



Colgate Palmolive
Clinical Research Training Program

Module 3

**Data Collection, Management and
Basic Statistical Concepts in
Clinical Research**

developed in conjunction with:





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Module 3 Goal

Provide an overview of data collection, data management, some basic statistical concepts in clinical research

Overall references for this module:

- Gallin JI, & Ognibene, FP. (2012) *Principles and Practice of Clinical Research*, 3rd ed., London: Academic Press, pp 780.
- Hulley SB, Cummings SR, Browner WS, Grady DG, Newman TB. (2013) *Designing Clinical Research* 4th ed. Philadelphia PA: Lippincott Williams & Wilkins, pp.367.
- Dye BA, Mitchel JT. Data management in oral health research. In: Giannobile WV, Burt BA, Genco RJ. *Clinical Research in Oral Health*. (2010) Hoboken NJ: Wiley Blackwell, pp103-122.
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- Borkowf CB, Johnson LL, Albert PS. Power and sample size Calculations. In: Gallin JI, Ognibene FP. (2012) *Principles and Practice of Clinical Research*, 3rd ed., London: Academic Press, pp243-253.
- Shaw PA, Johnson LL, Borkow CB. Issues in Randomization. In Gallin JI, Ognibene FP. (2012) *Principles and Practice of Clinical Research*, 3rd ed., London: Academic Press, pp243-253.
- Pihlstrom BL, Barnett ML. Design, operation and interpretation of clinical trials. J Dent Res. 2010 Aug;89(3): 759-772.



Learning Objectives

- Describe and understand what data should be collected
- Describe and understand how data should be managed
- Describe and understand some basic statistical concepts in clinical research

Data Collection in Clinical Research

Dye B.A., Mitchel J.T. Data management in oral health research. *In: Giannobile WV, Burt BA, Genco RJ. Clinical Research in Oral Health.* (2010) Hoboken NJ: Wiley Blackwell, pp.103-122



What Data Should Be Collected?

- The data collected depends on the question being asked, the testable research hypothesis and type of study that is conducted
- Minimum data for any study:
 - Demographic characteristics of sample
 - Independent variables – input, potential causes for variation in outcome variables
 - Dependent variables - primary and secondary outcomes, variation studied
 - Confounding variables that may influence the study outcome

Example: Data collected in an observational prospective cohort study of preterm birth and periodontal disease⁷

- Demographic data:
 - Age, Ethnicity, Education
- Independent variable (exposure)
 - Maternal periodontal disease among Sri Lankan women who were tobacco, alcohol and drug free
- Dependent variable (outcome)
 - Preterm birth (prior to 37 weeks of gestational age) with low birthweight (< 2500 grams)

Rajapakse PS, Nagarathne M, Chandrasekra KB, Dasanayake AP. Periodontal disease and prematurity among non-smoking Sri Lankan women. J Dent Res. 2005 Mar;84(3):274-277.



Example: Data collected in an observational prospective cohort study of preterm birth and periodontal disease⁸

- Possible confounding (independent) variables
 - Body mass index (BMI)
 - Occupational status
 - Obstetric history
 - Medical history
 - Pre-natal care

Rajapakse PS, Nagarathne M, Chandrasekra KB, Dasanayake AP. Periodontal disease and prematurity among non-smoking Sri Lankan women. J Dent Res. 2005 Mar;84(3):274-277.



Standardization of Data Collection

1. Identify data to be collected
2. Create a codebook or “data dictionary” that defines data:
 - Variable names (and abbreviated names)
 - Description of each variable
 - Range of acceptable values for each variable
 - Code used for values

Standardization of Data Collection

3. Develop standard forms for collection and entry of data into data base for study
4. Test data collection methods
 - Archival data (i.e. dental records)
 - Questionnaires
 - Clinical examination data

Standardization of Data Collection

5. Train and calibrate personnel who will be collecting data
 - Dental assistants
 - Dentists
 - Hygienists
 - Others

Training and Calibration of Study Examiners

- Establish quality standards for intra and inter-examiner reproducibility
- Establish a “gold-standard” examiner to whom all other examiners are compared
- Train and calibrate examiners to meet standards
- Test examiners to ensure that they meet established standards at beginning of study
- Re-calibrate and re-test examiners periodically to ensure that they continue to meet quality standards throughout duration of study

Standardization of Data Collection

- Standardized methods are defined in study manual of operations:
 - Who collects data?
 - Who enters data in data base?
 - Manual data entry?
 - Electronic data entry / data capture?
 - Internet data entry?

