CLINICAL PROTOCOL DEVELOPMENT SERIES (DAY 2)

Kim Brownley, PhD, CIP
Monica Coudurier, BA

Online Logistics - Questions

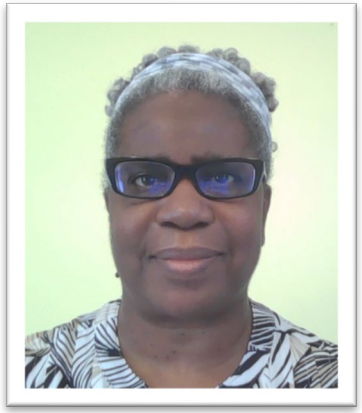
- To avoid connectivity issues, we ask that participants please turn off their video.
- Please enter questions using the Chat Function. We will be monitoring the chat and saving questions until the end.
- Any questions we do not get to will be compiled into a Q&A document and distributed to registered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

Protocol Development Support Team

NC TraCS

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 2

Kim Brownley PhD, CIP
Co-Director

Monica Coudurier, BA
Clinical Trials
Project Manager

- Develop understanding of study design, statistical principles and data management for clinical research
- Recognize protocol problem spots and ways to improve protocol writing
- Understand importance of the protocol for registration & results entry in clinicaltrials.gov
- Identify resources & other trainings to assist with protocol development

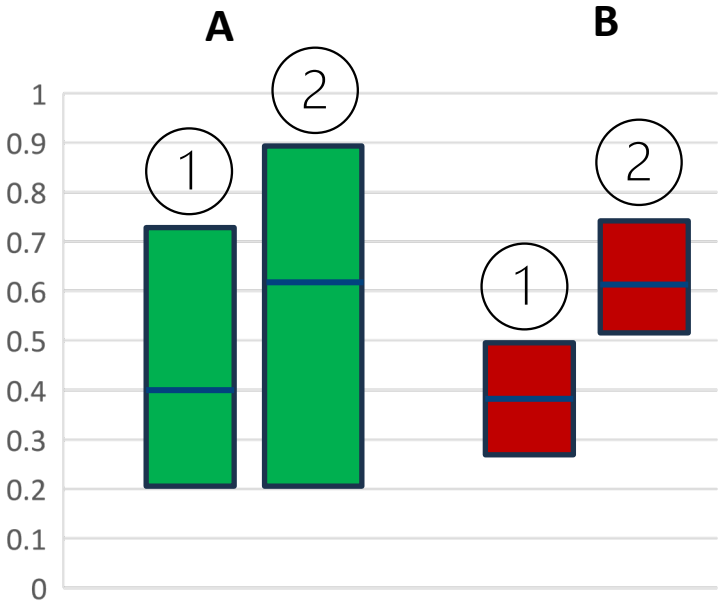
Day 1 Key Take Aways

- Use consultative resources
- Choose the “right” template
- PI and statistician hands-on in early stages
- Prioritize sound study design
  - Background, including pilot data when available, justifies the aims and the outcomes
  - Procedures are clear and measures are specific
  - Sample size and analysis plan fit the study intent
  - Monitoring plan reflects the study risks

Common Errors of Protocol Misalignment

Feasibility study with no feasibility aims or outcomes 

Pilot study for planning larger trial but analysis focuses on p-values rather than estimates of variability (C.I.s) to assess outcomes "stability" = will over- or under-estimate sample size



Some outcome measures are not mentioned in the statistical analysis plan – looks like collecting data for no reason, unjustified subject burden

Phase 3 trial without disease- and/or patient-specific adverse event assessment plan

Study Design – Align aims, design, outcomes

Specific Aim	Patient-Level Outcomes Measures	Typical Results of Interest
Evaluate **feasibility** of wearing a prototype glucose monitor to be used in a future study	• Questionnaire scores for acceptability • Occurrences of device failures	• Drop-out rate estimate • Go/no-go decision for the future study
Pilot test a new procedure with N=5 to identify problems and demonstrate abilities for a grant proposal	• Measures to use in future RCT • Occurrences of missing values • Occurrence of problems	• List of problems • % of values missing • Descriptive summary for the grant proposal
Perform a Phase 1 **dose-finding experiment**	• Dose-specific occurrences of toxicity	• Point- and interval- estimates of the max tolerated dose • Listings of AEs and SAEs
Perform a Phase 3 RCT to **compare the safety & efficacy of two treatments** for diabetes	• Longitudinal HbA1c measures • Occurrences of AEs	• Point- and interval- estimates of treatment effects on HbA1c • Listings of AEs and SAEs

1 Study with Several Aims & Analysis PlanS

Aim 1: RCT to evaluate safety and efficacy of X

- Primary outcomes:
  - Stroke incidence at week 52 → Sample size
  - # treatment discontinuations due to SAE → Monitoring plan
- Secondary outcomes:
  - % Δ Systolic blood pressure at week 52
  - Incidence grade 3 hypotension
- Tertiary or exploratory outcomes
  - Stroke incidence at week 104
  - % Δ Systolic blood pressure at week 104

Aim 2: Exploratory analyses of stroke biomarkers

Aim 3: Pilot test a new biomarker assay

Writing Clear Study Objectives

Clear objectives help focus the study to avoid collection of unnecessary data.

