Colgate Palmolive
Clinical Research Training Program

Module 1
Clinical Research: An Overview

developed by:

AAL
ACADEMY FOR ACADEMIC LEADERSHIP
Content Creator and Trainer: Bruce Pihlstrom, D.D.S., M.S.

Professor Emeritus, University of Minnesota
Associate Editor for Research, Journal of the American Dental Association (JADA)
Independent Oral Health Research Consultant
Former Director of Extramural Clinical Research, National Institute of Dental and Craniofacial Research (NIDCR), National Institutes of Health (NIH)

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Module 1 Goal

Define clinical research and provide an overview of objectives, design and outcomes of various types of clinical research

Main references for this module:


Learning Objectives

- Define clinical research

- Describe and outline methods, differences, and outcomes among:
  - Observational clinical research
  - Interventional clinical research – *clinical trials*
  - Internal vs. external *validity*
Clinical Research Definition

A. Patient-oriented research
   - Living human subjects, tissues, specimens, cognitive information
   - Researcher directly interacts with human subjects
   - Excludes *in vitro* studies that utilize human tissues that cannot be linked to a living individual

B. Epidemiologic and behavioral studies

C. Health services and outcomes research
Observational Clinical Research

Observational Clinical Research

- Fundamental Design Characteristics
  - Makes observations only
    - Does not intervene or assign treatment to human subjects
  - Time of making observations
    - **Cross-sectional study** - Data are collected at one time point
    - **Retrospective study** - Data are collected about disease and past exposures or risk factors
    - **Prospective study** - Data are collected in the future over time (prospective longitudinal data)
Observational Clinical Research

- Fundamental Design Characteristics
  - Outcome Measures
    - Prevalence
    - Incidence
    - Association of diseases and various factors, such as other diseases, potential etiological agents or risk factors
Observational Clinical Research

- Common types of Observational Clinical Research
  - Case reports and case series
  - Cross-sectional studies
  - Retrospective (case-control) studies
  - Longitudinal cohort studies
Cross-sectional Design  
Survey of current status (one time point)

- Often used to assess disease prevalence
- May be used to associate presence of disease with current exposure or current reflection of past exposure to potential risk factors or etiologic agents
- Relative to other designs is easy & inexpensive
  - No follow-up
  - Requires limited or no collection of past history data
- No time sequencing of exposure to risk factors with disease onset
  - Causal inference is weak at best
Retrospective Case-Control Design

1. Identify case subjects with disease

2. Identify healthy control subjects without disease

3. Look back and compare cases and controls for past exposures to possible risk factors
Retrospective Design
Looks backward in time at data that were previously collected

- Often used to identify factors that may have been associated with a disease
- Difficult to establish temporal relation between exposure to risk factor and development of disease
- Has serious potential for bias because:
  - Cases may not be representative of all subjects who develop disease
  - Controls may not be representative of healthy subjects who do not develop disease
  - Retrospective data may have been collected in a non-standardized way, may be inaccurate
Retrospective Design
Looks backward in time at data that were previously collected

- May give some idea of association between a disease and potential causes or risk factors…BUT,

- Causal inference is weak at best
Prospective Cohort Design

1. Identify subjects exposed to potential risk factors

2. Identify subjects not exposed to potential risk factors

3. Follow subjects prospectively over time and compare incidence of disease between exposed & non-exposed subjects

Time
Prospective Cohort Design
Collects data going forward in time

- Often used to assess disease incidence
- Used to identify associations between a particular exposure or risk factor and subsequent development of disease
- Can establish a temporal association of risk factor and subsequent development of disease
Prospective Cohort Design
Collects data going forward in time

- Has less potential for bias than retrospective studies
  - Data collection can be planned and standardized according to question being asked

- Causal inference is stronger than retrospective design, but still not conclusive
Retrospective Design vs. Prospective Cohort Design

- **Retrospective (Case-control) Design**
  - Identifies cases and controls
  - Looks for past exposure to risk factors for the disease
  - Purpose: Identify risk factors that may have been associated with the disease

- **Prospective (Longitudinal) Cohort Design**
  - Identifies possible risk factors for disease
  - Looks forward in time for development of disease
  - Purpose: Identify risk factors that may be associated with subsequent development of disease
Discussion Questions

- What type of observational study attempts to determine the presence of dental caries in Swedish children 5-8 years of age?

- What type of observational study attempts to determine how many new teeth become decayed in children between 5 and 8 years of age?
Discussion Questions

- What type of observational study attempts to determine the presence of dental caries in Swedish children 5-8 years of age?
  
  **Answer:** Cross-sectional epidemiologic study of caries prevalence

- What type of observational study attempts to determine how many new teeth become decayed in children between the 5 and 8 years of age?
  
  **Answer:** Prospective epidemiologic study of caries incidence
Example of a Case-Control Study

- **Research Question:**
  
  Is maternal periodontal disease (exposure) associated with pre-term low birthweight (PLBW) newborn infants?

