Supporting Clinical Trials Research and Building your Research Team

Ralph Nitkin, PhD

National Center for Medical Rehabilitation Research

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NIH *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

Topics for Discussion

- Clinical Trial Design

- The Treatment Package

- Recruitment and Randomization

- Outcome Measures

- Building the Research Team

- Developing an NIH Clinical Trials Research Application

- NIH Policy and Oversight of Clinical Trials

Clinical Trial Design

Why do Clinical Trials?

- Assess new therapeutic approaches

- Modify and optimize current therapies

- Adapt existing therapies to new clinical populations or to other clinical contexts

- Challenge existing treatment practice/beliefs

- Investigate safety and efficacy; adverse effects

- **Evidence-based medicine** is central to health-care management and policy

Are you at the Appropriate Career Stage?

Early in your research career, in might not be appropriate to initiate and lead a major clinical trial:

- Tremendous amount of work in getting the trial funded, as well as other administrative and regulatory burdens in human subject research

- You may not yet have status and experience to coordinate efforts of clinical referral, treatment delivery, assessment, and data analysis

- Peer review would be looking for administrative as well as clinical experience on the CV of the clinical trial PI

- Initial years of the study do not translate into research publications and productivity on your CV; and the tenure clock is ticking . . .

- In the early stages of your career, consider building up experience working on someone else's clinical trial - in recruitment, subject support, assessment, or other roles

Theory Development for Clinical Trials

A simple trial of two treatments merely establishes that one may be better than the other:

- It provides no guidance how that treatment acts, how it could be optimized, or how the delivery could be further refined or simplified

- However, a mechanistic, theory-based trial may provide broader information maximizing efficacy, what other classes of treatments should be considered/eliminated, and what future trials should focus on

- Thus, a well-designed clinical trial not only provides a yes/no answer,   but also provides mechanistic* information.

*The "mechanism" may not just be molecular or pathophysiological but could also include behavioral or psychosocial components.

Role of Exploratory Trials

- Phase I Studies

  - Initial information regarding the intervention (e.g., safety, tolerability, dosing, practicality, and/or logistics)

- Phase II Studies:

  - Provide evidence of short-term activity in the target population

  - Evaluating across potential interventions or dosing strategies

Basically, is there evidence for continued research on that approach?

Exploratory Trials – Concluding Remarks

- Exploratory studies are often funded through pilot grants from federal funding agencies, research foundations, or local institutional funds

- But please do not rush to propose major, efficacy trials before you have explored the necessary logistical and safety issues

- And optimized dose and delivery strategies

- Also, consider specifically which patients would most benefit from the proposed treatment (inclusion/exclusion criteria)

We do not need more underpowered 'efficacy trials' to further confuse the clinical literature!

The Gold Standard is Still Considered to be The Randomized Clinical Trial

- Importance of randomization to reduce confounds and some biases

- Balanced treatment groups (including control/contrast arm)

- Double-Blinded: neither participant nor assessor knows the assignment

But other valid clinical trial models exist!

Summary Considerations in Clinical Trial Design

- What is the likely mechanism of action?

- What is the "active ingredient(s)" in your treatment?

  - Have you optimized the dose and delivery of that active ingredient?

- What would be the appropriate contrast/control groups – that incorporate all the other potential positive factors except the proposed active ingredient

- How could you support and document subject compliance through the trial?

- Are your outcomes clinically significant and robust?

  - Are you measuring outcomes most directly linked to likely mechanism of action?

- Accounting for other factors in patient population that could affect outcomes:

  - Premorbid health and secondary conditions

  - Outside medications and concurrent treatments

  - Patient goals, motivations, and resources

- Will results be scalable to the real world? Supported under healthcare constraints

The Treatment Package

Treatments may be Multifaceted

- "Treatment" could be a drug, device, or set of tasks and activities - delivered through an operationalized protocol

- Have you optimized dosing: amount, frequency, timing?

- Treatments could be multifactorial or combinatorial

- Treatments may be affected by patient behaviors and activities, which could occur outside the clinical setting

- Would these factors affect treatment efficacy or outcome variables?

