Center for Scientific Review
Center for Scientific Review Advisory Council Meeting
National Institutes of Health
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September 25, 2017

The Center for Scientific Review Advisory Council (CSRAC) convened at 8:30 a.m., Monday, September 25, 2017, 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

Alfred L. George, M.D. *(ad hoc)*
Michael Hollingsworth, Ph.D.
Yasmin Hurd, Ph.D. *(ad hoc)*
José López, M.D. *(ad hoc)*
Scott Miller, Ph.D. *(ad hoc)*
Richard Nakamura, Ph.D.
Julie C. Price, Ph.D. *(ad hoc)*
Stephan Targan, M.D.
Louis Weiner, M.D.
Jennifer West, Ph.D.

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

I. Welcome and Introductions

Dr. Nakamura, CSR Director, welcomed CSRAC ad hoc and regular members, CSR staff, and other attendees in person and via webcast. He asked for a motion to approve the minutes from the Committee's March 27, 2017, meeting. CSRAC approved the minutes.

II. NIH Update

NIH Principal Deputy Director Lawrence Tabak, D.D.S., Ph.D., outlined three main topics he would cover: the Next Generation Researchers Initiative, rigor and reproducibility in biomedical research, and research to address the opioid crisis.

Next Generation Researchers Initiative

Dr. Tabak framed this initiative in the context of the NIH Strategic Plan, which calls for enhanced stewardship by recruiting and retaining the research workforce, and by enhancing diversity, among other efforts. Observations from the extramural community underscore the hypercompetitive system that impedes many from entering or remaining in research careers. An analysis of applicants who received NIH Research Program Grants (RPGs) from 1990 to 2015 shows a decrease in percentage of early (to age 45) and mid-career (ages 45–60) investigators funded, while the percentage of funded late-career investigators rose. This latter group is "outcompeting" the younger groups due to increased resiliency. Obtaining a new grant is more difficult that obtaining a renewal.

The 21st Century Cures Act requires that NIH establish the Next Generation Researchers Initiative to promote earlier independence and increase funding for new investigators. On August 31, NIH released a policy to support it. It calls for funding 200 more early stage investigators

(ESIs) and 200 more early established investigators (EEIs) across NIH in FY 2017 compared to FY 2016. The goal is to stabilize the career trajectories of these two more junior groups.

NIH also needs to develop metrics of productivity, especially in the shorter term, to assess impact. Tools include the Relative Citation Ratio (RCR) and a new dashboard tool called iCite. Additional approaches are needed.

Considerations going forward include how Institutes and Centers (ICs) will fund the Next Generation grants. They will use a variety of mechanisms. Other considerations include monitoring of workforce size and diversity, scientific excellence and outcome, and IC funding decisions. A working group of the Advisory Committee to the Director (ACD), consisting of investigators at all levels, is refining and implementing the initiative.

Rigor and Reproducibility

NIH is taking steps to strengthen rigor and reproducibility, but universities, professional societies, journal editors and reviewers, and others also play a role. One step to raise community awareness is to enhance the principles and guidelines for reporting preclinical research, similar to changes related to clinical research implemented a few years ago.

It is also important to share data and other information in a broad and transparent way. NIH is moving in the direction of making more data repositories publicly available through the Big Data to Knowledge (BD2K) and other efforts.

Research to Address the Opioid Crisis

With overdose death rates on the rise across the country, NIH is involved in a public-private partnership built on three pillars: new and innovative medications and biologics; safe, effective, and nonaddictive strategies to manage chronic pain; and research into the neurobiology of chronic pain. The Administration and governors are behind the work.

