U.S. Department of Health and Human Services
National Institutes of Health

Minutes of the Fourth Joint Meeting of the National Advisory Council on Alcohol Abuse and Alcoholism, National Advisory Council on Drug Abuse, and National Cancer Advisory Board

February 11, 2016
Rockville, Maryland

Members of the National Advisory Council on Alcohol Abuse and Alcoholism (NIAAA), National Advisory Council on Drug Abuse (NIDA), and the National Cancer Advisory Board of the National Cancer Institute (NCI) convened for their fourth joint meeting on February 11, 2016, in Rockville, Maryland. Chaired by Dr. George Koob, Director of NIAAA, and Dr. Nora Volkow, Director of NIDA, this open session convened at 9:03 a.m.

National Advisory Council on Alcohol Abuse and Alcoholism Members Present:

Carmen E. Albizu-Garcia, M.D.
Carol A. Casey, M.D.
Carlo C. DiClemente, Ph.D.
Thomas Donaldson
Karen Drexler, M.D. (Ex Officio)
James H. Eberwine, Ph.D.
Joseph Thomas Flies-Away, J.D., M.P.A.
Paul J. Gruenewald, Ph.D.
Paul Kenney, Ph.D.
Joe L. Martinez, Ph.D.
Sarah N. Mattson Weller, Ph.D.
Robert O. Messing, M.D.
Patricia E. Molina, Ph.D.
Adolf Pfefferbaum, M.D.
Arun J. Sanyal, M.D.
Rajita Sinha, Ph.D.
Frank A. Sloan, Ph.D.
Constance M. Weisner, D.R.P.H.

National Advisory Council on Drug Abuse Members Present:

Anne C. Andorn, M.D.
Judith D. Auerbach, Ph.D.
Laura J. Bierut, M.D.
Julie A, Blendy, Ph.D.
Regina M. Carelli, Ph.D.
John Carnevale, Ph.D.
Arthur T. Dean
Marie Gallo Dyak (ad hoc)

Jay N. Giedd, M.D. (ad hoc)
Lisa A. Marsch, Ph.D. (ad hoc)
Edward V. Nunes, M.D. (ad hoc)
Robert G. Rancourt, J.D. (ad hoc)
Eric M. Verdin, M.D.

National Cancer Advisory Board Members Present (via telephone):

Peter C. Adamson, M.D.
Yuan Chan, M.D.
Deborah Watkins Bruner, R.N., Ph.D
Judy E. Garber, M.D.
William R. Sellers, M.D.
Max S. Wicha, M.D.

Chairs: George Koob, Ph.D., and Nora Volkow, M.D.

National Institute of Alcohol Abuse and Alcoholism (NIAAA) Director: George Koob, Ph.D.

National Institute on Drug Abuse (NIDA) Director: Nora D. Volkow, M.D.

Acting NIAAA Deputy Director: Patricia Powell, Ph.D.

NIDA Deputy Director: Wilson Compton, M.P.E., M.D.

NIAAA, Director, Office of Extramural Activities: Abraham P. Bautista, Ph.D.

NIDA, Director, Division of Extramural Research: Susan B. Weiss, Ph.D.

NCI, Director, Division of Extramural Activities: Paulette S. Gray, Ph.D.

NIDA Senior Staff: Joellen M. Austin, M.P. Aff., M.S.M.; Carlos Blanco, M.D., Ph.D.; Cheryl Boyce, Ph.D.; Kevin Conway, Ph.D.; Dave Daubert; Gaya Dowling, Ph.D.; Roger Little, Ph.D.; Ivan Montoya, M.D.; Joni Rutter, Ph.D.; Phil Skolnick, Ph.D., D.Sc.; Jack Stein, Ph.D.; Mark Swieter, Ph.D.; Betty Tai, Ph.D.

NIAAA Senior Staff: Vicki Buckley, M.B.A; Ralph Hingson, D.Sc.; Robert Huebner, Ph.D.; Gary Murray, Ph.D.; Antonio Noronha, Ph.D.; Kenneth Warren, Ph.D.

NCI Senior Staff: Robert Croyle, Ph.D.; Michele Bloch, M.D., Ph.D.; Glen Morgan, Ph.D.

Additional Participants

Seventy-seven observers joined the meeting, including representatives of constituent groups, liaison organizations, and members of the general public.

Call to Order and Introductions

Dr. Nora Volkow, NIDA Director, called to order the fourth joint meeting of the National Advisory Councils of NIAAA, NIDA, and NCI in open session at 9:03 a.m. on Thursday, February 11, 2016. She noted how rapidly the partnership of the three Institutes has coalesced over two years, and thanked Council members for their contributions. Council members and Institute leaders introduced themselves.

NCI Director's Presentation

Dr. Croyle presented an overview of tobacco control research at NCI, which is one of the prime areas of its collaboration with NIAAA and illustrates how NCI's work complements that of NIAAA and NIDA. NCI is the only Institute or Center (IC) that has a Presidentially-appointed director, originating in the 1971 Cancer Act which assigned NCI some special authorities, including the Frederick National Laboratory for Cancer Research in Frederick, MD, and bypass legislation, which allows NCI to release its own budget request, in addition to the President's budget request. For the past several years, tobacco research has been an important component of the bypass budget. In the Congressional justification for the President's Fiscal Year (FY) 2017 budget request, there is a focus on smoking cessation representing the work of several ICs, including NIDA; it also emphasizes low-income populations.

NCI's tobacco use research is concentrated in the Tobacco Control Research Branch, rather than being spread across portfolios as it is at other ICs. The NCI Board of Scientific Advisors established a Tobacco Control Working Group, which was co-chaired by Michael Fiore, M.D., University of Wisconsin, and Robin Mermelstein, Ph.D., University of Illinois at Chicago, to develop a set of tobacco research priorities for NCI in the context of what other agencies are doing. Their report will be presented in late March, 2016.

