CLINICAL INVESTIGATOR CERTIFICATION

foundation programs

2021 CLINICAL INVESTIGATOR CERTIFICATION PROGRAM

Course Curriculum

American Academy of Optometry
FOUNDATION
Advancing Optometry's Future

Presented by the American Academy of Optometry Foundation

The Clinical Investigator Certification Program is an eight week (two hours a week) virtual program in which practicing optometrists will learn skills required to serve as a clinical investigator for sponsored research within their current practice setting. Additionally, attendees will gain an understanding of prerequisites to serving as an investigational site, conducting rigorous, sponsored, clinical trials. Each of the outlined sessions will involve a lecture component as well as breakouts for open discussion.

Learning Objectives:

- Understand the responsibilities of an investigator conducting a clinical trial
- Pearls for investigational study involvement
- Understand the basic concepts of clinical trial design (three sessions)
- Understand the concepts related to human subject research (two sessions)
- Review basics in statistics specific to clinical trials, and learn how to avoid data bias and error
- Understand the administrative/management aspects of research

Course Curriculum Outline:

Session 1: Pearls on Getting Involved in Clinical Research

Instructor: Katherine Weise, OD, MBA, FAAO

I. What's Your "Why" to Becoming a Clinical Investigator?

A. Take your learning to a new level
   1. Enhance writing and literature review skills
   2. Broaden your areas of expertise for speaking opportunities

B. Answer your patient's questions with the latest research--your own!

C. Offer novel treatments to patients

D. Create a higher standard of care for patients

E. Foster creative thinking in patient management

F. Become a key opinion leader

G. Boost office prestige

H. Generate an alternative revenue stream

I. Create variety within the workday

J. Become part of a multi-center team of investigators

K. Impact future clinical care of patients well outside the walls of your office

L. Collaborate with diverse colleagues

M. Propel academic advancement

II. Should I Conduct a Trial in My Office?

A. Investigator Responsibilities
   1. Do I have time for this endeavor?
   2. A brief overview and checklist

B. Team Responsibilities: Sub-investigators and Coordinators
   1. Are they on board?
   2. Do I have time to train them?

C. Study Concepts important for Rigor and Ethics
   1. Equipoise: What is it and do I have it?
      a. Investigator
      b. Professional/Community
      c. Recruitment Pool
   2. Conflict of Interest:
      a. Do I have a conflict that would prevent me from ethically moving forward?
   3. Scientific Misconduct:
      a. What is it?
      b. Do I know enough to know how to do it right and am I willing to take on study risks and remain dedicated to the study?

III. Potential Course Outcome Measures: Get More Involved in Research and Advance Your Research Skills

A. Serve on a local Investigational Review Board (IRB)
   1. Qualification requirements
   2. Time commitment

B. Join a multi-centered research network on your topic of interest

C. Explore the method for study question generation, study development, and research team selection

D. Experience new positions in clinical trials

E. Network with sponsors and mentors

F. Serve as a reviewer for a journal

G. Serve as a reviewer for grants

H. Attend research-oriented meetings

I. Join field-specific societies or research networks

IV. Getting Started: Critical Reading of Peer-Reviewed Research Articles

A. Bootcamp basics

Session 2: Basic Concepts of Clinical Trial Design - Part 1

Instructor: Robin Chalmers, OD, FAAO

I. What is a Clinical Trial?

A. Prospective

B. Employs one or more interventions

C. Compares effects and value of intervention against a control or other comparator (e.g. placebo or other interventions)

D. Human subject clinical trials

II. What isn't a clinical trial?

III. Study Types

A. Descriptive (Non-analytic): Provides an overview of what is happening in a population (e.g. prevalence, incidence, or experience of a group) but does not try to quantify relationship

1. Case Reports
2. Case Series
3. Survey (Cross Sectional)
4. Qualitative

B. Analytic: Attempts to quantify the relationship between two factors, the effect of intervention, or exposure on an outcome

1. Observational
    a. Types:
        i. Cohort
        ii. Cross Sectional
        iii. Case Control
2. Experimental (Randomized Controlled Trials)
    a. Types:
        i. Parallel (Non-crossover)
            a. One group receives treatment A while another receives treatment B
        ii. Cross-over
            a. One group receives treatment A followed by treatment B while the other group receives treatment B followed by A
        iii. Factorial
            a. Multiple factors manipulated or allowed to vary

