CTN Web Seminar Series: Research 101

INTRODUCTION TO CLINICAL TRIALS: THE BASICS

A REVIEW OF CLINICAL TRIAL DESIGNS, PHASES, AND OTHER ESSENTIALS FOR THE NEW RESEARCHER

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AGENDA

- What is clinical research?
- Terminology
- Phases of Clinical Trials
- Types of Research Studies
  - Observational Studies
  - Experimental Studies

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WHAT IS CLINICAL RESEARCH?

Clinical research is the comprehensive study of the safety and effectiveness of an intervention for patient care. Intervention can include medication, devices, tools, diagnostic tests, technique, and technology.

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TERMINOLOGY

- Placebo – An inactive substance or other intervention that looks the same as, and is given the same way as, an active drug or treatment being tested.
- Control group – The group that does not receive the new treatment being studied
- Experimental group – The group that receives the medication/treatment being tested
- Cohort – Group of people with a shared characteristic
- Target population – Total group of individuals to be studied or group of interest
- Sample population – Subset of the target population that is representative of the target population

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TERMINOLOGY

- Randomized control trial (RCT) – A study design that randomly assigned participants into an experimental group or a control group.
- Open label study – Study participants and researchers both know which treatment is being administered.
- Double-blind study – A study in which neither the participants nor the researcher(s) know which treatment/intervention participants are being administered.
- Single-blind study – A study where only the researcher(s) conducting the study know which treatment/intervention the participant is receiving.

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TERMINOLOGY

- Prospective study – Individuals are followed over time and data about them is collected as their characteristics or circumstances change.
- Retrospective study - Individuals are sampled and information is collected about their past.
- Bias – Occurs when systematic error is introduced into sampling or testing by selecting or encouraging one outcome or answer over others.
  - Information bias - a distortion in the measure of association caused by a lack of accurate measurements of key study variables.
  - Selection bias - a kind of error that occurs when the researcher decides who is going to be studied.
  - Confounding - A systematic distortion in the measure of association between exposure and the health outcome caused by mixing the effect of the exposure of primary interest with extraneous risk factors.

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POP QUIZ!

Which question aligns with the aims of Phase 2 clinical trials?

A. Is the medication safe and what is the right dose?

B. Is the new treatment/intervention more effective than existing treatments?

C. Is the new treatment/intervention effective and safe over the long term?

D. Does the new treatment/intervention work and what are the side effects?

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PHASES OF CLINICAL TRIALS

- Phase I
  - Is the medication safe and what is the right dose?
- Phase II
  - Does the new treatment/intervention work and what are the side effects?
- Phase III
  - Is the new treatment/intervention more effective than existing treatments?
- Phase IV
  - Is the new treatment/intervention effective and safe over the long term?

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PHASE I

- Is the medication safe and what is the right dose?
  - Tests the safety, side effects, best dose, and timing of new treatment
- Small sample size, in most cases 20-80 healthy volunteers
- Phase I can answer other questions as well, including:
  - How much drug is measured in the blood after administration?
  - How does the drug work in the body?
  - What are the side effects associated with increased dosage?

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PHASE II

- Does the new treatment/intervention work and what are the side effects?
  - Further tests safety and effectiveness and determine the optimal dose and how best to administer the medication/intervention to maximize possible benefits while minimizing risks
- Sample size is typically larger, 100-300 study participants who have the disease or condition for which the medication is being developed

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PHASE III

- Is the new treatment/intervention more effective than existing treatments?
  - Tests whether a medication/treatment offers a treatment benefit to the intended population
- Sample size is typically 300 to 3,000 participants from patient population for which the treatment is intended
- Participants are assigned to receive either the medication/intervention or a control group that receives either placebo or the current standard of care treatment.
- When one or more Phase 3 trials are completed and the medication/intervention shows results, researchers can then submit a New Drug Application (NDA) to the FDA for consideration for marketing approval.

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PHASE IV

- Is the new treatment/intervention effective and safe over the long term?
  - Studies the side effects caused over time by a new treatment after it has been approved and is on the market
- Sample size can be several hundred or thousands of study participants.
- Phase IV trials begin after the medication/treatment has been approved for use in the general population following phase 1, 2, and 3 trials to rigorously test efficacy and safety.
- Can also be referred to as post marketing surveillance

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POP QUIZ!

