The minimum everyone should know about clinical trial methodology What makes a good clinical research?

Introduction to Clinical Trial Methodology

Workshop PO 'Train the trainers' - 16 & 17 Sept 2020

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What about methodology ?

Our objectives:

1. To get basics of clinical trial methodology:
   - What you should know ?
   - What will help you in reviewing clinical trial protocols ?

2. To be able to train other patients, families, patient organizations.

What will we do ?

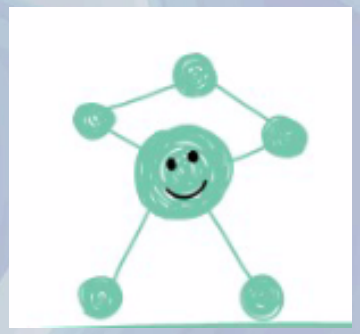
1. Talk about basics of clinical trials
2. Apply what we have seen and review a protocol

Please use the chat box at anytime !

What about methodology

What is the first word that comes to your mind when talking about methodology of clinical trials ?

Please insert one word in the app!



What about methodology

From the molecule to the drug

1. FIND THE RIGHT MOLECULE : Therapeutic interest

↓

2. PRE CLINICAL EVALUATIONS: Laboratory, animal studies

↓

3. CLINICAL EVALUATIONS: Phases I to IV

What about methodology

Phase I

Not in children

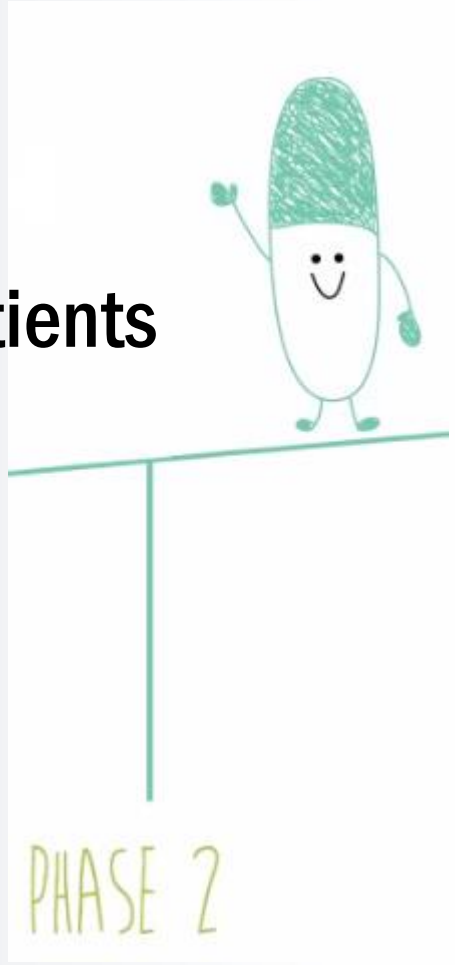
- First administration in Human
- Healthy volunteers
- Tolerance
- Absorption, Diffusion, Metabolism, Excretion (pharmacokinetics)

Healthy volunteers

What about methodology

Phase II

- Dose effect relationship
- Optimal dose
- Homogenous and limited number of patients



What about methodology

Phase III

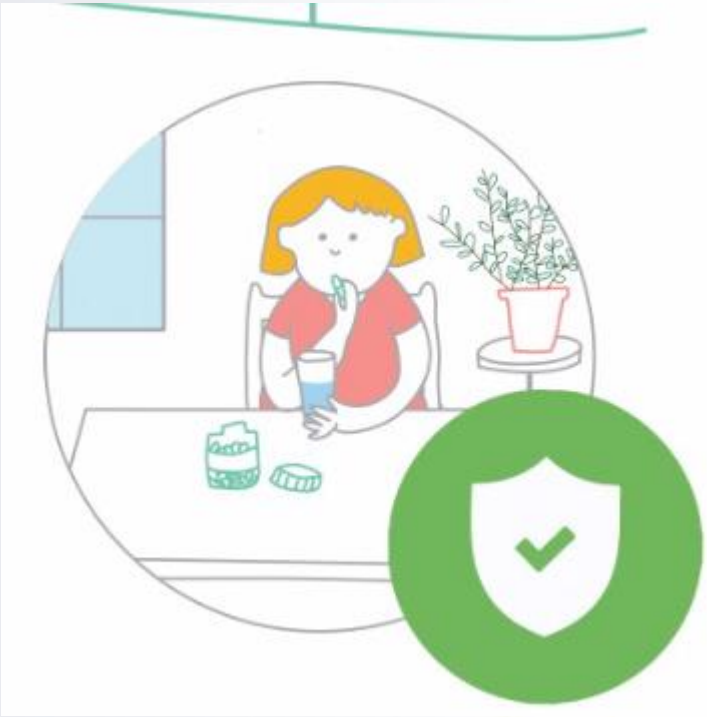
- Efficacy of the therapeutic
- Clinical outcomes
- Benefit risk ratio
- Large number of patients, representative population

