Lecture 1
RCT design

Major types of experimental studies
Placebo vs active comparison
Superiority vs non-inferiority
Blinded vs unblinded studies,
   Single/double/triple blinding
Randomization methods
   Individual vs group randomization
Controlled trials

A control group is used – to compare the effect of a new intervention against standard therapy (‘positive control’) or no therapy (placebo).

Can be assigned purposely – MD selects treatment based on patient characteristics,

Assigned quasi-randomly – based on day of week, or chart number

Randomly - best way to assign participants to control and intervention groups
Non-Randomized Concurrent Controlled Trial

Comparative study with intervention and control group
Subjects are treated at the same time;
But the assignment is not done by a random process.
In truth this is simply two case series.
Non-randomized concurrent trials – example: A retrospective TBNET assessment of linezolid safety, tolerability and efficacy in MDR-TB

G.B. Migliori, B. Eker, M.D. Richardson, G. Sotgiu et al

Comparison of efficacy end-points for treatment of MDR TB

<table>
<thead>
<tr>
<th></th>
<th>Linezolid</th>
<th>No Linezolid</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients n</td>
<td>45</td>
<td>110</td>
<td></td>
</tr>
<tr>
<td>Sputum smear conversion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>102.9 ± 74</td>
<td>65.4 ± 80.1</td>
<td>0.007</td>
</tr>
<tr>
<td>Culture conversion time</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>109 ± 71</td>
<td>69 ± 63</td>
<td>0.007</td>
</tr>
<tr>
<td>Treatment outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Success</td>
<td>36 (80.0)</td>
<td>90 (81.8)</td>
<td>0.88</td>
</tr>
<tr>
<td>Failure</td>
<td>0</td>
<td>1 (0.9)</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>9 (20)</td>
<td>19 (17.3)</td>
<td>0.65</td>
</tr>
</tbody>
</table>
## Non-Randomized Concurrent Controlled Trial

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
</table>
| - Easier to select patients (increased investigator and subject acceptance);  
- More inclusive;  | - Many potential biases  
- Patient selection  
- MD selection |
Non-randomized and Non-concurrent (Historical Controlled) Trial

Comparative study with an intervention and a control group where a new intervention is used in a series of subjects and the results are compared to the outcome in a previous series of comparable subjects; Essentially two case series
Non-randomized and Non-concurrent Controlled trial – example: MDR-TB Treatment outcomes.

Edward D. Chan, Valerie Laurel, Matthew J. Strand, Julanie F. Chan, Mai-Lan N. Huynh, Marian Goble, and Michael Iseman

• Retrospective comparison of MDR-TB patients treated in 2 time periods at NJMC
• 205 patients in 1984-1998, vs 171 in 1975-83
• Initial favorable response: 85% recent cohort vs 65% prior cohort.
• Long term success: 75% versus 56%.
• TB deaths: 12% versus 22%.
## Non-randomized and Non-concurrent (Historical Controlled) Trial

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>• All new subjects can receive the new intervention;</td>
<td>• Potential bias introduced by time changes in the nature of the patient population, in exposure to pathological agents, or in supportive care and diagnostic criteria;</td>
</tr>
<tr>
<td>• Easier to select patient (increased investigator and subject acceptance);</td>
<td>• Missing data.</td>
</tr>
<tr>
<td>• Ethical aspects;</td>
<td></td>
</tr>
<tr>
<td>• Rapid and relatively inexpensive.</td>
<td></td>
</tr>
</tbody>
</table>
Randomized experimental controlled clinical trial

Prospective study comparing the effect and value of intervention(s) against a control in human subjects

RCT are considered the design that offers the best control of all possible confounding factors
Evidence from Non-randomized vs randomized trials

Systematic review of 145 papers in the treatment of acute MI over 35 years:

• Non-randomized trials: 14 times more likely to find a difference in case fatality rates than Randomized Trials
Randomized Controlled Trial

Comparative study with intervention and control groups; Assignment is by **formal procedure of randomization**

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Removes the potential of bias in the allocation of subjects to the study groups</td>
<td>- Emotional and ethical aspects</td>
</tr>
<tr>
<td>- Tends to balance study groups in covariates</td>
<td>- Can only study one thing at a time</td>
</tr>
<tr>
<td>- Guarantees the validity of statistical tests of significance</td>
<td>- Complex, expensive and time-consuming</td>
</tr>
</tbody>
</table>
Ethical Considerations

Randomized controlled trials entail important ethical issues.