NCI contributes a strong research infrastructure to support the Collaborative Research on Addiction at NIH (CRAN) initiative. Elements of the infrastructure include 69 NCI-designated cancer centers across the country; the National Clinical Trials Network (NCTN) with over 3,000 clinical recruitment sites that focus on cancer patients, and can be leveraged to address issues of addiction, tobacco use and other drug use among the cancer patient and cancer survivor population; cancer epidemiology cohorts enrolling about 1.6 million individuals; and cancer registries that cover about 30% of the population and are currently being expanded to include NCI's specimens collection, electronic health records, and epidemiological data, to support health services research.

Currently NCI's Tobacco Portfolio is unique among ICs in its policy focus. In recent years, it has focused less on prevention than on cessation. In 2015, 43 grants (43.4%) emphasized a special population, such as low income populations, racial/ethnic minorities, members of the military, youth/young adults, pregnant women, and comorbid conditions, among others.

NCI is solely responsible for research on tobacco in cancer patients, who are often highly addicted to tobacco. A new Request for Applications, RFA CA-15-011, seeks to generate a greater number of cessation strategies among patients undergoing lung cancer screening using low dosage computed tomography, a rapidly expanding technology.

There is also a proposed Program Announcement with Review (PAR) on Improving Smoking Cessation in Socioeconomically Disadvantaged Populations via Scalable Interventions. Other research priorities include cancer communication, such as the CRAN program on new media research; predicting

behavioral responses to population-level cancer control strategies; cancer-related behavioral research through combining existing data; dual and poly tobacco product use among youth and young adults; and second hand smoke policy research.

NCI also conducts activities to support research, such as its ongoing NCI Monograph series and supporting supplements to journals such as *Tobacco Control*. The Institute also manages smokefree.gov, which is one of the smoke-free e-Health projects.

NCI established the State and Community Tobacco Control (SCTC) Research Initiative in 2009 to address high-priority research gaps in state and community tobacco control research, including secondhand smoke policies, tax and pricing policies, mass media countermeasures, community and social norms, and tobacco industry marketing and promotion and company practices.

NCI also plays a prominent role in collecting data about tobacco use trends. These activities include supporting the tobacco use supplement in the Current Population Survey that collects national, state, and sub-state level data on tobacco use patterns, policies, and attitudes. Data collected in 2014-15 (co-sponsored by the Food & Drug Administration [FDA]) will be released to the public in the fall of 2016 and is available for secondary analysis. The Health Information National Trends Survey (HINTS) collects data about the use of cancer-related information; it is also available for secondary analysis.

NCI is also active in global research on tobacco. Its Center for Global Health co-funds grants with Fogarty International Center and the U.S. Agency for International Development, and participates in tobacco-related initiatives of the World Health Organization (WHO). The Vice President's Moonshot cancer research initiative, which was announced in January 2016 during President Obama's State of the Union address, has been launched and received media coverage. Its Task Force met on February 1, 2016, for the first time. NCI is developing opportunities for public input and a set of plans for the end of this year. Although this initiative began late in the current administration, the hope is that it will lay the groundwork for an expanded cancer research effort across NCI and the federal government.

NIAAA Director's Presentation

Dr. George Koob began his presentation with a review of NIAAA's goals and activities, including the obtaining of FDA approval of more medications for alcohol use disorder (AUD); implementation of effective behavioral treatments for AUD; implementation of effective prevention strategies for adolescent drinking; implementation of effective prevention strategies for drinking during pregnancy; development of effective treatments for fetal alcohol spectrum disorders (FASD); elimination of alcohol-related HIV pathology; development of effective treatments for alcoholic liver disease; appropriate treatment of co-morbidities associated with AUD; successful recruitment of young investigators to the alcohol field; elimination of disparities in the alcohol field; and equal pay for women and minorities in the alcohol field.

To accomplish these goals, NIAAA is developing a strategic plan for 2016-2020, guided by four priorities: Identifying the basic mechanisms of alcohol action and alcohol-related pathology; tracking, preventing, and diagnosing alcohol misuse, AUD, and alcohol-related consequences; developing and improving treatments for AUD, co-occurring disorders, and alcohol-related consequences; and strengthening the public health impact of NIAAA-supported research. The report also has four cross-cutting themes: Addressing alcohol misuse across the lifespan, addressing co-occurring disorder, advancing precision medicine (previously called individual differences), and reducing health disparities.

NIAAA has embraced the consortia concept for initiating and strengthening priorities in the Institute. The consortia help NIAAA focus its priorities, bring in new people to the alcohol research field, and stimulate new research, including the development of new R01s. They include:

The Collaborative Initiative on FASD (CIFASD): A multi-disciplinary consortia of clinical and basic science projects, the goal of this initiative is to improve capabilities in FASD clinical case recognition, interventions and prevention through structural & functional brain imaging; neurobehavioral phenotypes; 3D facial imaging; and nutritional therapeutics.

Collaboration on FASD Prevalence (CoFASP): The goal of CoFASP is to determine a prevalence rate for FASD among young children within defined geographical areas of the country, using case ascertainment methodology.

Neurobiology of Adolescent Drinking in Adulthood (NADIA): This consortium looks at the neurobiological mechanisms by which alcohol affects the developing adolescent brain. New research is looking at specific brain changes and where they occur.

National Consortium on Alcohol and Neurodevelopment in Adolescence (NCANDA): With a goal of studying the impact of alcohol on brain structure and function during adolescence and into early adulthood, NCANDA operates at five sites across the country. It has successfully recruited 831 adolescent participants who are now beginning their third longitudinal follow-up assessment. Early results indicate that those adolescents who are heavy alcohol consumers are demonstrating untoward effects on their brains' structural development.

Adolescent Brain Cognitive Development (ABCD): Launched in September 2015, ABCD is the largest long-term longitudinal study of cognitive and brain development in children in the U.S. to date.

