What information should be included in protocols submitted to the NIH IRP IRB?

AKA: How to write a protocol 101

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Objectives

- Understand how to write clear, specific and descriptive inclusion/exclusion criteria
- Recognize how justification of inclusion or exclusion of various vulnerable populations should be addressed in research protocols
- Identify what activities need to be described in the protocol (i.e. those that are research related) and what activities do not need to be described (those that are purely clinical and not driven by the protocol)
- Understand the need to describe how investigational devices will be used in the protocol
- Identify the factors that make a protocol “multi-site” and recognize specific information that needs to be included in the protocol regarding activities at the non-NIH site(s)

Protocol = Recipe or Plan

"A document that describes the objectives(s), design, methodology, statistical considerations and organization of a trial."

(ICH GCP 1.44)

What:

- Purpose of the study

Why:

- Background/References

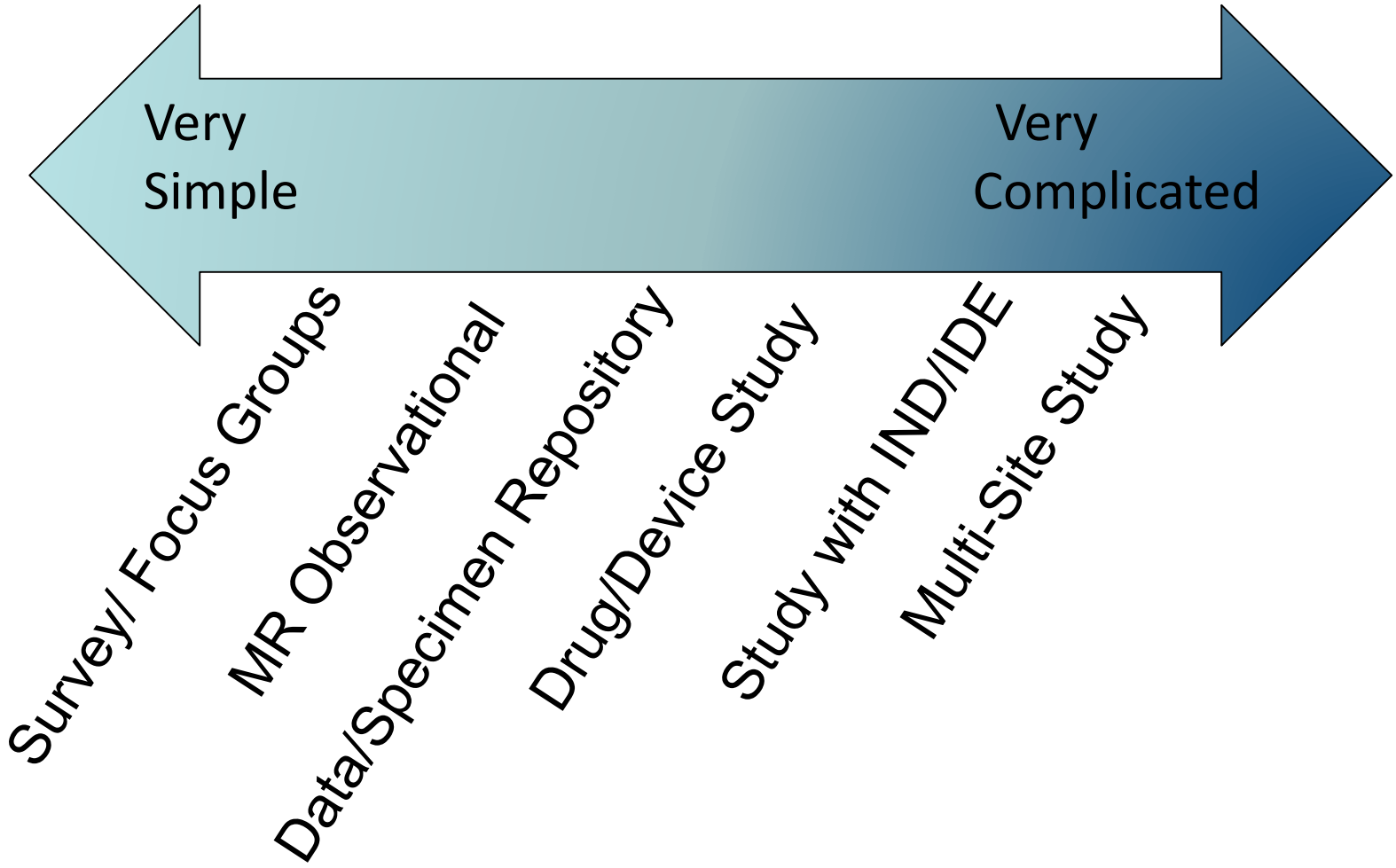
Who:

- Characteristics of the Populations

Where, When, and How:

- Subject's Identification, Recruitment and Consent/Assent
- Methods and Study Procedures
- Risk/Benefit Assessment
- Data Analysis

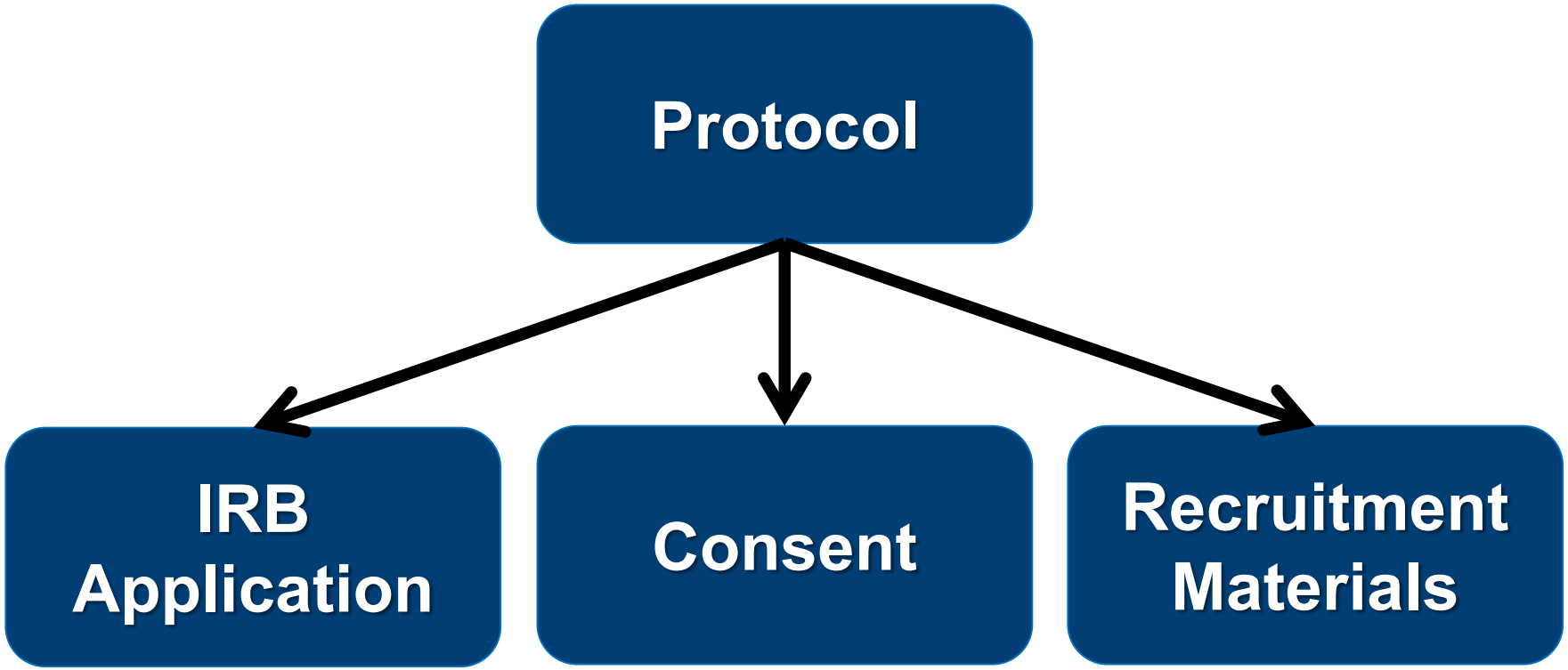
Protocol Complexity



Recipe or Plan… AND Rule Book

- Must comply with every word
- These “rules” are not meant to (and should not) be broken

Protocol, Application & Consent



PROTOCOL ≠ Protocol Document + Application + Consent

Purpose of the Study

- State the specific scientific objectives/aims of the research
- Should concur with:
  - Background
  - Eligibility Criteria (inclusion/exclusion)
  - Study Procedures
  - Plan for Data Analysis

What is your question?