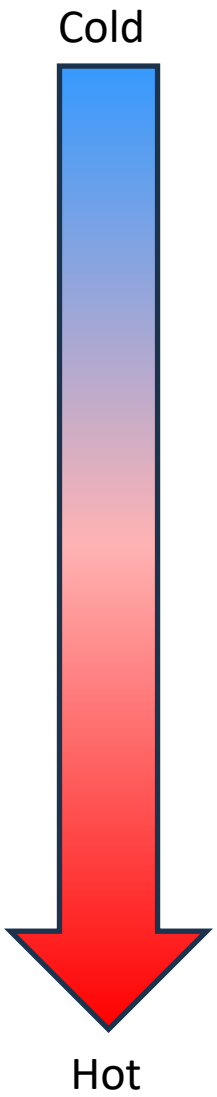
SMART:

- **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** - when the objective will be measured/met

*objectives stated in **action verbs** that illustrate their purpose (e.g., to determine, compare, verify, calculate, reduce, describe)

Clear Objectives are SMART Objectives

- Intervention A benefits patient group B
- Intervention A benefits patient group B by increasing C
- Intervention A benefits patient group B by increasing C at timepoint D
- Intervention A benefits patient group B by increasing C at timepoint D, as indicated by a clinically relevant 10-point increase on scale E



Objectives

Before:

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

After:

Specific

Time-based

- Primary: To identify demographic and clinical factors (age, race, disease severity, steroid 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, death)

2. Define change in [x] during hospitalization and identify clinical factors related to change.

3. Estimate associations between discharge [x] level and 30- and 90-day readmission.

Objectives and Endpoints

OBJECTIVES	ENDPOINTS / OUTCOMES	JUSTIFICATION FOR ENDPOINTS / OUTCOMES	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.

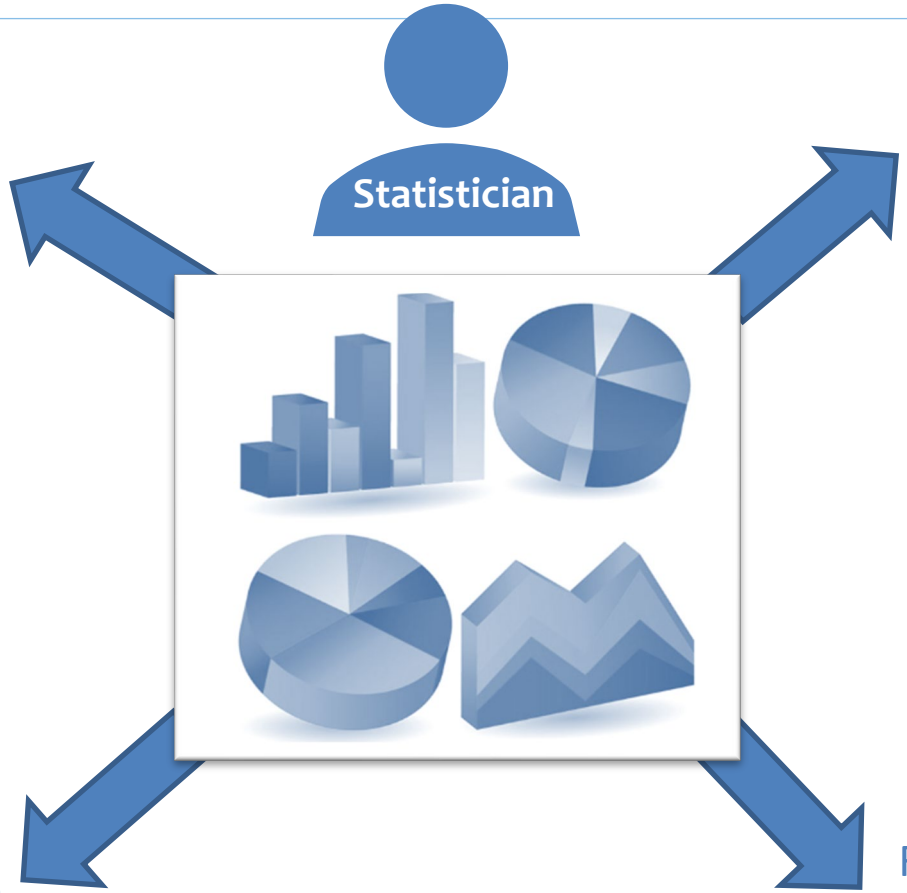
Objectives and Endpoints

OBJECTIVES	ENDPOINTS/ OUTCOMES	JUSTIFICATION FOR ENDPOINTS/ OUTCOMES	PUTATIVE MECHANISMS OF ACTION
To determine the safety and efficacy of 24 weeks o daily oral 10 mg drug X in patients with binge eating disorder (BED)	Efficacy outcomes, week 24: Primary: Change (from baseline) in binge eating freq Secondary: Change in mood symptoms Tertiary: Change in body weight Exploratory: Change in novel glucose regulation biomarker Primary Safety: # discontinue due to grade ≥3 nausea	Reduced BE is the hallmark of an effective treatment Depression and anxiety are highly comorbid in BED Weight loss is associated with treatment adherence in overweight BED Hypoglycemia may trigger BE Nausea is most common side effect	Drug X improves insulin sensitivity, DA and 5HT transmission, which may contribute to improved glucose regulation and eating control, mood and body weight. Biomarker may be highly sensitive to daily fluctuations in binge eating

Statistical Considerations

Has every measure of interest been addressed?

Is there a detailed statistical analysis plan for each specific aim?



Is there a rationale for the sample size?

