Some Statistical Issues in the Design and Conduct of Clinical Trials

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The importance of:

• Control group
• Randomization
• Blinding
• Intent-to-Treat: follow-up on everyone
• Keeping track of and reporting CONSORT info
Why do we need to do a Randomized Controlled Trial (RCT)?

Instead just do one of these:

• Pre-Post study
  – No Control group

• Non-Randomized Control group
  – Historical control study
  – Non-equivalent control group
  – Clinical epidemiology study
Pre-Post Study, no Control group

Did subjects improve after treatment, compared to before?
Pre-Post Study, no Control group

Did subjects improve after treatment, compared to before?
Pre-Post Study, No Control Group

• Would have gotten better anyway
• Placebo effect
• Attention effect
• Experience with outcome measures
Example: control group improves
Pre-Post Study, No Control Group

• Bias in outcome measurements
  – Tape measure waist circumference

• Completers only
  – Exercise
  – PTSD – exposure therapy

• Regression to the mean
  – High symptoms is an entry criterion
Regression to the Mean
Regression to the Mean
Regression to the Mean
Regression to the Mean
Pre-Post Study – when is it OK?

• Pilot study, feasibility study

• Know what would happen without treatment

• Outcome measure is objective, not self-report

• No selection for high symptoms in condition with fluctuating symptoms
Control Group, non-Randomized

Historical Control Group

Supplemental ascorbate in the supportive treatment of cancer: Reevaluation of prolongation of survival times in terminal human cancer*

(vitamin C)

Ewan Cameron† and Linus Pauling‡

Linus Pauling – Vitamin C & Cancer

• **100 terminal cancer** patients who were given supplemental ascorbate, usually 0 g/day, as part of their routine management

• **1000 matched controls**, similar patients who had received the same treatment except for the ascorbate.

• Tests confirm that the ascorbate-treated patients and the matched controls are representative subpopulations of the same population of "untreatable" patients.
Linus Pauling – Vitamin C & Cancer
Possible biases in Vitamin C study

- Selection of patients getting vitamin C, and of controls
  - Treating doctor decided who got Vitamin C, a subset of those are included in this analysis.
  - Database search to randomly select 10 control patients, matched for age, sex, tumor organ and histology.
- Date of ‘untreatability’
RCT of Vitamin C vs Placebo

• A double-blind RCT of 100 patients with advanced colorectal cancer.

• “On the basis of this and our previous randomized study, it can be concluded that high-dose vitamin C therapy is not effective against advanced malignant disease regardless of whether the patient has had any prior chemotherapy.”

Clinical Epidemiology Study

• Compare outcomes of patients who got treatment A versus patients who got treatment B, based on medical records.

• Attempt to control for confounders
Clinical Epidemiology Study

• Why did one person get treatment A and another person got treatment B?
• Patient choice, physician choice?
• Related to disease characteristics, prognosis?
• Related to comorbidities?
• Related to unmeasureable factors?
Randomized Controlled Trial

- Randomly assign subjects to treatment A or B
- Ensures that (in expectation) the two treatment arms do not differ in any respect except for treatment A versus B.
RCT – Random Assignment violated

- Lack of clinical equipoise
- Clinical versus research
  - This patient would benefit from treatment A
  - This patient could not tolerate treatment A

- Intentional fraud
  - Ensure better prognosis patients get treatment A
Manipulate Randomization process

- Researcher overrides random assignment

- Researcher figures out what next treatment assignment will be
  - Cheats to look at it
  - Can guess because it is predictable
  - If ‘wrong’ treatment, not enroll or delay enrollment
Manipulate after Randomization

• If subject gets randomized to the ‘wrong’ treatment, drop the subject from the study.
  – Decide subject is ineligible
  – Tell subject to not take the treatment
RCT – Non-adherence

• Patient does not receive treatment to which they are assigned.

