Matched Studies in Medical Research

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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 radio-active 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

μ_j—Patient effect τ—Effect of Treatment A

λ_A (λ_B)—Carryover effect of A (B) in Period 1

	Period 1	Period 2	Crossover Difference Trt A-Trt B	Sum
A/B	$\mu_j+\tau$	$\mu_j+\lambda_A$	$\tau-\lambda_A$	$2\mu_j+\tau+\lambda_A$
B/A	μ_k	$\mu_k+\tau+\lambda_B$	$\tau+\lambda_B$	$2\mu_k+\tau+\lambda_B$

- 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 μ_X (M_X) Variance σ_x^2 Y has mean μ_Y (M_Y) Variance σ_Y^2

Cov(X,Y)=σ_{xy}

- Test based on (M_X - M_y)
- Variance of (M_X - M_y) =Var[M_X]+ Var[M_Y]-2 Cov[M_X,M_X]
- Test Statistic

$$T= (M_X - M_y) /(S_x^2/n +S_y^2/n-2*S_{xy}/n)$$

Two Approaches with Normal Data

- $(M_X - M_y)$ = average values of the d's in approach 1
- $Var[M_X - M_y]$ =Variance of d'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 ρ, 100,000 samples

ρ	Unpaired	Paired	ρ	Unpaired	Paired
-0.9	0.157	0.048	0.9	0.000	0.049
-0.8	0.145	0.051	0.8	0.000	0.049
-0.7	0.133	0.050	0.7	0.001	0.050
-0.6	0.120	0.050	0.6	0.004	0.050
-0.5	0.108	0.051	0.5	0.007	0.049
-0.4	0.096	0.050	0.4	0.013	0.050
-0.3	0.087	0.051	0.3	0.021	0.051
-0.2	0.073	0.050	0.2	0.030	0.051
-0.1	0.061	0.049	0.1	0.039	0.050
0	0.051	0.050			

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

	Difference in Means = 0.5		Difference in Means=1.0	
Paired Design---Number of Pairs				
rho	80% power	90% power	80% power	90% power
-.5	97	129	26	34
-.3	84	112	23	30
-.1	72	95	20	26
0	65	87	18	24
.1	59	78	17	21
.3	46	61	14	17
.5	34	44	10	13
Parallel Design				
N per arm	64 per arm	86 per arm	17 per arm	23
N total	128 patients	172 patients	34 patients	46 patients

Examples
Biological Examples

- Study of a surgical device to show tumor cells
  - Mice have tumor implanted in one flank
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  - Small pen like counter used to measure radio-active count
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Number of radioactive counts in 60 seconds

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

Sign Test

- H_o: Median Difference=0

  H_A: Median Difference > 0
- Test based on the number of positive differences B =11 n=12
- Reject H_o if B is too large
- p-value $Pr[B>b_{obs}|p=1/2]$ with B~Binomial or

- $Pr[Z>(b_{obs}-(n/2))/\{n/4\}^{1/2}]$ if n is large Z~Normal[0,1]

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

Wilcoxon Sign Rank Test

- H_o: 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 $E_o[T^+]=n(n+1)/4$, $Var_o[T^+]=\{n(n+1)(2n+1)\}/24$
- Standardized test statistic is $Z=\{T^+-E_o[T^+]\}/(Var_o[T^+])^{1/2}$
- p-value=Pr[Z>z], Z~Normal(0,1)

- In example $T^+=71$, $E_o[T^+]= 39$, $Var_o[T^+]=162.5$, 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

		Cream A	
		yes	no
cream B	yes	75	45
	no	25	35

- 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={Number A no, B yes}/n
- Test statistic $Z=\{p-1/2\}/\{.5/n^{1/2}\}$
- Here p=25/70=0.357
- Z=-2.39
- p=2*Pr[Z>-2.39]=.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

- The Biostatistics Consulting Service provides comprehensive statistical support 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?