Discussion Highlights

- ***Next Generation funding:*** In answer to a question from Stephan Targan, M.D., Dr. Tabak said ICs will decide how to award the ESI and EEI grants. For example, they can identify areas where they want to catalyze research or give preference when they have two applications of equal merit.
- ***Next Generation impact:*** Louis Weiner, M.D., asked about the impact of research by the different age groups. Dr. Tabak noted more senior researchers have an advantage because they have had more time to demonstrate impact. Michael Hollingsworth, Ph.D., said the RCR does not reflect impact well. He also suggested linking impact with rigor and reproducibility.
- ***Demographics:*** José López, M.D., said researchers are retiring at later ages, which contributes to the imbalance. Scott Miller, Ph.D., said it was important to understand what is happening to EEIs at institutions. He noted they often have to take on more responsibilities compared to more junior and more senior scientists. He asked if 200 additional grants to ESIs and 200 to EEIs is the right balance. Dr. Tabak said the ACD working group will look at the distribution. Julie Price, Ph.D., asked about the role of mentorship in the new initiative. Dr. Weiner noted the long-term implications of shortened careers.

- ***Opioid research:*** Yasmin Hurd, Ph.D., said the mechanisms for increasing clinical trials, along with working groups and other discussions, take time. She urged accelerating the process, given the crisis.

III. Improving Openness and Reproducibility of Scientific Research

Tim Errington, Ph.D., Lead of Metascience Activities, Center for Open Science (COS), spoke about a COS project focused on cancer biology research and about other insights related to openness and reproducibility. These practices increase efficiency and reveal gaps in knowledge. Yet, a survey in *Nature* showed more than 50 percent of researchers across disciplines see a reproducibility crisis (https://doi.org/10.1038/533452a). He defined three types: computation, empirical, and replicability, which encompasses direct and conceptual replication.

COS Reproducibility Project

The COS Reproducibility Project: Cancer Biology (RP:CB) project will try to replicate a sample of high-impact, preclinical studies, making its own study process openly available (https://osf.io/e81xl/wiki/home/). He stressed RP:CB will not prove or disprove the original studies but rather analyze publications to see if the methods are clearly and openly communicated. Roadblocks to reproducibility include lack of error reporting, incorrect reporting of statistics, inaccessible original data, missing methodological details, and missing information about minimum standards for quality control checks. These challenges are not new and have been pointed out conceptually before, but the project hopes to illustrate empirical evidence of the challenges and suggestions for some new solutions, including workflow management, repositories, new funder/journal policies, and rewards for open practice. Incentives to implementation must be addressed. Among a number of barriers, the central issue is that incentives for individual success are focused on getting research published, not on getting it right. Because science is decentralized, incentives to embrace change must be generalizable and flexible simultaneously.

Transparency and Openness Promotion Standards

The Transparency and Openness Promotion (TOP) Standards (https://cos.io/our-services/top-guidelines/) -- adopted by more than 5,000 journals and 74 organizations -- address transparency, openness, and reproducibility. The eight standards are modular and agnostic to discipline.

Preregistration

Research has two aims: exploratory/discovery-based and confirmatory, both of which are important to accumulate knowledge. Confusing the two decreases reproducibility. Preregistration allows studies to be discoverable and interpretable by others. Required for clinical trials, preregistration consists of a time-stamped, read-only version of a research plan. Preregistration can also be integrated into the publishing model to increase rigor and transparency of research. In the traditional publishing model, peer review takes place between writing and publishing a report. A publishing format, call Registered Reports (https://cos.io/rr/) inserts preregistration as an early stage of peer review after study design with the results given in-principle acceptance regardless of outcome, which eliminates the bias against negative results in publishing because results are not known at the time of review.

Technology

New tools can enable changes because they can help manage research that involves collaboration, multiple versions, and the like. COS is developing an open-source science framework, OSF (https://osf.io) to help. He provided examples from RP:CB to illustrate the framework.

