U.S. Department of Health and Human Services (HHS)
National Institutes of Health (NIH)
Office of the Director (OD)
Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI)

Council of Councils Meeting
May 11, 2023

Meeting Minutes

I. CALL TO ORDER AND INTRODUCTIONS

Robert W. Eisinger, Ph.D., Acting Director, DPCPSI, welcomed participants, NIH staff members, and members of the public to the meeting of the Council of Councils. The virtual meeting began at 10:15 a.m. on Thursday, May 11, 2023. The meeting attendees are identified below.

Dr. Eisinger announced several DPCPSI staff changes, including the appointment of Dr. Beverly X. Watkins as DPCPSI Scientific Diversity Officer, the transition of Dr. Maureen Goodenow from the Office of AIDS Research (OAR) Director and NIH Associate Director for AIDS Research to the role of Senior Advisor in the NIH Office of the Director; the appointment of Dr. Bill Kapogiannis to fill Dr. Goodenow's roles in an acting capacity; and the appointment of Dr. Karina Walters as Director of the Tribal Health Research Office (THRO). Dr. Eisinger thanked the Council members who have rotated off for their service—Drs. Patricia Hurn, Paul Johnson, Sachin Kheterpal, Jian-Dong Li, Edith Mitchell, Charles Mouton, and Scout. Dr. Eisinger then reviewed the day's agenda.

A. Attendance

1. Council Members

Council Members Present

Chair: Robert W. Eisinger, Ph.D., Acting Director, DPCPSI
Executive Secretary: Franziska Grieder, D.V.M., Ph.D., Director, Office of Research Infrastructure Programs (ORIP), DPCPSI
Maria Rosario G. Araneta, Ph.D., M.P.H., University of California, San Diego, La Jolla, CA
Kristin Ardlie, Ph.D., Broad Institute of Massachusetts Institute of Technology and Harvard, Cambridge, MA
Linda Chang, M.D., FAAN, FANA, University of Maryland School of Medicine, Baltimore, MD
Graham A. Colditz, M.D., Dr.P.H., M.P.H., Washington University School of Medicine in St. Louis, St. Louis, MO
Monica Gandhi, M.D., M.P.H.,* University of California, San Francisco, San Francisco, CA
Rick Horwitz, Ph.D., Allen Institute for Cell Science, Seattle, WA
Barbara Kelley,* Hearing Loss Association of America, Bethesda, MD
Paul J. Kenny, Ph.D., Icahn School of Medicine at Mount Sinai, New York, NY
Jean A. King, Ph.D.,* Worcester Polytechnic Institute, Worcester, MA
Richard D. Krugman, M.D., University of Colorado School of Medicine, Aurora, CO
Kevin C. Kent Lloyd, D.V.M., Ph.D., University of California, Davis, Davis, CA
Jennifer Jaie Manly, Ph.D.,* Columbia University Medical Center, New York, NY
Rhonda Robinson-Beale, M.D., UnitedHealth Group, Minneapolis, MN
Susan Sanchez, Ph.D., The University of Georgia, Athens, GA

Jean E. Schaffer, M.D., Joslin Diabetes Center, Harvard Medical School, Boston, MA
Anna Maria Siega-Riz, Ph.D., M.S., University of Massachusetts Amherst, Amherst, MA
Lauren Silvis, J.D.,* Tempus, Inc., Washington, DC
Russell N. Van Gelder, M.D., Ph.D., University of Washington, Seattle, WA

Council Members Absent

Andrew P. Feinberg, M.D., M.P.H., Johns Hopkins University School of Medicine, Baltimore, MD
Rafael Irizarry, Ph.D.,* Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA
Kevin B. Johnson, M.D., M.S., FAAP, FACMI, FAMIA, Annenberg School for Communication, University of Pennsylvania, Applied Informatics, University of Pennsylvania Health System, and Children's Hospital of Philadelphia, Philadelphia, PA
Karen C. Johnston, M.D., M.Sc., University of Virginia, Charlottesville, VA
Gary A. Koretzky, M.D., Ph.D., Weill Cornell Medical College, New York, NY
Michael Kotlikoff, V.M.D., Ph.D.,* Cornell University, Ithaca, NY
Megan O'Boyle, Phelan-McDermid Syndrome Data Network, Arlington, VA

*** Pending approval**

2. Liaisons

Janine A. Clayton, M.D., FARVO, Director, Office of Research on Women's Health, DPCPSI
Susan K. Gregurick, Ph.D., Director, Office of Data Science Strategy, DPCPSI
Franziska B. Grieder, D.V.M., Ph.D., Director, ORIP, DPCPSI
Christine M. Hunter, Ph.D., ABPP, Acting Director, Office of Behavioral and Social Sciences Research, DPCPSI
Bill G. Kapogiannis, M.D., FIDSA, Acting Director, Office of AIDS Research, DPCPSI
Christopher J. Lynch, Ph.D., Acting Director, Office of Nutrition Research, DPCPSI
David M. Murray, Ph.D., Director, Office of Disease Prevention, DPCPSI, and Acting Director, Office of Dietary Supplements, DPCPSI
Karen L. Parker, Ph.D., M.S.W., Director, Sexual & Gender Minority Research Office, DPCPSI
Rebecca A. Meseroll, Ph.D., on behalf of **George M. Santangelo, Ph.D.,** Director, Office of Portfolio Analysis, DPCPSI
Douglas M. Sheeley, Sc.D., Acting Director, Office of Strategic Coordination, DPCPSI
Marina L. Volkov, Ph.D., Director, Office of Evaluation, Performance, and Reporting, DPCPSI
Karina L. Walters, Ph.D., M.S.W., Director, THRO, DPCPSI

