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

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

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's specificities,
- 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 lysosomes.

Cysteamine could improve kidney function and avoid kidney failure.
What about methodology

Disease mechanism

Effect of a molecule

IDEA OF TREATMENT = THERAPEUTIC HYPOTHESIS

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

When possible and ethically acceptable
No loss of chance!
What about methodology

PARALLEL

CROSS-OVER

RANDOMIZED WITHDRAWAL

EARLY ESCAPE

PLAY THE WINNER

DROP THE LOOSER

Nof1
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

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

End of treatment

Is this working?
Patients

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

End of treatment

End of treatment
Background, genetics, severity of the disease, psychological considerations... etc...

+ know nor unknown factors

Patients

Still missing something?

End of treatment

End of treatment
Patients

End of treatment

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

End of treatment

RANDOMIZATION

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
Other treatments

Background, genetics

Severity of the disease

Psychological considerations… etc…

+ known nor unknown factors

Patients

RANDOMIZATION

DOUBLE BLIND

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) | 9 Direct Access to Source Data/Documents |
| 2 Background Information | 10 Quality Control and Quality Assurance |
| 3 Trial Objectives and Purpose | 11 Ethical and regulatory considerations |
| 4 Trial Design | 12 Data Handling and Record Keeping |
| 5 Selection and Withdrawal of Subjects | 13 Financing and Insurance |
| 6 Study treatment | 14 Publication Policy |
| 7 Efficacy and safety assessments | 15 Supplements |