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**College of Health Sciences
and Professions**

CLINICAL RESEARCH PRIMER

Jennifer Horner, PhD, JD

Professor and Associate Dean for Research and Graduate Studies

Janet Simon, PhD

Assistant Professor, School of Applied Health Sciences and Wellness

College of Health Sciences and Professions

1 Ohio University
W380 Grover Center
Athens, OH 45701

Acknowledgment: We appreciate the constructive suggestions offered by Dr. Laura Rush, Director of the Clinical Translational Research Unit, Heritage College of Osteopathic Medicine.

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- What makes clinical research ethical?
- What are the responsibilities of the principal investigator (P.I.)?
- What is research?
- What is clinical research?
- How is a “clinical trial” different from “clinical research”?
- What is the relationship of clinical research to bench, bedside, and community health research?
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- What are the main types of research using quantitative data?
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What are several fundamental principles governing research ethics?¹

Respect for persons



Respect for persons entails respecting the dignity of research participants and ensuring their autonomy. In cases where autonomy may be diminished, people should be protected from any exploitation that results due to their vulnerability. This principle is important because adherence to it entails that people will not be merely a means to achieve the research objectives.

Beneficence



Beneficence requires a commitment to minimizing the risks associated with research, including psychological and social risks, and maximizing the benefits that accrue to research participants. Researchers must articulate specific ways this will be achieved. [Many contemporary ethicists separate this principle into two principles: beneficence and nonmaleficence.]

Justice



Justice requires a commitment to ensuring a fair distribution of the risks and benefits of research. Research participants should share in the benefits of the knowledge gained. Therefore, the research participants should be people who are expected to benefit from the knowledge gained through the study.

What makes clinical research ethical?²

According to Emanuel, Wendler, and Grady (2000), clinical research has seven ethical requirements:

- Social or scientific value
- Scientific validity
- Fair subject selection
- Favorable risk-benefit ratio
- Independent review
- Informed consent
- Respect for potential and enrolled subjects.

What are the responsibilities of the principal investigator (P.I.)?

The P.I. is responsible for the project as a whole. Elements include: articulating the scientific question; designing the methodology; assuring the reliability and validity of data collection, recording, and analysis; supervising research personnel; producing scholarly articles; and, assuring the ethics of the research from scientific, social, and regulatory perspectives.

In a famous early article on research ethics in the New England Journal of Medicine, exposing ethics abuses in pediatric research (Beecher, 1966) articulated his two most important concerns.

The ethical approach to experimentation in man has several components; two are more important than the others, the first being informed consent. . . [I]t is absolutely essential to *strive* for it for moral, sociological and legal reasons.

“Secondly, there is the more reliable safeguard provided by the presence of an intelligent, informed, conscientious, compassionate, responsible investigator.”³ (p1360)

What is research?

“A systematic investigation designed to develop or contribute to generalizable knowledge.”⁴

- **Investigation:** The gathering and analysis of information to answer a research question.
- **Systematic:** Deliberately organized around a specific research question and objective, and governed by rigorous (reliable and valid) methods of data collection and analysis.
- **Generalizable knowledge:** Research designed to inform questions of incidence/prevalence, correlation, and causation that both the scientific and lay communities can rely on to inform clinical choices.

What is clinical research?

Clinical research is patient-oriented research. It is a systematic investigation of humans, human biologic specimens, and human data to identify factors that affect (cause, exacerbate, or ameliorate) health, health risks, and health outcomes. Variables of interest include behavioral, genetic, environmental, and socioeconomic, all of which may predispose individuals to poor health.

How is a “clinical trial” different from “clinical research”?

According to the National Institutes of Health (2015)⁵:

[Clinical research] includes:

- Mechanisms of human disease, therapeutic interventions, clinical trials, development of new technologies;
- Epidemiological and behavioral studies;
- Outcomes research and health services research.

