RANDOMIZED CONTROLLED TRIALS

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Objectives

- understand fundamental principles of comparative clinical trials in investigating effectiveness, efficacy and safety of interventions
- understand the need for and selection of a control group
- understand the benefits of randomization and methods for randomization
- understand the concept of allocation concealment and the use of blinding
- understand the need for an adequate sample size

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.

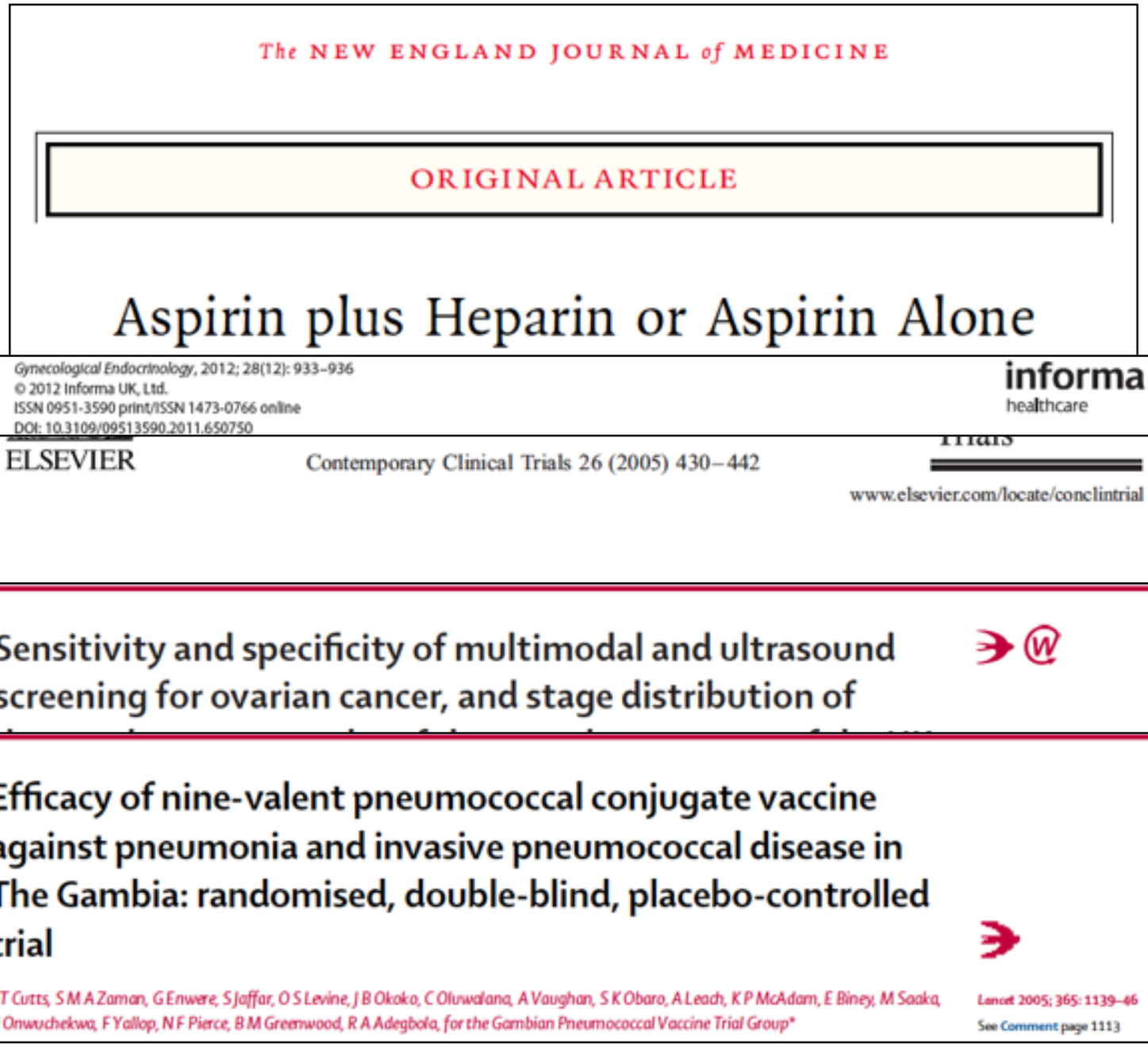
Clinical Trial, a.k.a. RCT

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.