3. *Ex Officio* Member Absent

Tara A. Schwetz, Ph.D., Acting Principal Deputy Director, NIH

4. Presenters

Noni Byrnes, Ph.D., Director, Center for Scientific Review (CSR)
Walter J. Koroshetz, M.D., Director, National Institute of Neurological Disorders and Stroke (NINDS), Co-Chair, Researching COVID to Enhance Recovery (RECOVER) Senior Oversight Committee
Stephanie J. Murphy, V.M.D., Ph.D., DACLAM, Director, Division of Comparative Medicine (DCM), ORIP, DPCPSI

Jennifer Roberts, Ph.D., Director, Resilient Systems, Advanced Research Projects Agency for Health (ARPA-H)

5. NIH Staff and Guests

In addition to Council members, presenters, and Council liaisons, others in attendance included NIH staff and interested members of the public.

B. Announcements and Updates

Franziska Grieder, D.V.M., Ph.D., the Executive Secretary for the NIH Council of Councils, reviewed the following:

- Council members are Special Government Employees during the days of Council meetings and are therefore subject to the rules of conduct governing federal employees.
- Each Council member submitted a financial disclosure form and conflict-of-interest statement in compliance with federal requirements for membership on advisory councils. The financial disclosures are used to assess real and perceived conflicts of interest, and Council members must recuse themselves from the meeting during discussions of any items for which conflicts were identified.
- Time is allotted for discussion between the Council members and presenters, but time for comments from other meeting attendees is limited. The public may submit comments in writing; instructions are available in the *Federal Register* notice for the meeting, which was published on April 13, 2023.
- Minutes from the January 19–20, 2023, meeting are posted on the DPCPSI website. The minutes from this meeting also will be posted there.

C. Future Meeting Dates

The next Council meeting is scheduled for September 7 and 8, 2023.

II. NIH PROPOSED CHANGES TO THE PEER REVIEW CRITERIA

Noni Byrnes, Ph.D., Director, CSR, outlined CSR's initiatives to strengthen peer review. CSR ensures grant applications for 24 of the funding institutes and centers (ICs) and the Office of the Director receive fair, independent, expert, and timely scientific reviews free from inappropriate influences so that NIH can fund the most promising and highly meritorious research. In fiscal year 2023 (FY23), NIH received approximately 79,000 applications; CSR reviewed approximately 60,000 (76%) of these. CSR reviews the majority of R01, Small Business Innovation Research/Small Business Technology Transfer Research, and National Research Service Award (NRSA) Fellowship applications. CSR has about 275 scientific review officers (SROs) and 19,000 reviewers; in FY23. CSR held 1,200 review meetings and reviewed 161 special initiatives.

In 2019, CSR began implementing a strategic framework utilizing the Evaluating Panel Quality in Review (ENQUIRE) process for optimizing peer review. Study sections are evaluated for structure, output, and process; reviewers receive training; and the reviewer pool has been broadened and diversified. CSR prioritizes transparency in this process—decisions are driven by data, and CSR has worked to ensure stakeholder engagement in these changes. About 20 percent of CSR study sections are assessed per year, so each study section is assessed every 5 years.

The current scope of the study section is assessed by external scientific evaluators to determine how well it matches the state of the research field. Emerging and declining areas of science are identified, and study sections are created, merged, or sunset as needed. Next, an internal NIH panel conducts a process evaluation and reviews the report of the external evaluators. The panel is provided with application number trends, score distributions, roster expertise, reports of study section site visits, and program feedback, and then it develops a set of recommendations that are sent to the CSR Advisory Council (CSRAC) for approval. The entire ENQUIRE process is overseen by CSR's scientific division directors. Multiple steps follow CSRAC approval; the process typically takes 12 to 18 months from initiation to implementation of new or restructured study sections. Reviews of 13 scientific clusters—152 study sections—have been completed or are in progress. ENQUIRE generally results in substantive changes, such as elimination or merging of smaller panels, refreshing scientific guidelines, creating new study sections, and incorporating expanding or emerging scientific areas.

CSR has also led the development of recommendations to simplify the review of NIH research project grant (RPG) applications, including R01s and R21s. One of the goals of the proposed changes is to refocus peer review on its unique role of providing advice regarding the scientific or technical merit of grant applications. The recommended changes will relieve reviewers of responsibility for administrative or policy compliance items, reducing burden and incentivizing participation in review. The second goal of the proposed changes is to mitigate reputational bias in the peer review process; specifically, considering investigator and environment only in the context of the proposed research project. These changes will facilitate achievement of the overarching goal of peer review: identification of the strongest, highest-impact research for potential NIH funding.

