr>
<tr>
<td>-.1</td>
<td>72</td>
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<tr>
<td>0</td>
<td>65</td>
</tr>
<tr>
<td>.1</td>
<td>59</td>
</tr>
<tr>
<td>.3</td>
<td>46</td>
</tr>
<tr>
<td>.5</td>
<td>34</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Parallel Design</strong></th>
<th><strong>Parallel Design</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N per arm</strong></td>
<td>64 per arm</td>
</tr>
<tr>
<td><strong>N total</strong></td>
<td>128 patients</td>
</tr>
</tbody>
</table>
Examples

Biological Examples

• Study of a surgical device to show tumor cells
  – Mice have tumor implanted in one flank
  – Mouse injected with radioactive iodine. Theory is tumor will pick up iodine have higher radioactivity count then opposite side.
  – Small pen like counter used to measure radioactive count
  – Experiment complicated by iodine absorption in thymus
### Number of radioactive counts in 60 seconds

<table>
<thead>
<tr>
<th>control flank</th>
<th>Tumor flank</th>
<th>difference</th>
<th>Rank of</th>
<th>diff</th>
<th>Sign</th>
</tr>
</thead>
<tbody>
<tr>
<td>117</td>
<td>121</td>
<td>4</td>
<td>1</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>279</td>
<td>336</td>
<td>57</td>
<td>8</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>259</td>
<td>400</td>
<td>141</td>
<td>11</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>432</td>
<td>521</td>
<td>89</td>
<td>10</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>455</td>
<td>399</td>
<td>-56</td>
<td>7</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>601</td>
<td>798</td>
<td>197</td>
<td>12</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>43</td>
<td>14</td>
<td>4</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>58</td>
<td>69</td>
<td>11</td>
<td>3</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>93</td>
<td>114</td>
<td>21</td>
<td>5</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>88</td>
<td>156</td>
<td>68</td>
<td>9</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>132</td>
<td>174</td>
<td>42</td>
<td>6</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>159</td>
<td>169</td>
<td>10</td>
<td>2</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>
Sign Test

• $H_0$: Median Difference = 0
• $H_A$: Median Difference > 0
• Test based on the number of positive differences $B = 11$, $n = 12$
• Reject $H_0$ if $B$ is too large
• p-value $Pr[B > b_{obs} | p = 1/2]$ with $B \sim \text{Binomial}$ or
  
  • $Pr[Z > (b_{obs} - (n/2))/\{n/4\}^{1/2}]$ if $n$ is large, $Z \sim \text{Normal}[0,1]$

Here $p = Pr[B \geq 11 | n = 12, p = 1/2] = 12 \cdot p^{12} + p^{12} = .003174$
Wilcoxon Sign Rank Test

- \( H_0 \): Median Difference = 0
- \( H_A \): Median Difference > 0
- Rank Absolute Values of Differences--- \( R_i \) rank of \( i^{th} \) pair
- Add up ranks associated with positive differences \( T^+ \)
- Compute \( E_o[T^+] = \frac{n(n+1)}{4} \), \( \text{Var}_o[T^+] = \frac{n(n+1)(2n+1)}{24} \)
- Standardized test statistic is \( Z = \frac{T^+ - E_o[T^+]}{\text{Var}_o[T^+]^{1/2}} \)
- \( p \)-value = \( \text{Pr}[Z > z] \), \( Z \sim \text{Normal}(0,1) \)

- In example \( T^+ = 71 \), \( E_o[T^+] = 39 \), \( \text{Var}_o[T^+] = 162.5 \), \( z = 2.51 \), \( p = 0.006 \)
Binary Data

McNemar Test

• Comparison of two skin creams
  – Put different cream on each arm
  – Measure yes or no did cream cure rash

<table>
<thead>
<tr>
<th></th>
<th>Cream A</th>
<th>Cream B</th>
</tr>
</thead>
<tbody>
<tr>
<td>yes</td>
<td></td>
<td>75</td>
</tr>
<tr>
<td>no</td>
<td>25</td>
<td>45</td>
</tr>
</tbody>
</table>

• Test based on n=25+45=70 discordant pairs
Binary Data

McNemar Test

• If no difference in treatments the chance of A yes, B No= chance of A no, B yes=1/2
• Test statistic based on $p=\frac{\text{Number A no, B yes}}{n}$
• Test statistic $Z=\frac{p-1/2}{\sqrt{0.5/n}}$
• Here $p=\frac{25}{70}=0.357$
• $Z=-2.39$
• $p=2\times\Pr[Z>-2.39]=0.0168$
Paired Survival Data
CTSI Supplemental Grant

- Paired data problems are more complex due to censoring
- Major complication is that in most techniques for comparison pairs where the patient with the smallest on study time is censored are omitted
- Coming soon an annotated bibliography of techniques on the CTSI webpage
Summary

• Paired data designs are a useful tool in medical studies
  – if they are analyzed by proper statistical techniques
  – if there is no expectation of studying variables patients are matched on
  – if the data is biologically matched
  – for crossover designs with no carryover effect
Summary

• Paired data designs may not be the best when they are drawn from large data bases
• Paired data designs require more logistical work then parallel data designs
• Paired data designs may suffer a loss of efficiency when patients drop out
• For many parameters point and interval estimation in paired designs is hard to do
Resources

- The **Clinical and Translation Science Institute (CTSI)** supports education, collaboration, and research in clinical and translational science: [www.ctsi.mcw.edu](http://www.ctsi.mcw.edu)

- The **Biostatistics Consulting Service** provides comprehensive statistical support [www.mcw.edu/biostatistics.htm](http://www.mcw.edu/biostatistics.htm)
Free Drop-In Consulting

- **MCW**: Tuesdays & Thursdays 1– 3 pm
  - Health Research Center, H2400
- **Froedtert**: Mondays, Wednesdays, Fridays 1 – 3 pm
  - Froedtert Pavilion, L772A- TRU offices
- **VA**: Every Monday, 9:30 – 10:30 am
  - VA Medical Center, Room 70-A 314-A
- **Marquette**: Every Tuesday, 8:30 – 10:30 am
  - School of Nursing-Clark Hall, Office of Research & Scholarship: 112D
Questions?