=> MA

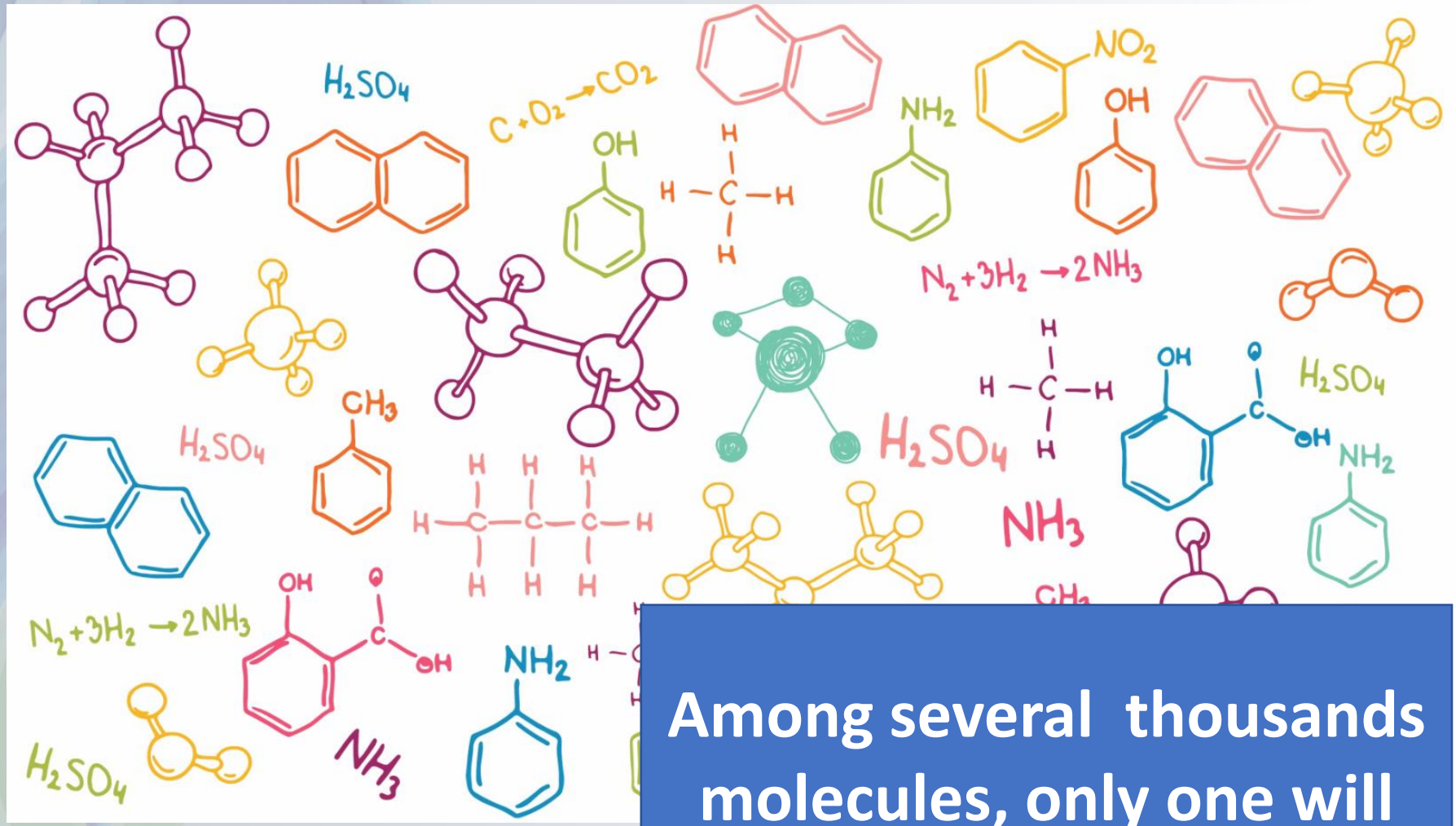
What about methodology

Phase IV

- Strategies,
- Pharmacovigilance (rare adverse reactions)
- Epidemiology, large population
- Real-life conditions
- After MA



What about methodology



Among several thousands molecules, only one will make it as a medicine

What about methodology

Evidence based medicine

Sacket : "Use of current best evidence in making decisions about care of individual patients"

Individual clinical expertise

Best available external evidence

Environment
Patient's specificities

What about methodology

Evidence based medicine

What does it mean?

Individual clinical expertise

Role of the physician
To provide the best care to the patient

- To prescribe a treatment only if useful