CSR convened two overlapping CSRAC working groups to consider non–clinical trial RPG applications, which represent 90 percent of NIH applications, and clinical trial RPGs. The five existing review criteria—significance, investigators, innovation, approach, and environment—cannot be changed, but they can be interpreted, grouped, or scored at NIH's discretion. Input on the proposed changes was gathered from January 2020 through March 2021 via blog posts, content analyses provided to working groups, and 11 virtual meetings. In April 2021, the CSRAC approved the recommendations and publication of the working group report. From July 2021 through September 2022, internal NIH input and modifications to the framework were provided, and the review was approved by IC and NIH leadership. From December 2022 through March 2023, public input was sought through an NIH request for information (RFI).

In the proposed new peer review framework for NIH RPGs, the criteria are grouped by three main factors that consider whether the research should, can, and will be conducted. Factor 1 is the Importance of the Research, including significance and innovation. Reviewers report that innovation is a difficult concept to grasp, so the committee recommended a factor based on importance, which allows reviewers flexibility to weigh both significance and innovation. Factor 2 is Rigor and Feasibility, which covers the approach and focuses on strong experimental design underlying the study. Factor 3 is Expertise and Resources, including the investigators and environment. Factors 1 and 2 are scored individually from 1 to 9, and Factor 3 is not individually scored, but assessed as either "appropriate" or "gaps identified," and gaps identified must be described. Most "Additional Review Criteria," which may affect the overall impact score, remain unchanged. Most "Additional Review Considerations," which do not affect the overall impact score, have been removed from first-level peer review.

The RFI closed on March 10, 2023, with responses from 780 individuals, 30 societies, and 23 academic institutions. Most respondents were very supportive of these changes; a minority felt that Factor 3 should be scored, and a similar minority suggested blinded reviews. Most of the responders recommended that CSR develop extensive training resources to socialize the changes for the community. An NIH-wide interdisciplinary committee is developing an implementation strategy that considers the RFI input, with

implementation planned for October 2024 receipt dates, February and March 2025 review, and May 2025 Council meetings.

CSR is also implementing improvements to the NRSA Fellowship application review process. The CSRAC Working Group convened in 2022, gathered data and community feedback, and held 14 virtual meetings to develop recommendations. Feedback noted that fellowships are concentrated in a small number of institutions and that applications from those do better in review. The review outcomes for fellowships improve as the rank of the sponsor increases. It was recognized that NIH may be missing highly promising scientists because the process favors institutions and senior and well-known sponsors with an emphasis on traditional markers of early academic success.

The first recommendation is to eliminate grades from the fellowship application, which are not indicative of success in research, and focus the application more on the potential and training needs of the applicant. No changes to the current Research Training Plan are recommended. The "Sponsors, Collaborators, and Consultants" section should be revised to align with proposed review criteria, emphasize the sponsor's training plan for this particular student, and eliminate the peer review of financial support. Letters of support will be revised to address trainee-specific questions in structured fields, which will discourage boilerplate language and make applications easier for reviewers to differentiate and evaluate. An optional statement of special circumstances should be allowed to address situations that might have hindered the trainee's progress. The second recommendation is to change the fellowship review criteria to focus on the potential of the applicant, the strength of the science, and the quality of the training plan to concentrate on the goals of the fellowship rather than the individual sponsor or institution. The CSRAC and NIH leadership endorsed these recommendations in 2022, and an RFI is open through June 23, 2023, for additional input on these proposed changes to the review process of these applications.

CSR is collaborating with its constituents to promote fairness during the review process. The center conducts about 10 orientation sessions per year with approximately 90 incoming study section chairs to discuss how the chair can improve impartiality of the peer-review process. CSR's bias awareness training for reviewers is focused on mitigating the most common biases in the peer-review process, rather than implicit bias. More than 19,000 CSR reviewers have taken the training, which has been well received by the scientific community. The training will be required for all NIH reviewers beginning with the February/March 2024 review meetings. CSR's Review Integrity Training Module, updated August 2022, is an interactive, scenario-based training on the reviewer's role in protecting the confidentiality and integrity of the NIH review process, with content based on actual cases. More than 12,000 CSR reviewers have completed the training, which will be required for all NIH reviewers beginning with the May 2024 Council round of review meetings.

Applicants, reviewers, and NIH institute and center program staff can report bias directly by emailing Dr. Gabriel Fosu, CSR's Associate Director for Diversity and Workforce Development, whose email is fosug@csr.nih.gov. Every allegation of potential bias is carefully investigated. If CSR agrees the review was compromised, it will re-review the application in the same council round, and if not, investigators can use the official NIH appeals process. CSR follows up with the individual reporting bias and the reviewer and takes actions as necessary to foster culture change in the review community. Dr. Byrnes pointed out that the majority of reviewers contacted are contrite, while the minority who disagree with the findings provide information about whether that reviewer should continue to serve on study sections.

