CLINICAL PROTOCOL DEVELOPMENT WORKSHOP

Kim Brownley, PhD, CIP
Marie Rape, RN, BSN, CCRC
Monica Coudurier, BS
Caron Modeas
Amanda Wood, BS, CCRP, RAC

Introduction
&
General Background

Kim Brownley, PhD, CIP
Co-Director, TraCS Regulatory Service
Co-Chair, Biomedical IRB
Member, Scientific Review Committee

Disclaimer

Registration Question: ***List topics about protocol development you find difficult or would like us to address in this workshop.***

- Wide variety of responses. Some obvious to address in this workshop, others didn't fit with theme and really would be better addressed as separate presentation.

- Unable to address everything requested in 2 hours so if we don't cover your topic, can meet with us 1:1 after workshop.

Objectives

- Understand when and why a protocol is required
- Review how a protocol is helpful to researchers
- Review available protocol templates
- Discuss content expectations for sections of the protocol
- Recognize protocol problem spots and ways to improve protocol writing
- Understand importance of the protocol for results entry in clinicaltrials.gov
- Identify resources to assist with protocol development

What is a Clinical / Research Protocol?

- The protocol is a document that describes how a study will be conducted.
- A research protocol is a document that describes the background, rationale, objectives, design, methodology, statistical considerations, and organization of a clinical research project.

Grant proposal versus protocol

- A **proposal** is a rhetorical document, comparable to an artist's painting of a concept car or a rendering of an architectural vision. **Its primary purpose is to motivate the sponsor to believe that the idea, plan, and researchers—as a whole—are worth funding**.
- A **protocol** **is an analytic document, meant to identify the parts and specifications of the project**, comparable to a schematic drawing, recipe, or blueprint. The goal of the protocol is to **present an effective and practical plan for conducting research and analyzing the results.**

Steve Maas, TraCS Institute

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** (full board) must undergo scientific review.

Industry-sponsored, multi-site trials generally excluded

Scientific Review – Why?

Scientific review of human subjects protocols is required as there is ***no acceptable risk*** to human subjects ***in the absence of valid scientific benefit***. The regulatory rationale for requiring science merit reviews emanates from 45 CFR 46.111(a)(1) as follows:

- Risks to participants are minimized by using procedures consistent with ***sound research design*** and which do not unnecessarily expose participants to risk.
- Risks to participants are reasonable in relation to anticipated benefits, if any, to participants, and the ***importance of the knowledge*** that may reasonably be expected to result.

"Bad" science is unethical

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
  - Ensures the safety of the trial subjects
  - Ensures the integrity of the data collected
  - Reduces noncompliance/unanticipated problems
  - Multicenter trials – all sites follow same protocol
- Facilitates IRB Review
  - Maps onto and supports the IRB application
  - Signals attention to detail ("bad" science → unethical)
- Source material for writing manuscripts or other submissions

Protocol Templates

Marie Rape, BSN, RN, CCRC
Associate Director, TraCS Regulatory Service
UNC IRB Board Member

Clinical Protocol Templates available

- NIH/FDA Phase II/III Template
- Social Behavioral Protocol (draft)
- NIH Institute Specific Templates
  - NCI-CTEP - Phase I or dose escalation
  - NIDCR
  - DMID / NIAID (templates for interventional protocol or for minimal risk sample collection)
- SPIRIT Checklist (serves as an outline)
- Scientific Review Committee Templates
  - NIH/FDA, observational, interventional, registry
- LCCC Protocol Templates (Cellular therapy, Chemo, Radiation, Health Services, Specimen-based research)

Protocol Template Resources

- UNC Scientific Review Committee (SRC): https://research.unc.edu/clinical-trials/scientific-review-committee/
- Online NIH Protocol Tool: https://e-protocol.od.nih.gov/#/home
- Spirit checklist: http://www.spirit-statement.org/
- Lineberger Cancer Center Protocol Templates: https://unclineberger.org/research/iit/forms-templates
- ReGARDD: http://regardd.org/resources

Why Use a Protocol Template?

- … template was created to guide investigators through the systematic development of a comprehensive clinical protocol, especially for investigators less familiar with the information and level of detail expected in a clinical protocol.
- … this template may be a useful tool for anticipating decision-points and potential challenges before a study launches, so that comprehensive planning ensures smooth and systematic study operations.

NIH/FDA Protocol Template Introduction

Choosing a Protocol Template

- Templates follow similar outline of topics to address
- Instructional text explains what to include in each section
- Some protocol templates include example language or graphics
- Use template that best fits your study
- Customize template with specific details about YOUR research and delete instructions

Basic Protocol Template Outline

- Title Page
- Table of Contents
- 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
- References

Starting to Write the Protocol

- You will have several drafts of the protocol before it is finalized!
- Write it, Review it, Improve it
- Get input from others:
  - Consult with study team, collaborators, MDs
  - Involve a statistician early on
  - Discuss with study coordinator / nurse logistics the feasibility of doing study (clinic flow, patient concerns, blood volumes, etc.)
  - Talk to finance/budget staff about costs
  - Have study team read protocol and offer comments before finalizing research plan

Writing the Full Protocol

- Read and follow protocol instructions!
- Prepare 5-10 page protocol outline, get agreement on critical issues before expanding to full protocol
- Work with statistician on objectives, study design and statistical analysis plan
- Address each item in template to ensure necessary content not inadvertently omitted (or mark N/A)
- Review full protocol for consistency after changes made

How much Detail to Include in Protocol?