- Based on evidences of the effect of the treatment

=> Integrating results from randomized clinical trials in his practice

What about methodology

Evidence based medicine

What does it mean?

Level of evidence

Case study

Uncontrolled studies (cohorts)

Controlled studies (randomized CT)

Meta analysis (several randomized CT)

Best available external evidence

What about methodology

Evidence based medicine

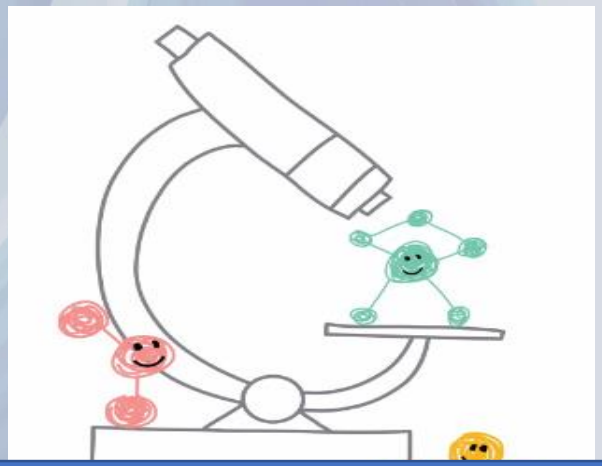
What does it mean?

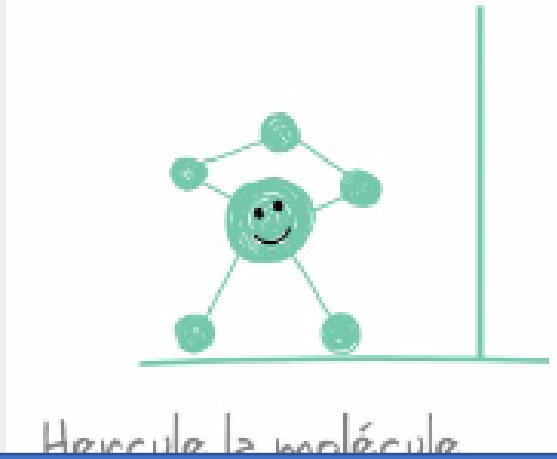
Taking into account the patient

- specificities,
- wishes,
- medical environment

Environment
Patient's specificities

What about methodology





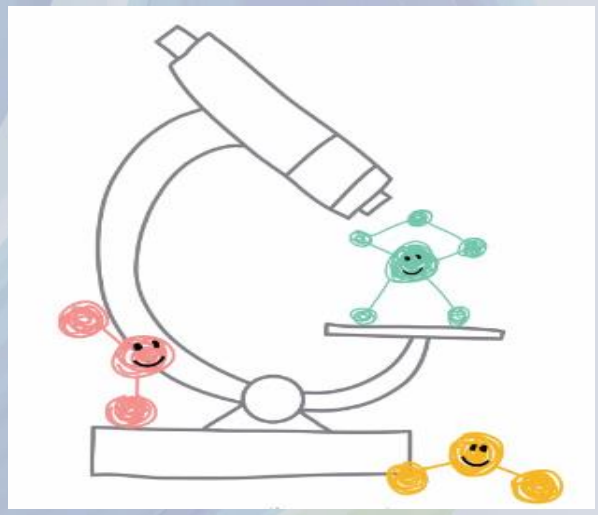
In cystinosis, a compound called cystine accumulates in lysosomes and lead to kidney failure