For all variables provided in the study, have you provided the unit of measurement?

Statistical Analyses Tip #1

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?
- Specify the unit of measure for each variable

Ex: blood pressure (mmHg)

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

Statistical Analyses Tip #2

Clearly state how *each and every* variable

- **Relates 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?

Elements of a well-developed Statistical Analysis Plan

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, incl. covariates and assumptions	A strategy for addressing multiplicity (potential false positive result; e.g., Bonferroni)	Sensitivity analysis to examine robustness of the main results	Distributional assumptions (normal/skewed) – *a priori* considerations

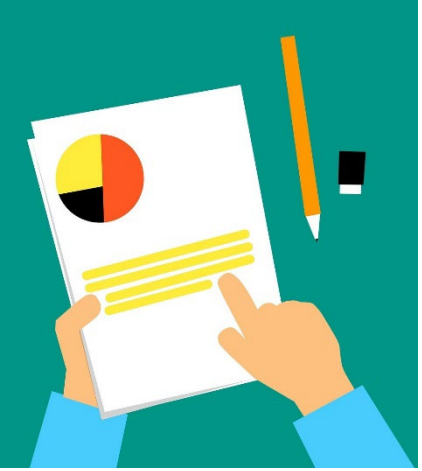
Statistical Analyses Variable Specification

Variable Name	Units	Time Point	Outcome	Objective
Binges past mo.	Count	Week 0, 24	Primary	Efficacy
Binges past mo.	Count	Week 0, 12	Secondary	Efficacy
Body weight	kgs	Week 0, 24	Secondary	Efficacy
Glycomark	µg/mL	Week 0, 24	Tertiary	Efficacy
D/C due to TEAE	Count	ALL	Primary	Safety
Nausea	Gr 1-4	ALL	Secondary	Safety
Sex	M/F	Screening		Covariate
Age	Years	Screening		Covariate

Variables of Interest Table – Helpful Alignment Tool

Variables within Domains	Scale	Occasions[1]	Aims	Main Roles
Identifiers				
Participant ID #	nominal	all	all	identifier
Date of birth	nominal	S	all	eligibility
Telephone number	nominal	E	--	follow-up
Clinical Health Profile				
Weight	ratio	0	all	covariate
Height	ratio	0	all	covariate
Tobacco use (current, former, never)	categorical	0	all	covariate
Medical Records				
pregnancy status	binary	S	--	eligiblity
Preoperative medications list	nominal	0	all	covariate
Patient-Reported Outcomes				
PROMIS 29+2 Profile v2.1[i]	Nominal	0, wk 1, 2, 4, 6, 8, 10, 12	1	Primary outcome
Post-traumatic stress disorder (PCL-5)[l]	Nominal	0, Wk 2, 6, 12	2, 3	Secondary outcome
Research Lab Assays				
Interleukin-6	Nominal	Day 0, 2	Aim 3	Exploratory outcome

[1] Occasions: **S** = screening, **E** = enrollment, **0** = baseline clinic visit



SRC Feedback on Data Analysis and Management

- 1:1 Match (Aims/Analysis)
- Sample size
  - Valid rationale, incl. pilot data when available
  - Enough detail to replicate
- Randomization, blinding, allocation
- Data Management Plan

1:1 Match – An Analysis Plan for Each Aim

Before (General):

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.

After (Specific):

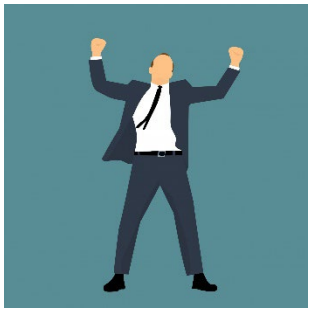
Aim 1: [Outcome a] will be analyzed using a 2 (male/female) x 5 (timepoints 1, 2, 3, 4, 5) repeated measures ANOVA.

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.

Sample Size Rationale

Sample size impacts the degree of “research risk.” Increasing the sample size +/or number of repeated measures may



Reduce the risk of a failed trial

Increase the financial risk

A reasoned explanation in simple language why you believe the proposed sample size is a good choice for successfully achieving each of the study aims.

Valid Considerations for Choosing a Sample Size

How much risk the investigator/funding agency are willing to take - time requirements and costs always play a role