Background/References

- State the problem
- Provide justification & rationale for why the proposed research is important
- Provide a summary of prior experience important for understanding the proposed study and it's procedures
- Include references to relevant literature

Why does this question exist?

Characteristics of the Population

- Describe your study subjects
  - Number of Subjects
  - Gender, Age, Racial/Ethnic Background
  - Vulnerable Populations (children, prisoners, cognitively impaired, NIH employees, etc.)
  - Eligibility Criteria (Inclusion/Exclusion)
    - BE SPECIFIC
    - Concur with purpose
    - Base criteria on scientific rationale
    - Don’t include criteria that are not necessary or will cause violations to occur

Who does this question affect?

Subject Identification & Recruitment

- Describe:
  - How you will identify potential subjects?
  - How, where and when potential subjects will be approached for participation?
- Both processes must:
  - Protect subject's privacy
    - Initial contact must come from someone with routine access→ No cold calling!
  - Be free of undue influence
    - Avoid (or manage) recruiting subordinates

Subject Identification & Recruitment

- Identify and explain all recruitment material
  - e.g. Flyers, letters, brochures, etc.
- If no subject contact: Explain how you will access specimens/data
  - e.g. Retrospective chart review: Identify subjects via MRN, imaging databases, etc.

Process of Consent

- Describe the Process: Who? How? Where? When?
- Address any additional requirements and/or considerations for vulnerable populations
- Address how subject comprehension will be assessed
  - i.e., How will you determine the subject understood the information presented?

Process of Consent

- Describe how the consent will be documented and stored
  - How will consent be documented?
    - Signed consent? What if you're only obtaining verbal consent?
    - Will you document the process beyond a signature on a form? (**Required for studies involving an IND & studies in the CC must have documentation in CRIS)
  - How/where will documentation be stored?

Methods & Procedures

- Where will the study be carried out?
  - If research activities are taking place at more than one site, describe which specific activities are taking place at each site.
  - Include: the site(s) where subjects are being enrolled/evaluated, and any other site where activities are taking place (e.g. analysis of identifiable specimens) which *engage* the site in human subjects research.
  - The contact information about each site should be listed in the study application in iRIS (not in the protocol)
  - If subjects are being enrolled at more than one site, a model consent should be provided to the NIH IRB.

Methods & Procedures

- Identify and describe **ALL** research procedures
  - What will be done? How often? How will it be done?
  - Describe in step-by-step format
    - Start at the beginning, end at the end
  - Use a Schedule of Activities table/grid when possible
  - Describe all procedures that will be done for research purposes. For example, all protocol specified labs, imaging studies etc. Do not describe procedures that are not done as part of the research, i.e. procedures done solely for the clinical care of the patient.
  - Details and risks of standard of care procedures should not be described in the protocol

What needs to be done to answer this question?

Schedule of Activities

Procedures	Screening Day -7 to -1	Enrollment/ Baseline Visit 1, Day 1	Study Visit 2 Day 7 +/-1 day	Study Visit 3 Day 14 +/- 1 day	Study Visit 4 Day 21 +/-1 day
Informed consent	X				
Demographics	X				
Medical history	X				
Physical exam	X	X			X
Vital signs	X	X			X
Height	X				
Weight	X	X		X	
Performance status	X	X		X	
Hematology	X	X	X	X	X
serum chemistry [a]	X	X	X	X	X
Pregnancy test [b]	X				
EKG	X				

Methods & Procedures

- Specifics:
  - What procedures will be done in each population (e.g. children, pregnant women)
  - How much total blood will be drawn at each time point?
  - What information will be collected from the medical record?
  - What surveys or interviews will be done?
  - What are the randomization procedures? Is it blinded?
  - What treatment phases/ doses/ scheduling are involved?
  - Will data/specimens be stored for future use?

Methods & Procedures

- YES – specimens will be stored for future use
  - What specimens will be stored?
  - How will they be identified?
  - Who will have access?
    - Investigators on the project only
    - Will they be shared with other Investigators…if shared with other Investigators how will they be identified? Coded, de-identified?
  - Will they be used for just this disease/disorder or possibly used for any type of research?
  - Is it ***required*** or ***optional***?

Investigational Drugs & Devices

- Any drug, biological product, imaging intervention, or device that is intended for administration in humans or use in humans, and has not yet been approved by the FDA is considered investigational and can only be used in a research protocol, except expanded access.
- The protocol must be submitted to the FDA for review (as part of an IND/IDE application) or justification provided in the protocol as to why the investigator thinks the use of the product is IND/IDE exempt.
- Indicate if the product is commercially available and being used according to approved labeling or note how it is being used differently.

