PAR-23-199 – NICHD Genomic Clinical Variant Expert Curation Panels (U24 Clinical Trial Not Allowed): Frequently Asked Questions (FAQs) and Answers

The following FAQs and answers are for PAR-23-199.

What is the objective of the Program Announcement (PAR)?

The objective of this Notice of Funding Opportunity (NOFO) is to establish or support existing expert curation panels that will select candidate genes and genomic variants associated with diseases or conditions of high priority to the participating NIH institutes and that will have a high impact on clinical practice. The expert curation panels will analyze all relevant data utilizing the ClinGen (https://www.clinicalgenome.org/) resource tools, and based on this analysis, establish the clinical relevance of these genes and/or variants tosupport clinical practice.

What are the priority conditions or diseases for the NIH curation panels?

For the purpose of this NOFO, genes and variants should be associated with but not limited to one or more of the following topic areas:

- *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD): gynecologic, andrologic, and reproductive health; poor pregnancy outcomes; high-risk newborn conditions; structural birth defects; intellectual and developmental disabilities; and susceptibility to infections
- National Cancer Institute (NCI): genes and germline variants associated with inherited susceptibility to cancer development and/or response or resistance to therapy; somatic variants associated with cancer diagnosis and treatment
- National Eye Institute (NEI): diseases of the eye, central visual, and oculomotor pathways
- National Institute of Mental Health (NIMH): severe mental illnesses, e.g., autism and schizophrenia
- National Institute of Neurological Disorders and Stroke (NINDS): neurological, neuromuscular diseases and stroke
- National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS): rheumatic, musculoskeletal and skin diseases
- National Center for Advancing Translational Sciences (NCATS): rare diseases
- National Institute on Deafness and Other Communication Disorders: hearing loss and auditory system

If you are not sure whether your condition(s) would be considered for funding by one of the sponsoring institutes, we strongly recommend that you reach out to the most appropriate program contact listed at the end of this FAQ.

How should expert panel members be listed in the application?

Each panel member can be listed in one of the following ways:

- Key Personnel or Other Significant Contributors (OSC) under personnel on the R&R Senior/Key Person Profile Form. Note that this choice requires an eRA Commons ID (NOT-OD-24-042) and requires you to submit their NIH biosketch.

- Non-Senior/Key Consultant. Consultants who are not listed on the R&R Senior/Key Person form do not require an eRA Commons name and should only be paid nominal fees (if any). Note that this choice does not allow submission of an NIH biosketch, so pertinent information about their expertise should be included in their Letter of Support for reviewers to assess.

Are foreign subawards allowed? Are foreign collaborators allowed and how should they be listed in the application? What else is required for applications with foreign personnel?

Per NOT-OD-25-104, NIH will no longer allow new subawards to foreign institutions. Consultants receiving nominal fees are still allowed, as are foreign collaborators who do not receive any financial compensation. We strongly recommend that you list all foreign personnel as **non-Senior/Key Consultants**.

Note that all applications that include a foreign component (such as collaborators/expert panel members/consultants) are required to submit a Foreign Justification. Please reference these Application Instructions which indicate the information must be submitted with the application in Field 12, Other Attachments. For each of the foreign collaborators/sites, it is helpful to include their name(s) and expertise and note if any funding is going towards that site. Be aware that Field 12, Other Attachments, is the only method that NIH will accept the Foreign Justification, and that post-submission is not allowed. Applications that have a foreign component but have not submitted the proper documentation will be withdrawn for being incomplete; see NOT-OD-25-098 for details.

What genes and/or variants should be selected for curation? Is it required to curate both genes and variants?

Selection of genes and/or variants is at the discretion of the Principal Investigator (PI) and panel members. Applicants may propose curation of only genes, only variants, or both. There is no minimum or maximum number of genes and/or variants required for a successful application. Applicants should justify their proposed scope of work in terms of the clinical importance of the disease area as a whole and the impact that their work is expected to have on clinical diagnosis and management of patients. Additionally, the proposed scope of clinical domain(s)/disorder(s) and the number of genes and/or variants to be curated should be feasible within a three-year project period. The panel should identify those genes/variants that are most likely to impact clinical practice and for which evidence is available. The justification for selecting the genes/variants to curate should be based on this principle rather than a sample of convenience.

How many genes and/or variants do expert panels typically tackle?

In general, gene curation expert panels tend to cover a larger number of genes, whereas variant curation expert panels typically focus on a smaller number of genes due to the need to establish variant classification guidelines and then curate hundreds or thousands of variants within each gene. Proposals that include both gene and variant curation activities should clearly describe the subdivision of these efforts within the grant period. For cancer-related curation of variants, applicants can propose to curate germline variants, somatic cancer variants, or both germline and somatic cancer variants.