Integrated Neuroscience Initiatives on Alcoholism Consortium (INIA). This consortium is a merger of the INIA Stress and INIA Neuroimmune consortia. INIA Stress' s goal is to elucidate adaptations to chronic alcohol in corticolimbic and corticostriatal brain circuitry and to understand synaptic mechanisms that underlie altered response to stress, which in turn can facilitate the transition from moderate/controlled drinking to excessive and habitual drinking. INIA-Neuroimmune's goal is to identify the genomic, cellular, and behavioral neuroadaptations related to excessive alcohol consumption, focusing on the importance of neuroimmune and inflammatory signaling systems in promoting and maintaining excessive drinking; and to use this information to determine & test medication(s) in the treatment of an AUD.

Collaborative Study on the Genetics of Alcoholism (COGA): This long-term study examines the genes that may contribute to the heredity of alcoholism.

Alcoholic Hepatitis Consortia: This initiative is composed of four individual consortia. The goals are: 1) to advance the understanding and treatment of alcoholic hepatitis (AH); and 2) to identify and test new mechanisms and strategies for the treatment of AH. An important question facing the field is what should be the guidelines for liver transplants e among those with alcoholic liver disease

Consortia for HIV/AIDs and Alcohol-Related Research Trials (CHAART): This program is made up of five individual consortia across the country, CHAART's goal is to advance operations or implementation

research in the context of alcohol and HIV/AIDS in order to develop a broader systems approach for monitoring complex HIV and alcohol-related morbidity and mortality; and to intervene to reduce the impact of alcohol and HIV disease progression and transmission.

Other programs ongoing at NIAAA independent of the Consortia framework include the following:

NIAAA Medications Development Program: The NIAAA Division of Medications Development, created in 2015, supports human laboratory screening studies to bridge the gap between preclinical and clinical trials; a Small Business Innovation Research/Small Business Technology Transfer (SBIR/STTR) program to facilitate studies leading to the development of an Investigational New Drug (IND) application; and the operation of the NIAAA Clinical Investigations Group (NCIG) to streamline the AUD medications development process. NIAAA's intramural program also conducts clinical studies on novel compounds with AUD treatment potential.

Wearable Alcohol Biosensors: This initiative seeks to promote the design and production of a wearable device to monitor blood alcohol levels in real time for use in research, clinical, and treatment settings and for individual health monitoring. NIAAA has launched a design competition; eight entries are currently being judged. It has also awarded six SBIR grants.

Stages of the Addiction Cycle (Associations with Neurocircuits & Addictions Neurochemical Assessment): Dr. Laura Kwako from NIAAA's intramural program is working on new ways to diagnose AUD using a research domain criteria approach where the domains form the framework of the addiction cycle. The objective is not to replace DSM-5, but to develop a heuristic framework using neuropsychological measures, imaging and biomarkers.

CollegeAIM: Launched in the fall of 2015, CollegeAIM is an evidence-based resource from NIAAA that guides colleges to strategies to address harmful and underage student drinking. Regional workshops about how to use CollegeAIM will occur in 2016.

Surgeon General's Report on Substance Use, Addiction, and Health: NIAAA and NIDA have played major roles in the development of the first Surgeon General's Report on Substance Use, Addiction, and Health, to be released in 2016. The report will present the state-of-the-science on alcohol and other substance misuse from the perspectives of neurobiology, prevention, treatment, recovery, and delivery of care. It will provide a comprehensive review of the research literature on alcohol, drugs, and health; outline potential future directions; and educate, encourage, and call upon all Americans to take action.

Publications: An NIAAA priority is to educate and inform health care professionals and the public about the effects of alcohol and treatment options. Publications are available on the NIAAA website.

Discussion: Mr. Robert Rancourt noted the central role that alcohol and drug use plays in the criminal justice system and the scarcity of resources to address the issue. He asked if NIAAA had established protocols for early intervention/treatment within the justice system and if it had reached out to the judiciary to share them. Dr. Koob responded that NIAAA has not yet done so, but the issue has been raised in Council discussions and he expects it will be part of the NIAAA strategic plan. Dr. Volkow explained that NIDA has a research network in the judicial system, which is now focused on juvenile offenders. This could provide an infrastructure for disseminating information. Dr. Arun Sanyal pointed

out the critical need to translate basic research into implementation in the field. Dr. Koob said NIAAA is working with other government agencies, such as the Substance Abuse and Mental Health Services Administration (SAMHSA), the Office of National Drug Control Policy (ONDCP), and the Center for Disease Control (CDC) to accomplish this goal.

NIDA Director's Report

Dr. Volkow's presentation focused on emerging trends and changes in policies as they relate to alcohol, tobacco, and other drugs of abuse. Marijuana use is one of three extremely important issues for NIDA, and a large summit, hosted by multiple NIH ICs is planned on this topic on March 22-23. The other two priority issues that NIDA is facing are an opioid abuse epidemic and the rise of electronic cigarettes.

Although NIDA's funding has increased, its actual buying power is the same as it was in 1999 after taking inflation into account. Today, only about one in five grant applications is funded. This forces NIDA to focus its grant making on research that has the highest likelihood of impact on substance use disorders.

Data from the 2015 Monitoring the Future (MTF) survey of high school students (8^{th}, 10^{th}, and 12^{th} graders), which includes ~ 45,000 participants from schools across the Country, revealed that overall trends in 2015 were in a positive direction, many with large effect sizes. Over the past five years, the survey has shown decreases in illegal and legal drug use, except for marijuana. For tobacco smoking, there has been a 50% decrease over the past five years. More students report past month use of marijuana than tobacco. There are also decreases in alcohol use, but these are not as steep as those for tobacco. And for both alcohol and marijuana, there is not a clear sense of how much people are using. For alcohol, we suspect that the amount consumed is increasing, since adverse consequences (ER admissions, overdoses) are increasing. Dosage is important to establish because the amount consumed will determine the downstream consequences.