Clinical trial

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



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Aspirin plus Heparin or Aspirin Alone

Gynecological Endocrinology, 2012; 28(12): 933–936
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ISSN 0951-3590 print/ISSN 1473-0766 online
DOI: 10.3109/09513590.2011.650750

informa
healthcare

ELSEVIER

Contemporary Clinical Trials 26 (2005) 430–442

Trials

www.elsevier.com/locate/conclintrial

Sensitivity and specificity of multimodal and ultrasound screening for ovarian cancer, and stage distribution of

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

*F T Cutts, S M A Zaman, G Enwere, S Jaffar, O S Levine, J B Okoko, C Oluwalana, A Vaughan, S K Obaro, A Leach, K P McAdam, E Biney, M Saaka, U Onwuchekwa, F Yallop, N F Pierce, B M Greenwood, R A Adegbola, for the Gambian Pneumococcal Vaccine Trial Group**

Lancet 2005; 365: 1139–46
See Comment page 1113

Aim of a Clinical Trial

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

efficacy = explanatory trial

vs

effectiveness = pragmatic trial

- ultimate aim is <u>to change clinical practice</u>.

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.

Resources

Staff

Infrastructure

Patients
Participants

Medication

Lab. Imaging etc.

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.

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.

The research question

Population

Intervention

Control

Outcome measure

Time

Trial hypothesis

Population

- Eligibility criteria must be comprehensively defined.
- They are determined by the nature and severity of the condition of interest.
- Usually, patients, whose health can be jeopardised by the experimental intervention will be excluded.
- Eligibility criteria determine generalizability

Antiretroviral drug for AIDS

- Adults aged > 18 years
- WHO clinical stage III or IV
- any stage but CD4 count < 250/mm^3
- pregnant and lactating women to be excluded
- BMI < 18 kg/m^2

Intervention

- Each intervention should be described throughly, allowing replication.
  - Drug name
  - Dosage
  - Route of administration
  - Timing and duration of administration
  - Indications to withhold treatment
  - Titration protocols
- Non-pharmacologic treatments:
  - Standardisation of procedures, allocation of care givers.

POISE trial

- extended release metoprolol 100 mg p.o.
- if heart rate > 50 bpm & BPs > 100 mmHg
- first dose 2 - 4 h before surgery
- first post operative dose 6 h after surgery
- if HR >80 bpm or BPs>100 mmHg, stat
- then every 6 h

The Control Group

- Should be similar to the intervention group in terms of important prognostic characteristics at the start of the trial.

The Journal of Reproductive Medicine®

Effect of High-Dose Estrogen in Luteal Phase Support on Live Birth Rates After Assisted Reproduction Treatment Cycles

Baris Ata, M.D., Mert Kucuk, M.D., Ayse Seyhan, M.D., and Bulent Urman, M.D.

- 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)

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.

How can we allocate?

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

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.

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

Equipoise

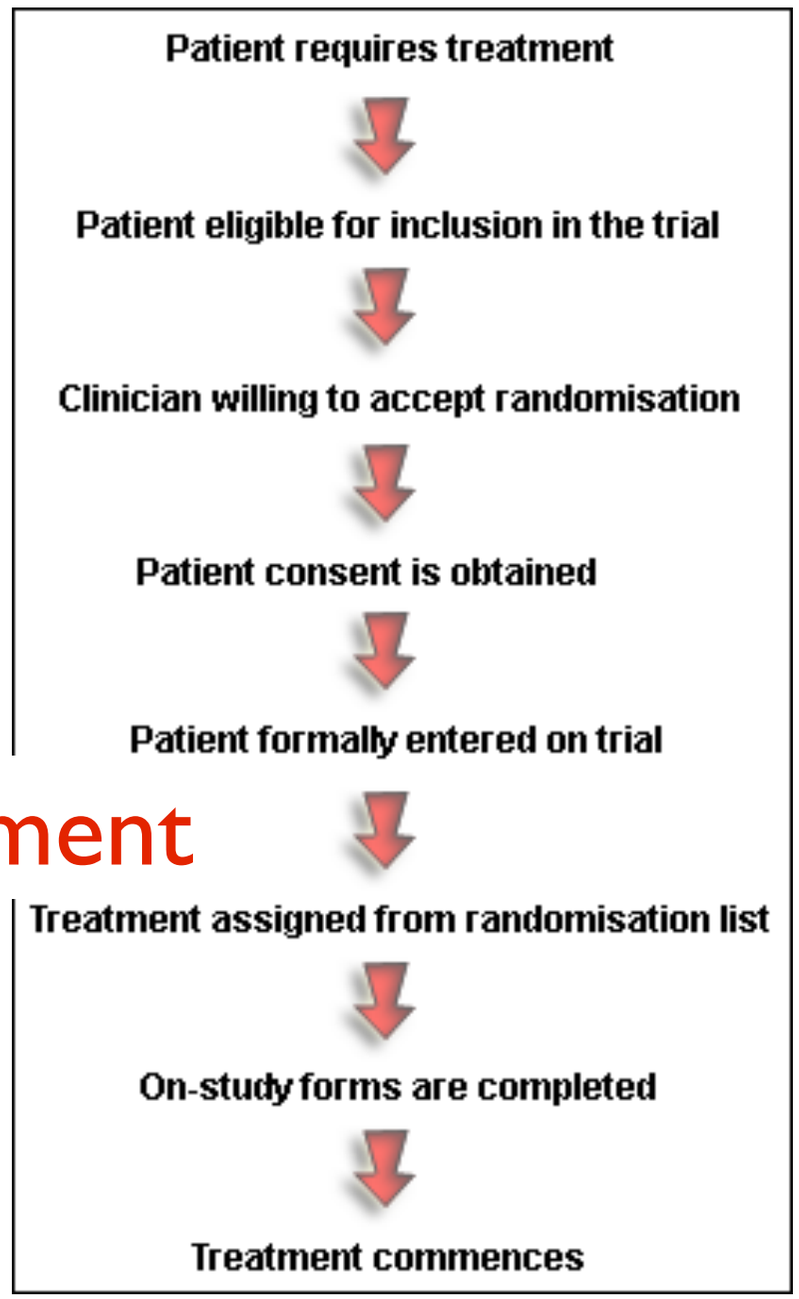
There should be genuine uncertainty about the comparative treatments among the expert medical community, but such uncertainty is not required of individual investigators.

