NINDS Clinical Trials Methodology Course (CTMC)
2017 Syllabus and Expectations

This course involves distance learning in small groups and webinars in the spring, followed by a residential experience in August, then additional small groups and a mock study section in the fall. The goal is to design a clinical trial by first developing a PROTOCOL, followed by a grant PROPOSAL. The course faculty will invest time in your project; therefore, your participation in ALL aspects of the course, including the residential course, is required to ensure your success.

The goal of the Clinical Trials Methodology Course (CTMC) is to assist trainees in the design of practical and successful clinical trials. The first step is to help you clearly define your experimental intervention. The next is to create a protocol which accurately describes a reproducible clinical research study, and a proposal which effectively provides the background scientific justification and summarizes the approach. The ultimate goal of a proposal is to gain the funding that will be necessary to conduct your protocol. Incorporating well-defined details into the protocol will make proposal development a much smoother process, and make implementing the project (if funded) considerably easier.

The CTMC is supported by NINDS R25: NS088248 and is administered by the University of Michigan, the University of Iowa, and Los Angeles BioMed. Additional support is provided by the American Academy of Neurology.

Certificates
Each trainee will receive a certificate based on the following criteria:
i. Letter of attendance (attended residential course)
ii. Certificate and letter of completion (submitted a protocol *and* consent)
iii. Certificate and letter of completion with distinction (submitted a protocol, consent, and proposal; participated in mock study section)

Publications
Please remember to acknowledge the support of NIH grant R25: NS088248 in publications or clinical trials developed from your work in the course. Each publication, press release, or other document about research supported by an NIH award must include an acknowledgment of NIH award support and a disclaimer such as *"Research reported in this publication was supported by the National Institute of Neurological Disorders and Stroke of the National Institutes of Health under Award Number R25NS088248. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health."*

Course website, Adobe Connect, Basecamp and Blue Jeans

Course website – the CTMC website is https://nett.umich.edu/training/ctmc

Adobe Connect – all live webinars will be held in Adobe Connect
https://connect.umms.med.umich.edu/ctmc-webinars/

Basecamp – web-based project management and collaboration tool used throughout the course to submit documents, manage tasks, and track due-dates. A Basecamp account will be created for you upon your acceptance to the course. You will receive an email from Basecamp with log in information. You will upload assignments, and communicate with faculty and your small group, through Basecamp.

Blue Jeans – cloud-based meeting platform used for small group meetings and for the Mock Study Section in the fall. We strongly encourage each participant and faculty member to use a webcam within the virtual conference rooms. Appointments, which can be added to your calendar, will be sent from Blue Jeans. An app is available for tablets or smartphones.

MBox – document sharing service. Links will be provided to any readings assigned during the course.

Course text and other recommended websites

We encourage you to purchase Clinical Trials in Neurology: Design, Conduct, Analysis (Ravina et al, 2012). Follow the link to selected chapters from the text which are available in MBox
https://umich.box.com/s/clhd0b3viwenrah7e6zu8084yk9k341v

Qualtrics™

We will send various surveys via Qualtrics™. Some surveys will be focused on your progress throughout and after the course (e.g. about your professional accomplishments). Another survey will be sent to collect demographics data that is required by the NINDS. We will also send a travel form through Qualtrics™ for the residential course. Surveys will include:

1. Demographics form
2. Travel form
3. Small group evaluations
4. Outcome Assessments (what has happened to you and your project after the course).

Course Stages and Task List

Points are used to determine the minimum threshold required to be granted a completion certificate for the course. Timely completion of each task below earns 3 points (unless otherwise specified). A penalty of 1 point is applied for each task that is completed within 1 week of the due date. A penalty of 2 points is applied for each task that is completed great than 1 week after the due date. No points are given for uncompleted tasks. No points are given for completing the anonymous residential course evaluations, but you are strongly encouraged to evaluate each session. Links to survey instruments in Qualtrics™ will be provided.

Stage 1: Baseline

1.1 Baseline tasks

Tasks and due dates are tracked in your Basecamp!

☐ Demographics survey
☐ Review 2017 Syllabus and Expectations document
☐ Attend or review the introduction webinar
☐ Review instructions for Blue Jeans and practice logging in (test http://bluejeans.com/111)
☐ Complete travel form (link will be sent in spring)
☐ Read and review the NINDS Transparency in Reporting Guideline: (no points)
https://www.ninds.nih.gov/sites/default/files/transparency_in_reporting_guidance_1.pdf

Stage 2: Spring/Summer 2017

2.1 Spring/Summer Webinar series

All webinars are held at 12PM EST https://connect.umms.med.umich.edu/ctmc-webinars/

Real-time attendance at and participation in the webinar series is strongly recommended. Recordings will be posted to the course website https://nett.umich.edu/training/ctmc/ctmc-webinars for those who cannot attend in real time. 3 points are earned if completed within 1 week of the webinar; 2 points if within 2 weeks; 1 point if done before the August in-person course.

