Writing a Study Protocol:
Critical Pieces to Include

Sharon Herring, MD, MPH

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What is a research protocol?

- A predefined written procedural method in the design and implementation of experiments
  - Answers specific research questions
  - Safeguards the health of participants
  - Allows for standardization and dissemination

It is the detailed, written plan of the study

Key pieces/format

1) Title
2) Summary/Abstract
3) Project narrative
   - Aims/hypotheses
   - Rationale
   - Methodology/approach
4) Ethical considerations
5) References

1) Title

- Should be descriptive and concise
- Sometimes requires revision at protocol completion to better reflect the study purpose

1) Title

- Search NIH reporter in your field of study for ideas

5 R01 MH084897 05	FOR MOMS:CULTURALLY RELEVANT TREATMENT FOR PERINATAL DEPRESSION	GROTE, NANCY K	UNIVERSITY WASHINGTO
5 K23 HL106231 03	PREVENTING POSTPARTUM WEIGHT RETENTION AMONG LOW-INCOME, BLACK WOMEN	HERRING, SHARON J	TEMPLE UNI COMMONWE
5 U01 HD072834 03	PREGNANCY AND EARLY LIFESTYLE IMPROVEMENT STUDY (PEARLS)	JOSHIPURA, KAUMUDI J et al.	UNIVERSITY PUERTO RIC SCIENCES
5 R01 HD068802 02	RELATIONSHIP OF LOSS OF CONTROL EATING TO EXCESSIVE GESTATIONAL WEIGHT GAIN	LEVINE, MICHELE D	UNIVERSITY PITTSBURGH PITTSBURGH
5 U01 HL096760 05	ELECTRONICALLY-MEDIATED WEIGHT INTERVENTIONS FOR PREGNANT AND POSTPARTUM WOMEN	OLSON, CHRISTINE MARIE et al.	CORNELL UN
5 R01 DK087889 03	PREVENTION OF POSTPARUTM WEIGHT RETENTION IN LOW INCOME WIC WOMEN	PHELAN, SUZANNE	CALIFORNIA STATE U SAN OBISPO
5 K24 HL096141 09	UNIQUE CARDIOVASCULAR RISK FACTORS IN WOMEN RESEARCH AND MENTORING PROGAM	SEELY, ELLEN W	BRIGHAM AN WOMEN'S HO

Keyword search:
Postpartum
weight retention

2) Summary/Abstract

- Should summarize all elements of protocol
  - Rationale
  - Aims/hypotheses
  - Overview of methods (study design, independent/ dependent variables, measures)
- Should stand on its own
- Be concise (aim for 250 words)
- Often written last (grabs from all sections of protocol)

Example abstract and identification of critical pieces

Protocol: *The Influence of Postpartum Sleep Duration on Adiposity and Cardiometabolic Risk Factors in Urban Mothers: Project SLEEP*
PI: Sharon J. Herring, MD, MPH

1) Abstract of the study

Low-income, ethnically diverse women have the highest rates of obesity in the United States. The childbearing period represents a critical life stage of heightened vulnerability for excess weight gain and thus obesity risk. However, efforts to develop effective peripartum obesity prevention interventions among racial/ethnic minorities have been hampered by the lack of data about modifiable determinants of weight retention and adverse physiological outcomes in the year after childbirth. One novel, potentially modifiable predictor of increasing interest is sleep duration, as numerous epidemiologic studies have found that insufficient sleep is linked to obesity and cardiometabolic disease. Most mothers experience sleep deprivation during the first postpartum year, yet few investigators have examined the influence of sleep curtailment on adiposity and cardiometabolic risk factors after childbirth, and no studies have explored these relationships in ethnically diverse, socially disadvantaged mothers. The scientific goal of the proposed research is to use observational epidemiology to examine the influence of postpartum sleep duration on adiposity and cardiometabolic risk factors in a cohort of 540 urban, low-income mothers. An additional goal is to explore factors influencing postpartum sleep time. Findings from this study have the potential to inform and change clinical care to reduce low-income mothers' risk of obesity and cardiometabolic morbidity through modifications in sleep duration.