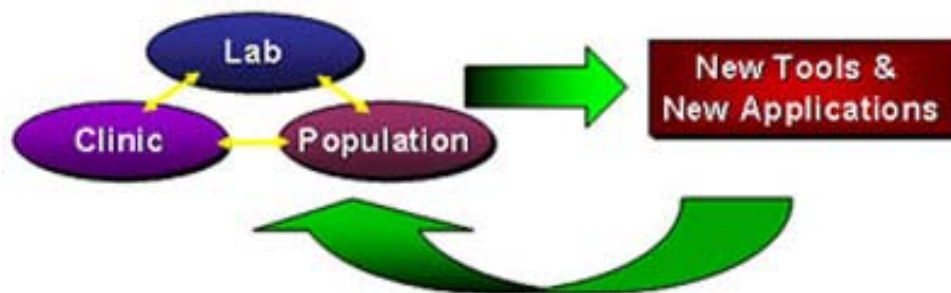
Clinical trials are a subset of clinical research. To be classified as a clinical trial, a clinical research project must involve the following three key characteristics:

- Prospective assignment of subjects through a pre-defined process;
- An intervention; and,
- Evaluation of a health–related biomedical or behavioral outcome.

What is the relationship of clinical research to bench, bedside, and community health research?

Clinical research is part of a continuum of research known as “translational research,” because clinical research is a fundamental bridge between basic science and patient care and, ultimately, population health.

Bench, Bedside & Community Health Research



"Translational research fosters the multidirectional integration of basic research, patient-oriented research, and population-based research, with the long-term aim of improving the health of the public."^{6(p4), 7}

What are some differences between quality improvement and research projects?

Table 1. Comparison Between Quality Improvement and Human Research Projects

	Quality Improvement	Human Research
Purpose	Designed to implement knowledge, assess a process or program as judged by established/accepted standards.	Designed to develop or contribute to generalizable knowledge.
Design	Adaptive, iterative design.	Follows a rigid protocol that remains unchanged throughout the research.
Benefits	Directly benefits a process, system or program; might or might not benefit patients.	Might or might not benefit current subjects; intended to benefit future patients.
Risks	Does not increase risk to patients.	Level of risk varies depending on the project.
Participant obligation	Expectation of participation as a component of care.	No obligation of individuals to participate.
Endpoint	Improve a program, process or system.	Answer a research question.
Analysis	Compare program, process or system to established standards.	Statistically prove or disprove hypotheses or otherwise support, refute or refine theories about mechanisms of, or influences on, human health.

Note. This table was compiled from numerous references, including Lynn J. When does quality improvement count as research? Human subject protection and theories of knowledge. *Qual Safety Health Care.* 2004;13(1):67-70.

What are the main types of research using quantitative data?

Quantitative data in clinical research are discrete, measurable units of behavior or behavioral outcomes, collected with standardized or calibrated test instruments with good reliability and validity (to assure accuracy and reproducibility across samples of subjects).

The main types of clinical research are:

- **Descriptive/observational:** Convert observations to numbers. Capture data to reflect average (mean), spread of scores around the mean (standard deviation), and frequency of occurrence.
- **Correlational:** Convert observations to numbers. Capture data points to determine whether they are related (ie, whether the rate of occurrence of one variable occurs at a similar rate and direction relative to one or more additional variables).
- **Inferential:** Convert observations of dependent variable(s) relative to independent variable(s) to numbers. Capture and compare data points to determine whether changes in the dependent variable vary systematically with respect to the independent variables. Subject the observed group data to well-selected statistical tests to determine probability values, effect sizes, and confidence intervals.

What is qualitative research?

Qualitative research involves the collection of individualized, subjective information that is converted to generalizations about phenomenon influencing the experience of disease, quality of life, and dynamics involved in health, wellness, and recovery from illness.

Qualitative data are typically acquired through 1:1 interviews and focus groups. Transcripts are then analyzed by the investigator to extract common themes. Clinical research can be quantitative, qualitative, or both (“mixed methods”).

What are several core features of a clinical research prospectus?

A research prospectus is the research plan and guideline for a research study, which stipulates the research question, the value of the research, and the research methodology. It is a roadmap that includes the project director, collaborators with the requisite expertise, research objectives and hypotheses, and timeline.

A research prospectus is developed *before* embarking on recruitment of volunteers and project implementation. Articulating a research prospectus is a *requirement for prior approval* by a duly constituted Institutional Review Board to assure compliance with federal guidelines for the protection of research participants.⁴

In summary, essential elements of a research prospectus are:

- **Principal investigator (PI):** Individual who takes overall responsibility for the design and execution of the research project.
- **Collaborators:** Individuals who share responsibility for all, or defined parts, of the research project.