Session 3: Basic Concepts of Clinical Trial Design - Part 2

Instructor: Bill Gleason, OD

I. Design of Clinical Trials

- A. Purpose
  - 1. Safety and efficacy
  - 2. Marketing claims (for regulatory)
- B. Study Objectives or Hypotheses
  - 1. Masking
    - a. Prevent bias (not always possible)
      - i. How it helps
    - b. Single, double, triple
      - i. May require more staff
  - 2. Maintaining a confidential, local log which links the study identification (ID) with the patient record ID
  - 3. Randomization
    - a. Definition
    - b. Helps prevent bias
    - c. Methods
- C. Human Pharmaceutical Trials
  - 1. Phase I
    - a. Proves no harm
      - i. Small number of participants (usually less than 100)
      - ii. Tests various doses of a drug to find appropriate dose
  - 2. Phase II
    - a. Assesses whether a drug has clinical efficacy
    - b. Usually involves 100-300 participants
    - c. Verifies dosage and frequency by increasing number of exposures
  - 3. Phase III
    - a. Demonstrates conclusively how well a drug works
    - b. Assess safety and efficacy
    - c. Usually involves 100-1000 subjects
    - d. Multiple locations
    - e. Representative subject population
  - 4. Phase IV: Post-market
    - a. Occurs after FDA approval

b. Further monitoring of drug in real-world environment
    i. E.g. Continuous wear contact lenses, pediatric trials, etc.
c. Very large population, multi-center

D. OTC Drug Trial

E. Medical Device Trials

1. Medical Device
    a. "Any article, instrument, apparatus, or machine that is used in the prevention, diagnosis, or treatment of illness or disease, or for detecting, measuring, restoring, correcting, or modifying the structure or function of the body for some health purpose."(World Health Organization)
    b. In different jurisdictions, there may be differences within medical devices (e.g. invasiveness/ insertion/radiation, etc.)
2. Stages
    a. Pilot/Early Feasibility/First-in-Human
        i. Usually 10-30 subjects
        ii. Collect preliminary safety and device performance data
        iii. Guides device modifications and/or future study design
    b. Traditional Feasibility
        i. Usually 20-30 subjects
        ii. Assess safety and efficacy
        iii. Guides design of pivotal study
    c. Pivotal
        i. Number of subjects in the 100s
        ii. Confirms clinical efficacy, safety, and risks
    d. Post-Market
        i. Number of subjects in the 1000s
        ii. Monitors long term effectiveness, safety, and usage in general population
        iii. May be mandated by FDA for devices with pediatric indication (myopia control contact lenses or spectacles)
        iv. Unscheduled

Session 4: Basic Concepts of Clinical Trial Design - Part 3

Instructor: Thomas Quinn, OD, MS, FAAO

I. Adverse Events (AE)

A. Timely reporting to study sponsor is imperative
   1. Depends on type of adverse event and IRB

B. Classifications
   1. Adverse event
   2. Serious adverse event
   3. For contact lens studies
      a. Significant adverse event
      b. Insignificant adverse event

C. Are they related or not related to investigational treatment?

D. Collect any AE for the participant during the study
   1. Include collecting data on administered, on-going, or completed treatments (allows for comparison to baseline data collected at the beginning of the study to help determine if pre-exsisting conditions worsened)

II. Study Flow

A. Interaction with study sponsor

B. Evaluation of protocol

C. Acceptance of participation with sponsor

D. Assign/hire study team members

E. Make sure all Good Clinical Practice (GCP) training is up to date

F. IRB submission

G. IRB revisions

H. IRB approval

I. Recruitment

J. Informed consent

K. Eligibility/exclusion criteria

L. Randomization

M. Visits
   1. Date ranges
      a. Enrollment period
      b. Individual visits
   2. Types of Visits
      a. Screening
         i. Inclusion/exclusion

