The Center for Scientific Review Advisory Council (CSRAC) convened at 8:30 a.m., Monday, March 14, 2016, at the Center for Scientific Review (CSR), 6107 Rockledge Drive, Bethesda, MD. The entire meeting was held in open session. Richard Nakamura, Ph.D., presided as chair.

Members Present
Roberta Diaz Brinton, Ph.D.  Mary Sano, Ph.D. (special guest)
Susan Essock, Ph.D.  Lewis Weiner, M.D.
Michael Hollingsworth, Ph.D.  Jennifer West, Ph.D. (ad hoc, via phone)
Richard Nakamura, Ph.D.

Rene Etcheberrigaray, M.D., was the executive secretary for the meeting.

I. Welcome, Introduction, and Overview

Dr. Nakamura, CSR Director, welcomed CSRAC members, CSR staff, and other attendees. He introduced the CSRAC members and thanked them for advising CSR about the future of peer review. He asked for a motion to approve the minutes from the CSRAC September 28, 2015, meeting. CSRAC approved the minutes.

II. Evidence-Based Funding: Thoughts about Extramural Research

Michael Lauer, M.D., Deputy Director for Extramural Research, NIH, and Director of the NIH Office of Extramural Research (OER) discussed metrics to view the success of NIH-funded research.

A New Finish Line

Dr. Lauer pointed out the goals in the Southwest Airlines’ mission statement are connected to metrics that determine whether the company achieves its goals. He argued that the amount of money spent on research is not a measure of NIH success. Others have suggested such measures as the number of publications and patents from funded research, or the annual growth of the biomedical enterprise. He reviewed metrics NIH could use:

- **Number of scientists versus projects funded**: The relative success of a grant encompasses many factors, from its potential to maximize discoveries to its ability to foster career development, which Dr. Lauer illustrated with a schematic developed by Jon Lorsch, Ph.D., Director of the National Institute of General Medical Sciences (NIGMS). Dr. Lauer discussed the number of scientists funded, rather than the number of projects, as a metric. The number of unique scientists with at least one Research Program Grant (RPG) is constant at least since 2011, at about 27,500. However, the number of applicants has grown, leading to a larger gap between those funded and those seeking funding.
• **Publications and citations:** Another output to look at is publications and citations. An author in *JAMA* proposed a metric termed PQRST—Productivity, Quality, Replication, Sharing, and Translation\(^1\). An article in *Nature* proposed “binning” research by scientific field, since different fields have different practices related to citations\(^2\).

• **Power Law:** Another metric to consider is the Power Law. Applied to research, funding as large a number of projects as possible will yield great discoveries, but the results are unpredictable. The Power Law says extreme events happen and they matter. They can take the “finish line” beyond the amount of dollars spent, publications, and other metrics. For instance, scientists at the University of California at San Francisco analyzed development of the drug Ivacaftor. They mapped the work of more than 2,500 scientists and 2,500 institutions, over 60 years, who contributed in some way. OER is developing tools to map extreme events, so better data can drive decisions.

**Other Issues**

Dr. Lauer highlighted other OER issues, including the NIH strategic plan and application of the scientific method to NIH’s own funding practices. As the new OER director, he said he welcomes dialogue on these and other issues.

**Discussion Highlights**

• **Policy implications:** Lewis Weiner, M.D., asked about other implications of the Power Law. Dr. Lauer noted NIGMS applies the concept by funding people, not projects, through the R35. Roberta Diaz Brinton, Ph.D., asked how the R35 dovetails with the emergence of team science. Dr. Lauer said different areas of science might point to announcements for teams or development of program- or lab-based awards.

• **Rise in applications:** Dr. Nakamura asked about projections on the number of applicants for 2016, based on the estimate of 27,500 that Dr. Lauer used in his presentation. Dr. Lauer clarified he used rolling numbers of applicants over the last five years.

• **Explosive events:** Michael Hollingsworth, Ph.D., noted the concept of an explosive event captures that, in science, everyone stands on the backs of others. Dr. Lauer suggested looking at time as a function of productive science. Often, papers from R01 research are not published until a few years into a grant. This is hard, especially for first-time investigators, when applying for renewals. A little more time might result in proportionately more output. But a policy implication is that longer grant durations, which become out-year obligations, are hard for Institutes and Centers (ICs) when budgets are cut.

