Developing Protocols and Manuals of Operating Procedures

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NIH – Introduction to the Principles and Practice of Clinical Research
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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

Related Announcements

Issued by

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How to Submit a Response

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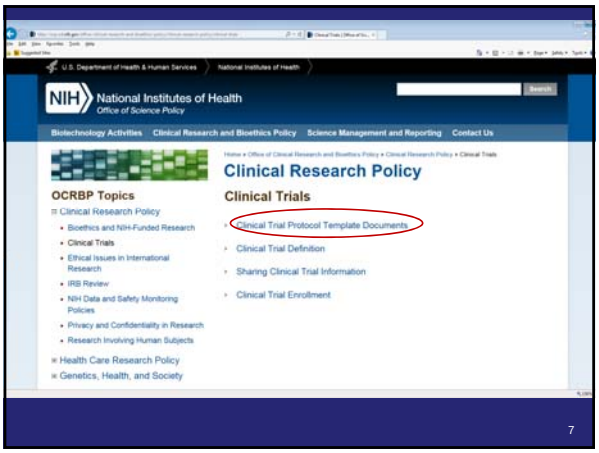

Protocol Components

- 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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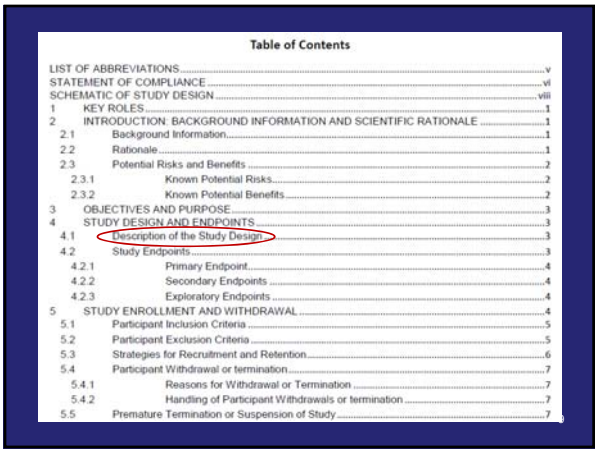

Statement of Design

- "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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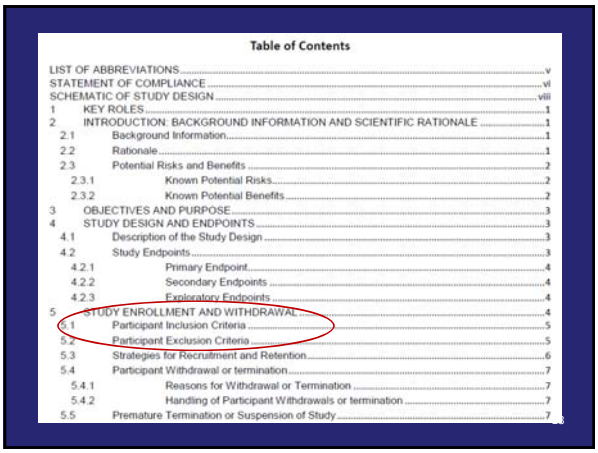

Table of Contents

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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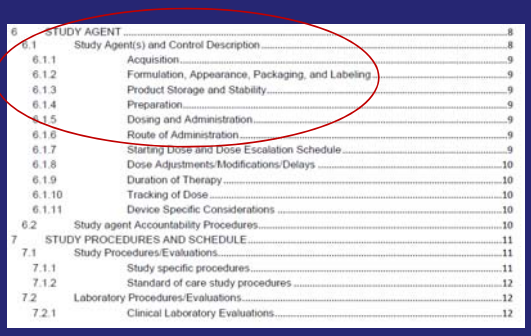

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Treatment Definition

- 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 Chemistries	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
  - Reconsider 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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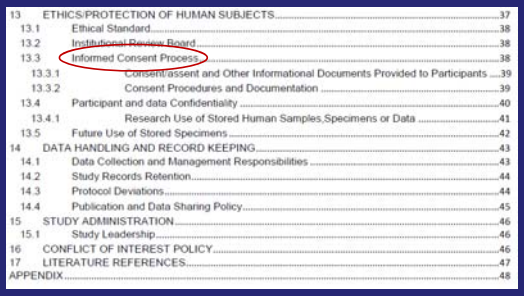

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Protection of Human Subjects

- 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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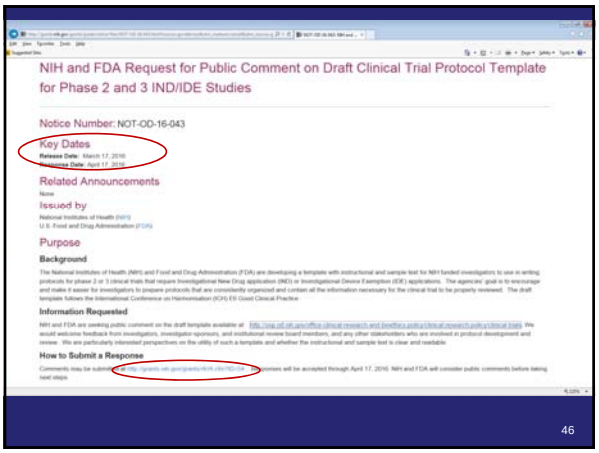
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Questions

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Resources: General Books

- Hulley et al (2001) *Designing Clinical Research, 2nd 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
- Software: nQuery, EpiTable, SeqTrial, PS (http://biostat.mc.vanderbilt.edu/twiki/bin/view/Main/PowerSampleSize)
  - http://tinyurl.com/zoysm

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