CLINICAL PROTOCOL DEVELOPMENT SERIES (DAY 1)

Kim Brownley, PhD, CIP
Joyce M. Lanier, MSRC, RRT, CCRC

Online Logistics - Questions

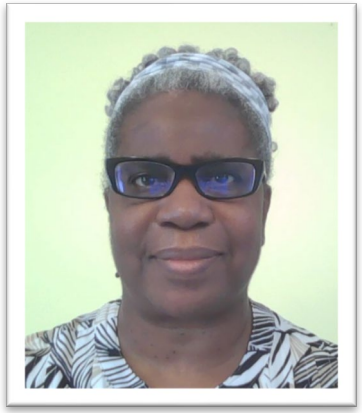
- To avoid connectivity issues, we ask that participants please turn off their video.
- Please enter questions using the chat function. We will be monitoring the chat and saving questions until the end.
- Any questions we do not get to will be compiled into a Q&A document and distributed to registered attendees.

Protocol Development Support Team

NC TraCS Team

Kim Brownley PhD, CIP
Co-Director

Marie Rape RN, BSN, CCRC
Associate Director

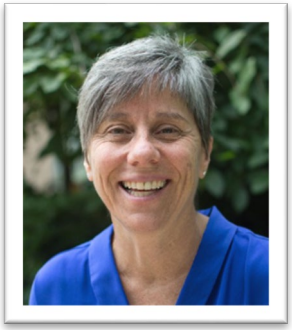


Joyce M. Lanier, RRT, MSRC, CCRC
Protocol & Quality Assurance Specialist

Office of Clinical Trials

Monica Coudurier, BA
Clinical Trials
Project Manager

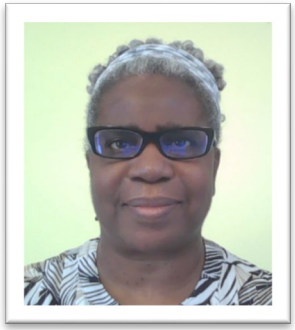
Objectives for Day 1



Kim Brownley PhD, CIP

Faculty Co-Director,
TraCS Regulatory Service

- Discuss how a clinical protocol differs from a grant or IRB application
- Explain clinical protocol requirements at UNC
- Review how a protocol is helpful to researchers
- Describe the Scientific Review Process at UNC



Joyce M. Lanier, RRT, MSRC, CCRC

Protocol & Quality Assurance Specialist

- Review available protocol templates and resources
- Discuss expectations for protocol section
- Provide resources for support

Grant Proposal vs Protocol – Key Differences

GRANT

Rhetorical document, comparable to an artist's painting of a concept car or a rendering of an architectural vision

- Page limitations per funder
- Document to propose an idea worth funding
- Summary of clinical plan
- May include a component for training researchers

PROTOCOL

Analytic document, comparable to a schematic drawing or recipe meant to present an effective plan for study conduct and data analysis

- No page limitations
- Sections describe all aspects of clinical plan
- Roadmap for study teams to implement study
- Dynamic document (updates, changes)

What is a Clinical / Research Protocol?

A document that describes:

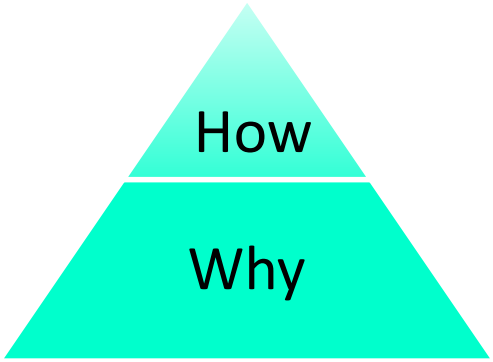
Why a study will be conducted

- Background and rationale
- Objectives and aims

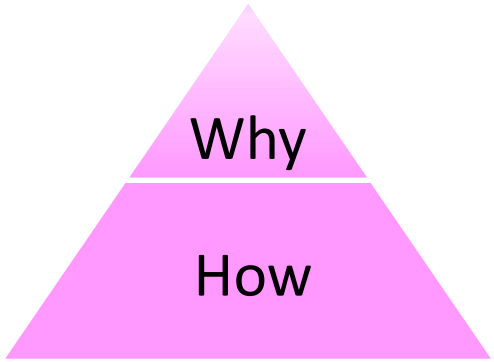
How, when, where, by whom a study will be conducted

- Design
- Methodology
- Statistical considerations
- Organization of the project

Grant Proposal



Protocol



How is a Protocol Helpful?

Helps PI translate scientific aims into actionable steps and clear deliverables/outcomes

Standardizes processes and provides a detailed plan for the study team to implement

- Clarifies role responsibilities (who does what, when, and how)
- Reduces noncompliance/unanticipated problems and helps ensure
  - The safety of the trial subjects
  - The integrity of the data collected
- Multicenter trials – all sites follow same protocol (rigor, reproducibility)

Source material for other submissions (CT.gov, IRB, future manuscripts)

Facilitates IRB Review

- More details
- Cross-reference (“see protocol section X.X”)

Why Require a Protocol?

- **FDA** IND or IDE submission
- **NIH** clinical trial grant submission (protocol synopsis)
- **Single IRB review** many IRBs require a protocol (not just IRB application)
- ClinicalTrials.gov registration & results reporting
- **UNC** = “industry standard” for scientific review

UNC Scientific Review Policy

All **clinical** research conducted at the University of North Carolina at Chapel Hill involving **greater than minimal risk** must undergo scientific review.

Industry-sponsored, multi-site trials generally excluded

Scientific Review – Why?

Regulatory Criteria to Approve Humans Subjects Research:

- ***Risks are minimized*** through ***sound research design***.
- ***Risks are reasonable in relation to anticipated benefits*** and the ***importance of the knowledge*** to be gained.

There is ***no acceptable risk*** to human subjects ***in the absence of valid scientific benefit***.

UNC Scientific Review – Who?

- Externally by an independent organization that has no COI with the research activity
  - Not NIH study section
  - Not Foundation peer review
- LCCC PRC for oncology research ★
- UNC SRC for all other clinical/biomed research ★

★ **Both require a protocol!!**

PRC Process

PI may request support from the Clinical Development Team

PI submits protocol and cover sheet (w/ biostatistician sign-off if an IIT) to PRC coordinator christinegrace_narag@med.unc.edu

PRC Coordinator previews submission, assigns to the next available PRC meeting (every 2 weeks)

Study team attaches the PRC approval letter to the IRB application and submits

SRC Process

PI may request help from the TraCS Protocol Specialist

PI submits protocol to SRC coordinator UNC Office of Clinical Trials *SRC Portal*

SRC Coordinator and Chair evaluate protocol "readiness"

"Ready" protocols assigned to 3 reviewers, 1 to 2 weeks turnaround

Post review: Investigator advised of next steps

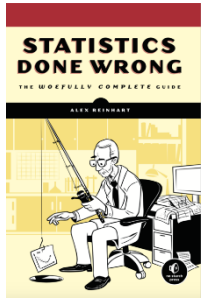
Revise, resubmit	Submit to the IRB

WHO ARE THE CURRENT SRC MEMBERS?

Chair **Eric T. Everett, PhD** (*Oral/Dental/Craniofacial, Genetics*)