- Never underestimate the role of subject expectations and the placebo effect

Operationalizing Treatment Delivery

- Need to standardize the delivery of treatment

  - Develop a manual of operations, with contingency responses to   likely subject responses and actions

  - Train and certify the treatment providers and assessors

    - And consider periodic re-certification to maintain fidelity

  - If multisite, standardize delivery and fidelity across sites

- Consider monitoring alterations in subject's outside activities, especially those associated with the treatment and/or those that could also impact outcome variables

  - Consider asking subject to keep an activity log or daily diary

- Detailed plans to monitor for adverse events

What about "Controls" or Contrast Groups?

- Given your hypotheses about "active ingredient" in your therapy, what are the proper contrasting treatments (control) groups?

- Merely using "historical controls" is not ideal:

  - Changes in base population, disease rates, disease definition, disease treatments, and available health resources may render historical data no longer comparable to your current study population

  - Seek clinical equipoise: balanced uncertainty of benefit across all the treatment arms

  - Treatment arms should also be balanced for psychosocial impact and subject's belief in efficacy

  - Don't underestimate the power of subject expectations **(placebo effect)**

Other Strategies for Treatment Arms

- What are appropriate controls or contrast treatment arms:

  - Standard of care

  - Sham treatment

  - Alternative, active procedure

- Escalating Dose-response arms

  - Assumption is improved outcomes with increasing dose

- Cross-over design: Treatment A -> Treatment B versus B -> A

  - Must leave sufficient time for "wash out" between treatments

  - Essentially, each subject serves as own control

  - Especially good for heterogeneous patient populations

- Delayed treatment: For each subject, establish initial baseline then examine treatment effects (analysis helps when dealing with heterogeneous subject populations)

Other Considerations in Treatment Arms

- Researcher must "sell" potential benefits of the treatment arm to the subjects enrolled in that treatment

    - Helps balance expectations, compliance (especially if placebo potential)

    - Avoids subjects dropping out after being randomized to the "wrong" group

- Balance quality of delivery (e.g., therapists) and support across each treatment arm

- If drug study, placebo pills should be matched for appearance, maybe even for well-known side effects of the expected drug

- Minimize potential for subjects within the study to compare notes with each other

- Consider debriefing subjects after study on their expectations as to which group they thought they were in whether they thought they were in the "preferred" treatment arm

Recruitment and Randomization

Recruitment

- A study a few years ago indicated that:

- $1.76 billion of $8 billion total annual clinical research spending is dedicated to patient enrollment efforts

- Only 1 out of 20 patients who respond to clinical trial recruitment promotions eventually enrolls in a study

- 85% of trials do not finish on time due to low patient accrual

  - 65-80% of U.S. clinical trials don't meet their end points, largely due to challenges in patient recruitment

  - 30% fail to enroll even a single patient

Targeting Study Participants

- Given the proposed mechanism of action, which range of subjects can realistically benefit?

- Special populations (women, minorities, elderly, rural, and poor) often require specially targeted plans with grassroots outreach activities

- A recent study showed that:

  - 1/3 of African-American women avoided clinical trials because they didn't trust scientists

  - 37% expressed a preference to be treated by an African-American doctor

  - Only 28% felt clinical research in the U.S. is ethical

To the Participants in an RCT, We:

- Admit that we don't know how best to treat their serious illness

- Introduce them to a lot of scientific jargon, and then ask them to sign a paper often agreeing:

  - to not take something that could help them

  - to take something that could harm them

  - that we will flip a coin to decide which treatment they get

And this process is called "Informed Consent"

What Study Subjects Want..

