Human Subject Research Protocols:

If you write it *(well)*, they will come

Helpful Tips and Tricks for Developing and Amending Protocols for the Rare Disease Clinical Research Network

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Presentation Overview

1. Introduction
2. DMCC Protocol Review Process
3. DMCC Resources Available
4. Protocol Sections
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Introduction

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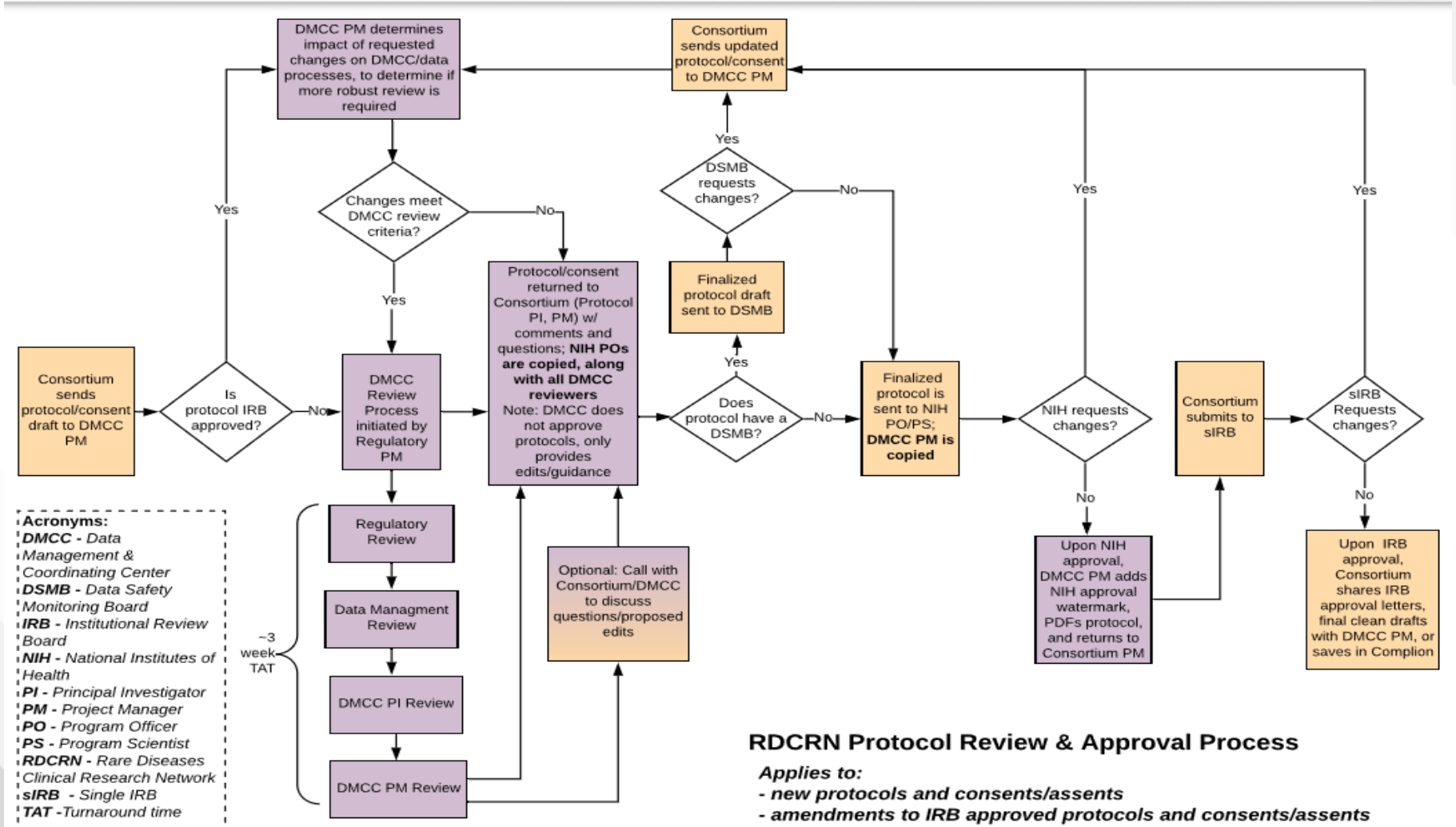
- PhD in Biochemistry and Molecular Biology
- Experience in both the Contract Research Organization (CRO) and Academic Regulatory Landscapes.
  - At Medpace, Inc., I spent 2 years as a Medical Writer and Regulatory Affairs Project Manager. Responsible for creating protocols and clinical study reports as well as being the regulatory lead for the successful submission of multiple INDs and an NDA to the FDA.
  - At CCHMC, I've spent approximately 1 year as a Senior Specialist Regulatory Affairs working on generating new content and reviewing protocols for the RDCRN and work as a regulatory lead for IND submissions for groups at CCHMC.

