

STUDY DESIGN

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Before we get into the types of study design,
let's discuss **ETHICAL APPROVAL** of a study.

A bit of history...



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Louis Pasteur- 1800's

- Founder of 'germ theory'
- Even though he was confident of the results obtained through animal trials, Pasteur "agonized over treating humans," and finally did so only when he was convinced the death of the child, the first test subject, "appeared inevitable."



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Nuremberg Code (after Nazi trials)

- The Nuremberg Code includes the following guidance for researchers:
 - Informed consent is essential.
 - Research should be based on prior animal work.
 - The risks should be justified by the anticipated results.
 - Only qualified scientists must conduct research.
 - Physical and mental suffering must be avoided.
 - Research in which death or disabling injury is expected should not be conducted.



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Declaration of Helsinki

- In 1964, the World Medical Association developed a code of research ethics that came to be known as the Declaration of Helsinki.
- It was a reinterpretation of the Nuremberg Code.
- Subsequently, journal editors required that research be performed in accordance with the Declaration.
- Revised in the year 2000



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Belmont Report

- After the Tuskegee Syphilis Studies, the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research adopted a code of ethics in 1979.
- Federal law now mandated regulations affecting research sponsored by the federal government.
- The regulations are referred to as the Belmont Report.



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The Belmont Principles

- The *Belmont Report* identifies three basic ethical principles that underlie all human subject research in the United States.
- The Belmont Principles are:
 1. Respect for persons (informed consent; protected populations)
 2. Beneficence (above all, do no harm; risk benefit ratios)
 3. Justice (all people are created equal)



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Institutional Review Board

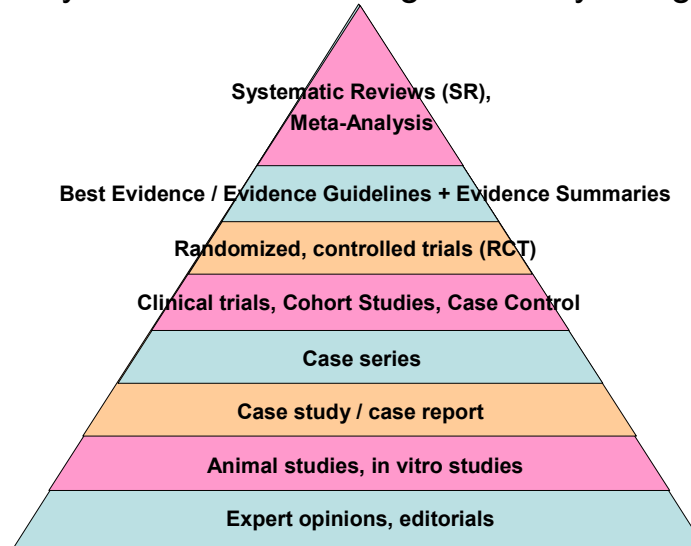
- Before undertaking a research study, researchers must submit research plans to the IRB
- The duty of the IRB is to ensure that the proposed plans meet the federal requirements for ethical research based on the Belmont principles
- An IRB can approve of the plan, require modifications, or disapprove the plan



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Hierarchy of Evidence: strength of study design



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Analytical Research

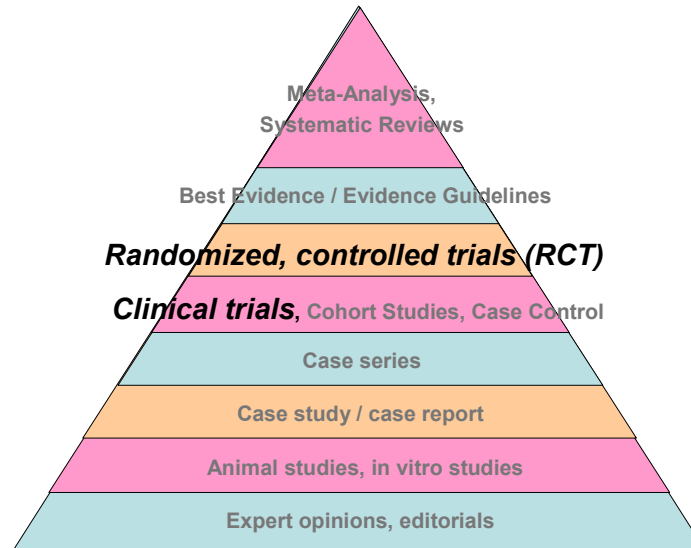
1. Observational (non-experimental) research: Researchers collect data without making changes to patient's lives or introducing treatments. Researchers 'observe' only.
2. Experimental research: Researchers actively introduce a risk factor, intervention, or treatment. Offers the greatest control. Researchers 'do experiments' by introducing new variables.