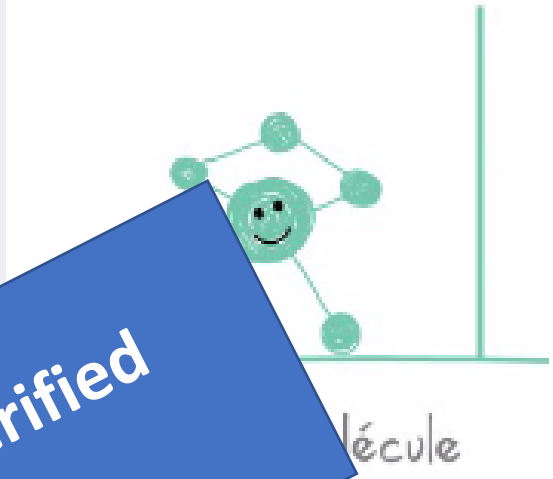
Cysteamine can linked to cystine and help cystine out of the lisosomes

IDEA C YPOTHESIS

Cysteamine could improve kidney function and avoid kidney failure

What about methodology





Disease mechanism

of a molecule

This hypothesis needs to be verified
=> principle of clinical trials

ID MENT = THERAPEUTIC HYPOTHESIS

What about methodology

The objectives and endpoints

1 CLINICAL TRIAL

↓

1 HYPOTHESIS (issued from adequate background)

↓

1 PRIMARY OBJECTIVE (clear and clinically relevant)

↓

CORRESPONDING ENDPOINT(S) = to evaluate the effect of the treatment on a well-defined population in specific conditions

The number of subjects needed is calculated from this hypothesis

MULTIPLE SECONDARY OBJECTIVES POSSIBLE (exploratory)

What about methodology

How would you demonstrate the efficacy of a therapeutic ?

1. By giving the drug to some patients and observe what happens after a sufficient time.
2. By giving the drug to some patients and not giving it to others and compare what happens after a sufficient time.
3. By giving the drug to some patients then not giving it to the same patients and observe the differences, after a sufficient time.

Please answer!

What about methodology

Clinical trial = tool measuring efficacy

Measure

=

TRUE VALUE OF EFFICACY

+

+ errors (random)

+

confounding factors

Role of methodology : Get the true value of efficacy

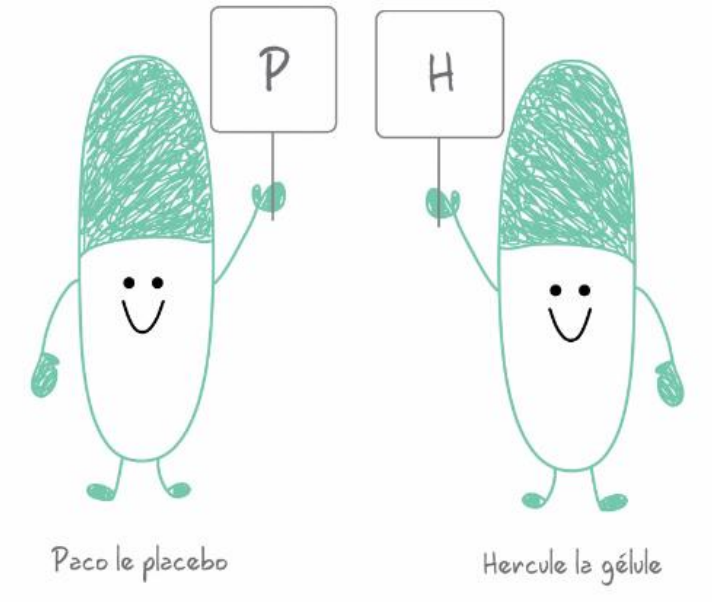
What about methodology

How to demonstrate the efficacy of a therapeutic?