CSR has developed a tool for investigators submitting transformative R01 applications that allows investigators to check that all identifiers are redacted from specific aims and research strategy sections. This increases the number of applications that reach peer review rather than being withdrawn for noncompliance with partially blinded review.

CSR is currently working to broaden the pool of study section reviewers and has developed a CSR Reviewer Finder Tool for SROs to find "underused" qualified reviewers. Dr. Byrnes emphasized that diversifying review panels requires more than just providing a tool, as a culture change is needed. CSR has focused on promoting that change by emphasizing the importance of diverse perspectives in identifying the most innovative and novel science. She pointed out that scientific diversity requires consideration not only of demographic and geographic diversity, but also diversity in scientific expertise and career stage. As the standing study section membership process includes multiple levels of oversight and approval, the diversity on those committees has been enriched. CSR has focused its efforts on special emphasis panels (SEPs), which are assembled more quickly and often involve gathering reviewers from existing networks. CSR is trying to raise collective awareness about the need for diverse perspectives. Dr. Byrnes noted that one of the most effective strategies so far has been sharing best practices for recruitment.

Dr. Byrnes shared the current percentages of women and underrepresented minorities in study sections, SEPs, and the principal investigators that contact CSR. The numbers have increased, reflecting CSR's recent efforts to increase diversity. Dr. Byrnes invited attendees to review the data and reports available on CSR's website.

Discussion Highlights

- When asked whether Factor 3 in the RPG reviews will drive scores, Dr. Byrnes explained that reviewers will be trained how to assess and report gaps, but socializing the changes will take time.

- In response to a comment about training NRSA Fellowship sponsors, Dr. Byrnes commented that the changes are intended to focus the application on the strengths of the individual trainee, so a targeted training plan will need to be included.

- Dr. Byrnes clarified that any reviews for which bias has been identified should not be reviewed by the same study section. In order to conduct the re-review in the same council round, the application should be re-reviewed by a SEP.

- In response to a question about adjustments to the review of NRSA Fellowship applications for early career mentors, Dr. Byrnes explained that the proposed changes are not intended to reduce the success of investigators with established mentors.

- When asked if NIH IC councils could provide input on ENQUIRE results, Dr. Byrnes noted that CSR currently does not plan to involve IC advisory councils in the process. Input is gathered from a broad community that has relevant expertise but no vested interest in the study section. This includes input from IC program staff and from IC leadership during the process. An evaluation process is in place for study sections in which the changes are not working as planned.

- In response to a question about reducing the influence of the environment on the overall impact score, Dr. Byrnes clarified that the environment criteria have been moved into Factor 3, which is not individually scored, and thus should have less influence on the score.

- Dr. Eisinger commented that the Office of Extramural Research closely monitors the number of early-stage investigators funded each year, and building the next generation of investigators continues to be a high priority for NIH.

- Dr. Byrnes explained that reviewers in the first level of the peer review process need not be academics, but should be active researchers in the field. CSR includes these researchers to broaden the pool of reviewers, particularly for study sections focused on community health.

III. ANIMAL MODELS AND ANIMAL AND BIOLOGICAL MATERIALS CENTER AND RESOURCE PROGRAM REISSUE (VOTE)

Stephanie Murphy, V.M.D., Ph.D., Director, DCM, ORIP, DPCPSI, introduced the reissue of the Animal Models and Animal and Biological Materials Center and Resource Programs for concept clearance. These programs support special colonies of laboratory animals, animal-related models, and other related resources that serve the national biomedical research community in a variety of research areas. The funds available and the anticipated number of awards for this program are contingent upon NIH appropriations and the submission of highly meritorious applications. The award project periods range from 4 to 5 years, depending on the grant mechanism.

The ORIP 2021–2025 Strategic Plan emphasizes development and enhancement of research-related center and resource programs to advance biomedical research and promote expansion and accessibility of animal models and animal and biological materials, as well as support exploration of ways to improve the reproducibility of research using these models. ORIP supports numerous center and resource programs in diverse areas of biomedical science that serve multiple purposes for the broad research community, including creating, collecting, developing, characterizing, preserving, and distributing animal models. Some centers and resources also provide informatics tools, data, biological materials, other types of tools, or services that support research projects in the scientific community and improve and expand animal model systems.

As part of ORIP's NIH-wide emphasis, animal model and animal and biological materials centers and resources to be developed must address the research interests of multiple NIH institutes, centers, and offices (ICOs). Applications must show that the biomedical research community's need for the proposed centers and resources is significant. Centers and resources must be available and used by investigators on a national basis. These awards should ensure the quality and welfare of distributed animals and biological materials, as well as supply expertise to guide reliable studies.

Animal and biological materials centers and resources must generate program income that will support efforts to enhance the volume of their operations to ensure use, document impact, and preserve valuable materials and animals. Applications must include marketing or distribution plans, community outreach strategies, approaches for tracking metrics, and a disaster response plan to minimize loss of animals and animal and biological materials should an adverse event occur. Collection and reporting of data related to animal models and animal and biological materials is expected.

