

# Clinical Trials

## Section 1

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## 2002 VA Distance Learning/Cyber Session

### SHORT COURSE IN CLINICAL TRIALS

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## COURSE OVERVIEW

- **MONDAY**
  - INTRODUCTION TO CLINICAL TRIALS, DEFINING HYPOTHESIS AND RESEARCH COMPONENTS
    - HENDERSON
  - DESIGNS FOR CLINICAL TRIALS -- REDA
  - HOMEWORK: CONSORT STATEMENT AND PROTOCOL/PAPER
- **TUESDAY**
  - CHOOSING SUBJECTS, INTERVENTIONS, ENDPOINTS
    - REDA
  - STATISTICAL INFERENCE, SAMPLE SIZE, POWER
    - HENDERSON

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## COURSE OVERVIEW

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- WEDNESDAY
  - PLANNING DATA COLLECTION & STUDY MONITORING -- REDA
  - ISSUES IN DATA ANALYSIS -- HENDERSON
- THURSDAY
  - PUBLISHING THE TRIAL -- HENDERSON
  - DISCUSSION OF CONSORT STATEMENT AND PROTOCOL/PAPER -- ALL

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## HISTORY OF CLINICAL TRIALS

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- 1700s - Lind, on board Salisbury, evaluated 6 treatments for scurvy in 12 patients; found 2 patients given oranges and lemons recovered the best
- 1926 - R.A. Fisher introduced concepts of randomization in agricultural experiments

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## HISTORY OF CLINICAL TRIALS

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- 1931 - First clinical trial to use randomization by Amberson studying sanocrysin, a gold compound, in pulmonary TB; carefully matched 24 patients into comparable groups of 12 each and then flipped coin to determine which group received sanocrysin; also introduced blindness, patients not told whether they received IV sanocrysin or distilled water

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## HISTORY OF CLINICAL TRIALS

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- 1938 - Diehl's trial of cold vaccines, referred to control saline solution as a placebo
- 1938 - The Federal Food, Drug, and Cosmetic Act requires new drugs to be shown to be safe

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## HISTORY OF CLINICAL TRIALS

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- 1948 - British Medical Research Council trial of streptomycin in TB patients first to use random numbers to allocate patients to experimental or control groups
- 1940s - First VA/Armed Forces multicenter clinical trials to evaluate chemotherapies for TB; first trial was not randomized!

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## HISTORY OF CLINICAL TRIALS

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- 1950s-1960s - Principles of RCTs laid out by Bradford Hill
- 1950s-1960s - Noteworthy VA cooperative trials conducted by individual groups in hypertension, psychiatry, cardiovascular diseases, gastroenterology, oncology
- 1960s-Present - Major large-scale multicenter clinical trials funded by NIH (NHLBI, NCI cancer groups, NIDDK, NEI, NINDS, NIMH, etc.)

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## HISTORY OF CLINICAL TRIALS

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- 1962 - FDA Kefauver – Harris Drug Amendments, after the thalidomide occurrence, requires drugs to be proven effective
- 1972 - Development of the VA Cooperative Studies Program as it exists today (4 statistical coordinating centers and central research pharmacy)

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## HISTORY OF CLINICAL TRIALS

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- 1974 - National Research Act – Created National Commission for Protection of Human Subjects, regulations focused on concepts of informed consent and decision making in local IRBs
- 1976 - FDA Medical Device Amendments requires medical devices to be shown safe and effective

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## HISTORY OF CLINICAL TRIALS

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- 1980 - Establishment of the Society for Clinical Trials, a society of clinical trialists from government, academia, and industry (physicians, biostatisticians, nurses, computer scientists, data coordinators)

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**1980's – PRESENT  
(BURGEONING FIELD)**

- Emergence of technological advances in computers (PCs, laptops, handheld devices, Internet, etc., software – SAS, NQuery, SOLAS, Equiv Test, Meta Analysis)
- Emergence of large simple trials and multi-national trials (ISIS, Physicians Health Study, etc.)

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**1980's – PRESENT  
(BURGEONING FIELD)**

- Good Clinical Practices, SOPs
- Improved statistical methodologies – Longitudinal analysis with missing data, regression methods in survival analysis, Bayesian approaches, interim monitoring
- Emergence of non-traditional endpoints (cost, quality of life, etc.)

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**1980's – PRESENT  
(BURGEONING FIELD)**

- Emphasis on IRB issues
- Genetic applications
- Meta-analysis, levels of evidence, guidelines development, research dissemination

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## WHAT IS A CLINICAL TRIAL?

- Prospective study
- Comparing an experimental intervention vs. a control
- Random allocation of subjects to interventions
- Involving human beings
- Patients directly observed
- Not a case-control study, case series, medical record review study

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## WHAT IS A CLINICAL TRIAL?

