ENSURE - Educating students for developing high quality research skills

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The conduct of clinical trials/framework

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Educating students for developing high quality research skills (ENSURE)

PARTNERSHIP

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Partner

Knowledge

Science

Scientific methods

Assessment of science

Implementation of best practice

Goals: To make a better world for all

Challenge knowledge: **Is it true?**
Can we do better?

Perspective:
Educating students for developing high quality research skills (ENSURE)

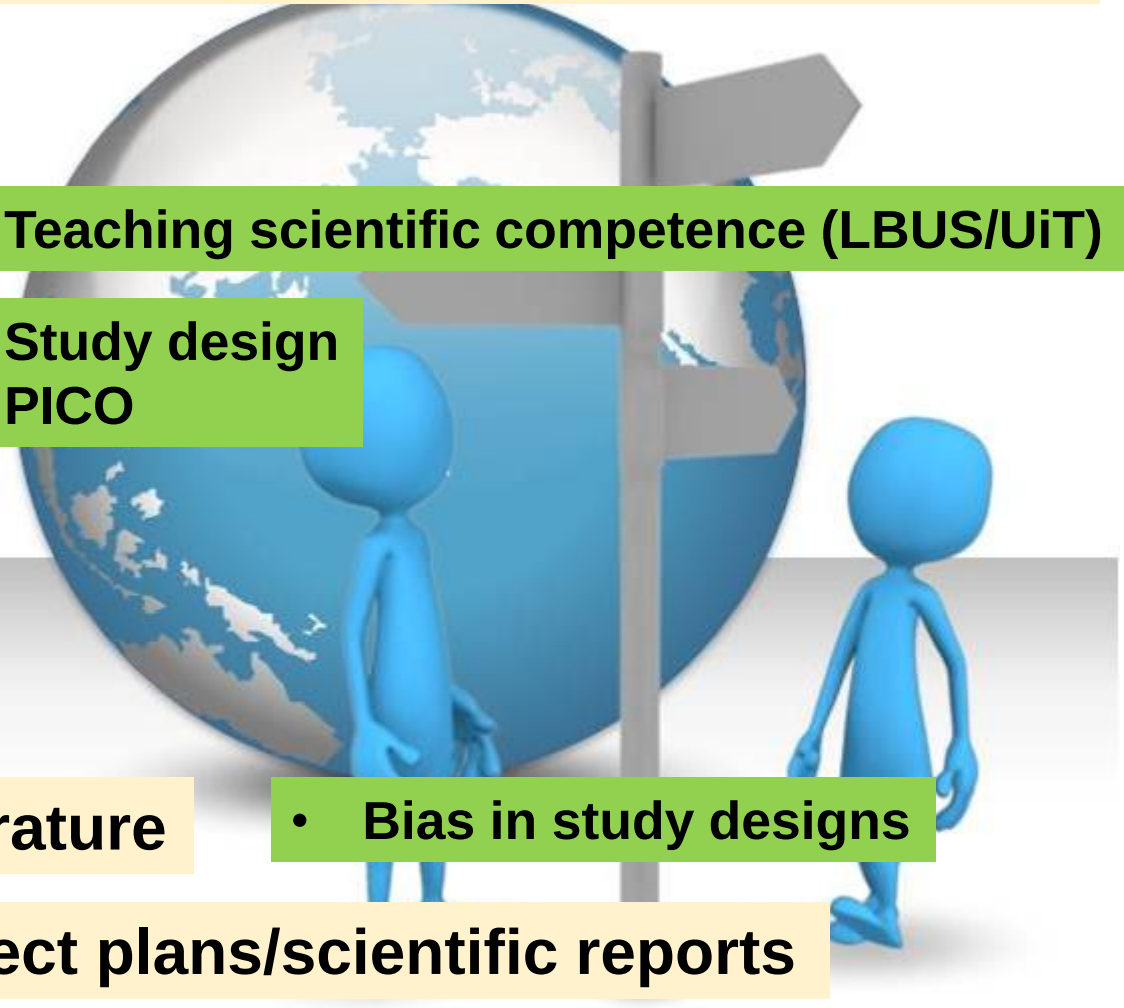
Define the research question?

