RANDOMIZED
CONTROLLED TRIALS

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<table>
<thead>
<tr>
<th>Objectives</th>
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<tbody>
<tr>
<td>• understand fundamental principles of comparative clinical trials in investigating effectiveness, efficacy and safety of interventions</td>
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<td>• understand the need for and selection of a control group</td>
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<td>• understand the benefits of randomization and methods for randomization</td>
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<td>• understand the concept of allocation concealment and the use of blinding</td>
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<td>• understand the need for an adequate sample size</td>
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Historical perspective

• 1753 - Controlled trial for treatment of scurvy by Lind

• 1795 - Rush on treatment of yellow fever by bleeding: “Thank God” of the 100 patients I visited, or prescribed for, this day I lost none.

• 1834 - Louis: need for the “numerical method”

• 1948 - First RCT. Streptomycin for treatment of pulmonary tuberculosis.
Clinical Trial

• **Planned experiment** to evaluate the benefits of one or more treatments usually for **patients** with a specific condition.

• A well designed trial provides the most rigorous method for evaluating treatment methods.
General patient population

Limited sample
General patient population

Limited sample
Clinical trial

- Drug therapy
- Medical procedures
- Educational intervention
- Screening trial
- Vaccine

Aspirin plus Heparin or Aspirin Alone

Sensitivity and specificity of multimodal and ultrasound screening for ovarian cancer, and stage distribution of patients with ovarian cancer in the USA

Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in The Gambia: randomised, double-blind, placebo-controlled trial
Aim of a Clinical Trial

• To provide reliable evidence of treatment efficacy (or effectiveness) and safety.

• efficacy = explanatory trial
• effectiveness = pragmatic trial

• ultimate aim is to change clinical practice.
Key design issues

• CONTROLLED: a new treatment should be compared with the standard of care or placebo/no intervention.

• UNBIASED: Fair comparison. No deliberate or accidental bias. Randomization.

• LARGE: Precise estimate requires sufficiently large numbers.
Ethical issues

• No patient should suffer as a result of participation.

• No patient should be denied known effective treatment.

• Known effective treatment relies on OBJECTIVE EVIDENCE, not subjective belief.

• Participants should be well informed of potential risks.
Clinical trials in context

• Ensure that the research question has not already been answered.
• Ensure that the correct question will be answered.
• Avoid misleading interpretations.
• Results should be placed in context of the initial review to provide answers using totality of the evidence.
The research question

• Population
• Intervention
• Control
• Outcome measure
• Time
The need for a control group

- Any effect of treatment can not be distinguished from an effect due to other reasons.
- Natural improvement over time.
- Placebo effect.
- Hawthorne effect.
With the experimental intervention we had a live birth rate of 33%.

The live birth rate in the control group was 36%. (p=0.79)
Randomization

- Key design feature of a clinical trial.
- Allocation of participants to one of the treatments under investigation by chance.
- Any differences between the outcomes can be reliably attributed to the treatment under investigation.
- Helps the groups to be similar at baseline in terms of known and unknown factors.
How can we randomize?

• a) Let the investigator decide.
• b) Let each center to choose the treatment to be used for all patients in that center.
• c) Allocate treatment according to the day of the week.
• d) Allocate treatments alternatively as patients present.
• e) None of the above.

Tim Clayton, LSHTM
The two key principles that apply to the randomization process are:

- that each patient has a known (usually equal) chance of receiving either treatment
- that neither the investigator nor the patient can predict in advance which treatment a particular patient will receive (allocation concealment)
In which of the following situations do you think a randomized trial cannot be undertaken?

1) The investigator believes the treatment under investigation will be effective
2) Observational studies suggest the treatment to be effective
3) The treatment is already used to treat patients
4) None of the above
5) All of the above

Tim Clayton, LSHTM
Non random methods

- Alternative methods of randomization are likely to produce biased and often over-optimistic results.

- Randomization can be problematic and even unethical.