What are typical curations rates for variant and gene expert panels?

Variant curation expert panels typically curate between ~3-10 variants per month, while gene curation panels average ~1 gene per month. Rates may also differ for variant curation in many genes, and for proposals curating both genes and variants. For panels early in their lifespan, curation rates are anticipated to be on the lower end of these ranges as they will spend more time in the establishment phase – recruiting and training the biocurator and expert curation workforce, setting up meeting cadences, and developing rule specifications. Once approved by the ClinGen consortium to proceed with curation activities, established expert panels will scale up their curation activities to address their scope of work.

May investigators propose gene precuration activities as part of the workflow for an expert panel?

In the context of ClinGen, "gene precuration" refers to the initial process of gathering information and determining which disease entity(s) a gene should be curated for, using lumping and splitting guidelines, before a full gene-disease validity curation is performed. This step may be important when there is potential overlap with other expert panels because a gene is associated with more than one disease area, a variable single organ phenotype, or a syndrome. For example, genes being curated by the Epilepsy Expert Panel may have been curated in a different context as a gene for brain malformation.

What if other groups/panels are evaluating the same domain or group of genes?

PIs are encouraged to work with the other groups to establish a single working group rather than duplicating effort. If this cannot be accomplished, a strong justification must be provided as to why the work of this panel will be unique, and any area of overlap must be described. As the goal of the PAR is to provide expert panel evaluation of gene-disease or variant pathogenicity assessments to support variant curation, having two groups duplicate efforts is not an efficient use of resources and will not be prioritized for funding consideration.

Is a single expert panel or multiple expert panels allowable or preferred for submission when an expert panel already exists?

The intent of the PAR is to support individual expert panels, as the awarded funds are expected to support a coordinator, curators, the PI, and, if applicable, co-PI(s). As stated in the PAR, if there are questions regarding overlap with existing expert panels, clarification is required in the application. Applicants are encouraged to reach out to existing expert panels that can be found on the ClinGen website (https://clinicalgenome.org/affiliation/) and determine whether there is scientific overlap; if so, the applicant should provide supporting evidence that the scope of the application will not overlap with an existing panel's curation activities.

How should the genomic expert panel be structured?

The panel should be led by a chair or co-chairs (who should serve as the PI or co-PI(s) of the grant). Members of the panel should include experts from at least three different institutions.

Expert panels should include supporting personnel that include a project coordinator; biocurators, who will provide the panel members with primary curation and

documentation of the selected genes/variants; and bioinformatics specialists.

Are multiple PIs allowed?

Multiple PIs are allowed. Funds are available to support partial salary of the PI who serves as the expert panel chair of the working group and, if applicable, the co-chair(s). Please see the

Does the PI have to be U.S.-based even though the proposals are encouraged to be international?

Yes, because it is a U.S.-based initiative, the PI for any expert panel proposal needs to be based in the United States. However, we encourage foreign consultants, with appropriate justification.

What experts should be included on the expert panel?

For the purpose of this NOFO, membership of the expert panel should include domain and condition experts reflecting the breadth of expertise required to ascertain the clinical actionability of the genes and/or variants to be curated. The panels should include medical professionals, medical geneticists, clinical laboratory diagnosticians and/or molecular pathologists, researchers, and statisticians. Since the goal of the PAR is to assess the clinical validity of the selected gene-disease associations or genetic variant pathogenicity, based on current knowledge that could support guidelines for clinical practice, multiple institutions and organizations must be represented and international participation is strongly encouraged, keeping in mind NIH policy related to data access (https://grants.nih.gov/grants/guide/notice-files/NOT-OD-25-083.html), where applicable.

Critical to the success of gene/variant curation are a project coordinator, biocurator(s), and bioinformatics specialist(s). Additional considerations for staffing are in another FAQ, below.

Can all members of the expert panel be from the same institution?

No, in order to qualify for a ClinGen expert panel, members are expected to be from multiple institutions, and foreign members are encouraged. Formation of expert panel guidance can be found at: https://www.clinicalgenome.org/docs/guidelines-for-applying-for-variant-or-gene-curation-expert-panel-status/

How should conflicts of interest be managed?

Conflicts of interest (COI) should be identified for each member of the working group and managed by the curation panel PI and the PI's institution. These should be kept up-to-date and reported to ClinGen. Please refer to ClinGen's Conflict of Interest Policy and COI reporting process outlined in the GCEP and VCEP applications.

How should expert panels organize their curation activities?