Standardization of Data Collection

- Quality control of data entry
 - Double entry from paper forms
 - Electronic checks of variable ranges, missing and illogical data
 - Data checking should be done as soon as possible after data is entered into data base to make it more likely that issues regarding ambiguous data, missing data or data that is out of the pre-specified ranges can be easily resolved

Standardization of Data Collection

- Quality control of data entry (cont.)
 - Study examiners should avoid performing calculations when entering data
 - Data that requires calculation should be done by computer after input data is entered
 - Example: Clinical attachment level is calculated by computer after probing depth and location of cemento-enamel junction relative to the free gingival margin is entered in the data base
 - Example: Body mass index (BMI) is calculated by computer after height and weight are entered into data base

Data Management

Dye B.A., Mitchel J.T. Data management in oral health research. In: Giannobile WV, Burt BA, Genco RJ. *Clinical Research in Oral Health*. (2010) Hoboken NJ: Wiley Blackwell, pp.103-122



Data Management

- Important considerations
 - Storage – electronic or paper?
 - How is data backed up?
 - How is data confidentiality assured?
 - How is data security assured?

Data Management

- Transmission to statistician or study sponsor
 - Paper transfer?
 - Electronic transfer?
 - Security?
 - Confidentiality?

Basic Statistical Concepts in Clinical Research

Basic Statistical Concepts in Clinical Research

- Sampling in clinical research
- Errors in hypothesis testing
- Sample size and statistical power
- Randomization in clinical trials
- Statistical and clinical significance

Sampling in Clinical Research

1. Identify the population of subjects for the study
2. Determine how the population will be sampled
 - Convenience sampling
 - Probability (random) sampling

Convenience Sampling

- Subjects in a population are identified and asked to participate in a study because they are easy to identify, available, and are likely to participate in the study
- Disadvantage:
 - May be a biased sample because the subjects may not be representative of the population of interest
 - Results of study will likely not be viewed as generalizable to the population of interest

Probability/Random Sampling

- Subjects in a population are identified in way that each has an equal chance (probability) of participating in a study
 - Subjects are selected by a random method of sampling
 - Subject selection not dependent on availability, likelihood to participate or any other factor that might bias the sample

Probability/Random Sampling

- Advantage:
 - Results of study will be viewed as generalizable to population of interest as a whole
- Disadvantages:
 - Difficult
 - Expensive
 - Often impractical or impossible

Errors in Hypothesis Testing

- **Type I Error** – Finding an association or effect in a study when it is not true
 - Failure to accept the null hypothesis of no difference
- **Type II Error** – Finding no association or effect in a study when there is one
 - Failure to reject the null hypothesis of no difference

Probability of Errors in Hypothesis Testing

- **Type I Error** – Finding an association or effect in a study when it is not true
 - False positive result
 - Probability of Type I error is called alpha (α) or statistical significance
- **Type II Error** – Finding no association or effect in a study when there is one
 - False negative result
 - Probability of type II error is called beta (β)

Statistical Significance (α) and Probability Value (p-value): Separate but Related

- Statistical significance (Type I error or α) sets the standard for how extreme the data must be to reject the null hypothesis of no difference
 - Value of α is arbitrary, but often is set at 5%; the smaller the value of α , the more unlikely it is to find a statistically significant result
- Probability value (p-value) is the likelihood of finding a study result by chance
 - If the p-value is less than or equal to α (i.e., 0.05), the null hypothesis is rejected and we would state that the result is statistically significant at $p < 0.05$

Required Sample Size of a Clinical Study

- It is critical to accurately determine sample size of a clinical study before beginning a study because:
 - Clinicians and statisticians must work together to establish the required sample size
 - Sample size has major influence on the likelihood of Type II error (false negative result or finding no difference when there is a one)

Required Sample Size of a Clinical Study

- It is critical to accurately determine sample size of a clinical study before beginning a study because:
 - Sample size has a major influence on the complexity and cost of a study
 - It is unethical to enroll subjects in a study that is under-powered and has little chance of finding a difference in study outcomes
 - It is unethical to needlessly enroll subjects in a study that is excessively large and is “over-powered” to find a difference study outcomes

Required Sample Size of a Clinical Study

- Required sample size is affected by:
 - Statistical significance (α)
 - Statistical power ($1-\beta$)
 - Size of association in observational studies
 - Effect size of a treatment in a clinical trial
 - Variability of the outcome in the population
(population standard deviation)
 - Drop-out rate in study
 - Outcome prevalence in population

Statistical Power

- Statistical power is:
 - Likelihood of finding an association or effect if there is one, or...
 - Probability obtaining a true positive finding
- Calculation of statistical power:
 - Power = 1- probability of a false negative finding
 - Power = $1 - \beta$

Example of 80% Statistical Power

- Statistical Power = Likelihood of finding an association or effect if there is one
- Statistical Power = $1 - \beta$
- Type I error (false positive result) rate (α) $\leq 5\%$
- Type II error (false negative result) rate (β) = 20%
- Power: $100\% - 20\% = 80\%$
 - Study has a 80% chance of finding a statistically significant ($\alpha \leq 0.05$) result if there really is one

Example of 90% Statistical Power

- Statistical Power = Likelihood of finding an association or effect if there is one
- Statistical Power = $1 - \beta$
- Type I error (false positive result) rate (α) $\leq 5\%$
- Type II error (false negative result) rate (β) = 10%
- Power: $100\% - 10\% = 90\%$
 - Study has a 90% chance of finding a statistically significant ($\alpha \leq 0.05$) result if there really is one

