NCCIH Clinical Research Studies Oversight Process Technical Assistance Webinar
December 7, 2021

Purpose of the Webinar

On Tuesday, December 7, 2021, the National Center for Complementary and Integrative Health (NCCIH) of the National Institutes of Health (NIH) hosted a technical assistance webinar to provide current and potential clinical researchers with a hands-on opportunity to familiarize themselves with new features of the National Center for Complementary and Integrative Health (NCCIH) Clinical Research Oversight process and learn how NCCIH is implementing clinical research oversight to ensure rigor and efficiency across the NCCIH portfolio.

Webinar Speakers

- Robin Boineau, M.D., M.A., Director, Office of Clinical and Regulatory Affairs, NCCIH
- Emmeline Edwards, Ph.D., Director, Division of Extramural Research, NCCIH
- Christine Wishnoff, M.P.H., Health Specialist, Office of Clinical and Regulatory Affairs, NCCIH
- Lanay M. Mudd, Ph.D., Program Officer, Clinical Research Branch, Division of Extramural Research, NCCIH
- Anita McRae-Williams, M.A., Outreach Communications Program Manager, Division of Extramural Research, NCCIH (Webinar Moderator)

Clinical Trials at NIH and NCCIH: The Role of the Office of Clinical and Regulatory Affairs (OCRA) at NCCIH

Dr. Boineau gave an overview of the NCCIH organization chart and explained the role of OCRA. OCRA is a resource for planning, implementation, and along with the Division of Extramural Research, providing oversight of clinical research funded by NCCIH. The primary goals of oversight are to minimize the risk for research participants and maximize the scientific potential, success, and future impact of funded research.

Dr. Boineau noted that researchers need to be aware of the governing laws, regulations, and policies for clinical trials, both international and NIH-specific, that relate to human protections. Among them are the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, the World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects, the Belmont Report of the U.S. Department of Health and Human Services, and Public Law 105-115 in the U.S. Food and Drug Administration Modernization Act of 1997.

Dr. Boineau shared an opinion piece/viewpoint article on trust and transparency in clinical trials that was written by Kathy L. Hudson, Ph.D., Michael S. Lauer, M.D., and Francis S. Collins, M.D., Ph.D., NIH, and published in *JAMA*. It discusses NIH's interest in rigor and reproducibility of research and mentions efforts toward harmonization across the NIH Institutes and Centers (ICs). She noted that the other NIH ICs are increasingly moving toward NCCIH's oversight approach as the NIH-wide harmonization efforts unfold.

Dr. Boineau said that OCRA had collaborated with NCCIH's Division of Extramural Research (DER) and Office of Communications to update the NCCIH Toolbox's information on the clinical study oversight levels.

NIH/NCCIH Clinical Trials: The Role of the Division of Extramural Research (DER)

Dr. Edwards said that NCCIH is unique in that 60 percent of its funded research is for clinical research, whereas other NIH ICs only allocate, on average, about 40 percent of their funding for clinical research. The remaining funds are allocated to basic science in both cases.

Another unique aspect of NCCIH's clinical research portfolio is its diversity, Dr. Edwards said. NCCIH funds research on mind and body therapies and natural products as well as outcomes and effectiveness studies. NCCIH's research portfolio also includes diverse study designs and grant mechanisms that have expanded over time.

Dr. Edwards explained that the role of DER is to provide scientific leadership, direction, development, and implementation of all NCCIH research programs. DER's staff plans, develops, and evaluates NCCIH's research programs. They also provide oversight and administrative management to NCCIH's research portfolios. In addition, DER staff oversee training and career development at NCCIH, and they have strong communications and collaborations with other NCCIH units, including the Office of Scientific Review and Grants Managements (OCRA).

Dr. Edwards shared DER's organizational chart and outlined its structure. She explained that the NCCIH research portfolios reside in the Clinical Research and Basic and Mechanistic Research Branches, headed by Wendy Weber, N.D., Ph.D., M.P.H. and Wen Chen, Ph.D., respectively. She noted that DER is currently recruiting, and she invited the participants to contact her office if they are interested in learning more. Contact information is available at nccih.nih.gov/grants/contact.