- IRB / other reviewers need sufficient details to fully understand the research plan.
- Provide
  - Supporting evidence for conducting the study
  - Sufficient background information to justify study population
  - Describe all study activities – the what, where, and how and by whom study conducted
  - All activities should support a primary, secondary, or exploratory aim of the study

TIPS ON Using the Protocol Template

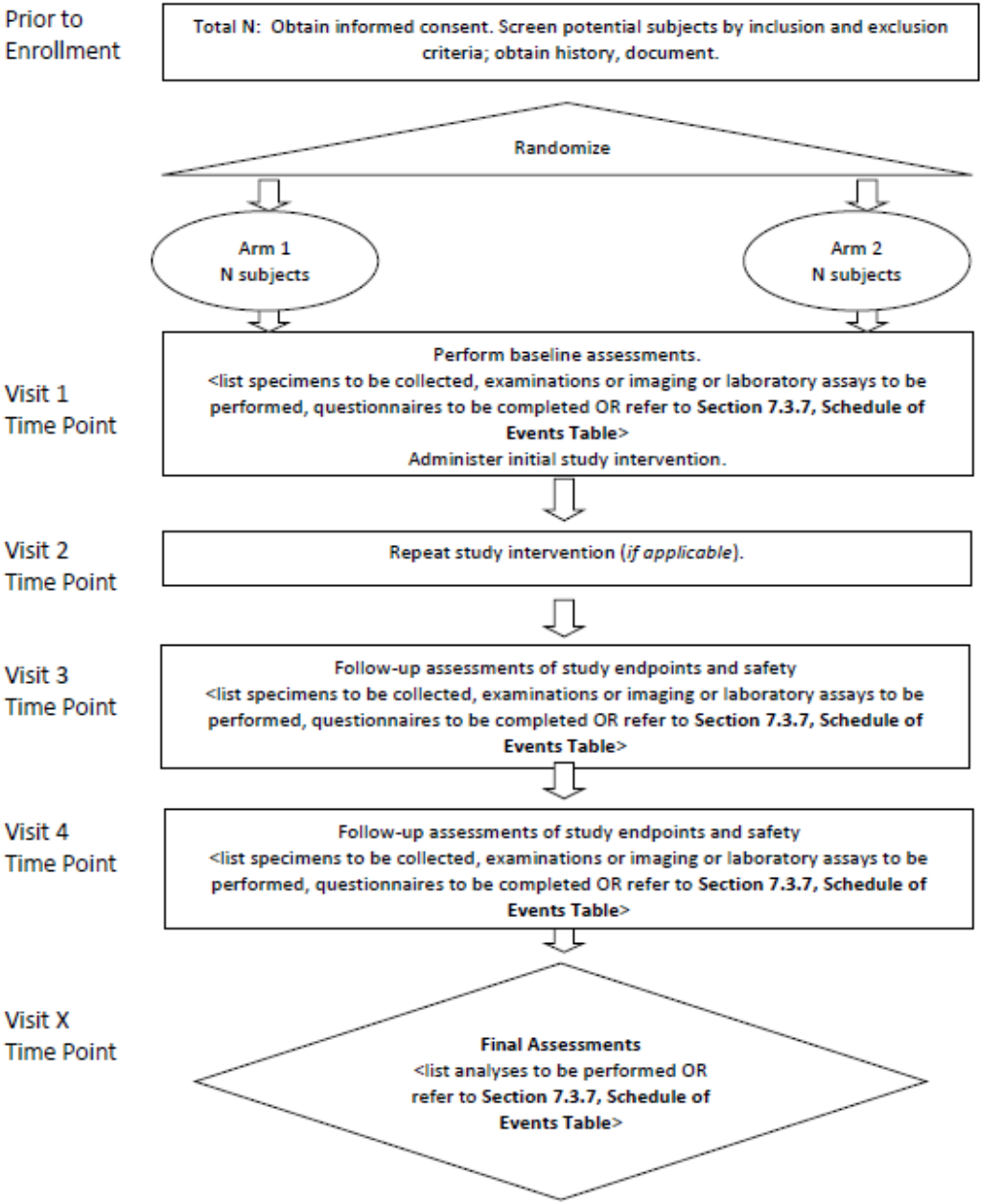
PROTOCOL SUMMARY OR SYNOPSIS

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;**
Estimated Time to Complete Enrollment:	

Study Schema

Example #2 provided as a guide, customize as needed: Flow diagram (e.g., randomized controlled trial)



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	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

2.1 Study Rationale

- Clearly state the importance of the problem or research question
- Reason for conducting the clinical trial
- Rationale underlying the intervention
- Name and nature of the intervention
- Clinical outcome of interest
- Justification for performing the study

The definition of the problem should be clear so a reader can recognize the real meaning of it.

2.2 Background

- Relevant basic, pre-clinical and clinical research
- Important literature and relevant data that provide background for the study (data supporting rationale)
- Identify gaps in the literature
- Any relevant treatment issues or controversies

Objectives and Endpoints

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS	PUTATIVE MECHANISMS OF ACTION
Primary			
The primary objective is the main question. This objective generally drives statistical planning for the trial (e.g., calculation of the sample size to provide the appropriate power for statistical testing).	The primary endpoint(s) should be clearly specified and its importance and role in the analysis and interpretation of study results should be defined. The primary endpoint(s) is the basis for concluding that the study met its objective.	Briefly identify the hypothesized role that each measure plays in the study objectives, e.g., moderator, mediator, causal mechanisms, covariate.	This column is optional and can be included when appropriate.

Writing Clear Study Objectives / Aims

SMART:

- **Specific** - who and what, use one action verb
- **Measureable** - quantify the amount of change
- **Achievable** - within a given time or with available resources
- **Relevant** - accurately address the scope of the problem
- **Time-based** - timeline when the objective will met/measured

- Objectives are stated in **action verbs** that illustrate their purpose (i.e., to determine, to compare, to verify, to calculate, to reduce, to describe, etc.)
- Do not make general or ambiguous statements

Study Population

- **Inclusion Criteria**
- **Exclusion Criteria**
- **Strategies for Recruitment & Retention** (summarize and refer to separate detailed plan in manual of procedures)
  - UNC Health Science Library: guide for community engagement & recruitment resources, easy background & literature searches https://guides.lib.unc.edu/c.php?g=787212&p=5636824
  - TraCS Resources
    - Emily Olsson, Recruitment Specialist - emolsson@unc.edu
    - Alicia Bilheimer, Community & Stakeholder Engagement (CASE) - alicia_bilheimer@med.unc.edu
    - Integrating Special Populations (Abigail Haydon, ahaydon@email.unc.edu)

Study Assessments and Procedures

- **Efficacy Assessments** (study procedures & evaluations to support determination of efficacy of primary & secondary endpoints)
  - Biological specimen collection
  - Assessments of intervention adherence
- **Safety and Other Assessments** (study procedures and evaluations to monitor safety)
  - Physical Exams, Vital signs, EKGs, X-rays
  - Laboratory evaluations
  - Questionnaires
  - Adverse event monitoring

Study Assessments and Procedures

Adverse events, Serious Adverse Events, Unanticipated Problems

- Definitions of AEs & SAEs, UPs
- Classification scale for AEs (use to grade severity – CTCAE scale)
- Reporting of events
- Reporting problems to participants