Required Sample Size Increases as:

- Level of statistical significance (α) decreases (from <0.05 to <0.01 for example)
- Power ($1-\beta$) increases
- Effect size decreases
 - Magnitude of association in an observational study decreases
 - Treatment effect in a clinical trial decreases
- Population variability (standard deviation) of the association or effect size increases
- Drop-out rate increases

Required Sample Size Decreases as:

- Level of statistical significance (α) increases
(from <0.01 to <0.05 for example)
- Power ($1-\beta$) decreases
- Effect size increases
 - Magnitude of association in an observational study increases
 - Treatment effect in a clinical trial increases
- Population variability (standard deviation) of the association or effect size decreases
- Drop-out rate decreases

Randomization (Random Allocation) in Clinical Trials

- **Definition:** Each patient has an equal chance of being assigned to the interventions tested in a clinical trial
- Creates study groups at baseline (before study begins) that are comparable
- As number of patients that are randomly assigned to the treatment groups in a trial increases, the likelihood of having large differences between the groups decreases

Randomization (Random Allocation) in Clinical Trials

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- An essential component in clinical trials
- Minimizes likelihood of bias from known and unknown factors
- Equipoise is a fundamental ethical principle of randomization in clinical trials
 - Means that investigators must have true uncertainty about the comparative effectiveness and safety of treatments being studied

Randomization (Random Allocation) in Clinical Trials

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- Prevents researcher from creating comparison groups that are different in systematic ways
- Helps make groups comparable in terms of known and unknown baseline characteristics that are related to the outcome of the trial
- Part of the masking (blinding) process that keeps investigators and subjects unaware of treatment that subjects are receiving

Common Randomization Methods

- Simple randomization
 - Subjects are randomly assigned to treatment groups regardless of treatment assignment of other participants
- Block Randomization
 - Subjects are randomly assigned in “blocks” to assure that the number of enrolled of subjects in each intervention group is consistent with desired sample size
- Stratified Randomization
 - Subjects are randomly assigned in a way to minimize potential imbalance between groups in factors that may be related to the study outcome

Randomization Example

- Multi-center clinical trial designed to determine if periodontal treatment affected rate of preterm birth
- Conducted at 4 centers in the U.S. (Minnesota, Kentucky, New York, and Mississippi)
- 823 pregnant women were randomly assigned to receive periodontal treatment either:
 - Before 21 weeks of pregnancy (n= 413 women)
 - After delivery (n= 410 women)
- Random assignment was stratified by center in blocks to minimize imbalance in treatment groups among the 4 centers

Michalowicz BS, Hodges JS, DiAngelis AJ, Lupo VR, Novak MJ, Ferguson JE, Buchanan W, Bofill J, Papapanou PN, Mitchell DA, Matseoane S, Tschida PA; OPT Study. Treatment of periodontal disease and risk of preterm birth. N Engl J Med. 2006 Nov 2;355(18):1885-1894.



Statistical and Clinical Significance

Greenstein G. Clinical versus statistical significance as they relate to the efficacy of periodontal therapy. J Am Dent Assoc. 2003 May;134(5):583-91

Pihlstrom BL, Barnett ML. Design, operation and interpretation of clinical trials. J Dent Res. 2010 Aug; 89(3):759-772.



Statistical and Clinical Significance

- **Statistical significance** is:
 - Chance of a Type I error (α) in a study
 - Mathematically defined by the probability that the null hypothesis is falsely rejected when it is true
 - Likelihood that the alternative hypothesis of a research study is false
 - Often called the false positive rate

Statistical and Clinical Significance

- **Clinical significance** is not mathematically defined – it is a matter of judgment
- May be defined in a clinical trial as the magnitude of difference between test and control treatments that would be important for clinical decision-making
- May be different for patients, health care practitioners, third-party payers, government regulatory agencies, industry

Statistical and Clinical Significance

The Key Question: **Does anyone care?**

- “Is the difference between groups in a clinical trial large enough to justify a change in patient behavior, clinical practice, third-party reimbursement, or public health policy?”

- Differences in the primary outcome of clinical trials that are large enough to be statistically significant but too small to be clinically meaningful would be unlikely to change anything



Module 3 Key Points

- To successfully conduct a clinical research study, it is critical that investigators understand the importance of data collection, data management, and some basic statistical concepts
- The type of data collected depends on the question being asked, the testable research hypothesis, and the type of study being planned (observational study or clinical trial)

Module 3 Key Points

- Important issues in data collection involve deciding who collects data, data quality assurance procedures, training and calibrating study personnel who collect and enter data, data storage and transmission
- Fundamental statistical concepts involved in clinical research include convenience and probability (random) sampling, statistical power and sample size, type I and type II errors, and distinguishing between statistical significance and clinical significance

End of Module 3