☐ **April 28:** Asking a good early phase clinical trial question – Roger Lewis, MD, PhD
☐ **May 12:** Rigor and Transparency. How to use preclinical data to inform trial design – Laurie Gutmann, MD, Will Meurer, MD, MS
☐ **May 26:** Small sample size clinical trials – Chris Coffey, PhD
☐ June 2: Crafting a specific aims page for an early clinical trial https://youtu.be/2gEz10pcqP4 This is a pre-recorded webinar from the 2016 webinar series.
☐ **June 9:** What you need to know before talking to your statistician about sample size – Sharon Yeatts, PhD

☐ **June 23:** Creating a budget for a single-site clinical trial – Valerie Stevenson, BAS, RRY, CCRP
☐ **July 14:** Data Management – Catherine Dillon, CCRP
☐ **July 21:** Study drug formulation and supply issues – Pat Bolger, R.Ph., MBA

AMA Credit Designation Statement
The American Academy of Neurology Institute designates this enduring material (April 28 - November 21, 2017) for a maximum of 11 *AMA PRA Category 1 Credit(s)™.* Each webinar is eligible for up to 1 *AMA PRA Category 1 Credit(s)™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Accreditation Statement
This activity has been planned and implemented in accordance with the accreditation requirements of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of the American Academy of Neurology Institute, the University of Iowa, Los Angeles BioMed, and the University of Michigan. The American Academy of Neurology Institute is accredited by the ACCME to provide continuing medical education for physicians.

In order to obtain CME credits you must complete an evaluation form (a link to the evaluation form will be provided during webinar) and provide your email address.

2.2 Spring Small Group Sessions ALL TIMES EST and subject to change

Small Group 1 – **Monday: 1:00 – 2:30 pm.** Laurie Gutmann, Sharon Yeatts
Small Group 2 – **Monday: 5:00 pm – 6:30 pm.** Michelle Detry, Wendy Galpern, Pooja Khatri
Small Group 3 – **Tuesday: 4:00 pm – 5:30 pm.** Robin Conwit, Eric Foster, Adam Hartman
Small Group 4 – **Tuesday: 4:00 pm – 5:30pm.**, Bill Barsan, Kristine Broglio (Advanced Track)
Small Group 5 – **Wednesday: 9:00 am – 10:30 am.** Erica Augustine, Valerie Durkalski-Mauldin
Small Group 6 – **Wednesday: 1:00 pm – 2:30 pm.** Chris Coffey, Jeremy Shefner
Small Group 7 – **Thursday: 4:00 pm – 5:30 pm.** Brett Kissela, Kert Viele
Small Group 8 – **Thursday: 4:00 pm – 5:30 pm.** Roger Lewis, Anna McGlothlin (Advanced Track)
Small Group 9 – **Friday: 10:00 am – 11:30 am.** Jordan Elm, Will Meurer
Small Group 10 – **Friday: 3:00 pm – 4:30 pm.** Ken Cheung, Dietrich Haubenberger

The goal of the small group sessions is protocol and proposal development. Small groups will be 90-minute sessions, which will occur by Blue Jeans video teleconference. There are two or three core faculty members in each small group. Each group has a biostatistical and clinical core faculty member. Each trainee will be primarily assigned to one of the group core faculty members who will be responsible for primary feedback on submissions. Each of the core faculty within a group will be familiar with all of the projects in the group.

2.2.1 Session 1 Introductions and Project Descriptions

☐ Complete your project information form
https://umich.box.com/s/w0vvu871oqyd60t6pkrndkr0capbrzph

☐ As soon as possible and no later than 48 hours prior to the first session, upload the research plan from your CTMC application AND the project information form into your Basecamp for the faculty to review.

☐ Prepare a five-minute introduction presentation about your clinical trial and why it is important. Each trainee will present (with 5 minutes of feedback from faculty) during the first session. Slides are not required. You should use the project information form as a guideline for the high yield topics you should cover during the presentation (e.g. disease, phenotype, preclinical justification).