- **Key personnel:** Others who are integral to the project, serving as content or technical experts.
- **Literature review:** To demonstrate a need for the research.
- **Research question(s):** Who, what, why questions aimed at filling the gap in the literature.
- **Research design:** The research question, the research objective, the characteristics of the research participants, the instruments to be used and other related methods and procedures, and the statistics to be employed.
- **Other elements:** Potential overall significance and impact of potential research findings; possible venues for research dissemination (conferences and journals); a tentative list of authors (based on their substantive contribution to the research project).⁸

What is a research question?

A research question addresses a gap in knowledge pertaining to *who, what and why* surrounding a specific area of clinical interest.

- **Who:** *Population of interest* (rural populations? youth? older people? stroke patients? etc).
- **What:** *Problem area of interest* (community populations at risk for cardiac arrest? youth involved in athletics? older people with back pain? stroke patients with swallowing disorders? etc).
- **Why:** *Gap in knowledge:* A significant absence of scientific data to support “best practice,” eg, lack of effectiveness data about prevention programs; lack of research on outcomes of a particular diagnostic group; lack of data comparing the relative effectiveness of common or new interventions; lack of translation of data from basic science (eg, cellular or animal research) to clinical or community applications.
- **Significance/impact/value:**
 - Is my research question important enough to solicit volunteers and expend resources on this clinical problem?
 - Is my research approach (design, methodology) valid?
 - Will the results of my research be important? Will my results have a significant impact on the health of the population of individuals who are being studied or on public health generally?

What are some real-world examples of research questions (RQ), research objectives (RO), and their associated design features?

First, the investigator asks a research question; second, narrows the question to a specific research objective; and, third, designs the methods and procedures to assure that they will accomplish the research objective.

Table 2. Illustrative Sketches of RQs, ROs, and Associated Design Features

Research Question (RQ)	Research Objective (RO)	Basic Features of the Quantitative Research Design
<i>The question the clinical researcher wants to answer.</i>	<i>What the clinical research intends to do to systematically address the research question.</i>	<i>“Design” features determine how we will select subjects, how we will group them for comparison, how we will measure behaviors using reliable and valid instruments, and how we will statistically compare the data.</i>
RQ1: What is the incidence among newborn babies of deafness in rural Appalachia?	RO1: To determine the incidence of deafness in newborns born at Hospital X over a 1-year period.	One group; descriptive.
RQ2: In individuals at risk for HIV/AIDS, what factors are associated with acquiring the disease?	RO2: To correlate new incidences of HIV/AIDS in X County over a 1-year period with “risk behaviors” as defined by the CDC.	One group; correlation of risk with outcome (HIV/AIDS). This is a one-group correlational study.
RQ3: Is continuous passive motion (CPM) therapy effective in achieving optimal range of motion following knee replacement?	RO3: To describe the effect of continuous passive motion (CPM) therapy after surgery for knee replacement by comparing the immediate post-operative range of motion (ROM) with ROM 1 month later.	One-group; comparison before and after an intervention (based on medical [EMS] record). This is a one-group repeated measures design.
RQ4: Does handwashing among healthcare workers reduce hospital-acquired infections (HAIs)?	RO4: To determine whether handwashing among healthcare workers reduces hospital-acquired infections (HAIs) in long-term care residents by comparison to the current	Two groups: one is historical; the other is the new intervention (hand-washing) with defined endpoint (outcome = infection).

frequency of hospital-acquired infections over a 6-month period.

RQ5: Is there a difference in mortality between hands-only CPR versus hands-plus breathing-CPR in community dwelling adults?

RO5: In community-dwelling adults who experience cardiac arrest, to compare the relative effectiveness of hands-only CPR versus hands-plus-breathing CPR on the rate of death.

Two-groups with defined endpoint (outcome = mortality) to determine relative effectiveness of two CPR techniques.

RQ6: Is an exercise program designed to strengthen the pharyngeal muscles more effective than diet modifications alone in preventing post-stroke pneumonia?

RO6: To determine whether there is a statistically significant difference in the incidence of aspiration pneumonia in individuals 1-3 months after stroke when comparing patients randomly assigned to one of three conditions: (a) diet modification treatment or (b) pharyngeal exercise alone, or (c) diet modification plus pharyngeal exercise.

Three experimental groups with defined endpoint (outcome: aspiration pneumonia) to determine relative effectiveness of the intervention programs.

What is the hypothesis?