What is a device?

A medical device is an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is—

- recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,
- intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
- intended to affect the structure or any function of the body of man or other animals, and

which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes (21 U.S.C. 321(h)).

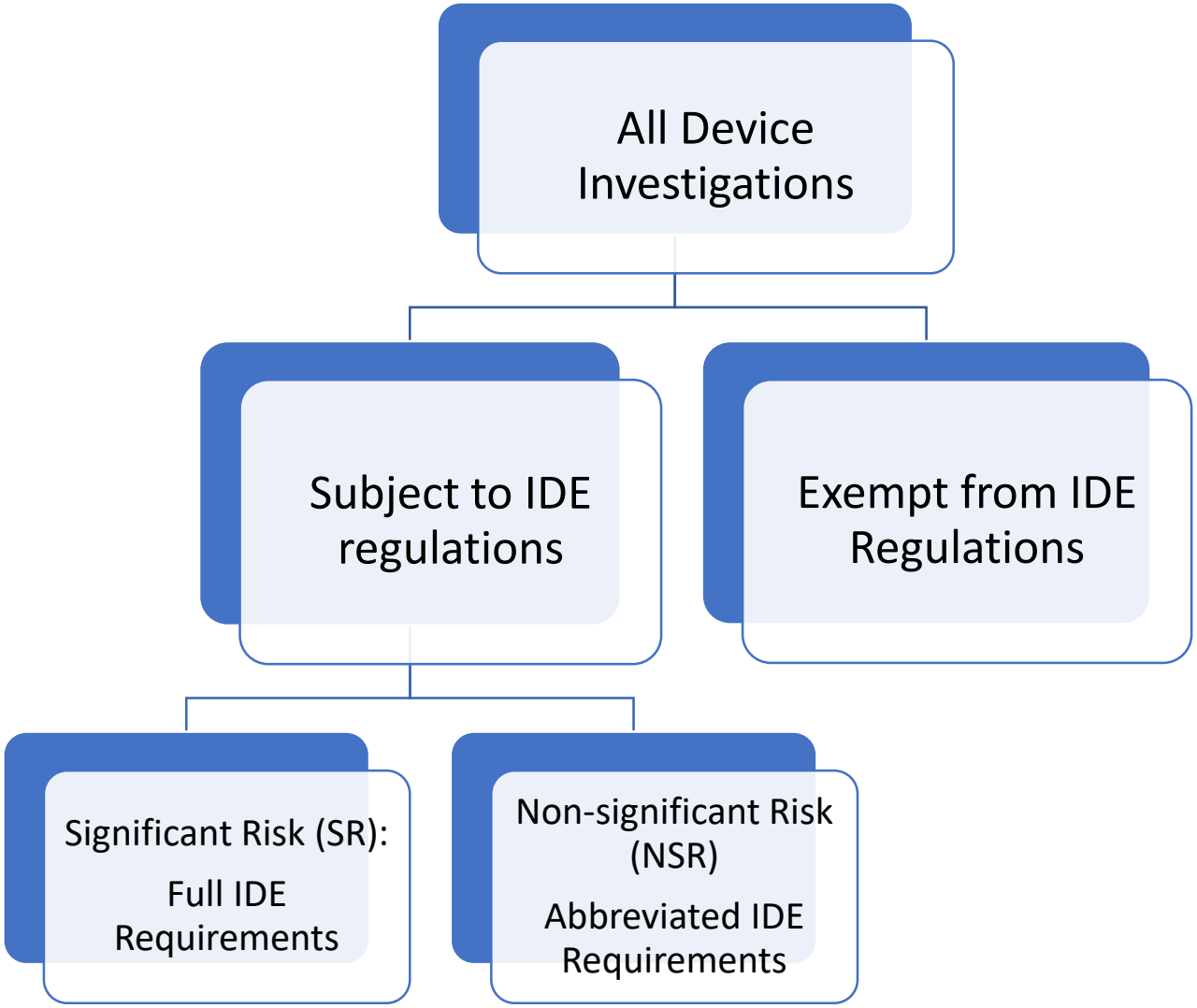
What is an investigational device?

- Investigational device means a device, including a transitional device, that is the object of an investigation (21 CFR 812.3(g)).
- Investigation means a clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device (21 CFR 812.3(h)).