Types of questions	
Intervention	What should be done
Risk factors	What causes the prol
Diagnosis	Does a person suffer
Prognosis	Who will suffer from
Frequency	How common is the
Contextual phenomena	Which other factors a positively/negatively

Educating students for developing high quality research skills (ENSURE)

Course plan

Educating students for developing high quality research skills (ENSURE)



Curriculum plans

- **Teaching scientific competence (LBUS/UiT)**

Framework

- **Study design**
- **PICO**

Ethics

Legal aspects

Search for literature

Read and assess literature

- **Bias in study designs**

The structure of project plans/scientific reports

Communicate scientific work

Course plan

Educating students for developing high quality research skills (ENSURE)

Curriculum plans

Framework

Ethics

Legal aspects

Search for literatu

Read and assess

The structure of p

Communicate sci

This week comprises:

- Lectures
- Group work
- Process

- Lectures
- Group work
- Process

- Lectures
- Group work
- Process

- Fun
- Friendship
- Pleasure


Systematic Reviews and Meta-analyses
Randomized Controlled Double Blind Studies
Cohort Studies
Case Control Studies
Case Series
Case Reports
Ideas, Editorials, Opinions
Animal research
In vitro ('test tube') research
Basic study designs

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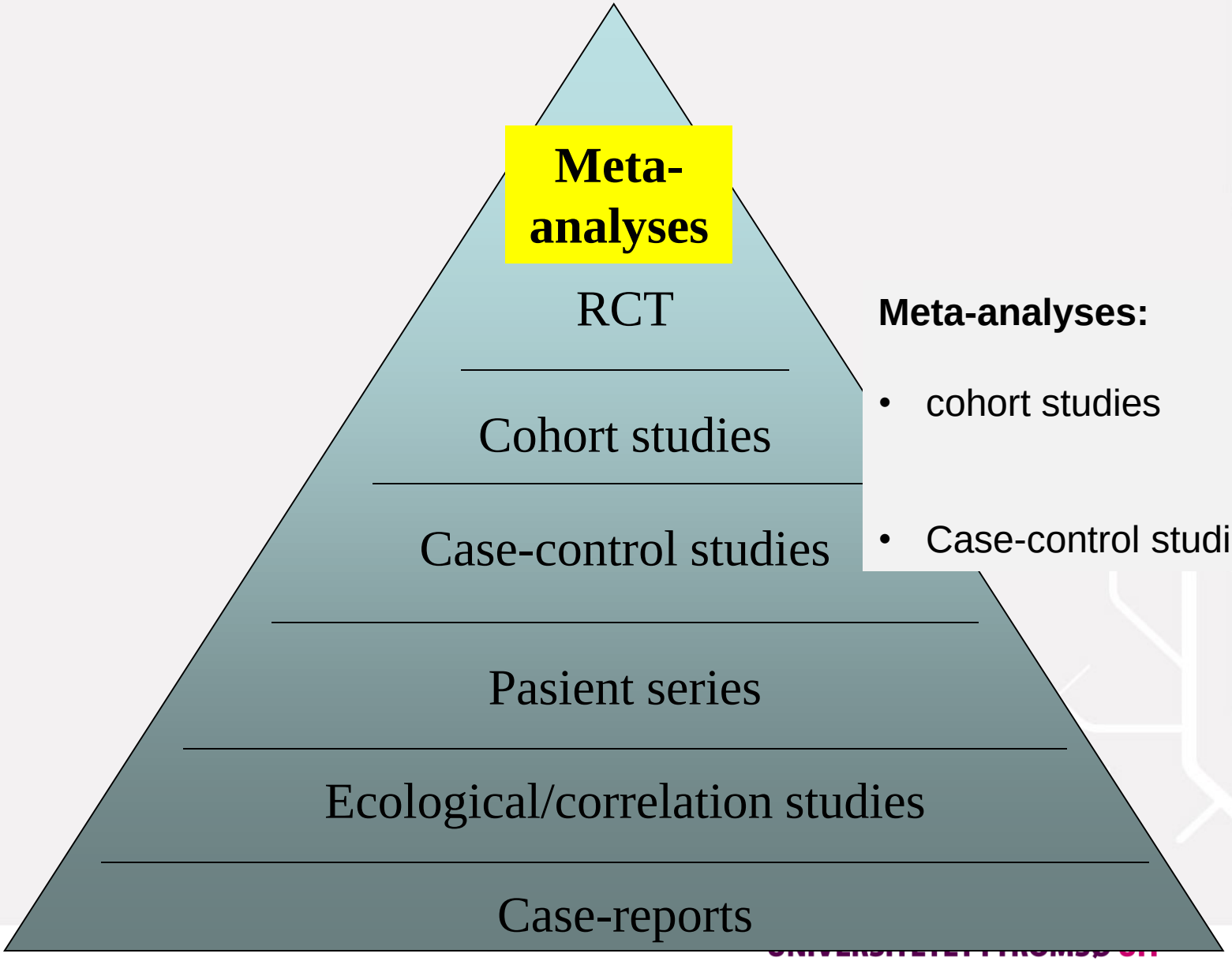
RCT randomized clinical trials

Learning aims

- Know the need for different study designs for different clinical questions
- Be able to explain how to conduct an RCT
- Know the limitations of the application of RCT and the applicability of results.