Studies where researchers observe the effect of a risk factor, test, treatment, or other intervention without trying to change who is or isn't exposed to it. This type of study is considered a(n)….

A. Experimental study
B. Randomized Controlled Trial (RCT)
C. Observational study
D. Correlational study

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C. **Observational study**
D. Correlational study

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TYPES OF RESEARCH STUDIES

Observational Studies

- Observe the effect of a risk factor, test, treatment, or other intervention
- Aim to identify and analyze patterns in medical data or biological samples, such as tissue or blood provided by study participants

Experimental Studies (Clinical Trials)

- Aim to test the safety and effectiveness of medication/interventions, medications, procedures, tools, technology, treatment trials, prevention trials, screening trials

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OBSERVATIONAL STUDIES

- Registries – Collection of information about individuals, usually focused on a specific diagnosis or condition.
  - Breast Cancer Surveillance Consortium, Cystic Fibrosis Foundation Patient Registry
- Cohort study: Follows a group of participants over a period of time, examining how certain factors, such as exposure to a risk factor, affect their health outcomes.
  - Prospective or retrospective
  - Framingham Cohort study
- Case control study: Compares two groups of people, those with the disease/condition (cases) and a group of people without the disease/condition (controls).
  - Foodborne illness outbreaks, like Hepatitis A infection

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- **Ecological** - This study design compares clusters of people, usually grouped based on their geographical location or temporal associations.
- **Proportional mortality** - Proportional mortality ratio studies (PMR) utilizes the defined well recorded outcome of death and subsequent records that are maintained regarding the decedent.
- **Case-crossover** – Relies upon an individual to act as their own control for comparison issues, thereby minimizing some potential confounders.

TYPE OF STUDY: OBSERVATIONAL

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- **Cross-sectional** - These studies consist of assessing a population, as represented by the study sample, at a single point in time.
- **Case-control** - Identify study participants based on their case status, i.e. diseased or not diseased.
- **Retrospective and Prospective Cohort** - Involve identifying study participants based on their exposure status and either following them…
  - through time to identify which participants develop the outcome(s) of interest (prospective) or
  - look back at data that were created in the past, prior to the development of the outcome (retrospective).

TYPE OF STUDY: OBSERVATIONAL

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Study Design	Strengths	Weaknesses	Temporality
Ecological	Inexpensive, fast, easy to assign exposure levels	Inaccuracy of data, inability to control confounders, hard to identify denominator	Retrospective
Proportional Mortality	Inexpensive, fast, outcome (death) well captured	Utilize deaths only, inaccuracy of data, inability to control confounders	Retrospective
Case-crossover	Reduces some types of bias, good for acute health outcomes, cases act as own control	Selection of comparison time point difficult, hard to execute, prone to recall bias, no temporality	Retrospective
Cross-sectional	Inexpensive, timely, individualized data, ability to control for multiple confounders, can assess multiple outcomes	No temporality, not good for rare disease, poor for diseases of short duration	Retrospective
Case-control	Inexpensive, timely, individualized data, ability to control for multiple confounders, good for rare diseases, can assess multiple exposures	Cannot calculate prevalence, can only assess one outcome, poor selection of controls can introduce bias, may be hard to identify enough cases, prone to recall bias, no temporality	Retrospective
Retrospective and Prospective Cohort	Temporality shown, individualized data, ability to control for multiple confounders, assess multiple exposures/outcomes	Expensive, time intensive, not good for rare diseases	Retrospective and Prospective

Citation: Thiese, M. (2014). Observational and interventional study design types; an overview. *Biochem Med*, 2014 Jun; 24(2):199-210.

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EXPERIMENTAL STUDIES (INTERVENTIONAL)

- **Randomized Controlled Trial (RCT)** – Most common type of interventional study, compares an intervention group to a control group utilizing randomization of participants.
- **Pre-post Study Design** - Measures the occurrence of an outcome before and again after a particular intervention is implemented.
- **Non-randomized Trial** - Compare a group where an intervention was performed with a group where there was no intervention, without randomization (not considered a strong design).
- **Crossover RCT** - where study participants intentionally "crossover" to the other treatment arm.

