DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Office of the Director

Report of the Director's Discretionary Fund
Third and Fourth Quarter of FY 2017

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Report of the Director's Discretionary Fund

Introduction

The following report of obligations for the third and fourth quarters of fiscal year (FY) 2017 has been prepared by the National Institutes of Health (NIH), part of the Department of Health and Human Services (HHS), in response to this request.

"The Committee continues the bill language for specific funds authorized by the Gabriella Miller Kids First Research Act within the CF to support the third year of the 10-year Pediatric Research Initiative. The Committee urges the Director to use a portion of the $10,000,000 made available to the Director's Discretionary Fund (DDF) to support additional pediatric research. The Committee requests, within 30 days after the end of each fiscal year quarter, a quarterly report on DDF obligations for each activity supported. The report should include a description of the program, which ICs are to provide continuation costs, and how this research serves a high priority for pediatric diseases. The quarterly reports shall be posted on-line via the NIH web-site within 30 days after being released to the Committee."

Background

The Director's Discretionary Fund (DDF) is used annually to enable NIH to address high-priority research opportunities and respond to new scientific issues, including through the development of improved management, planning, and analytical tools.

Director's Discretionary Fund
FY 2017
Third and Fourth Quarter Obligations
(Dollars in Thousands)

IC	Approved Projects	Obligations
NINDS	Myalgic Encephalomyelitis/Chronic Fatigue Syndrome ME/CFS)	$1,000
FIC	African Research Consortium (ARC)	$136
OD/OER	World RePORT Enhancements	$150
ORF	Current Good Manufacturing Practice (CGMP) Modular Facility	$2,500
OD/OER	Assessing the Implementation of the NIH Rigor and Reproducibility Policy	$517
OD/OER	Electronic Research Administration (eRA) IT Upgrades	$898
NIDA	Meetings to Address Opioid Epidemic	$150
NIDA	Treatment and Study of Opioid Use Disorders	$3,500
OD/DPCPSI	RNA-Sequencing in the Undiagnosed Diseases Network (UDN)	$500
NINDS	Pain Management Best Practices Inter-Agency Task Force	$50
NHGRI	Global Alliance for Genomics and Health	$150
OD/COSWD	NIH Workplace Harassment and Climate Survey	$55
	Total Obligations as of 9-30-17:	**$9,606**

Projects Supported by FY 2017 DDF during the Third and Fourth Quarters

Myalgic Encephalomyelitis /Chronic Fatigue Syndrome (ME/CFS) Collaborative Research Centers (CRC)

ME/CFS is a debilitating and complex disorder characterized by profound fatigue that does not improve with rest, and may include a range of other symptoms that negatively impact everyday life. The disorder severely impacts the lives of an estimated 800,000 to 2 million Americans, with 25% or more of the individuals either house-or bed-bound. The underlying causes of ME/CFS, however, are unknown and there are currently no diagnostic tests. The ME/CFS Collaborative Research Centers were established to create a network of researchers, clinicians, and patient advocates that will work collaboratively to rapidly advance biomedical ME/CFS research. The Data Management and Coordinating Center (DMCC) was established to facilitate efficient collection, storage, and analyses of data across the Centers.

Funds were obligated to award three CRC grants and one DMCC grant as follows:

- The Cornell ME/CFS CRC will be led by Maureen Hanson, Ph.D. at Cornell University. This Center will investigate the role of the immunological and neurological systems in ME/CFS by obtaining blood samples and conducting brain scans on individuals with ME/CFS before and after exercise testing.
- The Center for Solutions for ME/CFS CRC will be led by W. Ian Lipkin, M.D. at Columbia University. This Center will conduct the most extensive investigation to date examining the potential role of abnormal immune system responses in ME/CFS. The research team will use cutting-edge technology to test for microbial agents, such as viruses and bacteria in ME/CFS.
- The Topological Mapping of Immune, Metabolomic and Clinical Phenotypes to Reveal ME/CFS Disease Mechanisms CRC will be led by Derya Unutmaz, M.D. at the Jackson Laboratory. This Center will examine how the immune, microbiome, metabolic systems interact in ME/CFS.