Hierarchy of studies



Meta-analyses:

- cohort studies
- Case-control studies

Why randomize?

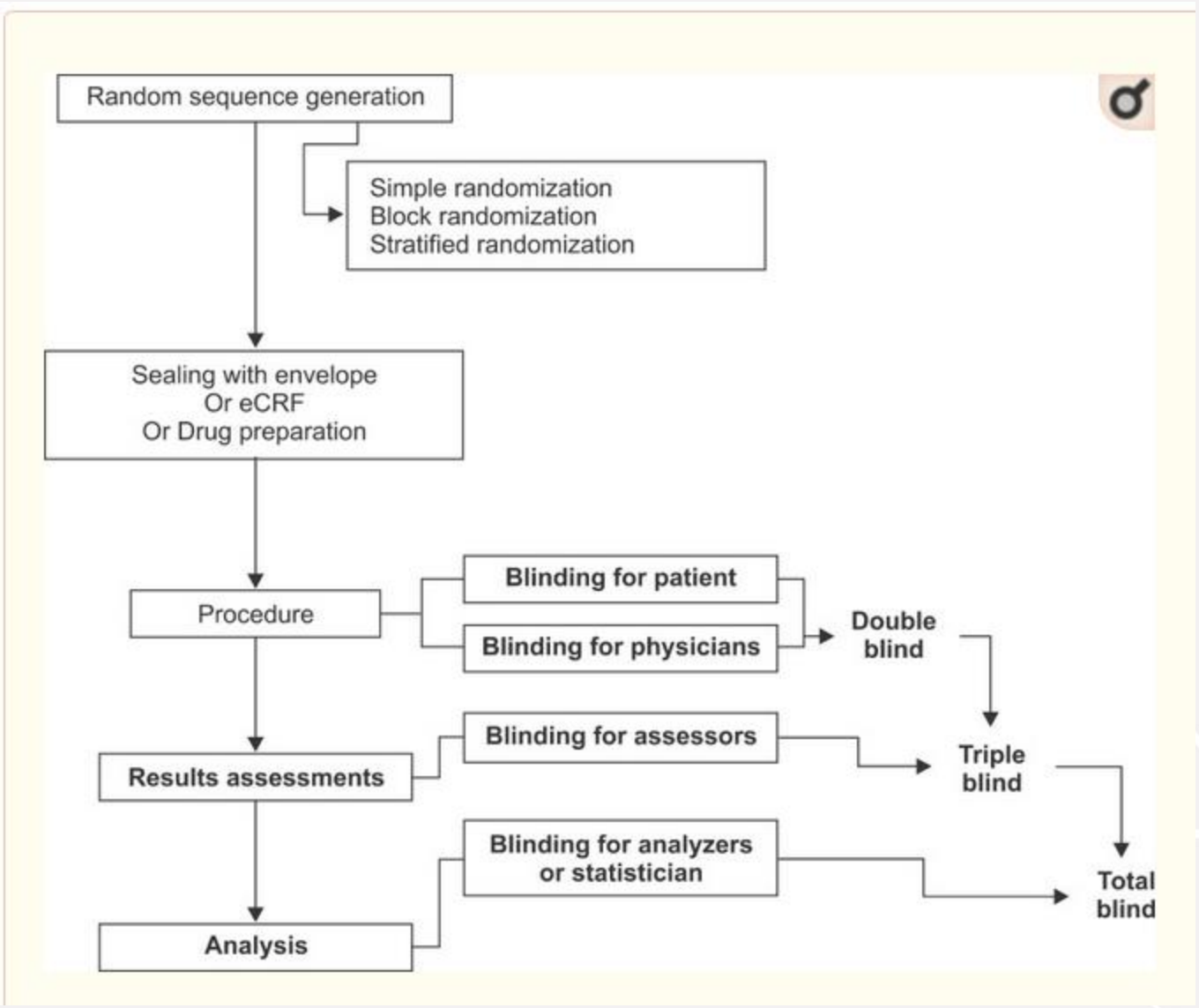
…to ensure that the two (or more) groups we compare should be equal in every way

History of randomized controlled trials

- 1920s - RA Fisher developed randomization as a basic principle of experimental design
  - predominantly in agricultural research
- 1940s - Sir Austin Bradford Hill, London School of Hygiene and Tropical Medicine, published use of ran
  allocate trial participants. ….