b. Baseline (Begin treatment)
    i. Randomization
c. Follow-up
d. Exit

III. Clinical Trial Endpoints

A. Primary
B. Secondary
C. Tertiary
D. Exploratory

IV. Source Documents vs. Case Report Forms (CRF)

V. Trends in Clinical Trial Designs*

A. Migration of more clinical trials to North America
    1. Increase new investigators
        a. 2010: 26%
        b. 2020: 31%
B. Focus on populations generalizability (e.g. FDA is looking for subject population representative of U.S.)
    1. Gender
    2. Ethnicity
C. Higher investigator turnover for those that only do a few studies
D. Nearly half of sites under-enroll → increases length of enrollment time
E. Most study funds go to contract service providers instead of "in-house"
F. Increase in tertiary endpoints → increased complexity → relaxed recruitment criteria (number one reason for protocol amendments)
G. Twice as much data collected today versus 10 years ago; most to prove tertiary endpoints
H. The Future
    1. Increased complexity
        a. Supported by computerization
    2. More options for volunteers (subjects)
        a. Remote technology

* *Future State of Clinical Research, Ken Getz, MBA, Tufts Univ. School of Medicine, webinar 4/29/2020*

Session 5: Concepts Related to Human Subjects Research - Part 1

Instructors: Allison Summers, OD, MCR, FAAO & Jack Phu, OD, PhD, FAAO

I. Good Clinical Practice (GCP) Training Certification

A. Review history of clinical trials in the United States
B. Ensures rights, safety, and well-being of human subjects
C. Ensures clinical trials are conducted with rigor and integrity
D. Ensures data collected is reliable
E. Refreshed based on the schedule of your institute and/or sponsor (time frames may vary)
F. National Institutes of Health (NIH)/Collaborative Institutional Training Initiative (CITI) options
G. Additional device requirements may vary depending on country/state regulations
H. Oversight/regulations may vary for non-device and non-drug studies

II. Investigational Review Board (IRB) and Ethics Committees

A. Definition and purpose
    1. Patient protection
B. Approval required (Regardless of intent to publish)
C. Approves protocol
D. Approves informed consent/assent documents
E. Approves study site
F. Approves study modifications and renewals
G. May elect to audit your study
H. Check with study sponsor on who is paying for IRB review; it can be costly
I. Reliance agreements between local IRB and central IRB
J. Protection against liability

III. Data and Safety Monitoring Committee (DSMC) and other institutional requirements

A. DSMC is independent and advises on continuation or stopping study based on safety and efficacy

Session 6: Concepts Related to Human Subjects Research - Part 2

Instructors: Allison Summers, OD, MCR, FAAO & Jack Phu, OD, PhD, FAAO

I. Informed Consent and Ethical Considerations

A. Informed Consent

1. Basic Elements
    a. Description of Clinical Investigation
    b. Risks and Discomforts
        i. Handling of incidental findings
    c. Benefits
    d. Alternative Procedures or Treatments
    e. Confidentiality
    f. Compensation and Medical Treatment in Event of Injury
    g. Contacts
        i. How to contact an appropriate individual for pertinent questions about the clinical investigation, the subjects' rights, and in case of an emergency
        ii. Includes names and telephone numbers
    h. Voluntary Participation
    i. Review for implicit bias
        i. As inclusive as possible
        ii. Scientifically sound reason for exclusion criteria
        iii. No exclusions for convenience only (e.g. if including pregnant women would require a pregnancy test, adding expense and inconvenience, not justification for exclusion)
2. Process
    a. Quiet, private environment (e.g. examination lane) to:
        i. Encourage subject to read consent form
        ii. Ensure subject has the opportunity for questions/answers
        iii. Accommodations and procedures for low literacy
        iv. Accommodations and procedures for low vision
        v. Accommodations and procedures for translation and interpretation
            a. Coordinating center policy/central IRB policy
            b. Local IRB/institution policy
            c. Short forms
            d. Certified medical interpreters
        vi. Signed, dated copies for investigator and subject
        vii. Once Informed Consent Document signed and witnessed, subject is considered enrolled and is assigned a study number

B. Assent Form
    1. Developed to prevent children from unwittingly being volunteered for studies by guardians for profit. Written in age-appropriate language.
    2. Children under 18 years sign
        a. Minimum age is IRB dependent (often 7 yo)
    3. Children above a certain age, dependent on central and local IRB
    4. Special exceptions not requiring assent
    5. Licensed investigator signs
        a. Stating the investigation was explained to the minor
    6. Parent or legal guardian signs consent form
        a. Cannot be foster parent or grandparent

C. Legally Authorized Representative
    1. Developed to protect the rights of adults who are cognitively impaired or otherwise unable to give informed consent

D. Revocation of Consent
    1. E.g. Study intervention discontinuation versus study participation discontinuation versus revoking the consent
    2. Processes need to be in place to ensure that clinical care is not compromised (part of the Ethics Committee Review)
    3. How is previous data handled?