The hypothesis is an assumption—an informed speculation—based on prior knowledge and clinical experience about whether we expect the within- or between-group comparisons to be different (or not), and the direction of the data.

For example, if one is comparing two interventions, the research question is: *Will the effect of two interventions differ significantly when subjected to rigorous statistical analysis?*

- **A “null hypothesis” states:** There will be **no difference** in the effect (within or between groups) of interventions X vs Y.
- **An alternative *nondirectional* hypothesis is:** There **will be a difference** in the effect of X intervention (repeated comparisons within a group) or between X and Y intervention (between two or more groups). It is a “nondirectional” hypothesis because it does not speculate about which intervention will be superior.

- **An alternative *directional hypothesis* is:** There **will be a difference**, and X intervention will be statistically significantly superior to Y intervention. It is a “directional” hypothesis because it predicts that one intervention will have a greater effect than the other.

What are common descriptive statistics? (See definitions, Appendix I)

Derived from raw data, the mean (or median, or mode) and standard deviation (the “spread” of scores around the mean) “reduce” raw data to summary terms.

What are common inferential statistics?

The type of statistical test depends on the *type of data* and the *nature of the research question*. Ideally, an expert in biostatistics should be consulted at the time the research prospectus is written.⁹

Standard statistical analyses are:

- **probability testing** (to test hypotheses or to make causal *inferences* about the meaning of data based on the probability that the observed effect is, or is not, due to chance);
- **correlational analysis** (to determine the relationships among variables);
- **effect size**; and,
- **confidence intervals**.

How should we display the data?

Displaying data in tables and figures enhances report of results, including the statistical analyses. (See Appendix II for examples.)

How should we interpret the data?

The interpretation section of a research report represents both the science and the art of clinical research. This section should explain the meaning of the data and avoid “over-interpretation” or “speculation.”

Interpretation should include:

- Limitations of the present study;
- New or significant insights from the research project in light of prior work;
- Implications for clinical practice and population health;
- Revisions to theories about health-related phenomena; and,
- Suggestions for future research.

APPENDIX I

Glossary of Select Terms

Confidence interval: Can we be confident that the effect is real and reproducible? Because we are only sampling some of the population of interest, we can expect that other samples of the population might show a different result. The confidence interval captures our *level of confidence* that *our result* will be replicated in a similar sample of subjects, tested under the same methods and conditions. When comparing two (or more) sets of data, **nonoverlapping confidence intervals** bolster our confidence in the observed differences. In contrast, **overlapping confidence intervals** suggest that the datasets are not as different as the *P*-value might suggest.

Correlation: The relationship among two or more variables to determine whether they change (increase or decrease) under the same conditions (eg, a correlation of advancing age and level of performance on a particular test). If performance improves with advancing age, a positive correlation exists. If performance deteriorates with advancing age, a negative correlation exists. Correlational values are amenable to statistical testing. (Variants of correlational analysis, linear and multiple regression, identify “predictor variables” to determine whether they, singly or in combination, predict a particular outcome.)

Dependent variable: The variable of interest selected for measurement; the variable that is expected to change in response to select independent variables or to experimental interventions (eg, does X performance change in relationship to demographic factors, risk factors, or the intervention(s) employed).

Effect size: The effect size is the magnitude of the difference between group means or between correlations between two or more groups.¹⁰ The effect size helps us understand whether the “statistically significant” result based on the *P*-test is small or large and, as such, helps us understand the *clinical significance* of the data rather than merely the *statistical significance*.

Independent variable: The variables that describe the subject sample (eg, age, SES, IQ; other test scores); the setting (eg, hospital versus home), or the conditions that are systematically manipulated with the purpose of influencing the dependent variable (eg, task instructions; task difficulty; treatment versus no treatment; treatment A versus treatment B).

Mean: After all raw data points are summed and divided by the total number of subjects, the result is the average, or mean.

Median: When all raw data points are rank-ordered, the absolute middle of the range of scores is the median.

Mode: After all raw data points are recorded, the mode is the most frequently occurring value.

PICO: The PICO approach helps generate a question that aids in constructing the framework of the study and subsequently in protocol development by alluding to the inclusion and exclusion criteria and identifying the groups of patients to be included.