- There are many examples of the results from clinical trials contradicting established beliefs in treatment often based on observational studies.
Equipoise

- There should be genuine uncertainty about the comparative treatments among the expert medical community, but such uncertainty is not required of individual investigators.
Randomization

Allocation concealment

Allocation concealment

- Prior knowledge of treatment allocation can lead to bias;
- investigators not entering a patient into the trial.
- the patient not getting the allocated treatment if it is not his/her preferred option.
Methods of randomization

- Not foolproof.
- Envelopes may be resealed or re-ordered.
Methods of randomization

RANDOMISE A PATIENT
The patient will be randomised to either Control group - no PGD or Study group - IVF with PGD. The randomisation result will be emailed to you and to the trial administrator (barisata@hotmail.com).

Trial password:
Password

Your email:
Email

A notification email will be sent to this address

Patient ID:
E.g. study number

Inclusion criteria
Female age between 30 - 42 years (inclusive) on the date of oocyte collection

US CGH trial
Created: April 4, 2012 at 01:15 PM
18 of 200

An RCT to assess the effectiveness of pre-implantation genetic diagnosis (PGD).

18 randomisations to date (limit is 200 - extend limit).

Email randomisations for this trial
Enter the trial password below to email the list of all randomisations to the trial administrator.

Password
Send list

Randomise by text message
New! You can allow randomisation by text message for this trial. Learn more …
Simple randomization

• Tossing an unbiased coin.
• Ensures each patient has an equal chance of either treatment with no connection between assignments!
Simple randomization

- Random number table or computer program.
- Read in a systematic manner.
- e.g. allocate the numbers 0 - 4 to trt. A and 5 - 9 to trt. B.
Why not use simple randomization?

• In the long run simple randomization should guarantee similar numbers on each treatment.

• However, given that clinical trials are of limited size, there is the possibility that substantial imbalance might occur.

• Even in large trials early interim analyses are often undertaken potentially leading to a similar problem of imbalance.
Restricted randomization

- Random permuted blocks.
- The number of patients allocated to each treatment is the same at certain points in the recruitment process.
GnRH agonist protocol administration in the luteal phase in ICSI–ET cycles stimulated with the long GnRH agonist protocol: a randomized, controlled double blind study

B. Ata¹, K. Yakin, B. Balaban and B. Urman

Randomization protocol and data management

Women were randomized according to a computer generated randomization list prepared by the chief investigator. Study subjects were randomized in blocks of 10; i.e. of every 10 subjects randomized, five were allocated to the GnRH agonist, and five were allocated to the placebo arms in a random manner. Opaque envelopes, which
Effect of block size

• Too small a block:
  • ABAB   BBAA   AABB
• What’s the problem?
• If this is an unblinded trial treatment allocation can be predicted at the end of each block.
Which of the following are potential solutions to the problem of predictability at the end of each block in such a situation?

a) Avoid block sizes that are too small
b) Keep the block size and method of randomization secret from the investigators
c) Vary the block size used
d) All of the above
e) None of the above

Tim Clayton, LSHTM
Differences between baseline characteristics complicate the interpretation of the trial results.

<table>
<thead>
<tr>
<th>IVF STUDY</th>
<th>Treatment A</th>
<th>Treatment B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean female age at baseline</td>
<td>35 y</td>
<td>28 y</td>
</tr>
<tr>
<td>Live birth rate</td>
<td>29%</td>
<td>35%</td>
</tr>
</tbody>
</table>
Stratified Randomization

Image from London School of Hygiene and Tropical Medicine
Stratified randomization

• A separate randomization sequence is produced for each stratum.
• Can we employ simple randomization to produce randomization lists for each stratum?
### Stratification

<table>
<thead>
<tr>
<th># failed cycles</th>
<th>&lt;3</th>
<th>≥3</th>
<th>&lt;3</th>
<th>≥3</th>
</tr>
</thead>
<tbody>
<tr>
<td>female age</td>
<td>&lt;35 y</td>
<td>≥35 y</td>
<td>&lt;35 y</td>
<td>≥35 y</td>
</tr>
<tr>
<td>H</td>
<td>C</td>
<td>C</td>
<td>H</td>
<td>C</td>
</tr>
<tr>
<td>C</td>
<td>H</td>
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<td>C</td>
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<td>C</td>
</tr>
</tbody>
</table>

X participating center
Stratification

Trial of a new treatment for IVF.