Dr. Edwards said that NCCIH has updated the oversight process to ensure adherence to the guiding principles for oversight that it shares with NIH—minimize risk to participants; maximize success, scientific potential, and impact of funded work; and maximize productivity and relevance of NCCIH programs.

Dr. Edwards said there are two broad categories of oversight for clinical studies at NCCIH—routine and enhanced oversight. The oversight activities that researchers need to comply with depend on the level of oversight that NCCIH assigns to their grants. For grants assigned a routine oversight level, NCCIH program staff engage in pre-award discussions with the principal investigators (PIs), obtain pre-award written communication from the PIs, and receive post-award accrual information. PIs of grants assigned to enhanced oversight will need to submit routine and enhanced-level study documents to NCCIH, and potentially, comply with onsite monitoring.

Dr. Edwards shared a graphic outlining the NCCIH clinical trial project lifecycle, from the idea stage through receipt of the award and registration of the clinical trial. She emphasized two areas that are particularly pertinent for this webinar. First, once their application has been reviewed, researchers must complete a set of pre-award activities, which can be found in the clarification letter they will receive from NCCIH. Activities include milestones (if applicable) that must be met and submission of routine documents, including the Study Accrual and Retention Plan (SARP) and the Data and Safety Monitoring Plan (DSMP). Second, once the project has been funded, researchers must also complete a post-award process, outlined in the study documents request letter, including submission of study documents and arrangement of onsite monitoring, if applicable. DER and OCRA collaborate extensively to oversee these activities for NCCIH-funded studies.

NCCIH Oversight Levels: Live Demo

Ms. Wishnoff shared the NCCIH Clinical Research Toolbox and said that the content on the new clinical study oversight levels is now available through the Toolbox. The new page starts by outlining NCCIH's guiding principles on oversight, followed by a list of the oversight levels. There are six main levels as well as additional links for grants with multiple clinical studies or studies of regulated products.

The exempt oversight level applies to studies that are exempt from NCCIH oversight, either because they do not involve human subjects or because they have an Institutional Review Board (IRB) exemption. These studies do not have any study review. NCCIH does not collect study documents or track accrual on these studies, Ms. Wishnoff said.

The excluded level applies to small, qualitative studies involving human subjects, such as small focus groups or survey studies. NCCIH does not collect study documents or track accrual on these studies, Ms. Wishnoff said.

The most common level of oversight is routine oversight. Researchers involved in studies assigned to routine oversight must submit study documents prior to the award, including the SARP and DSMP. NCCIH provides templates for the SARP and DSMP and asks that researchers use those templates to provide the required information. NCCIH also requires researchers to register their routine oversight studies and report results in ClinicalTrials.gov. Registration and submission of results is recommended for all studies, even those that do not meet the NIH definition of clinical trial. Ongoing reporting requirements for routine oversight studies consist of the submission of enrollment reports, which must be submitted every 4 months beginning 4 months following the expected accrual start date, and annual independent monitoring reports.

Ms. Wishnoff said that routine oversight study documents should be approved before the award is issued, a process that typically takes 2 to 4 weeks. Revised documents generally require an additional 2 weeks for review. If NCCIH is unable to approve the study documents prior to the award, the award will be issued with a human subjects' restriction.

Routine plus oversight applies to studies with complex data collection or analytic design. A statistical review will be performed by an NCCIH biostatistician to enhance success of study implementation. Researchers involved in these studies also must submit the SARP and DSMP, register and report results in ClinicalTrials.gov, and submit enrollment and independent monitoring reports. The timeframe for review is the same as for routine oversight.

Enhanced oversight applies to studies where NCCIH requests the basic study documents and a protocol. In addition to the SARP and DSMP, researchers will need to also submit the study protocol, informed consent document, and upon request, case report forms for these studies. There are three different protocol templates in the NCCIH Toolbox that researchers can use to submit their protocols. In addition, researchers must also register the studies and report their results in ClinicalTrials.gov, and submit enrollment and independent monitoring reports. The timeframe for reviewing study documents is typically 5 to 7 weeks for the first round, and revised documents generally require 2 weeks for subsequent reviews.