- P: Population
- I: Intervention
- C: Comparison group
- O: Outcome of interest

Power: “Statistical power is the probability that your study will find a statistically significant difference between interventions when an actual difference does exist. If statistical power is high, the likelihood of deciding there is an effect, when one does exist, is high . . . power depends on effect size and sample size.”^(10 p281) One must have an adequate number of subjects to achieve adequate power. In general, the larger the sample of subjects, the greater the power.

Probability testing: Probability testing involves the use of statistical tests that help us determine whether the result is due to chance or is due to the influence of external factors and variables. Probability testing helps us determine the validity of our results when comparing one group with repeated tests (over specific time intervals) or comparing more than one group across time intervals or types of interventions (“conditions”). (See *P*-value.)

***P*-value:** The *P*-value is the level of probability set by investigators in advance of statistical testing that will be used to determine whether a null hypothesis will be rejected. Typically, the *P*-value is set at $< .05$, which means that 95% of the time we can believe the result to be true, knowing that there is a 5% probability that the observed difference is due to chance, bias, or to an uncontrolled variable. If the actual *P*-value is $> .05$, this increases the likelihood that we will accept a null hypothesis (that there is no difference when, in fact there is a real difference), or that we will erroneously reject a null hypothesis (believing there to be a difference when, in fact, there is a no difference). $P < .05$ must be interpreted with caution. We should also use *effect size* and *confidence intervals* to avoid misinterpreting the *P*-value.

Standard deviation: The spread of raw data above and below the mean, ie, the *variance* around the mean. Population data follow a normal curve (ie, half the data will be -1, 2 or 3 *SD* below the mean, and +1, 2 or 3 *SD* above the mean). In contrast, *sample* data may skew to the left or right, implying that the data need to be analyzed using nonparametric rather than parametric statistics. (See Figure 1.)

