Introduction;
Understanding Clinical Trials

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Objectives

- Understand the ABC of clinical trial in regards of;
  - Design.
  - Analysis.
  - Reporting.

In a very simple manner
Types of studies

- Experimental study
- Observational study
- Reviews
Types of studies

- Experimental study
  - Controlled
  - uncontrolled
- Observational study
Types of studies

- Experimental study
  - Controlled
    - Parallel
    - Sequential
  - Uncontrolled
- Observational study
Types of studies

- Experimental study
  - Controlled
    - Parallel
      - Randomized
      - Non randomized
    - Sequential
  - Uncontrolled
- Observational study
Types of studies

- Experimental study
  - Controlled
    - Parallel
    - Sequential
      - Self control
      - Crossover
  - Uncontrolled

- Observational study
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Types of studies

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- Observational study
Randomized Controlled Clinical Trials (RCT) is considered the key means by which treatments and interventions are evaluated for their safety and efficacy. “they are the cornerstone of evidence-based medicine in current practice”
Randomized Control Trial

RCT characteristics

- Evaluate the effect of a new drug, device or procedure.
- Using Human volunteers (who should sign a consent).
- Include comparison arm (old treatment or placebo).
Randomized Control Trial

RCT characteristics

- Sponsored by pharmaceutical companies in case of new medication.

- Sometimes sponsored by the government in case of old medication in treating new disease area.

- Both patients and trial personnel are unaware of which patient is on the new drug.

- It should be run in ethical manner so that no patient is to be deprived from the benefit of usual treatment.
Types of clinical trials

Depends on the Sponsorship and the Aims.
Phases

- Phase I

  The new medicine is tried on healthy volunteers or in patients unresponsive to usual therapy. Mainly to look at:
  - Pharmacokinetics.
  - Pharmaco-dynamics.
  In respect to immediate short term safety of higher doses.
Phases

- Phase II
  - Examine dose response curves in patients.
  - Look at the benefit that might be seen in a small group of patients with particular disease.
Phases

- **Phase III**
  - The new drug is tested in controlled fashion in a large patient population against placebo or standard therapy.

  “it is a key phase where the drug either make or break its reputation with respect to safety or efficacy before marketing begins”
Phases

- Phase III
  Landmark study: is a phase III trial with positive results.

  This will make the new drug gains a license to be prescribed for the treatment of certain disease.
Phases

- **Phase IV**
  
  Post marketing study: as the drug has granted license or approval.
  
  These studies are crucial in gathering further safety information from a larger group of patients in order to understand the long term safety of the drug and address drug interactions.
Types of (RCT) clinical trials

According to the Design
Design

- Parallel group trial
- Crossover trial
- Factorial trial
Design

- Parallel group trial
  - Patients are randomized to the new treatment or to the standard treatment and followed to determine the effect of each treatment in parallel groups
Design

Crossover trial

- Where patients are randomized to different sequences of treatments, but all patients at the end get all treatments in varying order.
- The patient is his own control.
Design

Factorial trial

- Assign patients to more than one treatment-comparison group.
- Randomization occur twice at one trial at same time
- While drug A is being tested against placebo patients in the trial are randomized once more to drug B or placebo, thus producing 4 treatment groups in total;
  - Group A
  - Group B
  - Group A+B
  - Placebo
Types of (RCT) clinical trials

According to the number of centers involved in the trial.
Number of centers

- **Single center trial**
  - Involves patients of one specialized clinic or ward;
  - Used for phase I or phase II studies

- **Multi-center trial**
  - Involves patients at different centers
  - Can be done at any stage of clinical development.
What necessitate performing a Multi-center trial?

Two major reasons:

1. To evaluate a new medication or procedure more efficiently in terms of recruiting sufficient subjects over a shorter period of time.

2. To provide better bases for the subsequent generalization of the trial’s finding.
Types of (RCT) clinical trials

According to the aim that the study was designed to prove
Designed to prove what?

