

## Developing Protocols and Manuals of Operating Procedures

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(Laura Lee Johnson, PhD)

NIH – Introduction to the Principles and Practice of  
Clinical Research  
March 29, 2016

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### Objectives

- Define several parts of a protocol document
- Identify resources to assist in development of study designs and documents

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### Application vs. Protocol vs. MOP

- **Application**
  - NIH limits 6-12 pages, concise justification and design of clinical study
- **Protocol**
  - Detailed plan of the clinical study (no page limit)
- **Manual of Operations and Procedures (MOP)**
  - Finely detailed information describing the conduct and operation of a clinical study

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## Protocols and Manuals of Procedures

- Studies vary
  - Single detailed protocol
  - Protocol + Manual of Procedures (MOP)
- Multi-site studies
  - Different institutions may have varying protocol requirements
  - Using study MOP very useful
- Complicated or long procedures: MOP may be more useful
- Documents have to all agree!

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## Study Protocol: Purpose

- Road map for performance of study
  - Next step to operationalize application
  - Track changes recommended by IRB, clinical monitors, funding agency
  - Anticipate problems
- Safeguard participants' health and safety
- Facilitates communication among
  - Collaborators, employers, funding agency
- Assists in manuscript authorship/preparation

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NIH and FDA Request for Public Comment on Draft Clinical Trial Protocol Template for Phase 2 and 3 IND/IDE Studies

Notice Number: NOT-OD-16-043

**Key Dates**  
 Release Date: March 17, 2016  
 Response Date: April 17, 2016

**Related Announcements**  
 None

**Issued by**  
 National Institutes of Health (NIH)  
 U.S. Food and Drug Administration (FDA)

**Purpose**

**Background**  
 The National Institutes of Health (NIH) and Food and Drug Administration (FDA) are developing a template with instructional and sample text for NIH funded investigators to use in writing protocols for phase 2 or 3 clinical trials that require Investigational New Drug application (IND) or Investigational Device Exemption (IDE) applications. The agencies' goal is to encourage and make it easier for investigators to prepare protocols that are consistently organized and contain all the information necessary for the clinical trial to be properly reviewed. The draft template follows the International Conference on Harmonisation (ICH) E6 Good Clinical Practice.

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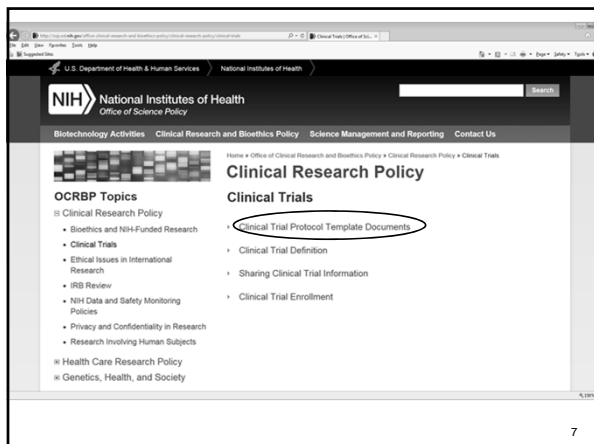
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## Protocol Components

- Specific objectives (3-5 aims of study)
- Background and rationale
- Concise statement of design
- Selection and enrollment of participants
- Interventions (if applicable), safety
- Methods or procedures, statistical considerations, data collection and quality assurance
- Participant rights and confidentiality
- Responsibility and authorship

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### Statement of Design

- "An observational study of decline in pulmonary function in persons living in heavily industrialized areas compared to persons in non-industrial areas."
- "A prospective, non-concurrent study of postoperative pneumonia in patients receiving regional vs. general anesthesia for peripheral vascular grafting."

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### What is the question of interest?

- Interpreting work into new population
- Making decision about individual case
- Looking at change in a population
  - Diabetes management
- Differences between groups in a study
- Biomarker or another outcome?
- Level of evidence
- Evaluation of evidence

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### Design and Analysis Problems

- Would XYZ be a more appropriate study design to answer the study aims?
  - Toxicity, tolerability, some efficacy
  - Pharmacodynamics, pharmacokinetics
  - Phase I, II, or an observational study
  - Which adaptive design?
- Not everything needs to be on the Phase III design framework
- Wide variety of question-appropriate designs

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## Participant Enrollment

- **Study enrollment procedures – address**
  - **How** will you identify and recruit?
  - **Where** will you recruit?
  - How will you document **ineligibility** and **nonparticipation** of **eligible** candidates?
  - Define consent procedure
  - Define randomization procedure if applicable