• If they are assigned to the ‘wrong’ treatment – Switches to the other treatment

• Example: Surgery versus Medical treatment for heart disease
Randomized

Received

"As Treated"

50

Surg

40

Surg

50

Med

10

Med

15

Surg

35

Med

15

Surg

35

Med

"As Treated"
Randomized | Received | "As Treated"

Surg  | Surg  | Surg

Surg  | Med   | Med

Med   | Surg  | Med

Med   | Med   | Med

50    | 15    | 35

35    | 15    | 35
Randomized  

Received  

Analyzed  

Exclude non-Adherent  

Surg  

Med  

Surg  

Med  

Surg  

Med  

Med
“As Randomized (Intent-To-Treat )”

Randomized | Received | Analyzed

50 Surg

15 Surg

35 Med

15 Surg

35 Med

50 Med

35 Med

50 Med
RCT – Non-adherence

• Patient does not receive treatment to which they are assigned.

• If they are assigned to the ‘wrong’ treatment
  – Switches to the other treatment
  – Drops out of the study
  – Physician choice
  – Patient choice
RCT – Non-adherence (NA)

- **Medication:**
  - Miss doses, take lower dose
  - Stop taking medication partway through
- **Psychotherapy**
  - Miss sessions, reschedule, delay
  - Do not do homework
  - Stop coming to therapy sessions
- **Includes those who never get any doses**
Prophylactic oral antibiotics in cancer chemotherapy

Rate of infection

<table>
<thead>
<tr>
<th>Compliance:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Excellent</td>
<td>32% (46/141)</td>
</tr>
<tr>
<td>• Good</td>
<td>44% (7/16)</td>
</tr>
<tr>
<td>• Poor</td>
<td>100% (9/9)</td>
</tr>
</tbody>
</table>

Prophylactic oral antibiotics in cancer chemotherapy

Rate of infection

<table>
<thead>
<tr>
<th>Compliance:</th>
<th>Placebo</th>
<th>Antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Excellent</td>
<td>32% (46/143)</td>
<td>18% (19/105)</td>
</tr>
<tr>
<td>• Good</td>
<td>44% (7/16)</td>
<td>36% (9/25)</td>
</tr>
<tr>
<td>• Poor</td>
<td>100% (9/9)</td>
<td>69% (18/26)</td>
</tr>
</tbody>
</table>

Adherence and Mortality

**TABLE I—RELATION BETWEEN ADHERENCE AND 1-YEAR MORTALITY**

<table>
<thead>
<tr>
<th>Adherence level</th>
<th>All patients (n=3381)</th>
<th>Psychosocial interview</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total (n=2175)</td>
<td>Propranolol (n=1081)</td>
</tr>
<tr>
<td>&lt; 75%</td>
<td>246</td>
<td>129</td>
</tr>
<tr>
<td>% dead</td>
<td>4.9</td>
<td>5.4</td>
</tr>
<tr>
<td>≥ 75%</td>
<td>3135</td>
<td>2046</td>
</tr>
<tr>
<td>% dead</td>
<td>2.5</td>
<td>2.2</td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>2.0 (1.1, 3.6)</td>
<td>2.6 (1.2, 5.6)</td>
</tr>
</tbody>
</table>

Adherence and Mortality

<table>
<thead>
<tr>
<th>Model</th>
<th>Propranolol (n = 1081)</th>
<th>Placebo (n = 1094)</th>
<th>Total (n = 2175)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adherence only</td>
<td>Coeff: 1.13, OR: 3.1, p: 0.08</td>
<td>Coeff: 0.90, OR: 2.5, p: 0.10</td>
<td>Coeff: 0.94, OR: 2.6, p: 0.02</td>
</tr>
<tr>
<td>Adherence, clinical severity*</td>
<td>Coeff: 1.07, OR: 2.9, p: 0.11</td>
<td>Coeff: 0.90, OR: 2.5, p: 0.12</td>
<td>Coeff: 0.89, OR: 2.4, p: 0.04</td>
</tr>
<tr>
<td>Adherence, clinical severity, sociodemographic†</td>
<td>Coeff: 1.02, OR: 2.8, p: 3.13</td>
<td>Coeff: 0.92, OR: 2.5, p: 0.12</td>
<td>Coeff: 0.82, OR: 2.3, p: 0.06</td>
</tr>
<tr>
<td>Adherence, clinical severity, sociodemographic, psychological‡</td>
<td>Coeff: 1.01, OR: 2.8, p: 0.14</td>
<td>Coeff: 1.03, OR: 2.8, p: 0.09</td>
<td>Coeff: 0.93, OR: 2.5, p: 0.03</td>
</tr>
<tr>
<td>Adherence, clinical severity, sociodemographic, psychological, smoking status</td>
<td>Coeff: 1.03, OR: 2.8, p: 0.13</td>
<td>Coeff: 0.97, OR: 2.7, p: 0.10</td>
<td>Coeff: 0.92, OR: 2.5, p: 0.04</td>
</tr>
</tbody>
</table>

