Department of Health and Human Services
Part 1. Overview Information

Participating Organization(s)

National Institutes of Health (NIH (http://www.nih.gov/))

Components of Participating Organizations

National Human Genome Research Institute (NHGRI (https://www.genome.gov/))
Office of Research on Women's Health (ORWH (http://orwh.od.nih.gov/))

Funding Opportunity Title

Human Genome Reference Center (HGRC) (U41 Clinical Trial Not Allowed)

Activity Code

U41 (//grants.nih.gov/grants/funding/ac_search_results.htm?text_curr=U41&Search.x=0&Search.y=0&Search_Type=Activity)
Biotechnology Resource Cooperative Agreements

Announcement Type

New

Related Notices

- **January 30, 2019** - Notice of Participation of the Office of Research on Womens Health (ORWH) in RFA-HG-19-004. See Notice NOT-OD-19-068 (/grants/guide/notice-files/NOT-OD-19-068.html).
- NOT-OD-19-068 (https://grants.nih.gov/grants/guide/notice-files/NOT-OD-19-068.html)

Funding Opportunity Announcement (FOA) Number

RFA-HG-19-004

Companion Funding Opportunity

RFA-HG-19-002 (https://grants.nih.gov/grants/guide/rfa-files/rfa-hg-19-002.html) (U01) Research Project with Complex Structure Cooperative Agreement

RFA-HG-19-003 (https://grants.nih.gov/grants/guide/rfa-files/rfa-hg-19-003.html) (U01) Research Project-Cooperative Agreements

Number of Applications

Only one application per institution is allowed, as defined in Section III. 3. Additional Information on Eligibility.

Catalog of Federal Domestic Assistance (CFDA) Number(s)

93.172, 93.313

Funding Opportunity Purpose

The National Human Genome Research Institute (NHGRI) seeks applications for a Human Genome Reference Center (HGRC). The HGRC will be the central group within a multi-component Human Genome Reference Program (HGRP) that will maintain and update the human genome reference and provide it to the scientific community. This group will also work with other HGRP members and the larger scientific community to prioritize sample choice and develop quality standards for new high-quality genome assemblies to add to the human genome reference; support state-of-the-art representations of alternate haplotypes (including representations developed by other program components); identify and respond to diverse community needs (e.g. clinical and basic) for use of the human genome reference; liaise or coordinate with other (international) resources that represent human genomic sequence and variation and/or that provide reference resources for human and other organisms.

Key Dates

Posted Date

January 30, 2019

Open Date (Earliest Submission Date)

March 2, 2019

Letter of Intent Due Date(s)

March 2, 2019

Application Due Date(s)

April 2, 2019, by 5:00 PM local time of applicant organization. All types of non-AIDS applications allowed for this funding opportunity announcement are due on this date.

Applicants are encouraged to apply early to allow adequate time to make any corrections to errors found in the application during the submission process by the due date.

AIDS Application Due Date(s)

Not Applicable.

Scientific Merit Review

June 2019

Advisory Council Review

October 2019

Earliest Start Date

September 2019

Expiration Date

April 3, 2019

Due Dates for E.O. 12372

Not Applicable

Required Application Instructions

It is critical that applicants follow the Multi-Project (M) Instructions in the SF424 (R&R) Application Guide (//grants.nih.gov/grants/guide/url_redirect.htm?id=12000), except where instructed to do otherwise (in this FOA or in a Notice from the *NIH Guide for Grants and Contracts (//grants.nih.gov/grants/guide/)*). Conformance to all requirements (both in the Application Guide and the FOA) is required and strictly enforced. Applicants must read and follow all application instructions in the Application Guide as well as any program-specific instructions noted in Section IV. When the program-specific instructions deviate from those in the Application Guide, follow the program-specific instructions. **Applications that do not comply with these instructions may be delayed or not accepted for review.**

There are several options available to submit your application through Grants.gov to NIH and Department of Health and Human Services partners. You **must** use one of these submission options to access the application forms for this opportunity.

1. Use the NIH ASSIST system to prepare, submit and track your application online.

   Apply Online Using ASSIST

2. Use an institutional system-to-system (S2S) solution to prepare and submit your application to Grants.gov and eRA Commons (http://public.era.nih.gov/commons/) to track your application. Check with your institutional officials regarding availability.

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- Section VI. Award Administration Information
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Part 2. Full Text of Announcement

Section I. Funding Opportunity Description

Background

The human genome reference resource, currently provided by the Genome Reference Consortium (GRC) https://www.ncbi.nlm.nih.gov/grc (https://www.ncbi.nlm.nih.gov/grc), is used by essentially all researchers who need to align and assemble experimental or patient genome sequence data. It also serves as a consensus coordinate system for reporting results.

Since the origin of the human reference in the completion of the International Human Genome Project there has been a need to maintain and improve the human reference and to make it available to the community. This has included resolving error reports, adding information to the reference from new high-quality genomes as they became available, and developing ways to represent alternative haplotype information derived from them. Improved or updated reference versions are curated and released to the community.

On March 1, 2018, NHGRI convened a web meeting of over 65 basic research, clinical, and bioinformatic scientists to discuss scientific opportunities for the genome reference. (https://www.genome.gov/pages/research/sequencing/meetings/hgr_webinar_summary_march1_2018.pdf (https://www.genome.gov/pages/research/sequencing/meetings/hgr_webinar_summary_march1_2018.pdf)) The meeting addressed key research and resource opportunities for improving the human reference; activities necessary to keep the reference relevant and useful; clinical and research community needs (including education); related resources; and collaborations.

The high-level conclusion of the meeting was that the current version of the human reference does not adequately represent human haplotype variation, that the existing tools to include alternative haplotype information in analyses are not well-used, and

that there is an opportunity to significantly improve the human reference by developing it into a “pan-genome”. One goal of a pan-genome reference is to represent as much as possible of human haplotype variation, implying that any newly sequenced experimental or patient haplotype will be readily alignable to the reference. This would include the multiple types of human genomic variation phased in chromosomal regions. This would require addition of many more high-quality human genome assemblies chosen to maximize haplotype diversity. This would also require the adoption of better ways of representing the data (e.g., as a genome graph), along with the development of new informatics tools to make use of the new reference.

As a result of these discussions, NHGRI will re-organize and re-focus its contribution to the genome reference to create a multi-component Human Genome Reference Program (HGRP) intended to enable an improved human genome reference for the community, and to foster its long-term sustainability and improvement.

Based on the Concept for this program presented to the National Council on Human Genome Research (https://www.genome.gov/pages/about/nachgr/september2018agendadocuments/genome_reference_foa_concept_clearance.pdf (https://www.genome.gov/pages/about/nachgr/september2018agendadocuments/genome_reference_foa_concept_clearance.pdf)) the components will be:

1. A Human Genome Reference Center (HGRC; This FOA)
2. High Quality Human Reference Genomes (HGRQ) see NIH Guide notice NOT-HG-19-008
3. Genome Reference Representations (GRR) see NIH Guide notice NOT-HG-19-009
4. Informatics tools for use of the human genome reference (see Concept documents)
5. Technology development for complete sequencing of genomes (see Concept documents)

Purpose

This FOA will establish a Human Genome Reference Center (HGRC), the central component of the HGRP. The HGRC will provide a high-quality human genome reference to the scientific community in order to enable genome sequence analysis by the community. The HGRC will integrate the products of, and help coordinate, the other elements of the HGRP. The HGRC will liase with other related resources worldwide (including other reference resources, groups maintaining genomic standards, human variation data resources, etc.) in a way that will add value for the genomic community as a whole. The HGRC will help determine and respond to potential needs of various sectors of the research community (e.g. basic population genetics, genomic medicine, comparative genomics, etc.) that depend on the human reference. The HGRC will also provide outreach to the community of users both to provide them with information about how to use the reference and also to obtain feedback for improvement of the reference. More detail about these objectives is provided below.

This FOA (and FOAs for other HGRP components) are intended to revise and improve NHGRIs current funding contributions to genome reference efforts, in line with the conclusions of the March 1, 2018 meeting described above, and replacing NHGRIs current funding of genome reference activities, which ends in 2018. The GRC currently operates as an international consortium, with support (in the form of funding and direct effort) provided by a number of entities, including NHGRI, whose main recent role has been to fund correction of errors in the reference, the addition of new high-quality genomes, and overall coordination. Others have ongoing roles, including the National Center for Biotechnology Information (NCBI) and the Wellcome Trust (funding the Sanger Center and the European Bioinformatics Institute (EBI)); these roles include supporting the underlying data, help in provision of the reference to the community, developing standards and policies, aspects of project coordination, and work on non-human genome references. These interactions have been, and will continue to be, essential to the success of the human reference. NHGRI’s future contribution to genome references will be most effective in collaboration with these and other ongoing international efforts to build, maintain, and serve references to the worldwide genomics community.

These NHGRI HGRP FOAs seek applications for work only on human; we note that the larger GRC currently supports references for mouse, zebrafish, and chicken as well.

Objectives: The HGRC will be the central component of the HGRP. It will:

1. Provide a state-of-the-art human genome reference to the community.

- Construct and release new human reference sequence versions (including patches and full updates), incorporating high quality human genome sequence data provided by another HGRP component (HQRG) and from elsewhere, anticipating and planning for the transition from the current reference representations to newer ones as the state of the art improves.
- Receive and resolve error reports. The HGRC will need to provide (direct or subcontracted) sequencing capacity to resolve error reports or obtain this capacity from another program component. However, to the extent that resolution of an error will require complete high-quality sequencing of a genome, this task should be left to another HGRP component, the High Quality Human Reference Genomes center (HGRQ). It is expected that the HGRC will work with the HGRQ, after awards are made, to address this need in an efficient way.

2. Integrate and coordinate with and between the other HGRP elements

- A separate HGRP component (HGRQ; FOA HG-2019-002) will sequence additional human genomes to very high quality for incorporation into the reference. An existing NHGRI-funded effort (ending in 2018) has produced eight assemblies, with six in progress, and 3-5 more planned from diverse populations (>75% non-European Ancestry).
    - The HGRC will integrate these assemblies into the reference cohort.
    - The HGRC will foster the discussion within the consortium, and with outside experts, as needed, regarding the prioritization of new high-quality genomes in order to improve representation of haplotype diversity.
    - An essential part of this prioritization is the identification of sample sets that are adequately consented for use in the reference cohort, and will meet requirements for added population diversity, quality of samples, and long-term availability of samples. Although NHGRI believes that the 1000 Genomes (1000G; http://www.internationalgenome.org/ (http://www.internationalgenome.org/)) samples are a good source, there may be other samples that are available. During the course of this program, the HGRP and NHGRI may determine that additional samples should be identified, and obtained. Resources for that effort, if needed, will be provided to the HGRP through the HGRQ.
    - The HGRC will foster the discussion within the consortium about the desired cost/quality point, and tradeoffs between quality and quantity, that is needed for new high-quality genome assemblies, considering different uses by the community (e.g., basic population genetics vs clinical).
- Implement, in the context of providing the reference, state-of-the-art representations that include alternative haplotypes.
    - Another HGRP component (Genome Reference Representations (GRR)) will be funded to undertake research and development on new reference representations (e.g., graph-based). The HGRC should adopt--or foster the adoption of--one or more of these as they mature. The HGRC should help establish performance metrics and benchmarks for these, together with the other component grantees.

3. Provide liaison to, and where appropriate, establish collaboration with, other investigators and organizations that undertake activities related to genome references.

- Collaborate with other funders and resources that have a direct role in genome references, especially NCBI, The Wellcome Trust, and EBI. NHGRI considers that effective collaboration with these other existing entities that provide the genome reference resource to the community will be essential.
- Communicate with organizations that set standards in this or related areas, e.g. Global Alliance for Genomics and Health (GA4GH; https://www.ga4gh.org (https://www.ga4gh.org)) or "Genome in a Bottle" (GIAB; http://jimb.stanford.edu/giab/ (http://jimb.stanford.edu/giab/)).
- Comply with widely used data standards; where appropriate contribute to development of standards (e.g., for data quality, meta-data, interoperability).
- Liase and coordinate with other major resources that provide human variation information (for example, ClinVar https://www.clinicalgenome.org/ (https://www.clinicalgenome.org/) and ClinGen https://www.ncbi.nlm.nih.gov/clinvar/ (https://www.ncbi.nlm.nih.gov/clinvar/) and the Human Genome Structural Variation Consortium http://www.internationalgenome.org/human-genome-structural-variation-consortium/ (http://www.internationalgenome.org/human-genome-structural-variation-consortium/)) to the community. From a high-level perspective, NHGRI regards the HGRP as representing an aspect of human variation for a particular use. As such, connections with other human variation resources will be important in the long term, for example to remain aware of community needs, to avoid unproductive duplication of effort, and to help work towards an overall presentation to the community of an integrated view of human variation.