DMCC Protocol Review Process



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DMCC Resources Available

1. DMCC Protocol Template and Checklist

- Checklist details each section to allow you to decide what is needed.
- The template provides some standard language to assist in writing certain protocol sections.

2. DMCC Pilot Project Protocol Template

- Template for small initial studies or studies involving only human samples, existing data, etc.
- Based on the standard Protocol Template but trimmed down.

3. Grant to Protocol Conversion Document

- The document highlights key differences between a Grant application and Human Subject Research Protocol.

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Human Subject Research Protocols

- With a Grant, the focus is on Scientific Merit, but with a Protocol, the focus should be on **study design and its ability to be implemented in keeping with regulatory requirements**.

- Write the protocol with your coordinators in mind.
  - A team member should know what to do at each study visit(s) after reading the protocol and be able to easily use the protocol as a reference.

- Remember things will change (team members, equipment, test supplies) so being appropriately general in the protocol can prevent the need for amendments to adjust protocol details, but not so general that key human subjects concerns are omitted or that new personnel cannot carry out study visits and procedures according to plan

Protocol Synopsis

Protocol/IND Number

Sponsor/Investigator
Version Number/Date of Version

Protocol Synopsis

Protocol Number	
Title of Study	
Phase of Clinical Trial	
Indication	
Study Objectives	
Study Design	
Treatment Duration	
Study Center(s)	
Study Endpoint(s)	
Study Treatment	
Inclusion/Exclusion Criteria	
Sample Size	
Statistical Analysis	
Protocol Version	

- The protocol synopsis should be viewed as a Quick-Use Guide.
- The Synopsis should be written so that it could be used without the rest of the protocol.
- The Synopsis should detail the major components of your study (i.e., Objectives, Endpoints, I/E Criteria, Analysis).
- Text in the Synopsis should be identical to text used in the key sections of the protocol. This should make it easy to update protocol and synopsis as the protocol changes.

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Adapted from RDCRN DMCC Protocol Template V4

Protocol Background

- This section is quite different from the Specific Aims, Significance and Innovation sections of a Grant.

- A Protocol's Background section should *succinctly* do the following:
  - Introduce the disease.
  - Discuss any previous nonclinical or clinical work.
  - Discuss the Study Intervention (Drug/Device), if applicable, along with the proposed Risks/Benefits of that Intervention.

- The DMCC requests that a subsection be included that discusses how the protocol will lead to Clinical Trial Readiness, since this is a major objective of the RDCRN to which human subjects research should be aligned.

- The Specific Aims section of your Grant will be better used in the Study Objectives section of the Protocol than detailed in the background.

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Study Objectives/Endpoints

- Study Objectives should be clear, concise statements that are being evaluated during the study.
  - Grant Hypotheses can be used to create your Study Objectives.
  - Based on your overall objective your Objectives should be subdivided into Primary, Secondary, and if applicable Exploratory.

- Study Endpoints detail the specific measurements/outputs that will support the evaluation of the Study Objectives.
  - Endpoints should be associated with a Study Objective.
  - Endpoints can also be divided into Primary, Secondary, and if applicable Exploratory.

- You do not need to provide the rationale for your Study Objectives and Endpoints in those sections.

- You should compare your Study Endpoints with your Schedule of Activities/Events Table to ensure you have accounted for every output.

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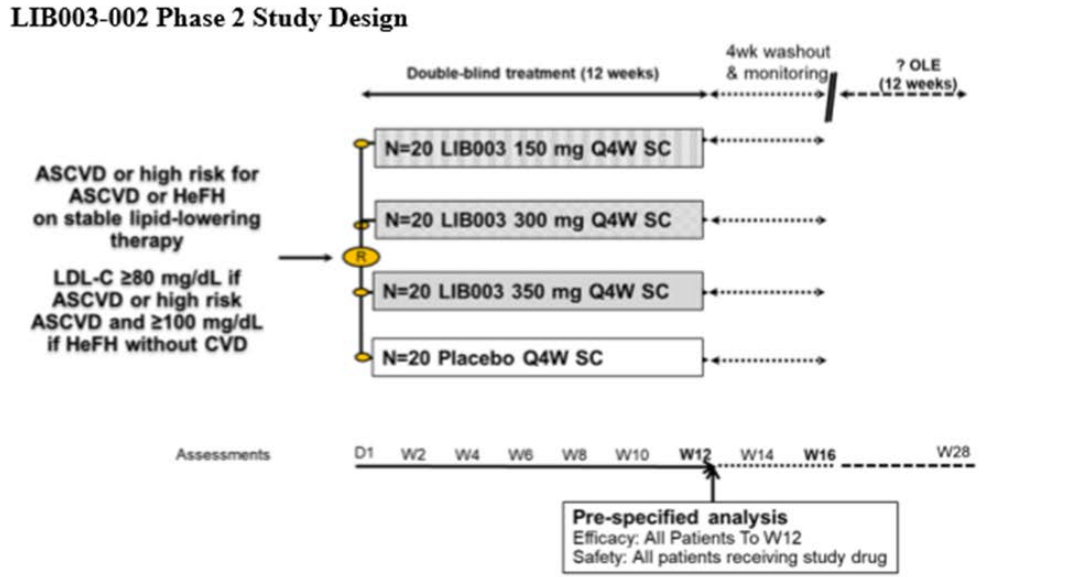
Study Design, Enrollment, and Retention