Biostatisticians

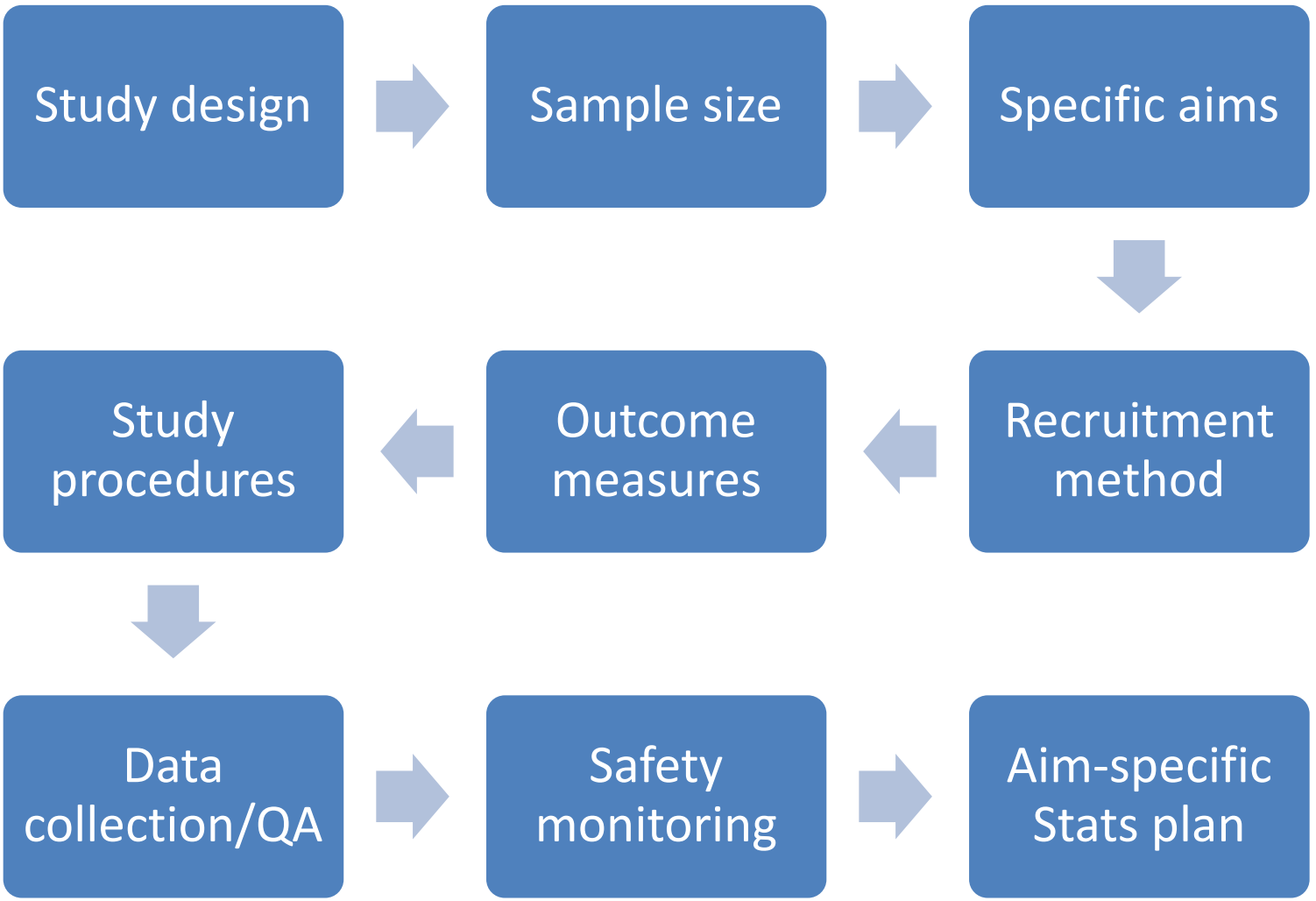
Feng-Chang Lin, PhD, Jipcy Sulbaran, PhD *Candidate*



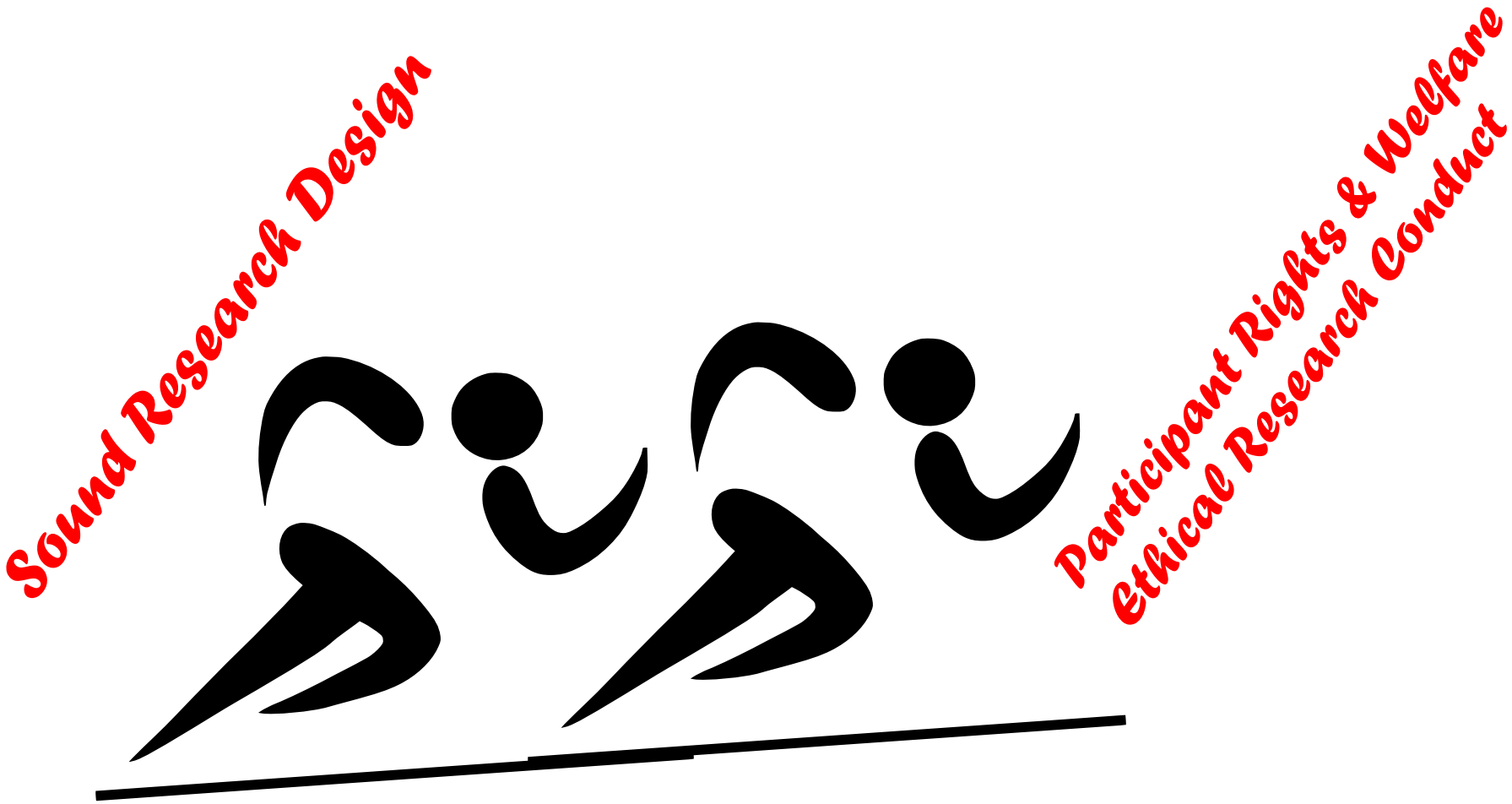
Reviewers

- **Kim Brownley, PhD, CIP** (*Psychology, Mental Health, HSR-regulations*)
- **Christne Chu, MD, MPH** (*OB-Gyn, Urogynecology*)
- **Michelle Floris-Moore, MD, MS** (*Infectious Diseases*)
- **Marianne Muhlebach, MD** (*Pediatrics, Pulmonology*)
- **Claudia M. Testa, MD, PhD** (*Neurology, Genetically-based Therapeutics*)
- **Michael Wagner, PhD** (*Genetic Medicine, Pharmacogenetics, Genomics*)
- **Laura Young, MD, PhD** (*Endocrinology*)