# prior failed cycles (<3 or ≥3)

Age (<35 or ≥ 35)

Duration of infertility (<4 years or ≥4 years)

Etiology of infertility (ovulatory, tubal or male factor)

How many strata?
<table>
<thead>
<tr>
<th></th>
<th>Vitamin E</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=1035)</td>
<td>(n=967)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>848 (82%)</td>
<td>842 (87%)</td>
</tr>
<tr>
<td>Female</td>
<td>187 (18%)</td>
<td>125 (13%)</td>
</tr>
<tr>
<td>Blood pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>135 (21)</td>
<td>133 (20)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>79 (13)</td>
<td>78 (12)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>61.8 (9.3)</td>
<td>61.8 (8.9)</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>26.5 (3.5)</td>
<td>26.4 (3.4)</td>
</tr>
<tr>
<td>T. cholesterol (mmol/l)</td>
<td>5.96 (1.19)</td>
<td>5.81 (1.11)</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>149 (14%)</td>
<td>121 (13%)</td>
</tr>
<tr>
<td>Ex</td>
<td>300 (29%)</td>
<td>269 (28%)</td>
</tr>
<tr>
<td>Never</td>
<td>586 (57%)</td>
<td>577 (60%)</td>
</tr>
<tr>
<td>Planned therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bypass</td>
<td>402 (40%)</td>
<td>352 (27%)</td>
</tr>
<tr>
<td>Medical</td>
<td>355 (35%)</td>
<td>324 (34%)</td>
</tr>
<tr>
<td>Angioplasty</td>
<td>257 (25%)</td>
<td>265 (28%)</td>
</tr>
<tr>
<td></td>
<td>Vitamin E (n=1035)</td>
<td>Placebo (n=967)</td>
</tr>
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<td>---------------------------</td>
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What’s the most likely reason for these imbalances?

- a) Simple randomization was used in error
- b) A number of patients in the placebo group had missing values for the stratifying variables
- c) There were many incomplete blocks among the strata when recruitment ended
- d) The randomization of patients was poorly conducted

Tim Clayton, LSHTM
Blinding (Masking)

• Knowledge of which treatment a patient is receiving can bias the results of a trial.

• Why this might be so if:
  
  i. Patient
  
  ii. Investigator
  
  iii. Outcome assessor

• has this knowledge?
The patient

- Knowledge of receiving the new treatment may lead to better outcomes.
- The impact of bias depends on the nature of the condition.
- More pronounced if a subjective outcome is measured by the patient themselves, e.g. pain score.
- Can also affect participation, adherence to the treatment, and motivation to stay in the trial.
Investigators

• Experimental intervention
• Ancillary care
• Monitoring frequency
• Reporting of adverse events.
• Consciously or subconsciously.
Outcome assessors

• Natural enthusiasm for new treatment.
• Especially important if clinical judgement is required, e.g. semi-structured interviews.

The impact of blinding on the results of a randomized, placebo-controlled multiple sclerosis clinical trial.
Noseworthy JH, Ebers GC, Vandervoort MK, Farquhar RE, Yetisir E, Roberts R.
Department of Neurology, Mayo Clinic and Foundation, Rochester, MN 55905.
Double Blind Design

- The patient, investigator and evaluator do not know which treatment a patient is receiving.
- Often the investigator and evaluator are the same person, hence the term double-blind.
Placebo

- A treatment or intervention that has no therapeutic effect on the outcome of interest but in other respects is the same as the real drug or intervention under investigation.
• Whether any apparent treatment effect is due to the treatment itself or due in some way to the process of receiving an intervention irrespective of whether this intervention has any therapeutic effect.
When the comparator should be an alternative treatment rather than placebo?