II. How to Offer Study Participation

A. Differentiating between research and clinical care

B. Advertising and promotion to patients and referring doctors

C. Cherry-picking your research participants

D. Avoiding inappropriate enticements z

III. How to End an Individual's Study Participation

A. Lost to Follow-up/Attrition
    1. Reason
    2. Documentation of attempts to contact
        a. Email, phone log, certified letter

B. Discontinuation of study subjects
    1. Subject withdraws from study
    2. Investigator withdraws subject
    3. Sponsor stops study
    4. Regulatory agency stops study

Session 7: Avoiding Data Bias and Error; Statistics Specific to Clinical Trials

Instructor: Jack Phu, OD, PhD, FAAO

I. Avoiding Bias and Data Error

- A. Know and follow the protocol
- B. Have a method
- C. Adhere to randomization schedule
- D. Adhere to masking
- E. Selection bias - how to identify deviations from protocol
- F. Making corrections
  1. Paper
     - a. Use ball point pen (black or blue preferred; no gel pens)
     - b. No white out
     - c. Draw a single, horizontal line through error
     - d. Write the correction
     - e. Initial and date the correction
  2. Electronic
     - a. Varies with system
       - i. Many will have keystroke logs

II. Review Basics in Statistics Specific to Clinical Trials and Comparative Studies

- A. Generating appropriate subject number
- B. Generating randomization codes
- C. Descriptive statistics
- D. Standard deviation
- E. What is normative data?
- F. Count data, proportions, Fisher's exact test, and McNemar's test
- G. Students' t-tests
- H. Analysis of Variance (ANOVA)

Session 8: Administrative/Management Aspects of Research

Instructor: Amy Nau, OD, FAAO

I. Investigator Qualification Documentation

A. Universal Documents

1. Documentation of human subject protection and Good Clinical Practice (GCP) training
2. Updated investigator and sub-investigator Curriculum Vitae (including study coordinator; often signed and dated)
3. Optometry license for the Primary Investigator (PI) and co-investigators, if licensed
4. Certificate of Insurance

B. Study-specific Documents

1. Non-Disclosure Agreement
2. Signed Investigator Agreement
3. Signed Financial Disclosure Forms for the PI and co-investigators (including study coordinator)
4. Signed Protocol Page
5. Delegation of Authority Log
6. Certification of Electronic Data Entry
    a. May be combined with Delegation of Authority Log
    b. Certifies electronic signature
7. Statement of Investigator (FDA Form 1572 or equivalent)
    a. Understands study protocol
    b. Agrees to:
        i. Supervise or conduct the investigation trial according to the current study protocol
        ii. Report all adverse events
        iii. Obtain informed consent
        iv. Maintain adequate and accurate records
        v. Accept oversight by Investigational Review Board (IRB)

II. Clinical Site Visits/Inspections

A. Frequency

1. Occurs more often (one-third of sites) in clinical studies involving an FDA Investigational Device Exemption (IDE)
    a. The purpose of the study is to evaluate effectiveness and safety of a new treatment such as an eyedrop or contact lens
2. For a site inspection, provide full disclosure on any issues relating to study
    a. If you do not know, say so
    b. Do not lie

3. Be professional
4. Be prepared, organized, and available during visit
5. Access to records for study subjects only
    a. Institutional rules likely require study team present
6. Demonstrate safe storage of documents/investigational products

B. Safe storage of documents/investigational product
1. Institutional and study group rules
2. HIPAA regulations
3. Computer security
4. Drug versus device storage
5. Length of storage requirements for documents
    a. Varies by state
    b. Pediatrics versus adults

C. Pearls
1. Ensure your research data is always entered into the Case Report Form (CRF) completely at the time of the study visit
2. Ensure legibility (ALCOA)
3. Ensure you regularly audit your study documents
4. Ensure you have an organized study binder
5. Ensure study information is not spread all over your office
    a. The local IRB will specify how information is to be stored
    b. May include password protected electronic documents
        i. Ensure digital data is also compliant and protected