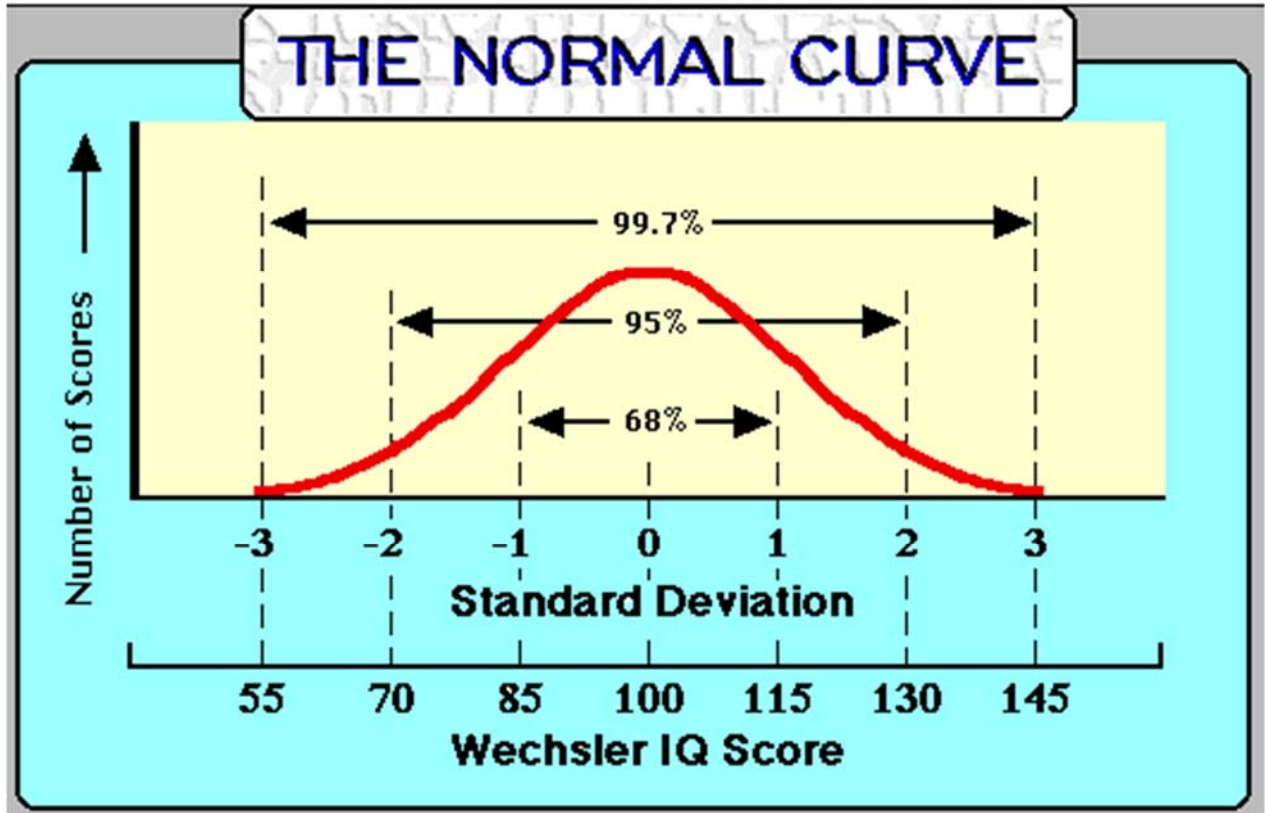


Figure 1. The normal curve represents the distribution of data for a population (or a representative sample of the population). This figure illustrates the normal curve for IQ scores in the population. http://www.igs.net/~cmorris/the_normal_curve...socialworktools.wordpress.com. Accessed September 14, 2016.

Statistical tests: Before choosing a statistical test, one needs to know whether the data to be collected are representative of the population (a “normal curve”) or not, and meet other criteria. This will inform whether a parametric or a nonparametric statistical test is appropriate.

Statistical significance: “Statistical significance is the probability that the observed difference between two groups is due to chance.”^{10(p 279)}