The enhanced oversight with site monitoring level requires a site visit by an NCCIH contractor at the start and at various points in the study's life cycle. Before the initial site visit occurs, all the required study documents (i.e., SARP, DSMP, study protocol, informed consent, case report forms) must be reviewed and approved by NCCIH. The timeframe for reviewing study documents is typically 5 to 7 weeks, and revised documents generally require 2 weeks for review. Scheduling the site visit requires a 4-week lead time as well as a 6-week follow-up period following the visit, Ms. Wishnoff explained.

One of the oversight categories applies to grants with multiple oversight levels, Ms. Wishnoff said. For such grants, there may be restrictions on the Notice of Award that apply to certain studies but not to all. Thus, researchers should read the Notice of Award carefully.

The final category applies to studies that propose the use of products or devices regulated by the U.S. Food and Drug Administration or the U.S. Drug Enforcement Administration. Grantees in this category must submit an NCCIH Regulatory Tracking Form along with supporting documentation prior to enrollment. In addition, the NCCIH Natural Product Integrity Policy may apply to these studies; if so, this will be outlined in the Notice of Award.

Case Study Examples

Dr. Mudd provided several examples of the processes that Ms. Wishnoff explained previously.

The first example was a routine oversight study involving a randomized clinical trial to test the feasibility of telehealth yoga versus health education in a sample of 60 adults with chronic low-back pain. The elements that will be required for this routine oversight study include:

- Pre-award: Researchers would need to submit the SARP and DSMP.
- Post study implementation: NCCIH would follow the progress on the SARP and the DSMP via the accrual reports and independent monitoring reports.

The second example was an enhanced oversight study of a pragmatic trial using a sequential multiple assignment randomized trial (SMART) design to test the effectiveness of a stepped care management involving physical therapy and mindfulness for pain management in 1,200 adults across four sites. Rather than requiring the SARP and DSMP documents in the pre-award period, NCCIH instead requests that they be submitted in the post-award period, along with the study protocol, informed consent document, and case report forms. Delaying their submission allows investigators more time to complete the documents using post-award funding. Once these documents are approved and the study begins, NCCIH will monitor progress through the accrual reports and independent monitoring reports.

Dr. Mudd said that for both examples, NCCIH would send the investigators a clarification letter that would outline their study oversight levels and provide links so you, the researcher, would know where to find the required documents and when they need to be submitted.

Dr. Mudd emphasized that whenever investigators were unclear about the requirements or had questions, they should ask their program officer (PO). POs can help clarify what the study's oversight level is and which documents are required and when. They can also provide additional information on any comments that were not clear. If you want to make changes to the study protocol after the study starts, you can talk to your PO to find out if you need pre-approval from NCCIH. Also, if you are having trouble with recruiting participants for the study, POs can assist, as well.

Dr. Mudd also provided some tips to help researchers stay on track with document reviews. She strongly urged investigators to use the NCCIH templates in the Clinical Research Toolbox. Doing so will expedite the review process by ensuring that investigators include all the required elements in their documents. She also noted that documents *must* be provided as Microsoft Word documents (not PDF files) to facilitate NCCIH's ability to add comments and to use track changes when responding to comments so that both the investigators and NCCIH staff can easily locate queries and your responses. Finally, she advised participants to keep the expected timelines in mind.

Questions and Answer

Prior to opening the floor for questions, Ms. McRae-Williams said that this webinar is an inaugural webinar, conducted via a collaboration between OCRA and DER. She invited the participants to suggest topics for future webinars. She said that the NCCIH clinical study oversight webinar provides clarity on the NCCIH oversight requirements. NCCIH staff want to ensure that people who participate in NCCIH-funded studies are protected. In addition, she said that NCCIH wants funded studies to be air-tight, reproducible, and ripe for success and publication. She added that NCCIH provides great tools and resources to the investigators to maximize their success.