Fisher's exact test

Bradford Hill's criteria for causality


Random sequence generation
Simple randomization
Block randomization
Stratified randomization
Sealing with envelope
Or eCRF
Or Drug preparation
Procedure
Blinding for patient
Blinding for physicians
Double blind
Results assessments
Blinding for assessors
Triple blind
Analysis
Blinding for analyzers or statistician
Total blind

RANDOM SEQUENCE GENERATION

Judgement of 'Low risk' of bias.	• Referring to a random number table • **Using a computer random number generator** • Coin tossing • Shuffling cards or envelopes • Throwing dice • Drawing of lots • Minimization* *Minimization may be implemented without a random element, and this is considered to be equivalent to being random.
'High risk' of bias	• Sequence generated by odd or even date of birth • Sequence generated by some rule based on date (or day) of admission • Sequence generated by some rule based on hospital or clinic record number • **Allocation by judgement of the clinician** • **Allocation by preference of the participant** • **Allocation based on the results of a laboratory test or a series of tests** • **Allocation by availability of the intervention**
`Unclear risk'	• **Not enough information**

ALLOCATION CONCEALMENT	
'Low risk' of bias	• Central allocation (including telephone, web-based and pharmacy-controlled randomization) • Sequentially numbered drug containers of identical appearance • Sequentially numbered, opaque, sealed envelopes
'High risk'	• Using an open random allocation schedule (e.g. a list of random numbers) • Assignment envelopes were used without appropriate safeguards **(e.g. if envelopes were unsealed or nonopaque or not sequentially numbered)** • Alternation or rotation • Date of birth • Case record number
`Unclear risk'	• Not enough information

Simple randomisation – randomization tables

For equal allocation to two groups, predetermine the direction to read the table: up, down, left, right, or diagonal **(in protocol).**

Then select an arbitrary starting point—ie, first line, 7th number:
56 99 20 20 52 49 **05 78 58 50 62 86 52 11 88**
31 60 26 13 69 74 80 71 48 73 72 18 60 58 20
55 59 06 67 02 . . .
For equal allocation, equate **odd and even numbers to interventions A and B**.
Therefore, a series of random numbers 05, 78, 58, 50, 62,
86, 52, 11, 88, 31, represent allocation to intervention A or B.

Alternatively, 00–49 could equate to A and 50–99 to B, or numbers 00–09 to A and 10–19 to B, ignoring all numbers greater than 19 **(in protocol).**

Any of a myriad of options suffice, provided the assignment probabilities and the investigator adhere to the predetermined scheme **(in protocol).**

Block Randomization

- Block randomization is balanced within each block
- The basic idea of block randomization
  - divide potential patients into m blocks of size 2n
  - randomize each block such that n patients are allocated to A and n to B
  - then choose the blocks randomly
- Example: Two treatments of A, B and Block size of 2 x 2= 4
  - Possible treatment allocations within each block are (1) AABB, (2) BBAA, (3) ABAB, (4) BABA, (5) ABBA, (6) BAAB
  - Block size depends on the number of treatments, it should be short enough to prevent imbalance, and long enough to prevent guessing allocation in trials

Block Randomization Design With 3 Blocks of Size 4, Treatments of A & B

Obs	Block	Size
1	1	B
2	1	A
3	1	B
4	1	A
5	2	A
6	2	B
7	2	B
8	2	A
9	3	B
10	3	B
11	3	A
12	3	A

- Sample size 12
- 3 centers (blocks)
- Treatment A or B

Stratified randomization

- To ensure that the treatment and control groups are balanced on important prognostic factors that can influence the study outcome (e.g., gender, ethnicity, age, socioeconomic status).
- Before doing the trial, the investigator decides which strata are important and how many stratification variables can be considered given the proposed sample size.
- A separate simple or blocked randomization schedule is developed for each stratum.
- Large trials often use randomly permuted blocks within stratification groups.

Stratified Randomization (2)

- **Define strata**
- **Randomization is perf… and is usually blocked**
- **Example: Age, < 40, 41… Total number of strata**

Why stratified randomization?