Don't use boilerplate language; be specific to your study and population

- What is known & expected, what events will you watch for
- Identify specific timelines for evaluating AEs (e.g., how long post intervention will you collect AEs or consider events related to the intervention)
- Describe **reporting requirements** based on UNC IRB SOP for Reporting New Safety Information: https://ohresop.web.unc.edu/files/2018/04/1401-Reporting-New-Safety-Information.pdf

Study Design

General Features:

- Type/design of trial
  - RCT, observational, cross-sectional, parallel arm, open label, etc.
  - Single site or multi-site
- Target enrollment
  - # of participants
  - # of groups/arms
- Randomization /method for assigning participants to study groups/arms
- Allocation and blinding
- Study duration and “phases”
  - Screening/baseline
  - Intervention/treatment
  - Follow up
  - Unscheduled visits

Study Design

Match study design with specific aims/outcomes

Design	Aim	Outcome
Pilot	Feasibility, acceptability	Enrollment target/rate/timeline Drop out Go/no-go decision @ future study
Phase 1	Dose escalation TEAE	Max tolerated dose w/in acceptable safety limits
Proof-of-Concept	Preliminary efficacy	Sample size estimate Mean group difference w/ confidence intervals
Phase 3 RCT	Efficacy Safety	Clinically meaningful difference Statistically significant difference

Statistical Analyses

Clearly state *all* the variables measured in the study, with their corresponding baseline and follow-up assessments

- Direct measures – what source?
- Derived measures – how computed?
- Unit of measure

Ex: blood pressure (mmHg)

- SBP or DBP or MAP?
- If MAP, is that direct from the instrument or computed?

Statistical Analyses

Clearly state how *all* the variables

- **Relate to a specific study aim(s)**
  - Primary
  - Secondary
  - Exploratory
- **Will be used in the analysis plan**
  - Efficacy outcome
  - Safety outcome
  - Covariate

* If no clear purpose, why allocate resources and why burden participants?

Statistical Analyses

Well-developed statistical analysis plans include:

- *All* statistical estimates (e.g., medians, proportions, incidence rates, mean differences, correlations, etc.) that will be tabulated along with corresponding confidence intervals (CIs).
- Complete list of the null hypotheses including the outcome measures involved and the details of the test procedures
- When applicable:
  - Complete specifications of the statistical models to be fitted, including covariates and assumptions
  - A reasoned strategy for dealing with the multiplicity of hypothesis tests
  - Sensitivity analysis to examine robustness of the main results
  - Distributional assumptions – *a priori* considerations

Data Management Plan

Basic Elements:

- Data security and confidentiality
- Data quality (accuracy, completeness, missing data)
- Role responsibilities
  - ➢ Develop/maintain the database
  - ➢ Create the codebook
  - ➢ Enter the data
  - ➢ Verify data accuracy
  - ➢ Create and review queries re: questionable values.

Get Statistical Input

- Consult with a statistician early on in development of your protocol!
- For Protocols going through LCCC PRC review, required UNC Biostatistician sign off
  - Ensures statistical input into trial design
  - Ensures pilot and feasibility trials include clear measure of success
- Access statistical resources on campus to help you with study design, statistical analysis plan, data management best practices

Statistical Resources

Some are free, others charge on a fee-for-service basis depending on association with the department:

- NC TraCS Biostatistics Consults (1 hour free): https://tracs.unc.edu/index.php/consultation
- LCCC Biostatistics Core support: cancer@bios.unc.edu
- UNC CFAR Biostatistics support: CFARbios@bios.unc.edu
- Center for Gastrointestinal Biology and Disease: https://www.med.unc.edu/cgibd/cores/biostatistics/
- Biometric Consulting Laboratory (School of Global Public Health): https://sph.unc.edu/bios/bios-research-units/biometric-consulting-laboratory/ or email to bcl@bios.unc.edu

Protocol Problem Spots: Tips from the Scientific Review Committee (SRC)

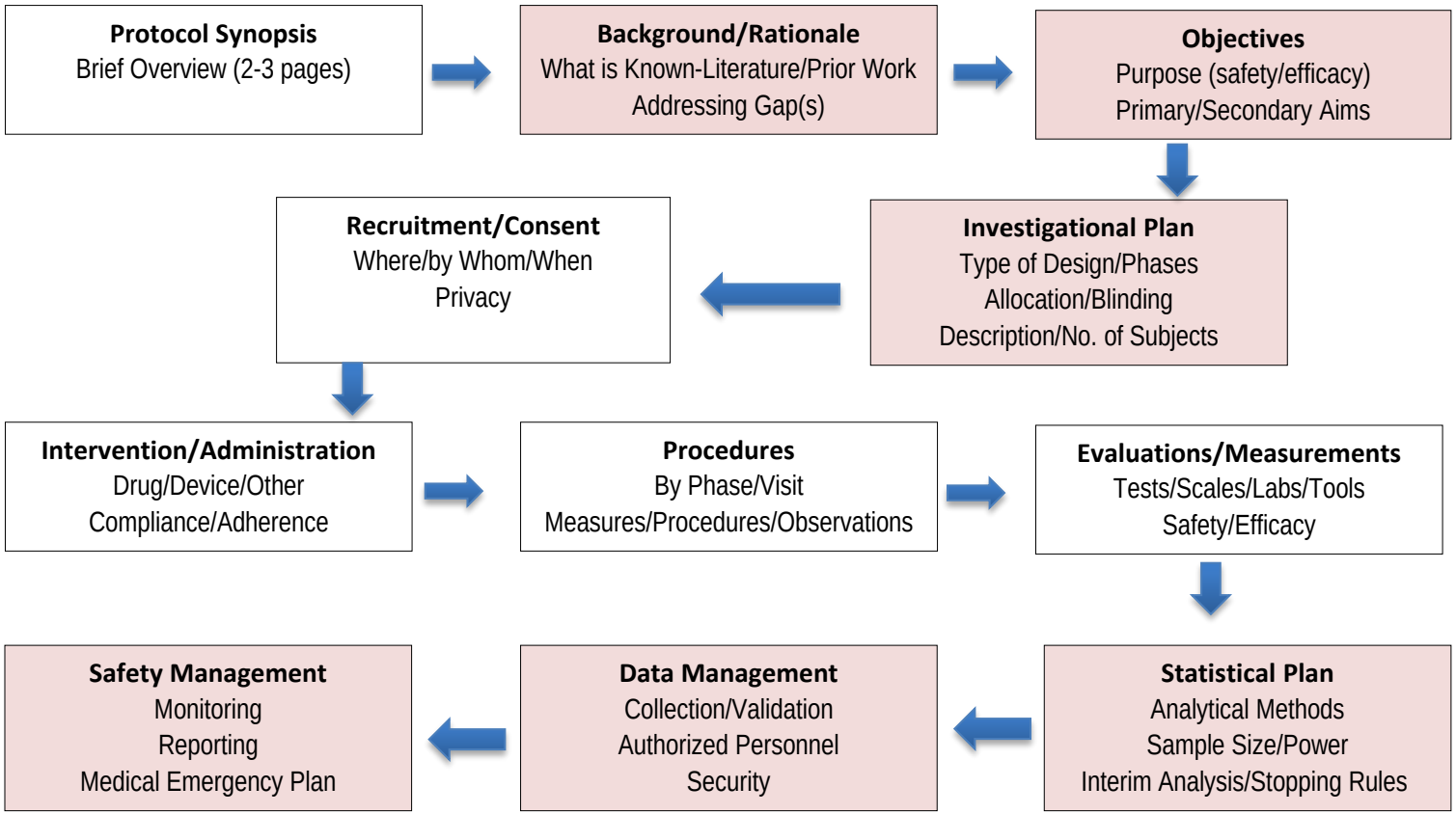
Caron Modeas, Coordinator
Scientific Review Committee
Office of Clinical Trials