Depending on the number of genes or variants, either a single panel could meet regularly to review individual genes/variants, or subpanels could be established that will focus on specific subsets of genes/variants. These subpanels/working groups could then report to the entire expert panel to determine final assertions. The investigators should build on the experience of ClinGen Clinical Domain Working Groups (CDWG) and curation panels in organizing the work of the expert panel. The following options exist for coordination of NIH expert curation panels with ClinGen activities: placement

within an existing ClinGen CDWG if appropriate, formation of a new CDWG if appropriate, or support of a standalone “expert panel.”

For new expert panels that are not part of an existing CDWG, applicants should articulate plans to engage with the ClinGen consortium. For new expert panels that are being initiated from within an existing CDWG, applicants should describe the need for a new expert panel in their broad disease area. Examples of ClinGen curation working groups can be found at: https://clinicalgenome.org/affiliation/.

How should the expert panels be staffed?

The PI (and possibly co-PI(s)) will be responsible for leading the panels. However, experience has shown that the availability of a project coordinator, biocurator, and bioinformatician are critical to the success of the curation panel. The biocuration staff are expected to perform data collection and primary analyses for genes and variants. Biocurators may be genetic counselors, clinical fellows, or researchers in the field. In addition, bioinformatics specialists should be engaged to help analyze existing datasets within the framework of the tools available through ClinGen. Both the biocurators and bioinformatics specialists are expected to utilize the ClinGen tools and to participate on appropriate ClinGen working groups.

How will NIH-funded expert curation panels interface with ClinGen, ClinGen working groups,and ClinVar?

Expert curation panels are expected to utilize the ClinGen/ClinVar framework and curation tools to assess current evidence supporting disease associations for the chosengenes and/or variants (https://clinicalgenome.org/tools/). Expert panel curation staff are expected to receive training on ClinGen tools and resources through distance and/or in-person educational modules. Expert panel members are expected to participate in monthly ClinGen meetings. The PI(s) and curation staff are expected to participate on appropriate ClinGen working groups and to deposit final determinations and supporting evidence into ClinGen and ClinVar databases. Applicants are encouraged to review ClinGen curation and education tools at https://clinicalgenome.org/curation-activities/.

ClinGen’s CDWGs serve strategic and organizational functions for horizon scanning and fostering the expert curation groups. Each CDWG coordinates one or more expert panel groups undertaking gene and/or variant curation and is an umbrella over a cluster of related expert panels. Coordinators and curators are expected to participate in regularly scheduled monthly calls with relevant Clinical Domain Working Groups, per PAR requirements.

What is the correct Biosketch format? And Current and Pending (Other) Support format?

NIH applicants and recipients must continue to use the current NIH Biosketch and Other Support format pages for applications, Just-in-Time (JIT), and progress reports (RPPRs) until further notice. For most up-to-date information, please see https://grants.nih.gov/policy-and-compliance/implementation-of-new-initiatives-and-policies/common-forms-for-biosketch.

What are the allowable costs?

Partial salary support for expert panel chair and, if applicable, the co-chair(s), is

allowed. The primary emphasis should be on supporting a project coordinator, biocurators, and bioinformatics specialists. Both domestic and international expert panel members can receive nominal consulting fees. Funds can also be used for meeting support and travel to face-to-face meetings and the annual *Curating the Clinical Genome Conference* (https://clinicalgenome.org/about/events/) by the PI and other appropriate members. There may be additional costs associated with training on ClinGen tools. Regarding budgeting for consultants, if they will not be conducting a substantive portion of the research, their fees are not considered to be a sub-award, and therefore, no indirect costs would be involved. If they are conducting a substantive portion of the research, a sub-contract will be required. Please note, however, that the NIH is no longer allowing foreign subawards (per NOT-OD-25-104). All costs, including indirect costs, should be described in the parent award proposal.

Are functional studies to support curation calls allowed?

No, only evaluation of existing functional data is supported through this initiative.

Are renewal applications allowed, or can existing expert panels apply through this PAR?

Yes, established expert panels, including those previously supported by a NIH ClinGen NOFO, can apply through this PAR. However, there needs to be adequate justification regarding the work that the panel proposes to do, and the scope or scale needs to be sufficiently new or expanded to justify continued support. For example, an approved variant curation expert panel engaged in ongoing curation might propose to establish a new set of rule specifications for an additional gene within their disease area. Past productivity of the existing Expert Panel should be provided, including metrics such as those described here: https://search.clinicalgenome.org/kb/reports/stats. If milestones from a previous application were not met, applicants should address this.

How do I address the Innovation section?