- **Case-Control Method:**
  
  - Compares exposure - presence of periodontal disease among:
    - Case subjects - women who delivered PLBW infants
    - Control subjects - women who delivered normal weight infants

Example of a Case-Control Study

- **Case-Control Method (cont.):**
  - **Case subjects (n=93):**
    - Mothers giving birth to infants with low birth weight (<2500g) plus one or more of following:
      - Pre-term labor (PTL)
      - Premature rupture of membranes (PROM)
      - Infant gestational age <37 weeks
  - **Control subjects (n=31):**
    - Mothers having normal birth weight infants
  - **Study compared exposure among case and control subjects to a potential risk factor:**
    - Evidence of past periodontal disease

Example of a Case-Control Study

- **Results:**
  
  Periodontal disease is a statistically significant risk factor for PLBW.

  - OR for PLBW=7.5 (95% CI=1.95-28.8) for all PLBW cases (with periodontal disease) compared to controls (without periodontal disease)

- **Conclusion:**
  
  “These data indicate that periodontal diseases represent a previously unrecognized and clinically significant risk factor for pre-term low birthweight as a consequence of either PTL or pre-term PROM.”

WILL future pre-term birth (disease or disorder) be more common among mothers who have periodontal disease (exposure) than among mothers who do not have periodontal disease (no exposure)?

Prospective Cohort Design
Example of a Prospective Cohort Study

- **Research Question:**
  
  Is there an association between maternal periodontal disease and birth of pre-term low birthweight infants among rural Sri Lankan mothers who do not smoke or chew tobacco, drink alcohol, or use drugs?

- **Prospective Cohort Study Method:**
  
  - Prospective follow-up study of 227 rural pregnant women who were free of tobacco, alcohol, and drug use
  - Exposure studied prospectively: Periodontal disease
  - Outcome studied prospectively: Preterm birth

Example of a Prospective Cohort Study

- **Results:**
  - Pre-term low birthweight rates:
    - 12% among “exposed” to periodontal disease
    - 5.6% among “unexposed” to periodontal disease
    - **Odds Ratio (OR) = 1.9** for pre-term low birthweight in relation to “exposure” (95% CI = 0.7-5.4)*
      *CI includes 1 so OR of 1.9 is not statistically significant

- **Conclusion:**
  “Our results are only suggestive of an association between periodontal disease and pre-term low birthweight perhaps indicating that previously reported associations may have been subjected to residual confounding due to tobacco, alcohol, and drug use.”

Interventional Clinical Research

Clinical Trials


Clinical Trial

- What is a clinical trial?

- What are the essential elements for a successful clinical trial?
Randomized Clinical Trial

- Traditionally considered to be highest form of evidence for a prevention or treatment of disease
- Exposure or intervention may be
  - Preventive
  - Therapeutic agent, drug, device, procedure
- Assignment of treatment is determined by objective, reproducible process and not governed by patient or clinician on basis of preconceptions
- **Equipoise** = Genuine uncertainty within the expert medical/dental community about preferred treatment
Randomized Clinical Trial

- Essential Components
  - Involves humans
  - Involves an intervention (treatment)
  - Random assignment of treatment is an essential component to minimize bias
  - Equipoise is essential
Randomized Clinical Trial

- Essential Components (Continued)
  - Depending on design - may involve masking (blinding) of subjects, outcome examiners, investigators, statisticians
  - Has a clinically meaningful outcome
  - Involves prospective, longitudinal (over time) collection of data
Types of Clinical Trials

- **Efficacy trial:**
  - Compares treatments under controlled conditions in well-defined populations

- **Effectiveness (pragmatic) trial:**
  - Compares treatments in daily clinical practice, e.g. Practice-based research

- **Superiority, non-inferiority & equivalence trial:**
  - Compares new treatment to standard or established treatment
Types of Clinical Trials

- **Multicenter Clinical Trial**
  - Increases availability of subjects for enrollment
  - Increases **generalizability** to population at large
  - Complicates:
    - Study coordination
    - Data collection
    - Standardization of procedures
    - **IRB** approval
    - Data and safety monitoring
Use of Controls in Clinical Trials

- **Placebo Controls**

  Question: Is there an established (or proven) treatment available?

  - If yes, it may not be ethical to use placebo control arm
  - If yes, trial may have to be a superiority or equivalence trial using the standard treatment as the control arm of the trial
Phases of Clinical Trials

- **Phase I**
  First human study of a few subjects to evaluate safety, dosage range & side effects. Involves relatively high risk – are often non-randomized

- **Phase II**
  “Proof of principle” preliminary study of effectiveness and further evaluate safety in a limited number of subjects – may be non-randomized

*Phases I & II are primarily for new drug development.*
Phases of Clinical Trials

- **Phase III**
  
  Definitive randomized trial in large numbers of subjects (100s to 1000s) to evaluate safety and effectiveness of new or existing interventions:
  
  - Drug
  - Device
  - Procedure
  - Behavioral Intervention

  *Aim is often to provide evidence for a change in health policy or standard of care.*
Phases of Clinical Trials

- Phase IV
  Post marketing studies to monitor effectiveness and adverse events in the general population

  *In U.S., may lead to recalls of devices, loss of regulatory approval of drugs, or “black-box warnings” in drug brochure.*
Primary and Secondary Outcome Variables

- Sample size and power estimate are based on primary outcome variable.