Availability of eligible subjects

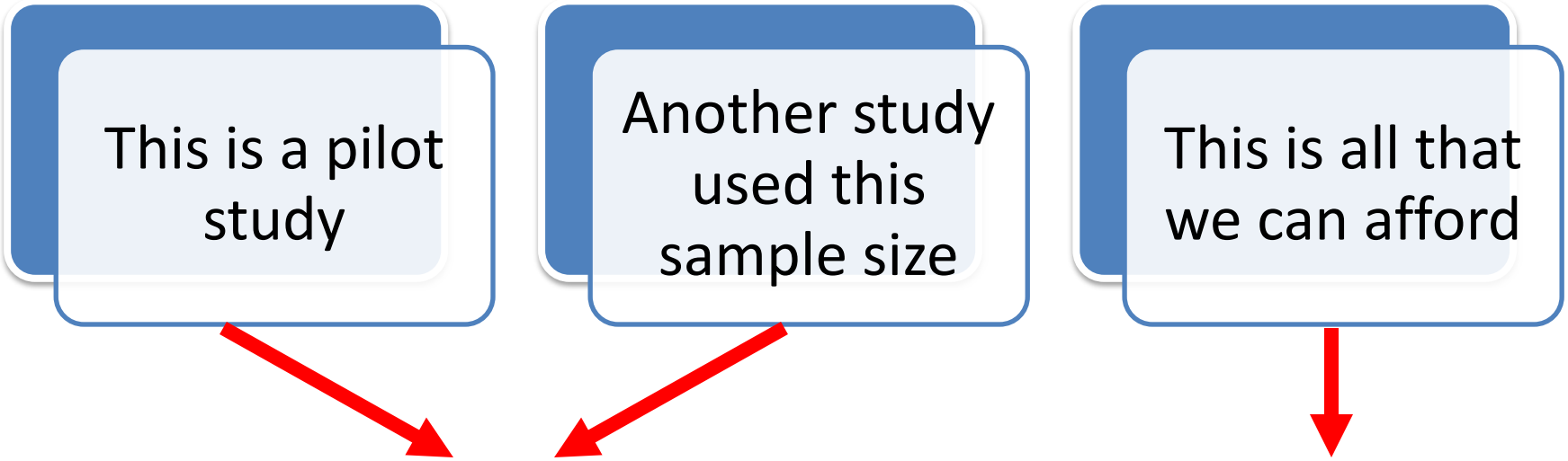
Expert opinion

Anticipated confidence interval widths – how precise are your measures?

Anticipated levels of power of the hypothesis tests under reasonable realistic conjectures

Anticipated probability that the null hypothesis will be rejected but the sign of the treatment effect will be wrong

Invalid Considerations for Choosing a Sample Size



If one simply uses the sample standard deviation from a small pilot sample, the chances of actually achieving the planned power may be as low as 40 percent." (Browne (1995, Statistics in Medicine, 14, 1933-1940).

Revise the study aims
Reduce the study aims
Change study design (cross-over vs. between-group)
Secure more funding

Key Points to Remember About Sample Size

* The anticipated precision of key estimators should be an important consideration when justifying or choosing a target sample size.

* Inflate the chosen target sample size for enrollment to take into account rates of dropout/withdrawal and missing data; explain assumptions about these rates and discuss whether data from withdrawn subjects will be evaluable.

* Each estimator, each test, each specific aim will have a different sample size need. Explain how these needs were prioritized to arrive at the final sample size choice.

Sufficient Detail to Replicate Power/Sample Size Calculation for each Aim

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.

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 [see section X, Table Y for primary outcome A]. The sample size estimate is based on the weakest effect being tested. We will also have 80% power to declare that primary outcome 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.

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.

What additional information can better describe this Randomization, Allocation & Blinding Section?

- ❑ Information about the randomization ratio between the subjects
- ❑ Information about who will perform the randomization
- ❑ Information on how the randomization will be accomplished
- ❑ All of the above

SRC: Specify details of the randomization/blinding procedures and identify the personnel involved

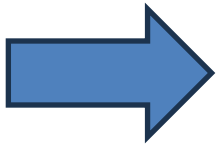
Before:

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.

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.

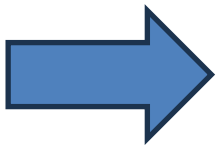
Allocation concealment



prevents selection bias

- ✓ conceals 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.