TIPS for Speedy Scientific Review

- Submit a template-based protocol, not a grant proposal
- 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

Required Protocol Elements

for UNC SRC Review



Common Problem Areas @ SRC Review

Background/Rationale

Before:

Postpartum depression (PPD) is common and causes enormous human suffering and societal cost. PPD is the leading cause of maternal morbidity/mortality and is a critical public health threat. There is a need for PPD treatments that can reach large numbers of people, such as the proposed use of technology to deliver a PPD intervention.

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 onset of psychiatric disorders, including postpartum depression (PPD), with potentially harmful outcomes for mother and child. Prevalence is estimated at 10-15% in Western societies. Studies of Latinas in the US show higher than average rates, especially among women in [x region]. This study will evaluate PPD in mothers living in [x region] and will assess feasibility and efficacy of a mobile intervention.

Objectives

Before:

To determine clinical factors associated with initial [x substance] level and the prognostic value of [x substance] to predict adverse clinical outcomes in patients with [y condition].

Objectives

What SRC Reviewers Look For…

Well-conceived objectives are the backbone of a protocol, succinctly describing what is hoped to be achieved. There may be one (primary) or more (secondary or exploratory) objectives, each of which is to be described individually.

Objectives

After:

- Primary: To identify demographic and clinical factors (age, race, exacerbation history, medication use) that may be associated with initial [x substance] level.
- Secondary:
- 1. Evaluate the association between initial [x] level and hospital events (LOS, floor to ICU, ventilation, death).
- 2. Define change in [x] during hospitalization and identify clinical factors (steroids, antibiotics) related to change.
- 3. Estimate associations between discharge [x] level and 30- and 90-day readmission, and combined 90-day readmission and death.

Specific Aims/Analyses

Before:

All variables will be assessed for normality using the Shapiro-Wilk test. For those that pass the Shapiro-Wilk test (nonsignificant result), medians and interquartile range will be reported. For those that fail (significant result), medians and interquartile range will be reported. Non-normal data will be log transformed for subsequent analysis.

Specific Aims/Analyses

What SRC Reviewers Look For…

Specific aims are investigations to be undertaken using study data to achieve the objective. Each specific aim has one or more outcome measures that will be analyzed; these should include unit of measure. There is to be a 1:1 match between specific aims and the planned statistical analyses; analysis plans should be aim-specific.

Specific Aims/Analyses

After:

Aim 1: [Outcome a] will be analyzed using a 2 (male/female) x 5 (timepoints 1, 2, 3, 4, 5) repeated measures ANOVA.

Aims 2 and 3: [Outcome b] will be compared between sexes using an independent samples t-test and a 1 x 2 ANCOVA, with [c] as the covariate.

Aim 4: [Outcome d] will be analyzed using a 2 (male/female) x 3 (timepoints 3, 4, 5) ANOVA.

If a significant group x time interaction is detected by ANOVA, a Bonferroni post-hoc test will be used to identify the interactions.

Investigational Plan
Allocation and Blinding

Before:

As a secondary measure, we will test the effect of a small monetary incentive on adherence. Participants will be randomized to receive the extra monetary incentive or no extra incentive.

Investigational Plan-Allocation and Blinding

What SRC Reviewers Look For…

Allocation concealment prevents selection bias by concealing the allocation sequence from those assigning participants to groups - until the moment of assignment - using a blinded randomization schedule generated via an appropriate algorithm prior to subject recruitment. The protocol is to specify details of randomization/blinding procedures and explicitly identify the personnel involved.

Investigational Plan - Allocation and Blinding

After:

Subjects will be randomized in a 1:1 ratio to receive additional monetary incentive or no additional incentive. Randomization procedures will be performed by the statistician. Allocation will be balanced between arms within each age group. The order of assignments will be shuffled *a priori* using a random number generator. Assignments will be placed in sequentially numbered opaque sealed envelopes. Upon confirmation of eligibility, study personnel open the next envelope in the subject's age group to obtain the assignment.

Statistical Plan-Sample Size

Before:

A proposed sample size of 50 subjects per group (total n=100) will provide 80% power to detect a minimal effect size of 0.36 between pre- and post-surgery groups at type I error of 0.05. Determination of noninferiority of the post-surgery group to the pre-surgery group in terms of primary outcomes can also be made with 80% power.

Statistical Plan - Sample Size

What SRC Reviewers Look For…

Regarding likelihood of achieving a study's specific aims, it should be explained in simple language why the proposed sample size is a good choice. Provide sufficient details of power calculations for verification purposes. In the presence of multiple aims, each aim requires its own power analysis or sample size computation. The final sample size will be the largest among all the computed sample sizes.