Electronic cigarettes became popular among teens recently. About 18% of teens have used e-cigarettes in the past month. NIDA and NCI have discussed initiating clinical trials to evaluate whether electronic cigarettes can function as smoking cessation aids since there are currently no data from randomized clinical trials (RCTs) on this topic. Two studies on adolescent use of e-cigarettes have been published, one by Leventhal in the *Journal of the American Medical Association (JAMA)* in 2015, and one by Wills and colleagues in *Tobacco Control* in 2016. Both show that adolescent e-cigarette users are more likely to smoke tobacco than non-users.

A troubling trend is the rising morbidity/mortality rate among white non-Hispanic Americans. A 2015 study by Deaton and Case in the *Proceedings of the National Academy of Sciences* showed that mortality among middle-aged whites began increasing for the first time in the United States in 1998, after several years of decrease. Chronic liver disease, suicide, and poisonings (mostly opioid) are the factors driving this trend. A major challenge facing NIDA is the opioid prescription epidemic. A study by Pierce and others in *Addiction* using data from England reported an increase in deaths from drug-related poisoning. The data indicate that if someone not in treatment, his or her chance of experiencing an overdose is twice that of someone who is in treatment. It also showed that medications are important for preventing overdoses.

Dr. Volkow highlighted two approaches from NIDA's Medications Development Division that reflect our priorities. The first is the development of a naloxone nasal spray that was approved by the Food and Drug Administration (FDA) in 2015. It is inexpensive ($37.50/dose) and easy to use for reversing an

opioid overdose, if it is given soon enough. The second, not yet approved by the FDA, is an extended release subdermal formulation of buprenorphine (Probuphine®), which will also facilitated the treatment of opioid addiction, since it requires dosing only once every 6 months. The FDA will review it again at the end of February.

Dr. Volkow also mentioned the ABCD study, which will be discussed further by Dr. Dowling later in the session. NIDA released its 2016-2020 Strategic Plan in December 2015, which is available on the NIDA website.

Discussion: Dr. Judith Auerbach asked if the three ICs are looking at self-controlled medical monitoring devices as part of the "big picture." Dr. Volkow responded that each IC has initiatives to develop devices to track intake and provide biofeedback to achieve better outcomes. Dr. Koob agreed that this was an important area of development. Dr. Croyle noted that there have been mixed results in past atheoretical e-Health studies. Dr. Volkow suggested that SBIR/STTR funding is one area where the ICs could collaborate on this research. Ms. Marie Dyak noted that the field is moving from prevention to harm reduction to self-regulation. Such devices could be helpful; however, she also noted the designated driver model as an analogy, which can also unintended consequences (implicit OK for heavy drinking among those not driving).

Dr. Carlo DiClemente asked if integration of research on multiple substances will be reflected in new Requests for Proposals. Dr. Susan Weiss responded that CRAN is starting to develop Funding Opportunity Announcements that involve participation from all of the institutes. Dr. DiClemente recommended that applicants should be encouraged to collect data that might be used across other topics, even in FOAs that address a specific substance. Dr. Volkow pointed out this would be a good opportunity for supplements.

Dr. James Eberwine stated that a big problem in the past has been underpowered studies. If hypotheses are generated but studies aren't publishable, can they be made public in other ways so that researchers can use the data? Dr. Volkow replied that the ICs are aware that creating registries of databases may be useful but also expensive. It is important that the data be of sufficient quality, and that the dataset that is created is used. NIH can't make all data accessible because of cost, but the agency is open to discussions of the value of particular datasets.

Dr. Laura Bierut noted that she sits on the Big Data to Knowledge (BD2K) Council and wondered how the Institutes are thinking about their interaction with BD2K. Dr. Volkow responded that the ABCD and the Precision Medicine Initiative provide opportunities for the ICs to contribute. Dr. Koob stated that Dr. Philip Bourne, NIH Associate Director for Data Science, has been reaching out to the ICs on this topic, and NIAAA is actively working on these issues. Dr. Croyle noted greater interaction between the ICs and BD2K can be anticipated; a broader challenge 10-15 years out is integration of NIH data with the data systems of healthcare organizations outside the government.

42 CFR & Precision Medicine

Dr. Volkow introduced Dr. Maureen Boyle, Chief of the Science Policy Branch in NIDA's Office of Science Policy and Communications. Dr. Boyle's presentation focused on including sensitive data and vulnerable populations in the NIH Precision Medicine Initiative (PMI) cohort program, an initiative to build a national research cohort of one million or more U.S. participants in order to advance research to

develop personalized disease treatment and prevention interventions that takes into account individual variability in genes, environment, and lifestyle.

Sensitive data and vulnerable populations are critical to include in the long-range implementation of the PMI Cohort Program since NIH is seeking a nationally representative dataset. If the technological infrastructure for the PMI Cohort Program is built without considering all possible use cases, it may be difficult to retrofit the system to include vulnerable populations later leading to a biased data set. This has the potential to exacerbate health disparities.

There is a complicated regulatory framework that must be addressed. Federal and state regulations on health information privacy and research pose challenges for inclusion of substance use disorder (SUD) treatment data (42 CFR Part 2); specialty mental health treatment data (laws vary by state); incarcerated populations (45 CFR Part 46, Subpart C); children and adolescents (45 CFR Part 46, Subpart D); and people who are decisionally impaired (45 CFR Part 46). Three PMI Cohort Program workgroups are addressing these issues, including one on sensitive data and vulnerable populations, chaired by Dr. Boyle; one on addressing state laws; and one on policy issues related to PMI.

SAMHSA is currently updating the substance use disorder treatment confidentiality regulations – 42 CFR Part 2. The original law was written in 1975 and the regulations were last updated in 1987. Since then, significant changes have occurred within the U.S. health care system that were not envisioned by these regulations, including new models of integrated care and expansion of electronic health records. A Notice of Proposed Rulemaking (NPRM) on 42 CFR Part 2 was released on February 9, 2016, with comments due by April 11, 2016. SAMHSA's goal is to have regulations in place by the end of the current administration, but the rule is very controversial so this may not be feasible.