• **Missing data:** A participant from the audience commented on what is not known about unfunded scientists. Ability and quality are not spread out evenly. Dr. Lauer agreed some applicants should not be funded. However, he said, with more resources, many more investigators of high-quality research could be funded.

• **R01s versus R21s:** In answer to a question from Dr. Nakamura, Dr. Lauer said the citation impact of R21-funded research is not as high as R01s. He also noted the success rate of R21s is now lower than R01s.

**III. Studying Both Sexes: A New Frontier for Discovery**

\(^1\) Ioannidis JP, Khoury MJ. *JAMA* 2014 (June 9).

Janine Clayton, M.D., Director of the Office of Research on Women’s Health (ORWH), spoke about the trans-NIH initiative to consider sex as a biological variable (SABV). Distinguishing between sex and gender, she stressed the importance of reporting and transparency in all stages of the scientific continuum from basic-basic to population health. There tends to be more data on sex effects as one moves along the continuum.

The initiative resulted from three considerations:
- Default biology has used a 70-kg male in the clinic and male animals/cells in the lab, but such decisions should be made by design, not default;
- Fundamental biology should look not only at what is shared, but also what differs between males and females;
- Enhanced reproducibility throughout the biomedical enterprise is enhanced by expanding the knowledge base about both male and female biology.

As shown in a 2010 paper, males dominate animal studies³, while a 2016 article found only 53 percent of animal studies report the age and sex of the animals used⁴. The lack of reporting creates a reproducibility challenge and makes results confusing to interpret. As an example, a stroke treatment that seemed to have similar results looking at the whole population actually had very different results dependent on sex.

Dr. Clayton and NIH Director Dr. Francis Collins co-authored a paper calling for a concerted effort to address sex differences in pre-clinical research and explaining the NIH policy⁵. Implementing the policy is a team effort involving stakeholders within and outside NIH. Congress has expressed interest. Two guide notices address the reproducibility issue and consideration of SABV in NIH-funded research⁶. A third notice provides further information for applicants and reviewers⁷. She stressed the SABV policy does not require looking for sex differences in every study. The first round of scientific review that includes SABV is now underway. NIH provides online tools and resources to assist applicants and other stakeholders in implementing the policy.

She closed with “4 Cs” of studying sex to strengthen science: Consider sex, Collect information, Characterize the information in the context of sex, and Communicate the information.

Discussion Highlights
- **Powering of studies**: Susan Essock, Ph.D., praised NIH for attention to this area and asked about the expectations of the policy. Dr. Clayton said not all experiments can be powered to detect sex differences, but they can account for SABV in their factorial design. Dr. Essock said some applicants might use this argument as a hedge not to consider sex. Dr. Clayton reiterated by providing the information by sex, others can use it in the future.
- **Process**: Dr. Weiner asked about the practical implications when studying, for example, female cancer of the breast, which is a larger public health problem than male breast cancer.

⁷ NOT-OD-16-011
For sex-specific diseases, Dr. Clayton said it comes down to the research question. The justification for not considering both sexes should be included. Dr. Brinton asked about resources or examples of adaptive designs for preclinical research. She also asked about programs or initiatives to collect bioinformatic data around sex differences. She noted the data could spur basic science. Dr. Clayton said a workshop was conducted on preclinical research, available online, with more resources in development. The Big Data to Knowledge (BD2K) initiative will help provide data.

- Other variables: Mary Sano, Ph.D., asked about other variables such as age. Dr. Clayton said the policy calls for consideration of all relevant variables. Dr. Sano noted the interaction among variables has value in some settings but is unreasonable in others. Dr. Clayton said an inclusion governance committee is looking at this issue.

- Application considerations: Dr. Nakamura asked how to advise applicants who have to include the additional information in the existing 12-page application. Dr. Clayton said there is not one, correct way, but should be part of presenting a rigorous approach.

IV. National Institute on Neurological Disorders and Stroke Update

National Institute on Neurological Disorders and Stroke Update

Walter Koroshetz, M.D., Director of the National Institute on Neurological Disorders and Stroke (NINDS), presented an update. He first thanked CSR since review is at the core of NIH research.