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## Participant Selection

- **Define participant / patient population**
  - Specific enough ↔ not too restrictive
- **Inclusion criteria**
  - Disease or condition under study
    - Examples: History of chronic pain, sleep disorder
  - Demographic characteristics
    - Age range
    - Sex
  - Required laboratory results, diagnostic tests
  - Ability to understand & comply with procedures

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### Participant Selection

- **Exclusion Criteria**
  - Each participant must meet specified criteria
    - Precludes participation: Specify clinical condition or health status that would make study difficult
    - Participants for whom one treatment or another would be unethical or inappropriate
    - Laboratory results or diagnostic tests (provide range)
  - Participants who take certain meds or are engaged in behavioral interventions

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### Participant Selection

- **Exclusion Criteria**
  - **Safety of participants is primary concern**
    - Pregnancy or pregnancy testing
    - Drug/alcohol dependence
  - “Logistic” concerns
    - Less than 18 years of age
    - Critically ill
    - Expected to leave area
  - Circumstances likely to make determination of outcome **difficult** or **impossible**

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### Protocol Components

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  - Responsibility and authorship

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### Treatment Definition

- Specify as much as possible without interfering with patient management
- Realize that generalizability often lost in quest for specificity
- Specify criteria for withdrawal from study or deviation from protocol
- List concurrent medications, procedures, etc. that are prohibited or permitted

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### Interventions

- Product
- Dose
- Quality
- Administration and reproducibility of interventions (including training)
- Participant Implications

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### Dose can be Many Things

- Number of sessions/pills/treatments/social media attempts
- Frequency
- Length of sessions (each, total treatment time)
- Amount of practice
- Leader
  - Contact time
  - Who that person is
- Many different combinations

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### Time and Other Elements

- Time is our favorite confounder in uncontrolled studies
  - Differential time participating is an issue
  - Differential drop-outs
- Social support
  - Meeting in a group may have an impact
  - Talking to someone, empathy, may impact
- Exercise
  - Exercise helps cardiovascular risk factors
  - Exercise helps stress

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### What is the control group?

- Placebo
- Most widely accepted treatment
- Standard treatment
- Most accepted prevention intervention
  - Condoms and HIV?
- Usual care
- Accepted means of detection or diagnostic test

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## Concomitant Interventions

- Allowed
- Required
- Prohibited

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## Study Procedures

- Schedule of evaluations
- Description of evaluations
  - Screening through final evaluation
  
- Overall study time line
  - Impacts ability to perform study
- Timeline for individual study participant
  - Impacts people wanting to participate

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Assessment	Screening: Visit 0 (Day-14 to Day -1)	Baseline, Enrollment, Randomization Visit 1 (Day 0)	Treatment Visit 2 (W1)	Treatment Visit 3 (W2)	Treatment Visit 4 (W3)	Treatment Visit 5 (W4)	Treatment Visit 6 (W5)	Followup Final Visit (W10)
Informed Consent Form	X							
Demographics	X							X
DXA	X							X
Medical History	X							
General Physical Examination	X	X	X				X	X
Current Medications	X	X						
Blood Chemistry	X	X	X			X		X
Hematology	X	X	X			X		X
Urine Analysis	X	X	X			X		X
Vital Signs	X	X	X	X	X	X	X	X
Inclusion/Exclusion Criteria		X						
Enrollment/Randomization		X						
Treatment Administration Form			X	X	X	X	X	
Concomitant Medications		X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X

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### Outcome Definitions

- Appointed panel of experts
- Previously widely-recognized study (SHEP, WHI, SOLVD)
- Adjudication: submit to panel of masked, unbiased "experts"

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### Measurement

- What difference is scientifically important in units
  - 0.01 inches?
  - 10 mm Hg in systolic BP?
- How variable are the measurements (accuracy)? – *Pilot!*
  - Plastic ruler, Micrometer, Caliper
- Can others measure this and will anyone understand the difference intuitively?

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### Outcome Measures

- Sensitive to the magnitude of change expected
- Specific to changes expected in your outcome based on your study hypothesis
- May or may not have been used in pervious research
- Need to know the reliability and validity of the measure
  - Preferably in population under study

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**Is it a good measure?**

- Do you have reasonable reliability and validity data?
- Cost is a study budget question, not a “good” determinant
- May not have been published or used in previous research; you may be first!
  - That is ok, if you have the data to back it up
  - Other measurements help, too

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**Statistical Considerations**

- General design issues
- Describe treatment assignment or randomization procedures (if applicable)
- Interim analyses and stopping rules
- Data analyses

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**Sample Size**

- Specific analyses to answer each hypothesis
  - Appropriate to study design
- Why not use a 2-sided test?
- Attrition/drop-outs/missing data
- Multiple comparisons
  - Clarity
  - Multiple outcomes, interventions, time points
- Longitudinal/repeated measures
- Interim analyses of the outcome data

