CHR FOA Technical Assistance Teleconference

Call Summary

Call date: Tuesday, December 17, 2019 3:00pm EST

NIMH attendees:

- **Sarah Morris** (Division of Translational Research)
- **Greg Farber** (Office of Technology Development and Coordination)
- **Holly Lisanby** (Division of Translational Research)
- **Linda Brady** (Division of Neuroscience and Basic Behavioral Science)
- **Gene Kane** (Office of Clinical Research)
- **Nikki North** (Division of Neuroscience and Basic Behavioral Science)
- **Tamara Kees** (Division of Extramural Activities)
- **Jeena Thomas** (Division of Translational Research)

Program Contact (U01 and U24): Dr. Sarah Morris

This call summary will be posted on the website for these RFAs. The PowerPoint slides and call summary can be obtained upon request via email to the CHR FOAs email address (chrfoas@mail.nih.gov).

Welcome to attendees by Sarah Morris. Attendees were informed that all will be on mute during the presentation of slides and that NIMH will open the phone line at the end of the presentation for questions. Attendees were also informed that all were welcome to submit via the chat room to Dr. Sarah Lisanby and those would be answered during the teleconference as well. Notification to attendees that the call is being recorded for the purpose of creating the summary.

The purpose of this teleconference is to provide technical assistance for the Request for Funding Announcements (RFAs) for Clinical High Risk (CHR) for Psychosis. These RFAs are for cooperative agreements and will involve substantial involvement by NIMH staff, an external workgroup, and a steering committee. It was emphasized that these RFAs are a different kind of collaborative project and applicants are strongly encouraged to read the applicant instructions, review information, and terms and conditions which are specific to these funding opportunities. The U01 and U24 mechanism are different from typical R type grants.

Background

Clinical heterogeneity within the CHR population presents a substantial challenge for intervention development. Approaches for addressing this heterogeneity to enable future intervention trials require the development of tools to define a core sent of clinical and functional outcomes not just related to the onset of psychosis but a broad spectrum of

outcomes and then to prospectively stratify individuals into more homogenous subtypes to predict the likelihood of those various clinical outcomes.

Right now, over 30 academic research centers and community clinics in the US conduct translational research studies of psychosis risk or provide evidence-based treatment for CHR individuals, so it is a growing area. The NIH Accelerating Medicines Partnership program is encouraging public-private partnerships to exploit CHR risk prediction and biomarker finding to support future clinical trials. (Dolgin, *Nat Rev Drug Discov* 2019; "Accelerating Treatment Development Research in Clinical High Risk for Psychosis" NAMHC Concept Clearance, presented to open session of National Advisory Mental Health Council meeting, May 30, 2019).

Purpose

The purpose of these RFAs specifically is to develop a set of validated tools including biomarkers, biomarker algorithms, and outcome measures, for selection of help-seeking/CHR subjects for enrollment in future clinical trials, to serve as readouts of early treatment effects, and/or to monitor disease progression and clinical and functional outcomes.

Timeline for both RFAs is as follows:

- Letter of intent due: December 31, 2019
- Applications due: January 31, 2020
- Scientific merit review: May 2020 (locus of review is NIMH)
- Advisory Council review: August 2020
- Earliest start date: September 2020

There are no late applications allowed under these RFAs so the continuous submission policies do not apply to these RFAs. There is only one submission date.

General Q&As applicable to both the U01 and U24

Q. Will the RFAs be re-issued or submission dates added?
A. There is no plan to re-issue the RFAs or add submission dates.

Q. Are the set-aside amounts that are provided in the RFA for the full duration of the grant or only the first year?
A. The set-asides are for the first year of the grant. Specifically, up to $4 million total costs in year 1 of the U24 and a combined total of up to $11 million total costs in year 1 of the U01(s). Subsequent years will be paid from general NIMH funds.

Q. The set-aside amounts are a virtual cap on year 1 budgets. Should budgets for years 2-5 stay approximately within that ballpark or could they be higher if well-justified?
A. Budgets for years 2-5 should stay within the same annual ballpark.