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RANDOMIZED CONTROLLED TRIAL (RCT)

PROSPECTIVELY ASSIGNS PARTICIPANTS RANDOMLY INTO AN EXPERIMENTAL GROUP OR A CONTROL GROUP

MEASURES THE EFFECTIVENESS OF NEW MEDICATIONS OR TREATMENT

REDUCES BIAS AND HELPS EXAMINE CAUSE-EFFECT RELATIONSHIPS BETWEEN AN INTERVENTION AND AN OUTCOME

WIDELY CONSIDERED THE "GOLD STANDARD" FOR CLINICAL RESEARCH STUDY DESIGNS

MUST CAREFULLY DEFINE THE POPULATION, INTERVENTION, AND OUTCOMES OF INTEREST *A PRIORI*

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PRE-POST STUDY DESIGN

Measures the occurrence of an outcome before and again after a particular intervention is implemented

May be single arm, one group where outcomes are measured before the intervention and again after the intervention.

May be multiple arms, where there is a comparison between groups. Sometimes that includes an arm with no intervention, which acts as the control group in a multi-arm pre-post study.

Strength of temporality but doesn't account for other confounding elements. Changes in disease occurrence during the study period cannot be fully attributed to the intervention.

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NON-RANDOMIZED TRIAL

Interventional design that prospectively compares a group where an intervention was performed with a group where there was no intervention.

There is NO randomization.

This design is convenient can suggest possible relationships between the intervention and the outcome but are subject to many types of bias and error.

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CROSS-OVER RCT

RCT where study participants intentionally "crossover" to the other treatment arm.

Begins the same as a traditional RCT, however at the end of the first treatment phase, each participant is reallocated to the other treatment arm.

Strengths of this design include demonstration of reversibility, compensating for unsuccessful randomization, and improving study efficiency by not using time to recruit subjects.

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POP QUIZ!

What study design measures the occurrence of an outcome before and again after a particular intervention is implemented?

A. Randomized Controlled Trial (RCT)
B. Observational study
C. Cross-sectional study
D. Pre-post study

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POP QUIZ!

What study design measures the occurrence of an outcome before and again after a particular intervention is implemented?

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QUESTIONS?

Please send any questions to ctntraining@emmes.com

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Pop Quiz Time

The first documented occurrence of clinical trial methodology in the western world was found in _____?

A. A ship's manifest
B. The Bible
C. The lost continent of Clinicalia
D. An oyster shell

B. The Bible

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Research is…

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Introduction To Clinical Trials: The Basics

- Protocol Components
- Human Subjects Protection
- Informed Consent Form
- Good Clinical Practices and Data Management
- The Research Assistant and Research Coordinator

4

Protocol Components

Get familiar with these sections

- Synopsis
- Study Flow
- Inclusion/Exclusion
- Safety
- Regulatory

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Synopsis

- Succintly states the purpose
- Statement necessitating study and potential impact
- Easy to Read
- Snack sized summary

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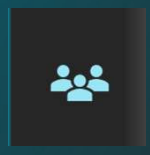
Study Flow

Design

Intervention
Randomization
Visit Schedule

Methods

Assessments
Data collection/entry
QA



Study Population and Study Staff

Recruitment/Retention strategies
Staff delegation and responsibilities
Anticipate potential challenges

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Study Eligibility

Inclusion Criteria

- Demographic and geographic characteristics
- Clinical characteristics related to the condition/disease being studied
- All must be answered "Yes"

Exclusion Criteria

- Narrows down the list
- Defines safety, privacy, feasibility rule-outs
- All must be answered "No"

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Regulatory Matters

Institutional Review Board (IRB)

- Submissions
  - Study Startup
  - Continuing Review(s)
  - Study Closeout
- AE/SAE
- Protocol Departures

Sponsor/
Clinical Coordinating Center (CCC)

- Inventory/Equipment
- Investigational Product (IP) Accountability
- Checklists
  - Study startup
  - Study visits
- Regulatory Binders
- Audits/Monitoring Visits

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Participant Safety

- Differentiate expected side effects and unexpected reactions
- Contraindications
- Participant withdrawal parameters
- Measures to monitor safety
- Data Safety Monitoring Board (DSMB)

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Pop Quiz Time

This President declared war on drugs and signed into law the National Research Act of _____?

