

Young Investigators' Guide to Research Mentoring

Protocol Writing and Submission

Meet With Your Mentor About The Nature of Clinical Research: Plan to spend *sufficient time* with your mentor to discuss clinical research. Proceed if you are committed to conducting a clinical research study. Discuss and grasp the difference between clinical care and clinical research, and, the funding issues related to conducting clinical research. Discuss the regulatory requirements of the researcher; IRBs, Federal regulations (FDA, RAC et al), HIPAA, and any institutional compliance components that bear on your field. Make certain that you have access to the software tools and administrative support that you need to write a protocol and conduct research; a database program, the tracking function in Word, a reference management software such as EndNote, and any templates that your mentor uses for writing protocols. Learn how to conduct Medline, Pubmed or other database searches. In addition, many useful books and on-line resources are available for the young investigator.

BOOKS:

Principles and Practice of Clinical Research, Ed. John I. Gallin, Academy Press, 2002, ISBN 0-12-274065

Ethical and Regulatory Aspects of Clinical Research: Readings and Commentary, Ed. Ezekiel J. Emanuel et al, The John's Hopkins University Press, 2003, ISBN 0-8018-7813-6

ON-LINE RESOURCES:

St. Jude's Children's Research Hospital

http://www.cure4kids.org/ums/home/courses/detail/content.php?courses_id=10

Registration and use of resources is free.

NIH Clinical Center; Training and Education, <http://www.cc.nih.gov/>

Colorado Pediatric General Clinical Research Center, electronic application,

<http://www.uchsc.edu/pedsgcrc/>

Public Health Service Form 398,

<http://grants.nih.gov/grants/funding/phs398/phs398.html>

Colorado Multiple Institutional Review Boards, <http://comirbweb.uchsc.edu/>

Meet With Your Mentor About Your Research Idea: Present the hypothesis of the research, relevant design issues, background, significance, scientific questions, reasons for questions, statistical analysis planned, and population to be studied. The idea for a research project should be, based upon your previous work or the work of others, responsive to the work of others, or an extension of the work of others. Recognize and master the skills of doing straightforward clinical research before tackling revolutionary or risky research or research with a large population. The purpose of the research should be stated in a few short, declarative sentences. Study design issues involved in the proposal must be discussed.

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What if you have difficulty adequately addressing the above?

- Seek assistance from your mentor to articulate what needs to be done and for instruction.
- If necessary, your mentor can provide you with on-line, literature and other resources.

If you have successfully accomplished articulation of the hypothesis, purpose and initial study design issues for your research, the next step is to:

- Gain more understanding of the background of the topic of interest
- Provide support – theoretical or practical – for thinking these are the right questions
- Construct a final plan for study design, e.g. a challenge paradigm, an observational study, a clinical trial, et al.
- Create inclusion and exclusion criteria for the study.

What if you haven't sufficiently demonstrated the above?

- Seek direction from your mentor.
- Remedy any inadequacies before proceeding.

Obtain Protocol Writing Resources: It is ideal to receive an example of a well-written protocol that was both approved by the IRB, and successfully funded. Your mentor will provide: on-line resources (NIH, PHS, GCRC), names of local experts, references for pivotal work in the field, contact information for persons available to assist; colleagues, GCRC core managers, SAC chairs, institutional research authorities et al. Obtain the protocol format required by your IRB and sources of support e.g. NIH, GCRC, PHS 398. Set a date and time to meet with your mentor again to discuss the protocol draft.

Meet With Your Mentor To Review And Critique Protocol Draft: Have a draft of your protocol to your mentor 5-7 days before the scheduled Draft Meeting time. Remind your mentor 48 hours before the meeting. Be prepared to articulate issues that arose in writing each section. Your draft should contain at least a rudimentary section on Background and Significance, Hypotheses and Specific Aims, Research/Study Design, Methods, and Inclusion/Exclusion Criteria. It is probably too soon for you to produce a robust data and safety monitoring plan, human subject consideration or biostatistics sections. Once your mentor has what you consider a final draft expect that he/she will give a thorough and robust critique (with both positive and negative criticisms). Ideally, your mentor should send you written comments on your draft a day or two before your next meeting. Consider the critique carefully and prepare a response – agreement or refutation of your mentor's comments – with sufficient support from literature etc.

The Protocol Draft Meeting:

- Your mentor will want to know answers to questions like “What issues arose while writing the Methods section?”. He/she is looking for evidence that you are growing in your appreciation of the complexity, significance, and difficulties posed by your proposed research. The well-prepared young investigator will come to this meeting with a great many new concerns, possible solutions and requests for the mentor's expertise and advice.