From FY18 to FY22, ORIP received 61 applications and made 36 awards across the centers, pilot centers, and resource programs, for an overall award rate of 59 percent. Center and resource programs resulted in more than 900 publications across multiple areas during this time frame. ORIP's current centers portfolio has wide utility for investigators and includes grants for development and distribution of biological materials, informatics, and animal models from the species most used in biomedical research.

Dr. Murphy provided several examples of centers and resources that included use and impact measures monitored by ORIP and each center. The Zebrafish International Resource Center (ZIRC), the only national repository for zebrafish genetic stock, has provided animals, materials, and services to the research community for more than 22 years. ZIRC provides the highest quality of animal lines raised under stringent health monitoring, and it develops, characterizes, maintains, cryopreserves, and distributes wild-type, transgenic, and mutant zebrafish. ZIRC also provides pathology and consultation services, as

well as develops diagnostic platforms to screen for pathogens common to laboratory zebrafish. In 2022, ZIRC distributed more than 75,000 animals to 376 national and international laboratories.

The Bloomington *Drosophila* Stock Center (BDSC) collects, curates, maintains, and distributes genetically defined *Drosophila* strains that have significant research value. As of February 2023, BDSC supports at least 836 active NIH grants from 21 ICOs, with significant increases in the number of stocks at the center over the past three decades.

ORIP has also supported pilot centers for precision disease modeling. Centers are located at Baylor College of Medicine, The Jackson Laboratory, and the University of Alabama at Birmingham (UAB). At each center, an interdisciplinary research team of scientists and physicians works to address specific medical conditions by creating new animal models that more precisely mimic patient-specific disease processes and are used in developing treatment options. Current technology has been able to produce animal model phenotypes closely analogous to human patients. These new animal models have accelerated the generation of precision diagnostic and therapeutic approaches for cancer, Alzheimer's disease, diabetes, and rare diseases.

Dr. Murphy outlined how the UAB Pilot Center for Precision Animal Modeling (CPAM) solicits and prioritizes variants for creation of animal models across a precision disease model that carries the exact patient-specific variant thought to underlie the diseases of interest. One treatment intervention is under study, and four bioinformatic tools have been developed. Overall, CPAM's contributions have led to one funded and five pending NIH and U.S. Department of Defense grants focused on rare diseases.

Dr. Murphy provided examples of other limited competition resources supported through this concept. The Specific Pathogen–Free Macaque Breeding Colonies program provides specific pathogen–free macaques of defined major histocompatibility complex class type I for HIV/AIDS research in 10 awards to 8 institutions. The Human Tissue and Organ Research Resource provides human tissues, cells, and organs for scientific research through a human tissue acquisition network of 130 sites among 45 states. The National Swine Resource and Research Center (NSRRC) provides specific pathogen–free swine, reagents, organs, and tissues for the research community; its services include genetic modification and cryopreservation of strains. NSRRC provides resources and services to investigators supported by active NIH grants from at least 14 ICOs. NSRRC supports many key research areas and offers state-of-the-art biosecurity (including being specific pathogen free for 14 pathogens), animal care, and laboratories.

Dr. Murphy requested that the Council vote to approve the Animal Models and Animal and Biological Materials Center and Resource Program reissue.

Discussion Highlights

- The discussants, Drs. Susan Sanchez and Kevin C. Kent Lloyd, provided their comments. Dr. Sanchez supported reissuing the concept. She emphasized the importance of animal models and recommended that resources be allocated to improve data sets across models, and she noted that developing alternative animal models in the future would be beneficial. Dr. Murphy pointed out that DCM has taken steps to improve data curation and informatics in the P40 Centers program, and these can be added to other programs if appropriate.

- Dr. Lloyd concurred with Dr. Sanchez and noted the training opportunities provided by this concept. He asked about interactions among resource centers. Dr. Murphy explained that ORIP supports a biennial meeting of all the comparative medicine resource directors to share best practices and address common issues/challenges.

- When asked about tracking publications and animal use, Dr. Murphy clarified that each center and resource submits an annual progress report with publications from each grantee. A supplemental progress report allows them to list many other metrics, including the number of animals distributed. A common set of metrics is used, but the diversity of the centers and resources requires ORIP to follow up individually about any unique components. An evaluation platform is in development to assess common metrics and address the variations. Dr. Sanchez recommended making this information available to the public. Dr. Murphy explained that some data are available, but ORIP can reevaluate what additional data can be posted.

Vote

A motion to approve the Animal Models and Animal and Biological Materials Center and Resource Program reissue was forwarded and seconded. The motion passed.