- A Study Schema is a helpful way to illustrate the overall design/flow of a protocol.
  - An easy point of reference for study team members.
  - Most useful when there are multiple visits.
  - Figure legend should provide details and definitions of any abbreviations.



ASCVD = atherosclerotic cardiovascular disease; CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; HeFH = heterozygous familial hypercholesterolemia; OLE = optional longer-term extension; Q4W = every 4 weeks; SC = subcutaneous; W = week; wk = week.

From LIB Therapeutics LLC, Clinical Trial Experience: NCT03549260

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Study Design, Enrollment, and Retention (con't)

- The Protocol should discuss how recruitment and retention will be handled.
- Study Retention is important to consider when your study requires any of the following: a) a high number of visits, b) invasive procedures, or c) a long duration.
- Screen Failure should be considered:
  - Will Subjects be allowed to be rescreened?
  - If they rescreen, is there a necessary time between screenings?
  - How many times can they rescreen?
  - Do all Screening Tests need to be repeated during a Rescreen?

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Study Design, Enrollment, and Retention (cont'd)

- Subject Withdrawal:
  - What circumstances will determine if/when a subject will withdraw?
    - Patient withdraws consent
    - Lost to follow-up
    - Non-compliance or missed visits(s) and/or procedures
    - Safety Events
    - Other reasons?
  - If the subject withdraws, are there special procedures that need to be followed?
  - Will there be an Early Termination Visit?
  - Will the subject be replaced to achieve the target study size?
    - Does replacement depend on the characteristics of the withdrawn subject?
  - These criteria are often more relevant for Protocols that involve a study intervention but should still be considered for other types of studies.

Inclusion/Exclusion Criteria

- Well designed I/E Criteria can help avoid unnecessary protocol deviations or missing out on potential subjects.

- Consider what activities will occur during Screening:
  - Discuss which I/E Criteria can be completely evaluated during Screening.
  - Consider which I/E Criteria can be found in the medical record vs what needs to be collected during the Screening Visit.
  - Which, if any, I/E Criteria require a test result that can't be obtained during the Screening Visit?

- Compare your Inclusion Criteria (IC) to your Exclusion Criteria (EC). Avoid redundancy (mirroring) of IC and EC.
  - For Example, only one of the following is necessary:
    - IC#1 Patients between 8 and 18 years of age.
    - EC#1 Patients under 8 and over 18 years of age.

Inclusion/Exclusion Criteria (cont'd)

- Consider the timeframe of your study. Will a subject fail a criterion at a later time point based on how your criteria are written?
  - For Example:
    - IC#1 "Patients ≥8 and ≤18 years of age".
    - The study lasts for 2 years.
    - Patient #7 enrolls at the age of 18.
    - Consider changing IC#1 to "Patients ≥8 and ≤18 years of age at the time of Screening".

- A catch-all Exclusion Criterion is a useful way to ensure subjects that may have confounding conditions can be excluded.
  - For example: *"Has any other finding which, in the opinion of the Investigator, would compromise the subject's safety or participation in the study"*

- If your study will involve children/adolescents, remember that both Informed Consent and Assent will be needed.

- Number your criteria to allow for easy tracking of any Screen failures.

Study Procedures

- Study Visits should be appropriately detailed even when there is just one visit.
  - Make things clear for your Study Coordinators (Assume they may only read this Section):
    - What occurs?
    - Do events have to occur in a particular order?

- Be sure to specify visit windows for Study Visits and that windows are reasonable.

- A Schedule of Events (Activities) is a useful tool to ensure consistency in what is performed at each visit.
  - The SOE should present each Study Visit, Visit Window, Study Procedure, and the information needed to perform those procedures (timing, definitions for abbreviations).
  - Remember to compare the SOE with your Study Endpoints!
  - Remember to include Study Procedures like Adverse Events and Concomitant Medications
  - If your SOE is more than one page, repeat the header row.