4. Provide community outreach and training for using the reference. Provide basic tools for using the reference.

- Provide courses/trainings (e.g. at meetings and on-line) for use of the reference.
- Solicit and respond to community feedback about the resource; summarize feedback for discussion with NHGRI program and advisors.
- Aggregate informatics tools created by the community for use of the reference. The HGRP may propose development or refinement of their own basic tools for using the reference. However, significant new tool development should be funded from other sources. NHGRI intends to solicit applications for tool development separately, via its regular R01 program.

5. Be the logistical and scientific coordinating center for the NHGRI HGRP, working to implement a human "pan-genome" reference in a way that maximizes its value to the community.

- Organize one annual meeting of the consortium and any others that maybe required; organize necessary travel for any program advisors; organize consortium conference calls; provide minutes and summaries, maintain an internal consortium web interface, create and maintain a web interface for the community.
- Describe how the HGRP (in general) and HGRC (in detail) plans will interface with other non-NHGRI-funded components contributing to an overall genome reference effort.
- Help ensure that the HGRP meets expectations for data deposition and leads in the area of making consortium-generated data, tools and other products available to the community.

Objectives 3-5 are anticipated to require a high degree of community engagement, an ability to productively lead collaborations with a wide range of consortium members and outside members of the research community, spanning interest areas (both basic and clinical researchers) and various levels of user expertise. Applicants should include evidence of past successful experience in this area.

Overall, the HGRP is intended to realize the vision from the March 2018 web meeting to significantly improve the human reference by developing it into a "pan-genome", representing as much human haplotype variation as possible given the resources available, in a way that is demonstrably useful across a range of basic and clinical genomics applications. This will be combined with improved community tools for representing and using the reference.

Webinar

NHGRI will conduct a webinar to answer questions from prospective applicants. Webinar information and FAQs are available at https://www.genome.gov/27572476/human-genome-reference-program-webinar/ (https://www.genome.gov/27572476/human-genome-reference-program-webinar/)

See Section VIII. Other Information for award authorities and regulations.

Section II. Award Information

Funding Instrument

Cooperative Agreement: A support mechanism used when there will be substantial Federal scientific or programmatic involvement. Substantial involvement means that, after award, NIH scientific or program staff will assist, guide, coordinate, or participate in project activities. See Section VI.2 for additional information about the substantial involvement for this FOA.

Application Types Allowed

New
The OER Glossary (//grants.nih.gov/grants/guide/url_redirect.htm?id=11116) and the SF424 (R&R) Application Guide provide details on these application types.

Clinical Trial?

Not Allowed: Only accepting applications that do not propose clinical trials

Need help determining whether you are doing a clinical trial? (https://grants.nih.gov/grants/guide/url_redirect.htm?id=82370)

Funds Available and Anticipated Number of Awards

The National Human Genome Research Institute intends to commit $2,500,000 in FY 2019 to fund one award.

Award Budget

Application budgets are not limited but need to reflect the actual needs of the proposed project. **Award Project Period**

The maximum project period is 5 years.

NIH grants policies as described in the *NIH Grants Policy Statement (//grants.nih.gov/grants/guide/url_redirect.htm?id=11120)* will apply to the applications submitted and awards made from this FOA.

Section III. Eligibility Information

1. Eligible Applicants

Eligible Organizations

Higher Education Institutions

- Public/State Controlled Institutions of Higher Education
- Private Institutions of Higher Education

The following types of Higher Education Institutions are always encouraged to apply for NIH support as Public or Private Institutions of Higher Education:

- Hispanic-serving Institutions
- Historically Black Colleges and Universities (HBCUs)
- Tribally Controlled Colleges and Universities (TCCUs)
- Alaska Native and Native Hawaiian Serving Institutions
- Asian American Native American Pacific Islander Serving Institutions (AANAPISIs)

Nonprofits Other Than Institutions of Higher Education

- Nonprofits with 501(c)(3) IRS Status (Other than Institutions of Higher Education)
- Nonprofits without 501(c)(3) IRS Status (Other than Institutions of Higher Education)

Governments

- State Governments
- County Governments
- City or Township Governments
- Special District Governments
- Indian/Native American Tribal Governments (Federally Recognized)
- Indian/Native American Tribal Governments (Other than Federally Recognized)
- Eligible Agencies of the Federal Government
- U.S. Territory or Possession

Foreign Institutions

Non-domestic (non-U.S.) Entities (Foreign Institutions) **are not** eligible to apply.
Non-domestic (non-U.S.) components of U.S. Organizations **are not** eligible to apply.

Foreign components, as defined in the *NIH Grants Policy Statement* (//grants.nih.gov/grants/guide/url_redirect.htm?id=11118), **are** allowed.

Required Registrations

Applicant Organizations

Applicant organizations must complete and maintain the following registrations as described in the SF 424 (R&R) Application Guide to be eligible to apply for or receive an award. All registrations must be completed prior to the application being submitted. Registration can take 6 weeks or more, so applicants should begin the registration process as soon as possible. The NIH Policy on Late Submission of Grant Applications (//grants.nih.gov/grants/guide/notice-files/NOT-OD-15-039.html) states that failure to complete registrations in advance of a due date is not a valid reason for a late submission.

- Dun and Bradstreet Universal Numbering System (DUNS) (http://fedgov.dnb.com/webform) - All registrations require that applicants be issued a DUNS number. After obtaining a DUNS number, applicants can begin both SAM and eRA Commons registrations. The same DUNS number must be used for all registrations, as well as on the grant application.
- System for Award Management (SAM) (https://www.sam.gov/portal/public/SAM/) – Applicants must complete and maintain an active registration, **which requires renewal at least annually**. The renewal process may require as much time as the initial registration. SAM registration includes the assignment of a Commercial and Government Entity (CAGE) Code for domestic organizations which have not already been assigned a CAGE Code.
- o NATO Commercial and Government Entity (NCAGE) Code (//grants.nih.gov/grants/guide/url_redirect.htm?id=11176) – Foreign organizations must obtain an NCAGE code (in lieu of a CAGE code) in order to register in SAM.
- eRA Commons (//grants.nih.gov/grants/guide/url_redirect.htm?id=11123) - Applicants must have an active DUNS number to register in eRA Commons. Organizations can register with the eRA Commons as they are working through their SAM or Grants.gov registration, but all registrations must be in place by time of submission. eRA Commons requires organizations to identify at least one Signing Official (SO) and at least one Program Director/Principal Investigator (PD/PI) account in order to submit an application.
- Grants.gov (//grants.nih.gov/grants/guide/url_redirect.htm?id=82300) – Applicants must have an active DUNS number and SAM registration in order to complete the Grants.gov registration.

Program Directors/Principal Investigators (PD(s)/PI(s))

All PD(s)/PI(s) must have an eRA Commons account. PD(s)/PI(s) should work with their organizational officials to either create a new account or to affiliate their existing account with the applicant organization in eRA Commons.If the PD/PI is also the organizational Signing Official, they must have two distinct eRA Commons accounts, one for each role. Obtaining an eRA Commons account can take up to 2 weeks.

Eligible Individuals (Program Director/Principal Investigator)

Any individual(s) with the skills, knowledge, and resources necessary to carry out the proposed research as the Program Director(s)/Principal Investigator(s) (PD(s)/PI(s)) is invited to work with his/her organization to develop an application for support. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH support.

For institutions/organizations proposing multiple PDs/PIs, visit the Multiple Program Director/Principal Investigator Policy and submission details in the Senior/Key Person Profile (Expanded) Component of the SF424 (R&R) Application Guide.

2. Cost Sharing

This FOA does not require cost sharing as defined in the *NIH Grants Policy Statement*. (//grants.nih.gov/grants/guide/url_redirect.htm?id=11126)

3. Additional Information on Eligibility

Number of Applications

Only one application per institution (normally identified by having a unique DUNS number or NIH IPF number) is allowed.

The NIH will not accept duplicate or highly overlapping applications under review at the same time. This means that the NIH will not accept:

- A new (A0) application that is submitted before issuance of the summary statement from the review of an overlapping new (A0) or resubmission (A1) application.
- A resubmission (A1) application that is submitted before issuance of the summary statement from the review of the previous new (A0) application.
- An application that has substantial overlap with another application pending appeal of initial peer review (see NOT-OD-11-101 (//grants.nih.gov/grants/guide/notice-files/NOT-OD-11-101.html)).

Section IV. Application and Submission Information

1. Requesting an Application Package

The application forms package specific to this opportunity must be accessed through ASSIST or an institutional system-to-system solution. A button to apply using ASSIST is available in Part 1 of this FOA. See your administrative office for instructions if you plan to use an institutional system-to-system solution.

2. Content and Form of Application Submission

It is critical that applicants follow the Multi-Project (M) Instructions in the SF424 (R&R) Application Guide (//grants.nih.gov/grants/guide/url_redirect.htm?id=12000), except where instructed in this funding opportunity announcement to do otherwise and where instructions in the Application Guide are directly related to the Grants.gov downloadable forms currently used with most NIH opportunities. Conformance to the requirements in the Application Guide is required and strictly enforced. Applications that are out of compliance with these instructions may be delayed or not accepted for review.

Letter of Intent

Although a letter of intent is not required, is not binding, and does not enter into the review of a subsequent application, the information that it contains allows IC staff to estimate the potential review workload and plan the review.

By the date listed in Part 1. Overview Information, prospective applicants are asked to submit a letter of intent that includes the following information:

- Descriptive title of proposed activity
- Name(s), address(es), and telephone number(s) of the PD(s)/PI(s)
- Names of other key personnel
- Participating institution(s)
- Number and title of this funding opportunity

The letter of intent should be sent to:

Adam Felsenfeld
Telephone: 301-480-2269
Email: felsenfa@mail.nih.gov (mailto:felsenfa@mail.nih.gov)

Page Limitations

Available Component Types	Research Strategy/Program Plan Page Limits

Available Component Types	Research Strategy/Program Plan Page Limits
Overall (Human genome reference center)	12
Project 1 (Maintaining, improving, and providing the human reference)	12
Project 2 (Community outreach)	6
Project 3 (HGRP logistical coordinating center)	6

Additional page limits described in the SF424 Application Guide and the Table of Page Limits (//grants.nih.gov/grants/guide/url_redirect.htm?id=11133) must be followed.

Instructions for the Submission of Multi-Component Applications

The following section supplements the instructions found in the SF424 (R&R) Application Guide, and should be used for preparing a multi-component application.

The application should consist of the following components:

- Overall: Human Genome Reference Center: one required.
- Project 1: Maintaining, improving, and providing the human reference: one required
- Project 2: Community outreach: one required.
- Project 3: HGRP logistical coordinating center: one required.

Overall Component

When preparing your application, use Component Type 'Overall'.

All instructions in the SF424 (R&R) Application Guide must be followed, with the following additional instructions, as noted.

SF424 (R&R) Cover (Overall: Human Genome Reference Center)

Complete entire form.

PHS 398 Cover Page Supplement (Overall: Human Genome Reference Center)

Note: Human Embryonic Stem Cell lines from other components should be repeated in cell line table in Overall component.

Research & Related Other Project Information (Overall: Human Genome Reference Center)

Follow standard instructions.

Project/Performance Site Location(s) (Overall: Human Genome Reference Center)

Enter primary site only.

A summary of Project/Performance Sites in the Overall section of the assembled application image in eRA Commons compiled from data collected in the other components will be generated upon submission.

Research & Related Senior/Key Person Profile (Overall: Human Genome Reference Center)

Include only the Project Director/Principal Investigator (PD/PI) and any multi-PDs/PIs (if applicable to this FOA) for the entire application.

A summary of Senior/Key Persons followed by their Biographical Sketches in the Overall section of the assembled application image in eRA Commons will be generated upon submission.

Budget (Overall: Human Genome Reference Center)

The only budget information included in the Overall component is the Estimated Project Funding section of the SF424 (R&R) Cover.

A budget summary in the Overall section of the assembled application image in eRA Commons compiled from detailed budget data collected in the other components will be generated upon submission.

PHS 398 Research Plan (Overall: Human Genome Reference Center)

Specific Aims: Specific Aims should convey the entire planned effort.