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Hierarchy of Evidence: strength of study design



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What is a trial?

- Experimental study where the investigator decides who belongs in which group.
- Decision as to group allocation can be done by random or non-random methods.
- Study may or may not have control group.



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What are the different types of trials?

- Clinical trial
- Controlled clinical trial
- Randomized clinical trial
- Randomized controlled clinical trial



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What does randomization do?

1. Reduces bias by the investigator or the subject regarding group allocation.
 2. Evenly allocates subjects on basis of known and unknown characteristics.
- Baseline characteristics are usually shown in Table 1 of any article so you can assess internal validity.



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Table 1. Characteristics of each group at the beginning of the study

	Control group	Experimental group	<i>P</i>
No. of subjects	37	34	
Sex (male/female)	13/24	13/21	.7
Age (mean \pm SD)	39 \pm 10	35 \pm 10	.2
Length of neck pain	4.5 \pm 4.6	4 \pm 3.4	.6
Neck pain at rest	5.5 \pm 1.5	5.7 \pm 1.5	.4
Cervical flexion	43 \pm 9	45 \pm 7	.2
Cervical extension	55 \pm 7	57 \pm 9	.2
Left lateral flexion	35 \pm 7	37 \pm 6	.2
Right lateral flexion	33 \pm 6	34 \pm 7	.4
Left rotation	56 \pm 7	57 \pm 10	.8
Right rotation	53 \pm 6	55 \pm 9	.3

Scores are expressed as means \pm SD.

Study validity

- Internal validity: When the study groups are comparable in terms of demographics and clinical characteristics. (Table 1)
- External validity (generalizability): When the study groups are comparable to the target population such as the general public.

The term 'random'

- 'Randomization' deals with group allocation
- 'Random selection' deals with sampling
- 'Randomization' \neq 'random selection'
- Randomized clinical trials are called randomized because of 'randomization' which means the subjects are randomly allocated to groups.



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RCT ADVANTAGES

- Randomization decreases bias
- Blinding (single or double) decreases bias
- Very structured therapy or intervention so investigator can accurately describe
- Strongest study design because so much control over the study



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RCT DISADVANTAGES

- Structure may change the results a clinician would get in private practice
- No variation from the therapy by the research clinician
- Takes many research personnel to complete and can be very expensive



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What to look for in a clinical trial...



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Study objectives

- Purpose, objectives, and hypothesis
 - Were the objectives of the study clearly stated?
 - Was there a study hypothesis?
 - Was there a significant need for this study?
Was the study justified?



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Study design

- Was the study design stated and adequately described?
- If appropriate, was ethical approval of the study obtained?



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Subjects

- Who was included in the study?
- Who was excluded from the study?
- How were the subjects recruited?
- Was there any selection bias?



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Baseline differences

- Were there any differences noted between groups at the beginning of the trial?
- Should any differences be considered as possible confounders?
- If differences are present, are they acknowledged and addressed?
- Are any differences discussed as limitations?



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Intervention provided

- Description of interventions should be clear and reproducible
- Comparison groups: one intervention vs. another with both being of interest
- Control group: Usual and customary care group or a placebo group. You compare your experimental group to the control group.
- Placebo group: Treatment group with no expected physiological effect. Also known as 'sham' treatment.



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Description of Interventions

- What specific intervention or other maneuver was given to the subjects in the study?
- Was the intervention sufficiently described so that the reader (practitioner) could adequately deliver the same intervention?
- Were an adequate number of visits provided at appropriate intervals and frequency?
- Was the intervention similar to “real life” treatments?
- If a placebo or “sham” was utilized, was it realistic?



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Blinding

- Was the study population blind to the type of intervention they received (experimental or control/placebo)?
- Were experimental and control groups treated equally?
- Were the clinicians and/or patients “blind” to the treatment?
- Was there double blinding?