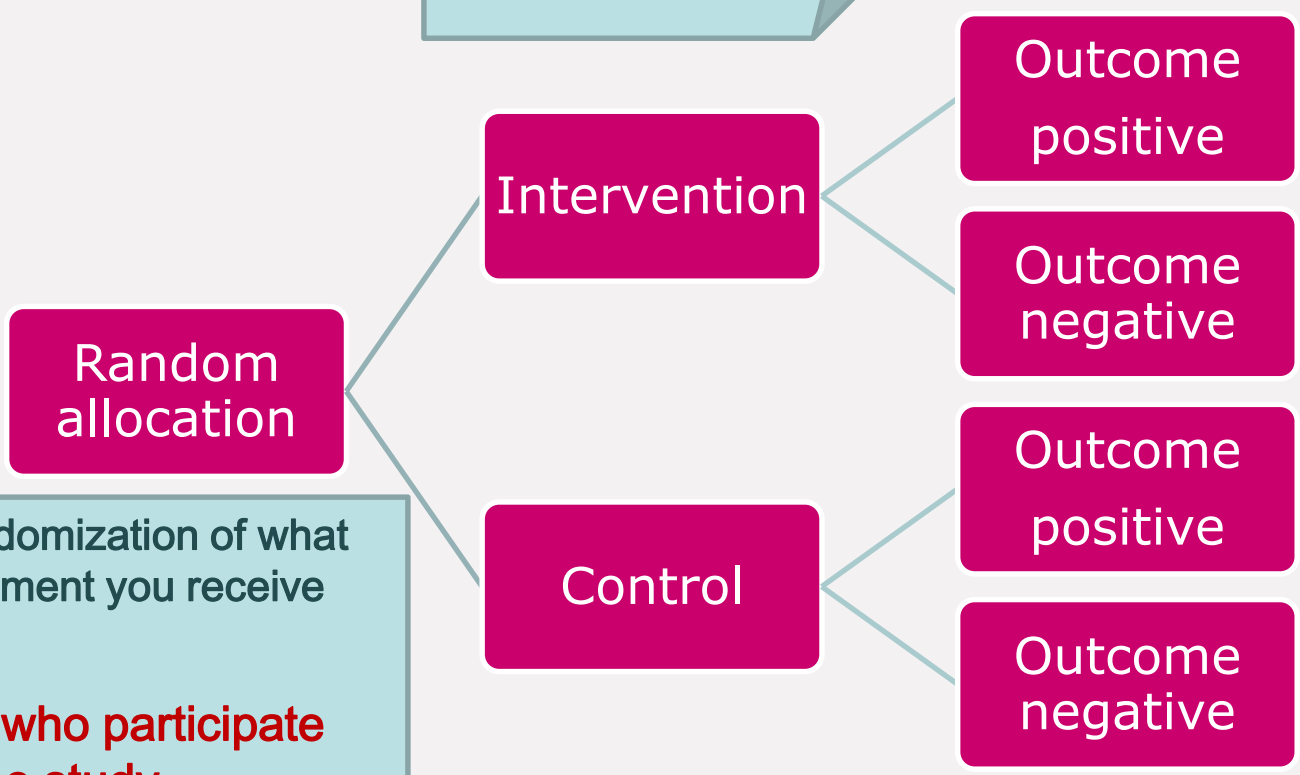
The **prevalence** and severity of disease varies considerably by age and sex

The **prognosis** of disease varies considerably by age and sex

Produce comparable groups with regard to certain characteristics as i.e. age and sex

Age	Male	Female
40	ABBA, BAAB, …	BABA, BAAB, …
41-60	BBAA, ABAB, …	ABAB, BBAA, …
≥60	AABB, ABBA, …	BAAB, ABAB, ..

- Open
- Single blind
- Doble blind
- Triple blind
- Total blind/ complete blind



Randomization of what treatment you receive …

Not who participate in the study

Conduct of a RCT

Enrollment
- Define study population
- Eligibility – inclusions/ **exclusions (generalisibility)**

Randomi-zation
- Interventioin (yes/no)

Allocation
- Concealment

Follow-up
- Same intervals for f-up, same diagnostic procedures….
- Blinded?

Analyse
- «Intention to treat» or «as treated»
- Blinded for intervention (?)

The Coronary Drug Project

***N. Engl. J. Med*.1980;303:1038-41**

- Men with ischemic heart disease (IHD).
- Intervention, clofibrat – lipid lowering drug. n=1103.
- Control group n=2789

- 5-year mortality
  - Intervention- 20.0%
  - Control - 20.9%

P=0.55

But they did not take the drug!

The Coronary Drug Project

***N. Engl. J. Med*.1980;303:1038-41**

- Subgroup analysis
  - Mortality in the intervention group
    - Good adherers to clofibrate 15.0%
    - Bad adherers to clofibrate : 24.6%

P=0.0001

That is what I told you! The drug works well!

The Coronary Drug Project

***N. Engl. J. Med*.1980;303:1038-41**

- Sub group analysis
  - Mortality in the control group
    - Good adherance to placebo: 15.1%
    - Bad adherance to placebo: 28.3%

P < 0.0001

May be the conclusion is that conscientious people have low mortality?