Q. What is the governance structure and decision-making process for the network(s), DPACC, steering group, and external workgroups?
A. We come back to the point about these being a cooperative agreement. This is a very collaborative process.
The CHR Steering Committee will serve as the operational governing board for the CHR Network(s) and the DPACC. The Steering Committee will include the U01 PI(s), the U24 PI(s), NIMH Program Officer, NIMH Project Scientist(s), and External Working Group members. External Working Group members will be identified after awards are issued.
The Steering Committee will coordinate activities of the DPACC and Network(s), advise on research priorities, and participate in reviewing scientific progress of the project.
See Section VI.2: Award Administrative Information: Cooperative Agreement Terms and Conditions of Award and Section V. Application Review Information

Q. What are the page limits?
A. Research strategy section is limited to 12 pages. *See NIH page limits tables (U01 and U24 appear in the "For R01, R03, R21, and all other Applications" sub-section of the table.)*

Q. Are sub-contractors allowed to issue sub-contracts (i.e., are third-tier subcontracts allowed)?
A. Third-tier subcontracts are highly discouraged and would only be allowable under unusual circumstances. Please contact Sarah Morris if you have an unusual circumstance before submission of your application

Q. Are applications from non-U.S. institutions allowable?
A. Applications from foreign institutions are allowable for RFA-MH-20-340 (U01) but not for RFA-MH-20-341 (U24), but foreign components are allowed for the U24. *See Section III. 1. Eligible Applicants: Foreign Institutions.*

Q. Are appendices allowed?
A. NIH policy regarding appendices (NOT-OD-17-098) is applicable.

Specifically, only the following documents are permitted:
- Blank data collection forms, blank survey forms and blank questionnaire forms;
- Simple lists of interview questions;
- Blank informed consent/assent forms.

Letters of support are not considered an appendix and can be submitted as part of the research plan.

Q. Could a large table of CHR studies used to select aggregated data be used in the appendix?
A. No, we would expect the source of the CHR studies be part of the main application instead of an appendix.

Q. Can an investigator be PI (or MPI) on both a U01 and a U24 application?
A. No. *See Section III. 1. Eligible Applicants: Eligible Individuals.* The reason for this is because we want to encourage different expertise coming in under the U01 and U24. Once the grants have been awarded those teams will work together and we expect a high level of collaboration.

Q. Can an investigator be PI (or MPI) on a U01 or a U24 application and be co-investigator or consultant on another U01 or U24 application?
A. Yes.

Q. Can an investigator be PI/MPI (or other role) on more than one application of the same type (*i.e.,* U01 or U24)?
A. Yes.

Q. The deadline for LOI is very soon, is it required?
A. No, it is optional. It is helpful for us to help plan with review but it is not required. The requirements for the letter are very minimal, so we do encourage it.

U24 Q&As

Q. Should specific datasets to be used in the analysis of existing data be identified in the application?
A. It isn't required that specific datasets be identified in the application, but doing so (and documenting that the investigator who controls the data agrees to share data) would help reviewers evaluate the feasibility of the planned analyses. It would be acceptable, however, to outline a plan for identify and selecting appropriate datasets and negotiating access to the data. Final decisions about the specific datasets to be included will be made by the steering committee in conjunction with the external working groups.

Q. Should specific data types be proposed?
A. Because the specific data types won't be finalized until after the grants are funded, applications should describe data infrastructure and pipelines necessary to gather, combine, store, and manipulate de-identified biomarker and clinical data as well as combined/multi-modal data from multiple network sites in a timely manner. *See Section IV.2. Content and Form of Application Submission: Approach and Section V. Application Review Information: Investigators.*

Q. Will the data include blood biomarkers such as metabolomic, proteomics, etc. or would blood be collected and stored for future hypotheses relevant to clinical trials, as opposed to part of the multi-modal data used to develop biomarkers?
A. It isn't possible to say for sure until the applications are reviewed and funded. U24 applicants should include descriptions of their capacity to handle and process data that they anticipate will be relevant to the scientific goals of the RFAs.

Q. If genetic variables are proposed, will the network sites acquire the blood and do analyses that are selected by consensus and then the specific variables of interest would be included in analyses by the U24?
A. As a general principle, it's optimal for data processing and analysis to be done centrally (i.e., by the DPACC) to avoid adding site-related variability in processes.

Q. Question about the blood analyses. Who should budget for the transfer, storage, and analyses of the samples? DPACC or Network?
A. The DPACC is not meant to be a tissue or blood bank but rather a data bank. Analyses that would need to be done would be done by the Network. Analyses of MRI, things that are intrinsically computational, are what the DPACC would be doing. Digital data would be transferred to the DPACC and would include results of the analysis of the sample as well as the scan data. Sites would do the analyses and then send the data to the DPACC. U01s would collect the tissue and send the digital data to the DPACC.