Randomization

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)

Randomization



Allocation concealment

Pocock. Methods of randomisation in Clinical Trials A practical approach. Wiley & Sons 1983

Allocation concealment

Prior knowledge of treatment allocation can lead to (selection) bias;

- investigators not entering a patient into the trial.
- the patient not getting the allocated treatment if it is not his/her preferred option.

Randomization sequence

Patient ID	Date	Investigator Initials	Randomization Number	Treatment Assignment
___				
_____	____/____/____	_____	JHOC-1	HEPARIN
_____	____/____/____	_____	JHOC-2	HEPARIN
_____	____/____/____	_____	JHOC-3	NO HEPARIN
_____	____/____/____	_____	JHOC-4	HEPARIN
_____	____/____/____	_____	JHOC-5	NO HEPARIN
_____	____/____/____	_____	JHOC-6	NO HEPARIN
_____	____/____/____	_____	JHOC-7	NO HEPARIN
_____	____/____/____	_____	JHOC-8	HEPARIN
_____	____/____/____	_____	JHOC-9	NO HEPARIN

1. How to generate the randomisation sequence?
2. How to implement the sequence while concealing allocation information.

Simple randomization

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

Simple randomization

7	0	2	8	9
6	1	5	6	6
9	9	7	9	1
5	1	6	7	3
6	5	4	4	1
8	1	4	8	9
1	4	4	8	6
7	1	5	6	9
5	5	7	0	2
9	9	4	1	8
5	1	5	3	5
5	3	9	2	2
6	4	8	3	7
0	8	9	1	1
6	9	9	6	3
0	8	4	0	3
9	0	6	5	8
5	3	2	1	2
0	2	1	8	2
5	1	2	8	8

- 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.

Human Reproduction Vol.23, No.3 pp. 668–673, 2008
Advance Access publication on January 12, 2008
doi:10.1093/humrep/dem421

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[1], 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

Block randomisation was used

IVF STUDY	Treatment A	Treatment B
Mean female age at baseline	35 y	28 y
Live birth rate	%29	%35

Differences between baseline characteristics complicate the interpretation of the trial results.