- A simple explanation of the study and translation of scientific jargon

- Clear understanding of what is expected of them

- Clear understanding of potential benefits and risks

- Whom to contact if they have questions or concerns

- To know that they can quit at any time

- To eventually find out about the results and outcomes of the trial

- And to feel appreciated and valued

Recruitment: Additional Considerations

- HIPAA compliance is time consuming and costly; budget sufficient staff and time

- Phone recruitment and access is more difficult due to use of caller ID

- Don't underestimate transportation and family issues

  - Costs and work-time lost by caregiver/transporter

  - Likelihood to remain in the area throughout trial

- Subject payment and reimbursement may be an appropriate budgetary cost on a research grant

- Consider complications due to pre-morbid interactions and secondary health complications

Recruitment Networks

- Consider networking with patient support and advocacy groups; build community trust

- Build recruitment networks among local clinicians and institutions

- Use of referral fees may raise ethical issues and create conflicts of interest for treating physicians

- Professional recruitment services have also sprung up to support clinical trials, but use them carefully

Why Randomize Assignment to Treatment Groups?

- To prevent investigator bias in distributing research subjects

- To prevent patient bias into "preferred" treatment

- To establish balance of subject characteristics at baseline

- To provide basis for statistical comparisons

However, subjects do not really like it . . .

Randomization Strategies

- Complete randomization ("coin flip")

- Objective algorithm to achieve balance across groups

- Ultimately want balance across:

- Disease severity, time since onset, and in the occurrence of associated and co-morbid conditions

- Gender, race/ethnicity, and age

- Across key physiological factors and major potential confounds

- Across socio-economic status (e.g., education level, resources)

Confounds: Concurrent Activities/Treatments

- Subjects may be taking other drugs or treatments, or may seek such treatments at some point after they enroll in study; what do you do?

  - Eliminate them through Inclusion/Exclusion criteria?

  - Ask them to voluntarily refrain from them during course of study?

    - Is this ethical? If so, what is appropriate washout period?

  - How do you ensure compliance?

    - Subjects may not admit to outside activities in order to get into or   remain in the study

    - Subjects may not want to disappoint the researchers

    - Consider blood tests, wireless monitors, or other objective ways to monitor compliance

- However, if concurrent treatments are really prevalent in the patient population, what is validity of a trial artificially suppresses access to them?

- Alternatively, allow access to other treatments but monitor as covariate

Recruitment: Concluding Remarks

- Don't underestimate how hard it is to recruit potential subjects

  - And to get them to actually enroll/consent into the clinical trial

  - And account for the possibility of subject drop out

- Document your catchment area and recruitment strategies

  - Demonstrate that you have access to sufficiently diverse population

- First-year approvals, logistics, training always take longer then expected

- Keep focused on maintaining recruitment goals throughout the study

- You may need to develop alternative recruitment strategies and broader catchment if recruitment falls behind

- And somehow your clinical trial will still fall behind in recruitment goals!

Outcome Measures

Outcomes: Initial Considerations

- Limit the number of primary outcomes

- Define which outcomes are primary vs. secondary

- Outcome measures should be at appropriate to the level of the intervention, and driven by your hypothesized mechanism of action

- Use outcomes that are widely accepted and clinically relevant (i.e., important) to the target patient populations

  - Use measures that have been validated for the subject population

  - This is probably not a good time to invent new measures

- Just because something can be measured does not mean that it is a necessary an appropriate outcome measure

Outcomes: Other Considerations

- Use measures that are most sensitive and selective for expected changes

- Avoid hitting ceiling or floor effects

- Limit the number of outcome measures in order to minimize subject burden and fatigue; avoid redundant measures

- Consider strategies to monitor change over time

- Minimize variability by doing assessment same time of day, same season

- Clinical trial should not take credit for what Nature does! That is, there may be some natural improvements over the course of the study due to disease progression and/or recovery processes

Outcomes: Other Considerations

- Timing: How soon after intervention should the outcomes be measured? How often?

- Consider follow-ups to test durability and robustness of treatment effect

- Ecological validity: Consider measures connected to real-world goals; outcomes that impact the subject's life

- Generalization: would clinical results extend to broader environments?

- Make sure that assessors are blinded as to which treatment arm the subject was in

  - Also make sure that the subjects do not accidently discuss their treatment assignment with the assessors

Building the Research Team

The Leadership Team

- Role of the PI; Possibly include Co-PIs

- Co-investigators may provide expertise to fully design, recruit, implement, and evaluate the trial

- If multisite, consider site-specific leaders

- Plan ahead!