NIH Investment in Neuroscience

At about $5.6 billion annually, neuroscience was the largest science area funded by Congress in FY 2015. This investment, which includes the BRAIN Initiative and Alzheimer’s disease research, spans 24 ICs and the NIH Office of the Director. Public interest in brain research is growing, and the number of trainees and fellows receiving Ph.D.s in neuroscience has risen exponentially since 2003. Through the NIH Blueprint for Neuroscience Research, multiple ICs are working together to fund projects that will benefit all of neuroscience, such as the Human Connectome Project and the Blueprint Neurotherapeutics Network.

NINDS Funding Decisions

Dr. Koroshetz reviewed the NINDS mission, noting it covers the full spectrum of basic, translational, and clinical research to seek fundamental knowledge about the brain and nervous system and to use that knowledge to reduce the burden of neurological disease. NINDS supports research across a wide spectrum of diseases, including between 200 and 400 rare diseases. Although no one rare disease receives a lot of funding, the hope is that work in one area will help other diseases. From a review perspective, the special expertise needed for research on these diseases is a challenge.

Following a flat budget for 12 years, NINDS received an increase starting in FY2014, including a percentage designated for the BRAIN Initiative. Application numbers have also risen, raising the percentile of applications funded only slightly, from the 14th to the 15th percentile. To protect the payline, the Institute decided to fund investigators, with less funding for Center, program project, and equipment grants. The number of R01 investigators has remained about the
same, but the number of R21 investigators increased. Dr. Koroshetz emphasized that many investigators need R21s to reach an R01 stage.

NINDS is considered a strict payline IC. Except for some funding outside the payline for early-stage investigators, NINDS does not fund an application above the payline in place of one below. If funds are available at the end of the year, NINDS funds above the payline, through high-priority grants. They also may offer bridge funding if funds are available.

**Support for Basic Research**

Dr. Koroshetz corrected the misperception that NINDS is not interested in basic research; in fact, a review of funding trends from 1997 to 2015 shows that basic applications have a slightly higher chance of success for funding at NINDS compared to applied translational or clinical applications. The reason for NINDS’ decline in funding for basic-basic applications, Dr. Koroshetz explained, is that fewer investigators submit applications for these kinds of grants. In trying to understand why the number of basic-basic applications has declined, a few potential reasons emerged, including that scientific progress has led to more opportunities for disease-related research, that disease foundations promote support for disease-related research and/or that there is a misperception by investigators that peer reviewers and NIH Institutes themselves favor disease-related research.

To address this issue, NINDS recently revised its mission statement to emphasize the importance of basic fundamental research. It also worked with CSR to educate study section members that basic science and applied research are equally important to the NIH mission. Recently, in partnership with NIDA, NIMH, and NIA, NINDS released a funding announcement that set aside funds (PAS-15-029) to stimulate research addressing fundamental questions in basic neuroscience at NINDS. The set aside ($5 million in FY16) will be used to support applications beyond the payline.

Dr. Koroshetz went on to discuss the need for more robust rigor and reproducibility in research, and the need for NIH to address these issues head on. Given the technology explosion and huge number of datasets available to researchers today, he said it is essential for scientists to be well-trained in quantitative skills and statistical analysis, rather than draw conclusions with too small an effect size. In June 2012, NINDS held a workshop on the topic, and NIH has released several notices for formal instruction in rigorous experimental design and transparency to increase reproducibility through institutional training grants, career development awards, and individual fellowships.

**R35**

NINDS is conducting a pilot with the R35 award, in which investigators are funded for eight years as their only NINDS grant. The purpose of the R35 is to provide investigators the freedom to pursue longer range, innovative or high risk research by reducing the amount of time spent writing and administering multiple grant awards. NINDS has committed $20 million per year to fund 20-30 awards. Review of these applications will focus on the merit and impact of the investigator’s previous accomplishments, the potential significance of the proposed research and whether it is of long-term importance, and the potential for the investigator’s productivity and impact to continue at a high level. Dr. Koroshetz also indicated that the R35 may strengthen
mentorship, as principal investigators spend less time writing proposals. He added that NINDS is also planning to pilot a mentorship award to reward outstanding mentorship for pre- and post-doctoral fellows to send a strong message that NINDS (and NIH) value good mentorship and welcomed input.