The purpose of the statute and regulations is to encourage patients to seek substance abuse treatment without fear that by doing so their privacy will be compromised. It is not meant to prevent information sharing but to set the standards for how to share. With limited exceptions, patient consent must be obtained before sharing information from a substance use disorder treatment facility that is subject to 42 CFR Part 2. There is an exception for research but the current provision has limitations. This regulation applies to any Federally-assisted individual or entity that "holds itself out as providing, and provides, alcohol or drug abuse diagnosis, treatment or referral for treatment." They govern any "communication of patient identifying information, the affirmative verification of another person's communication of patient identifying information, or the communication of any information *from the record* of a patient" (42 CFR 2.11). Even acknowledging that an individual is (or was) a patient at a Part 2 facility is a breach of the regulations.

There are nine required elements of a 42 CFR Part 2 compliant consent form, including who the information is coming from and to whom it will be released, patient name, disclosure purpose, amount and kind of information to be disclosed, signature, date, statement of revocation, and expiration conditions. These requirements can create problems with health information exchange and coordinated care organizations whose memberships are not static. The proposed updates to the regulations are intended to address this issue.

For the PMI, there are three issues of relevance related to 42 CFR Part 2. The first is the identification of the medical/treatment facilities to which 42 CFR Part 2 apply; the rule affects those who hold themselves out as providing alcohol and drug abuse treatment. This status can change over time, depending on how the facility advertises itself. The second is the release of Part 2 data to qualified

researchers; currently only the Part 2 program director can release data for research purposes, organizations that have data sets the include data from multiple Part 2 programs do not have the authority to release data to qualified researchers. Under the proposed rules, those in lawful possession of Part 2 data may now make the determination to disclose the data to qualified researchers who meet certain requirements under the Health Insurance Portability and Accountability Act (HIPAA) and the Common Rule. The third issue involves consent; under the proposed rules, the consent form can use a general designation of "treating provider," in the 'to whom' section. However the use of the general designation is limited to the sharing of information when a treatment provider relationship exists with the patient.

PMI needs to start by addressing the current regulations; however, it should also follow the new ones so they can adapt quickly when needed. The Advisory Committee to the Director (ACD) Proposal Registry for PMI is a hub and spoke model with the hub being core data and the spokes addressing more specialized information. In this hybrid data model, different levels of access based on data needs and security capabilities will be determined by a resource access subcommittee. Under the current rule patient consent would be required to contribute information to the registry and an additional consent would be required to send personally identifiable substance use disorder treatment information to any researchers not named in the original consent. Under the proposed rule the PMI registry would be a lawful holder of the Part 2 data and could make the determination to share the data with a qualified researcher as discussed above.

The implications of the regulations governing specific special populations, i.e., the incarcerated, adolescents, and the decisionally impaired, are currently being considered as well. There are IRB requirements about addressing the needs of those populations, so NIH needs to address these use cases within the context of the PMI Cohort Program. How the regulations are ultimately interpreted with be important.

Discussion: Dr. Lisa Marsch commented that the new rules are important in terms of the changing health care landscape and the integration of alcohol/drug treatment into general medical treatment. People are concerned about data integration/segmentation in the context of the primary care setting. How does one get around this challenge? Dr. Boyle responded that in her experience working on this issue at SAMHSA, compliance with 42 CFR Part 2 while integrating care depends on how organizations are structured. If behavioral health treatment is part of general health care, it's not covered under Part 2 but under HIPAA regulations. If one provider's primary function in a practice is to address substance use disorders, then their treatment records are protected by 42 CFR Part 2 and the electronic health record (EHR) has to segregate that data so it doesn't get shared without proper consent. So it's easier if it's built into the workflow to begin with, e.g., to have patients sign consent forms at the beginning of treatment.

Dr. Beirut stated that the field needs to change its thinking because everything needs protection, e.g., HIV status, pregnancy. Mental health is no different from any of those; behavioral health is part of health in general. The separation in general creates stigma, lack of research, etc. Dr. Boyle noted that behavioral health is different because of criminal and civic concerns, e.g., the data an individual gives to his or her doctor can't be used against the individual criminal case, by employers, in child custody decisions, etc. HIPAA doesn't provide that. It would be good to have one central set of standards that governs all sensitive health data so that organizations can implement one process to address them all and health information technology can be designed to address the single standard instead of having to

meet various standards across states. In addition, legislation that would protect patient reported information would go a long way, e.g., anything people tell their doctor can't be used against them.

Dr. DiClemente noted that SAMHSA is encouraging everyone to screen for a variety of substances. How does that initiative fit the new regulations? Dr. Boyle responded that Part 2 protection depends on the type of provider. A person is not protected if he or she is not part of a substance use disorder treatment program that is covered by 42 CFR Part 2, most general healthcare providers who would providing screening and brief intervention are not covered.

Ms. Dyak asked if training is provided to the health care team before the implementation of the new rule so they understand issues like stigma. Dr. Boyle explained that many organizations provide training and the Legal Action Center has a series of online training webinars. However, training is not mandated.

Dr. Volkow called for a 15 min break at 11:15 a.m. The meeting reconvened at 11:33 a.m.

Update on the Common Rule

Dr. Volkow introduced Taunton Paine, Science Policy Analyst at the NIH Office of Science Policy. Mr. Paine provided an overview of proposed changes to the Common Rule, i.e., regulations for human subjects' protection, which is followed by 18 Federal departments and agencies.

There have been dramatic changes in research since the Common Rule was established in 1991, including an expansion in clinical trials, more research conducted in clinical settings, more studies involving multiple institutions, greater scientific data sharing, and increased ability to extract information from biospecimens. Further, new initiatives such as PMI rely on a more participatory model of research.