Q: The human subjects in clinical trials form of grant submissions requires a data safety and monitoring plan, an accrual and retention plan, and a protocol synopsis. Can I just use that for the NCCIH-required documents?

A: Dr. Mudd said that while the grant application requests many similar elements, it often does not provide the level of detail needed for NCCIH's oversight processes. For that reason, NCCIH asks researchers to use the NCCIH templates within the NCCIH Clinical Toolbox to provide more complete documents for data safety and monitoring, accrual and retention, and the protocol, if required. Sometimes you can copy and paste this information from the grant application into the templates. However, the templates may have additional fields that you may not have considered previously or included in the grant submission.

Q: How do you suggest we plan for oversight level or review time when planning for study initiation for our grant application?

A: Dr. Boineau suggested looking at when you want to start your grant recruitment and working backwards from that date. She said that investigators should plan on having at least two rounds of review, particularly for enhanced oversight studies that submit protocols for review, which require the longest review times. Thus, after submitting their protocol, researchers should factor in an initial 5 to 7 weeks for the first review, plus 2 weeks for the second review. If investigators provide thorough answers to the questions raised in the first review, the project should move through the second review more quickly. In addition, investigators will need to factor in time to prepare their SARP and DSMP.

Dr. Boineau reiterated the importance of asking questions if anything is unclear. She said that her office staff and DER program staff often speak with statisticians and investigators at the time of document submissions. Having a call to address any questions that researchers may have can help expedite the process.

Q: Can we get copies of your slides?

A: Ms. McRae-Williams said that the webinar registrants and participants will receive the PowerPoint presentations along with a summary of the webinar in approximately 7 days. A benefit of registering for the webinar is that you will receive these documents even if you were unable to attend.

Q: What are the consequences if a clinician does not complete some of these steps?

A: Dr. Boineau said that it is very important to read the grant's terms and conditions because all the requirements are clearly spelled out in that document. NCCIH aims to help you be successful with meeting the requirements. However, you do put yourself at risk of not continuing to be funded if you do not complete the requirements in the terms and conditions.

Q: How do I know my oversight level? Could I have more than one oversight level for my grant?

A: Ms. Wishnoff said that many grants propose more than one clinical study, so yes, there can be more than one oversight level for grants. If your grant is selected for funding, you will receive a clarification

letter. That letter will provide the oversight level for each of the clinical studies that you have proposed. For example, if you proposed three clinical studies, it is possible that you may receive up to three different oversight levels. It is important to read your clarification letter carefully. This letter will list the oversight levels and provide the needed links to identify and comply with the requirements of those oversight levels. Thus, the clarification letter that you receive should provide all the information that you need for compliance.

Q: How does NCCIH determine the level of oversight in more detail?

A: Ms. Wishnoff said that NCCIH considers a range of factors—for example, the size of the study, the complexity of the study, the study participants and their level of vulnerability, the history of the institution, and the level of resources available at the institution. NCCIH considers many factors, and the determination is made very carefully and with a lot of consultation.

Dr. Boineau added that NCCIH will also consider the risk associated with the intervention and the number of sites, which may increase the complexity of being able to function consistently across the sites.

Q: Are the study population size and type big factors that NCCIH would consider when determining the level of oversight?

A: Dr. Boineau said that if the study is looking at a rare disease or an unusual population, investigators will often perform feasibility studies, which tend to require lower oversight unless they involve a vulnerable population such as a pediatric population. Through these feasibility studies, you will get a sense of how difficult it is to recruit study participants, which will enable you to show your success in identifying and recruiting subjects in a future application. You will also be able to show your success in getting the subjects to answer your questions and retaining them in the study throughout the study period, which helps to gauge your study's feasibility and acceptability.

Q: What is the current process or format for the Q4 month enrollment reports? Will investigators be sent a link in an email?