Statistical Plan - Sample Size

After:

With a sample size of 100 (n=50 per group), we will have 80% power to detect a minimal effect size of 0.36 between groups at two-sided $p<0.05$, including anticipated missing data. The effect size was drawn from our published work and preliminary data. The sample size estimate is based on the weakest effect being tested. We will also have 80% power to declare that primary outcomes in the post-surgery group is noninferior to the pre-surgery group assuming that the mean between-group difference in outcomes for Aims 1-4 is <32% SD and is not clinically significant.

Statistical Plan - Missing Data

Before:

In dealing with attrition/missing data, if a subject does not complete all sessions, he/she will be replaced. Our primary analysis will only include data from subjects who complete all 3 sessions; however, we will examine data from non-completers.

Statistical Plan - Missing Data

What SRC Reviewers Look For…

Missing data can reduce statistical power and bias estimates. Time/effort burden on research subjects may contribute to drop-outs and missing data; include only measures that are directly related to study aims. The Statistical Analysis Plan should specify/justify how non-adherence, protocol violations, and incomplete data/missing values will be handled and whether the method(s) used will induce or avoid selection bias.

Statistical Plan - Missing Data

After:

The General Mixed Model Analysis of Variance permits missing data, but assumes that data are missing at random. We will examine patterns of missing data and compare between-group rates and demographic/clinical characteristics of completers vs. non-completers. We will assess patterns to see if missing elements can be inferred from other responses. We may use multiple imputation to reduce risk of bias from missingness and to produce variance estimates that do not overstate statistical significance. We will compare results of "observed" and "imputed" models; for additional sensitivity, we may use shared-parameters to assess the impact of missingness.

Data Management

Before:

Identifying information will only be seen by members of the research team. All information will be kept in a secure computer and/or a locked cabinet. Access will only be granted to members of the research team. All subjects will be given a code number, which will identify all data about that subject. This code will be used when discussing subjects. No personal identifying information will be on any of the collected data.

Data Management

What SRC Reviewers Look For…

In addition to data security and confidentiality, provide sufficient detail regarding plans to ensure data quality, e.g.: accuracy, completeness, documentation of missing values. Describe WHO will: develop/maintain the database; create the codebook; enter the data; verify data accuracy; and create and review queries re: questionable values.

Data Management

After:

The PI will review screening questionnaires to ensure study eligibility. Additional paper forms include data collection sheets created by the PI, which will include subject ID only and be kept in a locked cabinet. The PI will enter data into REDCap on a password protected University computer. Only the PI and Faculty Advisor have access to study files. The PI will develop and maintain the database, create the codebook, verify data accuracy, and investigate questionable data.

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:

We have identified two independent monitors, Dr. [x] and Dr. [x], both board-certified and not otherwise involved in the study or treatment decisions. 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%.

ClinicalTrials.gov (CT.gov) Protocol Requirements

Study protocol relationship with CT.gov

Monica Coudurier, BS
ClinicalTrials.gov Coordinator
Office of Clinical Trials

What drives the need to register in CT.gov?

ICMJE
International Committee of Medical Journal Editors

NIH
National Institutes of Health

FDA
Definition of ACT (Applicable Clinical Trial) defined by Section 801/Code of Federal Regulations

CMS
Centers for Medicare & Medicaid Services

Trial Registration Overview

	Register WHEN?	Phase 1	Phases 2-4	Device	Other Interventional*	Observational	Post Results?
ICMJE	Before enrollment of 1st subject	Yes	Yes	Yes	Yes	No	No
NIH	Within 21 days of 1st subject's enrollment	Yes	Yes	Yes	Yes	No	**Yes**
FDA	Within 21 days of 1st subject's enrollment	No	Yes	Yes	No	No	**Yes**
CMS	Prior to claims submission (for Qualifying Clinical Trials)	Yes (if qualifying)	Yes	Yes	No	No	No

*Health-related or Behavioral Interventional Trials

CT.gov Study Protocol-Related Requirements

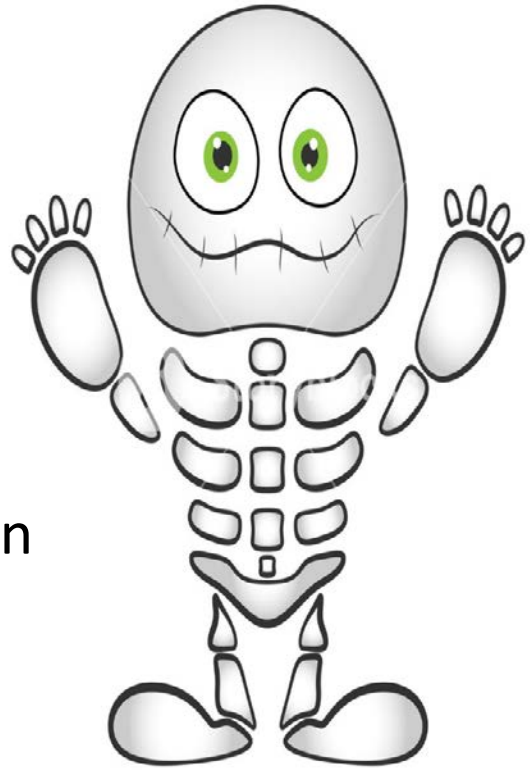
Protocol must be attached within CT.gov registry at the time of results submission

- Primary Completion Date on or after January 18, 2017

CT.gov Record Anatomy

Records consist of 3 parts:

1. Initial “Protocol” Registration
2. Results Reporting
3. Documents
   (Protocol + Statistical Analysis Plan [SAP])



Statistical Analysis Plan

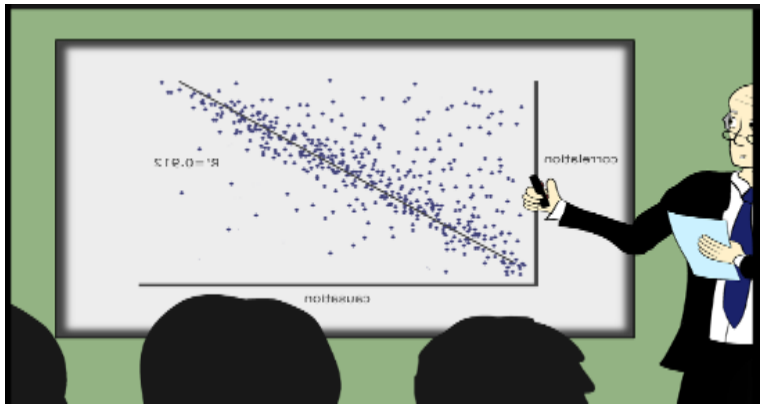
Within Protocol or Separate Document?