A randomized control study can be undertaken when:

• There is uncertainty about the value of a new therapy or dispute about the relative merits of existing therapies. This is termed equipoise.

Although studies might not actually prove the superiority of a new treatment, they can show that new or existing treatments are of no benefit, or even cause harm. This is important to discover.
Clinical trial phases (drugs)

Phase I Studies: *Pharmaco/Toxicity*

– Usually healthy volunteers.
– Pharmacological action, and safety – usually with escalating doses
– Best dose = maximal action with minimal side effects

Phase II Studies: *Treatment effect*

– Evaluate whether the drug has any effect in patients with a specific disease
– Monitor the rate of adverse events in these patients.
– Usually short term studies in small groups
Clinical trial phases (drugs)

Phase III: *Efficacy and Effectiveness*
Designed to assess the effectiveness of the new intervention, and thereby, its role in clinical practice.

Phase IV: *Post-marketing surveillance*
Surveillance for previously undetected adverse events. No control groups
Seed Trials (‘Marketing trials’): Large scale multi-centre studies. Small numbers of patients per centre (<10). Primary objective - marketing
Types of Study Designs
Simple randomization

- The simplest design is Group A gets active drug
- And Group B gets Placebo
- They get the placebo/drug for equal length of time.
- Then both stop
- Outcomes measured. Rate of outcomes compared
- Risk ratio = Incidence of outcome Group A/Group B
Simple randomization – example
Efficacy and Safety of a 4-Drug Fixed Dose Combination Compared with Separate Drugs
Lienhardt, et al JAMA

Treatment Outcomes

<table>
<thead>
<tr>
<th>Response</th>
<th>FDC (n=591)</th>
<th>Separate Drugs (n=579)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Favorable response</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Culture negative No. (%)</td>
<td>555 (93.9%)</td>
<td>548 (94.6%)</td>
</tr>
<tr>
<td><strong>Unfavorable response</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment failure (N)</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Relapse (N)</td>
<td>23</td>
<td>19</td>
</tr>
<tr>
<td>Death (N)</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>
### Simple randomization – example

**Feasibility...of Gene Xpert testing for TB in Africa**

*Theron et al, Lancet ID 2014*

- **Pragmatic Randomised multicentre trial**
- **Adults suspected of TB at primary care facilities**
- **Patients randomly assigned to Gene Xpert or AFB smear**
- **Outcome – TB related morbidity at 2 months and 6 months**

#### Outcomes of the study

<table>
<thead>
<tr>
<th>Days to start of TB treatment</th>
<th>Smear microscopy (N=758)</th>
<th>Xpert MTB/RIF (N=744)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>1 (0-4)</td>
<td>0 (0-3)</td>
<td>0.0004</td>
</tr>
<tr>
<td>In culture-positive patients</td>
<td>1 (0-3)</td>
<td>0 (0-1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>In culture-negative patients</td>
<td>2 (0-5)</td>
<td>1 (0-4)</td>
<td>0.12</td>
</tr>
<tr>
<td>In patients treated empirically</td>
<td>1 (1-6)</td>
<td>1(0-5)</td>
<td>0.38</td>
</tr>
</tbody>
</table>
Cross-Over Design

Each subject serves as own control.

Each subject receives intervention or control first, and then crosses over to the alternative next. Usually a ‘wash-out’ period between.

The order of intervention or control is randomized.