Discussion Highlights

- ***Impact on experimental science:*** Dr. Miller noted the field of chemical synthesis has a "check-in journal" to which researchers submit procedures. He asked whether the practice of including supporting information negatively affects experimental science. He also noted the high cost of electronic notebooks. Dr. Errington responded by saying that replication should not be seen as a threat, but acknowledged it requires a shift in culture. He said the next generation of scientists will more likely use electronic notebooks, and costs can be reduced if infrastructure is shared across institutions (i.e., public goods tools). Dr. George said the root of a lot of irreproducibility is mistaking exploratory research for confirmatory. It is important to distinguish between the two.
- ***Longitudinal studies:*** Dr. Price asked about reproducibility in longitudinal studies. Dr. Errington said privacy concerns may require slightly different rules.
- ***Preregistration:*** Dr. George asked about the venue for preregistering studies, as journals might not consider them publishable. Dr. Errington suggested a registry. Dr. Hollingsworth said preregistration can let others know what a researcher is working on to avoid asking the same question. Even if the study fails, it could provide valuable information. Dr. Hurd noted the community needs to work together on the issue. Guidance to study section reviewers is important, and NIH should dedicate a percentage of its budget to reproducibility. She noted the importance of failure in science as a way to learn.
- ***Disclosing information:*** Dr. Nakamura asked how the openness model affects careers, especially for younger researchers if their experiments fail. Dr. Weiner followed up to ask how the system accommodates shifts in experiments based on new directions. Dr. Errington said the key is transparency. Researchers can update their methods and explain why. Dr. Weiner asked about how to protect ideas in preregistration. Dr. Errington said researchers can timestamp ideas but embargo release. Dr. Targan asked how openness applies to pharmaceutical research. Dr. Errington said preregistration resonates with pharmaceutical companies, but not the idea of making data open. There may be other ways to expose information without compromising intellectual property.
- ***Working with journals:*** In response to a question from Dr. López, Dr. Errington said COS is working with journals on the TOP guidelines and offering tools for openness.

IV. Clinical Trial Reforms

Michael Lauer, M.D., Deputy Director for Extramural Research, updated CSRAC on NIH Clinical Trials Reforms. As background, a 2012 *British Medical Journal* article found fewer than one-half of NIH-funded clinical trials were published, either at all or in a timely manner. An analysis conducted by the National Heart, Lung and Blood Institute (NHLBI) found trials with clinical endpoints are usually published, but those that focus on other endpoints are far less likely to publish in a timely manner. A Yale study of academic medical centers showed 55 percent of trials conducted was the highest published two-year rate by a center, with most in the 20-30

percent range. A report by the Government Accountability Office concluded additional data would enhance the stewardship of clinical trials across NIH.

New Policy

In 2014 NIH issued a revised definition of clinical trials: "A research study in which one or more human participants are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes." A proposed rule about posting clinical trial results in the Clinical Trials.gov database and a Request for Information were also issued. Hundreds of comments came in. NIH released its policy in September 2016 on the dissemination of NIH-funded clinical trials, noting the ethical obligation to report on experimental research involving humans. The policy states main trial results should be reported in clinicaltrials.gov within 12 months of completion.

The pervasive failure to report main results of trials and the inadequacy of data to enable effective stewardship are systemic, requiring a number of reforms. The reforms include training, enhanced registration, changes to the grant application, and other measures. Accountability will come when clinical trial funding is withheld to those who do not comply.

Discussion Highlights

- ***Definition of clinical trials:*** Dr. Hurd asked about better definitions of clinical trials for potential participants on ClinicalTrials.gov. She also asked about placing basic science results in a database. Dr. Lauer noted more than 80 percent of NIH-funded trials do not focus on hard clinical endpoints. Some trials are address basic science questions about biological or behavioral mechanisms, rather than treatment of a disease. On Clinicaltrials.gov, researchers enter the primary purpose of their study. Dr. Weiner noted pharmaceutical companies may have their own requirements about reporting. Dr. Lauer clarified that observational studies are not covered by this policy.
- ***Reasons behind nonpublication:*** Dr. George asked what investigators said about why they had not published. Dr. Lauer said reasons included lack of success on the first few attempts, lack of time, and lack of expectations about publishing. Some investigators said trials with hard clinical endpoints were published more quickly. Dr. Price agreed a condition of a grant to publish will help shift the system.
- ***Use of preprints:*** Dr. George asked whether preprints, commonly used in other fields of science, might serve the same purpose. Dr. Lauer said respondents saw risks in that physicians would interpret the study as a finding to apply to patients. The policy's requirement is to post results on ClinicalTrials.gov as a minimum.
- ***Culture issue:*** Dr. Miller noted the role of publications on careers is an evolving topic. Some fields are creating archival journals to capture papers they do not publish. Dr. Hurd said different fields have different average lengths of time until publication. Dr. Lauer said their analysis did some breakout by field and by budget.