Patients who take the treatment **do better** than those who don't take it

- Curative treatment
- Prevention
- Safety

=> Need for comparison : control groups



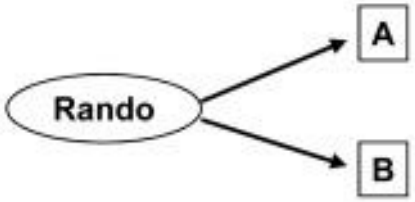
Placebo

Standard treatment

When possible and ethically acceptable

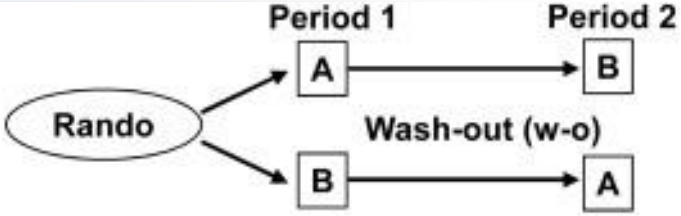
No loss of chance!

A



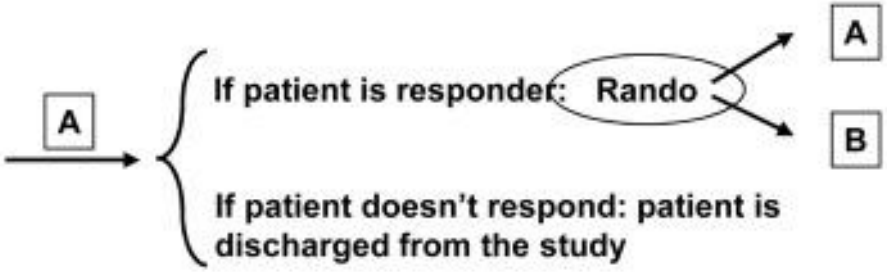
PARALLEL

B



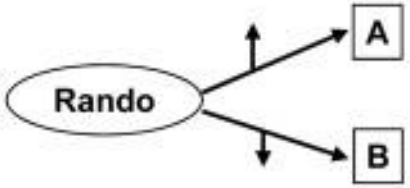
CROSS-OVER

C



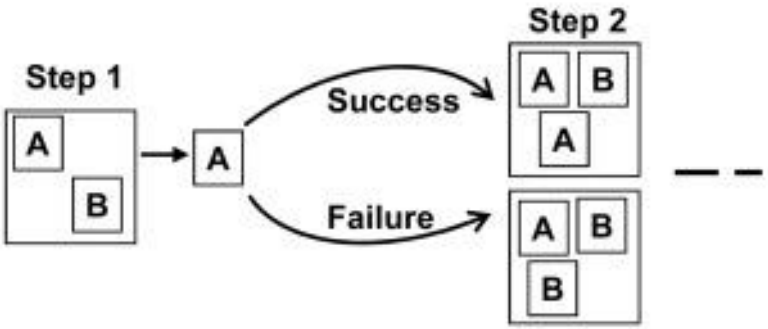
RANDOMIZED WITHDRAWAL

D



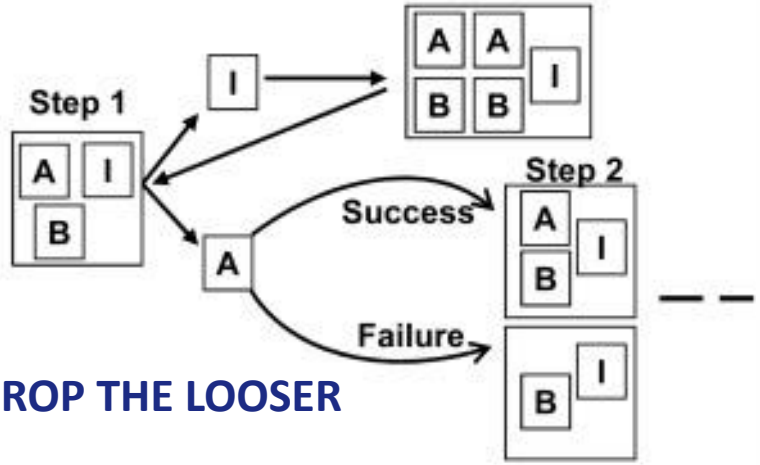
EARLY ESCAPE

E



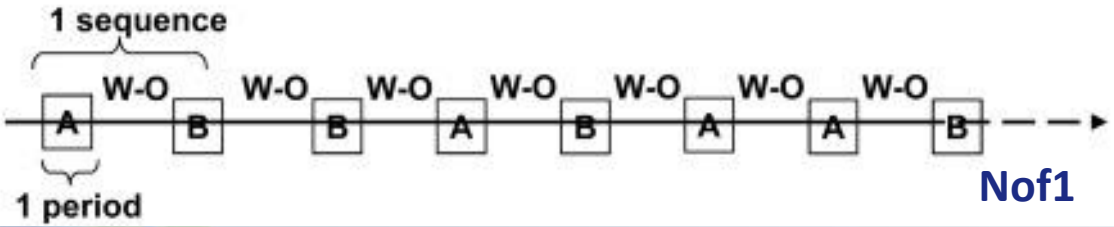
PLAY THE WINNER

F



DROP THE LOOSER

G



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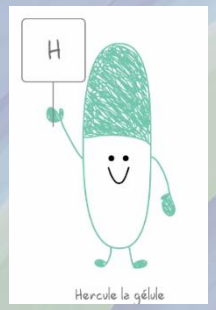