Research Strategy: The Overall: Human Genome Reference Center research strategy section should provide a scientific vision for, and integrated overview of, how the proposed center would accomplish the objectives of this FOA toward creating, providing, and maintaining a state-of-the-art human pan-genome reference resource, for multiple communities that will depend on it (e.g., basic and clinical genomics, different levels of user expertise). Applicants should discuss key decision points and trade-offs,

including how they would prioritize scientific and practical choices (e.g., resource allocation between center components, when to release new reference builds, prioritization of new genomes for the reference cohort, etc.). Applicants are encouraged to propose creative and practical ideas to attain the larger goals of this FOA as set out in the Funding Opportunity Description, particularly working towards the vision of the reference as a human "pan-genome". This section should also include:

- A high-level view and outline of a strategy for transitioning the current human reference representation to a pan-genome representation, considering that the current representation (e.g., GRCh38 and possibly further 'builds') will be in use until (at least) a transition is complete. (Details of this plan can be addressed in Project 2).
- An overall view of the proposed HGRC, including management of the HGRC components and reporting relationships. NHGRI anticipates that responses to this FOA are highly likely to be multi-PI applications. This view should convey how the HGRC will operate as a whole.
- An overall view of how the HGRC will coordinate with other NHGRI HGRP components, including the HQRG (which will provide high quality human genome assemblies) and the GRR (which will develop new reference representations).
- An overall view of how the HGRC plan will coordinate with other US and international efforts that produce the human genome reference in a way that effectively presents the genome reference resource to the community. The application as a whole should convey how different parts fit together and will be coordinated, even if some are funded by other means. For example, the HGRC will need access to computational resources to store, compute on/synthesize, and serve the reference. Applicants may propose to use grant funds for this, or may collaborate with existing informatics resources/facilities such as NCBI and the NHGRI Genomic Data Science Analysis, Visualization, and Informatics Lab-space (AnVIL) (https://www.genome.gov/27569268/the-nhgri-analysis-visualization-and-informatics-labspace-anvil/ (https://www.genome.gov/27569268/the-nhgri-analysis-visualization-and-informatics-labspace-anvil/)). NHGRI encourages these interactions because they represent a way to improve presentation and adoption of the reference, improve its sustainability, and will leverage NHGRIs funding.
- A description of how the HGRC will approach key decisions such as prioritization and incorporation of high quality, diverse human genome assemblies into the reference from all appropriate sources, and for prioritizing new genomes for addition. Is there a better way to do this than simply maximizing geographic diversity? Applicants should understand that final decisions on these questions will be made in concert with the HGRP as a whole.
- A view of how the HGRC will liase with other relevant genomic data resources; the application should state and justify the priorities for such collaborations, e.g. with reference to their ability to provide a coherent view of variation, or the reference itself, across different resources; or the importance of communicating to different communities about the reference, etc.
- A description of "added value" products and how the HGRC will release or otherwise provide them to the community.

Several of the objectives of this FOA require a high degree of community engagement, and the ability to productively lead collaborations with a wide range of consortium members and members of the research community, spanning interest areas (both basic and clinical researchers) and different levels of user expertise. Applicants should include evidence of past successful experience in this area.

Letters of Support: Applications should include letters of support from proposed collaborators, especially if they will be integral to the overall plan for the HGRC.

Resource Sharing Plan: Individuals are required to comply with the instructions for the Resource Sharing Plans as provided in the SF424 (R&R) Application Guide, with the following modification:

All applications, regardless of the amount of direct costs requested for any one year, should address a Data Sharing Plan. The Data Sharing Plan should cover aspects of data sharing that are not described elsewhere in the application.

Appendix:

Only limited items are allowed in the Appendix. Follow all instructions for the Appendix as described in the SF424 (R&R) Application Guide; any instructions provided here are in addition to the SF424 (R&R) Application Guide instructions.

PHS Human Subjects and Clinical Trials Information (Overall)

When involving NIH-defined human subjects research, clinical research, and/or clinical trials follow all instructions for the PHS Human Subjects and Clinical Trials Information form in the SF424 (R&R) Application Guide, with the following additional instructions:

If you answered “Yes” to the question “Are Human Subjects Involved?” on the R&R Other Project Information form, there must be at least one human subjects study record using the **Study Record: PHS Human Subjects and Clinical Trials Information** form or a **Delayed Onset Study** record within the application. The study record(s) must be included in the component(s) where the work is being done, unless the same study spans multiple components. To avoid the creation of duplicate study records, a single study record with sufficient information for all involved components must be included in the Overall component when the same study spans multiple components.

Study Record: PHS Human Subjects and Clinical Trials Information

All instructions in the SF424 (R&R) Application Guide must be followed.

Delayed Onset Study

Note: Delayed onset (https://grants.nih.gov/grants/glossary.htm#DelayedOnsetHumanSubjectStudy) does NOT apply to a study that can be described but will not start immediately (i.e., delayed start).

All instructions in the SF424 (R&R) Application Guide must be followed.

PHS Assignment Request Form (Overall: Human Genome Reference Center)

All instructions in the SF424 (R&R) Application Guide must be followed.

Project 1: Maintaining, improving, and providing the human reference

When preparing your application, use Component Type 'Project 1 .'

All instructions in the SF424 (R&R) Application Guide must be followed, with the following additional instructions, as noted.

SF424 (R&R) Cover (Maintaining, improving, and providing the human reference

Complete only the following fields:

- Applicant Information
- Type of Applicant (optional)
- Descriptive Title of Applicant's Project
- Proposed Project Start/Ending Dates

PHS 398 Cover Page Supplement (Maintaining, improving, and providing the human reference)

Enter Human Embryonic Stem Cells in each relevant component.

Research & Related Other Project Information (Maintaining, improving, and providing the human reference)

Human Subjects: Answer only the 'Are Human Subjects Involved?' and 'Is the Project Exempt from Federal regulations?' questions.

Vertebrate Animals: Answer only the 'Are Vertebrate Animals Used?' question.

Project Narrative: Do not complete. Note: ASSIST screens will show an asterisk for this attachment indicating it is required. However, eRA systems only enforce this requirement in the Overall component and applications will not receive an error if omitted in other components.

Project /Performance Site Location(s) (Maintaining, improving, and providing the human reference)

List all performance sites that apply to the specific component.

Research & Related Senior/Key Person Profile (Maintaining, improving, and providing the human reference)

- In the Project Director/Principal Investigator section of the form, use Project Role of 'Other' with Category of 'Project Lead' and provide a valid eRA Commons ID in the Credential field.
- In the additional Senior/Key Profiles section, list Senior/Key persons that are working in the component.
- Include a single Biographical Sketch for each Senior/Key person listed in the application regardless of the number of components in which they participate. When a Senior/Key person is listed in multiple components, the Biographical Sketch can be included in any one component.
- If more than 100 Senior/Key persons are included in a component, the Additional Senior Key Person attachments should be used.

Budget (Maintaining, improving, and providing the human reference)

Budget forms appropriate for the specific component will be included in the application package.

Note: The R&R Budget form included in many of the component types allows for up to 100 Senior/Key Persons in section A and 100 Equipment Items in section C prior to using attachments for additional entries. All other SF424 (R&R) instructions apply.

PHS 398 Research Plan (Maintaining, improving, and providing the human reference)

Specific Aims: Provide the aims for the construction, maintenance, improvement, and releases of the reference.

Research Strategy: This Project research strategy should focus on scientific details about how the human reference pan-genome resource will be constructed, maintained, improved, and provided to the community. It may include, for example:

- Plans for maintaining the reference, e.g., correcting errors, making updates, and new version releases.
- Plans for evaluation of the quality of the reference, evaluation of errors and ambiguities; this includes computational/analytic capabilities and genome sequencing capacity that will be required to resolve errors or ambiguities in the human reference. Applicants should be aware that another component, the HQRG, will have ample capacity to sequence entire high-quality human genomes if those are needed. Applications for this FOA should not duplicate that.
- Plans for how the reference will be constructed, represented, and made available to the community, including details about analytical methods and expertise needed. Plans should account for the near-term needs to serve the reference in its current representation (e.g. GRCh38 and future GRCh versions), as well as a transition to improved representations. Describe any computational resources and expertise needed to store and compute on data, serve the reference, etc., whether data resources are to be supported by grant funds or through other means.
- Technical and strategic plans for incorporating alternate haplotype information and/or new genomes into the reference, including existing and new high-quality genome assemblies produced by the HQRG. This should be related to the long-term goal of a practical representation of the human reference as a "pan-genome", and will have both technical and strategic aspects. Applicants should consider how they will manage the transition between the current representation of the human reference and a future pan-genome representation. Applicants should propose processes for evaluating required quality of the new assemblies to be added to the reference cohort (keeping in mind that final decisions on assembly quality needed will be made by the program as a whole). Applicants should discuss how they would consider tradeoffs, e.g., between adding new assemblies to the reference cohort that will tend to aid basic researchers vs clinical researchers. Applicants should discuss and justify their view of how new genomes should be prioritized (e.g. by population).

Applicants should address how various types of genomic variation will be represented in the reference. If applicants propose variant calling activities (for new genomic assemblies) they should anticipate that the HQRG will also do variant calling. A harmonized process will need to be developed after the consortium has formed.

- Plans for making reference versions "backwards compatible", or otherwise facilitating adoption of new versions by different sectors of the community through technical solutions. This refers to the tendency of e.g. consortia to resist updating their analyses to use newer reference versions because they have built those analyses on older reference versions.
- Plans for basic informatics tools for making the reference available, including alternate haplotype information available within the reference. As the GRR component matures we anticipate that the HGRC will likely adopt their representations, if they are successful. Overall the HGRC should use state-of-the-art tools to represent and provide this information to the community.

Letters of Support:

Resource Sharing Plan: Individuals are required to comply with the instructions for the Resource Sharing Plans as provided in the SF424 (R&R) Application Guide, with the following modification:

All applications, regardless of the amount of direct costs requested for any one year, should address a Data Sharing Plan. This section should not repeat information provided in the Research Strategy.

Appendix:

Only limited items are allowed in the Appendix.Follow all instructions for the Appendix as described in the SF424 (R&R) Application Guide; any instructions provided here are in addition to the SF424 (R&R) Application Guide instructions.

PHS Human Subjects and Clinical Trials Information (Maintaining, improving, and providing the human reference)

When involving NIH-defined human subjects research, clinical research, and/or clinical trials follow all instructions for the PHS Human Subjects and Clinical Trials Information form in the SF424 (R&R) Application Guide, with the following additional instructions:

If you answered “Yes” to the question “Are Human Subjects Involved?” on the R&R Other Project Information form, you must include at least one human subjects study record using the **Study Record: PHS Human Subjects and Clinical Trials Information** form or a **Delayed Onset Study** record.

Study Record: PHS Human Subjects and Clinical Trials Information

All instructions in the SF424 (R&R) Application Guide must be followed.

Delayed Onset Study

Note: Delayed onset (https://grants.nih.gov/grants/glossary.htm#DelayedOnsetHumanSubjectStudy) does NOT apply to a study that can be described but will not start immediately (i.e., delayed start).All instructions in the SF424 (R&R) Application Guide must be followed.

Project 2: Community outreach

When preparing your application, use Component Type ‘Project 2.’

All instructions in the SF424 (R&R) Application Guide must be followed, with the following additional instructions, as noted.

SF424 (R&R) Cover (Community outreach)

Complete only the following fields:

- Applicant Information
- Type of Applicant (optional)
- Descriptive Title of Applicant's Project
- Proposed Project Start/Ending Dates

PHS 398 Cover Page Supplement (Community outreach)

Enter Human Embryonic Stem Cells in each relevant component.

Research & Related Other Project Information (Community outreach)

Human Subjects: Answer only the 'Are Human Subjects Involved?' and 'Is the Project Exempt from Federal regulations?' questions.

Vertebrate Animals: Answer only the 'Are Vertebrate Animals Used?' question.

Project Narrative: Do not complete. Note: ASSIST screens will show an asterisk for this attachment indicating it is required. However, eRA systems only enforce this requirement in the Overall component and applications will not receive an error if omitted in other components.

Project /Performance Site Location(s) (Community outreach)

List all performance sites that apply to the specific component.

Note: The Project Performance Site form allows up to 300 sites, prior to using additional attachment for additional entries.