V. CSR Update

Dr. Nakamura updated CSRAC on issues that affect peer review, including management practices, communications, and workload. Later in the meeting (see below) he returned to issues related to workload, rigor and reproducibility efforts, and the CSR anonymization study.

Management and Communications

The underlying concern is to ensure that reviews are effective and identify good science, and that the scientific community, including reviewers, sees the process as fair and reasonable. The historic lows for success rates for grants have been challenging. Recent increases from Congress have provided a slightly greater sense of optimism.

CSR has conducted supervision and management retreats to see how to mitigate the effects of low success rates. One discussion defined a list of fundamental qualities of a good scientific review officer (SRO), such as flexibility and communications skills, to achieve through hiring, training, management, and supervision. NIH turns to CSR to communicate changes through the review process. The 250 SROs must communicate policy changes to 3,500 regular and 15,000 temporary reviewers. The changes cannot always be implemented in a single round, as reviewers must be convinced of the rationale behind a change. Chairs receive orientation on policy changes to understand the NIH context. Staff has expressed concern about lack of bottom-up input, micromanagement, trust, and variability of communication accuracy in dealing with the changes.

Quality and Workload

SRO workload is expected to increase because of staff departures that cannot be replaced, increases in applications, increases in special grants, and increased work per application with the anticipated policy changes. He identified a number of benefits to CSR, reviewers, and applicants if the overall number of applications declined. He asked for CSRAC feedback on potential solutions to reduce applications to about 40,000 applications per year, rather than the current average of 60,000:

- A quota for the number of applications reviewed per principal investigator (PI) per year
- Deferral of applications once that limit is reached
- Shift of the basic research grant from an R01 to a longer-term R35
- Elimination of grant deadlines
- Applicant reviewing of applications.

Discussion Highlights

- ***Accountability:*** Dr. Hurd commented on accountability when a reviewer's scoring skews the system. Dr. Nakamura explained SROs track scoring behaviors. Chairs are also involved. Some reviewers are not invited back. She suggested a more structured system.
- ***Training:*** Dr. Miller said the community appreciates mentoring workshops by ICs for new faculty. Dr. Nakamura said CSR SROs are involved in these efforts. Dr. Miller asked about the utility of shortened reviewers' summaries for applicants, rather than the previous "pink sheets" with more thoughtful essays. Dr. Nakamura said reviewers are encouraged to communicate complete thoughts but the switch related to workload. Dr. Price said interpretation of expectations across fields contributes to communications challenges.
- ***SRO experience:*** In response to a question from Dr. Targan, Dr. Nakamura estimated about

half of SROs have direct experience in submitting grant applications. Many come from extramural or intramural research labs.

- ***Confidentiality:*** Dr. López asked about expectations of confidentiality in review. Dr. Nakamura said this requirement is stressed before each round of review.
- ***Quota on applications:*** Dr. López and Dr. George said lower funding rates mean investigators must submit more applications. A quota would mean losing investigators because their institutions would not retain them if they went over their quota before funding.
- ***Impact of R35:*** Dr. George asked whether the R35 has affected the number of R01s. Dr. Nakamura said they have not seen an overall decrease in R01s. Dr. Weiner noted, if the R35s were used more NIH-wide, more impact might result, including possibly on institutional culture. Dr. Nakamura said R35 use by the National Institute of General Medical Sciences (NIGMS) will serve as a good test. Dr. Miller noted an advantage to receiving a lot of applications is that it shows researchers have the incentive to push beyond their existing programs.
- ***Deadlines:*** Dr. Hurd urged focus on projects, not just individuals. She said elimination of deadlines three times a year might help applicants to develop better projects. Dr. Nakamura said a test is being planned.
- ***Funding rates:*** Dr. George noted in the past, a single R01 could fund a lab, which is no longer the case. He asked about raising the cap on fixed modular budgets. Dr. Nakamura said NIH has proposed to ICs to increase the upper limit but they have not accepted the change.