When existing as a separate document, the **Statistical Analysis Plan** (SAP) must also be uploaded into ClinicalTrials.gov

- ❑ in addition to protocol

  (at the time of results reporting)

Statistical Analysis



WHAT?
HOW?
} To measure

PRINCIPAL INVESTIGATOR'S DISCRETION

What do the rules say?

42 CFR Part 11

Results must include all:

Primary and Secondary Outcome Measures (OM)

- No limit on number reported

Term Definitions

- **Primary** Outcome Measure

  The outcome measure(s) of greatest importance specified in the protocol

  — Usually the one(s) used in the power calculation

- **Secondary** Outcome Measure

  An outcome measure of lesser importance than a primary outcome measure, but is part of a pre-specified analysis plan for evaluating the intervention(s) effects and is not specified as an exploratory or other measure

  — OMs included in SAP should clearly state level of overall importance

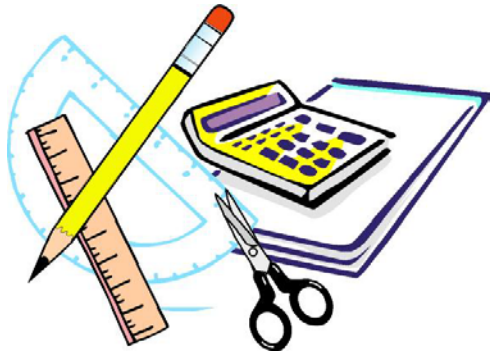
CT.gov Outcome Measure (OM) Entry

Outcome Measures have 3 Elements:

What? – OM Title

How? – OM Description

When? – OM Time Frame



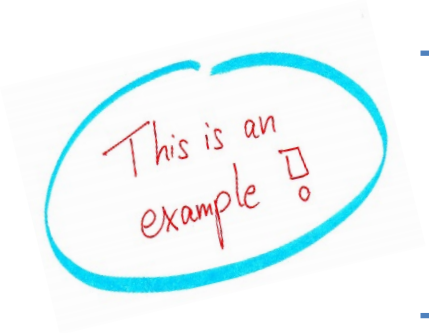
Outcome Measures (OM): CT.gov perspective

- Outcome Measures in protocol/registration records eventually become labels for results
- CT.gov reviews initial protocol/registration records with an eye toward this end regardless of actual results reporting requirement
  - Verbs not permissible (OM Title)
    (To: study, determine, seek, explore, analyze, etc.) ✗
  - Objectives or goals ≠ OM Titles
    (Feasibility, Adherence, Tolerability) ✗

OM: CT.gov perspective (continued)

- Each OM can report only 1 Time point unless:
  - A change (between 2 times) is being reported (OM Title should indicate this)
  - Data aggregated (e.g., AUC, TLFB)
- If multiple data measures combined, an explanation of how these data are aggregated must be provided (OM Description)
- Each OM can report only 1 unit of measure
- Provide reviewer(s) with an indication of what the numerical data being reported represent (OM Title)

Outcome Measure (OM) Title



Proportion of Patients Who Are Considered a Therapeutic Cure

- Answers WHAT? is being measured and reported
- Provides indication of numbers/units being reported (#s between 1-100)

OM Reported in CT.gov (Titles)

(n=38)

- Number of Participants With Local Tolerability Reactions by Severity
- Area Under the Plasma Concentration-Time Curve From Hour Zero to Hour 24 (AUC_{0-24}) of [Drug X]
- Percentage of Participants With Complete Cure of Target Great Toenail (TGT) at Week 52
- Percentage of Participants With Negative Fungal Culture of the TGT at Week 52
- Percentage of Participants With Almost Complete Cure of TGT at Week 52
- Percentage of Participants With Clinical Efficacy of TGT at Week 52
- Percentage of Participants With Mycological Cure of TGT at Week 52
- Percentage of Participants With Negative Fungal Culture of the TGT at Week 52
- Change From Baseline in Hematology Parameter (Hematocrit) at Week 24
- Change From Baseline in Hematology Parameter (Hematocrit) at Week 52
- Change From Baseline in Hematology Parameter (Erythrocytes) at Week 24
- Change From Baseline in Hematology Parameter (Erythrocytes) at Week 52
- Change From Baseline in Hematology Parameters (Hemoglobin) at Week 24
- Change From Baseline in Hematology Parameters (Hemoglobin) at Week 52
- Change From Baseline in Vital Sign (Respiratory Rate) at Week 24
- Change From Baseline in Vital Sign (Respiratory Rate) at Week 52

Outcome Measure (OM) Entry (Description)

Scales and Questionnaires Must Include:

- Full scale name
- All scale ranges (min and max scores) required to interpret data
    - Total score—overall range
    - If using subscales—specify range for each subscale
- Directionality
    - Those values considered to be a better (or worse) outcome

Those outcomes reporting scale or questionnaire results typically include the word ‘score’ within the OM Title

Outcome Measure (OM) Description

Scale/Questionnaire

Ocular comfort was assessed on an 11-point Visual Analog Scale (VAS) ranging from 0-10 where 0 = very uncomfortable and 10 = very comfortable. Higher scores reflect more comfort.

- Answers How? outcome is being measured and reported
- Includes mandatory scale information
  (Scale name, range, directionality)

Challenges with CT.gov Protocol Registry

Study Aim: Ascertain treatment-related blood pressure changes during initial treatment.