Research & Related Senior/Key Person Profile (Community outreach)

- In the Project Director/Principal Investigator section of the form, use Project Role of 'Other' with Category of 'Project Lead' and provide a valid eRA Commons ID in the Credential field.
- In the additional Senior/Key Profiles section, list Senior/Key persons that are working in the component.
- Include a single Biographical Sketch for each Senior/Key person listed in the application regardless of the number of components in which they participate. When a Senior/Key person is listed in multiple components, the Biographical Sketch can be included in any one component.
- If more than 100 Senior/Key persons are included in a component, the Additional Senior Key Person attachments should be used.

Budget (Community outreach)

Budget forms appropriate for the specific component will be included in the application package.

Note: The R&R Budget form included in many of the component types allows for up to 100 Senior/Key Persons in section A and 100 Equipment Items in section C prior to using attachments for additional entries. All other SF424 (R&R) instructions apply.

PHS 398 Research Plan (Community outreach)

Specific Aims: Provide Aims for community outreach for the HGRP.

Research Strategy: Describe how the HGRC will provide information to the community about the genome reference, and also obtain information about and respond to community needs. Applicants should keep in mind that the users of the reference encompass a range of research interests (e.g., from basic population genetics to interpretation of patient genomes) and levels of expertise, and should describe how they will meet these diverse needs. This section may include:

- The user interface for the reference
- Online provision of information to the community about the reference, updates, new features, etc.
- Online and in-person training and information sessions about the use of the reference.
- Indexes or aggregation of informatics tools (built by the community) for use of the reference.
- Use statistics, metrics, and other means to understand the uses and users of the reference and areas for attention.
- Proposed surveys, user focus groups, workshops, or other means to understand community needs and incorporate them into ongoing priorities for the reference.
- Generally increasing the community awareness about the reference, its uses, and its significance.

Applicants are encouraged to think creatively about how to make the most efficient use of the resources available, especially for training activities.

Letters of Support: Please do not duplicate letters of support that were included in the Overall section.

Resource Sharing Plan: Individuals are required to comply with the instructions for the Resource Sharing Plans as provided in the SF424 (R&R) Application Guide, with the following modification:

- The Resource Sharing Plan should include a high-level description of how HGRC resources will be shared. Because the overall intent of this FOA is to provide a resource, detailed resource sharing plans should be described and justified in the Research Strategy section.

Appendix:

Only limited items are allowed in the Appendix. Follow all instructions for the Appendix as described in the SF424 (R&R) Application Guide; any instructions provided here are in addition to the SF424 (R&R) Application Guide instructions.

PHS Human Subjects and Clinical Trials Information (Community outreach)

When involving NIH-defined human subjects research, clinical research, and/or clinical trials follow all instructions for the PHS Human Subjects and Clinical Trials Information form in the SF424 (R&R) Application Guide, with the following additional instructions:

If you answered "Yes" to the question "Are Human Subjects Involved?" on the R&R Other Project Information form, you must include at least one human subjects study record using the **Study Record: PHS Human Subjects and Clinical Trials Information** form or a **Delayed Onset Study** record.

Study Record: PHS Human Subjects and Clinical Trials Information

All instructions in the SF424 (R&R) Application Guide must be followed

Delayed Onset Study

Note: Delayed onset (https://grants.nih.gov/grants/glossary.htm#DelayedOnsetHumanSubjectStudy) does NOT apply to a study that can be described but will not start immediately (i.e., delayed start).All instructions in the SF424 (R&R) Application Guide must be followed

Project 3: HGRP logistical coordinating center

When preparing your application, use Component Type 'Project 3.'

All instructions in the SF424 (R&R) Application Guide must be followed, with the following additional instructions, as noted.

SF424 (R&R) Cover (HGRP logistical coordinating center)

Complete only the following fields:

- Applicant Information
- Type of Applicant (optional)
- Descriptive Title of Applicant's Project
- Proposed Project Start/Ending Dates

PHS 398 Cover Page Supplement (HGRP logistical coordinating center)

Enter Human Embryonic Stem Cells in each relevant component.

Research & Related Other Project Information (HGRP logistical coordinating center)

Human Subjects: Answer only the 'Are Human Subjects Involved?' and 'Is the Project Exempt from Federal regulations?' questions.

Vertebrate Animals: Answer only the 'Are Vertebrate Animals Used?' question.

Project Narrative: Do not complete. Note: ASSIST screens will show an asterisk for this attachment indicating it is required. However, eRA systems only enforce this requirement in the Overall component and applications will not receive an error if omitted in other components.

Project /Performance Site Location(s) (HGRP logistical coordinating center)

List all performance sites that apply to the specific component.

Note: The Project Performance Site form allows up to 300 sites, prior to using additional attachment for additional entries.

Research & Related Senior/Key Person Profile (HGRP logistical coordinating center)

- In the Project Director/Principal Investigator section of the form, use Project Role of 'Other' with Category of 'Project Lead' and provide a valid eRA Commons ID in the Credential field.
- In the additional Senior/Key Profiles section, list Senior/Key persons that are working in the component.
- Include a single Biographical Sketch for each Senior/Key person listed in the application regardless of the number of components in which they participate. When a Senior/Key person is listed in multiple components, the Biographical Sketch

can be included in any one component.
- If more than 100 Senior/Key persons are included in a component, the Additional Senior Key Person attachments should be used.

Budget (HGRP logistical coordinating center)

Budget forms appropriate for the specific component will be included in the application package.

The grant budget should include estimated funds for the meeting venue and travel for five advisors.

Note: The R&R Budget form included in many of the component types allows for up to 100 Senior/Key Persons in section A and 100 Equipment Items in section C prior to using attachments for additional entries. All other SF424 (R&R) instructions apply.

PHS 398 Research Plan (HGRP logistical coordinating center)

Specific Aims: Provide the aims for logistical coordination of the HGRP.

Research Strategy: Describe how the HGRC will serve as the logistical coordinating center for the consortium. This should include:

- Facilitating communications within the consortium. Scheduling/hosting consortium conference calls, meeting logistics; taking meeting and call notes and recording/following up on major action items; maintaining an internal web site, Wiki, or similar platform for communicating, retaining and tracking key program documents, policies, and action items.
- Organizing and supporting an annual consortium meeting including supporting travel for up to 5 NHGRI external scientific advisors (see Cooperative Agreement Terms and Conditions) to the annual meeting.
- Tracking publications and presentations of the program; maintaining a library of presentations including materials that can be re-used by consortium members.

Applicants are encouraged to anticipate other key logistical and coordination needs for the program.

Letters of Support: Please do not duplicate letters of support that were included in the Overall section.

Resource Sharing Plan: Individuals are required to comply with the instructions for the Resource Sharing Plans as provided in the SF424 (R&R) Application Guide.

Appendix:

Only limited items are allowed in the Appendix. Follow all instructions for the Appendix as described in the SF424 (R&R) Application Guide; any instructions provided here are in addition to the SF424 (R&R) Application Guide instructions.

PHS Human Subjects and Clinical Trials Information (HGRP logistical coordinating center)

When involving NIH-defined human subjects research, clinical research, and/or clinical trials follow all instructions for the PHS Human Subjects and Clinical Trials Information form in the SF424 (R&R) Application Guide, with the following additional instructions:

If you answered “Yes” to the question “Are Human Subjects Involved?” on the R&R Other Project Information form, you must include at least one human subjects study record using the **Study Record: PHS Human Subjects and Clinical Trials Information** form or a **Delayed Onset Study** record.

Study Record: PHS Human Subjects and Clinical Trials Information

All instructions in the SF424 (R&R) Application Guide must be followed

Delayed Onset Study

Note: Delayed onset (https://grants.nih.gov/grants/glossary.htm#DelayedOnsetHumanSubjectStudy) does NOT apply to a study that can be described but will not start immediately (i.e., delayed start).All instructions in the SF424 (R&R) Application Guide must be followed.

3. Unique Entity Identifier and System for Award Management (SAM)

See Part 1. Section III.1 for information regarding the requirement for obtaining a unique entity identifier and for completing and maintaining active registrations in System for Award Management (SAM), NATO Commercial and Government Entity (NCAGE) Code (if applicable), eRA Commons, and Grants.gov.

4. Submission Dates and Times

Part I. Overview Information contains information about Key Dates and times. Applicants are encouraged to submit applications before the due date to ensure they have time to make any application corrections that might be necessary for successful submission. When a submission date falls on a weekend or Federal holiday (https://grants.nih.gov/grants/guide/url_redirect.htm?id=82380), the application deadline is automatically extended to the next business day.

Organizations must submit applications to Grants.gov (//grants.nih.gov/grants/guide/url_redirect.htm?id=11128) (the online portal to find and apply for grants across all Federal agencies) using ASSIST or other electronic submission systems. Applicants must then complete the submission process by tracking the status of the application in the eRA Commons (//grants.nih.gov/grants/guide/url_redirect.htm?id=11123), NIH's electronic system for grants administration. NIH and Grants.gov systems check the application against many of the application instructions upon submission. Errors must be corrected and a changed/corrected application must be submitted to Grants.gov on or before the application due date and time. If a Changed/Corrected application is submitted after the deadline, the application will be considered late. Applications that miss the due date and time are subjected to the NIH Policy on Late Application Submission.

Applicants are responsible for viewing their application before the due date in the eRA Commons to ensure accurate and successful submission.

Information on the submission process and a definition of on-time submission are provided in the SF424 (R&R) Application Guide.

5. Intergovernmental Review (E.O. 12372)

This initiative is not subject to intergovernmental review. (//grants.nih.gov/grants/guide/url_redirect.htm?id=11142)

6. Funding Restrictions

All NIH awards are subject to the terms and conditions, cost principles, and other considerations described in the *NIH Grants Policy Statement (//grants.nih.gov/grants/guide/url_redirect.htm?id=11120)*.

Pre-award costs are allowable only as described in the *NIH Grants Policy Statement (//grants.nih.gov/grants/guide/url_redirect.htm?id=11143)*.

7. Other Submission Requirements and Information

Applications must be submitted electronically following the instructions described in the SF424 (R&R) Application Guide. Paper applications will not be accepted.

For information on how your application will be automatically assembled for review and funding consideration after submission go to: http://grants.nih.gov/grants/ElectronicReceipt/files/Electronic_Multi-project_Application_Image_Assembly.pdf (//grants.nih.gov/grants/ElectronicReceipt/files/Electronic_Multi-project_Application_Image_Assembly.pdf).

Applicants must complete all required registrations before the application due date. Section III. Eligibility Information contains information about registration.

For assistance with your electronic application or for more information on the electronic submission process, visit How to Apply – Application Guide (https://grants.nih.gov/grants/how-to-apply-application-guide.html). If you encounter a system issue beyond your control that threatens your ability to complete the submission process on-time, you must follow the Dealing with System Issues (https://grants.nih.gov/grants/how-to-apply-application-guide/due-dates-and-submission-policies/dealing-with-system-issues.htm) guidance. For assistance with application submission, contact the Application Submission Contacts in Section VII.

Important reminders:

All PD(s)/PI(s) and component Project Leads must include their eRA Commons ID in the Credential field of the Senior/Key Person Profile Component of the SF424(R&R) Application Package**.** Failure to register in the Commons and to include a valid PD/PI Commons ID in the credential field will prevent the successful submission of an electronic application to NIH.

The applicant organization must ensure that the DUNS number it provides on the application is the same number used in the organization's profile in the eRA Commons and for the System for Award Management (SAM). Additional information may be found in the SF424 (R&R) Application Guide.

See more tips (//grants.nih.gov/grants/guide/url_redirect.htm?id=11146) for avoiding common errors.

Upon receipt, applications will be evaluated for completeness and compliance with application instructions by the Center for Scientific Review and responsiveness by components of participating organizations, NIH. Applications that are incomplete, non-compliant and/or nonresponsive will not be reviewed.

In order to expedite review, applicants are requested to notify the NHGRI Referral Office by email at Pozzattr@exchange.nih.gov when the application has been submitted. Please include the FOA number and title, PD/PI name, and title of the application.

NHGRI strongly encourages prospective applicants to contact the scientific program officer to discuss applications and to address questions in advance of submission.

Post Submission Materials

Applicants are required to follow the instructions for post-submission materials, as described in the policy (//grants.nih.gov/grants/guide/url_redirect.htm?id=82299). Any instructions provided here are in addition to the instructions in the policy.

Section V. Application Review Information

1. Criteria

Only the review criteria described below will be considered in the review process. Applications submitted to the NIH in support of the NIH mission (//grants.nih.gov/grants/guide/url_redirect.htm?id=11149) are evaluated for scientific and technical merit through the NIH peer review system.