**Other Issues**
Dr. Koroshetz briefly touched on other topics, including:

- **Agreement index:** An experiment will look at outlier scores, in addition to final scores, to see how that information could supplement scores for applications right around the payline.

- **Reviewing networks:** Networks for clinical trials have improved efficiency and function very well. The challenge is to find reviewers to avoid conflicts of interest, given the large number of scientists involved.

- **Neuroethical issues:** Through the BRAIN Initiative, new tools will increase understanding about how brain circuits and networks generate thought and action. With these advances will come neuroethical issues, and a working group is being formed to consider them.

**Discussion Highlights**

- **Reproducibility:** Dr. Brinton noted the differences in standardization between discovery and translational research. She suggested finding aspects of the translational reproducibility framework to apply to discovery. Dr. Koroshetz noted that NINDS communicates with researchers about the risks of publishing data that cannot be reproduced. They are also working to change the culture among trainees. Dr. Brinton stressed the need to upgrade procedures for an entire lab, not just the newest members.

- **R50:** In response to a question from Dr. Hollingsworth, Dr. Koroshetz said they are interested in seeing how the R50 works among the ICs using it. Currently, R50s are only used by the National Cancer Institute.

- **Reviewers:** Dr. Hollingsworth also commented his institution conducted a review panel for an internal grant that consisted of the applicants themselves. Each stepped out when his or her application was discussed. The process was very fair.

- **Payline:** Dr. Weiner asked about analysis to see if a firm payline leads to improved grantee performance. Dr. Koroshetz said the payline is a convention with no difference between those who just miss or do not miss it. It shows NIH is resource-limited. With more funding, applications just above the payline, which represent more good science, could be funded.

**V. Quality Evaluations of Peer Review through Surveys and Focus Groups**
Mary Ann Guadagno, Ph.D., Senior Scientific Review Officer (SRO), spoke about several CSR studies. The goal of the studies is to obtain actionable feedback to enhance CSR’s best practices.

**Quick Feedback Surveys**
In these surveys, reviewers and program officers fill out a survey about the meeting in which they just participated or observed, with space for optional comments. She discussed findings related to the four questions about the quality of prioritization, collective expertise, assignments, and quality of discussion, noting overall positive feedback but some hesitation related to Internet Assisted Meetings (IAM). Program officers tend to have less favorable responses than reviewers. Dr. Guadagno said results are being further analyzed.
Many respondents included comments. With the Center for Information Technology, CSR is looking at how to automate the process of capturing and categorizing the responses. CSR defined 10 themes, or objects of sentiment, related to the study section chair, scoring, logistics, and other meeting aspects. The automated approach can allow CSR to evaluate thousands of comments more quickly to inform NIH leadership about stakeholder needs.

Focus Groups
Twenty-seven focus group sessions were conducted. Analysis will consist of detailed notes, as well as extraction of key themes and topics, open-ended coding, and analysis of themes related to current practices, strengths, and challenges of the peer review process.

Using the Findings
Dr. Guadagno said CSR will use the survey and focus group results to:
- Examine the utility of alternate scoring methods
- Design a study to understand the roles of principal investigator demographics, career stage, and institution in application outcomes
- Explore new technology to improve Program access to review discussions
- Continue to improve study section alignment
- Continue to pursue “the caffeine issue” to assist reviewers
- Improve communication and transparency with stakeholders.

Discussion Highlights
- **Takeaways:** In response to a question from Dr. Weiner about the impact of different review formats, Dr. Guadagno noted each format has advantages and disadvantages. The surveys also show how NIH can help applicants with the process, such as enhanced training and communications.

VI. CSR Updates
Dr. Nakamura highlighted staffing changes across NIH and within CSR. CSR expects to add 30 more SROs to meet the increased numbers of applications. NIH had its first significant budget growth in 12 years, but most funds are connected to specific programs, such as the Precision Medicine Initiative. The increase may result in more applications, although investigator-initiated research will not have greater access to the new money. There is some indication of support for more funding, but nothing concrete to report.