2.2.2 Session 2 Outcome Measures

☐ Review Chapter 7 "Selecting Outcome Measures" in Ravina (course text).
https://umich.box.com/s/clhd0b3viwenrah7e6zu8084yk9k341v
☐ Prepare a ½ to full-page description of the potential outcome measures you are considering using in your clinical trial. There aren't specific requirements for the format (bulleted list vs narrative paragraph) or for the level of detail, except that the sheet should be ½ to 1 page. Provide enough detail to allow a discussion of any outstanding questions which you may have struggled with in considering the proposed outcomes. Include sufficient information to allow your peers and the faculty to understand the problem, and consider critiques or possible weaknesses that you have not already considered.
☐ Turn outcome measure sheet into core faculty members at least 48 hours prior to session 2 by uploading the assignment in Basecamp (under Docs & Files).
☐ Core faculty will provide feedback on submitted outcome measure document during session 2 (10 minutes each)

2.2.3 Session 3 Hypotheses

☐ Review Chapters 2 and 4 in Ravina (course text)
☐ Prepare a ½ to full-page description of the planned hypotheses and main objectives of your clinical trial.
☐ Turn hypotheses and objectives sheet into core faculty members at least 48 hours prior to session 3 by uploading the assignment in Basecamp (under Docs & Files).
☐ Core faculty will provide feedback on hypotheses and objectives document during session 3 (10 minutes each)

2.2.4 Session 4 Specific Aims

☐ Prepare 1 page specific aims document to be used in grant application. Include additional 0.5-1 pages describing likely grant mechanisms used (due to core faculty 48 hours prior to session).

2.2.5 Session 5 Protocol Synopsis

☐ Review Chapters 27 in Ravina (course text). This reading is geared towards multi-center trials but it provides a good overview. https://umich.box.com/s/clhd0b3viwenrah7e6zu8084yk9k341v
☐ Prepare protocol synopsis. A template is available in your Basecamp.
☐ Turn protocol synopsis in to core faculty members at least 48 hours prior to session 5 by uploading the assignment in Basecamp (under Docs & Files).
☐ Core faculty will provide feedback on submitted clinical trial synopsis document during session 5 (10 minutes each)

2.2.6 Session 6 Budget

☐ Review the following article http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2793732/
☐ Review the following website and look at the schema examples http://research.unc.edu/offices/sponsored-research/resources/research-toolkits/developing-submitting-proposals/data_res_osr_proposalbudget
☐ Prepare budget and personnel justification draft. (Consider getting an example from your mentor and/or your departmental research administrator)
☐ Turn draft budget in to core faculty members at least 48 hours prior to session 6 by uploading the assignment in Basecamp (under Docs & Files).

2.2.7 Full protocol draft

We recognize that not all elements of the design, sample size and statistical analysis plan will be worked out after the small group sessions. It is important to attempt to fill out as much of a complete protocol template as possible, so that it will be feasible for you to revise and finalize this document while you are in Iowa City. Note: some elements of the protocol template may not apply (or may not seem to apply) for early phase trials so please mark sections as not applicable. These sections will be deleted when you finalize the protocol.
☐ Review clinical trial protocol template http://www.ninds.nih.gov/research/clinical_research/toolkit/protocoltemplate.doc OR drafts from NIH/FDA available here: http://osp.od.nih.gov/office-clinical-research-and-bioethics-policy/clinical-research-policy/clinical-trials (even if you are not planning an IND/IDE trial, many of these elements are extremely helpful to consider and include).
☐ Prepare first complete draft of your clinical trial protocol
☐ Turn draft protocol in to core faculty members by uploading in Basecamp (under Docs & Files).

Stage 3: Summer Residential Course 2017

3.1 Didactics

A variety of course lectures and other activities will occur during the summer residential course in Iowa City, IA. A complete agenda will be provided closer to the residential course. Attendance at the large group lectures is required. Readings will be assigned by lecturers from the residential course. A reading list will be provided in Box.

Stage 4: Fall 2017

4.1 Fall Webinar Series

All webinars are held at 12PM EST https://connect.umms.med.umich.edu/ctmc-webinars/

☐ September 1 Adverse event reporting and safety monitoring in clinical trials https://youtu.be/znv1YfY1aEk This is a pre-recorded webinar from the 2016 webinar series.
☐ **September 8:** Good Clinical Practice – Marianne Kearney Chase and Dixie Ecklund, RN, MSN, MBA
☐ **September 15:** Trial Management – Mary Farrant, MBA, RN
☐ **October 13:** Clinical trials study sections – Jaideep Kapur, MBBS, PhD, and David Wright, MD, FACEP
☐ **November 21:** Changes to the Common Rule – Judy Birk, PhD

4.2 Fall Small Groups Sessions

The goal of the fall small group sessions is continued protocol and proposal development. Small groups will be 90-minute sessions, which will occur by Blue Jeans video teleconference. The goal is to work towards getting a full version of a proposal (specific aims page plus 6 to 12-page grant depending on funding mechanism).