How do you know the FDA has approved the use?

- Look it up!
  - PMA approvals http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm
  - 510k approvals: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm
  - Exempt: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpcd/315.cfm

When do you need an IDE?



Who decides SR vs. NSR

- If previously decided by the FDA, sponsor should provide the determination letter.
- If no previous FDA decision, sponsor/PI makes initial determination.
  - The sponsor/PI MUST include in the protocol the rationale for why they think the device is IDE exempt, NSR or SR
- IRB must review and either agree or modify the sponsor/PI determination if they disagree.
- FDA is final arbiter if submitted.

Cost & Payments

- Costs - Describe and justify any cost to the subject
- Payment: Describe payments (cash, gift cards, extra credit, movie tickets, etc.)
  - How much? How often? How received?
  - Amount must be justified & pro-rated

Risk/Benefit Assessment

- Risks to Subjects
  - Describe any potential physical, psychological, sociological, economic and legal risks of the research procedures/interventions
    - Probability that the given harm may occur?
    - Reversibility?
  - How will you prevent and/or minimize risks?
    - Trained personnel?
    - Withdrawal of subject?
    - Referral for treatment, counseling or other necessary follow-up (including who will pay)

Risk/Benefit Assessment

- Potential Benefits *to the Subject*
  - DO NOT OVERSTATE
  - If none, this should be stated
  - However, if you actually know of some potential benefit, it is good to provide it. For example, it is way more informative to say something like "10% of subjects in earlier trials had some therapeutic benefit" then the typical."
  - Note: Payments and medical care the subject may receive while participating are not considered a benefit
- Alternatives to Participation
  - Biomedical: Treatment available outside the research (if none, this should be stated)

Privacy vs. Confidentiality

- Privacy
  - Protect access to individual/data/specimens
    - Access to an individuals information
    - “How did you get my name?”
- Confidentiality
  - Protect the research data once it’s collected
    - Who has access? How is the portable device that contains the data protected? Are the data collection forms in password protected?

Privacy vs. Confidentiality

- Describe what measures will be taken to protect the confidentiality of subjects?
  - Will datasets and/or specimens be coded or completely de-identified?
  - How will your data/specimens be stored?
  - Who will have access to data/specimens?
  - How will you protect against disclosures?
  - How long will the information be kept?

Reportable Events

- Describe the process for identifying and reporting any symptom, sign, illness or experience that occurs during the study
  - Timeframe for identification (e.g. consent to 30 days after, consent to last visit?)
  - Requirements for follow-up?
  - Who reviews? Forms completed?
  - Reporting requirements?
- Include a reference to the IRB reporting requirements (Policy 801)

Data & Safety Monitoring

- Data & Safety Monitoring
  - How will the safety of the subjects and continued validity, scientific merit and integrity of the data be monitored?
  - Who is monitoring? When?
  - The plan should be based on nature, size & complexity of the protocol
  - Range: PI → Independent DSMC

Data & Safety Monitoring Examples

a) Minimal Risk Observational Study

b) Multi-Site GTMR Study with an Investigational Device (with an IDE)

c) Single-Center GTMR Study with an Investigational Drug (IND exempt)

1) PI Monitors Study

2) PI with Independent Safety Monitor

3) Data Safety Monitoring Committee

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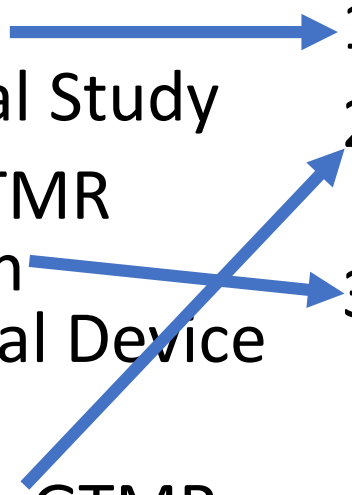


1) PI Monitors Study
2) PI with Independent Safety Monitor
3) Data Safety Monitoring Committee

***IRB makes the final decision on what DSM is appropriate

Data Analysis

- Planned Statistical Analysis
  - How will the data be evaluated in relation to the objective(s)
  - What statistical approach will be used?
  - How was the sample size determined?
    - Formal sample size calculations – dependent upon the type of study
    - Medical record review vs. randomized trial