Evolution of the disease

Patients



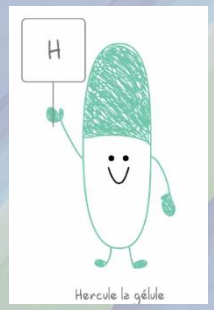
Other treatments
Background, genetics
Severity of the disease,
Psychological considerations
…etc…
+ known or unknown factors

End of treatment

Evolution of the disease

Is this working?

er treatments
round, genetics
y of the disease,
gical considerations
…etc…
+ known or unknown factors



End of treatment

Patients

Other treatments
Background, genetics
Severity of the disease,
Psychological considerations
…etc…
+ know nor unknown factors

End of treatment

End of treatment

Patients

Still missing something?

ments
genetics
disease,
siderations

+ know nor unknown factors

End of treatment

End of treatment

Patients

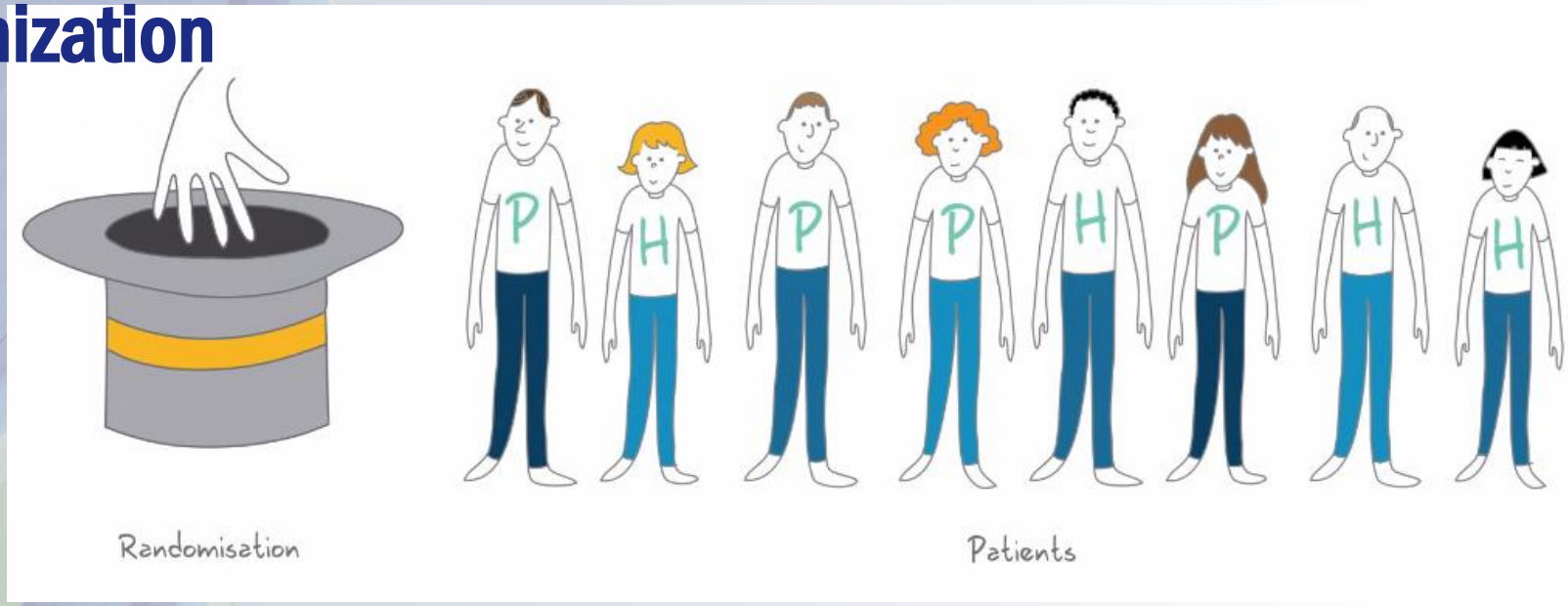
This one ?