Therefore, the two main goals of the proposed updates are to 1) enhance safeguards and respect for research participants and 2) simplify the current oversight system and reduce inappropriate administrative burdens. To accomplish these goals, the proposed new Rule includes six major reforms: matching oversight to the level of risk; requiring consent for research with biospecimens; allowing broad consent; simplifying consent documents; increasing privacy and security safeguards; and streamlining Institutional Review Board (IRB) review of research.

Matching Oversight to Level of Risk: The new Rule proposes to expand the scope of the Common Rule by covering clinical trials that are not currently subject to Federal regulation, including those conducted at an institution that received federal funding for non-exempt human subjects research and those conducted at U.S. institutions. The proposed Rule excludes activities that are considered 1) not to be research (e.g., collection of data and biospecimens for intelligence, national security and/or criminal justice; public health surveillance); 2) low-risk research (e.g., educational tests, surveys); 3) low-risk research with adequate protection (e.g., research covered under HIPAA or subject to requirements for notice and protections in by the Paperwork Reduction Act, E-Government Act, and Privacy Act); and 4) low-risk biospecimen research (e.g., non-identified biospecimens that will not reveal new information about an individual). There are also exemptions for some types of low-risk research, research with sensitive information, and biospecimens with identifiable data, provided specific protections (e.g., safeguards to protect information, limited IRB review) are in place. Special conditions apply for research with children, pregnant women and neonates, and prisoners.

Requiring Consent for Biospecimens: A change in the definition of a human subject requires consent for the collection, use, and analysis of biospecimens for research. The NPRM includes two alternative proposals for when consent is required: 1) for the generation or use of whole genome sequence data, whether identifiable or not; and 2) for the generation or use of data that is unique to an individual and could be used to identify that person if combined with publicly-available data. IRB waivers of consent for biospecimen use have new criteria added, and are expected to be rare.

Allowing Broad Consent: The proposed new Rule allows and defines broad consent for the collection and use of biospecimens and identifiable information for future, unspecified research. Broad consent elements will include a general description of the types of research that may be conducted, a description of the scope of the consent, the time period for availability for secondary research, a statement that participation is voluntary and may be withdrawn, and an option to decline inclusion of non-identifiable data in a public database.

Simplifying Consent Processes and Documents: Informed consent documents must first include the required elements of consent and participants must receive information that a reasonable person would need to make an informed decision about participation, as well as an opportunity to discuss that information.

Increasing Privacy and Security Safeguards: For biospecimens and identifiable data, research would be required to follow specific measures that will be published by the Secretary of Health and Human Services or those required by HIPAA. Sharing would be permitted if specific conditions were met.

Streamlining IRB Review: Institutions engaged in multi-site research located in the United States must rely on a single IRB of record. OHRP would be able to take compliance action directly against IRBs, which means that IRBs, rather than the research institutions, would be responsible if IRBs fail to follow the regulations. IRBs will no longer review grant applications and continuing review would be eliminated for research eligible for expedited research and studies that progressed to data analysis only or accessing follow-up data from standard clinical care.

Almost 2,200 comments were submitted during the public comment period on the NPRM that closed on January 6, 2016. Consideration of public comments is currently underway prior to development and publication of the final Rule. Provisions of the new Rule will become effective one year after publication, with the exception that compliance with new consent requirements for biospecimens and a mandate for a single IRB in cooperative research will be three years after publication.

Discussion: Dr. Eberwine inquired about how the Common Rule deals with metadata regarding biospecimens. Mr. Paine replied that it doesn't treat such data separately. What matters is if the data is identifiable or not. If it's not identifiable, then there are no new requirements. Judge Flies-Away noted that some tribal organizations have their own IRBs and their own regulations about data sharing.

CRAN Update

Dr. Peggy Murray, Office of the Director, NIAAA, and Dr. Susan Weiss, Director of Extramural Research, NIDA, updated meeting participants on Collaborative Research on Addiction at NIH (CRAN) in 2016.

Dr. Murray began by reviewing the CRAN mission. She shared the CRAN website and highlighted the CRAN Blog that can be found there.

In May, NIH brought together 80 CRAN grantees who received supplemental awards covering diverse areas from basic science to clinical environmental research, along with NIAAA, NIDA, and NCI program staff. An interesting lesson was that the grantees from these diverse areas admitted that they would likely not have come to the meeting had they not been required to do so, because they generally don't interact with those in other research realms. Another important comment from the grantees was that CRAN has elevated the status of doing polysubstance work, often not previously seen as valuable. Other comments encouraged a change in programs and reviews at NIH regarding the value of polysubstance use research.

A CRAN-sponsored RFA on "Using Social Media to Understand and Address Substance Use and Addiction" addressed using social media as surveillance tools to better understand the epidemiology, risks, attitudes, and behaviors associated with alcohol, tobacco, and other drug use, as well as studies on the use of social media in intervention research. NCI took the lead on the RFA, with support from NIAAA and NIDA staff. It received numerous applications and 11 awards were made in September 2014. In June 2015, an introductory webinar was held; and the first grantee meeting will occur on June 22-23, 2016.

IN FY15, two program announcements (PA 15-035 and PA 15-036) were released on improving adolescent and young adult substance abuse treatment and prevention, by targeting behavioral mechanisms such as impulsivity and sensation seeking relevant to substance abuse. There has not yet been a lot of response from the research community.

The CRAN committee has developed workgroups to develop additional Program Announcements, including: Implementation of System-Level Changes to Improve Substance Abuse Treatment and Prevention; Target Assessment, Engagement, and Data Replicability to Improve Treatment Outcomes; and Translational Studies on Poly-Substance Abuse and Addiction.