Additional Elements

- Rationale for Study Design, Dosage
- Subject Compliance Assessments
- Accountability & Administration of Investigational Products
- Return of Individual Research Results
- Concomitant & Disallowed Medications
- Subject Withdrawals
- Research Info in the Medical Record

Lessons Learned

- Use the NIH IRB protocol template
  - Ensures that you are addressing the essential elements
  - Don’t repeat yourself
  - Start with a new template each time; do not copy and paste from old protocols.
- Little things go a LONG way….
  - Title and Principal Investigator on the first page
  - Page numbering
  - Schedule of Activities (by cohort if applicable)
  - Version Control (update the version date with each amendment)
  - Track changes (with each amendment)

Lessons Learned

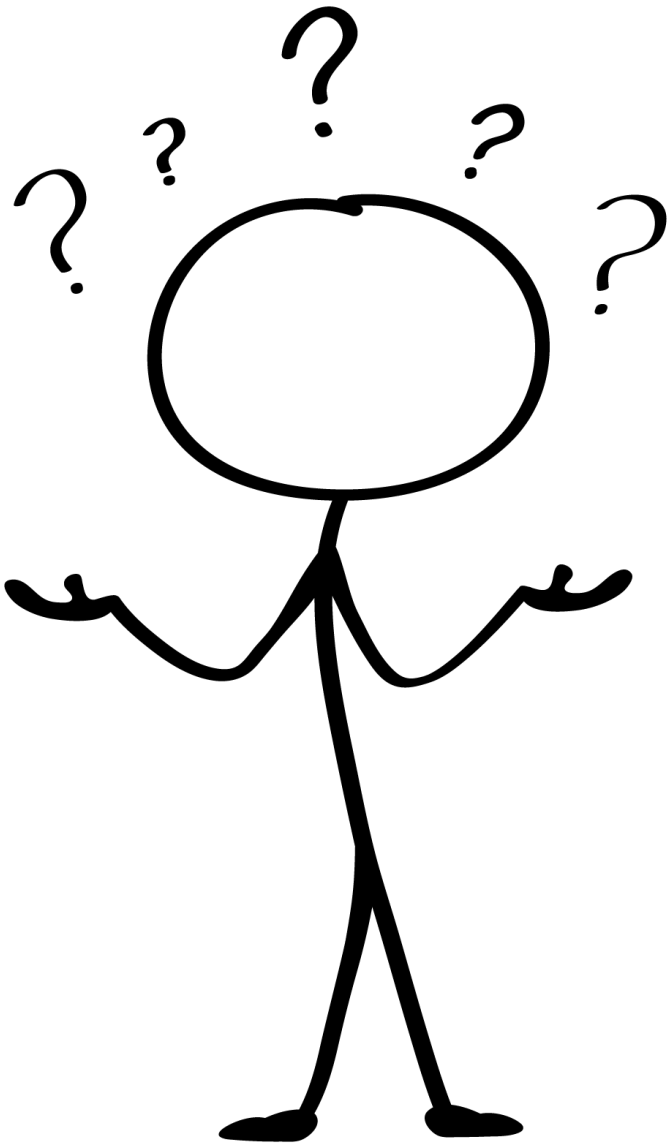
- Avoid “mad scientist” protocols
  - The more sub-studies, objectives, procedures, data, etc….the more likely to have compliance problems and issues with data reporting at the end of the study
  - Keep the protocol as “clean” and straightforward as possible

Lessons Learned

- Ask yourself:
  - Have I provided enough detail for another person to replicate the study?
  - Am I inadvertently including protocol defined procedures that may not apply or are unnecessary?
- Don’t leave items open for interpretation

Lessons Learned

- Don't shoot yourself in the foot. Write and review your protocol with an (overly) critical eye
  - Can you comply with *every* word you have written?
  - Are you inconsistent in the descriptions of your procedures?
  - Is your protocol inconsistent with the consent documents, study measures, recruitment materials & iRIS application?
  - Is everything do-able?
- Have a second set of eyes review the protocol!



Resources

- DHHS/OHRP Guidance: Regulations, Policy, & Posting | HHS.gov
- FDA-Clinical Trials and Human Subject Protection: Clinical Trials and Human Subject Protection | FDA
- FDA IND Applications for Clinical Investigations-Clinical Protocols: IND Applications for Clinical Investigations: Clinical Protocols | FDA
- ICH GCP E6: E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) | FDA
- NIH HRPP Policies and Guidelines: Policies and SOPs - Policies and SOPs - Confluence