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Outcomes, measurement, observation

- What outcome was measured, and how?
- Were outcomes clear and logical?
- Were outcomes valid? Standard? Objective?
- Were there alternative measurements which were considered “gold standards” ?
- Was the measurement clinically relevant?
- Was the study of adequate length in terms of outcomes assessment (ex: follow-up)?



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Key results

- Were the basic data adequately described?
- Were results presented clearly, objectively, and in sufficient detail to enable the reader to draw their own conclusions?
- Were adverse effects adequately described and explained?



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Statistical significance ($p < 0.05$)

- “Acceptable” level of probability (chance error) is set before the study begins, often set at 5% but could also be set higher. It is considered the tolerable amount of chance intrusion.
- Typically, statistically significant data has a p-value of < 0.05 . This means that there is a $< 5\%$ possibility that the result is due to chance.
- Ex: If you have a $p = 0.10$ then there is 10% possibility that the result is due to chance. And a $p = 0.32$ means a 32% possibility of chance.



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Follow-up / Accountability

- Were all study participants or subjects accounted for at the end of the study?
- Were the reasons why patients withdrew from the clinical trial included in the follow-up information?



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Follow up/Accountability

- Should use the Consolidated Standards of Reporting Trials (CONSORT guidelines)
- Follow-up of less than 75% should lead you to thoughts of bias.

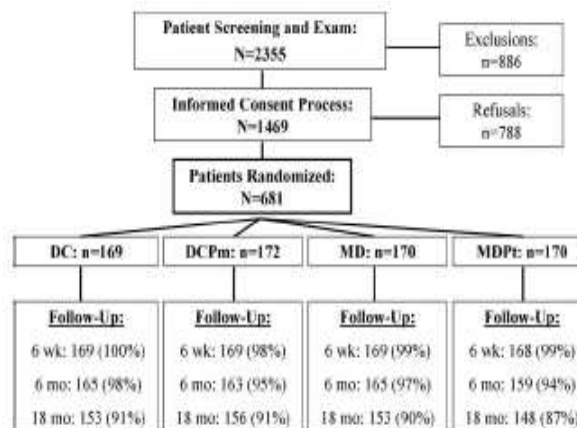


Figure 1. Flow diagram of patient screening, enrollment, and follow-up through 18 months.

Hurwitz et al. 2006



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Author's conclusions

- Have the authors expressed the effects of an intervention in terms of the likely benefit or harm which an individual patient can expect?
- Do the authors overstate any of their conclusions?
- Do the authors discuss limitations of the study?



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Statements of support/influence; Disclaimers

- Did any of the authors have affiliations with companies or organizations that may have affected their ability to be objective?
- Did any financial support potentially lead the investigators to be biased?



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Clinical impact statement

- Does this new research add to the literature in any way?
- Does this research impact your clinical decision-making within your practice?



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Critical appraisal of an RCT

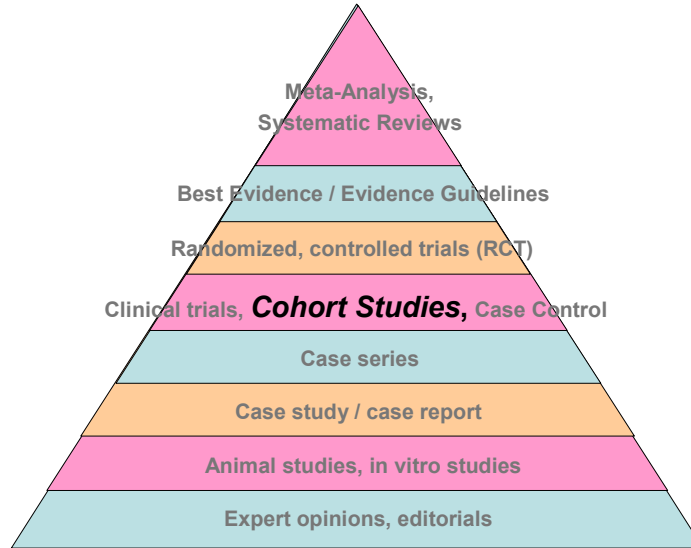
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Next study design...



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Any questions?



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