Appendix II Examples of Data Analysis and Data Displays

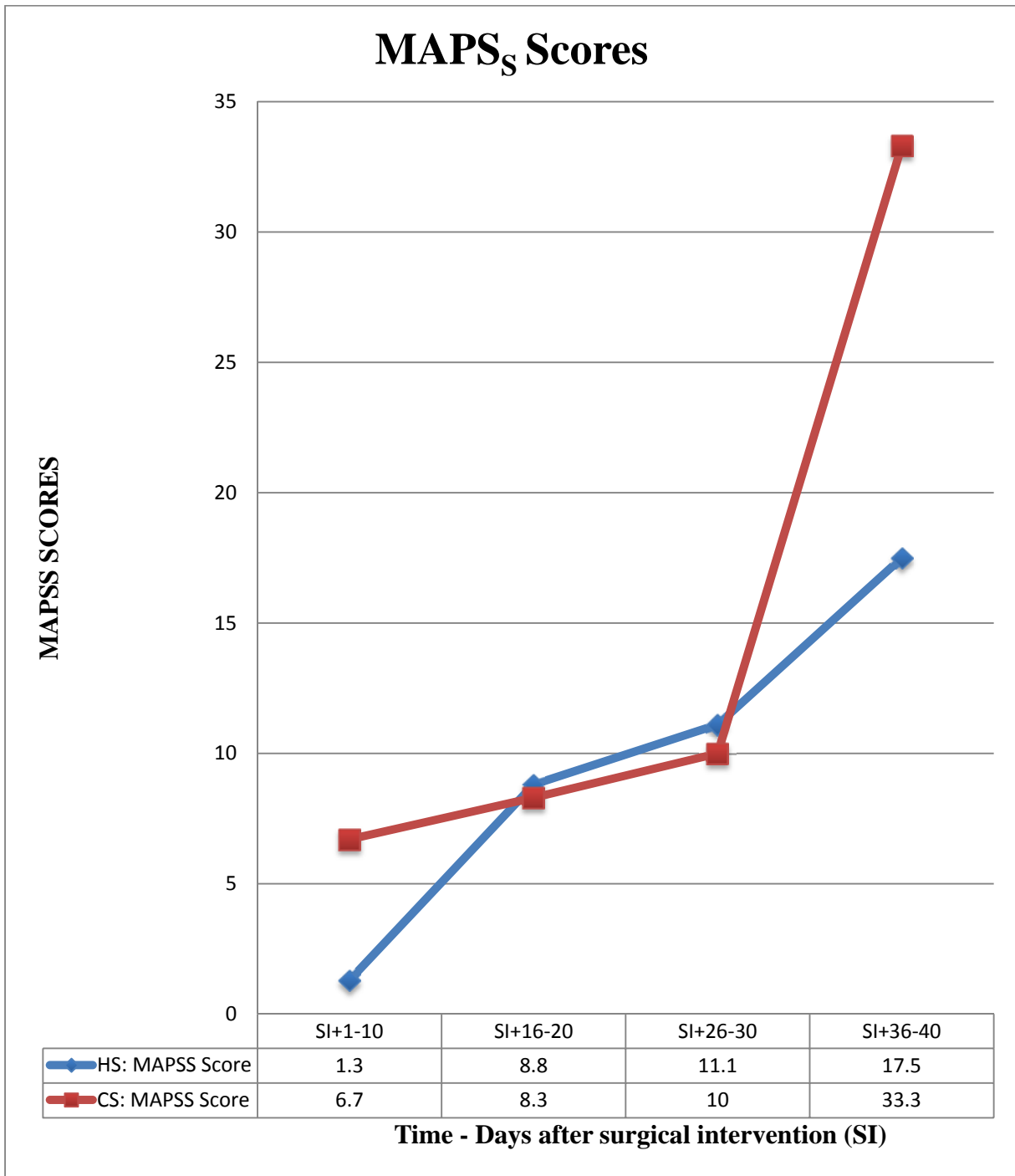


Figure 2. Difference between high school and college student MAPS_S scores. HS = high school students; CS = college students; MAPS_S = steps/time @ location/day; SI = surgical intervention, post-op days.¹¹