4.2.1 Session 7 Research Strategy/Research Plan

☐ Prepare a draft of the research strategy/research plan appropriate to the proposed grant mechanism.
☐ Turn research strategy/research plan in to core faculty members at least 48 hours prior to session 7 by uploading the assignment in Basecamp (under Docs & Files).
The research plan describes the proposed research, stating its significance and how it will be conducted. Remember, your application has two audiences: the majority of reviewers who will probably not be familiar with your techniques or field and a smaller number who will be familiar.

1. https://grants.nih.gov/grants/how-to-apply-application-guide/format-and-write/write-your-application.htm

2. http://www.niaid.nih.gov/researchfunding/grant/strategy/pages/3default.aspx (Particularly "Write the Research Strategy"). Provides a nice overview of how to write scientifically, and how to write a grant using the current strategy. The caveats are it is by NIAID, and it is targeted somewhat towards basic science. (However, science is science, and testable hypotheses are an important part of that. Particularly thinking about how to communicate clearly is something that this covers well.)

3. http://www.niaid.nih.gov/researchfunding/grant/Pages/appsamples.aspx has sample grant applications. They are almost all pre-clinical/translational. The McCune R03 application actually uses humans, and is most helpful. I recognize it is a completely different disease, design, etc. I think the above link "writing the research strategy" will be more helpful.

4. While not in the latest format, the following grant proposal shows how a research strategy for a clinical trial might be presented. Generally, you will want to organize the sections based on the modern requirements for Significance, Innovation, and Approach. The general strategy used to define the approach in this proposal should translate to the current grant writing instructions for NIH. In addition, there is a push for linking to the biological basis and scientific premise for your experiment and this will also need to be weaved in.
https://umich.box.com/s/6201xeey6xlp3j87rentyphw89ex5vfk

4.2.2 Session 8 Human Subjects Protection Sections

☐ Draft the human subjects' protection sections of your proposal, appropriate to the proposed grant mechanism. (Due to core faculty 48 hours prior to HSP session).

☐ Turn Human Subject Protection document in to core faculty members at least 48 hours prior to session 8 by uploading the assignment in Basecamp (under Docs & Files).

4.2.3 Session 9 Wrap Up and Finalize Proposal

☐ Wrap up and discuss any loose ends and plans for submission of grant/implementation of trial.

4.2.4 Proposal Submission

☐ A complete draft of your proposal revised based on feedback from above small groups and other iterative feedback is due by October 15. However, small groups completing proposals substantially earlier than this may be able to have study sections accelerated. You should include all required elements of your grant proposal (biosketches, budget, human subjects protection, research plan, specific aims, facilities and resources). If you are using an alternative mechanism to NIH (i.e. foundation or AHA) you may include a cover letter that describes the mechanism and the required elements. You may include your protocol as an appendix. You should not submit your protocol as a research plan as the structure of a grant proposal research plan is different from a protocol.

☐ Turn in all documents for review in the Mock Study Section by uploading the assignment in the submission portal. A link to the submission portal will be provided in future. Proposals without required elements will not be included in the Mock Study Section.

☐ Complete Evaluations of Small Groups

4.3 Mock Study Section

Trainees will be expected to turn in a protocol and proposal for inclusion in the Mock Study Section.

November 6 (4pm-8pm EST) and November 7 (10am – 2pm EST)

A consent form must be included as an appendix, as well as a screening and recruitment plan. A safety monitoring and adverse event reporting plan must also be included as an appendix if not addressed in protocol. The session will be recorded for later review by the trainees. Trainees will be permitted to attend sessions and observe but will generally only speak if called upon. Written feedback from the reviewers will be provided following the mock study section.

Stage 5: Beyond

5.1 Reunion at American Academy of Neurology Annual Meeting (Spring 2018)

Trainees from the 2017 and previous cohorts are invited to join the annual AAN-NINDS/CTMC Meeting and Reception at the AAN Annual Meeting. If you are unable to attend the reception, you will be asked to prepare an abbreviated single slide update to be shared at the reception. If you are able to attend the reception in person, you will be asked to prepare a 2-slide update of your project to present.

We regret that we cannot provide travel to the AAN meeting. Please email NINDS-CTMC-Info@umich.edu if you have any questions.