End of treatment

End of treatment

What about methodology

Randomization



Belonging to a group depends only from random ensuring:
Comparable groups with characteristics well distributed

A good randomization is centralized, unpredictable

Patients

RANDOMIZATION

Other treatments
Background, genetics
Severity of the disease,
Psychological considerations
…etc…
+ know nor unknown factors

End of treatment

End of treatment

What about methodology

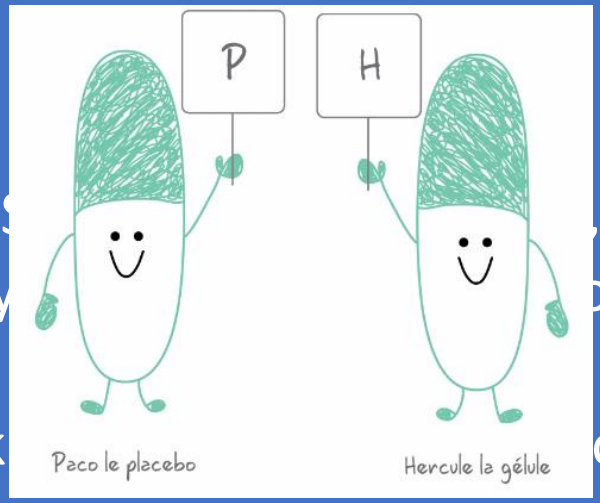
Double blind

- Neither the patient nor the physician knows what treatment the patient is receiving
- Use of a placebo
- Single blind assessment when double blind impossible

Patients

RANDOMIZATION

DOUBLE BLIND



Psy ons

+ k ors

End of treatment **End of treatment**

TRUE TREATMENT EFFECT

What about methodology

Population and patient follow-up

- Population needs to be defined very precisely
  - What is our targeted population ?
  - Is it representative ?

- Eligibility criteria
  - Demographic data
  - Definition of the disease
  - Authorized concomitant medications…
  - Other associated comorbidities?

What about methodology

Some statistics (the word that should not be pronounced!)

- Chance versus “real effect”
  - Can explain apparent results

- Probability : p to observe a difference only due to chance when there is no difference between the two groups

- Alpha : threshold to reject chance (5%)

- NSN : number of subjects needed; What is the expected difference between the two groups . The smaller it is the biggest NSN.

What about methodology

More statistics ….

- Interpretation of results :
  - Statistically significant or not (what does it mean ?)
    - p <0.05
    - If statistically significant, is it clinically relevant ? Is it due to treatment ?
    - If not statistically significant , is there no difference between groups? Was the power of the study sufficient (patients)? => NO CONCLUSION

What about methodology ?

THE STUDY PROTOCOL - CONTENT

- 1 General Information (trial title,, sponsor, date and version)
- 2 Background Information
- 3 Trial Objectives and Purpose
- 4 Trial Design
- 5 Selection and Withdrawal of Subjects
- 6 Study treatment
- 7 Efficacy and safety assessments
- 8 Statistics
- 9 Direct Access to Source Data/Documents
- 10 Quality Control and Quality Assurance
- 11 Ethical and regulatory considerations
- 12 Data Handling and Record Keeping
- 13 Financing and Insurance
- 14 Publication Policy
- 15 Supplements