SRC's Focus – Alignment



SRC and IRB Reviews are Complementary



Protocol Templates, Resources & Case Scenarios

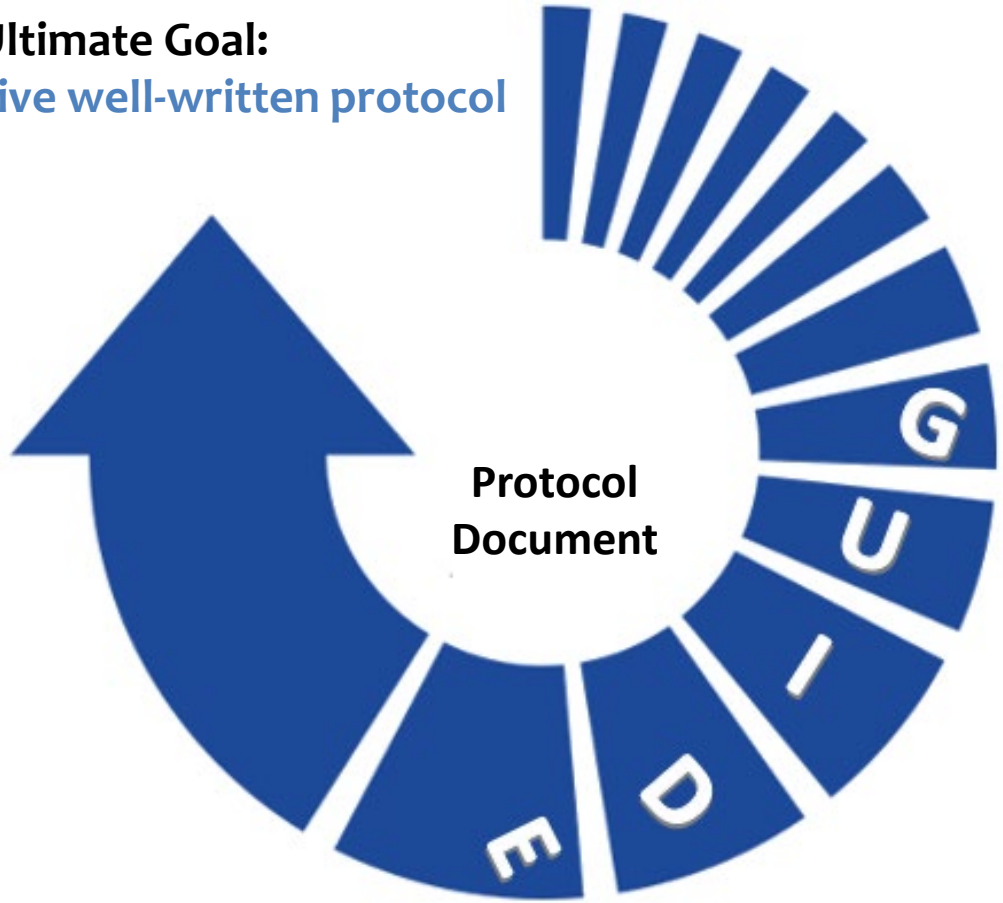
Joyce M. Lanier, MSRC, RRT, CCRC

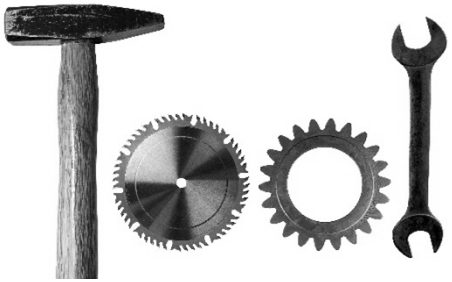
Protocol & Quality Assurance Specialist

North Carolina Translational & Clinical Sciences Institute

Why Use a Protocol Template?

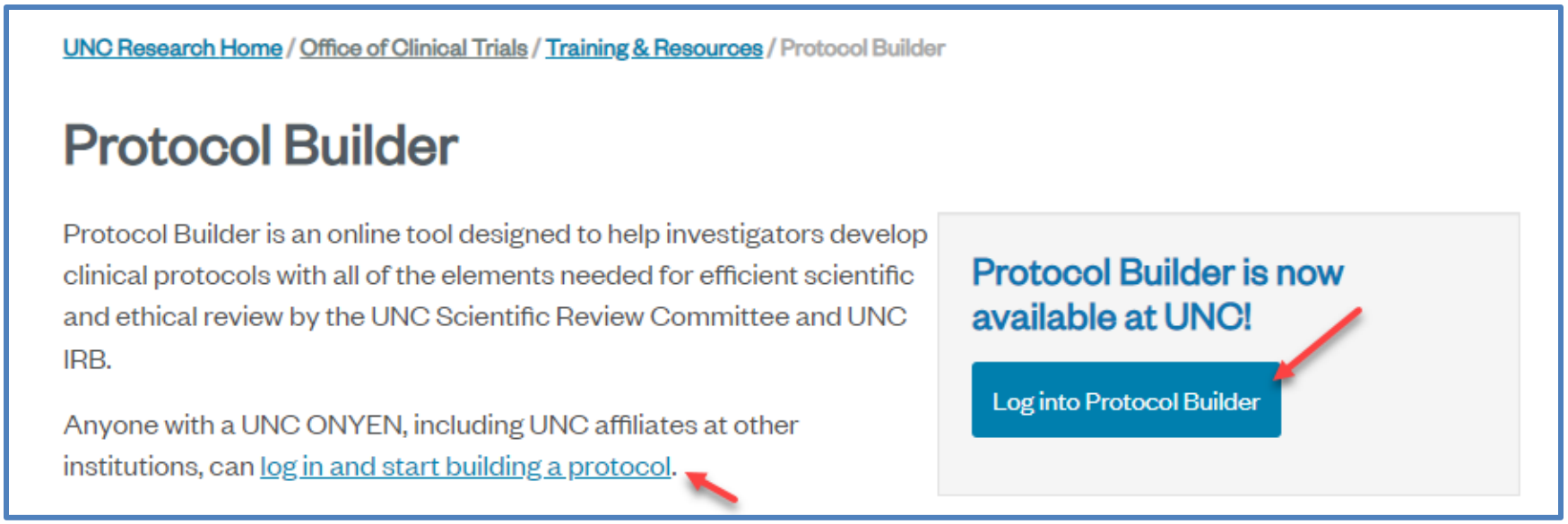
Ultimate Goal:
Comprehensive well-written protocol





To guide investigators through the systematic development of the document.

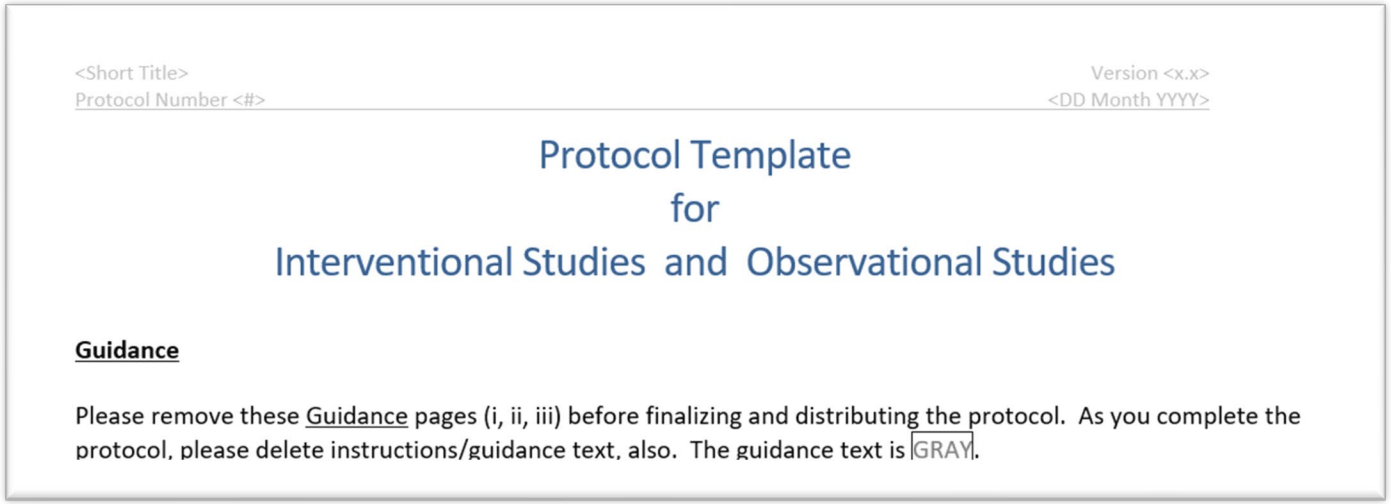
Protocol Builder Tool



Link: https://research.unc.edu/clinical-trials/training/protocol-builder/

PB administration contact: src@unc.edu

SRC Protocol Development Tips & Resources



https://research.unc.edu/clinical-trials/src/protocol-development/

SRC Protocol Development Tips & Resources

UNC Master Protocol Document Template

NIH-FDA Protocol Template

BSSR Protocol Template

Registry Repository Protocol Template

https://research.unc.edu/clinical-trials/src/protocol-development/

TIPS for Speedy Scientific Review

- Submit protocol to SRC early
- Pick the right protocol template . . .

- Cleary describe relationships and roles of the:
  - Sponsor
  - Institution
  - Investigator
  - IRB
  - Research Partners
- Clearly describe the investigational drug/device status
- Address all elements per the protocol template
- Be consistent (aims→ procedures → measures → analyses)

Clinical Protocol Templates (LCCC)

https://unclineberger.org/protocolreview/forms/
Writing Your Protocol - Investigator Initiated Trials (IITs) (unclineberger.org)
Investigator Initiated Trials (IITs) - Investigator Initiated Trials (IITs) (unclineberger.org)

Clinical Protocol Templates (LCCC)