Influence of Adherence to Treatment and Response of Cholesterol on Mortality in the Coronary Drug Project

The Coronary Drug Project Research Group

N Engl J Med 1980; 303:1038-1041

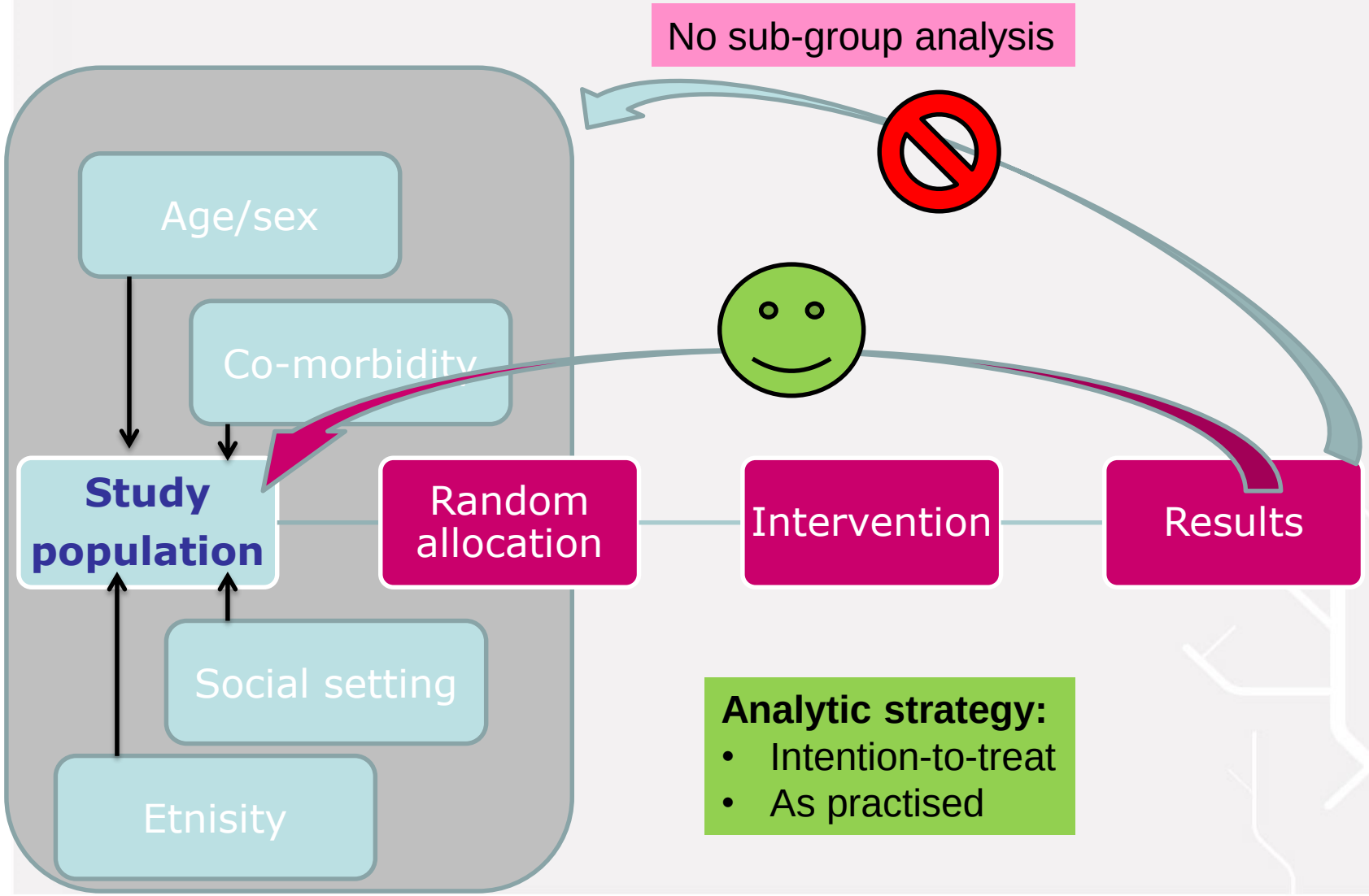
Abstract

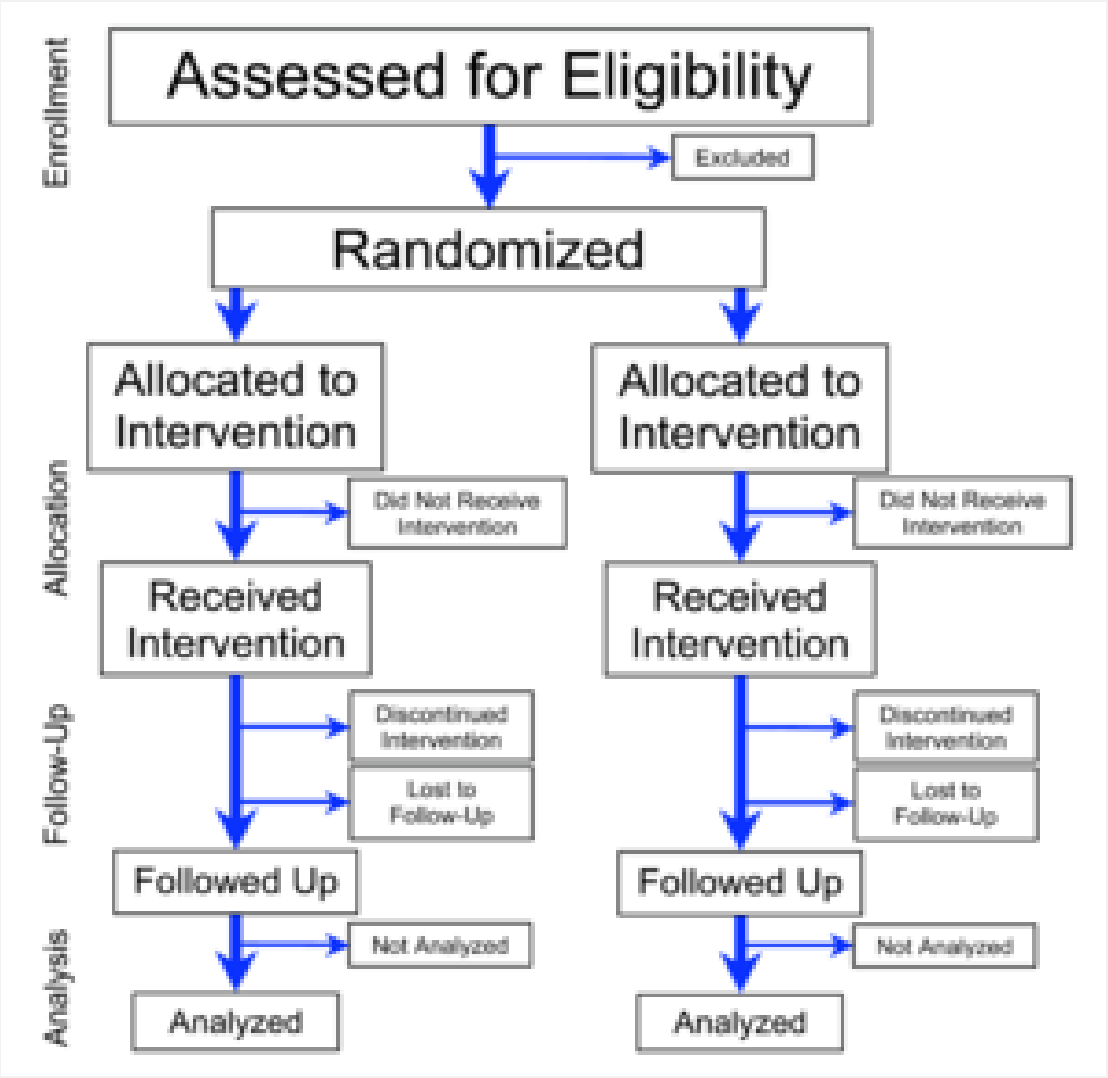
The Coronary Drug Project was carried out to evaluate the efficacy and safety of several lipid-influencing drugs in the long-term treatment of coronary heart disease. The five-year mortality in 1103 men treated with clofibrate was 20.0 per cent, as compared with 20.9 per cent in 2789 men given placebo (P = 0.55).

Good adherers to clofibrate, i.e., patients who took 80 per cent or more of the protocol prescription during the five-year follow-up period, had a substantially lower five-year mortality than did poor adherers to clofibrate (15.0 vs. 24.6 per cent; P = 0.00011). However, similar findings were noted in the placebo group, i.e., 15.1 per cent mortality for good adherers and 28.3 per cent for poor adherers ($P = 4.7 \times 10^{-16}$).

These findings and various other analyses of mortality in the clofibrate and placebo groups of the project show the serious difficulty, if not impossibility, of evaluating treatment efficacy in subgroups determined by patient responses (e.g., adherence or cholesterol change) to the treatment protocol after randomization.