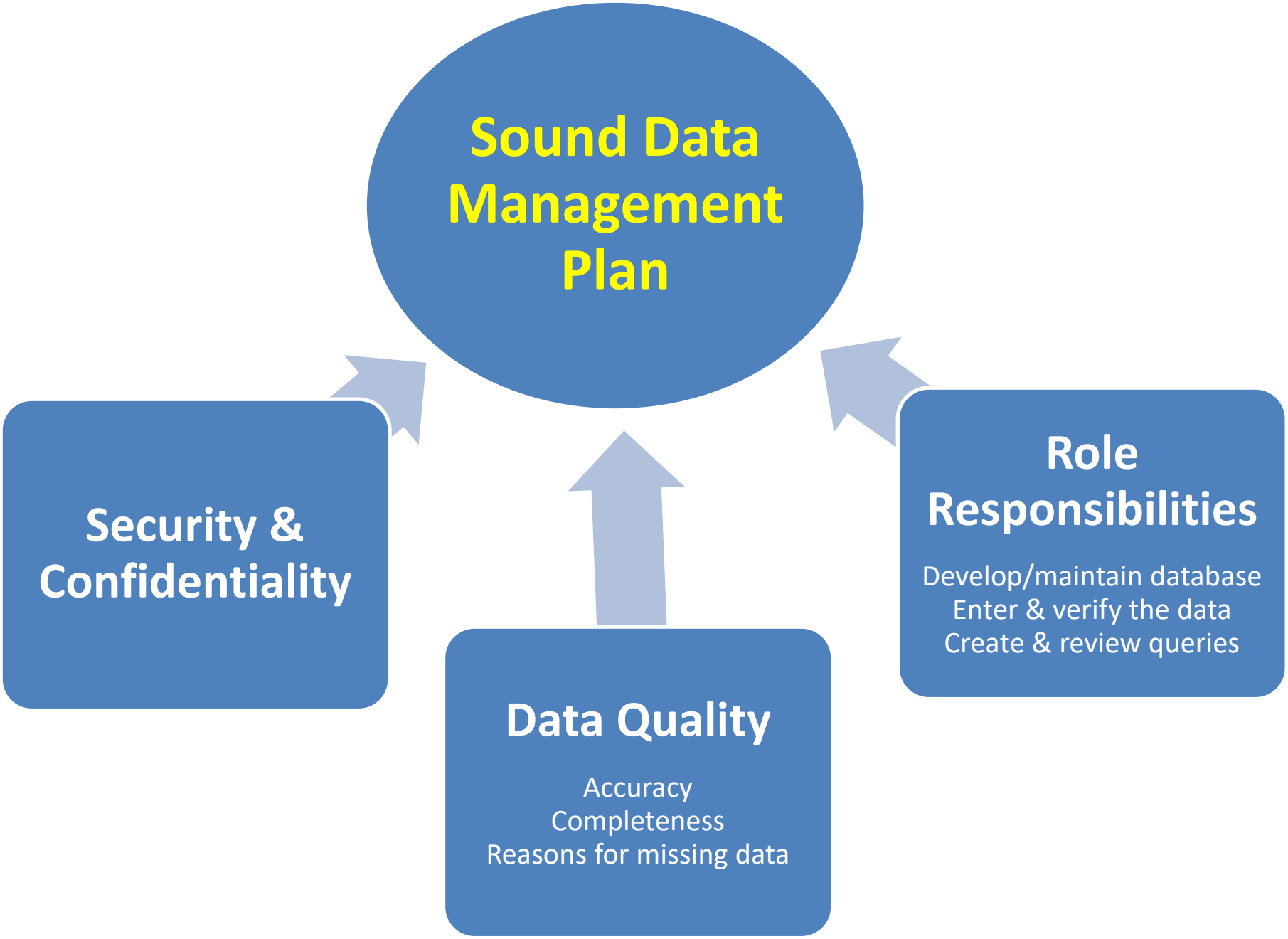
Blinding



prevents measurement bias throughout the study duration

Is Allocation Concealment Adequate?

Adequate	Sequence *Generation*	Sequence *Concealment*
YES	Random numbers generated by a computer-generated number, table of random numbers, drawing of lots or envelopes, tossing a coin, shuffling cards, throwing dice, etc.	Central randomization (site remote from trials location), sequentially numbered, sealed/opaque envelopes, coded drug containers of identical appearance prepared by an independent pharmacy
NO	Sequence could be related to prognosis or introduces selection bias: case record number, date of birth, day, month or year of admission.	Alternation, unsealed or non-opaque envelopes, dissimilar-appearing drug containers


Sound Data Management Plan
Security & Confidentiality
Data Quality
Accuracy
Completeness
Reasons for missing data
Role Responsibilities
Develop/maintain database
Enter & verify the data
Create & review queries

SECURITY & CONFIDENTIALITY

Plans to Protect Data Confidentiality & Participant Privacy

- How will you store identifiers?
  - Separately with a linkage file
  - Together with research data; if so, added protections
    - Encryption
    - Access limited to select study team personnel
- When will you destroy identifiers, if ever?
- How will you ensure safe electronic communication?

SECURITY & CONFIDENTIALITY

Risk Assessment / Security Review

- Two entities
  - SOM (School of Medicine IT | School of Medicine IT (unc.edu))
  - UNC Health ISD (ITS Policies, Standards, and Procedures - Information Technology Services (unc.edu))
- Cloud-based technology Home - Data Security: Policies and Regulations Impacting Research Data - LibGuides at University of North Carolina at Chapel Hill (unc.edu))
  - If database includes sensitive information, the database vendor must have a Business Associate Agreement with UNC. Business Associate Agreements (BAAs) - Institutional Privacy (unc.edu)

QUALITY & INTEGRITY/ROLE RESPONSIBILITIES

Accuracy –

- Data entry
- Data queries

Completeness –

- Real-time review of questionnaire responses

Reasons for missing data –

- Participant elected not to answer question
- Participant missed study visit
- Instrumentation failure

SRC: Specify Plan for 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.

After: We will . . .

- Examine patterns of missing data and compare between-group rates and demographic/clinical characteristics of completers vs. non-completers.
- Assess patterns to see if missing elements can be inferred from other responses.
- When appropriate, use multiple imputation to reduce risk of bias from missingness and to produce variance estimates that do not overstate statistical significance.
- Compare results of "observed" and "imputed" models; for additional sensitivity, we may use shared-parameters to assess the impact of missingness.

* Also include how protocol violations and non-adherence will be handled

QUALITY & INTEGRITY – UNC Resources

REDCap – Data Management System

- Reliability. Supported locally, sophisticated IT infrastructure , backed up multiple times per day.
- Security. Secure login page. Data storage per UNC's encryption policy. Audit trails.
- Ease of Use. Built-in training and free tutorials. Remote web-based data entry.
- Data Quality. Structured data dictionary, skip logic, mandatory fields, range checking, form locking/unlocking, customized data quality checks, data queries and resolutions. Reports/graphs.
- Features. Support for simple through complex longitudinal trials: survey scheduling, randomization and concealment, text and voice messaging.
- Data export. Exports CSV files along with Stata/SAS/R/SPSS code easily.

Qualtrics – Online Survey Tool

- Free to all UNC faculty, staff & students for UNC-related projects (*not available for UNC Healthcare)
- Survey construction & distribution
- Survey response analysis

We are here to help you!