  - Allow time for co-investigators to give input and edit the application

  - Know your institution's timelines/deadlines

  - If multisite, plan time to coordinate approvals across sites

  - Plan a timeline for writing and communicating with your team

  - Discuss authorship and publication of key research findings

  - It may take additional time to revise and resubmit the application

Statistical Expertise

- Get expert help and get it early, especially from those familiar with biomedical research and clinical trial design

  - Discuss your goals and hypotheses

  - Provide information on patient heterogeneity

  - Some sense of likely effect size and robustness of response

  - Discuss primary outcomes measures and their parametrics

- Provide sufficient time for discussion and be flexible in your design

- Together develop a power analysis (number of subjects required to get a conclusive answer)

  - Be willing to rewrite the hypothesis or scale-down the proposal if study appears to be underpowered

- Then add extra recruitment to account for potential drop-out

Other Key Team Members and Roles

- Research coordinator/project manager (at each research site)

- Clinical referral and recruitment staff

- Screener for eligibility, inclusion/exclusion criteria, and getting informed consent

- Clinicians/therapists delivering the respective treatment arms

- Outcome assessors (different and blinded from those delivering the treatments)

- Data manager and analysist

- Data safety and monitoring board (often independent of research team)

- Those involved in publication and dissemination of clinical trial findings

- Make roles and expectations clear from the beginning

- Have upfront discussion of potential publications, secondary papers, and authorship

- Keep your team psyched and engaged throughout the trial

- Provide feedback to your research participants, especially at end of trial
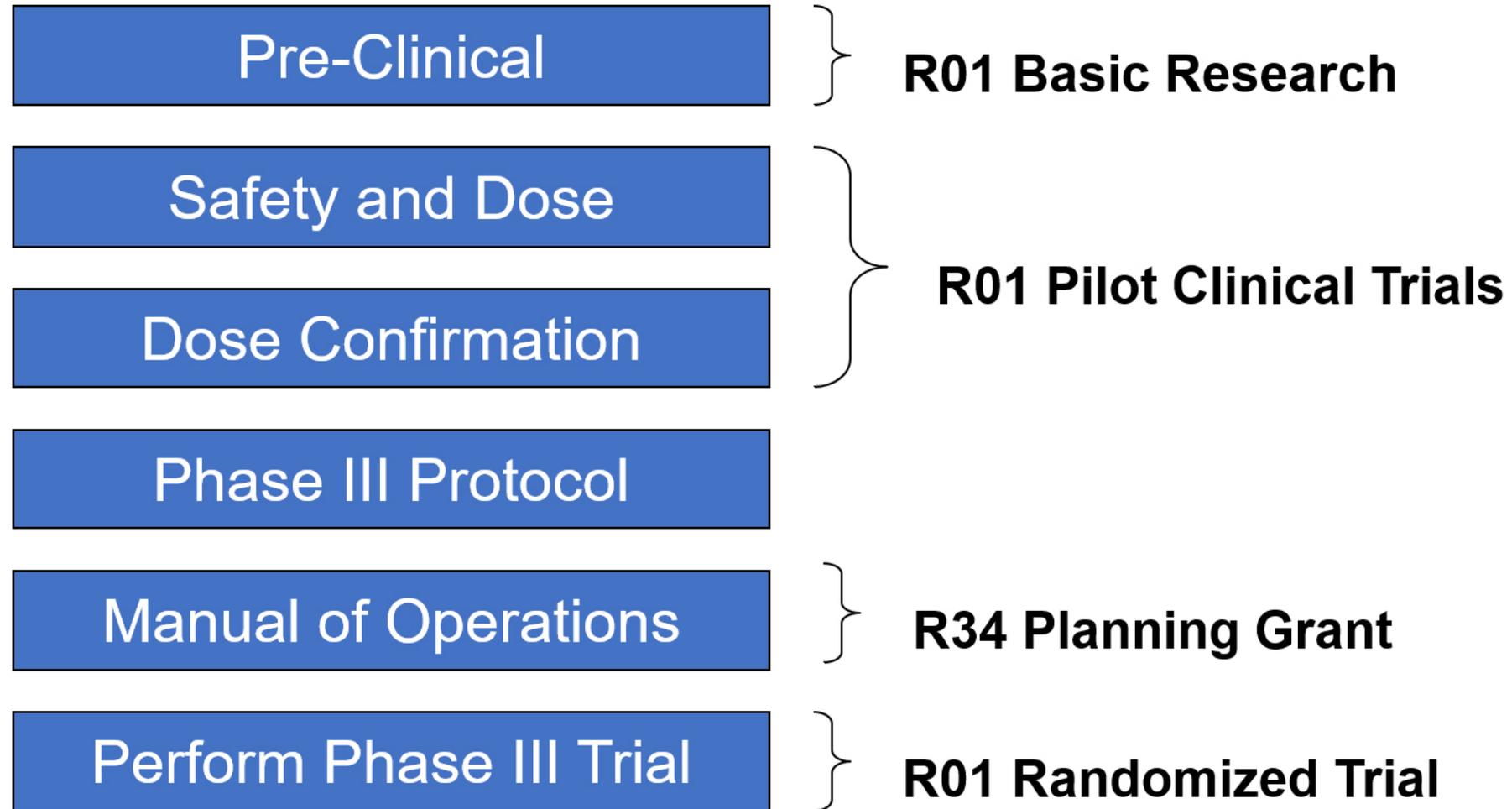
Developing an NIH Clinical Trials Research Application