African Research Consortium (ARC)

A range of African global initiatives are now directed at improving access to effective interventions for major diseases such as AIDS, tuberculosis (TB) and malaria; supporting the development and availability of vaccines; dealing with the increasing importance of non-communicable diseases; and broadening access to health information. However, these efforts confront multiple limitations due to lack of adequate local human capital and infrastructure. Current programs rely on limited existing local capacities, use of expatriate and off-shore consultants, and funding streams that are largely outside the country. This often results in poor integration of the finite human resources available to address the multitude of current and emerging health issues, and a continuing "brain drain" of talent to higher income countries. In the longer term, if leadership of these critical initiatives is to shift to national governments in Africa, supple thinking and greater emphasis must be directed to building sustainable capacity. Among critical priorities, is the need to bring to adequate scale the training of research professionals capable of developing and assimilating knowledge and approaches to prevention and care; incorporating new technologies; and monitoring impact. New tools and delivery strategies must be developed locally that achieve effective coverage in diverse settings.

There are many reasons to be optimistic that now is a critical moment for transformative change. The African-led Alliance for Accelerating Excellence in Science in Africa (AESA), with a substantive budget provided by the Wellcome Trust, the United Kingdom Department for International Development, and the Bill & Melinda Gates Foundation, has the potential to capitalize on African government commitments to science and technology. These include pledges in the Declaration of the African Heads of State (2007), the Algeria Declaration (2008), the Bamako Call for Action (2008), and the African Union Strategic Plan for Innovation and Science. Moreover, a number of pilot experiments by large national funding agencies including NIH and the Wellcome Trust have shown that direct and substantial awards to African institutions can be successful in building capacity and strengthening local leadership across Africa.

In June 2016, the Heads of International Research Organizations (HIROs)—a grouping of twenty-eight of the world's largest health research funding agencies—concluded that we have reached a tipping point where the empowerment of African countries to take charge of their own science, technology, and innovation agenda is compelling, with significant potential benefits in economic growth and job creation. Government leaders in the growing economics of Africa will need to be convinced that this kind of investment will not only advance health in their countries, but also provide a significant economic return on investment.

In light of these developments, AESA, NIH, the Wellcome Trust, and the Bill & Melinda Gates Foundation (ARC's Executive Committee members) organized a private session at the World Economic Forum (WEF) annual meeting January 17-20, 2017, in Davos-Klosters, Switzerland, regarding moving the center of gravity for African research capacity to Africa. The session was chaired by President Aminah Gurib-Fakim of Mauritius and brought together critical partners—African political leaders, corporate and philanthropic funders, and research agencies. Following and building upon the January 2017 WEF-Davos meeting, the Executive Committee will work to obtain informed input and buy in from key thinkers and stakeholders, both at key international meetings where these stakeholders will be present, and through 2-3 consultative meetings held by the different partners. The Executive Committee also expects to meet 3 times (Bethesda, Seattle, and London) for planning purposes. By WEF-Davos 2018, the Executive Committee plans to have a fully developed roadmap proposal to present, with buy in from key government and other stakeholders.

Dr. Francis Collins, with support from Dr. Roger Glass, Director, Fogarty International Center, serve as the key leadership for ARC at NIH with the assistance of a dedicated Project Manager to keep the initiative moving forward and running smoothly.

Funds were obligated to support the payroll costs of a full time Project Manager as well as travel and expenses related to organizing a consultative workshop in Durban, South Africa which resulted in the following deliverables:

- Organized World Economic Forum sessions involving African leadership in January 2017 and May 2017;
- Developed White paper on creative financing mechanisms;
- Formed Leadership Council of public and corporate leader;

- Established pharma leaders working group to create blueprint for coordinated actions to strengthen local research capacity;
- Initiated business plan in coordination with Nairobi-based consultant; and
- Developed scope of work and contracted London School of Economics to generate instructive case studies.

World RePORT Enhancements

The Fogarty International Center (FIC) and the NIH, Office of the Director's Office of Extramural Research have been working with members of the Heads of International Research Organizations (HIROs) to further develop World RePORT, an open access database of projects funded by HIRO members. World RePORT went public after Dr. Roger Glass, provided a demonstration at the HIROs meeting on November 9, 2016.

Funds were obligated to award a contract to implement enhancements to the World RePORT site as follows:

- Enhance the mapped display of multi-component projects, summarizing the multiple locations and details of institutions, investigators, and projects.
- Finalize a system to automatically load data from the UK Gateway to Research for Medical Research Council (MRC) into World RePORT, which can be leveraged towards other funders that publicly list their data in similar ways.
- Collaborate with NIH ICs to add intramural projects with international components, as available.
- Expand the scope of the site to include all indirect projects worldwide.
- Maximize the utility of the site and data by implementing minor enhancements and bug fixes to the site, as recommended by the steering committee and site users.