- a) Never since the comparison should always be with an inactive placebo to establish treatment efficacy.
- b) Always since the comparison should be with one of the alternative treatments.
- c) In situations where the efficacy of the alternative treatment is established.
- d) In trials among individuals with more serious disease.

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Double Dummy Trials

• Two active treatments are compared.
• A is q 24h and B is q 12 h
• A is vaginally administered B is orally.

• Placebo for both treatments is used.
• (A + placebo B) vs (placebo A + B)
Feasibility of blinding

• When theoretically possible but ethically or practically difficult.

Luteal phase empirical low molecular weight heparin administration in patients with failed ICSI embryo transfer cycles: a randomized open-labeled pilot trial

B. Urman¹, B. Ata, K. Yakin, C. Alatas, S. Aksoy, R. Mercan, and B. Balaban
When double blind design is unethical or impractical?

1) Consider the extent and importance of the bias that would be introduced without full blinding.

2) Consider whether a single blind study is possible where only the patient is unaware of treatment.

3) Consider whether the outcome being measured is appropriate to achieve a reliable result.

4) Consider blinding those responsible for measuring patient outcomes.

5) All of the above

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Blinding

- Careful organization is required to ensure that patients receive the correct treatment and usually involve a pharmacist preparing the blinded drug packages based on a pre-prepared randomization list.

- The code is kept secret until the end of the trial when the data are ready to be analyzed, unless there is a need to break the code for individual patients to ensure patient safety.
**Interventions**: Coronary angioplasty vs medical treatment alone.

**Outcome measures**: Death or myocardial infarction.

Who could be blinded:

- a) patient
- b) investigator
- c) outcome adjudicator
- d) all of the above
- e) none of the above
Which of the following are reasonable approaches for double-blinded drug studies?

a. Accept that blinding of the investigator is not possible.

b. Include the pharmacist responsible for preparing the drugs in the randomization process.

c. Supply the investigator with drugs coded as A or B and reveal the assignment simply as A or B.

d. None of the above.

Tim Clayton, LSHTM
GnRH agonist protocol administration in the luteal phase in ICSI-ET cycles stimulated with the long GnRH agonist protocol: a randomized, controlled double blind study

B. Ata, K. Yakin, B. Balaban and B. Urman

ICSI. The nurse coordinator informed the pharmacy regarding the number of patients that would be included in the study and received study medication every morning. Patients were assigned to the study groups in the hospital pharmacy. Syringes containing either triptorelin or sterile saline, according to the allocation information in the envelopes opened in an orderly fashion, were prepared in the pharmacy. Syringes were labeled with only the patient identification number, and sent to the assisted reproduction center nurse daily. Allocation information was kept in a file in the pharmacy. Study medications were administered to each woman by the assisted reproduction nurse, who matched the study subject with the syringe labeled with her patient identification number. Both the nurse injecting the study medication and women receiving injections were blinded for allocation. Patient records other than allocation information were kept in the assisted reproduction center. Hence, outcome assessors who performed the pregnancy tests and ultrasonographic examinations to determine if the patient was pregnant were also blinded for allocation. The allocation code was broken upon completion of the 20th gestational week of the last pregnant subject.
Blinding

• Blinding should be used in situations and to the level where such blinding is possible and ethically acceptable. Any potential impact of bias resulting from an unblinded trial needs careful consideration.
Size of trials

- A successful clinical trial is one that provides reliable evidence of the efficacy and safety of a treatment and not one that necessarily produces a positive outcome in terms of a statistically significant result.