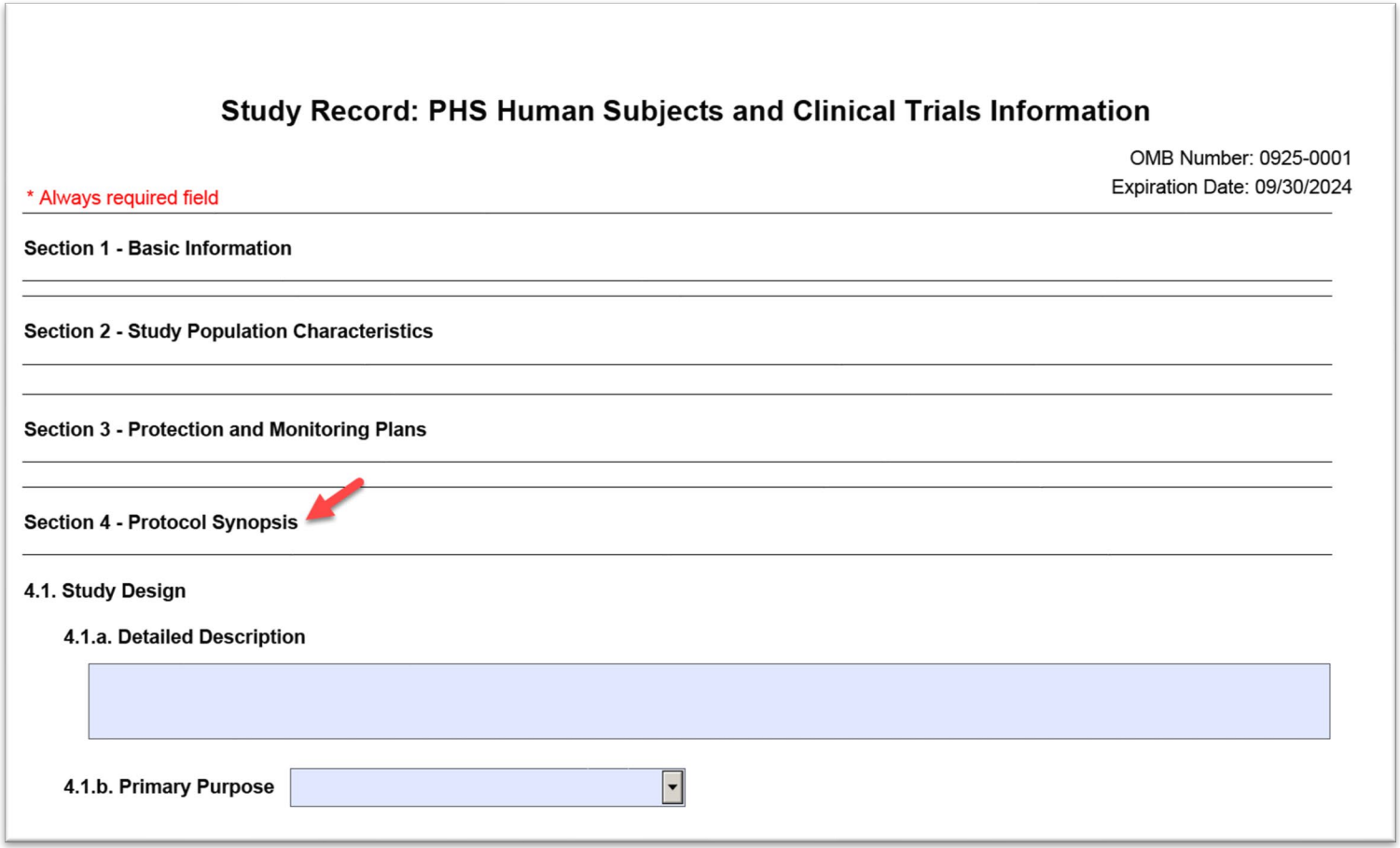
- Chemotherapy Treatment Protocol Template
- Cellular Therapy Protocol Template
- Health Services Research Protocol Template
- Imaging Study Protocol Template
- Biospecimen Protocol Template
- Radiation Treatment Protocol Template

Writing Your Protocol - Investigator Initiated Trials (IITs) (unclineberger.org)

Additional Protocol Templates

1. Protocol Templates and Guidelines | Protocol Development | CTEP (cancer.gov)
2. nidcr-clinical-trial-interventional-protocol-template.dotx (live.com)
3. Protocols and Informed Consent | NIH: National Institute of Allergy and Infectious Diseases