- Pick the right template
- Understand what information goes in what sections of the template
- Get 1-on-1 protocol writing assistance
- Access statistical support
- Respond to SRC comments
- Anticipate and avoid unnecessary CT.gov headaches

Break Time


05:00
Start
Stop
Reset
mins: 5
secs: 0
type: None
Breaktime for PowerPoint by Flow Simulation Ltd.
Pin controls when stopped

ClinicalTrials.gov (CT.gov)

Study protocol relationship with CT.gov

Monica Coudurier

Office of Clinical Trials (OCT)

What is CT.gov?

Web-based registry

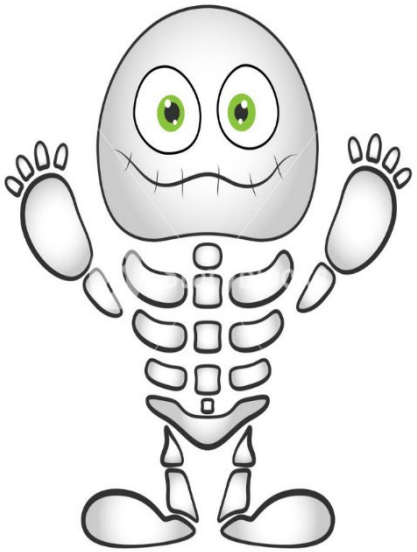
Maintained by National Library of Medicine (NLM)

Publicly available since Feb 2000

CT.gov Record Anatomy

Records consist of 3 parts:

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



CT.gov Registration/Reporting Drivers

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

CT.gov Registration Required For:

Studies meeting respective 'clinical trial' definitions:

1. Applicable Clinical Trials (**ACTs**)
2. NIH $$$ trials that meet **NIH** 'clinical trial' definition
3. Interventional study planning to publish (**ICMJE**)
4. Deemed & qualifying trials billing clinical-trial related services to Medicare/Medicaid (**CMS**)

Contractually required by funder:

- Patient-Centered Outcomes Research Institute (PCORI)
- Funding providers (Merck, DoD, VHA)

See OCT website: Registering an Investigator-Initiated Clinical Trial Overview

Registration driven by "Clinical Trial" Definitions

Feasibility, **Exploratory**, and **Pilot** studies

- require registration/reporting if they meet relevant 'clinical trial' definition (i.e., NIH, FDA [ACT], ICMJE)

CT.gov-Related Protocol Requirement

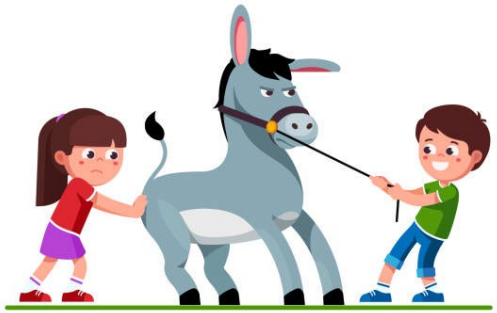
IRB-approved protocol must be attached in CTgov registry at the time of results submission

- Primary Completion Date on or after January 18, 2017

Formal Protocol Required for CT.gov

CT.gov vs. UNC Policy

No UNC protocol requirement ≯ "minimal risk"



CT.gov *requires* a formal protocol for all studies reporting results

Which Outcomes to Perform?

WHAT data to consider/study and **HOW** to analyze is entirely at the PI's discretion

. . . although

CT.gov has rigid ideas about HOW to enter

What do the rules say?

Per 42 CFR Part 11

Results must include all protocol pre-specified:

- Primary outcomes (POM)
- Secondary outcomes (SOM)

- At least 1 Primary Outcome Measure (POM) *required*
  - Most studies have 1 POM -- can have more than one
  - May also have one or more Secondary Outcome Measure (SOM)

- No limit on number of outcomes

Tertiary/Exploratory (Other Pre-Specified) Outcomes

- Must be prespecified in protocol
- May voluntarily include in CT.gov
- Less obligation than Primary or Secondary outcomes
  - Results reporting not required
  - Not used in determining Primary or Study Completion dates

- OMs discussed in SAP with unspecified level (not primary), CT.gov will interpret as secondary [reporting req'd]

Building Outcome Measures (OM)

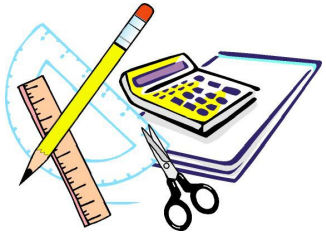
CT.gov Outcome Measure (OM) Entry

Outcome Measures have 3 Elements:

WHAT? – OM Title

HOW? – OM Description

WHEN? – OM Time Frame



Summary Data vs. Statistical Analysis

Outcome Measure (OM)Titles

"Summary data" must be reported for each POM and SOM

Examples:

- Number of Participants
- Mean
- Median
- Least Squares Mean
- Geometric mean
- Number: Percent (of something)

- Statistical analyses (e.g., p-value, ANOVA, chi-squared, hazard ratios, regressions, mean difference, slope, etc) are reported in separate statistics modules

- OM **Title** should reflect the summary data being reported (not supporting statistics)

Outcome Measure (OM) Do's and Don'ts

OM Titles do not reflect aims/goals (no verbs)

Examples: To assess, To evaluate, To Study, To Determine, Feasibility, Acceptability

. . . Do indicate:

- WHAT is measured & numerically reported
- Data measurements gathered by the study
- Quantifiable units (using nouns)

  Examples: "Number of [x]"; Proportion or Percent of [something]"; "Mean"; "Mean Change"; "Median"; "Geometric Mean"; "Change in [X] Over Time"

Example

CTgov QC Review Comment

MAJOR ISSUE:

The Outcome Measure describes the goal or objective of each assessment, rather than defining what will be assessed.