IV. RECOVER OVERVIEW

Walter J. Koroshetz, M.D., Director, NINDS, Co-Chair, RECOVER Senior Oversight Committee, presented on the RECOVER program, an effort of multiple ICs that focuses on subacute and chronic issues related to COVID-19, known as post-acute sequelae of COVID-19 (PASC) or Long COVID. Dr. Koroshetz pointed out that the COVID-19 pandemic has had a monumental effect on the health of the country, but long-term health consequences are not yet understood. COVID-19 affects nearly every organ system in the body, and people with Long COVID tend to have symptom clusters in multiple areas. Symptoms include difficulties with the heart and vascular system, pulmonary difficulties, diabetes, immune system abnormalities, gastrointestinal difficulties, neurological difficulties, dysautonomia, and small-fiber neuropathy. Almost 90 percent of those with PASC experience fatigue, and the incidence of post-exertional malaise, a signature of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), may be almost as high. RECOVER's focus is necessarily broad to investigate these many symptoms across many areas of the body.

People with ME/CFS experience many of the same symptoms as those with Long COVID. The leading theory about the cause of ME/CFS is that it is post-infectious caused by an acute infection that triggers a long-term disability. The mechanisms of ME/CFS and many other post-infectious conditions remain unknown. The significant number of people affected by Long COVID, which is clearly related to COVID-19, is resulting in physicians' taking these conditions more seriously. As ME/CFS patients often are not diagnosed for years after they begin having symptoms, the biologic causes are difficult to trace. Dr. Koroshetz pointed out that a rapid explanation is unlikely, and decades of research have failed to identify the cause of or effective treatments for ME/CFS. He noted that COVID-19 provides scientists the unique opportunity to study the post-infectious process immediately after infection.

Many federal agencies across HHS are collaborating to address the broad effects of Long COVID on all HHS areas of responsibility, including the workforce, in a coordinated program. There is a concern that the National Action Plan may not be funded, which will present many challenges.

The goal of the RECOVER Initiative is to rapidly improve the understanding of and ability to predict, treat, and prevent PASC. Key scientific aims are to better understand (1) the clinical spectrum and biology underlying recovery over time; (2) define risk factors, incidence and prevalence, and distinct PASC sub-phenotypes; (3) study pathogenesis over time, including decades after infection, and possible relation to other organ dysfunction or disorders; and (4) identify interventions for treating and preventing PASC. Dr. Koroshetz emphasized that although RECOVER's goals are long term, patients who are struggling now also need researchers to develop effective treatments for their symptoms. RECOVER is patient centered, operates on a national scale with inclusive and diverse participation and community

engagement, and uses platform protocols that include standardized methodologies and common data elements, as well as adapts approaches based on emerging science.

RECOVER has successfully recruited a diverse cohort of people with symptoms of Long COVID. Electronic health records (EHRs) from 60 million people provide longitudinal information, and the clinical cohort of 16,000 in-person participants is the largest in-person study of Long COVID in the world. Community-based cohorts of people in other NIH studies have enrolled in follow-up blood sampling, and pathobiology studies are used to search for biomarkers and identify circulating viral particles. Evidence of tissue damage has been assessed through autopsy reports. RECOVER is planning to conduct clinical trials of antiviral agents and nonpharmacological treatments for symptomatic cohorts. Biosamples also can be used for future studies with more advanced technology.

RECOVER's EHR studies already have resulted in 15 published reports, more than 10 manuscripts in preprint, and more than 50 manuscripts in preparation. One study published in 2022 showed that conditions including dyspnea, edema, cognitive difficulties, malaise and fatigue, abnormal heartbeat, sleep disorders, abdominal pain, chest pain, and constipation—many of which are related to Long COVID—were found more frequently than expected in people who had COVID-19. Comorbidities identified as predisposing people to developing PASC include cancer, chronic kidney disease, chronic lung disease, depression, mental health disorders, obesity, female sex, and being a minority. Dr. Koroshetz pointed out that some of these factors are related to an increased risk of contracting or becoming seriously ill with COVID-19, which complicates interpretation of the results.

Studies using EHRs also have identified Long COVID subphenotypes that overlap with clusters of self-reported symptoms and have shown that vaccination against COVID-19 offers some protection from both severe acute COVID-19 and PASC. A study of pediatric populations reported that 3.7 percent of children infected with SARS-CoV-2 develop PASC. They may experience some unique symptoms, such as myocarditis, acute respiratory distress syndrome, and myositis, which are subacute effects of organ damage.

Dr. Koroshetz noted that the adult cohort is 96 percent enrolled, with more than 18,100 adult patients who had an acute COVID-19 infection within the past 4 weeks. He commented that pediatric enrollment remains in progress. Whether a participant will develop PASC is unknown at the time of enrollment, so those who do develop it can be compared with those who do not. Dr. Koroshetz pointed out that this unique opportunity to identify PASC when it begins is possible because of the active monitoring by health departments and the Centers for Disease Control and Prevention of SARS-CoV-2 infections, which now has ended.

RECOVER's in-person cohort program enrolls national participants from 30 hubs for 15 adult cohorts, 2 pregnancy cohorts, 8 pediatric cohorts, and several autopsy centers. Studies are conducted in three tiers. Tier 1 studies are screening studies that allow researchers to categorize the participants into symptom classes. Tier 2 studies are more in depth and will be triggered by some of the symptom complexes identified in the Tier 1 studies. Tier 3 studies are investigator-initiated coordinated studies that assess the potential pathologic clues with great depth.