Major Discussion Points

- Why should it be done?

  - Need, relevance, timeliness

  - Current practice perspectives and treatments

  - Expected impact of the results on practice

- Who is the target patient population?

  - Disease, condition, subgroups

  - Inclusion/exclusion criteria

  - Access to patient population and adequate recruitment strategy

- Phase of the trial: pilot to efficacy

  - Appropriate study design

  - Outcome measure(s)

- Likelihood of success

- Scalability of the results to real world? To broader clinical populations?

What Stage is your Clinical Trial?

Pre-Clinical	**R01 Basic Research**
Safety and Dose	**R01 Pilot Clinical Trials**
Dose Confirmation	
Phase III Protocol	
Manual of Operations	**R34 Planning Grant**
Perform Phase III Trial	**R01 Randomized Trial**

Human Subjects Research Issues

- Protection of human subject includes:

    - Risks to subjects

    - Adequacy of protection against risks

    - Importance of the knowledge to be gained

    - Potential benefits of proposed research to participants

    - Recruitment and informed consent strategies

    - Data and Safety Monitoring Plan

- HIPAA and Patient Privacy

- NIH Policies on appropriate inclusion of children, of women, and of racial/ethnic minorities in the subject population

Specific Review Considerations

- Adequacy of preliminary data and experience of applicant team

- Appropriateness of inclusion exclusion criteria

- Protection from Type I and Type II errors

- Power analysis and sample size

- Recruitment and retention strategies; evidence of ability to recruit the projected number of patients

- Randomization and blinding strategies

- Outcome measures and data analysis; data security

- Primary outcome measure(s) clearly defined; clinical relevance; hierarchy of other outcomes