Current Good Manufacturing Practice (CGMP) Modular Facility

Funds were obligated to implement the design and construction of a Current Good Manufacturing Practice (CGMP) modular facility approximately 3,000 Gross Square Feet (GSF) on the East Terrace of Building 10 (Clinical Center (CC)). The new CGMP facility includes four manufacturing suites, administrative area, storage, and supporting area. It also includes required mechanical and electrical equipment including air handling units and chillers. The project includes the necessary infrastructure to support the facility including, but not limited to, utility connections, staff access, structure, and mechanical, electrical, plumbing and fire protection systems.

This facility will allow the Clinical Center's Department of Transfusion Medicine (CC-DTM) to prove that pre-clinical data to support treatment concepts are sound and these clinical protocols have been through the CCR review process. This will allow these drugs to move into the Investigational New Drug (IND) Applications phase which will in turn allow the NIH to treat many high-risk patients. Additionally, this facility will provide services to the NIH Institutes and Centers to support their intramural clinical trials. These services include (1) performing research aimed at development, evaluation and validation of new manufacturing processes for cellular therapies and (2) manufacture of cellular therapy products for approved clinical trials. The majority of these trials are early phase (I/II) trials not intended to result in the development of a commercial product. To provide these services, the CC-DTM Cell Processing Section (CPS)

operates a core facility for the manufacture, storage and distribution of cellular therapy products. This core facility produces clinical therapies from cells collected from NIH CC patients and healthy donors. The products manufactured by the laboratory are used to treat and often cure NIH CC patients with cancer, hematological malignancies, marrow failure, congenital immune disorders and autoimmune diseases.

The unique nature of these cellular therapy programs requires a separate CGMP facility to maintain segregation and aseptic process. The cellular therapy products manufactured in CPS requires aseptic processing facilities for specific cell population enrichment to achieve a high level of purity and recovery of the cells of interest and/or a high log depletion of the cells to be removed from the product. This modular facility is envisioned as a means to meeting the production needs of the NIH CGMP cellular therapy protocol program.

Assessing the Implementation of the NIH Rigor and Reproducibility Policy

NIH released updated instructions for applications and reviewer guidelines for rigor and reproducibility. The updates clarify the agency's expectations regarding how these issues should be addressed in grant applications. The updates encompass four areas of clarification: scientific premise, scientific rigor, relevant biological variables such as sex, and authentication of key biological and/or chemical resources. All grant applications submitted to NIH after January 2016 are expected to address these four elements in their proposed research.

Funds were obligated in FY 2016 to support a complete evaluation to assess NIH's implementation of the rigor and reproducibility policy. The evaluation (all phases) compared the rigor and reproducibility described in grant applications, and summary statements, pre-policy to post policy.

FY 2017 funds were obligated to support tasks in the original design of the Rigor and Reproducibility Evaluation including the development of an online platform which raters would use to assess applications and summary statements, pilot testing of the evaluation approach, development of a guidance document for raters, recruitment of raters, and redaction and assessment preparations. In spring 2017, the OD's Office of Extramural Research (OER) convened an internal advisory workgroup composed of members of NIH's Planning and Evaluation community to guide the evaluation moving forward. The group identified several concerns with the proposed evaluation. The assessment form remained in preliminary form, and no estimate of expected effect size and variability had yet emerged. Additionally, after 5 rounds of pilot testing, 10 of the 28 criteria were rated by at least one rater as "somewhat or very difficult to assess." Overall, the advisory workgroup questioned the complexity of the evaluation design in several key areas: 1) recruitment, selection, training, and management of hundreds of assessors; 2) large number of variables in the planned analysis; and 3) review of hundreds of scored applications and summary statements. Based upon this feedback, in June 2017, OER issued a stop work order on the Rigor and Reproducibility Evaluation project.

Electronic Research Administration (eRA) IT Upgrades

eRA provides critical IT infrastructure to manage over $30 billion in research and non-research grants awarded annually by NIH and other grantor agencies in support of the collective mission of improving human health. It is critical that NIH has reliable and secure systems that promote

efficient grants management and optimal decision making, while minimizing administrative activities required of grant applicants and recipients.
Funds were obligated to support the following two efforts:

- Supplement larger efforts to redesign the Committee Management module that was initially implemented in 1997 and to upgrade Commons Oracle Internet Directory (OID) that supports user authentication and handles over 600,000 external user accounts.