- Note that a detailed explanation of how a procedure or test is performed is better suited for a Manual of Procedures (MOP). This information will often be wordy and can include information that may change (i.e., software versions, hardware models, or kit numbers). Keep the description general to avoid the need for unnecessary amendments.

Study Procedures (cont'd)

APPENDIX C: SCHEDULE OF PROCEDURES

Table 6. Schedule of Procedures

Study Day / Study Procedure	-7 to -28 Screen/V1	1 V2	15 (±3) V3	29 (±3) V4	43 (±3) V5	57 (±3) V6	71 (±3) V7	85 (±3) V8	99 (±3) V9	113/ET (±3) V10
Informed consent	X									
Inclusion/exclusion criteria	X									
Demographics	X									
Medical history	X									
Prior/concomitant medications [1]	X	X	X	X	X	X	X	X	X	X
Physical examination	X [2]							X		X [3]
Weight	X [2]	X		X		X		X		X [2]
Height	X [2]									
Vital signs [4]	X	X	X	X	X	X	X	X	X	X
Full chemistry profile [5]	X [5a]	X		X		X		X		X
Brief chemistry profile [5]			X		X		X		X	
Hematology and urinalysis [5]	X	X		X		X		X		X
PK blood sample [6]		X	X	X	X	X	X	X	X	X
PCSK9 measurement [7]		X	X	X	X	X	X	X	X	X
Brief lipid panel only [5]	X		X		X		X		X	
Expanded lipid/apo panel [5]		X		X		X		X		X
Immunogenicity assessment		X		X		X		X		X [8]
Exploratory biomarkers [9]		X						X		X
12-lead ECG [10]	X							X		X [3]
Pregnancy/FSH test [11]	X									X
Randomization		X								
Study drug administration		X		X		X				
Injection site assessment		X [12]	X	X [12]	X	X [12]	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X

See footnotes on next page.

From LIB Therapeutics LLC, Clinical Trial Experience: NCT03549260

Study Procedures (cont'd)

- Be sure to review all procedures with all participating sites.
  - If you plan to use Standard of Care procedure data as part of your dataset, ensure that the data collected will be consistent across all sites.
  - It is best to have all data points collected at all sites, or you may be unable to compare all possible endpoints if a test is not performed.
  - Note: Even something as simple as a Physical exam may be different at different sites. Be sure the data is consistently collected.

- Be sure to consider the time it takes to perform each procedure. Can the necessary tests occur within one study visit?
  - Be careful when specifying time in your protocols
    - Example: "the patient will sit for 5 minutes before blood pressure is taken."
    - This means the patients has to sit for exactly 5 minutes, or it's a protocol deviation.
    - Change this to *"the patient will sit for approximately 5 minutes before blood pressure is taken."*

Statistical Analysis

- Should always be generated or at least reviewed by a Statistician.
  - Generally better to involve the statistician early in the hypothesis formulation/design process.

- Be sure that the analysis considers the Objectives and Endpoints and their feasibility with the planned study size. When possible include study size and power or precision calculations.

Other Protocol Components

- Risk and benefit analysis.
- Study drug supply, preparation and handling and administration by subjects/personnel, distribution, accountability, etc. (broad descriptions in protocol, details in MOP).
- Subject randomization, blinding (and unblinding) procedures, etc. when appropriate.
- Data management and monitoring plans, publication plans.
- Human subjects protections (privacy/confidentiality, informed consent process, funding source, etc.).
- Subject compensation (or not).

Additional Documents

- The PI should be sure that the documents that patients/subjects will be given from study personnel are consistent with the protocol:
  - Recruitment materials
  - Newsletters
  - Questionnaires

- However, the DMCC recommends against including these documents in the protocol as they are known to change frequently.

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Additional Tips and Tricks

- You know your terminology and abbreviations, but new team members or IRB/FDA reviewers may not.
  - Introduce abbreviations at first use.
  - An abbreviation list is an easy and helpful item to add to the protocol (the DMCC template has an abbreviation list after the Protocol Synopsis).

- Be cautious about specifying that a particular individual must perform a particular task unless there is a clear requirement. Excessive specificity can result in protocol deviations.
  - If you can be general in who performs a task (i.e., study team member, radiologist, etc.) be general.
  - This also applies to the names of Coordinators or other non-key personnel.

Additional Tips and Tricks (cont'd)

- Be consistent in formatting the document.
  - Font size, Font style(s), Margins
- Be sure any Figures or Tables in the Protocol are appropriately sized for easy review.
  - It is recommend not wrapping text around figures (protocols are not page-limited and wrapping text frequently interferes with formatting when templates are transferred to site-specific documents or when future amendments are made to the protocol).
- Be sure to review your references and list only the references that you cite in the body of the protocol.

Questions?

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