Overall Impact - Overall

Reviewers will provide an overall impact score to reflect their assessment of the likelihood for the center to exert a sustained, powerful influence on the research field(s) involved, in consideration of the following review criteria and additional review criteria (as applicable for the center proposed).

For this specific announcement, note the following: Because the overall purpose of this FOA is to seek applications that will produce, maintain, improve, and serve a state-of-the-art human genome reference resource to the community, the significance of the overall center plan is highly dependent on the quality of the product, how well it meets the current and future needs of the diverse genomics community, and how well the reference works together with other related resources. These aspects are reflected in Section IV, and in the added criteria descriptions below.

Scored Review Criteria - Overall

Reviewers will consider each of the review criteria below in the determination of scientific merit, and give a separate score for each. An application does not need to be strong in all categories to be judged likely to have major scientific impact. For example, a center that by its nature is not innovative may be essential to advance a field.

Significance

Does the center address an important problem or a critical barrier to progress in the field? Is the prior research that serves as the key support for the proposed project rigorous? If the aims of the center are achieved, how will scientific knowledge, technical capability, and/or clinical practice be improved? How will successful completion of the aims change the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field?

Does the proposed project address the needs of the HGRP research program? Is the scope of activities proposed for the project appropriate to meet those needs? Will successful completion of the aims bring unique advantages or capabilities to the research program?

Does the application present a coherent vision for how the center will produce, provide, improve, and maintain a state-of-the-art human genome reference?

Is the overall plan likely to result in a practical realization of the reference as a "pan-genome"?

Is the overall plan likely to result in a resource that is widely adopted, and that appropriately balances the diverse needs of a broad genomics community?

Has the application adequately and creatively considered the opportunities for working with partners to present the genome reference to the community in a way that will be most useful, for example working with other genomic variation resources to present a coherent view to the community?

Investigator(s)

Are the PD(s)/PI(s), collaborators, and other researchers well suited to the center? If Early Stage Investigators or those in the early stages of independent careers, do they have appropriate experience and training? If established, have they demonstrated an ongoing record of accomplishments that have advanced their field(s)? If the project is collaborative or multi-PD/PI, do the investigators have complementary and integrated expertise; are their leadership approach, governance and organizational structure appropriate for the project?

Does the application include evidence, including past relevant experience, that the principal investigators and other key staff will be able to productively lead and work within collaborations needed to build a successful community resource? This collaboration includes other project leads for the Human Genome Reference Center (HGRC), other HGRP grantees, international partners with an interest in producing genome references, and diverse users of the genome reference.

Innovation

Does the application challenge and seek to shift current research or clinical practice paradigms by utilizing novel theoretical concepts, approaches or methodologies, instrumentation, or interventions? Are the concepts, approaches or methodologies, instrumentation, or interventions novel to one field of research or novel in a broad sense? Is a refinement, improvement, or new application of theoretical concepts, approaches or methodologies, instrumentation, or interventions proposed?

Approach

Are the overall strategy, methodology, and analyses well-reasoned and appropriate to accomplish the specific aims of the center? Have investigators included plans to address weaknesses in the rigor of prior research that serves as the key support for the proposed project? Have the investigators presented strategies to ensure a robust and unbiased approach, as appropriate for the work proposed? Are potential problems, alternative strategies, and benchmarks for success presented? If the project is in the early stages of development, will the strategy establish feasibility and will particularly risky aspects be managed? Have the investigators presented adequate plans to address relevant biological variables, such as sex, for studies in vertebrate animals or human subjects?

If the center involves human subjects and/or NIH-defined clinical research, are the plans to address:

1) the protection of human subjects from research risks, and

2) inclusion (or exclusion) of individuals on the basis of sex/gender, race, and ethnicity, as well as the inclusion or exclusion of individuals of all ages (including children and older adults), justified in terms of the scientific goals and research strategy proposed?

For this specific announcement, note the following: the current human reference is produced in a highly collaborative manner, with NHGRI funding only part of the overall effort. This announcement anticipates that the continued effort is likely to require continued effective collaboration at a similar scale. Therefore, some of the criteria below reflect the need for reviewers to evaluate whether the key elements have been identified and described, and whether plans for coordination are adequate.

Is the overall center management plan adequate? Does it provide a coherent view of how the multiple elements of this application will be coordinated and managed?

Does the overall plan convey how the investigators will work towards a practical realization of the reference as a human "pan-genome"? Does the high-level plan for transitioning from the current representation to a future pan-genome representation take into account both the scientific factors and community outreach needs?

Does the application identify the key partners and address how the center will coordinate with other US and international efforts that work to produce the human genome reference? Is there a high-quality plan for successful coordination between collaborators funded by other sources, and with other components of the NHGRI Human Genome Reference Program (HGRP)?

If the applicant has identified key partners to undertake a critical element of the overall plan for this specific FOA, are those roles clearly defined and are they likely to be successful? Is the plan adequate for coordinating with other entities involved in producing genome references?

Has appropriate consideration been given to groups working on standards and policies relating to references, etc. (this could include, for example, Genome in a Bottle, and Global Alliance for Genomics and Health (GA4GH))?

Has the applicant identified the major issues, choices, and tradeoffs involved in producing a high-quality reference and serving it to the community? Does the application provide a clear view and justification of stated priorities?

Environment

Will the scientific environment in which the work will be done contribute to the probability of success? Are the institutional support, equipment and other physical resources available to the investigators adequate for the project proposed? Will the project benefit from unique features of the scientific environment, subject populations, or collaborative arrangements?

Additional Review Criteria - Overall

As applicable for the center proposed, reviewers will evaluate the following additional items while determining scientific and technical merit, and in providing an overall impact score, but will not give separate scores for these items.

Protections for Human Subjects

For research that involves human subjects but does not involve one of the categories of research that are exempt under 45 CFR Part 46, the committee will evaluate the justification for involvement of human subjects and the proposed protections from research risk relating to their participation according to the following five review criteria: 1) risk to subjects, 2) adequacy of protection against risks, 3) potential benefits to the subjects and others, 4) importance of the knowledge to be gained, and 5) data and safety monitoring for clinical trials.

For research that involves human subjects and meets the criteria for one or more of the categories of research that are exempt under 45 CFR Part 46, the committee will evaluate: 1) the justification for the exemption, 2) human subjects involvement and characteristics, and 3) sources of materials. For additional information on review of the Human Subjects section, please refer to the Guidelines for the Review of Human Subjects (//grants.nih.gov/grants/guide/url_redirect.htm?id=11175).

Inclusion of Women, Minorities, and Individuals Across the Lifespan

When the proposed center involves human subjects and/or NIH-defined clinical research, the committee will evaluate the proposed plans for the inclusion (or exclusion) of individuals on the basis of sex/gender, race, and ethnicity, as well as the inclusion (or exclusion) of individuals of all ages (including children and older adults) to determine if it is justified in terms of the scientific goals and research strategy proposed. For additional information on review of the Inclusion section, please refer to the Guidelines for the Review of Inclusion in Clinical Research (//grants.nih.gov/grants/guide/url_redirect.htm?id=11174).

Vertebrate Animals

The committee will evaluate the involvement of live vertebrate animals as part of the scientific assessment according to the following criteria: (1) description of proposed procedures involving animals, including species, strains, ages, sex, and total number to be used; (2) justifications for the use of animals versus alternative models and for the appropriateness of the species proposed; (3) interventions to minimize discomfort, distress, pain and injury; and (4) justification for euthanasia method if NOT consistent with the AVMA Guidelines for the Euthanasia of Animals. Reviewers will assess the use of chimpanzees as they would any other application proposing the use of vertebrate animals. For additional information on review of the Vertebrate Animals section, please refer to the Worksheet for Review of the Vertebrate Animal Section (//grants.nih.gov/grants/guide/url_redirect.htm?id=11150).

Biohazards

Reviewers will assess whether materials or procedures proposed are potentially hazardous to research personnel and/or the environment, and if needed, determine whether adequate protection is proposed.

Resubmissions

Not applicable.

Renewals

Not applicable

Revisions

Not applicable.

Additional Review Considerations - Overall

As applicable for the center proposed, reviewers will consider each of the following items, but will not give scores for these items, and should not consider them in providing an overall impact score.

Applications from Foreign Organizations

Not applicable.

Select Agent Research

Reviewers will assess the information provided in this section of the application, including 1) the Select Agent(s) to be used in the proposed research, 2) the registration status of all entities where Select Agent(s) will be used, 3) the procedures that will be used to monitor possession use and transfer of Select Agent(s), and 4) plans for appropriate biosafety, biocontainment, and security of the Select Agent(s).

Resource Sharing Plans

Reviewers will comment on whether the following Resource Sharing Plans, or the rationale for not sharing the following types of resources, are reasonable: 1) Data Sharing Plan (//grants.nih.gov/grants/guide/url_redirect.htm?id=11151); 2) Sharing Model Organisms (//grants.nih.gov/grants/guide/url_redirect.htm?id=11152); and 3) Genomic Data Sharing Plan (//grants.nih.gov/grants/guide/notice-files/NOT-OD-14-124.html) .

Authentication of Key Biological and/or Chemical Resources

For projects involving key biological and/or chemical resources, reviewers will comment on the brief plans proposed for identifying and ensuring the validity of those resources.

Budget and Period of Support

Reviewers will consider whether the budget and the requested period of support are fully justified and reasonable in relation to the proposed research.

Overall Impact - Project 1: Maintaining, improving, and providing the human reference

Reviewers will provide an overall impact score to reflect their assessment of the likelihood for the project to exert a sustained, powerful influence on the research field(s) involved, in consideration of the following review criteria and additional review criteria (as applicable for the project proposed).

Scored Review Criteria - Project 1: Maintaining, improving, and providing the human reference

Reviewers will consider each of the review criteria below in the determination of scientific merit, and give a separate score for each. An application does not need to be strong in all categories to be judged likely to have major scientific impact. For example, a project that by its nature is not innovative may be essential to advance a field.

Significance

Does the project address an important problem or a critical barrier to progress in the field? Is the prior research that serves as the key support for the proposed project rigorous? If the aims of the project are achieved, how will scientific knowledge, technical capability, and/or clinical practice be improved? How will successful completion of the aims change the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field?

Investigator(s)

Are the leads, collaborators, and other researchers well suited to the project? If Early Stage Investigators or those in the early stages of independent careers, do they have appropriate experience and training? If established, have they demonstrated an ongoing record of accomplishments that have advanced their field(s)? If the project is collaborative or multi-PD/PI, do the investigators have complementary and integrated expertise; are their leadership approach, governance and organizational structure appropriate for the project?

Innovation

Does the application challenge and seek to shift current research or clinical practice paradigms by utilizing novel theoretical concepts, approaches or methodologies, instrumentation, or interventions? Are the concepts, approaches or methodologies, instrumentation, or interventions novel to one field of research or novel in a broad sense? Is a refinement, improvement, or new application of theoretical concepts, approaches or methodologies, instrumentation, or interventions proposed?

Approach

Are the overall strategy, methodology, and analyses well-reasoned and appropriate to accomplish the specific aims of the project? Have the investigators included plans to address weaknesses in the rigor of prior research that serves as the key support for the proposed project? Have the investigators presented strategies to ensure a robust and unbiased approach, as appropriate for the work proposed? Are potential problems, alternative strategies, and benchmarks for success presented? If the project is in the early stages of development, will the strategy establish feasibility and will particularly risky aspects be managed? Have the investigators presented adequate plans to address relevant biological variables, such as sex, for studies in vertebrate animals or human subjects?

If the project involves human subjects and/or NIH-defined clinical research, are the plans to address:

1) the protection of human subjects from research risks, and

2) inclusion (or exclusion) of individuals on the basis of sex/gender, race, and ethnicity, as well as the inclusion or exclusion of individuals of all ages (including children and older adults), justified in terms of the scientific goals and research strategy proposed?

Are plans for maintaining and improving the human reference, such as correcting errors, making updates, providing new version releases adequate?

Are plans adequate for how the reference will be constructed, represented and made available to the community? Are resources including computational resources, adequate?

Are technical plans and strategic approaches for incorporating alternative haplotype information (existing and new high-quality human genomes) adequate? Do these plans thoughtfully identify and consider tradeoffs, e.g. between quality and quantity/diversity? Whether and how prioritization of new human assemblies may tend to help some sectors of the community vs others (e.g., clinical vs basic)?