Q. What type of expertise is optimal for the study team?
A. The team must be experienced in coordination and management of multi-site clinical studies. The team should be multidisciplinary and the application should reflect the team's background in acquisition, processing, aggregation, and analysis of multi-modal biomarker and clinical data, as well as study coordination and data dissemination.

The team members must have experience and expertise in:

- bioinformatics and large-scale longitudinal studies, including cloud computing and data science;
- establishment of cut-points that define subjects, at the individual level, who meet criteria for biomarker prediction/outcomes; and
- an understanding of the criteria needed for application of biomarker and/or clinical algorithms to inform planning of future clinical trials.

See *Section IV.2. Content and Form of Application Submission* and *Section V. Application Review Information: Investigators*

Q. In Section 2.1.2 of the RFA: "Applications in response to this FOA are encouraged to engage thought leaders in bioinformatics and large-scale multi-site longitudinal studies of multi-modal biomarker predictors…": What is meant by "thought leaders" and what would their role be?
A. The intent of this statement is to encourage applicants to seek out any appropriate additional expertise that the team might need to develop a state-of-the-art informatics

infrastructure. It would be up to the study team to decide whether or not to engage experts in this way and to define their role.

Q. Could you clarify further the role of the DPACC in setting up standardized measures, protocols along with training relevant to the U01?
A. The way it's written in the RFA, we give that responsibility to the DPACC (U24) to do it in a very centralized way but it will be done collaboratively with the Network sites. U01 should budget to train staff at their individual sites, rather than expect the DPACC to send someone out to the sites to train people, however it will depend on the details once the network is established.

Q. Could non-NIMH funded data be submitted to DPACC that is consistent with the protocol?
A. Data collected outside the network (not funded by NIMH) would likely be welcome to be deposited to the NIMH Data Archive directly, which will serve as the informatics framework for the U24, and then that data could be aggregated with the new data collected that will be submitted to DPACC.

Q. How many U24s are you planning to fund?
A. Only one U24 will be funded and this DPACC would be expected to work with both networks if two U01s are funded

U01 Q&A

Q. How many networks do you plan to fund?
A. 1 or 2

Q. The RFA says that the network(s) should focus on rapidly recruiting "a sufficient number of participants." What is a sufficient number?
A. The number of participants will depend on the types of data proposed to be collected and the statistical power needed to achieve the scientific aims. If proposed data types are low-burden/high throughput, total sample size might be more than 1,000.

Q. Is it allowable to propose a clinical trial?
A. No. Both of these RFAs are designated "No Clinical Trials Allowed. Trials to test for efficacy or effectiveness of interventions are not allowed. Studies that use clinical trial methodology to answer questions about predictive biomarkers are also not allowed. Applications that include a clinical trial will not be reviewed.

Q. Should applicants expect that the usual policy requiring a single IRB for multisite studies applies?
A. Yes, a network should plan to use a single IRB. If 2 different U01s are funded, it is not expected that both would use the same IRB. We anticipate that the U24 would have its own IRB.

Q. Can a site be included in more than one U01 application?
A. Yes, however, if both U01s are funded, the site would need to discontinue participating in one of the U01s (or it may be possible to negotiate ongoing participation in both networks if duplicative expenses can be avoided).

Q. The U01 Network RFA refers to the variety of outcomes "beyond psychosis." Does "beyond" psychosis mean "in addition to" the emergence of psychosis or does it mean that applicants should not propose to capture emergence of psychosis as one the several outcomes?
A. It means "in addition to" the emergence of psychosis, to capture the full range of clinical outcomes and possible predictors of those diverse outcomes.