- Superiority study
- Equivalence study
- Non inferiority study
Designed to prove

- **Superiority**
  - Aims to prove that the new drug is more effective than the comparative treatment
    - Placebo
    - Current best treatment
  - Represent most of the clinical trials

- **Equivalence**
- **Non inferiority**
Designed to prove

- **Superiority**
- **Equivalence**
  - Designed to prove that two drugs have the same clinical benefits
  - Such trial demonstrate that the effect of the new drug differs from the effect of the current treatment by a margin that is clinically unimportant
- **Non inferiority**
Designed to prove

- Superiority
- Equivalence
- Non inferiority

- Aims to show that the effect of a new treatment cannot be said to be significantly weaker than that of the current treatment
Designed to prove

- Superiority
- Equivalence
- Non-inferiority

In both the equivalence and non-inferiority studies the new treatment might still turn out to be more effective than the comparative treatment, but this is not the prior assumption of the trial.
Reporting of the Clinical Studies

- Anatomy of the clinical study as seen in the literature:
  - Abstract
  - Introduction
  - Methodology
  - Results
  - Discussion
  - Acknowledgement
  - References
# Anatomy of RCT

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<td>Brief overview of the research project.</td>
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<td>Introduction</td>
<td>Research background, and the clinical trial objectives.</td>
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<tr>
<td>Methodology</td>
<td>Study design, patient inclusion and exclusion criteria, intervention and control groups, randomization, blinding, endpoints, follow-up procedure, sample size calculations/power analysis, statistical analysis</td>
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# Anatomy of RCT

<table>
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M. Haji Faraji et al. (1998)

- The effect of sour tea (*Hibiscus sabdariffa*) on essential hypertension
Abstract

- We conducted this experimental study to evaluate the effect of sour tea (*Hibiscus sabdariffa*) on essential hypertension.

- For this purpose, 31 and 23 patients with moderate essential hypertension were randomly assigned to an experimental and control group, respectively.

- Patients with secondary hypertension or those consuming more than two drugs were excluded from the study.

- Systolic and diastolic blood pressures were measured before and 15 days after the intervention.

- In the experimental group, 45% of the patients were male and 55% were female, and the mean age was 52.6 ± 7.9 years.

- In the control group, 30% of the patients were male, 70% were female, and the mean age of the patients was 51.5 ± 10.1 years.
Abstract

- Statistical findings showed an 11.2% lowering of the systolic blood pressure and a 10.7% decrease of diastolic pressure in the experimental group 12 days after beginning the treatment, as compared with the first day.

- The difference between the systolic blood pressures of the two groups was significant, as was the difference of the diastolic pressures of the two groups.

- Three days after stopping the treatment, systolic blood pressure was elevated by 7.9%, and diastolic pressure was elevated by 5.6% in the experimental and control groups.

- This difference between the two groups was also significant.

- This study proves the public belief and the results of in vitro studies concerning the effects of sour tea on lowering high blood pressure.

- More extensive studies on this subject are needed.
Question

- What was the cause for the investigators to do this research?
Introduction

- Hypertension is one of the most prevalent and important health problems in developed as well as developing countries.
- 24.6–29.7% of the residents of Tehran are hypertensive.
- For high blood pressures, diuretics, CCB and ACEI.
- These drugs have multiple side effects such as vertigo, depression, tachycardia, angina, hypokalemia, gastrointestinal disturbances.
- Traditionally, drugs or herbs such as decoction olive leaf, garlic and specially sour tea (*Hibiscus sabdariffa*) are used for controlling hypertension.
- They have beneficial therapeutic effects and minimal side effects.
Introduction

- we conducted this study to evaluate of the effects of sour tea on the systolic and diastolic pressure of patients with essential hypertension in Tehran’s Shariati Hospital in 1995.

- This study may clearly define the effects of sour tea on hypertension, thereby providing a safe treatment for controlling hypertension and its secondary fatal effects.
Questions

- What was the design of the study?
- How many patients were initially recruited?
- What was their inclusion and exclusion criteria?
- What were the control subjects drinking?
- When did they measure the blood pressure?
- For how long was the study conducted?
- How did they analyze the data?
Methodology or (materials and methods)

- Sequential randomized controlled clinical trial.
- 80 patients meeting the inclusion criteria were selected among 162 patients registered.
Inclusion criteria were:

- a systolic pressure of 160–180 mmHg and/or a diastolic pressure of 100–114 mmHg, use of two or fewer antihypertensive drugs.