Additional Protocol & Template Resources



Study Record: PHS Human Subjects and Clinical Trials Information

OMB Number: 0925-0001
Expiration Date: 09/30/2024

* Always required field

Section 1 - Basic Information

Section 2 - Study Population Characteristics

Section 3 - Protection and Monitoring Plans

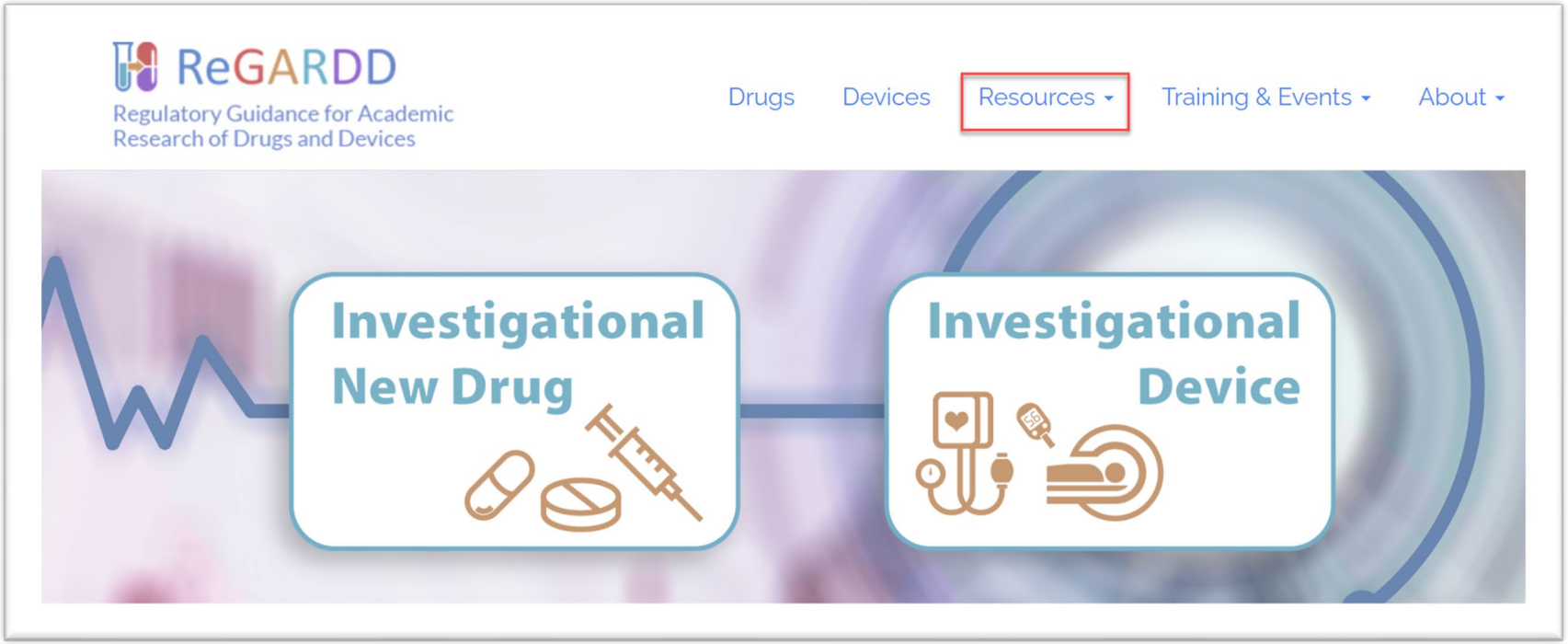
Section 4 - Protocol Synopsis

4.1. Study Design

4.1.a. Detailed Description

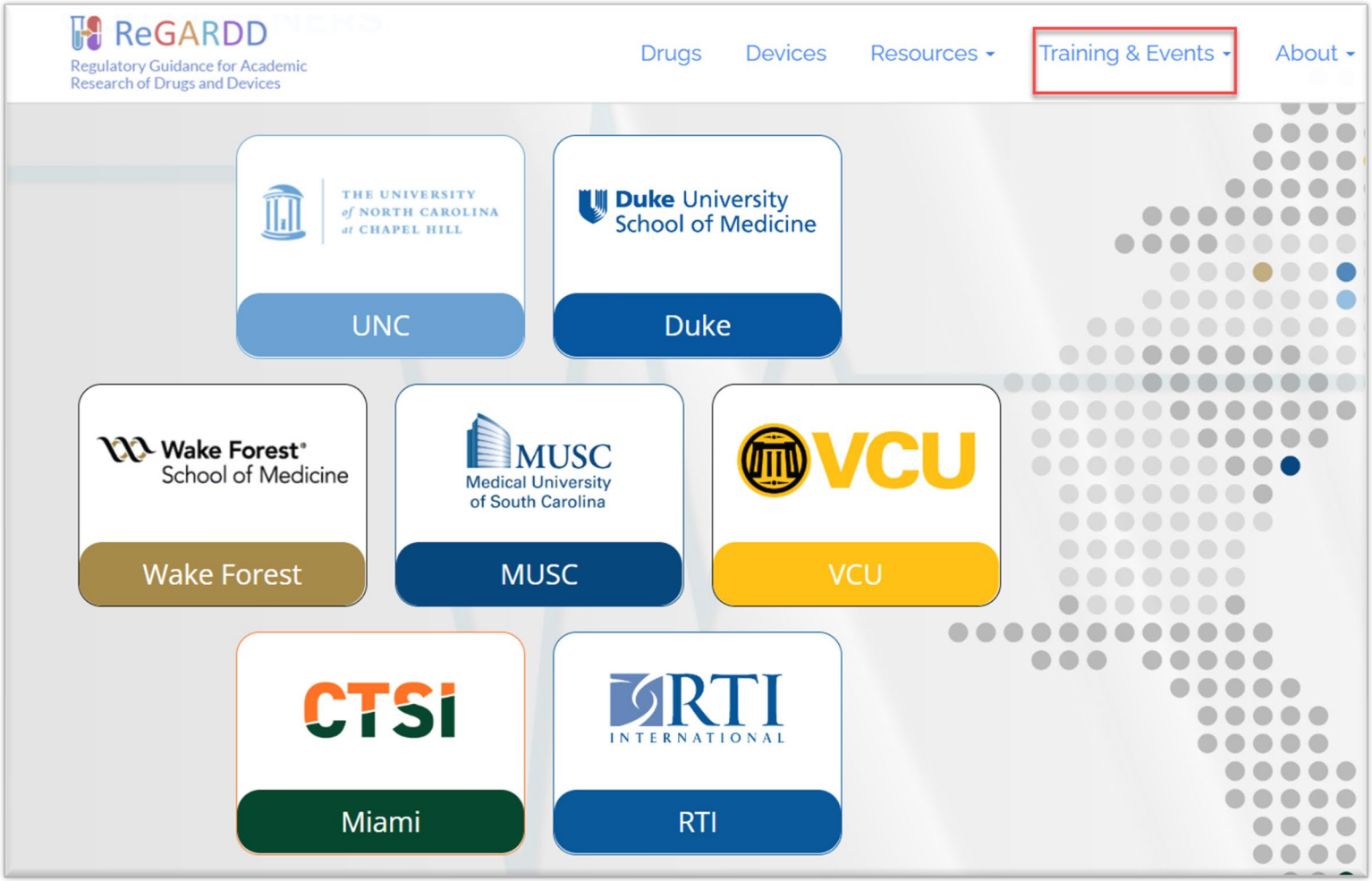
4.1.b. Primary Purpose

Additional Protocol & Template Resources



[ReGARDD.org (unc.edu)]
http://regardd.org/resources
ReGARDD - Regulatory Guidance for Academic Research of Drugs and Devices

Additional Protocol & Template Resources

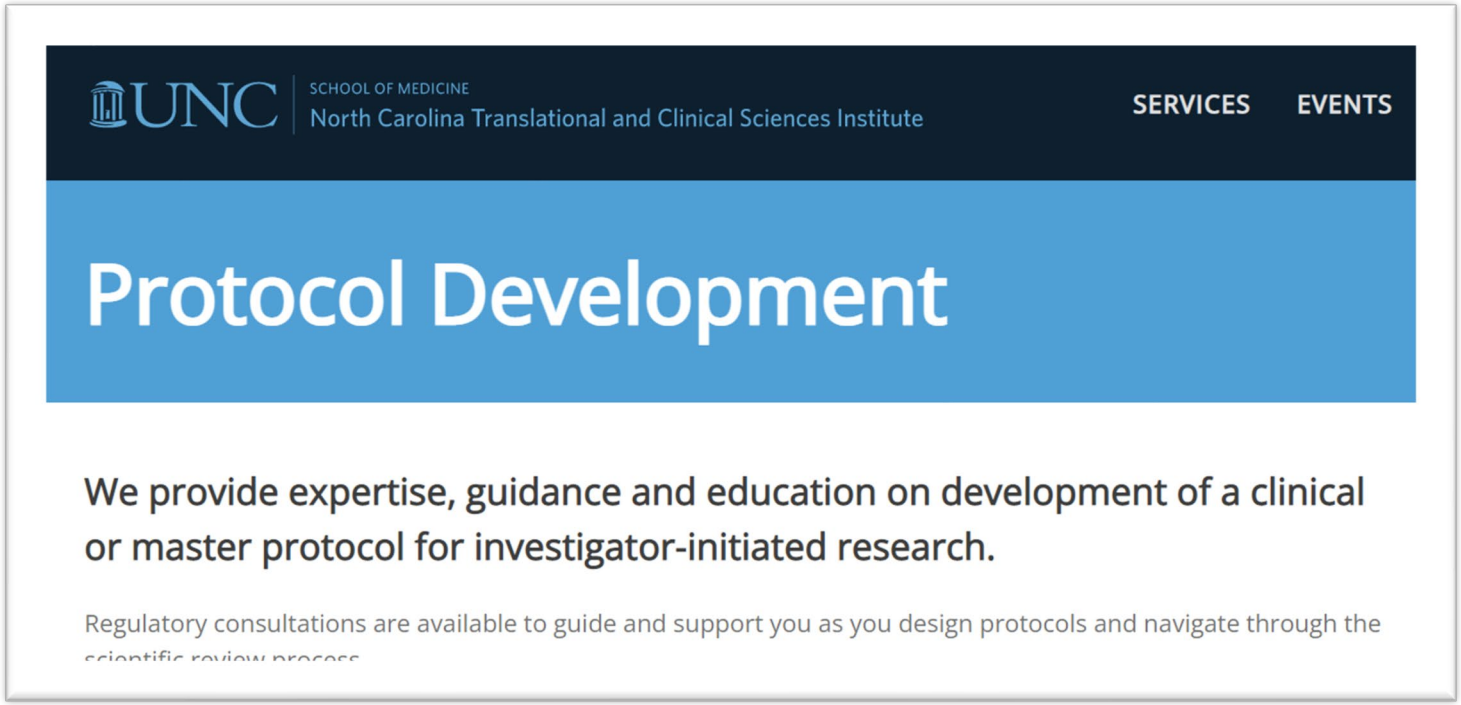


Additional Protocol & Template Resources

CITI Optional Module –
Research Study Design:
https://www.citiprogram.org/

Additional Protocol & Template Resources

TraCS Regulatory:



https://tracs.unc.edu/index.php/services/regulatory/protocol-development

Additional Protocol & Template Resources

Protocol Development Services

Virtual consultation services

Provide protocol templates

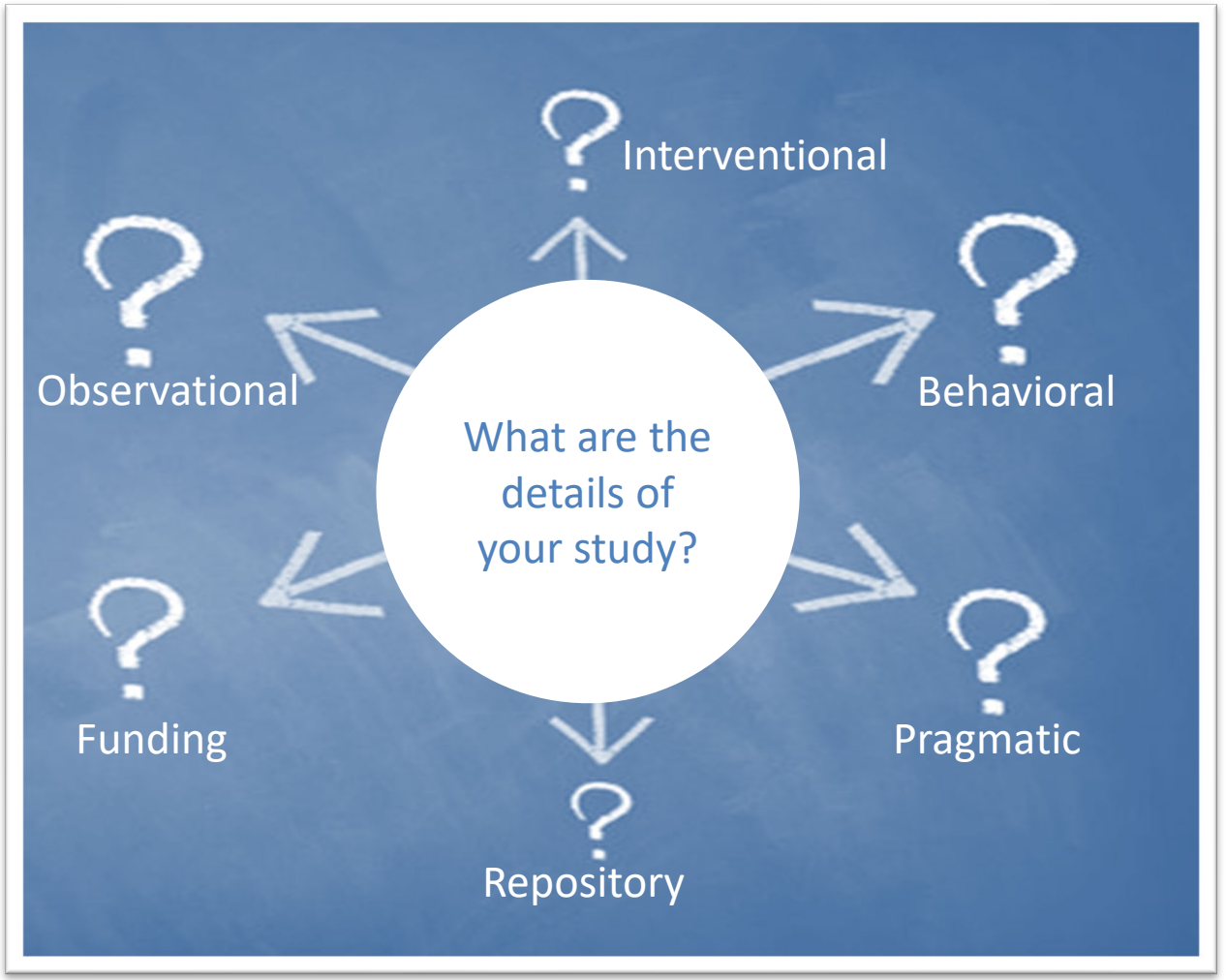
Protocol review with annotated recommendations