Changes are coming in the form of rigor/reproducibility and the new SABV criteria, as discussed earlier. NIH is also developing more specific language to clarify its support of basic science. Dr. Nakamura discussed a number of topics, followed by Council discussion on each.

Current Studies
CSR is undertaking other studies to improve peer review in addition to those discussed by Dr. Guadagno. A major study will be on anonymization, using 1,200 applications in original and redacted form reviewed by different groups. He explained further how CSR envisions carrying it out. CSR also recently conducted a post-meeting ranking study, a half-point pilot study, and a
pilot study to provide Program Officers with the means and distributions of percentiled applications so they have additional information for funding decisions.

**Discussion Highlights: Current Studies**

- **Applications for Anonymization:** In answer to a question from Dr. Hollingsworth, Dr. Nakamura clarified the anonymization study will use already-scored applications. In answer to a question from Dr. Sano, he said preliminary scores and critiques will be requested, but discussion and final scores will not take place.

- **Quality of review:** Dr. Weiner expressed concern that the reviews in the study would be less intense. From the audience, Lee Mann, J.D., Ph.D., who will coordinate the experiment, noted each reviewer will receive fewer applications than usual, with the hope they will read them thoroughly. Dr. Nakamura said follow-up studies, including a reliability study, will take place. Dr. Weiner said reviewers may still try to decipher the identity of the applicants, even if anonymized. Dr. Mann said a smaller sample will determine if complete anonymization is possible. Dr. Essock questioned whether calling attention to bias will influence the review. Dr. Mann said the focus is not race but is more general, as occurs with blinded journal reviews.

- **Hypothesis:** In reply to a question from Dr. Essock, Dr. Nakamura said they will register the study hypothesis and analysis plan but do not want to provide a detailed statement at this point. CSR is consulting with the central NIH Institutional Review Board.

- **Use of results:** Dr. Hollingsworth asked what NIH will do with the results. Dr. Nakamura said the study may provide an estimate of the effects of pieces of information on scoring as compared to differences in perceived quality. NIH will have input to develop interventions to achieve true parity across groups. Dr. Sano asked about options, noting as an example that gender bias is not necessarily solved with more gender diversity in a study section. Dr. Nakamura said hard data would help develop counter-measures. Dr. Mann said if bias is shown, CSR would do a second experiment to see the effects of a two-stage review.

- **Diversity in the experimental group:** Dr. Brinton said it is important to make sure there is comparability of research resources. One challenge for underrepresented minorities is when they are at institutions that fall below a competitive research environment. Dr. Nakamura clarified the disparity affects applicants in all types of institutions. From the audience, Bruce Reed, Ph.D., Director of the CSR Division of Neuroscience, Development and Aging, noted multiple patterns of disparity may be revealed.

- **Ranking approach:** Dr. Weiner said end-of-meeting rankings are useful. Dr. Nakamura said study sections generally do not have consensus discussions at the end of a meeting, because one or two people can dramatically influence the final ranking.

**Workload**

Dr. Nakamura reviewed data on application numbers by year and cycle. The growing number, especially when spread unevenly across review cycles, has increased the workload for SROs, reviewers, ICs, and applicants. Setting a maximum number of applications per applicant is not feasible, but he reviewed other possibilities:

- **Continuous submission:** The Scientific Management Review Board has suggested a test to drop deadlines, as the National Science Foundation (NSF) has done. Several ICs have expressed interest in exploring the possibility.
• **Pre-application process:** OER has suggested two routes: (1) everyone submits a full application, with an initial group selecting applications for further evaluation, or (2) applicants express a letter of intent and only those that might be competitive submit a full proposal.

• **R35:** Wider use of the R35 could mean fewer R01s to review.

• **Additional CSR staff and enhanced support:** These changes have helped CSR, but they do not affect reviewers or the competitive climate.

• **Learning from institutions:** A group will look at success rate by institution to learn if infrastructure or other practices in these institutions can apply elsewhere.

• **Editorial board:** This review method, used for some NIH initiatives, can reduce the review load and filter applications.