Stratified Randomization

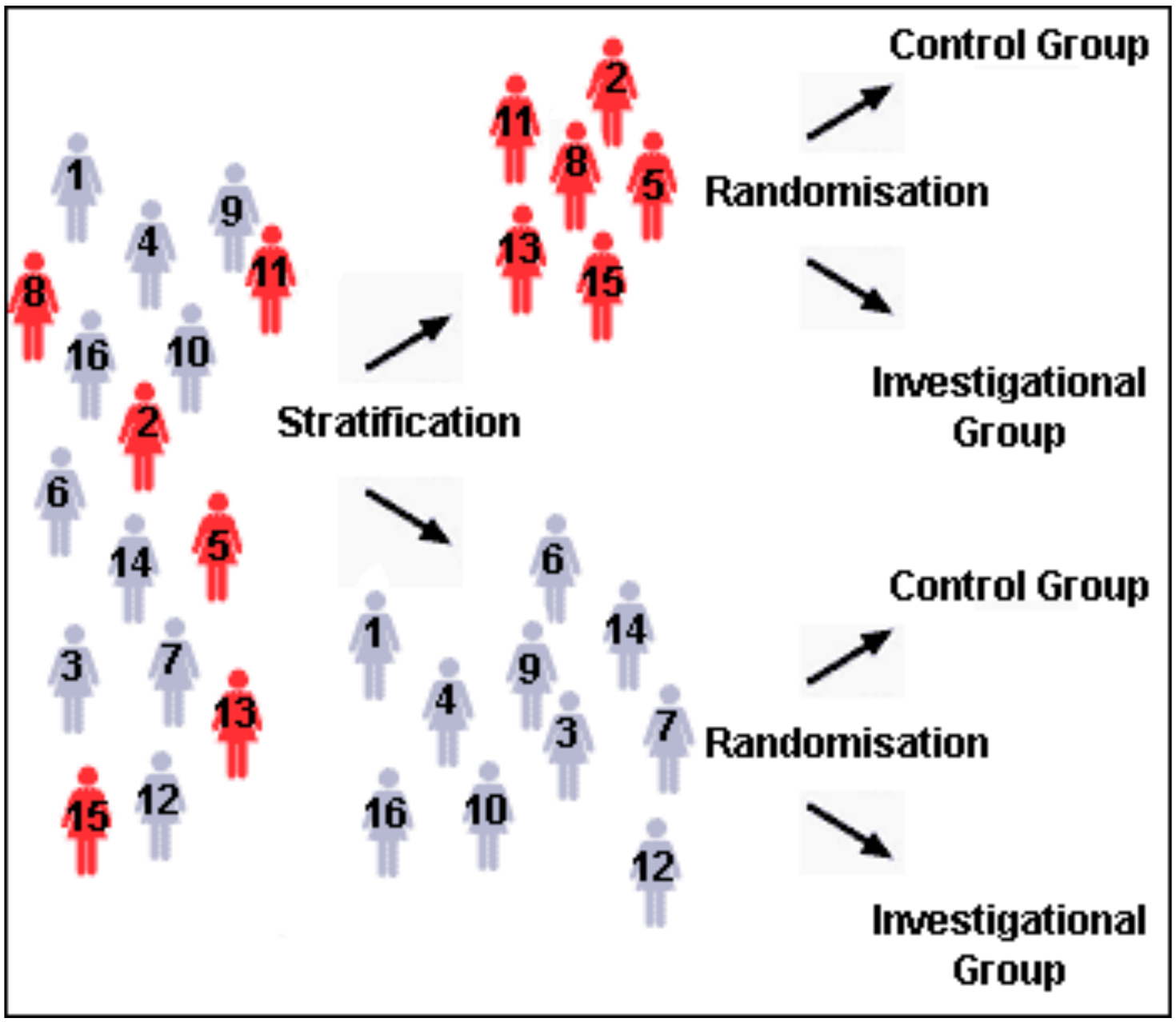


Image from London School of Hygiene and Tropical Medicine

Stratified randomization

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

Stratification

# failed cycles	<3	≥3	<3	≥3
female age	<35 y	≥35 y	<35 y	≥35 y
	H	C	C	H
	C	H	C	C
	C	H	H	C
	C	C	C	H
	H	H	H	C
	H	C	H	C
	C	C	H	H
	H	H	C	H
	H	H	H	H
	C	C	C	C