Meetings to Address Opioid Epidemic

As the leading medical research agency of the U.S. government, NIH is determined to take all possible steps to accelerate research to help end the opioid crisis facing our nation. NIH is doing so by focusing its efforts in three major areas: (1) new and innovative medications/biologics to treat opioid addiction and for overdose prevention/reversal; (2) safe, effective, and non-addictive strategies to manage chronic pain; and (3) neurobiology of chronic pain. At the request of Dr. Francis Collins, the National Institute on Drug Abuse (NIDA) coordinated a series of meetings to address the opioid epidemic. The first meeting took place on June 5, 2017, to stimulate innovative directions in preventing and treating opioid use disorders and overdoses. The second meeting convened on June 16, 2017, to discuss safe effective pain medication. The third meeting was held on July 7, 2017, to provide discussion on the neurobiology of pain. These meetings brought together some of the most creative and innovative experts from industry and academia to discuss scientific strategies with the greatest potential to expedite solutions for the opioid problem. These meetings were not intended to be traditional academic meetings—they focused on vigorous brainstorming opportunities to accelerate progress.

Funds were used to support the travel costs of 80 participants (domestic and international airfare, lodging and all necessary travel expenses) as well as logistical support in preparation for the meetings.

Treatment and Study of Opioid Use Disorders

A total of $2.4 million was obligated to award a grant with the goal of introducing Extended Release Buprenorphine (XR-BUP) into three Emergency Departments (EDs) to initiate treatment for a broad range of patients seen in these EDs, including patients presenting with opioid overdoses or in opioid withdrawal, others requesting opioid treatment, other issues around opioid dependence, and patients with unrelated presentation but who are opioid dependent and for whom an ED visit may be an opportunity to engage in treatment. Aims are (1) to learn about XR-BUP induction across this spectrum of intoxication-to-withdrawal, (2) to learn what resources are needed or need to be developed in the ED (e.g., holding beds or equivalent) and in the community (e.g., providers able to take on BUP maintenance), (3) to collect data on patient-level outcomes (treatment engagement, retention in treatment, overdoses, opioid use, etc.) over a 2-6 month period comparing a group treated with XR-BUP plus a warm-hand-off referral to treatment-as-usual (TAU), and (4) to collect data on provider- and provider-organization- level feasibility and acceptability.

In addition, $1.0 million was obligated to fund the cost of an opioid study on Pharmacokinetic (PK) evaluation of improvised vs. FDA-approved naloxone devices. Anecdotal reports of opioid (primarily fentanyl) overdoses that do not respond to treatment with naloxone have been widely reported in the media. However, as noted by Sharon Hertz (FDA) during the NIH hosted Opioid

meeting held on June 5, 2017 ("Medications Development for Opioid Use Disorders and for Overdose Prevention and Reversal"), there is no actual data on these events, including the type of naloxone device used. Prior to FDA approval of NARCAN® nasal spray, the only nasal naloxone product available was an unapproved "improvised device" consisting of a syringe filled with 2 milliliters of dilute naloxone solution (intended for injection), with the FDA-approved needle replaced by an adaptor to allow aerosolization. Two milliliters is a much greater dosing volume than any FDA-approved nasal product, and although there is no related data, it seems likely that much of the fluid goes down the back of the throat or flows back out of the nostril after the improvised device is used (greatly reducing the amount of naloxone available for nasal absorption). Despite the approval of NARCAN® nasal spray, sale and use of the improvised device continues, and this may be responsible for many overdose deaths that are purported to be "naloxone resistant." Instructions provided with the improvised device say that administration should be repeated in 2 to 5 minutes if there is no response; however, no PK study has ever evaluated 1 vs. 2 administrations of the improvised device. If nasal passages are filled with the maximum possible fluid volume after one administration, then a second administration, 2 minutes later, would only flush out the old fluid and replace it with new (with little change in the amount of naloxone available for nasal absorption). If first responders are under the impression that a second administration of the improvised device will provide a meaningful increase in naloxone plasma levels, this may be false hope. The proposed PK study will provide the first within-subject comparison of naloxone plasma levels following use of the improvised device and 3 different FDA-approved devices, as well as the first comparison of plasma levels following 1 vs. 2 administrations of the improvised device. In total, each subject will receive 5 treatments: 1) one administration of the improvised device; 2) two administrations of the improvised device, ~2 min apart; 3) one administration of 2 mg NARCAN® nasal spray; 4) one administration of 4 mg NARCAN® nasal spray; and 5) one administration of the EVZIO® auto-injector. The tentative plan is to publish the results in a journal that is widely read by emergency responders (TBD), and the results may finally result in discontinued sale/use of the improvised device.