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- The result of this meeting should be a clear understanding, preferably articulated by you regarding modifications needed to what has been written, and what must next be written. Basically, the writing process (when it involves protocol writing) is about gradually amplifying and expanding the depth and breadth of the protocol draft until it is adequate for submission. It is not uncommon to emerge from this meeting with only 25% of what you have produced judged useable.
- Once the essential components of the scientific portion of the protocol are at least in rudimentary form it is time for you to seek additional expertise; biostatistics, human subject issues, bioinformatics, regulatory, etc. It is best to seek these resources while the protocol is still being written as it will likely strengthen and improve it. If you are lucky enough to have a biostatistician in your department obtain his/her contact information from your mentor. If you will be using the Institution's Research Organization or the GCRC make certain to obtain that contact information.
- Whatever your research, data will be collected and must be stored. Expert assistance in setting up databases and data collection advice can mean the difference between meaningful research and unusable research. Obtain the contact information for the bioinformatics experts available in the institution. The GCRC bioinformatics manager can be reached at 303-764-8373.
- Set a time to meet again with your mentor for the purpose of reviewing and discussing the full **best-possible draft** of your protocol

Obtain Information About Additional Resources and Expertise: Obtain information from experts in DSMPs, DSMBs, HIPAA, FDA, informed consent, data handling, et al. as relevant to your research protocol. The regulatory climate at present is such that both the regulations and the required compliance documentation have become exceedingly complex. It is important that investigators have expert assistance. The GCRC contact who can best assist you is the Research Subject Advocate who can be reached at 303-764-8538.

Meet With Your Mentor to Review And Critique The Full Protocol Draft: Examine and discuss each section of the protocol. Expect to have the full protocol draft to your mentor 5-7 days before the meeting. Always, remind your mentor 48 hours before the meeting. Your mentor will expect that the draft will contain all the required sections and will expect an explanation if it does not. If you need more time to produce a full draft let your mentor know and think about rescheduling the meeting. If you need more guidance and assistance from your mentor tell him/her in a clear way. Expect a written review of your protocol a day or two before the scheduled meeting. Be prepared to respond: agree or refute criticisms et al. Bring to the meeting the bits and pieces that you considered including in the protocol but didn't. Discuss these decisions with your mentor.

Personally Contact GCRC Core Managers (RSA, Biostatistician, Bioinformatics, Administrative Manager): Take advantage of early protocol submission for pre-review. Investigators who submit early for GCRC Pre-Review have the benefit of the advice and contribution of those whose approval must be obtained before the GCRC will approve

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support for your research. Optimal use of this opportunity results in an improved protocol submission and fewer difficulties with the submission and approval process. The range of collective expertise provided exceeds that of both you and your mentors and serves to mitigate individual weaknesses in protocol writing and submission.

Meet With Your Mentor Post-GCRC Pre-Review: Assess the timing of formal submission, decide to proceed or delay. Once you have received a written response from the GCRC core areas, meet with your mentor to discuss the reviews. Each of the core areas has a variety of resources to enable you to construct the best possible protocol. The GCRC encourages protocol submissions from young investigators and welcomes the opportunity to work with you to maximize your research efforts.

Meet With Your Mentor Prior To The GCRC Scientific Advisory Committee (SAC) Review Meeting: Discuss the review process with your mentor; what to expect of the meeting, from reviewers, expected turn-around time et al. Your mentor should attend the GCRC Scientific Advisory Committee meeting with you. He/she is there to support you. Be prepared to address the questions raised. If your mentor cannot be present insist upon an experienced investigator accompanying you.

Attend Review Meeting With Your Mentor: Do not attend a review meeting without your mentor or an experienced investigator. Expect that you will be required to make revisions to the protocol and resubmit it.

Meet With Your Mentor Post-Review Meeting: Once you have received the SAC review, schedule a meeting with your mentor; both in cases of requests for revisions or a disapproval. You and your mentor should debrief and discuss your experience of the review process and what is now required. Send electronic copies of reviewers' comments to your mentor as soon as you receive them. Prepare responses to each of the reviewers' comments, concerns or requests for changes. Support each of these with reasons and literature if possible. Send these to your mentor for discussion. At this point this discussion may occur via e-mail if the revisions are not extensive or complicated. If they are, schedule a time to meet with your mentor. If a reviewer raises a concern then it is significant and must be addressed. If you do not understand the concern seek clarification from the reviewer. If you disagree with the reviewer, discuss it with your mentor and be prepared to clearly explain your position in your response letter with reference to literature where appropriate.

Meet With Your Mentor To Review And Assess Adequacy of Responses to Reviewers: Decide about proceeding with submission of revisions, or delaying. Provide your written responses to the reviewers' comments to your mentor as soon as they are in near-final form. If there are comments that you don't understand even after attempts to discuss them with the reviewer, bring these with you to the meeting with your mentor.

Protocol Approval or Disapproval: Proceed to protocol initiation, or regroup. If things have gone well, the protocol will be approved after minimal revisions and both IRB

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approval and funding/support source approval will be forthcoming. If this is the case, the mentor and student move to the next phase of research mentoring: Operationalizing the Protocol. If things have not gone as well as hoped you and the mentor must take a step back. This occurs when there is a clear disapproval of the protocol, or when there are significant revisions and changes necessary. It is important to reassess the protocol if it did not go as well as expected. If you feel that you have not obtained the mentoring you need from the mentor, discuss it with your mentor and consider changing mentors.