Implemented: Blood Pressure measured every 15 minutes for 4 hours

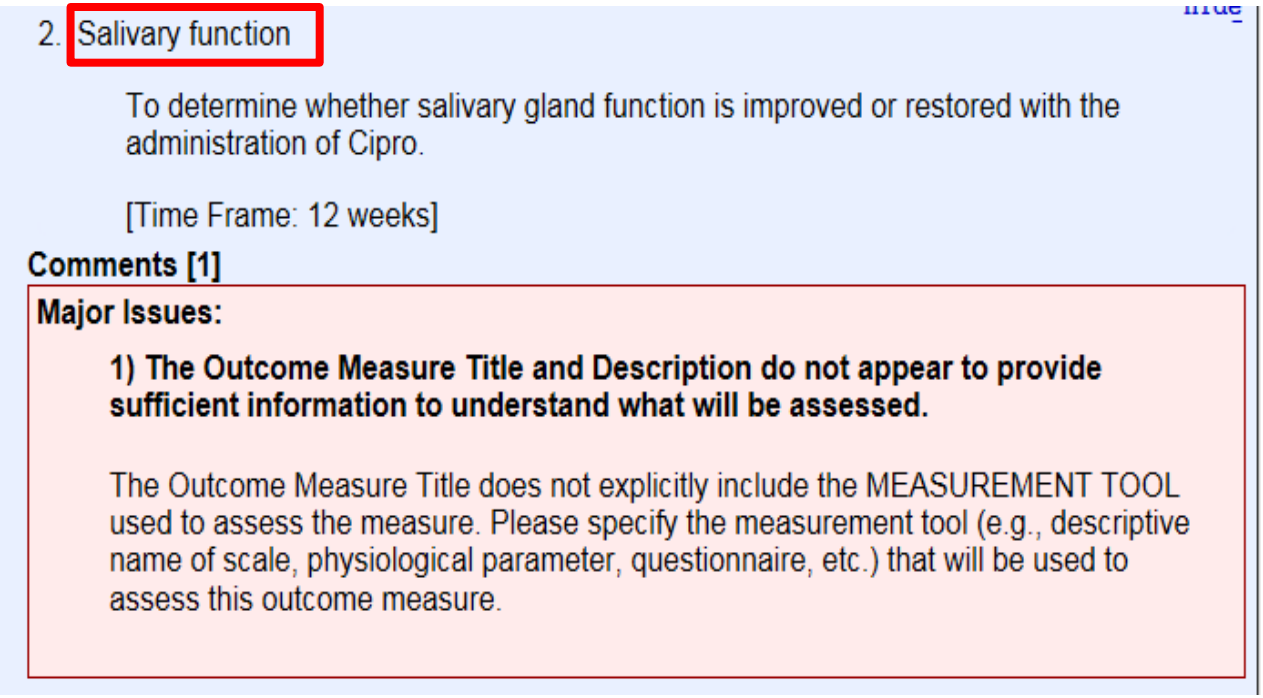
= 16 OMs (if reporting either systolic or diastolic BP measure alone)

= 32 OMs (if reporting both systolic and diastolic measures)

CT.gov formatting requirements: Multiple time points per outcome measure = multiple outcome measures

Example Outcome Measure (OM)

What? How? measured/reported?



2. Salivary function

To determine whether salivary gland function is improved or restored with the administration of Cipro.

[Time Frame: 12 weeks]

Comments [1]

Major Issues:

1) The Outcome Measure Title and Description do not appear to provide sufficient information to understand what will be assessed.

The Outcome Measure Title does not explicitly include the MEASUREMENT TOOL used to assess the measure. Please specify the measurement tool (e.g., descriptive name of scale, physiological parameter, questionnaire, etc.) that will be used to assess this outcome measure.

Major Issue cited by CT.gov

Stimulated vs. Unstimulated

Weigh gauze, suctioning, spit into collection tubes

Example Outcome Measure (OM)

Goal or Objective

Before

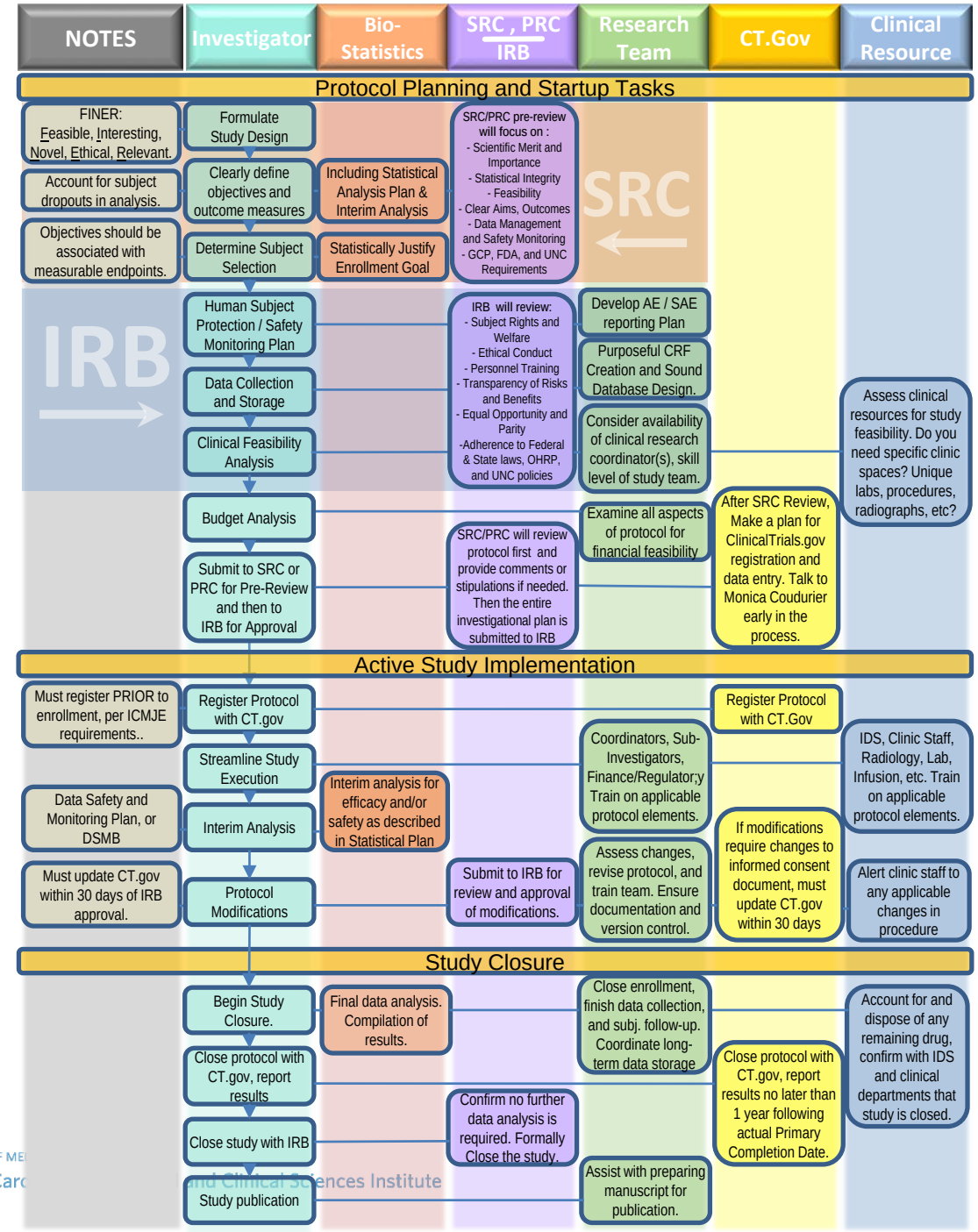
OM Title: Adherence
OM Description: Evaluate adherence to MRSA eradication protocol
OM Time Frame: Day 56