- Experimental interventions can be prophylactic agents, diagnostic agents, therapeutic agents, devices, procedures (angioplasty, surgery), lifestyle changes, psychological/educational, health services, strategies
- Control could be standard treatment, no treatment, placebo
- All groups may be on additional, concomitant treatments

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## WHAT IS A CLINICAL TRIAL?

- Efficacy vs. effectiveness trials
  - Efficacy trial measures what intervention accomplishes in ideal setting (protocol compliers only)
  - Effectiveness trial measures what intervention will do in actual practice – preferred analytic approach

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## PHASES OF CLINICAL RESEARCH

- In Vitro or Animal Studies
- Human Studies
  - Phase I – To determine maximally tolerated dose (MTD)
    - 3 patients given lowest dose
    - If toxicity not observed, next dose tried
    - If toxicity occurs, 3 more patients tried on same dose
    - If no toxicity, next dose tried
    - If toxicity occurs, dose escalation terminated, and that dose or next lower dose called MTD

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## PHASES OF CLINICAL RESEARCH

- Phase II – To determine if agent has any biologic effect at MTD and to estimate rate of adverse events
  - Two-stage design
    - Minimum response rate 20%
    - Enter 14 patients
    - If 0 responses, agent failure (Prob. < 5% of missing an effect)
    - If 1 or more responses, add 10-20 patients to estimate response rate

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## PHASES OF CLINICAL RESEARCH

- Phase III – To assess effectiveness and safety of agent (Clinical Trial)
- Phase IV – To observe effectiveness and safety of agent long-term as it would be used in clinical practice (no control group)

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## WHY ARE CLINICAL TRIALS NEEDED?

- Provides clearest method of determining whether intervention has a postulated effect and is safe
- Uncertain knowledge about disease course in population and individual patients
- Many examples of widespread adoption of interventions without good evidence of effectiveness and safety
  - Digitalis in CHF
  - Intermittent positive pressure breathing in COPD
  - High concentration of oxygen in premature infants
  - Antiarrhythmic drugs in patients with HX of MI

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## WHY ARE CLINICAL TRIALS NEEDED?

- They often can improve clinical practice
- Timing is important
  - Institute as early as possible in evaluation of new interventions
  - Before intervention becomes widespread
  - Feasibility (pilot data, outcomes to assess)
  - Stability of intervention (Cochlear implant study, PCI vs. CABG, DBS in PD)

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## ETHICS OF CLINICAL TRIALS

- Issues/debates center around physician's obligation to patient vs. societal good, informed consent, randomization, and use of placebo
- A well-designed and conducted RCT can answer important public health questions without impairing welfare of individual patients
- Proper informed consent is essential

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## ETHICS OF CLINICAL TRIALS

- Randomization is ethical if it is truly not known which intervention is better (Clinical equipoise – presence of uncertainty among expert medical community)
- If investigator believes one treatment is better than another, he/she should not participate
- Use of placebo does not necessarily mean no care in many trials, all patients receive standard care.

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## ETHICS OF CLINICAL TRIALS

- Interim monitoring of accumulating data can stop a trial early if the answer becomes known
- In many situations, patients receive better care inside vs. outside of a trial
- Individual patient welfare always takes precedence

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## STUDY PROTOCOL

- Every well-designed clinical trial requires a protocol
- Can be viewed as written agreement between PI, participant, IRB, and scientific community
- Ongoing changes should be carefully documented, dated and require IRB approval
- Minor changes only should be allowed; major changes should be rare; all changes should be clearly justified

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## TYPICAL CONTENTS OF STUDY PROTOCOL

- A. Background of study (possibly including meta-analysis of previous studies for effect size)
- B. Objectives
  - 1. Primary question and response variable
  - 2. Secondary questions and response variables
  - 3. Subgroup hypotheses
  - 4. Adverse effects

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## TYPICAL CONTENTS OF STUDY PROTOCOL

- C. Design of study (in order of chronology of patient going through trial)
  - 1. Study population
    - a. Inclusion criteria
    - b. Exclusion criteria
  - 2. Enrollment of participants
    - a. Informed consent
    - b. Assessment of eligibility
    - c. Baseline examination
    - d. Stratification and randomization

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## TYPICAL CONTENTS OF STUDY PROTOCOL

- C. Design of study (in order of chronology of patient going through trial)
  - 3. Interventions
    - a. Experimental
    - b. Control
    - c. Concomitant treatments
    - d. Measures of compliance
  - 4. Follow-up description and schedule
  - 5. Ascertainment of response variables
    - a. Training
    - b. Data collection
    - c. Quality control

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## TYPICAL CONTENTS OF STUDY PROTOCOL

- C. Design of study (in order of chronology of patient going through trial)
  - 6. Statistical issues
    - a. Effect size, sample size, and statistical power
    - b. Interim monitoring
    - c. Statistical analyses