Rationale

Aims,
Study Design,
Variables

3) Project narrative

- Aims/hypotheses
  - Statements of the research question(s)
  - Simple, specific, stated “a priori” - before the research is concluded
  - Need to have statistical power to test the main objectives – so resist the temptation to have too many aims!
    - Secondary or exploratory aims do not need to prove statistical power

Example aims/hypotheses for different study designs

The specific aims and hypotheses are:

Aim 1. To determine the extent to which postpartum sleep duration is associated with weight retention in the first year after childbirth. *Hypothesis: Shorter sleep duration in the early (< 6 months) postpartum period is directly associated with higher 1-year postpartum weight retention.*

Aim 2. To determine the extent to which postpartum sleep duration is associated with cardiometabolic risk factors in the first year after childbirth. *Hypothesis: Shorter sleep duration in the early (< 6 months) postpartum period is directly associated with higher blood pressure, higher waist circumference, greater insulin resistance, and dyslipidemia at 1 year after delivery.*

3. SPECIFIC AIMS

3.1 Primary Aim – Effects on Maternal Weight

To compare changes in weight from early pregnancy (weight at enrollment) to 6-months postpartum among Black mothers randomly assigned to the pregnancy and postpartum intervention (PP) versus usual care (UC).

We hypothesize that mothers assigned to PP will weigh 3.2 kg less at 6-months postpartum than those randomized to UC.

3) Project narrative

- Rationale
  - Equivalent to introduction in a research paper
  - Puts proposal in context
  - Answers why the research needs to done
  - Most relevant studies on the subject should be referenced
  - Aim for 2 pages maximum

3) Project narrative

- Methodology/approach
  - Research design
  - Research subjects
  - Measures (independent/dependent variables)
    - If independent variable is a treatment, more details need to be provided
  - Statistical analyses and power calculations

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Options in research designs

2 main study types

- **Analytic Studies**
  - Experimental Study: RCT
  - Prospective Cohort Study
  - Retrospective Cohort Study
  - Case-Control Study
- **Descriptive Studies**
  - Ecologic Studies
  - Cross-sectional Studies
  - Case Series / Case Reports

- Lacks a comparison group
- Hypothesis-generating
- 1st step in formulating a research questions
  - Prevalence of outcome
  - Prevalence of exposure
  - Useful in policy

Options in research designs

Hierarchy of studies

- **Analytic Studies**
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Best at establishing causal relationships (typically for treatments & dz prevention)

Provides weakest evidence for cause-effect

Options in research designs

Hierarchy of studies – WHY? Because of BIAS in Design

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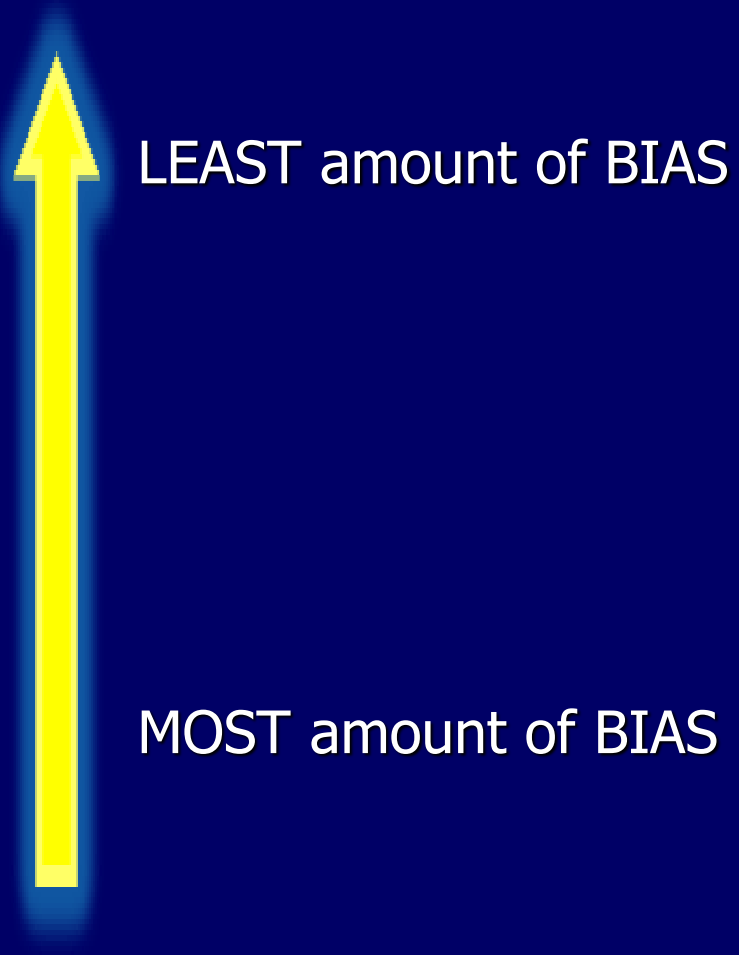