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Within-subject estimates means less variability. So need smaller sample size to detect a specific difference in treatment response.</td>
<td>• Effect of the intervention during the first period must not carry over into the second period; • Cannot be used for treatment of an acute disease.</td>
</tr>
</tbody>
</table>
Cross-Over Design - example

• New analgesic vs. Placebo for headache
• Consenting subjects enrolled
• Phase 1 – Randomization – ORDER of interventions:
  Group A – Placebo
  Group B – New analgesic

  Phase 1 ends – All subjects stop treatment
• Wash out phase – No drug for any subject for N weeks
• Phase 2 – No Randomization, just take the other:
  Group A – New analgesic
  Group B -- Placebo
• End of study – all drugs stopped
Cross-Over Design – example

Oral Bioavailability of H,R,E,Z, in a 4-Drug FDC compared to separate pills. Xu, et al

- Randomized single dose two period crossover trial
- PK studies with blood samples collected over 24 hours
- Healthy volunteers randomized to take FDC or separate drugs first
- Washout period of one week
- After one week all volunteers took the opposite formulation
Withdrawal Studies

Subjects on a particular treatment for chronic disease are taken off or have dosage reduced;

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Evaluate the duration of benefit of an intervention already known to be useful;</td>
<td>• Highly selected sample is evaluated, e.g. only subjects who had benefited from the intervention, AND never had a major side effect. Tends to overestimate benefit and underestimate toxicity.</td>
</tr>
<tr>
<td>• Alternate way to assess intervention that is believed but never proven to be beneficial.</td>
<td></td>
</tr>
</tbody>
</table>
Example

A long-term study of hydroxychloroquine withdrawal on exacerbations in systemic lupus erythematosus. The Canadian Hydroxychloroquine (HCQ) Study Group

47 patients with stable SLE on HCQ

- at least 6 mos on drug (average was 3 years)
- and at least 3 months stable

Randomized to stop drug (switch to placebo) or continue. Duration of study intervention period was 24 weeks. Most patients stayed on same therapy (drug or none) for 3 years after

Major disease flare: 50% if placebo. 28% if active drug
Factorial Design

Two interventions tested at same time:
Group A – Intervention A, Placebo B
Group B – Intervention A, Intervention B
Group C – Placebo A, Placebo B
Group D – Placebo A, Intervention B
Factorial Design Comparisons

Intervention A vs. Placebo A
Intervention B vs. Placebo B

Advantages:
- Can test two interventions for “same price,”
- meaning sample size as for one.

Disadvantage:
- Assumes NO interaction between interventions
- If Intervention A enhances or reduces effect of B, could make results invalid
Factorial Design Example

Moxifloxacin versus EMB in the first 2 months of treatment for TB \textit{Burman et al, AJRCCM}

- Adults with smear positive pulmonary TB
- Randomized in factorial design:
  - Received Moxi or EMB
  - And randomized to: 5 days/week or 3 days/week
- 2 month in culture conversion:
  - Moxi = EMB
  - 5/week = 3/week
- Four week culture conversion: Moxi > EMB, 5/wk = 3/wk
Placebo vs. Positive Control

Placebo is justified if there is uncertainty regarding whether the standard therapy helps (e.g., Headache, common cold).

or

Placebo / New drug may be added to an existing standard regimen. Test if the new drug adds to standard therapy. (e.g., New anti-TB or Placebo added to current MDR-TB regimen)

Positive Control – the new drug is compared directly to the standard therapy.

- Used when the standard therapy is known to be effective.
Superiority Studies

• Test New Interventions against a standard or placebo.

• Hypothesis: New intervention is better.

• New intervention will be adopted if patients’ outcomes are better.
Superiority Study: Example

Placebo controlled trial of Isoniazid for inactive TB:

Large study of 28,000 participants
  - Conducted in Eastern Europe, in 1968-1975
  - 7,000 in each group

Randomized to: placebo, 3 months INH, 6 months INH, or, 12 months INH

Hypothesis:

INH for 3, or 6 or 12 months would be more effective than placebo in preventing active TB. (Each INH group of 7,000 compared to same placebo group of 7,000)
Superiority studies – Concept: Selection of estimates of effect

Superiority: New treatment must be at least 50% times more effective than existing treatment.
Superiority studies – Design

Setting 95% confidence intervals

- No effect
- Standard Effect
- 1.5X Effect of New Therapy
- Upper Bound
Superiority studies:
Results: **CAN** conclude superiority
Superiority studies:
Results: \textbf{CANNOT conclude superiority}

<table>
<thead>
<tr>
<th>Effect of New Therapy</th>
<th>Effect of Standard Therapy</th>
<th>0 No Effect</th>
</tr>
</thead>
</table>
Non-inferiority Studies

If current therapy is effective
- But is very costly, or lengthy
- Or has major side effects

Alternate therapies must be cheaper, shorter, or safer.