A. President Nixon, 1974
B. President Carter, 1977
C. President Reagan, 1982
D. President Lincoln, 1864

A. President Nixon, 1974

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Belmont Report

Respect for persons

Beneficence

Justice

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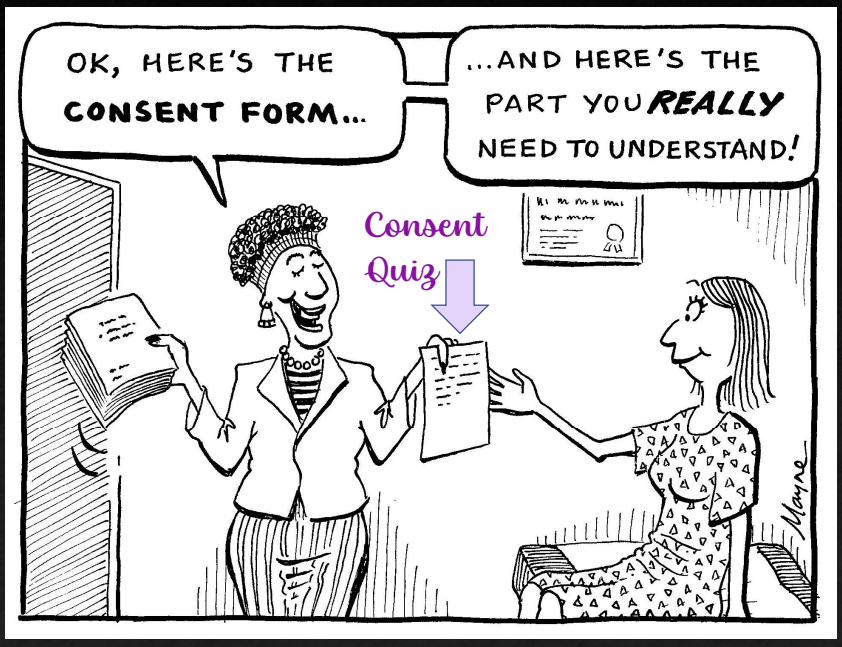

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Informed Consent... it's a process

- Build credibility, rapport, trust
- Establish ground rules and boundaries
- Maintain established communication, expectations
- If in doubt, ask first
- Purpose is to help the potential participant understand
- Must have it to gather any data beyond pre-screening

Etymology (Latin): Con (together) + Sentire (feel)

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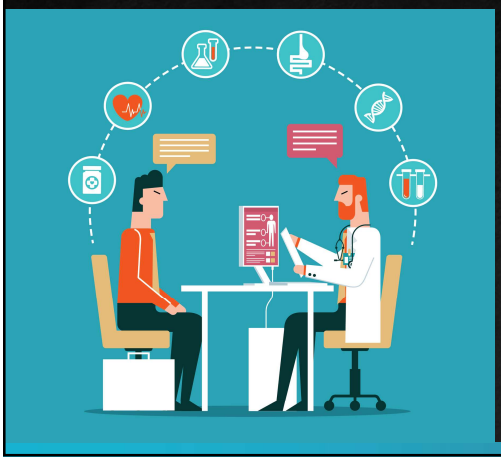
Informed Consent Process



- Information exchange
  - Q and A
- Wording/phrasing matters
- Know your audience
- Keep it simple, paraphrase
- Slow down, budget for time, time varies
- Choose a quiet, confidential space
- Practice with team members and family
- The more you know, the better you feel

You only get one first impression

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Pop Quiz Time - ICF

Which one of these does not belong?