Exclusion criteria

- Secondary hypertension
- Underlying diseases such as:
  - Cardiovascular abnormalities
  - Thyroid disease
  - Diabetes
Methodology or (materials and methods)

- One week after discontinuation of antihypertensive drugs, blood pressure was measured in the sitting position, from the right hand positioned at the level of the heart, by a Reister mercury sphygmomanometer with a 1450-cm cuff and a German stethoscope.

- Blood pressure was measured twice, at least 5–10 min apart. If there was more than 5 mmHg difference between the two recordings, blood pressure was measured for the third time.
Methodology or (materials and methods)

- instructions for the usage of sour tea were given.
- Boxes of 150 g of sour or ordinary tea were given to the patients, based on random numbers.
- They were instructed to use one glass of the decoction (two spoonfuls of blended tea in one glass of boiled water boiled for 20–30 min) at least 1 h before measuring the blood pressure.
- None of the patients knew the type and effects of the tea they consumed. Blood pressure was recorded at days 4, 8 and 12, and 3 days after stopping its use (day 15) by the described method.
Methodology or (materials and methods)

- Results of changes in blood pressure in the two groups were compared using the paired $t$-test, and between the groups using the $t$-test.
- Qualitative variables were tested with $x^2$. 
Results

- Of the 80 patients, 26 were excluded from the study due to a rise in blood pressure over the expected range, after discontinuation of their pharmacological drugs.

- Fifty-four patients (31 in the experimental group and 23 in control group) were evaluated.
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Results

Variables such as:

- Sex
- BMI
- Positive family history of hypertension
- Cigarette smoking
- The number of persons in the family (no significant difference) between the two groups.
Results

- The blood pressure was the lowest on the twelfth day in the experimental group, with an 11.2% decrease of systolic pressure and a 10.8% decrease of diastolic pressure, as compared to the first day.

- The difference of blood pressure between the control and experimental groups are significant (with $P < 0.00001$ for systolic pressure and $P < 0.00002$ for diastolic pressure).
Results

- On the fifteenth day after cessation of drinking tea for 3 days, there was a systolic pressure elevation of 5.6% and diastolic pressure elevation of 6.2% in the experimental group.

- In the control group, systolic pressure decreased 0.6% and diastolic pressure rose 0.4%.

- Comparing the two groups, we observe a 1.8-fold decrease in systolic pressure and a 2.1-fold decrease in diastolic pressure until the twelfth day in the experimental group as compared to the control group.
Question

- How did the author interpret the results?
- How the result comply with what is already known or compared with other similar studies?
The patients in the experimental group showed decrease in blood pressure that was greatest on the eighth day, and continued until the twelfth day.

The effect of sour tea on decreasing systolic and diastolic pressure increases by continuing its consumption.

This effect begins on the first day, gradually increases, and peaks on the eighth day.

From this day until day 12, systolic and diastolic pressure decrease equally.
Discussion

- The blood pressure of the patients in the control group who used ordinary tea decreased on the twelfth days of the study, which may be due to the application of the health advices given at the beginning of the study.
Discussion

- The use of sour tea for the treatment of hypertension has a long traditional history, especially in Iran, in which it is a popular belief.
- Is the antihypertensive effect of sour tea only due to its diuretic effect, or are there any other mechanisms?
- Is the antocianine in the extract of sour tea the effective antihypertensive substance of this tea which has a vasodilator or an angiotensin converting enzyme inhibitor mechanism?
Discussion

- One of the remarkable findings of this trial was the positive effect of regular consumption of sour tea on controlling blood pressure, as is the case in all antihypertensive drugs.

- Since the exact mechanism of the antihypertensive effect of sour tea is still unknown, its consumption must be supervised by a physician.
Acknowledgements

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References


Thank You