Then we want to show that the new treatment is not worse.

This is called a Non-inferiority study.
9 months INH - now the current standard for TB prevention.
- Greater than 90% efficacy in preventing TB
- but 9 months duration - reduces compliance
- And significant side effects

4 months Rifampin - much better compliance
- and lower rates of serious adverse effects

Therefore, objective is to demonstrate efficacy that is NOT (a lot) worse than 9 INH.
- because it is hard to beat 90% efficacy!
**Non-Inferiority studies - concept**

Inferiority: New treatment could be 30% worse and still acceptable.
Non-Inferiority studies - design

Setting 95% confidence interval for non-inferiority

- No effect
- Least Acceptable Effect of New Therapy
- Effect of Standard Therapy

Lower Bound of 95% Confidence Interval
Non-Inferiority studies - Results

CAN conclude non-inferiority

<table>
<thead>
<tr>
<th>Effort</th>
<th>No effect</th>
<th>0.7</th>
<th>1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Standard Therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard Therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Graph showing the results of non-inferiority studies with data points indicating the effect sizes for New Standard Therapy and Standard Therapy, with 95% confidence intervals.
Non-Inferiority studies - Results

CANNOT conclude non-inferiority

<table>
<thead>
<tr>
<th>No effect</th>
<th>Least Acceptable Effect of New Therapy</th>
<th>Effect of Standard Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.7</td>
<td>1.0</td>
</tr>
</tbody>
</table>

0 = No effect

0.7 = Least Acceptable Effect of New Therapy

1.0 = Effect of Standard Therapy
3 months once weekly INH & Rifapentine – Incidence of active TB  
*Sterling et al NEJM, 2011*

<table>
<thead>
<tr>
<th></th>
<th>9INH</th>
<th>3HP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized</td>
<td>3649</td>
<td>3895</td>
</tr>
<tr>
<td>Completed</td>
<td>2536 (69%)</td>
<td>3190 (82%)</td>
</tr>
<tr>
<td>TB Disease - All patients</td>
<td>12 (0.4%)</td>
<td>7 (0.2%)</td>
</tr>
<tr>
<td>- Completed</td>
<td>5 (0.2%)</td>
<td>4 (0.1%)</td>
</tr>
</tbody>
</table>
Non-Inferiority Study design - Example:
9H vs 3HP – Sterling et al NEJM, 2011

A  Modified Intention-to-Treat Population

Tuberculosis Rate Difference (%)

No. at Risk
Isoniazid only 3745 3644 3599 3555 3513 3484 3454 3405 3394 3310
Combination therapy 3986 3866 3827 3799 3783 3752 3726 3675 3661 3577
Non-Inferiority Study design - Example:
9H vs 3HP – Sterling et al NEJM, 2011

B Per-Protocol Population

- Noninferiority margin (delta)
- Upper limit of 95% CI
- Reference (no difference)
- Difference in rates
- Lower limit of 95% CI

Tuberculosis Rate Difference (%)

Days since Enrollment

No. at Risk
Isoniazid only
2585 2583 2580 2572 2552 2540 2525 2493 2487 2434
Combination therapy
3273 3246 3229 3210 3200 3177 3159 3118 3108 3042
**Optimal Background Therapy (OBT) trial design:**
Example - The enfuvirtide registration trials

**Study population**
- Prior therapy with 3 drug classes (NRTI, NNRTI, PI)
- Virological failure of current therapy: \( VL > 5000 \)