A. A newly signed ICFs should be double checked by a separate staff member before filing

B. Blue or black ink is the standard for documenting on paper documents

C. The participant should leave with the ICF or at least given the option to take a copy home

D. Study Staff should sign before the participant whenever possible

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Good Clinical Practice

GCP **helps protect participants by ensuring a high level of quality for each trial that is conducted**. The standards also ensure accurate reporting of study results and protect against fraudulent or misleading data so that consumers can trust the products they use.

GCP Data (GCDMP) Management

Runs GCP concepts through the lens of technology to define industry standards for computer applications and database systems as well as establishing conditions for electronic signatures on eCRFs (Case Report Forms).

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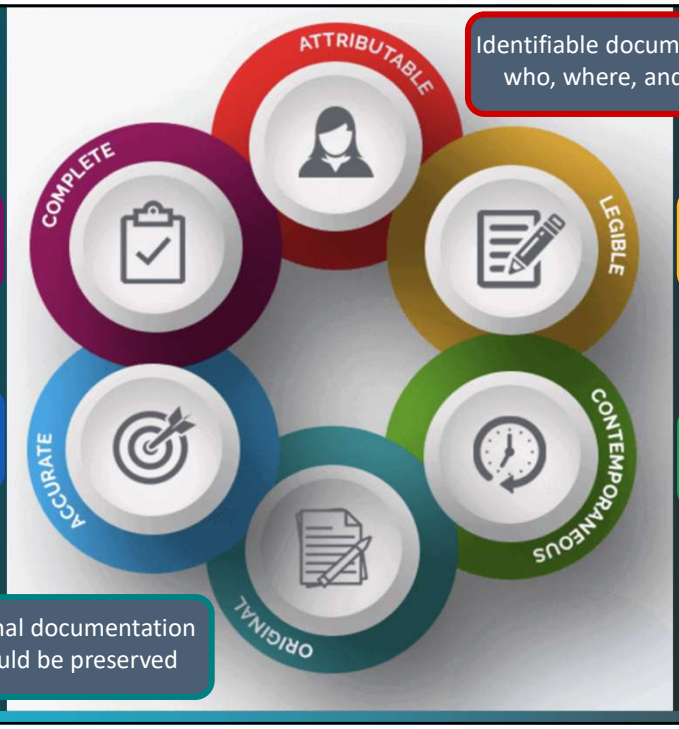
ALCOA



Identifiable documentation: who, where, and when

Can be "easily" read

Real-time data collection and data entry

Original documentation should be preserved

Viable data should be error free

No deletion or removal of data from sources

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Tips and Tricks of the trade for RA/RC Study Staff

- **Rapport building starts on day 1:**
  - Facilitates an information highway
  - Friendly but not friends
- **Establish internal QA procedures:**
  - Double check and document (temporary is fine)
  - Create hard rule about this
  - Identify refresher training or obsolete process
- **Proper Preparation Prevents Poor Performance**
  - Participant Data Binders
  - Reviewing site staff schedules regularly (holidays)
  - Thorough SOPs with contingency plans
  - You can never have too many back-up plans!

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Tips and Tricks of the trade for RA/RC Study Staff

Common Errors

- **Do not pick favorites or maintain boundaries:**
  - Each participant is equally deserving of your time
  - Participant self-reporting may be influenced by perceived shame or disappointment
- **Between the ears, is no place for data:**
  - Contemporaneous documentation dictates writing/ typing it as soon as possible
  - I you didn't write it down, it didn't happen
  - Procedures to aid appropriate documentation
- **<u>Exhaustively</u> complete Locator Information Form (LIF) with everyone.**
  - This alone will save time, save effort, increase performance metrics, indicate to the ppt that we take study participation seriously

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Questions?

Please send any questions to ctntraining@emmes.com

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1. Emma M. Nellhaus , Todd H. Davies, PhD. Evolution of clinical trials throughtot history. https://mds.marshall.edu/cgi/viewcontent.cgi?referer=&httpsredir=1&article=1101&context=mjm

2. Emanuel EJ, Boyle CW. Assessment of Length and Readability of Informed Consent Documents for COVID-19 Vaccine Trials. JAMA Netw Open. 2021 Apr 1;4(4):e2110843. doi: 10.1001/jamanetworkopen.2021.10843. PMID: 33909052; PMCID: PMC8082317.

Sources

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