A: Ms. Wishnoff said that in the NCCIH-approved SARP, you will identify an expected accrual start date. Four months after the expected accrual start date, you will begin to receive requests from NCCIH to submit accrual reports, and NCCIH will continue to ask for updated accrual information throughout the lifecycle of the recruitment period. Even if you are not recruiting at the time you receive the request from NCCIH, you should still access the link and provide an explanation of what is happening in the study and/or at the site. NCCIH strongly encourages investigators to complete all their reporting requirements, including the accrual report. Even if there is not much to say yet, NCCIH still needs to hear from you.

Additional information (not in response to a question): Dr. Boineau said that because of the pandemic this year, some studies had to stop operations for a time. They were later able to restart after moving to

a remote intervention or implementing new safeguards and procedures to protect participants. Most of the studies that needed to stop required a reset prior to restarting. This meant that a new SARP report was generated by the investigators with a new start date. In difficult situations that affect everyone, such as this pandemic, NCCIH is happy to work with you to look for and find ways to work through the difficulties and to overcome barriers. NCCIH can also help you determine if there are any barriers that cannot be overcome, so that you are not stuck doing a study that is not feasible under the current circumstances. In such cases, it may be best to stop and, instead, reflect on what has been learned prior to the stopping point. However, before making any decision, our first approach is always to work with you on identifying barriers.

Dr. Edwards said that if any of the requirements for your grant are not clear, you should contact your PO. If your PO cannot answer your questions, they will direct you to the appropriate person or resource to answer your questions. However, most of the time, your PO is your best advocate, and that person will be able to help answer your questions so you can meet all your requirements. For example, if you have problems with recruitment and enrollment, NCCIH POs can help you brainstorm and come up with potential solutions for those issues.

Q: What does a PI need to do if they want to include an international collaboration?

A: Dr. Boineau said that the first step is to look at the Funding Opportunity Announcement (FOA) to make sure it allows international collaborations. You should also talk with your PO. Some large clinical NCCIH-funded studies have been done in collaboration with Canada. NCCIH has also funded studies that were done in Brazil. However, while NCCIH does fund some international studies, steps need to be taken to move forward on these.

Dr. Mudd said that NCCIH will not consider applications involving clinical trials outside of the United States and Canada due to the difficulty involved in conducting oversight processes in different countries (this policy is described on NCCIH's webpage on International Health Research). She advised investigators to look at this policy as well as the FOA prior to initiating international collaborations.

Q: Will NCCIH fund complementary and integrative health studies among cancer patients, or do cancer studies go to the National Cancer Institute (NCI)?

A: Dr. Edwards said that NCI has a larger budget than NCCIH, so unless the study aims to look at a particular mechanism of how the complementary and integrative health approach exerts its effect, it would likely go to NCI. Studies of cancer treatments would go directly to NCI, whereas studies on the fundamental science of a complementary approach would come to NCCIH. However, the focus of the study will determine which Institute should receive the application.

Q: Are there any alternatives to the randomized controlled trial (RCT) methodology that reviewers may be receptive to?

A: Dr. Mudd said that it is hard to discuss study design in general terms because the study design will depend on the specific research questions being asked in the study. She suggested that the participant who posed the question contact NCCIH program staff to discuss their research interests so that NCCIH can provide a more thorough answer.

Conclusion

Dr. Boineau thanked the participants for attending the webinar and invited them to submit feedback on or questions about this webinar as well as topics or ideas for future webinars.

Dr. Edwards said that the collaboration between OCRA and DER also extends to and includes NCCIH investigators. All have a shared goal—to maximize the success of the studies that you are proposing.

Dr. Mudd said that the conversations between NCCIH staff and investigators revolve around troubleshooting problems and maximizing the likelihood of success. She also encouraged the participants to go to the NCCIH Toolbox and look at the information that is available on the website, including the information on the oversight levels, required documents, and templates. The Toolbox also has a large variety of resources that can help in grant application, study initiation, and post-initiation phases.

Ms. McRae-Williams ended the webinar by thanking the webinar speakers for their presentations and the participants for their attendance and questions. She reminded the participants that they would be receiving a written summary of the webinar and the webinar slides, and she invited them to submit additional feedback on this webinar or ideas on topics for future webinars after they receive these materials.