After

OM Title: Proportion of subjects with >80% compliance for study drug during the first 28 days
OM Description: Compliance refers to the amount of prescribed medication consumed as verified by patient diaries and drug reconciliation records.
OM Time Frame: Day 8

Takeaways for CT.gov

- CT.gov expects a level of granularity that needs to be anticipated when writing a protocol
- Be prepared to extract data from your protocol for easy entry into CT.gov
- Clearly indicate Primary and Secondary Endpoints
- Enlist biostatistical support


NOTES
Investigator
Bio-Statistics
SRC , PRC IRB
Research Team
CT.Gov
Clinical Resource
Protocol Planning and Startup Tasks
FINER: Feasible, Interesting, Novel, Ethical, Relevant.
Formulate Study Design
SRC/PRC pre-review will focus on : - Scientific Merit and Importance - Statistical Integrity - Feasibility - Clear Aims, Outcomes - Data Management and Safety Monitoring - GCP, FDA, and UNC Requirements
SRC
Account for subject dropouts in analysis.
Clearly define objectives and outcome measures
Including Statistical Analysis Plan & Interim Analysis
Objectives should be associated with measurable endpoints.
Determine Subject Selection
Statistically Justify Enrollment Goal
IRB
Human Subject Protection / Safety Monitoring Plan
IRB will review: - Subject Rights and Welfare - Ethical Conduct - Personnel Training - Transparency of Risks and Benefits - Equal Opportunity and Parity -Adherence to Federal & State laws, OHRP, and UNC policies
Develop AE / SAE reporting Plan
Purposeful CRF Creation and Sound Database Design.
Data Collection and Storage
Consider availability of clinical research coordinator(s), skill level of study team.
Assess clinical resources for study feasibility. Do you need specific clinic spaces? Unique labs, procedures, radiographs, etc?
Clinical Feasibility Analysis
Budget Analysis
Examine all aspects of protocol for financial feasibility
After SRC Review, Make a plan for ClinicalTrials.gov registration and data entry. Talk to Monica Coudurier early in the process.
Submit to SRC or PRC for Pre-Review and then to IRB for Approval
SRC/PRC will review protocol first and provide comments or stipulations if needed. Then the entire investigational plan is submitted to IRB
Active Study Implementation
Must register PRIOR to enrollment, per ICMJE requirements..
Register Protocol with CT.gov
Register Protocol with CT.Gov
Streamline Study Execution
Coordinators, Sub-Investigators, Finance/Regulator;y Train on applicable protocol elements.
IDS, Clinic Staff, Radiology, Lab, Infusion, etc. Train on applicable protocol elements.
Data Safety and Monitoring Plan, or DSMB
Interim Analysis
Interim analysis for efficacy and/or safety as described in Statistical Plan
If modifications require changes to informed consent document, must update CT.gov within 30 days
Must update CT.gov within 30 days of IRB approval.
Protocol Modifications
Submit to IRB for review and approval of modifications.
Assess changes, revise protocol, and train team. Ensure documentation and version control.
Alert clinic staff to any applicable changes in procedure
Study Closure
Begin Study Closure.
Final data analysis. Compilation of results.
Close enrollment, finish data collection, and subj. follow-up. Coordinate long-term data storage
Account for and dispose of any remaining drug, confirm with IDS and clinical departments that study is closed.
Close protocol with CT.gov, report results
Close protocol with CT.gov, report results no later than 1 year following actual Primary Completion Date.
Close study with IRB
Confirm no further data analysis is required. Formally Close the study.
Assist with preparing manuscript for publication.
Study publication

1:1 Guidance, Resources for Protocol Development

- TraCS Institute: https://tracs.unc.edu/index.php/consultation
  - Regulatory: Marie Rape & Amanda Wood
  - Research Coordination Management Unit: Laura Tuttle
  - Biostatisticians: John Preisser
  - Bioinformatics (database): Clarence Potter
  - Community Engagement, Integrating Special Populations
- UNC Office of Clinical Trials:
  - Scientific Review Committee:
    - https://research.unc.edu/clinical-trials/scientific-review-committee/
    - Caron Modeas, caron_modeas@unc.edu, (919) 843-4733
  - ClinicalTrials.gov:
    - https://research.unc.edu/clinical-trials/clinical-trials-gov/
    - Monica Coudurier, (919) 843-2333, m_coudurier@unc.edu
- Office of Human Research Ethics (OHRE): https://research.unc.edu/human-research-ethics/, 919-966-3113

Presenter Contact Information

- Kim Brownley, PhD, CIP (IRB, SRC, TraCS Regulatory)
  - kim_brownley@med.unc.edu
  - (919) 966-5276
- Marie Rape, RN, BSN, CCRC (TraCS Regulatory)
  - marie_rape@med.unc.edu
  - (919) 966-6844
- Caron Modeas, SRC Coordinator
  - caron_modeas@unc.edu
  - (919) 843-4733
- Monica Coudurier, BS (OCT, ClinicalTrials.gov)
  - m_coudurier@unc.edu
  - (919) 843-2333
- Amanda Wood, BS, CCRP, RAC (IND/IDE Specialist, TraCS Regulatory)
  - amanda_wood@med.unc.edu
  - (919) 843-9445

References

- Best Practices in Clinical Research Protocol Writing: Eight tips from an IRB member. https://kinetiqideas.com/educate-train/best-practices-in-clinical-research-protocol-writing/
- 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

Questions/Discussion

Thank you!