Research subjects

- What are the criteria for inclusion or selection?
- What are the criteria for exclusion?
- In intervention studies, how will subjects be allocated to index and comparison groups?
  - Random number generator (who is blinded to group allocation)
- What are the criteria for discontinuation?

Measures

- Description of specific variables, how they will be measured, frequency of measures
- Questionnaires should be appended to protocol
- Lab or other diagnostic procedures should be described

Example of table to present measures, frequency

Measure	In-Person Screening	Timepoint		
		Baseline (pregnancy study week 1)	6-months postpartum	1-year postpartum
Visit	**1**	**2**	**3**	**4**
Informed consent	X			
Past medical history	X			
Questionnaires	X	X	X	
Maternal weight	X	X	X	X
Maternal height		X		
Maternal waist circumference		X	X	
Maternal blood pressure		X	X	
Fasting blood collection (mothers only) * 6 teaspoons at each visit HbA1c Insulin Glucose C-peptide Cholesterol, LDL, HDL, Triglycerides Uric acid		 X X X X X X	 X X X X X X	
Infant weight			X	X
Infant length			X	X
Adverse events		X	X	X
Medications added/adjusted	X	X	X	X
Medical record review		X	X	
Treatment acceptability			X	

Treatment

- Description of treatment (e.g., drugs, devices, behavior therapy) to be used
  - Are these drugs/devices already commercially available?
  - Are these drugs/devices in phases of experimentation?
  - How is the study treatment administered?
- Description of literature (human and/or animal data supporting use of treatment)

Example of intervention administration instructions

5.3.1 Dose levels and escalation regimen for oral dosing

Subjects on the oral dosing (treatment arms 1-8) must administer the dose following specific rules:

- Fasting for at least six hours (e.g., in the morning following an overnight fast) before tablet ingestion
- Water and oral concomitant medication is allowed two hours prior to dosing
- Intake of maximum 120 mL of water is allowed when swallowing the tablet
- Subjects are required to abstain from food and fluid intake for at least 30 minutes after ingestion of oral semaglutide or placebo
- Oral concomitant medication can be taken two hours post-dosing. If taken with food, concomitant medication can be administered 30 minutes after ingestion of the semaglutide or placebo tablet

See illustration of oral dosing and fasting rules in Figure 5–2.