Randomized controlled trials




Enrollment
Assessed for Eligibility
Excluded
Randomized
Allocation
Allocated to Intervention
Did Not Receive Intervention
Received Intervention
Follow-Up
Discontinued Intervention
Lost to Follow-Up
Followed Up
Analysis
Not Analyzed
Analyzed
Allocated to Intervention
Did Not Receive Intervention
Received Intervention
Discontinued Intervention
Lost to Follow-Up
Followed Up
Not Analyzed
Analyzed

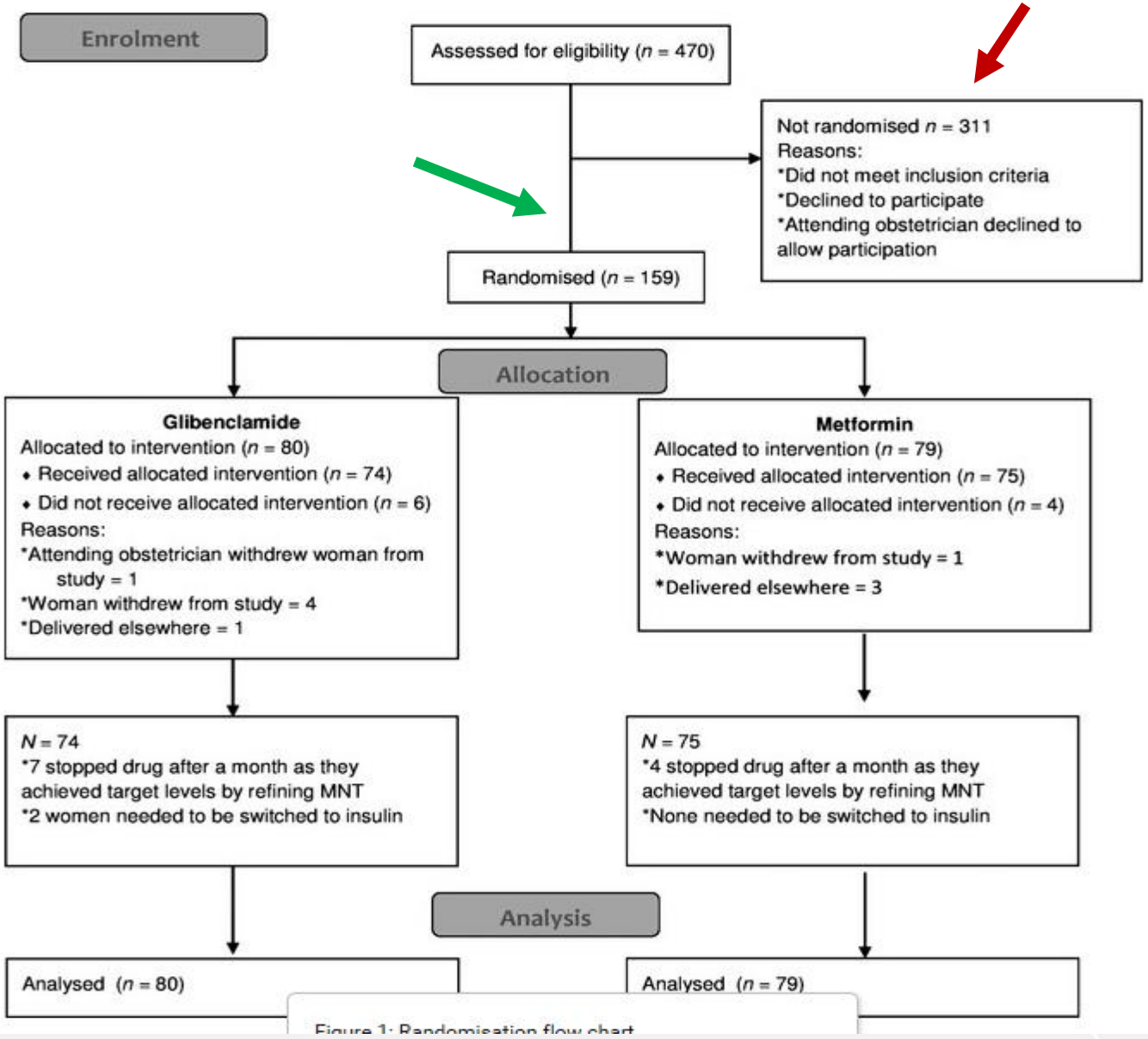


Figure 1: Randomisation flow chart

https://www.randomizer.org/

RCT – strengths and limitations

- Strength
  - Gold standard for assessment of interventions
  - Minimalize bias and confounding

- Limitations
  - Time-consuming
  - Costly
  - Limited generalisability
  - Ethical concerns

In summary

- **Questions of the nature of which treatment works best for RCT**
- RCT addresses problems with skew in the study population

  Excluded were….
- Ethical considerations limit the use of RCT
- **Results from the RCT apply to the study population, but cannot be readily transferred to other populations**