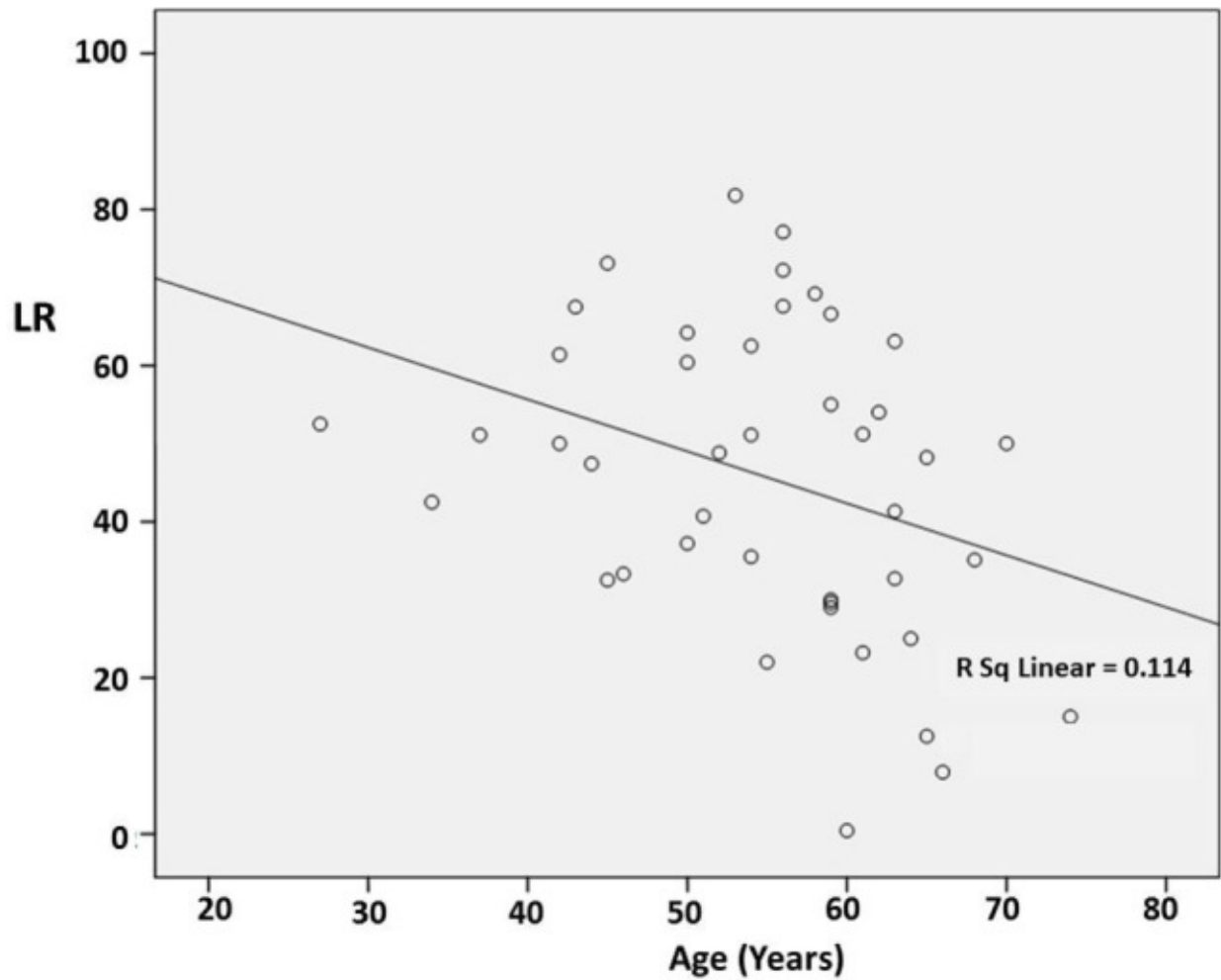


Figure 3. Scatter plot of the correlation between age and the preoperative levodopa response (LR). The line indicates a negative correlation ($r = -0.374$; $p = 0.013$).¹²(Figure 2 in the original)

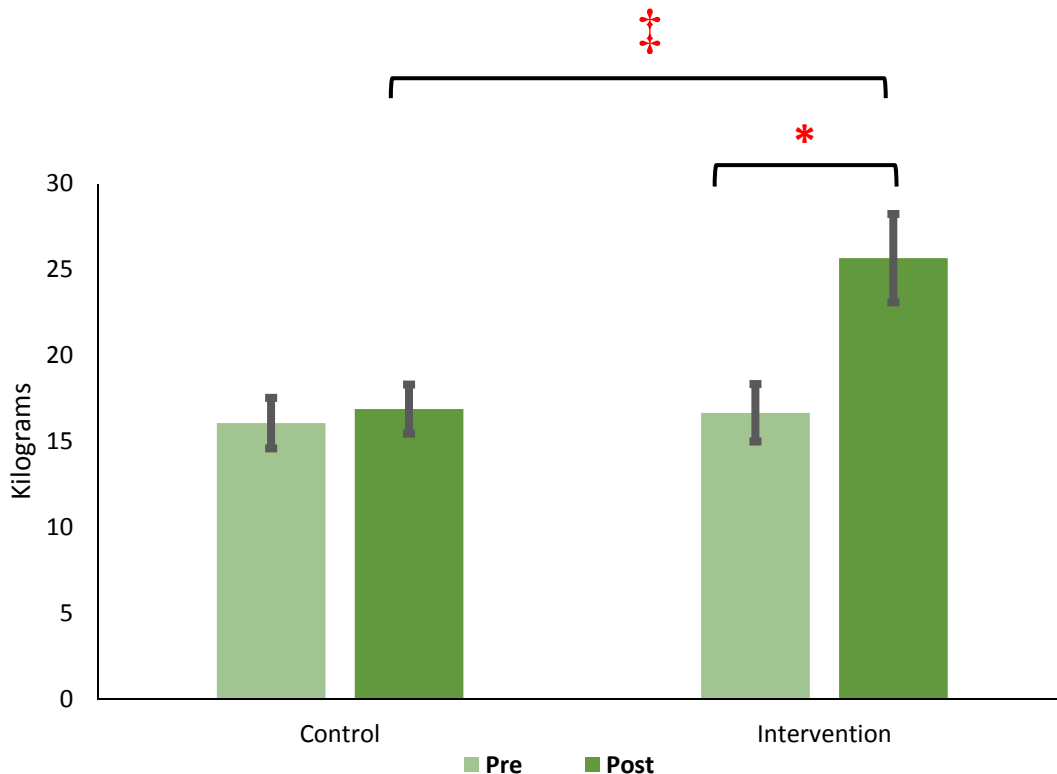


Figure 4. Dorsiflexion strength pre- and post-intervention (hypothetical example).

Dependent variable: strength

Independent variable: intervention

Within-group analyses:

- In the control group, no significant difference in strength when comparing pre- to post-intervention.
- In the intervention group, significant difference in strength when comparing pre- to post-intervention; *** 95% confidence intervals do not overlap and $p < 0.05$ (paired t-test) indicates statistically significant difference.**

Between-group analyses:

- Comparing control and intervention groups, no significant difference in strength pre-intervention.
- Comparing control and intervention groups, significant difference in strength post-intervention; **‡ 95% confidence intervals do not overlap and $p < 0.05$ (independent t-test) indicates statistically significant difference.**

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