How well are the detailed plans for this project related to the long-term goal of a practical representation of the human reference as a "pan-genome"? Are plans adequate for the short-term maintenance of the current representation, and the transition to a pan-genome?

Are there adequate plans for evaluating the quality of the reference, including evaluation and resolution of errors or ambiguities?

Are plans adequate for making the reference versions "backwards compatible" and do they otherwise minimize disruption for the community to switch to new reference versions when they are released?

Are plans adequate for provision of basic informatics tools to the community for making the reference (including alternate haplotype information) usable by the community?

Environment

Will the scientific environment in which the work will be done contribute to the probability of success? Are the institutional support, equipment and other physical resources available to the investigators adequate for the project proposed? Will the project benefit from unique features of the scientific environment, subject populations, or collaborative arrangements?

Does the overall plan provide for adequate computational resources to provide the reference to the community, whether these are funded by this FOA or are provided by a key collaborator?

Additional Review Criteria - Project 1: Maintaining, improving, and providing the human reference

As applicable for the project proposed, reviewers will evaluate the following additional items while determining scientific and technical merit, and in providing an overall impact score, but will not give separate scores for these items.

Protections for Human Subjects

For research that involves human subjects but does not involve one of the categories of research that are exempt under 45 CFR Part 46, the committee will evaluate the justification for involvement of human subjects and the proposed protections from research risk relating to their participation according to the following five review criteria: 1) risk to subjects, 2) adequacy of protection against risks, 3) potential benefits to the subjects and others, 4) importance of the knowledge to be gained, and 5) data and safety monitoring for clinical trials.

For research that involves human subjects and meets the criteria for one or more of the categories of research that are exempt under 45 CFR Part 46, the committee will evaluate: 1) the justification for the exemption, 2) human subjects involvement and characteristics, and 3) sources of materials. For additional information on review of the Human Subjects section, please refer to the Guidelines for the Review of Human Subjects (//grants.nih.gov/grants/guide/url_redirect.htm?id=11175).

Inclusion of Women, Minorities, and Individuals Across the Lifespan

When the proposed project involves human subjects and/or NIH-defined clinical research, the committee will evaluate the proposed plans for the inclusion (or exclusion) of individuals on the basis of sex/gender, race, and ethnicity, as well as the inclusion (or exclusion) of individuals of all ages (including children and older adults) to determine if it is justified in terms of the scientific goals and research strategy proposed. For additional information on review of the Inclusion section, please refer to the Guidelines for the Review of Inclusion in Clinical Research (//grants.nih.gov/grants/guide/url_redirect.htm?id=11174).

Vertebrate Animals

The committee will evaluate the involvement of live vertebrate animals as part of the scientific assessment according to the following criteria: (1) description of proposed procedures involving animals, including species, strains, ages, sex, and total number to be used; (2) justifications for the use of animals versus alternative models and for the appropriateness of the species proposed; (3) interventions to minimize discomfort, distress, pain and injury; and (4) justification for euthanasia method if NOT consistent with the AVMA Guidelines for the Euthanasia of Animals. Reviewers will assess the use of chimpanzees as they would any other application proposing the use of vertebrate animals. For additional information on review of the Vertebrate Animals section, please refer to the Worksheet for Review of the Vertebrate Animal Section (//grants.nih.gov/grants/guide/url_redirect.htm?id=11150).

Biohazards

Reviewers will assess whether materials or procedures proposed are potentially hazardous to research personnel and/or the environment, and if needed, determine whether adequate protection is proposed.

Resubmissions

Not applicable.

Renewals

Not applicable.

Revisions

Not applicable.

Additional Review Considerations - Project 1: Maintaining, improving, and providing the human reference

As applicable for the project proposed, reviewers will consider each of the following items, but will not give scores for these items, and should not consider them in providing an overall impact score.

Applications from Foreign Organizations

Not applicable.

Select Agent Research

Reviewers will assess the information provided in this section of the application, including 1) the Select Agent(s) to be used in the proposed research, 2) the registration status of all entities where Select Agent(s) will be used, 3) the procedures that will be used to monitor possession use and transfer of Select Agent(s), and 4) plans for appropriate biosafety, biocontainment, and security of the Select Agent(s).

Resource Sharing Plans

Reviewers will comment on whether the following Resource Sharing Plans, or the rationale for not sharing the following types of resources, are reasonable: 1) Data Sharing Plan (//grants.nih.gov/grants/guide/url_redirect.htm?id=11151); 2) Sharing Model Organisms (//grants.nih.gov/grants/guide/url_redirect.htm?id=11152); and 3) Genomic Data Sharing Plan (//grants.nih.gov/grants/guide/notice-files/NOT-OD-14-124.html) .

Authentication of Key Biological and/or Chemical Resources

For projects involving key biological and/or chemical resources, reviewers will comment on the brief plans proposed for identifying and ensuring the validity of those resources.

Budget and Period of Support

Reviewers will consider whether the budget and the requested period of support are fully justified and reasonable in relation to the proposed research.

Overall Impact - Project 2: Community outreach

Reviewers will provide an overall impact score to reflect their assessment of the likelihood for the project to exert a sustained, powerful influence on the research field(s) involved, in consideration of the following review criteria and additional review criteria (as applicable for the project proposed).

Scored Review Criteria - Project 2: Community outreach

Reviewers will consider each of the review criteria below in the determination of scientific merit, and give a separate score for each. An application does not need to be strong in all categories to be judged likely to have major scientific impact. For example, a project that by its nature is not innovative may be essential to advance a field.

Significance

Does the project address an important problem or a critical barrier to progress in the field? Is the prior research that serves as the key support for the proposed project rigorous? If the aims of the project are achieved, how will scientific knowledge, technical capability, and/or clinical practice be improved? How will successful completion of the aims change the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field?

For this particular announcement, note the following: This component of this FOA calls for community outreach, including both training as well as solicitation of community input. Much of the significance of this section relies on the effectiveness of the plans for community outreach.

Investigator(s)

Are the leads, collaborators, and other researchers well suited to the project? If Early Stage Investigators or those in the early stages of independent careers, do they have appropriate experience and training? If established, have they demonstrated an ongoing record of accomplishments that have advanced their field(s)? If the project is collaborative or multi-PD/PI, do the

investigators have complementary and integrated expertise; are their leadership approach, governance and organizational structure appropriate for the project?

Innovation

Does the application challenge and seek to shift current research or clinical practice paradigms by utilizing novel theoretical concepts, approaches or methodologies, instrumentation, or interventions? Are the concepts, approaches or methodologies, instrumentation, or interventions novel to one field of research or novel in a broad sense? Is a refinement, improvement, or new application of theoretical concepts, approaches or methodologies, instrumentation, or interventions proposed?

Approach

Are the overall strategy, methodology, and analyses well-reasoned and appropriate to accomplish the specific aims of the project? Have investigators included plans to address weaknesses in the rigor of prior research that serves as the key support for the proposed project? Have the investigators presented strategies to ensure a robust and unbiased approach, as appropriate for the work proposed? Are potential problems, alternative strategies, and benchmarks for success presented? If the project is in the early stages of development, will the strategy establish feasibility and will particularly risky aspects be managed? Have the investigators presented adequate plans to address relevant biological variables, such as sex, for studies in vertebrate animals or human subjects?

If the project involves human subjects and/or NIH-defined clinical research, are the plans to address:

1) the protection of human subjects from research risks, and

2) inclusion (or exclusion) of individuals on the basis of sex/gender, race, and ethnicity, as well as the inclusion or exclusion of individuals of all ages (including children and older adults), justified in terms of the scientific goals and research strategy proposed?

It the user interface with the reference likely to be accessible and readily usable?

Are plans adequate for provision of information about the reference to the community?

Are training plans well-described? Do they make efficient and creative use of resources (e.g., through online training, social media, etc.)?

Are plans adequate for aggregating or indexing useful informatics tools for use of the reference?

Is there a viable plan for gathering information on use of the reference (eg, via use statistics, metrics, surveys, focus groups, etc.) to understand uses and users of the reference? Does the application describe how this information will be used to improve the reference and its presentation?

Overall, is the plan for community outreach of adequate quality considering that the human genome reference is an essential and widely used community resource and that the HGRP aims to promote improvements in the reference that may entail significant change?

Environment

Will the scientific environment in which the work will be done contribute to the probability of success? Are the institutional support, equipment and other physical resources available to the investigators adequate for the project proposed? Will the project benefit from unique features of the scientific environment, subject populations, or collaborative arrangements?

Additional Review Criteria - Project 2: Community outreach

As applicable for the project proposed, reviewers will evaluate the following additional items while determining scientific and technical merit, and in providing an overall impact score, but will not give separate scores for these items.

Protections for Human Subjects

For research that involves human subjects but does not involve one of the categories of research that are exempt under 45 CFR Part 46, the committee will evaluate the justification for involvement of human subjects and the proposed protections from research risk relating to their participation according to the following five review criteria: 1) risk to subjects, 2) adequacy of protection against risks, 3) potential benefits to the subjects and others, 4) importance of the knowledge to be gained, and 5) data and safety monitoring for clinical trials.

For research that involves human subjects and meets the criteria for one or more of the categories of research that are exempt under 45 CFR Part 46, the committee will evaluate: 1) the justification for the exemption, 2) human subjects involvement and characteristics, and 3) sources of materials. For additional information on review of the Human Subjects section, please refer to the Guidelines for the Review of Human Subjects (//grants.nih.gov/grants/guide/url_redirect.htm?id=11175).

Inclusion of Women, Minorities, and Individuals Across the Lifespan

When the proposed project involves human subjects and/or NIH-defined clinical research, the committee will evaluate the proposed plans for the inclusion (or exclusion) of individuals on the basis of sex/gender, race, and ethnicity, as well as the inclusion (or exclusion) of individuals of all ages (including children and older adults) to determine if it is justified in terms of the scientific goals and research strategy proposed. For additional information on review of the Inclusion section, please refer to the Guidelines for the Review of Inclusion in Clinical Research (//grants.nih.gov/grants/guide/url_redirect.htm?id=11174).

Vertebrate Animals

The committee will evaluate the involvement of live vertebrate animals as part of the scientific assessment according to the following criteria: (1) description of proposed procedures involving animals, including species, strains, ages, sex, and total number to be used; (2) justifications for the use of animals versus alternative models and for the appropriateness of the species proposed; (3) interventions to minimize discomfort, distress, pain and injury; and (4) justification for euthanasia method if NOT consistent with the AVMA Guidelines for the Euthanasia of Animals. Reviewers will assess the use of chimpanzees as they would any other application proposing the use of vertebrate animals. For additional information on review of the Vertebrate Animals section, please refer to the Worksheet for Review of the Vertebrate Animal Section (//grants.nih.gov/grants/guide/url_redirect.htm?id=11150).

Biohazards

Reviewers will assess whether materials or procedures proposed are potentially hazardous to research personnel and/or the environment, and if needed, determine whether adequate protection is proposed.

Resubmissions

Not applicable.

Renewals

Not applicable.

Revisions

Not applicable.

Additional Review Considerations - Project 2: Community outreach

As applicable for the project proposed, reviewers will consider each of the following items, but will not give scores for these items, and should not consider them in providing an overall impact score.

Applications from Foreign Organizations

Not applicable.

Select Agent Research

Reviewers will assess the information provided in this section of the application, including 1) the Select Agent(s) to be used in the proposed research, 2) the registration status of all entities where Select Agent(s) will be used, 3) the procedures that will be used to monitor possession use and transfer of Select Agent(s), and 4) plans for appropriate biosafety, biocontainment, and security of the Select Agent(s).

Resource Sharing Plans

Reviewers will comment on whether the following Resource Sharing Plans, or the rationale for not sharing the following types of resources, are reasonable: 1) Data Sharing Plan (//grants.nih.gov/grants/guide/url_redirect.htm?id=11151); 2) Sharing Model Organisms (//grants.nih.gov/grants/guide/url_redirect.htm?id=11152); and 3) Genomic Data Sharing Plan (//grants.nih.gov/grants/guide/notice-files/NOT-OD-14-124.html) .

Authentication of Key Biological and/or Chemical Resources

For projects involving key biological and/or chemical resources, reviewers will comment on the brief plans proposed for identifying and ensuring the validity of those resources.

Budget and Period of Support

Reviewers will consider whether the budget and the requested period of support are fully justified and reasonable in relation to the proposed research.