These studies already have shown that of those adults recruited within a month of acute infection, 20 to 30 percent report symptoms 3 months after enrollment. Predominant symptoms are consistent across infection waves, with lower overall rates of symptoms observed in participants infected in later years of the pandemic. Vaccinated individuals infected with the omicron variant continue to be at risk for PASC, although the chance of developing PASC is lower than in individuals infected pre-omicron. Longitudinal cohort studies are being conducted with 49,000 adults from 14 existing community-based cohorts that can be followed over time. The studies include biospecimen collection. As some biosamples were collected prior to the COVID-19 pandemic, the specimens can be compared before and after COVID-19 infection.

Main theories for the causes of Long COVID include the following: persistent active virus or viral particles after acute infection that remain in the membranes of many body tissues and continue to activate the immune system for months or years; secondary damage caused by reprogramming of the host tissue or organ; immune response abnormalities; and epigenetic influences. An NIH intramural autopsy study on 44 COVID-19 patients from acute infection through more than 7 months following symptom onset shows that SARS-CoV-2 is widely distributed throughout the body, even in patients who had asymptomatic or mild infection. Virus replication is present in multiple pulmonary and extrapulmonary tissues early in infection, with viral RNA present in multiple anatomic sites, including the brain, for up to 230 days after symptom onset.

RECOVER plans to conduct clinical trials of antiviral agents and therapies for some of the common symptom complexes. Master protocols have been developed for each of these categories of symptom complexes to identify the outcome measures. Multiple treatments can be tried in succession. These outcome measures can be included in the broader protocol and help address the underlying biology that might connect the symptom complexes. Dr. Koroshetz commented that now that recruitment is almost finished, RECOVER investigators need to determine how to investigate each potential biological cause in a stepwise manner and with practical considerations.

Discussion Highlights

- When asked about criticism of RECOVER's recruitment speed, Dr. Koroshetz commented that an initial emphasis on rapid recruitment to the research cohort delayed clinical trials for symptomatic therapies. Time also was needed to develop protocols that would ensure that the trials could gather effective data. Although many early efforts in response to the COVID-19 pandemic focused on preventing deaths, Dr. Koroshetz noted that it was not anticipated that a large post–acute infection effect would occur. He noted that many patients studied between 3 and 6 months after their initial infection have not improved from their Long COVID symptoms and some members initially categorized into the control groups have developed symptoms of Long COVID. Dr. Koroshetz also emphasized the need to learn from these experiences to prepare for the next pandemic.

- Dr. Koroshetz commented that HIV/AIDS research has set a precedent for studies of viral persistence.

V. THE ARPA-H MISSION AND APPROACH

Jennifer Roberts, Ph.D., Director, Resilient Systems, ARPA-H, outlined ARPA-H's mission, progress, and procedures. ARPA-H funds research toward revolutionary breakthroughs with large investments over a short period of time to turn scientific advances into technical capabilities that can improve health outcomes for patients in the real world. While improved health outcomes could include traditional biomedical advances, ARPA-H also is looking across interdisciplinary fields to incorporate a variety of approaches. ARPA-H also supports advances that can help populations access interventions available today that are difficult to reach. ARPA-H's support will complement the work of organizations that conduct fundamental scientific research by ensuring that those advances are translated more quickly into interventions that can help patients. As an advanced research projects agency, ARPA-H will help eliminate risks that hinder commercialization of health products.

ARPA-H spent its initial year building necessary infrastructure and is currently developing its technical portfolio. Operating as an independent agency within NIH, ARPA-H has the authority to create its own policies necessary to support its mission. ARPA-H is expanding its network across the health ecosystem with health care providers, patients, community health centers, and others served by ARPA-H's activities,

including contacts across academia and industry and nonprofits and hospital systems that may participate in research. ARPA-H is building relationships with stakeholders throughout the federal government to address potential regulatory challenges as well. The agency collaborates with private investors and nongovernmental organizations to ensure that the technologies developed can continue after the ARPA-H program concludes.

ARPA-H recently released its first solicitations, including an open broad agency announcement (BAA) that seeks novel proposals about areas in which ARPA-H should invest, as well as a site selection solicitation. The BAA allows the research community to propose ideas that do not align with existing programs. When fully operational, ARPA-H will support a series of programs focused on specific areas, which will capture innovation across the ecosystem. The first program has been announced, titled "Novel Innovations for Tissue Regeneration in Osteoarthritis." The site selection solicitation will identify two locations in addition to the current ARPA-H site in the Washington, D.C., area. Congress has required three ARPA-H locations, but more likely will be needed to reach the populations ARPA-H must serve. The additional sites will support networks across the country that can test the technologies developed in patient populations and collaborate with the investment community. The top four entries from the ARPA-H Dash, a recently concluded ideas competition, will also be investigated for further investment.

ARPA-H's broad focus is divided into four areas: (1) health science futures (fundamental scientific advances); (2) scalable solutions (delivering existing interventions to populations that cannot access them); (3) proactive health (extending periods of health and helping people heal more quickly); and (4) resilient systems (enhancing the robustness of systems that affect health from the molecular to the societal scale).