**Discussion Highlights: Workload**

• **Continuous submission impact:** Dr. Brinton said deadlines can stimulate applicants to submit, whether ready or not. In addition to the reduced workload, applicants might have a higher chance of success with continuous submission. Dr. Weiner said applicants might submit more proposals, not fewer. Dr. Nakamura said this is not the case with NSF, but the experiment is worth trying. In answer to a question from Dr. Sano about any other impact NSF has seen, Dr. Nakamura said NSF has not measured aspects beyond workload. Dr. Hollingsworth noted continuous submission could benefit internal university systems, although it may not apply to all mechanisms.

• **Pre-application processes:** Dr. Weiner said he has been involved with funding mechanisms that use a filtering system. It provides an intense review of a smaller amount of information, and investigators have appreciated the process. Dr. Nakamura noted legal issues that always enable applicants to submit a full proposal if they choose. Dr. Weiner and Dr. Hollingsworth stated this option would eliminate the value of the process.

• **Review location for letters of intent:** Dr. Sano asked whether program staff or review groups would review the letters of intent. Dr. Nakamura noted program staff currently filter applications in some ICs, such as for clinical trial studies, but study sections could also do so. Dr. Sano said if reviewers do it, it re-creates the same concern. Dr. Essock observed the incentives are different if a pre-application is looked at by program versus review, and if voluntary or not. Dr. Brinton said the distinction between programs versus investigator-initiated research might make prior review difficult, although noted the Pioneer Awards have used sequential review successfully.

• **R35:** Dr. Sano asked about the impact of the R35 on the number of applications submitted. Dr. Nakamura said, because the mechanism is just beginning, there are no data yet.

• **Editorial boards and diversity:** In response to a question from Dr. Sano about the impact on diversity, Dr. Nakamura said the initial reviews of Pioneer Award applications were fairly catastrophic for diversity of all kinds. Dr. Sano asked about a strategy to anonymize information on these shorter applications. Dr. Nakamura said CSR would conduct the initial anonymization study, discussed previously, before expanding the concept.

**Alternative Award Systems**

While some people question whether peer review should be replaced, it has produced the dominant scientific system for more than 70 years. Alternative methods to fund research could range from using an applicant’s track record based on citation or publication analysis, to public
crowd sourcing, to use of a super-intelligent computer. Any replacement system must produce better outcomes for scientific knowledge and clinical advancement, combine high efficiency and performance, be fair, provide evidence of passing the renewal test, and provide relative immunity against inappropriate gaming.

Discussion: Alternative Award Systems

- **Quantifying the need:** Dr. Brinton noted the pressures caused by monetary limitations. She questioned the size of the scientific discovery engine necessary to sustain or exceed demand, now and in the future. That knowledge could be used to communicate the funding that science really needs. Dr. Nakamura said the Battelle Institute found the U.S. is one of the few countries whose proportion of Gross Domestic Product going into research and development has declined. Dr. Sano asked about models to determine the impact of the current emphasis on STEM (science, technology, engineering, and mathematics) education. Dr. Nakamura said an OER workforce study attempted to do some modeling, but had many unknowns. Dr. Hollingsworth said increased funding to support 25 to 30 percent of applications is a reasonable estimate to support high-quality science.

- **Sharing resources:** Dr. Weiner referred to his experience chairing the Board of Scientific Counselors for Clinical Sciences and Epidemiology of the National Cancer Institute. The intramural labs are small but very productive, in part because of infrastructure resources available to them. He suggested CSR could advocate for shared resources in the extramural community. Dr. Brinton noted this approach could also lower the cost per grant. Dr. Nakamura said NIH is doing several studies in this area. Dr. Hollingsworth asked about identifying areas of research in study sections that would be complementary to improve the system, while still honoring confidentiality. Dr. Nakamura noted a lot of interest in probing an intelligent database system like Watson to find linkages and reduce redundancy.

VII. Closing

Dr. Nakamura invited audience members to ask questions. When no questions were asked, he adjourned the meeting.

We do hereby certify that, to the best of our knowledge, the foregoing minutes of the March 14, 2016, meeting of CSRAC are accurate and complete. The minutes will be considered at the next meeting of the Advisory Council, and any corrections or comments will be made at that time.

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Rene Etcheberrigaray, M.D.
Executive Secretary
Center for Scientific Review Advisory Council

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Richard Nakamura, Ph.D.
Chair
Center for Scientific Review Advisory Council