**Randomization**
- OBT (could include other investigational or expanded access drugs) + placebo
- vs OBT + enfuvirtide
Enfuvirtide trial – results from OBT trial
(% with viral load > 5000 copies/ml)

N Engl J Med 2003; 348: 2175-85,
N = 501
Results from two OBT Enfuvirtide trials (% with viral load > 5000 copies/ml)

Enfuvirtide

Control

N = 501

Efficacy of etravirine in two OBT trials (% with viral load < 400 copies/ml)

Lessons from OBT trials

OBT design can provide highly reproducible estimate of the treatment effect, using a dichotomous endpoint (virological failure)

WHILE

Allowing for the diversity inherent in treating patients with advanced disease or MDR-TB

- Prior therapy
- Degree of baseline resistance
- Other drugs used at the time. The optimized regimen is selected by each treating MD, and is highly individualized
Pragmatic trials

Concept: trial that simulates real practice conditions

- Non-selective patient selection
- Realistic follow up

Patient selection should be truly representative

- Of all patients with target condition
- Includes patients at risk for adverse events
- Includes patients at risk for non compliance
Pragmatic trials: follow up

In a typical clinical trial, follow-up is very close and intense

– Adherence is usually over estimated
– Serious adverse events often under estimated

In pragmatic trial one attempts to simulate real life conditions

– Follow up by normal clinic staff and MDs
– Research staff play observer role
– Research staff “jump in” if outcome occurs

Intention to treat analysis will be more realistic

– And quite different from per protocol analysis
## What is Pragmatic research? Comparing to “Typical RCT”

<table>
<thead>
<tr>
<th></th>
<th>Typical Randomized Trials</th>
<th>Pragmatic research</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Question</strong></td>
<td>Efficacy. How well does it work under optimum conditions?</td>
<td>Effectiveness. How well does it work in real practice?</td>
</tr>
<tr>
<td><strong>Setting</strong></td>
<td>Well resourced ($$$)</td>
<td>Publicly funded ($)</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>Carefully selected. Likely non-adherent excluded</td>
<td>All comers</td>
</tr>
<tr>
<td><strong>Adherence</strong></td>
<td>Carefully monitored and enforced</td>
<td>Normal enablers and incentives. (Patients drop out, come late, forget)</td>
</tr>
<tr>
<td><strong>Relevance to practice</strong></td>
<td>Indirect</td>
<td>Direct</td>
</tr>
</tbody>
</table>
Pragmatic trials: example

Comparison between MGIT and LJ in detection of TB at public health care facilities...

*Moreira, Kritski and others*

- Practical clinical trial to evaluate clinical performance and cost effectiveness of two diagnostic methods
- MGIT 960 compared to smear microscopy
- Adults who were TB suspects were enrolled and randomized to one or the other diagnostic method
- Outcomes – change in initial treatment approach within 2 months of randomization
- Unblinded study except outcome assessors blinded
Cluster randomized trials

• Randomization in most RCT is by individual
  – One by one

• Cluster randomization – is by groups
  – Could be towns/villages (fluoridation of water)
  – Could be health facilities (introduction of XPert)
  – Could be school classes (polio)

• Why? – when the intervention is not at individual level, but affects entire group
Advantages and disadvantages of cluster randomized trials

• Advantages: For many interventions – it’s the only option

• Disadvantages:
  – Sample size must be larger
  – Accounts for group effect
  – May not be able to control confounding as well.
  – May not be able to measure confounding well either
Stepped intervention trials

• Stepped intervention – means interventions are introduced sequentially to different groups (goes with cluster randomized trial)

• Comparison: Outcomes during period before intervention with outcomes after intervention

• Advantage: Everyone eventually gets the intervention – resolves ethical issue
  – Plus – simply more feasible if intervention is complicated and takes time to introduce

• Disadvantage: Temporal effect – if other things change (improve) at same time
Randomization Units (clinics) receiving interventions

Control Period

Intervention Period

Intervention Follow up

First 2 months (0-2) No clinics have intervention
Last 4 months (16-20) All clinics have intervention
Thanks