Q. Should specific data types be proposed?
A. Applicants should propose a preliminary core assessment battery, including measures of baseline characteristics and illness features, multimodal biomarkers, and symptomatic and functional outcomes and justify the proposed measures in terms of reliability and validity, participant burden, and utility for dissecting the heterogeneity of CHR outcomes.
The applicant should describe the frequency and method of assessment, training required to administer measures, and the appropriateness of the measures for use in diverse populations.
The final assessment battery will be determined in partnership with the NIMH and external working groups.
See Section IV.2. Content and Form of Application Submission: Approach and Section V. Application Review Information

Q. Given likely delays in initiating data collection due to post-award consultation and protocol revisions, should U01 applicants indicate that the study will be Delayed Onset with regard to Human Subjects Protections or should U01 applications include the PHS Human Subjects and Clinical Trials Information form based on the network's preliminary proposed research in the application?
How should this anticipated delay be handled in the year 1 budget?
A. The network studies should not be marked as delayed onset. The Human Subjects and Clinical Trials Information form should be completed based on the proposed research. It's reasonable to include a period of protocol finalization, along with other estimated start-up costs, in the year 1 budget.

Q. The RFA refers to the *network's* information technology systems (p 10). Should applicants budget for their own information technology systems or should they plan to use the information technology systems supplied by the DPACC?

Similarly, one of the U01 review criteria is "Does the application include a data workflow designed to collect and aggregate data and provide data to the DPACC?" Does the "aggregate" part suggest that Network hub will be expected to operate its own electronic data capture/information technology system?

A. U01 applications should budget for and describe their plans for an information technology system that will allow data to flow quickly from the data collection sites to the DPACC (this could be directly or via a hub within the network). Before these plans are finalized and implemented, the network will need to coordinate with the DPACC to ensure smooth data transfer.

Q. How critical is it to have US sites involved in the U01 submission? Are US based sites viewed as critical to the application?

A. Applications from non-US institutions are allowed under the U01 RFA. It makes sense to think about it the same way you'd think about it for any other application coming from a non-US site. You would want to have a strong argument for why the non-U.S. site is optimal for the research and address any differences in the healthcare system that might relate to the interpretability of the findings. We encourage submission of the best applications, regardless of location. The review process will address the justification of the international site, including uniqueness of expertise, access to the participant population, and diversity of CHR and trajectories, all of which are critical.

Q. The network should budget for the electronic data capture system that transfers to DPACC, is that correct?

A. Yes. The DPACC will budget what they need for the data processing, aggregation, duration, and analysis.

Q. Given the parallel timelines of the U01 and U24, assuming both start at the same time, what is the expected timeline for data analysis by the U24 of newly collected data?

A. One of the first tasks for the U24 is looking at already collected data and so the U24 would not be receiving newly collected data until the network is functioning. We envision a phased approach where the U24 would start with already existing data. We realize the timing is a little difficult given that the network will have to get up and running. We do expect that to go pretty quickly and hope that there will be a lot of attention dedicated in the very early months of the U24 to analyze the existing data so any new discoveries coming out of that data could be integrated with the work to be done by the network.

Q. Can you comment more about trajectories? What sort of timeframes? Weeks? Months? Would this be chosen in consideration of the length of a typical randomized control trial?

A. These are not randomized control trials. This is cohort collection and characterization, phenotyping, and monitoring over time for longitudinal trajectory of clinical status and

biomarker information. There are two ways to think about this. There is an inherent timeframe imposed by the duration of the grant. We want to optimize the variability in the different outcomes of interest, including conversion to psychosis, and to maximize the power to have enough of those clinical events to do a pretty fine-grained analysis of different pathways to the different outcomes. That would suggest a longer follow-up period (perhaps up to approximately two years). However, we know from existing data that different types of measures change over different periods of time. It would be up to the investigators to think about what changes they expect to see in specific kinds of measures and how often they need to be measured in order to capture that trajectory. It will depend on the measure, the scientific justification for that measure, and over what timeframe you're expecting those measures to be changing in a predictively informative way.

Q. Since the network is responsible for the initial collecting of the data, is the network also responsible for developing the case report forms for data capture?
A. Yes, and the network would be responsible for developing the case report forms and that would be done in collaboration with the DPACC and the external advisory committee.

Q. For many projects, NIMH has indicated that the Rutgers repository would be the central repository for DNA and RNA, is this true for this network or do we need to propose our own repository?
A. You do not need to propose your own repository for RNA and DNA; NIMH expects that investigators would use the Rutgers repository, provided they have appropriate consent for sharing.

Q. Will specific datasets be available to the funded PIs?
A. Four to six high value datasets would be optimal but the RFA does not specify any specific dataset. These high value datasets will be identified in collaboration with the External Advisory Committee and Steering Committee.