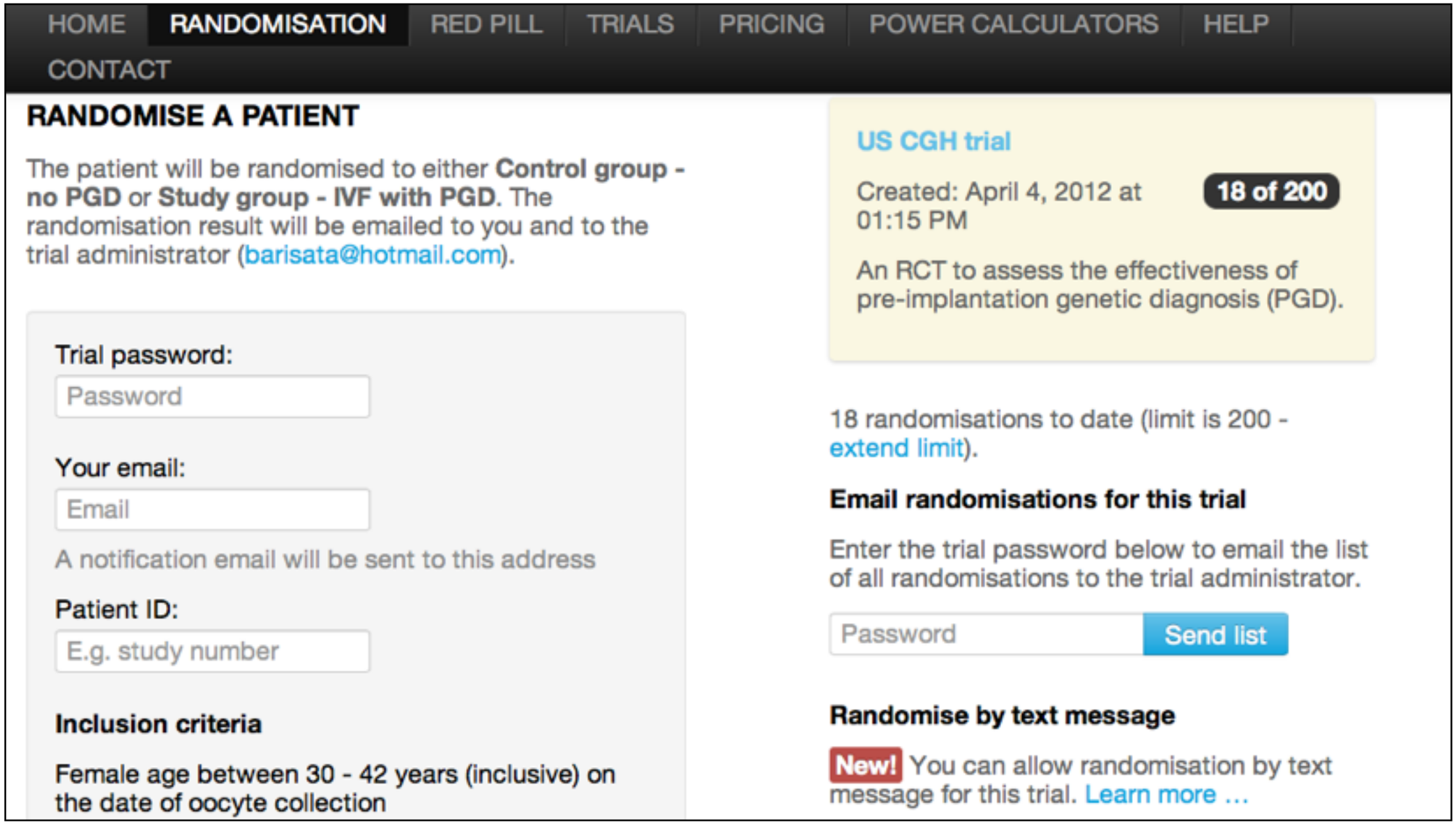
X participating center

Implementing the sequence

Not foolproof.

Envelopes may be resealed or re-ordered.

Implementing the sequence



Outcome measures

- Primary and secondary outcome measures, including how and when they will be assessed should be defined.
- The outcome that is of greatest impotence to relevant stakeholders is the primary outcome measure.
- Sample size calculation is usually based on the primary outcome measure.
- Nature of the outcome measures determine the need for blinding assessors.

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.

Neurology. 1994 Jan;44(1):16-20.

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.

No Placebo

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.

Tim Clayton, LSHTM

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.

The
pre
Albert J
Summ
Backgr

human reproduction ORIGINAL ARTICLE *Infertility*

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

B. Urman[1], B. Ata, K. Yakin, C. Alatas, S. Aksoy, R. Mercan, and B. Balaban

19–24

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

Tim Clayton, LSHTM

Blinding

- Ensure that patients receive the correct treatment
- 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.

RITA - 2

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

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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[1], 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

	TRUTH	
	No difference exists	Difference π_1-π_2 exists
No significant difference observed	1 - α	Type II error (β)
Significant difference observed	Type I error (α)	1 - β

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?

	Trial 1		Trial 2	
	Treatment X	Treatment Y	Treatment X	Treatment Y
Died	1 (10%)	2 (20%)	100 (10%)	200 (20%)
Alive	9	8	900	800
Total	10	10	1000	1000

	Trial 1		Trial 2	
	Treatment X	Treatment Y	Treatment X	Treatment Y
Died	1 (10%)	2 (20%)	100 (10%)	200 (20%)
Alive	9	8	900	800
Total	10	10	1000	1000

	Risk ratio	p	95% CI
Trial 1	0,5	> 0.99	0.05 to 4.67
Trial 2	0,5	< 0.0000001	0.40 to 0.63

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/