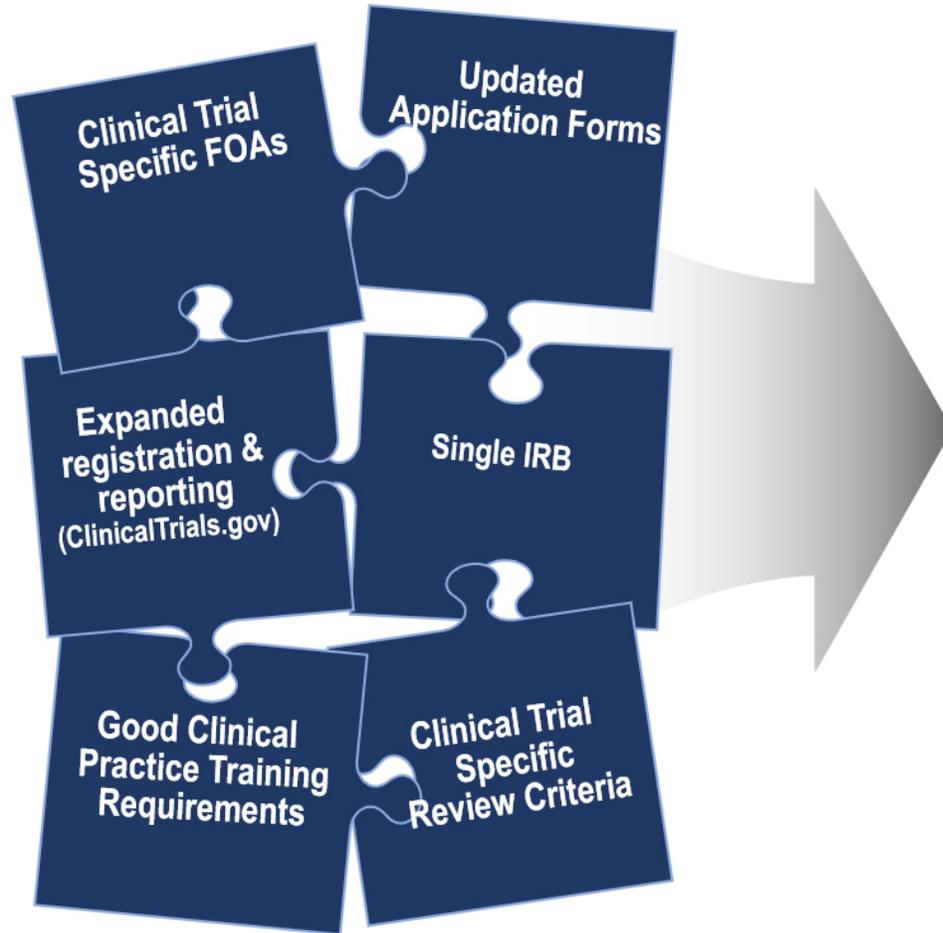# Top 10 Pitfalls in Clinical Trial Applications

10) Inadequate statistical expertise

9) Too many "outcomes" proposed

8) Overly restrictive inclusion/exclusion criteria

7) Insufficient resources and budget

6) Rush to propose efficacy trial, when more piloting/dosing required

5) Inadequate data management plans

4) Inadequate subject recruitment plans

3) Hypothesizing an unrealistically large treatment effect

2) Believing that submitting a lousy application will yield useful feedback from the review committee (First impressions count!)

1) Failing to consult with NIH staff before writing application

NIH Policy and Oversight of Clinical Trials Research

Enhanced Clinical Trial Stewardship

Learn more at https://grants.nih.gov/policy/clinical-trials.htm

Purpose of Reforms and Policy Changes

In 2016, NIH announced initiatives targeted to enhance and improve:

Efficiency

Enhance the efficiency of how research studies involving human participants are conducted

Transparency

Promote a culture of transparency in research in order to advance public health

Accountability

Ensure that NIH can appropriately identify and report on their clinical trials portfolio to ensure proper stewardship

Timely Reporting

Decrease the time it takes investigators to publicly report study results

Reforms and Initiatives

To enhance the stewardship of research involving human subjects, NIH implemented the following:

All Research Involving Human Participants

- New forms to collect human subjects information

- Use of a single Institutional Review Board (IRB) for multisite studies

- Certificates of confidentiality for all research that uses "identifiable, sensitive information"

Research that Meets the NIH Definition of a Clinical Trial

- Training in Good Clinical Practice (GCP)

- Clinical trial-specific Funding Opportunity Announcements (FOAs)

- New review criteria

- Expanded registration and results reporting in ClinicalTrials.gov

How Does NIH Define a Clinical Trial?
It's broader than you think!

A research study in which one or more **human subjects** are **prospectively assigned** to one or more **interventions** (which may include placebo or other control) to evaluate the effects of those interventions on **health-related biomedical or behavioral outcomes.**

Learn more at https://grants.nih.gov/policy/clinical-trials/definition.htm

Clinical Trial Checklist

Does your study…

- Involve one or more human subjects?

- Prospectively assign human subject(s) to intervention(s)?

- Evaluate the effect of intervention(s) on the human subject(s)?