Assist PI & study team with review committee responses

Protocol writing services – *Fee for Hire*

Joyce Lanier (Protocol Specialist) –
joyce_lanier@med.unc.edu

Choosing Appropriate Protocol Template



Interventional vs. Observational Studies

- **Interventional:** Participants are assigned (based on the randomization of the research study) to groups that receive one or more intervention / treatment (or no treatment) so researchers can evaluate the effects of the intervention on biomedical or health related outcomes. Assignments are determined by the protocol / study participation (typically prospectively assigned).
- **Observational:** Researchers observe the effect of a risk factor, diagnostic test or treatment or other intervention without trying to change who is or isn't exposed to it. Subjects receive treatment via standard of care typically determined by their health care provider (NOT assigned by study) .

Anonymous Case Scenario Poll #1

Study 1 is comparing the impact of **Drug A** versus **Drug B** for physiological changes in the liver.

Study Aim: To characterize changes in liver microbiome structure

Inclusion Criteria: Diagnosis of liver disease; Clinical decision to start Drug A or Drug B

Study Design: 4 study visits after starting the drug which includes specimen collection and the administration of questionnaires

Is this an interventional or observational study?

Case Scenario Poll #1 (Revised)

Study 1 is comparing the impact of **Drug A** versus **Drug B** for physiological changes in the liver.

Study Aim: To characterize changes in liver microbiome structure

Inclusion Criteria: Diagnosis of liver disease; Clinical decision to start Drug A or Drug B where drug has been prescribed by the treating physician as standard of care prior to enrollment.

Study Design: 4 study visits after starting the drug which includes specimen collection and the administration of questionnaires

Is this an interventional or observational study?

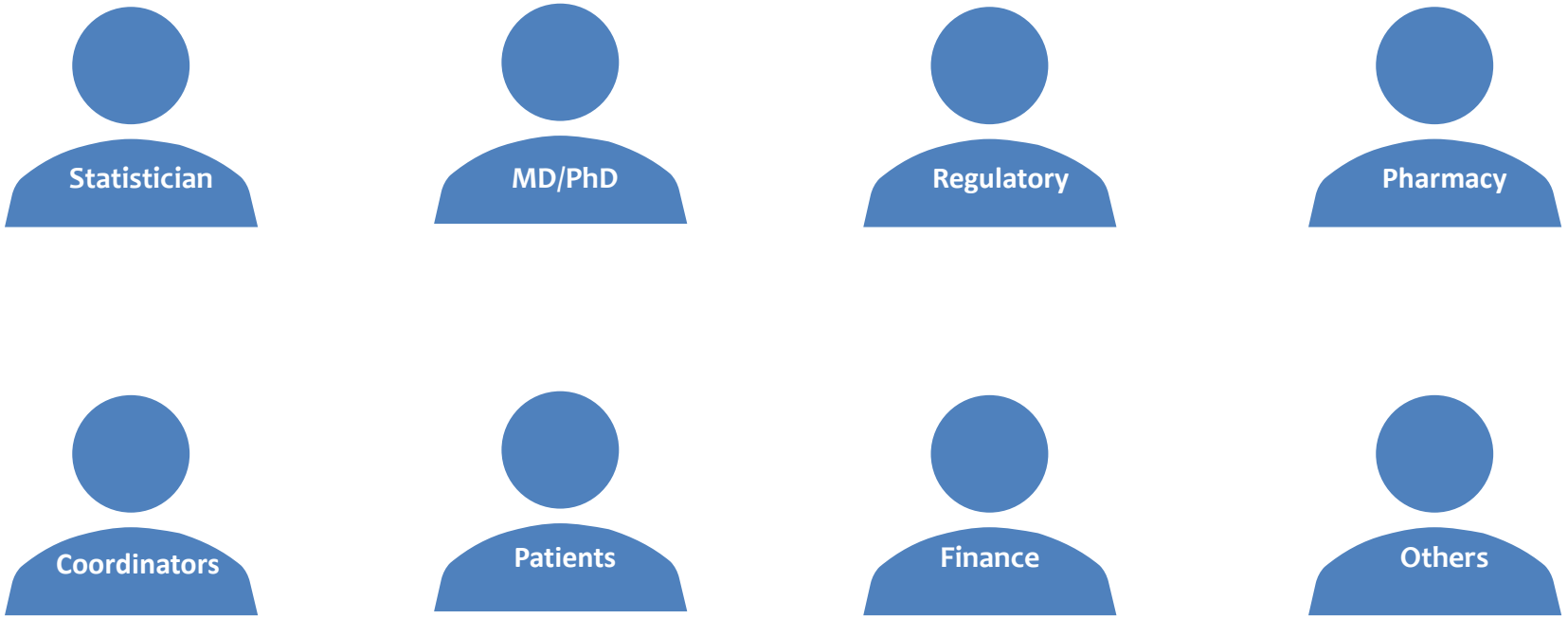
Pragmatic Trial = Clinical Trial = Interventional

- ***Pragmatic trial***
  - Typically randomized and controlled, but participants often randomized at the group level (hospital, nursing home, clinic) with a similar group matched as control group.
  - Purpose is to inform decisions about practice
  - Designed to evaluate the effectiveness of interventions in real-world clinical settings.

- Recommend use of an Interventional Protocol Template
- Resource: Pragmatic Elements: An Introduction to PRECIS-2 - Rethinking Clinical Trials

Break Time

How to Develop a Protocol



Additional tips:

- ❑ Anticipate several drafts of the protocol
- ❑ Check for consistency across protocol

Basic Protocol Template Outline

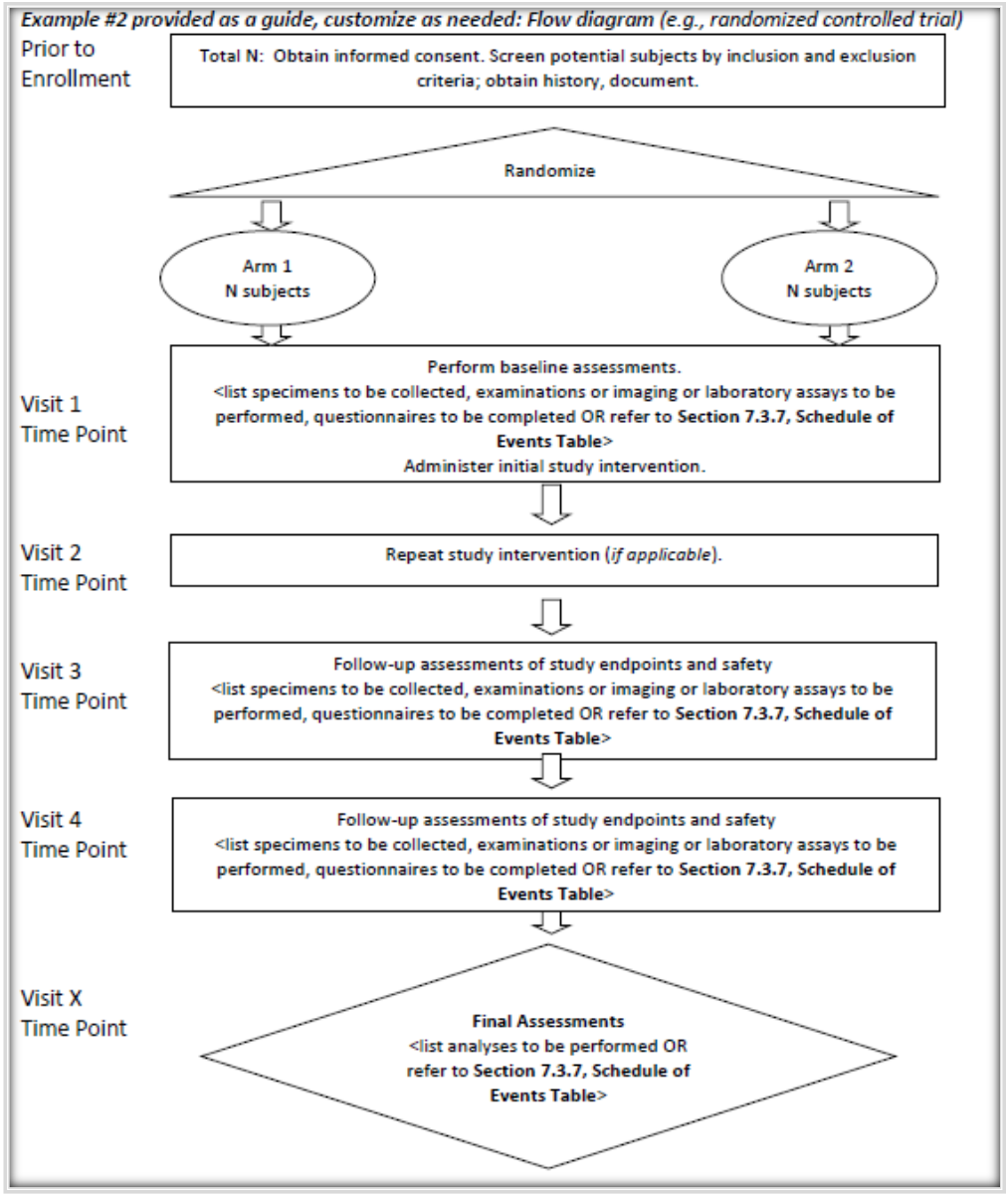
- Title Page
- Table of Contents
- Abbreviations
- Protocol Summary
- Study diagram, SOE
- Introduction (Background, Rationale, Risk/Benefit)
- Study Objectives, Endpoints
- Study Design
- Study Population (I/E criteria)
- Study Intervention Administration
- Assessments & Procedures
- Adverse Event & Safety Management
- Statistical Considerations
- Recruitment Strategy
- Consent Process
- Study Team, Oversight, Monitoring
- Data Collection/Management
- References
- Appendix