*Clinical severity = congestive heart failure, severity of myocardial infarction, and age
†Sociodemographic = non-white, unmarried, < 12th grade education
‡Psychological = composite variable of high life-stress and social isolation

“As Randomized (Intent-To-Treat)”

Randomized

Received

Analyzed

Drug

Placebo

Drug

NA

Drug

NA

Placebo

Placebo

Placebo

Drug

Drug

Drug

Placebo

Placebo

Placebo

Drug

NA

Placebo

Placebo

Placebo

Drug

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Drug

Drug

Drug

Placebo
“Intent-to-Treat” means:

• Get follow-up data on everyone, regardless of adherence

• Analyze data from all subjects, according to random assignment

• Missing data, lost to follow-up?
  – That is a different issue

• It is NOT true that
  – Intent-to-Treat = Impute missing data
“DROP OUT”

• Non-adherent
  – Does not get full dose

• Lost to follow-up
  – Does not provide follow-up data

• “The reliability and interpretability of results from clinical trials can be substantially reduced by missing data.”

• “Although rational imputation methods may be useful to treat missingness after it has occurred, these methods depend on untestable assumptions.”

• “Thus, the preferred and often only satisfactory approach to addressing missing data is to prevent it.”
Sample template for the CONSORT diagram showing the flow of participants through each stage of a randomized trial. The text boxes can be modified by clicking on them.
ASSESS FOR ELIGIBILITY (n = 126)

NOT MEETING INCLUSION CRITERIA (n = 6)

REFUSED TO PARTICIPATE (n = 60)

RANDOMISED (n = 60)

ALLOCATED TO TENS GROUP (n = 28)

LOST TO FOLLOW UP (n = 0)

DISCONTINUED INTERVENTION (n = 1)

ANALYSSED (n = 27)

EXCLUDED FROM ANALYSIS (n = 0)

ALLOCATED TO FAIRMED BACK 100 GROUP (n = 32)

LOST TO FOLLOW UP (n = 0)

DISCONTINUED INTERVENTION (n = 5)

ANALYSSED (n = 27)

EXCLUDED FROM ANALYSIS (n = 0)
190 initially responded to announcement (University: 96; SAAC: 94)

103 completed the screening assessed for eligibility (University: 53; SAAC: 50)

6 excluded (not meeting inclusion criteria):
1 under age
1 borderline personality disorder
3 not currently smoking
1 occasional (<10 daily cigarettes)
16 refused to participate

81 eligible for treatment

43 Allocated to ACT

27 Treatment completers (at least 5 sessions)
25 provided 3-month follow-up data
23 provided 6-month follow-up data
24 provided 12-month follow-up data
43 in intent-to-treat analyses

38 Allocated to CBT

29 Treatment completers (at least 5 sessions)
21 provided 3-month follow-up data
19 provided 6-month follow-up data
19 provided 12-month follow-up data
38 in intent-to-treat analyses
Preventing loss to follow-up

• Collect baseline data before randomization
• Subjects need to understand up front that giving outcome data is a commitment, separate from getting treatment
• Have different staff collect outcome data than those delivering intervention
• Pay subject for outcome data collection
• Methods for keeping in touch
• Reduced outcome data if needed
Summary

• Only way to definitively determine treatment effectiveness is an RCT that has
  – Intent-to-treat procedures and analysis
  – Very little loss of follow-up data
  – No other threats (randomization, blinding)

• Non-adherence is bad, but loss to follow-up is much worse

• Loss before randomization is OK, loss after randomization is not
Statistical Consultation Services

• ITHS – Center for Biomedical Statistics
• https://www.iths.org/CBS

• If affiliated with the School of Nursing:
• http://www.son.washington.edu/research/internal/Consultation/Consultants.asp