- Avoidance of bias
- Recruiting a sufficient number of patients
Key statistical concepts

• **Null hypothesis**: there is no difference between the treatments in their impact on that outcome, i.e. that the treatments have the same effect.

• **Alternative hypothesis**: there is a true difference between the two treatments in respect of their impact on some outcome of interest
Key statistical concepts

• **p value**: the probability that the results observed in a trial (or results more extreme) could have occurred by chance if the null hypothesis is true.
What’s adequately large?

a) 40
b) 200
c) 500
d) 1000
e) need more information
Key statistical concepts

<table>
<thead>
<tr>
<th></th>
<th>TRUTH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No difference exists</td>
</tr>
<tr>
<td>No significant difference observed</td>
<td>1 - $\alpha$</td>
</tr>
<tr>
<td>Significant difference observed</td>
<td>Type I error ($\alpha$)</td>
</tr>
</tbody>
</table>
Why an adequate sample?

• There should be enough subjects in a trial to give a good chance of detecting a clinically important treatment difference if such a difference exists, while being able to reasonably conclude that no such difference exists if our results do not show it.
### Why size does matter?

<table>
<thead>
<tr>
<th></th>
<th>Trial 1</th>
<th>Trial 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>X</td>
<td>Died</td>
<td>1 (10%)</td>
</tr>
<tr>
<td></td>
<td>Alive</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>10</td>
</tr>
<tr>
<td>Y</td>
<td>Died</td>
<td>2 (20%)</td>
</tr>
<tr>
<td></td>
<td>Alive</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Treatment X</td>
<td>Treatment Y</td>
</tr>
<tr>
<td>-------</td>
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<td>10</td>
<td>10</td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>Risk ratio</th>
<th>( p )</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial 1</td>
<td>0.5</td>
<td>&gt; 0.99</td>
<td>0.05 to 4.67</td>
</tr>
<tr>
<td>Trial 2</td>
<td>0.5</td>
<td>&lt; 0.0000001</td>
<td>0.40 to 0.63</td>
</tr>
</tbody>
</table>
Problems of a small trial?

a) The observed difference could be far from the true treatment difference
b) The risk of a false negative result is increased
c) The study will be underpowered to detect realistic clinically important differences
d) The treatment effect will be imprecisely measured
e) All of the above

Tim Clayton, LSHTM
The Trial Protocol

• providing a guideline for the conduct of a trial
• to enable funding to be obtained
• obtaining ethical approval from the relevant ethics committees
• providing a useful source of information for those undertaking and monitoring trials
Main features of a study protocol

1. Background and general aims
2. Specific objectives
3. Patient selection criteria
4. Treatment schedules
5. Methods of patient evaluation
6. Trial design (controls, blinding, randomization)
7. Patient consent
8. Registration and randomization of patients
9. Required size of study
10. Monitoring of trial progress
11. Forms and data handling
12. Protocol deviations
13. Plans for statistical analysis
14. Administrative responsibilities
Non-compliers

• do not receive the treatment to which they are randomized.
• Stop taking treatment.
• Switch to an alternative treatment.
• Withdraw from the trial.
Intention to treat

• inclusion of all randomized patients (where possible) and analyzing them according to the intervention group to which they were randomized irrespective of the actual treatment they receive.
Per protocol analysis

• To analyze only those individuals who are fully compliant with the randomized intervention according to the study protocol.

• The aim is to evaluate the true effects of an intervention when taken according to protocol i.e. under ideal conditions.
Recommended reading

http://www.consort-statement.org/consort-statement/
Interim analysis & data monitoring

• Recruitment occurs over a period of time.
• Can take years.
• Results accumulate gradually.
• Opportunity for repeated analysis.
• Trial can be stopped or modified.
Why stop early?

- Primarily based on ethical issues.
- One treatment clearly superior to the other.
- Adverse effects.
- Futility.
Who should decide?

• Is it appropriate for the investigators conducting the trial to be responsible for undertaking interim analyses and, based on these, deciding whether to stop a trial?