Protocol Summary or Synopsis

Limit to 1-2 pages – brief, concise, specific

Title:	**Include type of trial (e.g., dose-ranging, observational, double-blind)**
Phase:	**I, II, III, IV**
Population:	**Include sample size, gender, age, general health status, geographic location**
Number of Sites:	**3 or fewer, list here; otherwise, list only in Section 1**
Study Duration:	**Provide time from when the study opens until the monitor completes the close out visit.**
Subject Participation Duration:	**Provide time it will take to conduct the study for each individual participant.**
Description of Agent or Intervention:	**Include dose and route of administration**
Objectives:	**Copy objectives and clinical/laboratory outcome measures from the appropriate sections of the protocol. Include primary/secondary outcome measures and method by which outcome will be determined.** **Primary:** **Secondary:**
Description of Study Design:	**This schematic should provide an overview of the study design, including study arms, sample size and schedule of interventions (e.g., vaccine administration), if applicable;**

Study Schema



Study Schema: Dose Escalation Study (Phase I)

Dose Escalation Schedule	
Dose Level	**Dose of [IND Agent]***
Level 1	
Level 2	
Level 3	
Level 4	
Level 5	

* Doses are stated as exact dose in units (e.g., mg/m^2, mcg/kg, etc.) rather than as a percentage.

Schedule of Events / Activities (SOE)

	Pre-screening (Pre-consent)	Visit 1 Day 1	Visit 2 Day 14 ±7	Visit 3 Day 28 ±7	Visit 4 Day 42 ±7	Visit 5 Day 56 ±7	Visit 6 Day 365 ±30	Unscheduled Visit
EMR Review Eligibility	X							
Informed Consent		X						
Demographics		X						
Clinical history		X					X	
Height & Weight		X	X				X	
Outcome Evaluation								
Assessment		X			X		X	X
Questionnaire		X	X	X	X	X	X	
Randomization		X						
Control & Experimental Interventions		X	X	X	X			
Adverse Events Reporting		X	X	X	X	X	X	X

Introduction

Study Rationale
(*state the problem or research question*)

Background
(*summary of relevant clinical research*)

Known Risks
(*potential risks from clinical or nonclinical studies*)

Known Potential Benefits
(*relevant published data*)

Background/Rationale

Before:

Condition P is common and causes enormous human suffering and societal cost. P is the leading cause of psychiatric morbidity among minority US women. There is a need for culturally sensitive P treatments that can reach large numbers of women. This study proposes to use a mobile device app to deliver intervention for P.

Background/Rationale

What SRC Reviewers Look For…

There must be **thoughtful justification** for conducting a study. It should draw upon results from **previous or pilot studies** and investigator experience to identify knowledge gaps, and devise a strategy to answer one or more questions - while maximizing resources and minimizing burden on participants.

Background/Rationale

After:

Childbirth is a potent trigger for the condition, P, with potentially harmful outcomes for mother and child. Prevalence of P is estimated at 5% in Western societies but may be as high as 35% in minority women living in the southeastern US, especially among women in rural counties. The main feature of P is depression. Six of 8 women in our pilot feasibility study found the mobile app (called P-I) easy to use and helpful for dealing with feelings of depression. This study will assess feasibility and efficacy of P-I for mothers with P living in rural NC.

Study Objectives & Endpoints

What answers are you searching for through the conduct of your study?

Study Design

General Overview of the Study Features

Type: Randomized Clinical Trial, Observational, Cross-sectional, Parallel arm, Open-label

Single site or multi-site (and # sites)

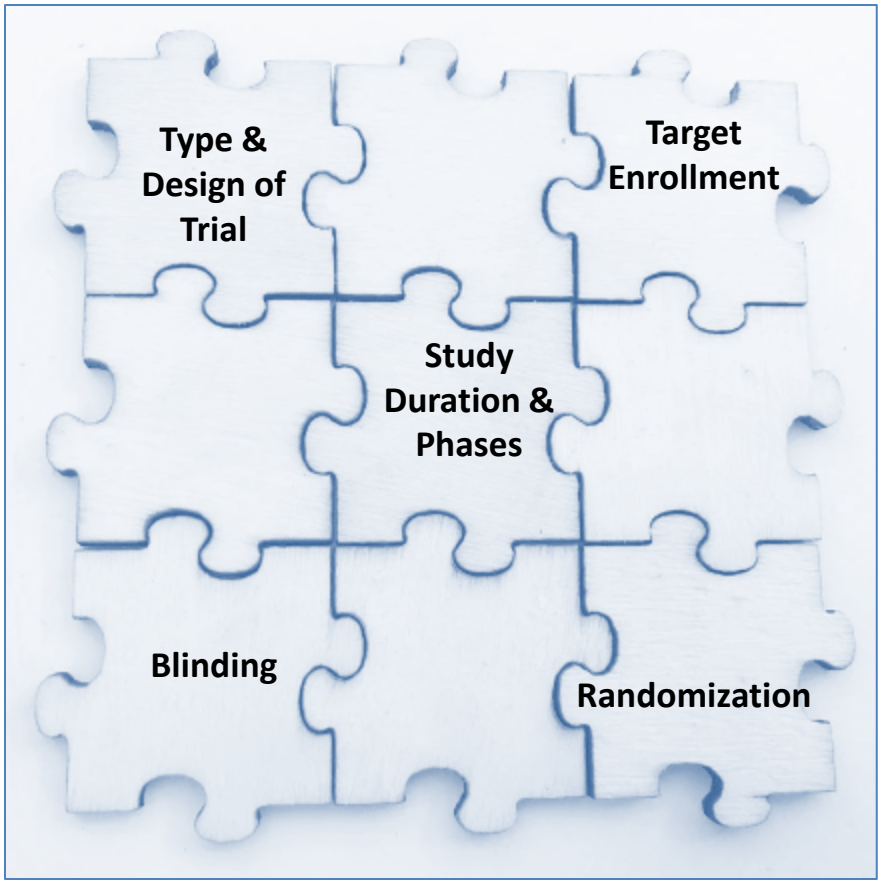
Target: # of participants, # of groups/arms

Randomization: method for assigning participants to study groups/arms

Blinding: Will there be blinding, who blinded (PI, subjects?)

Duration:

- Screening/baseline
- Intervention/treatment
- Follow up, Unscheduled visits



Study Population

Eligibility Criteria

Inclusion & Exclusion Criteria

- All aspects of selection procedures
- Specific criteria on who is and is not eligible
- I/E criteria both for scientific and safety purposes

Recruitment Retention

Strategies

- Summarize, can refer to detailed plan in manual of procedures
- TraCS Support
  - Recruitment Specialist (Summer Choudhury)
  - Community & Stakeholder Engagement (Alicia Bilheimer)

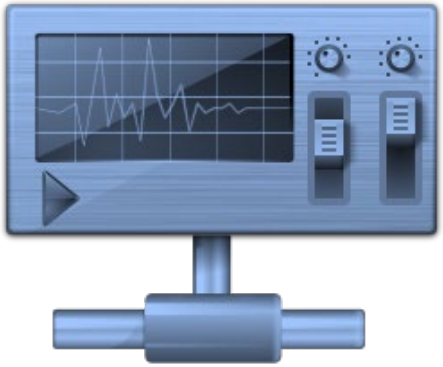
Recruitment Strategy

What are the strategies for achieving adequate participant enrollment in order to reach the proposed sample size?