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## TYPICAL CONTENTS OF STUDY PROTOCOL

- D. Organization
  - 1. Participating investigators
    - a. Clinical centers
    - b. Chairman's office
    - c. Statistical center
    - d. Special laboratories
  - 2. Study administration
    - a. Steering committees and subcommittees
    - b. Data monitoring committee
    - c. Funding organization

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## TYPICAL CONTENTS OF STUDY PROTOCOL

- Appendices
  - A. Budget and budget justification
  - B. Consent form and Human Rights Committee Review
  - C. Case report forms
  - D. Biostatistical and data processing procedures
  - E. Drug/device handling protocol
  - F. Medical center participation/patient availability
  - G. CVs of investigators

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## STATING THE RESEARCH OBJECTIVE(S)

*"The formulation of a problem is often more essential than its solution."*

– A. Einstein and L. Infeld

- Why is a clear statement of the research objective(s) so important?
  - It helps the researcher to constantly focus on the main issue(s)
  - The remainder of the research design follows from the objective(s)

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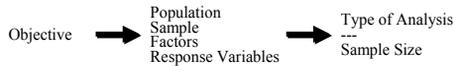
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## STATING THE RESEARCH OBJECTIVE(S)



- It helps the researcher to communicate his/her research ideas to others
- It helps prevent add-on projects that may interfere with main purpose
- It helps define priorities for data analysis and report writing

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## THE RESEARCH IDEA

- Probably the most important and most difficult aspect of the research proposal
- An immaculate design cannot save a poor idea
- How does one develop a good research idea?
  - Thorough familiarity with the research field (keeping up with the literature)
  - Motivated by an important medical problem faced routinely in the clinic
  - Feasibility of the idea

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**SOME STRENGTHS OF THE VA COOPERATIVE STUDIES PROGRAM MODEL**

- Research ideas come from VA clinicians from VAMCs all over the country and from many specialty areas
- The ideas are motivated by real clinical problems faced by the clinicians daily
- Brief planning request submitted through local research office and medical center director to VAHQ (a large investment of time is not required to obtain a preliminary evaluation of the idea)

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**SOME STRENGTHS OF THE VA COOPERATIVE STUDIES PROGRAM MODEL**

- Planning request sent to 4-5 experts in field for evaluation
- If this review is positive, researcher is immediately partnered with methodologists (CSPCC, CSPCRPCC) to develop full proposal

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**SOME GENERAL PRINCIPLES IN WRITING RESEARCH OBJECTIVES**

- Keep the number of objectives as small as possible; i.e., focus the research project
- If there are several objectives, try to divide them into primary and secondary objectives
  - Base sample size on primary objective(s). If more than one primary objective, calculate sample size for each and choose largest sample size.
  - Final analysis priorities should be in terms of primary and secondary objectives.

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## SOME GENERAL PRINCIPLES IN WRITING RESEARCH OBJECTIVES

- State the hypothesis/objectives as simply as possible
  - “[Intervention] compared to [control] will improve [response variable] in [population of interest]” or “To determine if ...”
- These elements should be included in the primary research objective:
  - Population to be studied
  - Experimental intervention
  - Comparison group
  - Outcome of interest

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## PRIMARY QUESTION

- Ideally, clinical trial should have one primary question
- Stated clearly and in advance
- Size of trial (sample size) based on this
- The question of most importance, and should be feasible
- Should be one which will change practice

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## PRIMARY QUESTION

- Should include population of interest, experimental intervention, control group, and outcome (major response variable)
- Encourages proper study design, enhances credibility of trial
- Must be emphasized in reporting of trial results

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**EXAMPLE OF “MARGINAL” PRIMARY QUESTION THAT MIGHT NOT CHANGE CLINICAL PRACTICE**

- Amiodarone compared to placebo in patients with congestive heart failure and ventricular arrhythmias will improve exercise tolerance

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**EXAMPLE OF IMPORTANT PRIMARY QUESTION THAT WOULD CHANGE CLINICAL PRACTICE**

- Amiodarone compared to placebo in patients with congestive heart failure and ventricular arrhythmias will increase long-term survival

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**SECONDARY QUESTIONS**

- Generally one of two types
  - Different response variable than in primary question (e.g., primary endpoint mortality; secondary – quality of life, morbidity, cost, patient satisfaction)
  - Related to results in a subgroup – e.g., gender, race, age, disease severity

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## SECONDARY QUESTIONS

- Secondary questions should be specified in advance, based on reasonable expectation (rationale based in literature or knowledge of biology), and limited in number
- Recognized to be exploratory in nature; hypothesis generating; sample size may be too small for definitive conclusions

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## OTHER QUESTIONS

- Adverse effects
  - Cannot always be specified in advance
  - Monitor a variety of laboratory and clinical measurements and symptoms and compare groups
  - Some adverse effects do not show up until post-marketing
- Ancillary questions
  - Secondary uses of database
  - Do not bear directly on intervention being tested

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## OTHER QUESTIONS

- Ancillary questions
  - Examples
    - Heart valve replacement trial – comparison of patient risk
      - adjusted mortality and morbidity for patients operated by residents vs. attendings
    - Comparison of local vs. central tumor measurements in a cancer trial
- Natural history of disease
  - In control group
  - Predictors of outcome

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## CSP #196

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- Study Objectives

The primary objective of this controlled study is to determine whether the Incidence of recurrent spontaneous pneumothorax can be decreased if tetracycline is instilled into the pleural space when the patient is initially treated with a tube for the pneumothorax.