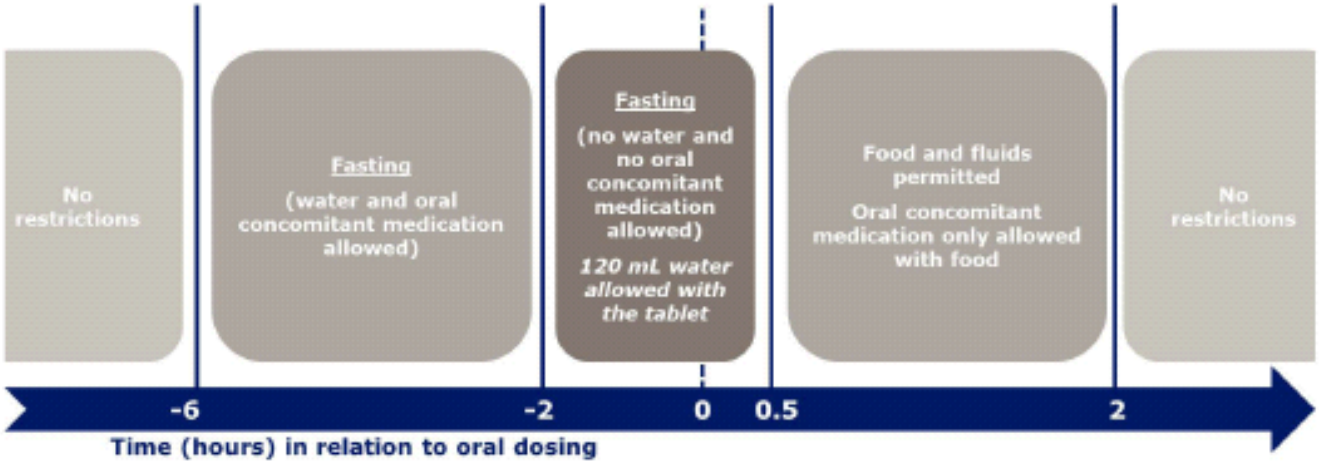

Figure 5–2 Dosing and fasting conditions for oral treatment (arms 1-8)

Statistical analyses

- A priori, statistical tests need to be identified to confirm/refute study hypotheses
- Additionally, information on how data will be managed (and kept confidential) must be included

Example of a statistical analysis section

Statistical analyses will be performed by the Center for Obesity Research and Education at Temple University's School of Medicine. All analyses will be produced using the latest version of SAS software (SAS Institute; Cary, NC).

Preliminary and descriptive analyses. Data integrity will be assessed by descriptive statistical and graphical methods to examine assumptions (i.e., normality) that underlie statistical models. Transformations will be applied to continuous variables that display markedly non-normal or skewed distributions. To assess the randomization procedure, baseline values of all variables will be compared between the PP and UC groups. Group differences for continuous variables will be assessed using t-tests or the Wilcoxon test. Proportions will be compared using the chi-square test or exact tests.

Primary Outcome (changes in weight from early pregnancy [weight at enrollment] to 6 months postpartum) and Secondary Outcomes (changes in blood pressure, and waist circumference] from early pregnancy to 6 months postpartum). Data will be analyzed using an intent-to-treat (ITT) model where subjects are analyzed according to their treatment assignment, not according to the dose of treatment they actually received. All randomized subjects will be included in analyses. Differences between treatment conditions will be assessed via analysis of covariance (ANCOVA) at each time point adjusted for baseline values. We will add additional covariates to the ANCOVA models to control for important predictors of each outcome that are unequally distributed between the treatment groups. Since an ITT analysis is planned, 2 methods are proposed for accounting for the missing data at follow-up. First, multiple imputation methods[71] will be used to estimate the 6-month outcomes based on intermediate outcomes, mediating variables, and data collected on subjects with complete follow-up. A second approach will be to perform model-based analyses with direct maximum likelihood methods.[72]

Additional analyses will be done to evaluate our exploratory outcomes: changes in weight from early pregnancy (weight at enrollment) to 1 year postpartum; changes in infant weight and length from birth to 6 months and from birth to 1 year; and changes in survey measures from early pregnancy to 6 months postpartum.

Sample size calculations

- Justification about sample size should be provided
  - A larger sample size than needed:
    - Increases the study cost and duration
    - Unethical if it exposes human subjects to any potential unnecessary risk without additional benefit
  - A smaller sample size than needed:
    - Can also be unethical if it exposes subjects to risk with no benefit to scientific knowledge
- Ask for help from a statistician!

4) Ethical considerations

- Risks, Benefits of the study
- Inclusion/exclusion of specific groups
- Confidentiality
- Compensation for subjects in study
- Informed Consent, IRB Approval

4) Ethical checklist

- Is the research design adequate to provide answers to the research question?
- Is the method of selection of research subjects justified?
- Are interventions justified, in terms of risks/benefits ratio?
- For observations made, have measures been taken to ensure confidentiality?

5) References

- The protocol should end with relevant references on the subject

Tips for a solid protocol

- EXAMPLES! Best is an example of a protocol in your topic area or an example submitted to the same funding source
- Read the instructions from the organization (e.g., IRB) or funding agency (e.g., NIH) where you are submitting the protocol
  - Protocol format is usually (a little) different
- Get input from collaborators/mentors
- Start early! May take at least 6 months