Study Intervention

Drug

Device



Behavior Modification

This section has sub-sections to describe…..

- administration of the study intervention, dosing, or info on the experimental manipulation
- preparation handling and storage of the product or device,
- randomization & blinding, placebo/control
- intervention compliance

Study Assessments and Procedures

- **Efficacy Assessments** (evaluations done to support determination of efficacy of the intervention on study endpoints)
  - Biological specimen collection, PKs, physical measures
  - Assessments of intervention adherence
  - Survey and interview data

- **Safety Assessments** (study procedures and evaluations done to monitor safety)
  - Physical Exams, Vital signs, EKGs, X-rays
  - Laboratory evaluations
  - Adverse event monitoring

Adverse & Serious Adverse Event Section

Include descriptions **specific** to your study (not boilerplate)

- Plan on how AEs / SAEs will be assessed by study team
- Specific events to monitor, based on what is known & expected from intervention (e.g., kidney or liver affects)
- Events that lead to stopping intervention in participant
- Events leading to stopping entire study
- Classification scale to evaluate severity of adverse events
  - e.g., GI side effects → nausea, vomiting, hosp. for dehydration

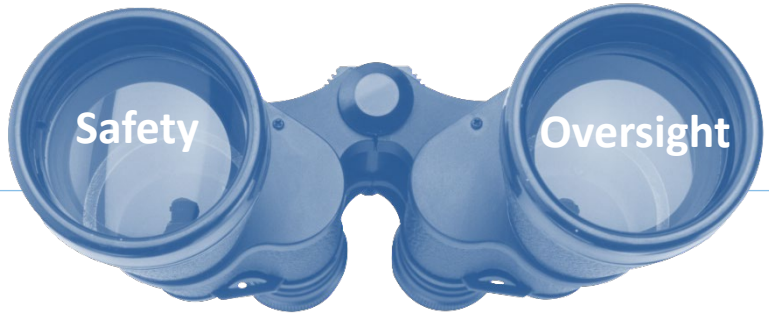
Evaluating Severity of AEs

When it comes to evaluating adverse events, you should have a scale to grade the **severity**, a **classification scale.**

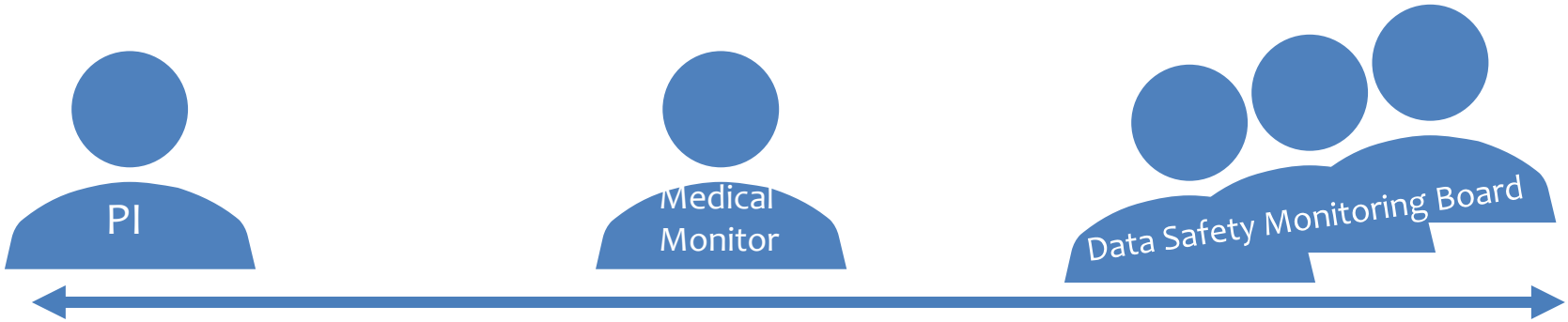
- Mild-Moderate-Severe Scale
- CTCAE scale (5 levels of severity)
- DAIDS AE Grading Table
- Other Specific Scale

The classification scale should be described in the protocol and used consistently for all subjects and by all investigators.

Safety Oversight



Entire Study



- ❑ Who would be providing the safety oversight?
- ❑ What are their responsibilities?
- ❑ What are the frequencies for when the reviews would be done?
- ❑ What data would they review to decide if the study was safe to continue?

Safety Management-Monitoring

Before:

No new safety evaluations will be implemented as the intervention is a reduction of doses compared to current practice. We do not anticipate any moderate or severe AEs from the intervention as compared to the usual care group. However, AEs will be monitored and recorded in both treatment groups.

Safety Management - Monitoring

What SRC Reviewers Look For…

When conducting a high risk research study, it is recommended to have independent Data Safety Monitoring (board or medical monitor) with ***a priori* stopping rules.** Such stopping rules should be **safety based** and not necessarily based on statistical numbers at interim review. This is especially important when the sample size is small and the literature suggests large variations in response.

Safety Management - Monitoring

After:

Dr. [x] and Dr. [y], both board-certified and not otherwise involved in the study or treatment decisions, will serve as independent safety monitors. AEs will be reported to the IRB and safety monitors through regular progress reports. In addition, AE reports will be generated every 3 mo. or after 20 participants are enrolled, whichever comes first. If any of the following are met in either arm we will suspend the study to investigate: death at 30 days-20%; pleural hemorrhage-15%; increase in pain medications-50%.

Consent Process

- ❑ Where will participants be consented?
- ❑ Is there any consent training required for the staff?
- ❑ Does your consent process require any waivers?
- ❑ Will interpreters be needed?
- ❑ Are you enrolling decisionally impaired individuals?
- ❑ What is the process for re-consent?

Study Team, Oversight, Monitoring

- ❑ What does your study team consist of? (PI, SC, research nurse etc…)
- ❑ Is there a manual of procedurals (MOP)?
- ❑ How is the conduct of the study being monitored?
- ❑ Who is responsible for monitoring your study?
- ❑ What is your process for ensuring the rights & welfare of study participants?
- ❑ Is there a clinical monitoring plan?

Questions/Discussion

Any questions we do not get to will be compiled into a Q&A document and distributed to registered attendees.

Also, email joyce_lanier@med.unc.edu if you would like to submit a question for the Q&A document or be included in distribution.

Thank you!

Protocol Development Workshop – Day 2

Study Design
Statistics
SRC Problem Spots
CT.gov Registration & Results reporting

Workshop Evaluation

- Please use the link provided to complete the online evaluation. Your comments are especially helpful as we update and improve the workshop for future sessions.
- If you would like an attendance certificate, which includes the equivalent of 2.0 Clinical Research Education Contact Hours, please complete the evaluation and email joyce_lanier@med.unc.edu

Workshop Evaluation QR Code

Workshop Evaluation Link:

https://reports.tracs.unc.edu/surveys/?s=PKCDETDPPLJ4334K

Thank you!

Websites, Links, Resources

- PRC Website: https://unclineberger.org/protocolreview/
  - kaitlin_morrison@med.unc.edu; stacy_maxwell@med.unc.edu, christinegrace_narag@med.unc.edu
- SRC Website: https://research.unc.edu/clinical-trials/scientific-review-committee/
- UNC CT.gov information: https://research.unc.edu/clinical-trials/clinical-trials-gov/overview-policy/
  - Monica Coudurier - m_coudurier@unc.edu
  - Melahat Canter - gmelahat@email.unc.edu
- Recruitment Resources at TraCS:
  - Recruitment Specialist (Summer Choudhury, summer.choudhury@unc.edu)
  - Community & Stakeholder Engagement (Alicia Bilheimer, alicia_bilheimer@med.unc.edu)
  - Inclusive Science Program (Laura Villa Torres) villal@unc.edu
  - UNC Health Science Library guide https://guides.lib.unc.edu/c.php?g=787212&p=5636824

References

- Best Practices in Clinical Research Protocol Writing: Eight tips from an IRB member. 10_Kinetiq_WP_BestPracticesinClinicalResearchProtocolWriting-EighttipsfromanIRBmember_020416-1.pdf (usc.edu)
- Minnesota Department of Health. Different Ways to Write SMART Objectives. http://www.health.state.mn.us/divs/opi/qi/toolbox/objectives.html
- SPIRIT Group:
  - http://www.spirit-statement.org/about-spirit/
  - http://www.spirit-statement.org/publications-downloads/
- Protocol Writing in Clinical Research. J Clin Diagn Res. 2016 Nov; 10(11): ZE10–ZE13. Published online 2016 Nov 1. doi: 10.7860/JCDR/2016/21426.8865. PMID: 28050522
- Rho Protocol Design presentation: https://www.slideshare.net/BrookWhitePMP/protocol-design-development-what-you-need-to-know-to-ensure-a-successful-study
- Workshop by Paul Stewart: Designing Your Research Study: Essential concepts, Best practices, Pitfalls, Speedy IRB approval