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### Analysis Plan

- Appropriate analyses for the study design
  - If it needs to be a two sample t-test, t-test
  - If it needs to be fancy, fancy
  - Reconsiders repeated measures ANOVA
    - Consider linear mixed models or generalized estimating equations
- Drop outs/missing data in the analyses

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### Analysis Plan

- Detail the interim analysis plan if interim analyses are anticipated (they may not be)
- Work with a statistician and/or epidemiologist
- Sample size must support analytic plan
- Clear can express research findings in a way that is relevant to the field and society AND will have information to plan future research

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### Intent to Treat versus Completers “How many in the data analysis”

- ITT = Intent To Treat analysis
  - Includes everyone randomized (if rand. study)
  - Assume all study participants
    - Adhered to the study regime assigned
    - Completed the study
- MITT = Modified ITT analysis
  - ITT, but only include people who start the intervention they are assigned to
- Completers or Adherers analysis
  - Only the well behaved

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## Protection of Human Subjects

- Monitoring for adverse effects
- Informing patient, physician of complications or abnormalities
- Interim analyses (*pre planned*)
- Data Safety Monitoring Board (DSMB) or other monitoring committee

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### Informed Consent

- Written informed consent
- Institutional review board (IRB): independent review and monitoring by panel including members outside institution

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### Write the Protocol

- Anyone can replicate the study
  - They may need the manuals of procedures, too
- Recommend one-stop document for all study needs
  - People will not flip to several different places
  - If information is in several different places it needs to match

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### Conclusion

- Document needs to make sense
- Statistical methods and sample size flow with the rest of the proposal
- Correctly staffed
- Implementable
- Practical
- Rigorous
- Testable hypotheses that address aims and goals of the research

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## Questions

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## Resources: General Books

- Hulley et al (2001) *Designing Clinical Research, 2<sup>nd</sup> ed.* LWW
- Rosenthal (2006) *Struck by Lightning: The curious world of probabilities*
- Bland (2000) *An Introduction to Medical Statistics, 3rd. ed.* Oxford University Press
- Armitage, Berry and Matthews (2002) *Statistical Methods in Medical Research, 4th ed.* Blackwell, Oxford

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### More Books

- *Statistical Reasoning in Medicine: The Intuitive P-Value Primer* by Lemuel Moye
- *Designing Clinical Research: An Epidemiologic Approach*, edited by Stephen Hulley
- *Critical Appraisal of Epidemiological Studies and Clinical Trials* by Mark Elwood

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### And More Books

- *Data Monitoring Committees in Clinical Trials: A Practical Perspective* by Ellenberg, Fleming, DeMets.
- *Fundamentals of Clinical Trials* by Friedman, Furberg, DeMets
- *The Statistical Evaluation of Medical Tests for Classification and Prediction* by Margaret Sullivan Pepe

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### Resources: Articles

- Simon R. Optimal two-stage designs for phase II clinical trials. *Controlled Clinical Trials*. 10:1-10, 1989.
- Thall, Simon, Ellenberg. A two-stage design for choosing among several experimental treatments and a control in clinical trials. *Biometrics*. 45(2):537-547, 1989.

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### Regulatory Guidances

- ICH E9 Statistical principles
- ICH E10: Choice of control group and related issues
- ICH E4: Dose response
- ICH E8: General considerations
- US FDA guidance and draft guidance on drug interaction study designs (and analyses), Bayesian methods, etc.
  - <http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234622.htm>

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### REDCap

- Research Electronic Data Capture
- <http://project-redcap.org/>
- Started by Vanderbilt University
- 450+ active institutional partners (US+)
- Secure web application
- Build and manage online surveys and databases quickly and securely
- 47000+ projects

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### AssessmentCenter

- <http://www.assessmentcenter.net/>
- Online research management tool
- Create study-specific websites
- Capture participant data securely
- PROMIS instruments (short forms, CATs, profiles) are a central feature
- Automated accrual reports
- Capture endorsement of online consent

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## Resources: URLs

- NIH Office of Science Policy Draft Clinical Trial Protocol Documents(templates)
  - <http://osp.od.nih.gov/office-clinical-research-and-bioethics-policy/clinical-research-policy/clinical-trials>
- Sample size calculations simplified
  - <http://www.jerrydallal.com/LHSP/SIZE.HTM>
- Statistics Guide for Research Grant Applicants, St. George's University of London
  - [www-users.york.ac.uk/~mb55/guide/guide.htm](http://www-users.york.ac.uk/~mb55/guide/guide.htm)
- Software: nQuery, EpiTable, SeqTrial, PS (<http://biostat.mc.vanderbilt.edu/twiki/bin/view/Main/PowerSampleSize>)
  - <http://tinyurl.com/zoysm>

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