VI. Review of Cancer Biology Scientific Review Groups

John Bowers, Ph.D., Director of the Division of Translational and Clinical Sciences, reported on a review of cancer biology scientific review groups (SRGs) and requested CSRAC consideration of recommended changes.

Review Process

CSR reviews scientific clusters across Integrated Review Groups (IRGs), from 12 to 20 SRGs at a time. A working group of scientifically broad, senior scientists focuses on the science of the SRGs, examines alignment with the current state of the science, and recommends changes as needed.

Working Group Recommendations

A CSR committee uses a number of analyses to form the scientific cluster. In Cancer Biology, the review encompassed basic and translational science, including seven SRGs in the Oncology 1 IRG, five in the Vascular and Hematology IRG, and seven in Oncology 2. The working group was asked to recommend changes if an SRG is under- or oversubscribed, or if the scope of the science it reviews is not adequately representative of the field and emerging fields. The group recommended: (1) no changes to two study sections; (2) some redistribution in seven study sections; and (3) charter of a standing special emphasis panel as a second mechanistic therapeutics SRG. They further recommended a distribution of topics related to mechanisms of cancer therapeutics between it and another new chartered SRG.

Council Approval

CSRAC moved, seconded, and approved a motion to accept the working group's recommendations.

VII. NSF Perspective on Basic Science, Review, and Funding

James Olds, Ph.D., Head of the Directorate of Biology, National Science Foundation, explained the National Science Foundation (NSF) structure, proposals, and award process timeline. One significant difference between NIH and NSF is that an NSF program director is more autonomous in funding decisions compared to the NIH system.

NSF review guidelines, compiled in the Proposal & Awards Policies & Procedures Guide (PAPPG), provide general principles related to merit review but not specifics, thus leading to variability across the agency. Flexibility in the process is common.

Program Officers (also called Program Directors) are at the heart of the process. They are either visiting scientists and engineers, known as rotators, or permanent, Ph.D.-level Federal employees. They serve as communicators, assessors, and directors.

External reviewers consider the review criteria, adequacy of the proposed project plan, priorities in the scientific field and at NSF, and the potential risks and benefits of a project. They provide independent written comments. They also look at the potential impact to the science and to society more broadly. Reviews are either ad hoc or conducted in in-person panels. Differing from NIH, review committees do not provide numbered ranks or paylines. The key output is a panel summary prepared by a scribe at the meeting. The panel is advisory, and high ratings do not guarantee funding. A program officer makes funding recommendations, and NSF Division Directors either concur with or reject the recommendations.

In 2012-2015, NSF piloted the concept of preliminary proposals to lessen the burden on reviewers and staff. Applicants submitted preliminary proposals in January and some were invited to submit full proposals in April. Applicants were limited to submission of two preliminary proposals as a PI or co-PI per year, but there was pushback. An evaluation showed applicant workloads increased, while workload for staff did not decrease. As another experiment, two tests to remove deadlines entirely have also been conducted. The practice resulted in fewer applications being submitted, so NSF might expand this practice.

Alternative mechanisms at NSF include the Ideas Lab to accelerate new science in focused areas. Dr. Olds described the process to select panelists and participants for these five-day workshops.

Discussion Highlights

- ***Success rates:*** Dr. Olds estimated at NSF, strong proposals worth about $3 billion are not funded for lack of budget. If the funds were available, about 30 percent of proposals would merit funding. Many proposals are submitted multiple times. Dr. Miller noted through the NIH process, applicants may get the message that their proposal is not compelling enough to be funded. Dr. Olds said he thinks the NIH process is better at communicating that message

than the NSF process. Dr. Hurd asked whether reviewers accept that the program director makes the decisions. Dr. Olds said reviewers willingly participate and do accept the process.