Overall Impact - Project 3: HGRP logistical coordinating center

Reviewers will provide an overall impact score to reflect their assessment of the likelihood for the project to exert a sustained, powerful influence on the research field(s) involved, in consideration of the following review criteria and additional review criteria (as applicable for the project proposed).

Scored Review Criteria - Project 3: HGRP logistical coordinating center

Reviewers will consider each of the review criteria below in the determination of scientific merit, and give a separate score for each. An application does not need to be strong in all categories to be judged likely to have major scientific impact. For example, a project that by its nature is not innovative may be essential to advance a field.

Significance

Does the proposed project address the needs of the research program that it will coordinate? Is the scope of activities proposed for the project appropriate to meet those needs? Will successful completion of the aims bring unique advantages or capabilities to the research program?

Investigator(s)

Is the project lead and other personnel well suited to their roles? Do they have appropriate experience and training, and have they demonstrated experience and an ongoing record of accomplishments in managing complex, multi-component research? Do the investigators demonstrate significant experience with coordinating collaborative research? If the Center is multi-PD/PI, do the investigators have complementary and integrated expertise and skills; are their leadership approach and organizational structure appropriate for the project? Does the applicant have experience overseeing selection and management of subawards, if needed?

Innovation

Does the application propose novel strategies or communications tools for helping to in coordinate the research program the project will serve? Are the concepts, strategies, or instrumentation novel to one type of research program or applicable in a broad sense? Is a refinement, improvement, or new application of strategies or communications tools proposed?

Approach

Are the overall strategy, operational plan, and organizational structure well-reasoned and appropriate to accomplish the goals of the research program the project will serve? Will the investigators promote strategies to ensure a robust and unbiased scientific approach across the program, as appropriate for the work proposed? Are potential problems, alternative strategies, and benchmarks for success presented? Are an appropriate plan for work-flow and a well-established timeline proposed? Have the investigators presented adequate plans to ensure consideration of relevant biological variables, such as sex, for studies of vertebrate animals or human subjects?

If the project involves human subjects and/or NIH-defined clinical research, are the plans to address:

1) the protection of human subjects from research risks, and

2) inclusion (or exclusion) of individuals on the basis of sex/gender, race, and ethnicity, as well as the inclusion or exclusion of individuals of all ages (including children and older adults), justified in terms of the scientific goals and research strategy proposed?

Are plans adequate for facilitating communication within the program consortium? Do they adequately anticipate needs for eg. meetings, conference calls, taking notes, tracking action items? Are plans adequate for creating a web interface and archive for the program (e.g., for key notes, publications, presentations, policies, etc.)?

Environment

Will the scientific environment in which the work will be done contribute to the probability of success? Are the institutional support, equipment and other physical resources available to the investigators adequate for the project proposed? Will the project benefit from unique features of the scientific environment, subject populations, or collaborative arrangements?

Additional Review Criteria - Project 3: HGRP logistical coordinating center

As applicable for the project proposed, reviewers will evaluate the following additional items while determining scientific and technical merit, and in providing an overall impact score, but will not give separate scores for these items.

Protections for Human Subjects

For research that involves human subjects but does not involve one of the categories of research that are exempt under 45 CFR Part 46, the committee will evaluate the justification for involvement of human subjects and the proposed protections from research risk relating to their participation according to the following five review criteria: 1) risk to subjects, 2) adequacy of protection against risks, 3) potential benefits to the subjects and others, 4) importance of the knowledge to be gained, and 5) data and safety monitoring for clinical trials.

For research that involves human subjects and meets the criteria for one or more of the six categories of research that are exempt under 45 CFR Part 46, the committee will evaluate: 1) the justification for the exemption, 2) human subjects involvement and characteristics, and 3) sources of materials. For additional information on review of the Human Subjects section, please refer to the Guidelines for the Review of Human Subjects (//grants.nih.gov/grants/guide/url_redirect.htm?id=11175).

Inclusion of Women, Minorities, and Individuals Across the Lifespan

When the proposed project involves human subjects and/or NIH-defined clinical research, the committee will evaluate the proposed plans for the inclusion (or exclusion) of individuals on the basis of sex/gender, race, and ethnicity, as well as the inclusion (or exclusion) of individuals of all ages (including children and older adults) to determine if it is justified in terms of the scientific goals and research strategy proposed. For additional information on review of the Inclusion section, please refer to the Guidelines for the Review of Inclusion in Clinical Research (//grants.nih.gov/grants/guide/url_redirect.htm?id=11174).

Vertebrate Animals

The committee will evaluate the involvement of live vertebrate animals as part of the scientific assessment according to the following criteria: (1) description of proposed procedures involving animals, including species, strains, ages, sex, and total number to be used; (2) justifications for the use of animals versus alternative models and for the appropriateness of the species proposed; (3) interventions to minimize discomfort, distress, pain and injury; and (4) justification for euthanasia method if NOT consistent with the AVMA Guidelines for the Euthanasia of Animals. Reviewers will assess the use of chimpanzees as they would any other application proposing the use of vertebrate animals. For additional information on review of the Vertebrate Animals section, please refer to the Worksheet for Review of the Vertebrate Animal Section (//grants.nih.gov/grants/guide/url_redirect.htm?id=11150).

Biohazards

Reviewers will assess whether materials or procedures proposed are potentially hazardous to research personnel and/or the environment, and if needed, determine whether adequate protection is proposed.

Resubmissions

Not applicable.

Renewals

Not applicable.

Revisions

Not applicable.

Additional Review Considerations - Project 3: HGRP logistical coordinating center

As applicable for the project proposed, reviewers will consider each of the following items, but will not give scores for these items, and should not consider them in providing an overall impact score.

Applications from Foreign Organizations

Not applicable.

Select Agent Research

Reviewers will assess the information provided in this section of the application, including 1) the Select Agent(s) to be used in the proposed research, 2) the registration status of all entities where Select Agent(s) will be used, 3) the procedures that will be used to monitor possession use and transfer of Select Agent(s), and 4) plans for appropriate biosafety, biocontainment, and security of the Select Agent(s).

Resource Sharing Plans

Reviewers will comment on whether the following Resource Sharing Plans, or the rationale for not sharing the following types of resources, are reasonable: 1) Data Sharing Plan (//grants.nih.gov/grants/guide/url_redirect.htm?id=11151); 2) Sharing Model Organisms (//grants.nih.gov/grants/guide/url_redirect.htm?id=11152); and 3) Genomic Data Sharing Plan (//grants.nih.gov/grants/guide/notice-files/NOT-OD-14-124.html) .

Authentication of Key Biological and/or Chemical Resources

For projects involving key biological and/or chemical resources, reviewers will comment on the brief plans proposed for identifying and ensuring the validity of those resources.

Budget and Period of Support

Reviewers will consider whether the budget and the requested period of support are fully justified and reasonable in relation to the proposed research.

2. Review and Selection Process

Applications will be evaluated for scientific and technical merit by (an) appropriate Scientific Review Group(s), convened by the National Human Genome Research Institute in accordance with NIH peer review policy and procedures (//grants.nih.gov/grants/guide/url_redirect.htm?id=11154), using the stated review criteria. Assignment to a Scientific Review Group will be shown in the eRA Commons.

As part of the scientific peer review, all applications:

- May undergo a selection process in which only those applications deemed to have the highest scientific and technical merit (generally the top half of applications under review) will be discussed and assigned an overall impact score.
- Will receive a written critique.

Appeals (//grants.nih.gov/grants/guide/notice-files/NOT-OD-11-064.html) of initial peer review will not be accepted for applications submitted in response to this FOA.

Applications will be assigned on the basis of established PHS referral guidelines to the appropriate NIH Institute or Center. Applications will compete for available funds with all other recommended applications submitted in response to this FOA. Following initial peer review, recommended applications will receive a second level of review by the National Advisory Council on Human Genome Research (NACHGR). The following will be considered in making funding decisions:

- Scientific and technical merit of the proposed project as determined by scientific peer review.
- Availability of funds.
- Relevance of the proposed project to program priorities.
- Overall ability of the proposed HGRC to interact productively with multiple collaborators and international partners for the purposes of producing a vital community resource for genomics.

3. Anticipated Announcement and Award Dates

After the peer review of the application is completed, the PD/PI will be able to access his or her Summary Statement (written critique) via the eRA Commons (//grants.nih.gov/grants/guide/url_redirect.htm?id=11123). Refer to Part 1 for dates for peer review, advisory council review, and earliest start date.

Information regarding the disposition of applications is available in the *NIH Grants Policy Statement (//grants.nih.gov/grants/guide/url_redirect.htm?id=11156)*.

Section VI. Award Administration Information

1. Award Notices

If the application is under consideration for funding, NIH will request "just-in-time" information from the applicant as described in the *NIH Grants Policy Statement (//grants.nih.gov/grants/guide/url_redirect.htm?id=11157)*.

A formal notification in the form of a Notice of Award (NoA) will be provided to the applicant organization for successful applications. The NoA signed by the grants management officer is the authorizing document and will be sent via email to the grantee's business official.

Awardees must comply with any funding restrictions described in Section IV.5. Funding Restrictions. Selection of an application for award is not an authorization to begin performance. Any costs incurred before receipt of the NoA are at the recipient's risk. These costs may be reimbursed only to the extent considered allowable pre-award costs.

Any application awarded in response to this FOA will be subject to terms and conditions found on the Award Conditions and Information for NIH Grants (//grants.nih.gov/grants/guide/url_redirect.htm?id=11158) website. This includes any recent legislation and policy applicable to awards that is highlighted on this website.

2. Administrative and National Policy Requirements

All NIH grant and cooperative agreement awards include the *NIH Grants Policy Statement (//grants.nih.gov/grants/guide/url_redirect.htm?id=11120)* as part of the NoA. For these terms of award, see the *NIH Grants Policy Statement* Part II: Terms and Conditions of NIH Grant Awards, Subpart A: General (//grants.nih.gov/grants/guide/url_redirect.htm?id=11157) and Part II: Terms and Conditions of NIH Grant Awards, Subpart B: Terms and Conditions for Specific Types of Grants, Grantees, and Activities (//grants.nih.gov/grants/guide/url_redirect.htm?id=11159). More information is provided at Award Conditions and Information for NIH Grants (//grants.nih.gov/grants/guide/url_redirect.htm?id=11158).

Recipients of federal financial assistance (FFA) from HHS must administer their programs in compliance with federal civil rights law. This means that recipients of HHS funds must ensure equal access to their programs without regard to a person's race, color, national origin, disability, age and, in some circumstances, sex and religion. This includes ensuring your programs are accessible to persons with limited English proficiency. HHS recognizes that research projects are often limited in scope for many reasons that are nondiscriminatory, such as the principal investigator's scientific interest, funding limitations, recruitment requirements, and other considerations. Thus, criteria in research protocols that target or exclude certain populations are warranted where nondiscriminatory justifications establish that such criteria are appropriate with respect to the health or safety of the subjects, the scientific study design, or the purpose of the research.

For additional guidance regarding how the provisions apply to NIH grant programs, please contact the Scientific/Research Contact that is identified in Section VII under Agency Contacts of this FOA. HHS provides general guidance to recipients of FFA on meeting their legal obligation to take reasonable steps to provide meaningful access to their programs by persons with limited English proficiency. Please see https://www.hhs.gov/civil-rights/for-individuals/special-topics/limited-english-proficiency/index.html (https://www.hhs.gov/civil-rights/for-individuals/special-topics/limited-english-proficiency/index.html). The HHS Office for Civil Rights also provides guidance on complying with civil rights laws enforced by HHS. Please see https://www.hhs.gov/civil-rights/for-individuals/section-1557/index.html (https://www.hhs.gov/civil-rights/for-individuals/section-1557/index.html); and https://www.hhs.gov/civil-rights/for-providers/laws-regulations-guidance/index.html (https://www.hhs.gov/civil-rights/for-providers/laws-regulations-guidance/index.html). Recipients of FFA also have specific legal obligations for serving qualified individuals with disabilities. Please see https://www.hhs.gov/civil-rights/for-individuals/disability/index.html (http://www.hhs.gov/ocr/civilrights/understanding/disability/index.html). Please contact the HHS Office for Civil Rights for more information about obligations and prohibitions under federal civil rights laws at https://www.hhs.gov/ocr/about-us/contact-us/index.html (https://www.hhs.gov/ocr/about-us/contact-us/index.html) or call 1-800-368-1019 or TDD 1-800-537-7697. Also note it is an HHS Departmental goal to ensure access to quality, culturally competent care, including long-term services and supports, for vulnerable populations. For further guidance on providing culturally and linguistically appropriate services, recipients should review the National Standards for Culturally and Linguistically Appropriate Services in Health and Health Care at http://minorityhealth.hhs.gov/omh/browse.aspx?lvl=2&lvlid=53 (http://minorityhealth.hhs.gov/omh/browse.aspx?lvl=2&lvlid=53).