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## CSP #196

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- There are also secondary objectives. These are:

- To determine whether the intrapleural instillation of tetracycline will diminish the length of the initial hospitalization.
- To determine whether the intrapleural instillation of tetracycline will lessen the need for thoracotomy.
- To determine whether there are significant short term or long term side effects associated with the intrapleural instillation of tetracycline.

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## CSP #207

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- Objectives of the Study

- Primary objective
  - The aim of this proposal is to determine the effect of antiplatelet therapy on graft patency in patients after coronary artery bypass surgery (CABG).
- The primary objective is to determine if antiplatelet therapy alters graft patency at one week and one year after CABG.

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## CSP #207

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- Secondary objective

- The secondary objectives are to determine:
  - If antiplatelet therapy alters progression of coronary artery disease in grafted (proximal and distal to insertion of graft), and ungrafted vessels at one year after CABG.
  - If antiplatelet therapy alters the development of the perianastomotic lesion after CABG.
  - Whether antiplatelet therapy alters the clinical course of patients with coronary artery disease after CABG. Specifically, does antiplatelet therapy decrease the incidence of angina and death?

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## CSP #411

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- Primary Hypothesis

- Prophylactic coronary artery revascularization (compared to no revascularization) in patients scheduled for elective vascular surgery and at high risk for coronary complications reduces long-term risk of mortality.

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## CSP #411

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- Secondary Hypotheses

- The intervention reduces long-term risk for myocardial infarction.
- The intervention improves both:
  - Cost-effectiveness of treatment
  - Quality of life of patients

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## COMPONENTS OF RESEARCH PROJECT

Population	- Total collection of objects that are of interest to the study (patients, animals, operations, etc.)
Experimental Unit (EU)	- Each individual object in population
Sample	- Group of EU's included in study
Response variable (dependent variable, outcome)	- Observation or measurement that records state of EU for phenomenon being studied (May be >1)

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## COMPONENTS OF RESEARCH PROJECT

Factor (independent variable)	- A set of treatments or some other effect that is to be evaluated; or groupings of EU's into subsets of the population for comparison (such as sex, race, and age, etc.)
Level of factor	- Each possible setting of factor (Treatment A, B, C; Dose of drug; male or female)
Qualitative Factor	- A factor that has levels that are categorical (e.g., type of drug, gender)

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## COMPONENTS OF RESEARCH PROJECT

Quantitative Factor	- A factor that has numerical levels (e.g., dose of drug, age)
Extraneous Factor	- Factor not of primary interest but may have effect on response variable and may influence the observed effect of the factor of interest on the response variable
Experimental Factor	- One in which researcher assigns factor levels to EU's randomly
Observational Factor	- One in which researcher observes level of factor present on EU but does not assign it

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## COMPONENTS OF RESEARCH PROJECT

Experimental Study - Research project that contains at least one experimental factor

Observational Study - Research project that contains only observational factors

- The goals of the observational and experimental study are the same – to determine the effect of the factor on the response variable. However, it is more difficult to accomplish with the observational study because the extraneous factors are not well balanced across the levels of the factor being studied.

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## CSP #411

Population - All (male?) patients undergoing elective vascular surgery and at high risk for coronary complications

Experimental unit - Each patient in this population

Sample - Patients included in the trial

Primary response variable - Long-term mortality

Primary factor or independent variable - Coronary revascularization (yes, no)

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## CSP #411

Levels of factor - Yes, no (Qualitative, experimental factor)

Extraneous factors - Many (e.g., age of patient, type of vascular surgery, severity of coronary disease, other comorbidities, etc.) These tend to be balanced by randomization.

- Experimental study since at least one factor is experimental.

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## SUMMARY

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- Clinical trials are considered to be the “gold standard” in clinical research due to the balancing of extraneous factors in an experiment
- VA is a major contributor to the field
- Research idea (hypothesis, objective) is the most important part of the research – needs to be important, potentially changing practice, and feasible

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## SUMMARY

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- One primary hypothesis, including population, intervention, control, primary response variable
- Secondary questions can relate to other outcomes, subgroups, adverse effects, ancillary questions, or natural history

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