Funds were obligated to award three contracts as follows: (1) an analytical contract to measure naloxone in plasma samples; (2) a clinical services contract to provide help with protocol writing, monitoring, and data analysis/report writing; and (3) a contract to conduct the actual human laboratory study. The contract Task Orders were awarded in September for which the data is anticipated to be available in late 2017 or early 2018, with publication shortly thereafter.

RNA-Sequencing in the Undiagnosed Diseases Network (UDN)

Currently, the Undiagnosed Diseases Network diagnoses ~22% of participants through complete clinical evaluations at the Clinical Sites and collaborative research at the UDN Metabolomics Core, Model Organisms Screening Center, and Sequencing Core resources. Some UDN Clinical Sites have been piloting RNA-Sequencing (RNA-Seq) as an additional component of their evaluations with preliminary success including identifying a second variant not seen in a patient through genome sequencing (UCLA Clinical Site – sequencing revealed paternally inherited pathogenic variant and RNA-Seq identified exon skipping) and work by the Stanford Clinical Site showing that blood can be used as a surrogate for diseases based in other tissues. As a result, funded was needed to run a larger pilot of RNA-Seq in the UDN to assess the impact of adding RNA-Seq to making diagnoses.

Funds were obligated to support an RNA-Seq analyses to the diagnostic assessments of 150 new pediatric UDN patients and their family members. These funds were awarded to the UDN Coordinating Center to distribute to UDN sites for RNA-Seq projects. Data produced from this RNA-Seq pilot will be compared to RNA-Seq data in other databases, including other Common Fund programs such as the Library of Integrated Network-based Cellular Signatures (LINCS), to find similar patients, identify the perturbed biological pathways and design potential approaches to therapy.

Pain Management Best Practices Inter-Agency Task Force

The Comprehensive Addiction and Recovery Act, enacted in July 2016, called for the HHS Secretary to establish a Pain Management Best Practices Inter-Agency Task Force to review, modify and update the best practices for prescribing pain medication and managing chronic and acute pain. The Task Force will function as a Federal Advisory Committee. Its activities will be overseen within the Office of the Assistant Secretary for Health (OASH).

Funds were transferred to OASH to support a portion the funding required for implementation of the Task Force's operations.

Global Alliance for Genomics and Health (GA4GH)

Sharing genomic and clinical data supports research in many ways. For example, studying the genetic contributions to common diseases requires large sample sizes, which are obtained by combining data from many studies. To understand the effects of variants associated with disease, it is valuable to examine the phenotypes of many people with those variants. The Global Alliance for Genomics and Health (GA4GH) is an international organization that aims to establish a framework for effective and responsible data sharing. They convene an international set of experts to develop technical approaches for data standards and sharing methods, as well as the policy frameworks to allow data to be shared between countries while protecting patient privacy. Examples of successful demonstration projects within the GA4GH include the Beacon, Matchmaker Exchange, and Breast Cancer (BRCA) Challenge projects. This work aligns with NIH's interest in promoting the integration of many NIH-funded data sets with each other and with data sets supported by other organizations, to allow discoveries to be made that cannot be made in individual data sets.

Funds were obligated to support the planning, coordination and communication of GA4GH activities, including two meetings and more than 600 calls.

NIH Workplace Harassment and Climate Survey

With increasing reports of sexual harassment in academic science, NIH has pledged to "identify the steps necessary to end this [sexual harassment] in all NIH-supported research workplaces and scientific meetings" (Nature, 531, 35; 2016). The first step in the identification process is to look within and investigate the prevalence and severity of workplace harassment and sexual harassment within NIH and their impact on people's careers and decision to stay in science.

The NIH Chief Officer for Scientific Workforce Diversity (COSWD), in collaboration with the OD's Office of Intramural Research, Office of Extramural Research, and Office of Equity Diversity and Inclusion, is launching a Trans-NIH Workplace Climate and Harassment Survey, and intends to survey all employees, contractors, fellows/trainees, and volunteers to assess the extent and severity of workplace harassment and sexual harassment at NIH.

The success of the survey depends on complete assurance of anonymity and privacy. Although COSWD is assuring complete anonymity and confidentiality on the online version of the survey, some may still be hesitant to complete the survey. Another way to assure anonymity is to offer a paper-pencil version of the survey that respondents can complete and mail-in. Similarly, COSWD can also provide a pdf version of the survey that respondents can download, print, and mail with pre-paid postage.

Funds were obligated to support the creation of a paper and pdf version of the survey, postage, mailbox hosting, and data entry.