In accordance with the statutory provisions contained in Section 872 of the Duncan Hunter National Defense Authorization Act of Fiscal Year 2009 (Public Law 110-417), NIH awards will be subject to the Federal Awardee Performance and Integrity Information System (FAPIIS) requirements. FAPIIS requires Federal award making officials to review and consider information about an applicant in the designated integrity and performance system (currently FAPIIS) prior to making an award. An applicant, at its option, may review information in the designated integrity and performance systems accessible through FAPIIS and comment on any information about itself that a Federal agency previously entered and is currently in FAPIIS. The Federal awarding agency will consider any comments by the applicant, in addition to other information in FAPIIS, in making a judgement about the applicant's integrity, business ethics, and record of performance under Federal awards when completing the review of risk posed by applicants as described in 45 CFR Part 75.205 "Federal awarding agency review of risk posed by applicants." This provision will apply to all NIH grants and cooperative agreements except fellowships.

Cooperative Agreement Terms and Conditions of Award

The following special terms of award are in addition to, and not in lieu of, otherwise applicable U.S. Office of Management and Budget (OMB) administrative guidelines, U.S. Department of Health and Human Services (DHHS) grant administration regulations at 45 CFR Part 75, and other HHS, PHS, and NIH grant administration policies.

The administrative and funding instrument used for this program will be the cooperative agreement, an "assistance" mechanism (rather than an "acquisition" mechanism), in which substantial NIH programmatic involvement with the awardees is anticipated during the performance of the activities. Under the cooperative agreement, the NIH purpose is to support and stimulate the recipients' activities by involvement in and otherwise working jointly with the award recipients in a partnership role; it is not to assume direction, prime responsibility, or a dominant role in the activities. Consistent with this concept, the dominant role and prime responsibility

resides with the awardees for the project as a whole, although specific tasks and activities may be shared among the awardees and the NIH as defined below.

The PD(s)/PI(s) will have the primary responsibility for:

- Developing scientific plans.
- Meeting the goals and objectives, as well as timelines and milestones set out in the funded application or amended as approved by NHGRI.
- Providing effective leadership and management for the Human Genome Reference Center
- Interacting effectively with the Human Genome Reference Program components.
- Accommodating any necessary changes to improve the efficiency of operations and services, and decrease costs.
- Providing interim reports or information requested by NHGRI staff.
- Providing logistical and administrative support for meetings of the Eternal Scientific Panel (ESP), as provided in HGRC project 4 (HGRP logistical coordinating center) and of any governance committee instituted to oversee and guide the HGRP operations.
- Addressing and implementing the guidance and recommendations of the ESP.
- Serving as active members of a HGRP Steering Committee (HGRP-SC) or similar coordinating unit for the program.
- Participating/leading working groups that focus on topics or activities that affect the value, quality, and efficiency of the operations and services provided by the HGRP. Participating effectively with collaborators that work to produce genome references, develop related standards, develop priorities for addition of new genomes, provide variation resources, etc.
- Assisting in the development of policies for dealing with situations that require coordinated action.
- Ensuring that the data underlying the human reference are available to the community in a manner consistent with policies, and according to best practices for handling the data.
- Adopting new solutions and technologies to ensure appropriate use of data underlying the reference.
- Data and software transition. At the end of the award, or if a new recipient has been selected prior to the end of the award, the awardee will work with NHGRI staff and the new award recipient to transition any data, product (reference) and software to the new service, or to the Government.
- Maintaining necessary regulatory and policy compliances related to data access and data security for both unrestricted and controlled access data (if applicable), including any NIH-designated best practices for genomic data sharing.
- Ensuring that the data and related tools and resources developed as part of the HGRP are made publicly available according to NHGRI and the NIH policies.
- Agreeing and accepting close coordination, cooperation, and participation of NHGRI staff in those aspects of scientific and technical management of the service as described under "NIH Program Staff Responsibilities."
- Agreeing to be subject to Government rights of access consistent with current DHHS, PHS, and NIH policies
- Data/software ownership and transition to another grantee:
- A fundamental objective of this cooperative agreement is to ensure that the valuable data, products, and resources provided by the HGRP remain available without interruption to the research community if awardee withdraws or otherwise can no longer manage the resource or the award is terminated by the NIH.
- Consistent with 45 C.F.R. 75.322, the awardee will own the data generated and software developed by the awardee, and it will be able to continue to use these data and software upon expiration or termination of the award. NIH will have unrestricted cost-free access and use of the data, resource and software generated by the awardee, including the right to transfer said data and/or software to other NIH-funded and/or managed resource projects, at the NIH's sole reasonable discretion upon termination or expiration of this cooperative agreement.
- Ownership of the data and software that may be hosted (but not created) by the HGRP remains with the data and software providers.
- Open Source Technology: Capabilities and software built as part of the NHGRI HGRP must be delivered under an open source model. Organizations may propose to use proprietary platforms, so long as the requirements for data transparency and interoperability are maintained.
- Awardees will retain custody of and have primary rights to the data and software developed under these awards, subject to Government rights of access consistent with current DHHS, PHS, and NIH policies.

NIH staff have substantial programmatic involvement that is above and beyond the normal stewardship role in awards, as described below:

- Participating with the HGRP-SC and all other relevant working groups in the group process of setting scientific, administrative and technical priorities, facilitating consensus around program policies and certain technical decisions (including metrics for sequence assembly quality and priorities for sample selection and adding new assemblies to the reference consortium) and deciding optimal approaches and protocol designs, and contributing to the adjustment to protocols or approaches as warranted.
- Serving as a liaison, helping to coordinate activities among and for the awardee(s), including acting as a liaison to the NIH, and as an information resource for the awardee(s) about scientific, administrative, and technical activities.

- Assist in coordinating the efforts of the resource with other groups conducting similar efforts at the NIH and worldwide.
- Periodically reporting on the progress of the program to NHGRI Division Directors, the NHGRI Director, and to the National Advisory Council for Human Genome Research.
- Serving as a liaison between the HGRP and the ESP.
- Serving as a liaison between the HGRP and other federal agencies.
- Providing advice in the management and technical performance of the award.
- Participating in data analyses, interpretations where warranted.
- The Program Official may withhold or reduce support from any awardee that fails to achieve its goals or comply with the Terms and Conditions of Award.
- Other NHGRI staff may assist the awardee(s) as designated by the Program Official.
- Additionally, an agency program official or IC program director will be responsible for the normal scientific and programmatic stewardship of the award and will be named in the award notice.

Areas of Joint Responsibility include:

- None; all responsibilities are divided between awardees and NIH staff as described above.

Dispute Resolution:

Any disagreements that may arise in scientific or programmatic matters (within the scope of the award) between award recipients and the NIH may be brought to Dispute Resolution. A Dispute Resolution Panel will be convened. It will have three members: a designee of the Steering Committee chosen without NIH staff voting, one NIH designee, and a third designee with expertise in the relevant area who is chosen by the other two; in the case of individual disagreement, the first member may be chosen by the individual awardee. This special dispute resolution procedure does not alter the awardee's right to appeal an adverse action that is otherwise appealable in accordance with PHS regulation 42 CFR Part 50, Subpart D and DHHS regulation 45 CFR Part 16.

3. Reporting

When multiple years are involved, awardees will be required to submit the Research Performance Progress Report (RPPR) (//grants.nih.gov/grants/rppr/index.htm) annually and financial statements as required in the *NIH Grants Policy Statement*. (//grants.nih.gov/grants/guide/url_redirect.htm?id=11161)

A final RPPR, invention statement, and the expenditure data portion of the Federal Financial Report are required for closeout of an award, as described in the *NIH Grants Policy Statement (//grants.nih.gov/grants/guide/url_redirect.htm?id=11161)*.

The Federal Funding Accountability and Transparency Act of 2006 (Transparency Act), includes a requirement for awardees of Federal grants to report information about first-tier subawards and executive compensation under Federal assistance awards issued in FY2011 or later. All awardees of applicable NIH grants and cooperative agreements are required to report to the Federal Subaward Reporting System (FSRS) available at www.fsrs.gov (//grants.nih.gov/grants/guide/url_redirect.htm?id=11170) on all subawards over $25,000. See the *NIH Grants Policy Statement (//grants.nih.gov/grants/guide/url_redirect.htm?id=11171)* for additional information on this reporting requirement.

In accordance with the regulatory requirements provided at 45 CFR 75.113 and Appendix XII to 45 CFR Part 75, recipients that have currently active Federal grants, cooperative agreements, and procurement contracts from all Federal awarding agencies with a cumulative total value greater than $10,000,000 for any period of time during the period of performance of a Federal award, must report and maintain the currency of information reported in the System for Award Management (SAM) about civil, criminal, and administrative proceedings in connection with the award or performance of a Federal award that reached final disposition within the most recent five-year period. The recipient must also make semiannual disclosures regarding such proceedings. Proceedings information will be made publicly available in the designated integrity and performance system (currently FAPIIS). This is a statutory requirement under section 872 of Public Law 110-417, as amended (41 U.S.C. 2313). As required by section 3010 of Public Law 111-212, all information posted in the designated integrity and performance system on or after April 15, 2011, except past performance reviews required for Federal procurement contracts, will be publicly available. Full reporting requirements and procedures are found in Appendix XII to 45 CFR Part 75 – Award Term and Conditions for Recipient Integrity and Performance Matters.

Section VII. Agency Contacts

We encourage inquiries concerning this funding opportunity and welcome the opportunity to answer questions from potential applicants.

Application Submission Contacts

eRA Service Desk (Questions regarding ASSIST, eRA Commons, application errors and warnings, documenting system problems that threaten submission by the due date, and post-submission issues)

Finding Help Online: http://grants.nih.gov/support/ (preferred method of contact)
Telephone: 301-402-7469 or 866-504-9552 (Toll Free)

General Grants Information (Questions regarding application instructions, application processes, and NIH grant resources)
Email: GrantsInfo@nih.gov (mailto:GrantsInfo@nih.gov) (preferred method of contact)
Telephone: 301-945-7573

Grants.gov Customer Support (Questions regarding Grants.gov registration and Workspace)
Contact Center Telephone: 800-518-4726
Email: support@grants.gov (mailto:support@grants.gov)

Scientific/Research Contact(s)

Adam Felsenfeld
National Human Genome Research Institute (NHGRI)
Telephone: 301-480-2269
Email: adam_felsenfeld@nih.gov

Rajeev K. Agarwal, Ph.D.
Office of Research on Women's Health (ORWH)
Telephone: 301-451-7058
Email: Rajeev.Agarwal@nih.gov (mailto:Rajeev.Agarwal@nih.gov)

Peer Review Contact(s)

Rudy Pozzatti
National Human Genome Research Institute (NHGRI)
Telephone: 301-496-7531
Pozzattr@exchange.nih.gov (mailto:Pozzattr@exchange.nih.gov)

Financial/Grants Management Contact(s)

Deanna Ingersolll
National Human Genome Research Institute (NHGRI)
Telephone: 301-435-7858
Email: Deanna.Ingersoll@nih.gov (mailto:Deanna.Ingersoll@nih.gov)

Section VIII. Other Information

Recently issued trans-NIH policy notices (//grants.nih.gov/grants/guide/url_redirect.htm?id=11163) may affect your application submission. A full list of policy notices published by NIH is provided in the *NIH Guide for Grants and Contracts* (//grants.nih.gov/grants/guide/url_redirect.htm?id=11164). All awards are subject to the terms and conditions, cost principles, and other considerations described in the NIH Grants Policy Statement (//grants.nih.gov/grants/guide/url_redirect.htm?id=11120).

Authority and Regulations

Awards are made under the authorization of Sections 301 and 405 of the Public Health Service Act as amended (42 USC 241 and 284) and under Federal Regulations 42 CFR Part 52 and 45 CFR Part 75.

Weekly TOC for this Announcement (/grants/guide/WeeklyIndex.cfm?02-01-19)
NIH Funding Opportunities and Notices (/grants/guide/index.html)

Note: For help accessing PDF, RTF, MS Word, Excel, PowerPoint, Audio or Video files, see Help Downloading Files (/grants/edocs.htm).