- Have a health-related biomedical or behavioral outcome?

If "yes" to ALL these questions, your study will be considered a clinical trial by the NIH

Why do I Need to Know Whether my Study is a Clinical Trial?

It impacts whether you need to:

- Submit through a Funding Opportunity Announcement (FOA) **that allows clinical trials**

- Take **Good Clinical Practice Training**

- Address additional **review criteria** specific for clinical trials (e.g., study timeline and milestones)

- Use new **Application Packages** (FORMS-E)

- **Register and report** your clinical trial in ClinicalTrials.gov

Clinical Trial Designations for FOAs

All NIH Funding Opportunity Announcements (FOAs) will be designated as one of the following, in Section II of the announcement:

- Clinical Trial Required

- Clinical Trial Not Allowed

- Clinical Trial Optional

- No Independent Clinical Trials: *only for Career Development (K) & Fellowship (F) applications

   Tip: Contact your Program Official or the Scientific/Research contact listed in Section VII of the FOA to ensure you are submitting to the correct announcement

Good Clinical Practice Training Requirement

NIH expects all NIH-funded clinical investigators and clinical trial staff who are involved in the design, conduct, oversight, or management of clinical trials to be trained in Good Clinical Practice

Good Clinical Practice training establishes:

- Standards for clinical trial implementation, data collection, monitoring, and reporting

- Responsibilities of investigators, sponsors, monitors, and institutional review boards

Expectations for Good Clinical Practice Training

- GCP training can be achieved through several ways:

  - class or course

  - academic training program

  - certification from a recognized clinical research professional organization

- Training should be refreshed every 3 years to stay up to date with regulations, standards, and guidelines

- Recipients of GCP training are expected to retain documentation of their training and make it available to NIH upon request

Learn more at https://grants.nih.gov/policy/clinical-trials/good-clinical-training.htm

For Multisite Trials: Single Institutional Review Board (sIRB) Policy

NIH expects that all multisite studies, which involve non-exempt human subjects research, will use a single Institutional Review Board (sIRB) to conduct the ethical review required for the protection of human subjects

sIRB policy aims to:

- Streamline IRB review process to enhance research efficiency

- Reduce unnecessary administrative burdens and inefficiencies

Learn more at https://grants.nih.gov/policy/clinical-trials/single-irb-policy-multi-site-research.htm

What Does the sIRB Policy Apply To?

- Domestic sites of NIH-funded multisite studies where each site will conduct the same protocol involving non-exempt human subjects research

- Includes research supported through:

    - Grants

    - Cooperative agreements

    - Contracts

    - NIH Intramural Research Program

- sIRB policy does not apply to career development, research training, or fellowship awards

Updated Certificates of Confidentiality Policy

- Requires investigators to only disclose information under specific circumstances

Certificates will be issued automatically for any NIH-funded project using identifiable, sensitive information

- Eliminates the need for NIH funded investigators to apply for a Certificate

- Enhances privacy protections of individuals participating in NIH-funded research

- Applies to NIH awards funded wholly, or in part, by NIH

- Disclosure restrictions also apply to anyone who receives a copy of identifiable sensitive information protected by the policy, even if they are not funded by NIH

- Certificate is issued as a term and condition of award (no physical certificate)

Learn more at https://humansubjects.nih.gov/coc/index

NIH Policy on Dissemination of NIH-Funded Clinical Trial Information

- All clinical trial applications requesting support for a trial must register and report the results in ClinicalTrials.gov

- NIH dissemination policy:

  - Extends previous HHS laws and regulations to apply to all NIH-funded clinical trials, including the defined subset of "applicable clinical trials"

  - Increases availability of information to the public about clinical trials

Learn more at https://grants.nih.gov/policy/clinical-trials/reporting/index.htm

Registering and Reporting Requirements for ClinicalTrials.gov

In order to comply with the NIH Policy on Clinical Trial Dissemination, awardees must:

- Submit a plan in the application that outlines compliance with the expectations of the policy

- Register the clinical trial no later than 21 days after enrolling the first participant

- Submit summary results no later than one year after primary completion date