III. Contents and Maintenance of Study Binder

A. Contents include:
1. Study Protocol and Amendments
2. The local IRB Approvals and Correspondence
3. Investigator Qualifications Documents
4. Financial Disclosure Forms
5. Study Correspondence (keep up to date with e-mails and mailed communications)
6. Enrollment Linking Log
7. Informed Consent Documents (signed copies kept here)
8. Delegation of Authority Form

B. Maintenance

IV. Characteristics of a Good Clinical Site

A. Investigator/Sub-investigator
   1. Committed
   2. Knowledgeable and willing to learn
   3. Detailed
   4. Resilient (e.g. may not be able to control timing)
   5. Flexible (e.g. may need to sign documents in a different way)
   6. Comprehensive
   7. Responsive
   8. Inclusive recruitment plan
   9. Appropriately trained
   10. Able to juggle the demands of clinical care with study responsibilities
   11. Able to evaluate a protocol to determine if it is feasible from a time management perspective, staff availability, and financial standpoint to engage in the study

B. In-office coordinator
   1. Key to success
      a. Pearl: Experience can be invaluable, particularly if you are inexperienced
   2. Organized
   3. Detailed
   4. Understands the gravity of responsibilities
   5. Able to recruit a diverse range of subjects
   6. Good communicator
      a. Bilingual may be helpful
   7. Needs:
      a. Time to dedicate to managing study
      b. Human subjects and Good Clinical Practice (GCP) training
      c. Understanding of protocol
         i. May be the one to discuss study with patients
      d. Shipping training

C. Diversity and inclusion
   1. Individuals from diverse backgrounds strengthen the team, lead to innovative thinking, and encourage enrollment of diverse subjects which increases the generalizability of the study
   2. Include diverse individuals in your local research team
   3. Encourage diverse individuals to join the larger research network
   4. Suggest diverse individuals to those selecting sites
   5. Provide mentorship and career support

6. Provide an inclusive and welcoming work environment at your site
7. Advocate for an inclusive and welcoming atmosphere in the larger research network meetings
    a. Access/timing for single parents
    b. Celebrate diversity
    c. Interrupt inappropriate comments
    d. Use your position to advocate for those who may feel uncomfortable speaking up

D. Appropriate patient base for the proposed study
1. Demographics (disease, age, ethnicity, other inclusion criteria)
2. Is the study designed in a way that your patient population will be able to enroll, complete treatment and follow up visits?
    a. Patient payments amount and method appropriate for your setting
    b. Transportation
    c. Home tech, internet, or other requirements
    d. Translation services (written consent and other documents)
    e. Interpreter services (verbal consent process and all visits)

E. Office Culture
1. Support of superiors
2. Efficient office systems
3. Support of peers and staff

F. Physical space
1. Set-up to accommodate chosen group from above
    a. E.g. If performing pediatric studies, have games/children's books in reception area
2. Space for study materials (e.g. logMar acuity charts)
3. Locked rooms/cabinets for study binders
4. Private area for informed consent process (e.g. examining lane)
5. Appropriate equipment
    a. Maintained and calibrated; must have some authority to purchase/replace/repair equipment needed for study
    b. Log documentation above
6. Compatible office systems with conduct of study
    a. Easily searched patient database
    b. Schedule allows for timely study visits
    c. Examination lanes/equipment availability
    d. Co-investigator(s)

7. Front desk schedule needs to:
    a. Flag study visit:
        i. For check-in and checkout
        ii. For billing
        iii. For documentation of study activity
    b. Reflects that study visits took place

G. Adequate time to conduct study is paramount
    1. Primary Investigator must have time to supervise study, conduct study visits in addition to seeing patients
    2. Clinical staff participating in study
    3. Regular meetings with study staff

V. Practical Considerations

A. Scheduling considerations
    1. Do not "squeeze this in"

B. Staffing considerations
    1. Compensation
        a. Funding allocation and recruitment policies should reflect no coercion
    2. Time required for training

VI. Closing Recommendations/Best Practices

A. Pitfalls to avoid

B. Key past learning experiences