Dr. Weiss continued the presentation by addressing research training and the CRAN strategic plan. Research training has come up repeatedly as a natural priority for CRAN. At the end of 2013, the CRAN Coordinating Committee brought together several NIDA/NIAAA Council members and training directors to talk about the issues that they saw as barriers to broadening their research training programs. NIAAA, NIDA, and NCI all support training, but there is limited "cross-Institute" training, as well as disincentives in review for programs that propose to train students in other IC priority areas. The workgroup recommendations were that Institute leadership convey to investigators and reviewers that cross-substance research/training is a priority; that workshops and symposia be conducted to communicate this to the field; and to solicit input on opportunities for both research and training in multi- or polysubstance use and disorders. In response, CRAN provided supplements T32 programs for additional training slots that expose trainees to cross-cutting research areas and prepare them to conduct independent research in those areas. Fourteen supplements were awarded to experiment with different strategies to expose trainees to research in other substances. These programs are now in their second year.

In addition, beginning in 2016, a common review panel will be established for NIAAA and NIDA institutional National Research Service Award (NRSA) applications. This strategy should increase the pool of reviewers, broaden their expertise, and address reviewer bias against trainees studying other IC's priority areas. It should also communicate to the research community that NIDA and NIAAA leadership support training that is broad and inclusive of multiple substances. This will not replace Institute-

specific training programs, which remain important to both Institutes, especially in certain topic areas (e.g., alcohol-related liver disease). It will be implemented by an NIAAA/NIDA working group.

Note that this will not apply to NCI training applications, because there are few that are specifically focused in this area.

Council members have copies of the CRAN Strategic Plan for 2016-2020 in their electronic packets and comments are welcomed. The goal is to make sure the research community knows NIH is serious about promoting research on poly-substance use, beyond the ABCD study.

The Strategic Plan states that CRAN seeks to fill in gaps in research by expanding research training to increase scientific research in multi-substance research; creating core technical facilities and common databases for such research; and facilitating a paradigm shift in addiction research culture both within NIH and across the research communities. This shift is happening in the extramural and intramural NIH community; there is much better communication today between ICs at both the leadership and grass roots levels.

The Strategic Plan lays out CRAN's goals and objectives of investigating and differentiating the common and distinctive features of addiction along the disease continuum and encouraging funding to target emerging and/or under-recognized opportunities addressing multiple substance abuse and comorbidity across the lifespan, involving different levels of analysis. It emphasizes the following strategic approaches: advancing basic science, promoting clinical research, improving public health and reducing health disparities, and leveraging data systems and sharing resources among the CRAN ICs.

Dr. Weiss summarized the presentation by stating that CRAN encourages the research community to leverage the opportunities provided by CRAN to consider their research priorities in order to develop a better understanding of the influence of multiple substances on brain development, drug use patterns and trajectories, health and public health consequences, treatment, prevention, and implementation science.

Discussion: Dr. Regina Carelli asked, given the enthusiasm that CRAN grantees experienced sharing their work in the grantee meeting, if there were additional plans within CRAN to bring preclinical and clinical researchers together. Dr. Volkow responded that NIDA's strategic plan identified opportunities in integrating science as a way to expand such opportunities. Dr. Paulette Gray said that the Institutes' T32 training programs would be a good place to do this, and they're interested in doing so. Dr. Weiss noted that CRAN has looked at where the training programs are located and despite significant Institutional overlap, the convened training workgroup (in 2013) commented that these are not well leveraged. CRAN wants to find ways to make the integration more natural. Dr. Koob noted that Scripps has an integrated program. Training is one aspect, but it needs to also occur for all medical training in addiction. He and Dr. Volkow are thinking about the need for a core curriculum for teaching about addiction from middle school on up. Another place is review. There is a need to educate reviewers and work with the Center for Scientific Review (CSR) on this. Dr. Murray stated that the CRAN committee is aware of the need for better integration. One suggestion was to enable researchers working on preclinical and clinical studies to be located in one building so that they would have more opportunity for interaction.

ABCD Update

Dr. Volkow introduced Dr. Gaya Dowling, Director of the Adolescent Brain and Cognitive Development (ABCD) study. ABCD is a longitudinal study of about 10,000 children from ages 9-10 through early adulthood to assess factors that influence individual brain development trajectories and functional outcomes. It began as a CRAN initiative, but has expanded to become an NIH-wide collaboration involving eight ICs and offices, including NIDA, NIAAA, NCI, the National Institute of Mental Health (NIMH), the National Institute on Minority Health and Health Disparities (NIMHD), the National Institute of Child Health and Human Development (NICHD), the National Institute of Neurological Disorders and Stroke (NINDS), and the Office of Behavioral and Social Sciences Research (OBSSR). Its research objectives include: identification of individual developmental trajectories and the factors that can affect them; development of national standards of normal brain development in youth; the role of genetic vs. environmental factors on development (enriched by comparisons of twin participants); the effects of physical activity, sleep, screen time, as well as sports and other injuries on brain development and other outcomes; the onset and progression of mental disorders, factors that influence their course or severity, and the relationship between mental disorders and substance use; and how exposure to different substances like alcohol, marijuana, nicotine, caffeine, and others, individually or in combination, affect various developmental outcomes and vice versa.

Funding Opportunity Announcements (FOAs) for the study were released in January 2015 and generated a robust response. Thirteen awards were made in September 2015, including one for a coordinating center at the University of California at San Diego (UCSD), one for a data analysis and informatics center (UCSD), and 11 for research grants representing 19 geographically-dispersed research sites. One research hub (4 research sites) is focused on recruiting 800 pairs of twins. The initial meeting of Principal Investigators was held in October, 2015.

ABCD has a complex governance structure; its primary decision-making body is a Steering Committee made up of representatives of the 13 grantees and NIH. An External Advisory Board, made up of national experts in relevant scientific fields, provides scientific and administrative oversight, such as guidance on the study protocol. An Observational Study Monitoring Board monitors the study and makes recommendations to NIH on issues such as participant safety, confidentiality and informed consent; participant burden; and the impact of proposed ancillary studies and sub-studies.