ARPA-H's structure centers on its program managers, who will be term-limited, allowing the agency to remain agile, pivot easily into new areas, and incorporate new perspectives. Program managers will start one program per year, each of which will last 2 to 4 years. Each program manager will use a specific set of questions to frame a problem area that has the potential to affect health outcomes meaningfully and identify a revolutionary approach. The program managers will provide concrete ideas about areas in which ARPA-H should invest, creating a "bottom-up" organization. The program managers are experts in their program areas and will have significant autonomy to develop a balanced portfolio that meets the program goals. They will launch the program through a BAA, create a team of performers to research several complementary approaches simultaneously, and actively manage the program with concrete metrics to adjust investments and focus based on which areas of the program are succeeding. Program managers also will determine a path to sustain new technologies through collaborations with investors or other government agencies after the ARPA-H funding concludes. ARPA-H is seeking program managers with dedicated drive, no fear of failure, curiosity, and technical honesty. Program managers will come from a variety of backgrounds and career phases. Dr. Roberts invited attendees to refer any candidates from their professional networks.

Discussion Highlights

- When asked how ARPA-H is incentivizing equity at every level, Dr. Roberts explained that ARPA-H is actively recruiting from diverse populations and noted that experts with community connections may have program manager candidates in their networks. The metrics built into each program from the beginning will include evaluations of equity. As the metrics are in the BAA, they can be included in contracts, so funding for aspects like clinical trials will be contingent on meeting equity goals to ensure that technologies reach the patient populations that need them. The hub-and-spoke networks will also help ARPA-H reach many populations.

- Dr. Roberts clarified that the point at which industry would become involved would vary based on the nature of each program. During program formulation, program managers will interact repeatedly with the groups that they anticipate will contribute to technical innovation, which may include small or large companies, academia, industry, or laboratories. There are no regulations that preclude early industry–academic collaborations. The BAA for each program will outline the nature of the effort and whether the program will be collaborative or competitive.

- Dr. Roberts noted that program managers report to an office director. Programs are approved only by the office director and agency director, contributing to the program managers' autonomy.

- Dr. Roberts invited attendees to send ideas about how ARPA-H could address social determinants of health and recruit more effectively in that area.

- When asked if ARPA-H will have a policymaking function, Dr. Roberts clarified that ARPA-H will not create any external policies, but that the agency has special authority to work with the U.S. Food and Drug Administration (FDA). Some programs may benefit from early involvement by the FDA. ARPA-H also will work with the Centers for Medicaid & Medicare Services to address potential reimbursement barriers.

- In response to a question about evaluating the cost of an innovation, Dr. Roberts explained that ARPA-H can conduct market research and financial analyses when programs are being formed to determine the feasible costs for a particular approach. Cost margins will become clearer later in development and in some cases can become program metrics. When the area to be addressed is more foundational and may not reach patients until later in the process, transparency in cost considerations will become critical. Dr. Roberts emphasized that funding paths will vary in complexity.

VI. CLOSING REMARKS

Dr. Eisinger reminded attendees that the next Council meeting will be held on September 7 and 8, 2023.

VII. ADJOURNMENT

Dr. Eisinger adjourned the open session at 2:11 p.m. on May 11, 2023.

VIII. REVIEW OF GRANT APPLICATIONS

This portion of the meeting was closed to the public, in accordance with the provisions set forth in Sections 552(b)(c)(4) and 552(b)(c)(6), Title 5, U.S. Code and Section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix).[1] Members were instructed to exit the meeting if they deemed that their participation in the deliberation of any matter before the Council would represent a real or perceived conflict of interest. Members were asked to sign a conflict-of-interest/confidentiality certification to this effect. The *en bloc* vote for concurrence with the initial review recommendations was affirmed by all Council members present. During the closed session, the Council concurred with the review of 125 ORIP applications with requested first-year direct costs of $36,585,464; 911 Common Fund applications with requested first-year direct costs of $945,266,085; and 70 Environmental influences on Child Health Outcomes (ECHO) applications with requested first-year direct costs of $142,000,972.

[1] For the record, it is noted that members absented themselves from the meeting when the Council discussed applications (a) from their respective institutions or (b) in which a conflict of interest may have occurred. This procedure applied only to applications that were discussed individually, not to *en bloc* actions.

IX. CERTIFICATION

I hereby certify that, to the best of my knowledge, the foregoing summary minutes are accurate and complete.

Robert W. Eisinger -S Digitally signed by Robert W. Eisinger -S Date: 2023.06.29 07:07:50 -04'00' 6/29/2023

Robert W. Eisinger, Ph.D.
Chair, NIH Council of Councils
Acting Director, DPCPSI, OD, NIH

Date

Franziska B. Grieder -S Digitally signed by Franziska B. Grieder -S Date: 2023.06.29 05:09:39 -04'00' 06/29/2023

Franziska Grieder, D.V.M., Ph.D.
Executive Secretary, NIH Council of Councils
Director, ORIP, DPCPSI, OD, NIH

Date