- ***Preliminary proposals:*** In response to a question from Dr. Hurd, Dr. Olds said the major concern of the preliminary proposal test was the limit on the number that tenure-line researchers could submit. He said in this test, pre-applications were not blinded so as to only deal with one variable in the pilot.
- ***Impact evaluation:*** Dr. Olds said when he is asked about the impact of NSF funding, he points to common technologies now used by Apple and Google, among others, that received initial funding through NSF. It is hard to evaluate the impact of an individual grant, since it is not known what will pay off over time.
- ***Legal authorities for NSF and NIH:*** Dr. Olds stressed Congress created NIH and NSF with different legal authorities related to the review process. He also noted NSF can fund high-risk expensive science, which works in the types of science under its purview. Dr. Miller pointed out that different ecosystems in fields of science lead to broad agreement about objectives in these large projects. Life sciences often thrive because of different objectives.
- ***Program officers:*** Dr. Hollingsworth asked how NSF evaluates the work of its program officers. Dr. Olds said he worries that some may become too insular so he likes to pair federal employees and rotators.

VIII. AARR SRGs Review

Valerie Durrant, Ph.D., Director, CSR Division of AIDS, Behavioral, and Population Sciences, presented results of a review related to AIDS and AIDS-Related Research (AARR) study sections. The review used a process similar to that presented by Dr. Bowers (see above). Several of the current nine AARR SRGs are undersubscribed.

The working group was asked to look at SRGs that review AARR science from basic to behavioral topics. ICs in related areas also provided feedback. The group recommended a change to six study sections. They recommended two sections with a basic science focus, one with a virology focus and the other with an immunology focus. They also recommended an SRG that broadly focuses on co-morbidities and one on co-infections, both of which take a bench-to-clinic perspective. They revised two SRGs related to behavioral and social science.

Council Approval

CSRAC moved, seconded, and approved a motion to accept the working group's recommendations.

IX. Closing Remarks and General Discussion

CSRAC continued discussion on issues raised by Dr. Nakamura in his earlier presentation: workload, rigor and reproducibility, and the anonymization study.

Workload

An additional way to ease workload has been to provide eSlate and electronic support to aid in locating and nominating reviewers.

Rigor and Reproducibility

Rigor and reproducibility efforts cover clinical trial review; animal studies may also undergo further scrutiny. The National Institute of Neurological Disorders and Stroke (NINDS) has suggested greater use of checklists. He asked for CSRAC feedback about checklists for reviewers.

Anonymization Study

Dr. Nakamura reviewed the assumptions and study aims of the study. A 90-application test is concluding. CSR has registered the study plan and analysis with the Center for Open Science. Possible recommendations if the study shows bias include two-stage reviews and training.

Discussion Highlights

- ***Checklists for rigor and reproducibility:*** Dr. George said checklists, if not mandated, could be useful reminders to reviewers. Dr. López suggested applicants could use a list as they develop their applications. Dr. Miller noted checklist use is field-specific. Dr. Hurd said the structure could help when reviewing many applications. Several members agreed that checklists provide useful structure to reviewers as long as they are not overinterpreted.
- ***Consolidation of review:*** Dr. Nakamura noted review offices in ICs have about the same number of SROs as CSR, but handle fewer applications.
- ***Abbreviated critiques:*** Dr. Weiner said if critiques become too short, they lose meaning. Dr. Miller agreed, noting they should provide constructive interaction. Dr. Hurd asked about the impact of triage and any scoring differences before and after discussion. Dr. Nakamura said this could be calculated.
- ***Multiple goals:*** Dr. Targan asked whether the workload impact on CSR staff or on external reviewers was more important. Dr. Nakamura said the issue is that a breaking point will be reached and asked for feedback about what to try. In reaction to the idea of eliminating deadlines, Dr. Jennifer West noted applicants would still know when the SRGs meet, so using NSF as a comparison might not be useful.

Closing Comments

Dr. Nakamura thanked the departing members of CSRAC for their service: Dr. Hollingsworth Dr. Weiner, and Dr. Targan, as well as Dr. Paula Hammond and Dr. Steven Mayo who could not attend. He asked CSRAC ideas for feedback and thanked all for their participation.

We do hereby certify that, to the best of our knowledge, the foregoing minutes of the September 25, 2017, 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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Noni Byrnes, Ph.D.
Acting Executive Secretary
Center for Scientific Review Advisory Council

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