Because each expert panel is expected to utilize pre-defined ClinGen tools and procedures, the innovation in proposed expert panels arises from their capacity to make substantial and significant new contributions to publicly available knowledge and understanding of genomic variants. There might also be innovation in the selection of variants or prioritization within the curation.

Is preliminary data required?

Preliminary data is not expected for new expert panels.

What information should ***not be included***?

Please do not include Justice, Equity, Diversity, and Inclusion (JEDI) language. Note that JEDI language is no longer included in the NOFO.

What ClinGen and ClinVar resources are available to guide andfacilitate the curation process?

ClinGen has posted guidelines for obtaining ClinVar expert panel status for gene and/or variant curation (https://clinicalgenome.org/docs/guidelines-for-applying-for-variant-or-gene-curation-expert-panel-status/). This includes the process of curation and criteria for the levels of clinical assertions as well as an expert panel toolkit: https://www.clinicalgenome.org/expert-groups/. In addition, ClinGen has provided demonstration curation interfaces. For further information about these interfaces, please

contact the ClinGen help desk at: clingen-helpdesk@lists.stanford.edu.

Is a Letter of Intent required?

No, a Letter of Intent is not required, but is strongly encouraged. Applicants should address letters of intent to Mollie Minear (mollie.minear@nih.gov) and Jiaqi O'Reilly (oreillyjj@nih.gov).

Is a Letter of Support from ClinGen required?

No, a letter of support from ClinGen is not required, although applicants are strongly encouraged to include one with their application to clearly define the type and status of their curation panel:

- New Expert Panel that is not part of an existing CDWG
- New Expert Panel that is being initiated from within an existing CDWG
- Established Curation Expert Panel

To request a letter of support from ClinGen, please email clingen@clinicalgenome.org with the subject line: "Request for LOS for NIH GCEP/VCEP application, in response to PAR-23-199 ."

ClinGen has a process to approve expert panels to ensure the number of curators experienced with ACMG guidelines are present. Will the groups submitting to this PAR need to first be approved by ClinGen, the step 1 approval, or would these be external to ClinGen?

ClinGen approval is not required to submit an application to NIH for this PAR. Applications for ClinGen expert panel approval can be submitted after obtaining funding. However, applicants are strongly encouraged to clarify the ClinGen approval status of the proposed expert panel in their application, including:

- The type of expert panel (gene curation expert panel, variant curation expert panel, and/or somatic cancer variant curation expert panel);
- Whether the expert panel has a relationship to an existing ClinGen CDWG; and
- Whether they have already submitted an expert curation application to the ClinGen Clinical Domain Oversight Committee for approval and, if so, the status of their application and, if applicable, their approved curation activities.

Applicants can submit a proposal in response to this NOFO to convene a curation expert panel that is anywhere along the continuum of curation activities for genes and/or variants, as long as the curation proposed is justified based on what is known about the disease(s) or condition(s) under study. Applicants are allowed to propose expert panels that will curate genes only, variants only (germline and/or somatic), or both genes and variants. If curation of both genes and variants is proposed, justification should be provided as to why both types of curation activities are needed and feasible. Additional guidance can be found within ClinGen's Guidelines for Applying for Variant or Gene Curation Expert Panel Status at: https://www.clinicalgenome.org/docs/guidelines-for-applying-for-variant-or-gene-curation-expert-panel-status/.

How can I contact ClinGen with questions?

For general inquiries, contact clingen@clinicalgenome.org or the NHGRI ClinGen team at: clingen@mail.nih.gov. For inquiries about the curation interface, contact clingen-helpdesk@lists.stanford.edu. For inquiries about the programmatic priorities of the NIH institutes participating in PAR-23-199, or for scientific questions, contact the NIH Contacts listed below.

NIH Contacts:

Institute	Contact
NICHD	**Jiaqi O'Reilly** Email: Jiaqi.OReilly@nih.gov
NCI	**Melissa Rotunno** Phone: 240-276-7245 Email: rotunnom@mail.nih.gov
NEI	**James Gao** Phone: 301-594-6074 Email: james.gao@nih.gov
NIMH	**Jonathan Pevsner** Phone: 301-728-5618 Email: jonathan.pevsner@nih.gov
NINDS	**Vicky Whittemore** Phone: 240-274-6696 Email: Vicky.whittemore@nih.gov
NCATS	**Tiina K Urv** Phone: (301) 402-7015 Email: urvtiin@mail.nih.gov
NIDCD	**Bracie Watson, Jr.** Phone: 301-402-3458 Email: watsonb@nidcd.nih.gov
NIAMS	**Marjorie Lindhurst** Phone: 301-451-8484 Email: marjr@mail.nih.gov