- The Outcome Measure should define what will be measured, not why it will be measured.
- For example, phrases such as "to assess", "to examine", and "to determine" should be deleted and replaced by an accurate description of what will be measured and reported (e.g., Number of Participants With Treatment-Related Adverse Events as Assessed by CTCAE v4.0, Change From Baseline in Pain Scores on the Visual Analog Scale at 6 Weeks).

Example

CTgov QC Review Comment

MAJOR ISSUE:

The Outcome Measure Title does not appear to provide sufficient information to understand what will be assessed.

- The Outcome Measure **Title** should clearly indicate what will be measured and reported. Terms such as "safety", feasibility, and "tolerability" do not convey what will be assessed and collected as outcome measure data.
- Please move or copy some of the information in the Outcome Measure Description to the Outcome Measure Title, if appropriate, to describe more specifically what is being measured (e.g., Incidence of Treatment-Emergent Adverse Events [Safety and Tolerability]).

Example

CTgov QC Review Comment

MAJOR ISSUE:

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

- The Outcome Measure is vague; it is unclear what will be measured and reported. In the Title field, specify the measurement that will be used (e.g., descriptive name of scale, physiological parameter, questionnaire) and, if relevant, how the collected measurement data will be aggregated. Use the Description field, for any additional information about the measurement or metric for summarizing the data. For example, an Outcome Measure Title of "Safety and Tolerability" does not sufficiently describe how quantitative data will be reported. A specific Title would instead be "Number of participants with treatment-related adverse events as assessed by CTCAE v4.0".

Outcome Measure (OM) Do's and Don'ts

Continued

Multiple time points not permitted in single OM unless assessing change (i.e., post-time minus pre-time)

Examples: "'X' over/across time", "Area Under the Curve (AUC)"

Only one assessment per OM

One Unit of Measure per OM

Scales & Questionnaires

OM Description must include:

1. Full scale name and construct
2. All scale ranges (min and max scores) required to interpret data
    - Total score—overall range
    - If using subscales—specify range for each subscale. Consider reporting subscales as separate OMs
3. Directionality
    - Those values considered to be a better (or worse) outcome

OMs reporting scale/questionnaire data typically include the word 'score' in the OM Title

Example

Major Issue: Outcome Measure with insufficient detail

Unacceptable	**Title:**	Change from Baseline in Clinical Chemistry Laboratory Tests
	Description:	Clinical laboratory tests of electrolytes assessed using blood samples.
	Time Frame:	Baseline, Week 1
Acceptable	**Title:**	Change from Baseline in Sodium Levels (mEq/L)
	Description:	Clinical laboratory tests of electrolytes (**sodium**) assessed using blood samples.
	Time Frame:	Baseline, Week 1

Example

Major Issue: Outcome Measure with insufficient detail

Unacceptable	**Title:**	Safety and Tolerability
	Description:	Evaluate the safety and tolerability of the intervention
	Time Frame:	Week 1
Acceptable	**Title:**	Number of Participants with Treatment-related Adverse Events as Assessed by CTCAE v4.0
	Description:	Common Terminology Criteria for Adverse Events (CTCAE) v4.0 uses a range of grades from 1 to 5: 1. = Mild 2. = Moderate 3. = Severe 4. = Life-threatening 5. = Death
	Time Frame:	Week 1

Example

Major Issue: Outcome Measure with insufficient detail

Unacceptable	**Title:**	Participants' Overall Assessment of Treatment
	Description:	Effectiveness of the intervention
	Time Frame:	Day 3
Acceptable	**Title:**	Number of Participants Who Rated Effectiveness of Treatment as Good, Very Good, or Excellent
	Description:	Each participant provided a response to the question "How effective do you think the study medication is as a treatment for pain?" Answers were rated on a five-point scale where 1 = poor, 2 - Fair, 3 = Good, 4 = Very good, and 5 = Excellent.
	Time Frame:	Day 3

Example

Major Issue: Outcome Measure (OM) with insufficient Time Frame

Unacceptable	**Title:**	Length of Hospital Stay in Days
	Description:	Length of stay will be defined by the duration between the time of first study treatment to the time a discharge order is placed.
	Time Frame:	From admission to discharge
Acceptable	**Title:**	Length of Hospital Stay in Days
	Description:	Length of stay will be defined by the duration between the time of first study treatment to the time a discharge order is placed.
	Time Frame:	From admission to discharge, **up to 90 days**

Example

Major Issue: Outcome Measure (OM) with insufficient Time Frame

Unacceptable	**Title:**	Number of Participants with Treatment-Emergent Adverse Events as assessed by CTCAE v4.0
	Description:	A treatment-emergent adverse event (TEAE) is defined as any unfavorable and unintended sign, symptom or disease temporally associated with the use of a study drug.
	Time Frame:	Through study Completion
Acceptable	**Title:**	Number of Participants with Treatment-Emergent Adverse Events as assessed by CTCAE v4.0
	Description:	A treatment-emergent adverse event (TEAE) is defined as any unfavorable and unintended sign, symptom or disease temporally associated with the use of a study drug.
	Time Frame:	Through study completion, **an average of 1 year**