- Secondary outcome variables may also be specified – and analyzed for treatment effects within subgroups of patients (subgroup analysis).

- Trials are **NOT** designed or powered to assess secondary outcomes!
Clinical Meaningful Endpoint/Outcome

- A characteristic or variable that reflects how a patient feels, functions or survives

  - Distinct measurement of disease that reflects effect of therapeutic intervention

  - Most credible characteristic used to interpret results of randomized clinical trials

Clinically Meaningful Endpoint/Outcome Example

- **Question**
  
  Does antibiotic use decrease pain after root canal treatment?

- **Efficacy Clinical Trial Design**
  
  - Test group: Root canal treatment + a systemic antibiotic
  
  - Control group: Root canal treatment + placebo
Clinically Meaningful Outcome/Endpoint Example

- **Primary outcome: Pain relief**
  - Measured on a VAS scale 5 days after root canal treatment

- **Secondary outcomes:**
  - Extra-oral swelling and patient temperature 5 days after root canal treatment + systemic antibiotic
Surrogate Outcome Measures

- A **surrogate outcome / endpoint** is a measure that is used as a substitute for a clinical outcome / endpoint.
- A surrogate endpoint is expected to predict clinical benefit, harm, lack of benefit or lack of harm.
- **IMPORTANT**: Surrogate endpoints must be verified as being valid substitute for a clinical endpoint / outcome before being used in a clinical trial as a primary outcome variable.
- **EXAMPLE**: Hb1Ac has been validated and is an acceptable outcome or endpoint in clinical trial of diabetes.

Example of a Clinical Trial

- **Purpose:**
  
  Determine if nonsurgical treatment of periodontal disease during pregnancy reduces risk of preterm birth.

- **Material and Methods:**
  
  - 823 pregnant women randomized to:
  
    - Treatment group: periodontal scaling and root planing before 21st week of pregnancy (n= 413)
    
    - Control group: Periodontal scaling and root planning after delivery (n=410)

Example of a Clinical Trial

- **Primary Outcome:**
  - Gestational age of newborn at end of pregnancy

- **Secondary Outcomes:**
  - Birth weight of newborn babies
  - Proportion of newborn babies who were small for gestational age

Example of a Clinical Trial

- **Results:**
  - Periodontal treatment improved measures of periodontitis.
  - Periodontal treatment did not have an effect on rate of preterm delivery, birth weight or proportion of babies that were small for their gestational age.

- **Conclusions:**
  “Treatment of periodontitis in pregnant women improves periodontal disease and is safe but does not significantly alter rates of preterm birth, low birth weight, or fetal growth restriction.”

Public Registration of Clinical Research

- To have a clinical trial published, ICJME Guidelines have been adopted by many dental journals that require registration of trials on a public website **prior to enrolling the first subject in the trial**

- **VERY IMPORTANT:** If the trial has not been registered prior to enrolling the first subject, the study is not eligible for publication under ICJME Guidelines!

Recommendations for Clinical Trial Registration. International Committee of Medical Journal Editors (ICJME)
Three Examples Cited:

- The case-control observational study showed an association between presence of maternal periodontal disease and birth of preterm low birth weight infants.

- The prospective cohort study (Sri Lanka) did not show a statistically significant association of maternal periodontal disease during pregnancy and future delivery of preterm low birthweight infants.

- Clinical trial (U.S.) reported no effect of periodontal treatment in reducing incidence of preterm birth.
Internal vs. External Validity of Clinical Research
Internal Validity

- Would results be the same if the study were repeated?

- Questions to ask (examples):
  - Design adequate?
  - **Masking (blinding)** appropriate?
  - Intervention administered consistently?
  - Randomization procedures appropriate?
  - Patients analyzed in groups to which they were randomized?
  - Outcome assessment appropriate and accurate?
External Validity

- Are results generalizable? - How likely is it that results are applicable to population as whole?

- Questions to ask (examples):
  - Were inclusion and exclusion criteria for patients narrowly or widely defined?
  - Was the study conducted in different practice settings?
  - Was study conducted among subject samples that are likely to represent the desired population?
  - What was the sample size? Small or large?
  - Large studies are more likely to represent the target population – but can they still be biased or not representative of the target population?
Module 1 Key Points

- Clinical research may involve patient-oriented research, epidemiologic or behavioral studies, and health services and outcomes research

  - Observational studies - only record observations; do not assign an intervention (treatment) to subjects; used to study prevalence, incidence and associations

  - Interventional studies (Clinical Trials) - assigns an intervention or treatment to human subjects; trials study outcomes of the assigned intervention or treatment
Module 1 Key Points

- Randomized clinical trials are considered the highest form of health care evidence.

- Multi-center trials increase availability of subject enrollment and increase generalizability of findings to population as a whole, but complicate operation of a trial.

- Clinical trials should have a clinically meaningful endpoint that reflects how a patient feels, functions or survives.
End of Module 1