Example

Major Issue: Outcome Measure (OM) with insufficient Time Frame

Unacceptable	**Title:**	Total Number of Cardiovascular Deaths
	Description:	Cardiovascular deaths defined as death due to myocardial infarction, congestive heart failure, cardiac valvular disease, arrhythmia, sudden death, stroke, or peripheral arterial disease.
	Time Frame:	From randomization to death
Acceptable	**Title:**	Total Number of Cardiovascular Deaths
	Description:	Cardiovascular deaths defined as death due to myocardial infarction, congestive heart failure, cardiac valvular disease, arrhythmia, sudden death, stroke, or peripheral aterial disease.
	Time Frame:	From randomization to death, **assessed up to 100 months**

Example

Major Issue: Outcome Measure (OM) with insufficient Time Frame

Unacceptable	**Title:**	Percentage of Participants Requiring Rescue medication During Cycle 2 of Treatment
	Description:	Rescue medication was initiated for participants who met progressively more stringent rescue criteria.
	Time Frame:	Cycle 2
Acceptable	**Title:**	Percentage of Participants Requiring Rescue medication During Cycle 2 of Treatment
	Description:	Rescue medication was initiated for participants who met progressively more stringent rescue criteria.
	Time Frame:	Cycle 2 **(each cycle is 28 days)**

Example

Major Issue: Outcome Measure (OM) with Multiple Assessments and/or Different Units

Unacceptable	Title:	1	Change from Baseline in Vital Signs including Pulse Rate, Systolic and Diastolic Blood Pressures, Respiratory Rate, and Oral Temperature. Change in Pain using VAS. Change in Health-Related Quality of Life using SF-36 and EQ-5D-3L.
	Description:		The effect of the study drug on vital signs, pain, and health-related Quality of Life.
	Time Frame:		Week 1
Acceptable	Title:	1	Change from Baseline in Pulse Rate
	Description:		Assessed in the morning while participant is resting calmly in a chair and recorded by the physician by placing two fingers over the wrists and counting the number of beats in 60 seconds.
	Time Frame:		Baseline, Week 1
	Title:	2	Change from Baseline in the Mean Seated Trough Cuff Systolic Blood Pressure
	Description:		
	Time Frame:		Baseline, Week 1

Example

Major Issue: Outcome Measure (OM) with Multiple Assessments and/or Different Units

Acceptable	Title:	3	Change from Baseline in the Mean Seated Trough Cuff Diastolic Blood Pressure
(continued)	Description:		
	Time Frame:		Baseline, Week 1
	Title:	4	Change from Baseline in Respiratory Rate
	Description:		
	Time Frame:		Baseline, Week 1
	Title:	5	Change from Baseline in Oral Temperature
	Description:		
	Time Frame:		Baseline, Week 1
	Title:	6	Change from Baseline in Pain Using VAS
	Description:		The Visual Analag Scale (VAS) is a self-reported instrument assess average pain intensity in the back over the past 24-hour period. Possible scores range from 0 (no pain) to 10 (worst possible pain). A clinical significant difference is considered to be a change by 3 points.
	Time Frame:		Baseline, Week 1

Example

Major Issue: Outcome Measure (OM) with Multiple Assessments and/or Different Units

Acceptable	**Title:**	7	Change from Baseline in Health-Related Quality of Life Using the SF-36
(continued)	**Description:**		The Short Form Survey (SF-36) is a self-reported instrument that is a general measure of perceived health status comprising 36 questions and yielding 8 separate scores for sub-scales that assess: 1) vitality; 2) physical functioning; 3) bodily pain; 4) general health perceptions; 5) physical role functioning; 6) emotional role functioining; 7) social role functioning; 8) mental health. Scores from each sub-scale are directly transformed into a 0-100 scale, with higher values representing a better outcome. Scores from the 8 sub-scales are averaged to provide a total assessment of physical and mental health status. Total scores range from 0 to 100 with higher values representing a better outcome.
	Time Frame:		Baseline, Week 1

Example

Major Issue: Outcome Measure (OM) with Multiple Assessments and/or Different Units

Acceptable	**Title:**	8	Change from Baseline in EQ-5D-3L Scores
(continued)	**Description:**		The EQ-5D-5L is a standardized non-disease specific instrument for describing and valuing health-related quality of life. The EQ-5D-5L descriptive system comprises 5 dimensions of health (mobility, self -care, usual activities, pain/discomfort, and anxiety/depression) to describe the subject's current health state. Each dimension comprises 5 levels with corresponding numeric scores, where 1 indicates no problems, and 5 indicates extreme problems. The health status is converted to an index value using the country-specific weighted scoring algorithm for the United States (US). The summary index value for the US ranges from a worst score of -0.109 to a best score of 1. An increase in the EQ-5D-5L total score indicates improvement.
	Time Frame:		Baseline, Week 1

Protocol Amendments

Best Practice

Within 30 days of IRB approval of protocol amendment:

- Update record for any existing outcome measures that are changed/deleted
- Incorporate new outcomes added
- Discuss outcomes removed in Study Description (Detailed Description)

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=NKYRLN8WXR4M3CMX

Thank you!

Biostatistical Support & Resources

Some services are free, others have fee-for-service charge:

- 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
- Research Electronic Data Capture or REDCap: https://tracs.unc.edu/index.php/services/informatics-and-data-science/redcap

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References

- Best Practices in Clinical Research Protocol Writing: Eight tips from an IRB member.Protocol Writing Tips from IRB Member
- 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