The study is currently in the protocol development stage, which is moving rapidly. Grantees have formed different groups, e.g., assessment groups covering various areas, a design and biostatistics group, an image analysis group, etc. There are also other advisory groups such as the bioethics and medical oversight group, which is developing policies for the sites for how to handle sensitive situations e.g., when child abuse is suspected. The development of a community advisory council of parents and others is also in process.

The study will use school-based sampling, except for the twins cohort which relies on birth registry records in four states. The demographics of the catchment area from which we will draw the sample is close to representative; with some populations overrepresented (e.g., Hispanics and Asians). These will be addressed by the individual site targets. The recruitment protocol is to ask schools to make initial contact with parents by distributing materials provided by the sites. The researchers will then interview parents for inclusion of their children in the study.

Researchers plan to do brain imaging and specimen collection for genetic analyses every other year. The baseline assessment is 7 hours in length (including consent, imaging, and breaks). Youngsters come to the study center in the off-years for additional neurocognitive and behavioral assessments and some biospecimen collection. In the interim, web-based or phone assessments are planned.

The protocol is being finalized. There will be a training in April at UCSD in how to use the study's informatics and conduct the assessments. Researchers will begin enrolling participants in May with a smaller sample of 25-30 children per site, who can be assessed during the summer. Based on what is learned in that effort, the sites can adjust their outreach so that they can do their major recruitment in the fall when students come back to school.

Outreach and dissemination group members are working together to develop a website for the study, but there is already information about ABCD on the NIDA and CRAN websites.

Discussion: Dr. Rajita Sinha asked about the types of data on child maltreatment included in the study, noting that CDC has addressed ways to include such information. Dr. Dowling acknowledged the importance of this topic and said she would check to see if it's currently included. Dr. Sinha also asked about socio-economic status (SES) and issues of poverty and stress. Dr. Dowling indicated that SES is included; the sample is seeking balanced demographics, including urban vs. rural.

Dr. Gray asked if the study will examine prenatal pediatric records. Dr. Dowling responded that she was not sure if that had been discussed yet. Dr. Eberwine followed up with a question about the inclusion of parental biospecimens. Dr. Dowling indicated that funding for this data source was not provided and that investigators had decided it wasn't essential. Dr. Volkow noted that the ABCD study will provide a platform for associated studies as new questions are raised. Dr. Sinha asked if the data would be publicly available, and Dr. Dowling responded affirmatively, noting the data would be shared as soon as possible.

Dr. Sanyal inquired if there was a robust nutritional assessment plan. Dr. Dowling explained that some nutritional information, including food insecurity, would be collected, but participants would not be asked to maintain food diaries. Pediatric records would also be examined.

Dr. Marsch asked about anticipated attrition and plans to combat it. Dr. Dowling responded that the study is anticipating an 87% retention rate. The sites will compensate parents and children for participation at different levels by degree of involvement and geography. The study is also compensating schools for their efforts. Many groups in the study have significant experience in recruiting and working with children and parents, so their experience can help with retention.

Dr. Frank Sloan wondered how researchers can conduct a 7-hour interview with "someone who moves." He commented that an 87% retention rate seems optimistic. Dr. Dowling explained that the baseline assessment includes an hour of intake, consents and administration; two hours of imaging; and breaks. Dr. Sloan asked how families could continue to participate if they move from one state to another. Dr. Dowling indicated that the goal would be to switch the family to a nearby site for the annual visit; the remainder of the data collection is online. Dr. Sloan pointed out the many issues, such as low SES, children placed in foster care, custody battles, etc., that could make this challenging. Dr. Dowling noted that the study leaders have received a lot of feedback from the external advisory board about the kind of intensive work that will be required to keep track of patients. Dr. Weiss stated that the investigators are very experienced; they anticipate 90% retention, which NIH thinks is high. Every effort will be made to send birthday cards and maintain contact so that parents see this as a valuable opportunity to learn about their children's brains and to contribute to science. Dr. Volkow interjected that the challenges are big, but the payback is immense. Another potential issue is ethical: if a teen gets pregnant, must the investigators tell the parents? The study is designed with a very strong structure so that it can draw on the expertise of researchers, ethicists, as well as the perspective of the community as such issues arise.

Dr. Beirut inquired if the study has considered providing feedback to the parents as an incentive to continue. Dr. Dowling responded that clinical information would not be provided to parents. One site plans to give out t-shirts with the participant's brain scan on the front. Dr. Volkow commented that the study needs to be mindful of not discriminating or creating stigma, e.g., for a child whose development is delayed.

Dr. Auerbach asked about the message given to potential participants about why they should participate. In the context of earlier discussion regarding CFR Part 2, how does consent work with a child and parents together? Whose consent is more important? Dr. Dowling said their elevator speech is that this is a national study of brain development and the opportunity to contribute to a body of knowledge that can help children develop in the future. NIH and study investigators think people are attracted to the brain images. There are a lot of issues around informed consent. Dr. Murray, who sits on the bioethics and medical advisory group, stated that both parent consent and child assent are required. As children get older, they will also have to give consent.

Dr. Carmen Albizu-Garcia urged caution about placing children's brain images on T-shirts because it could have unintended consequences, such as bullying.

Dr. Koob concluded the discussion by noting that these are all important comments, and encouraging Council members to send additional comments to Dr. Dowling.

Council Round Table Discussion

Dr. Koob opened the floor for a round table discussion. Dr. Joe Martinez asked about the data showing prevalence of e-cigarettes to be 18% among teenagers and how this data can be reconciled with declining tobacco use prevalence. Dr. Volkow stated that these are not necessarily the same populations. The decrease in tobacco use preceded e-cigarettes. NIH is worried that teens who wouldn't have started smoking may do so due to e-cigarettes. Another question is, are teens using e-cigarettes just for the flavors? If they start using e-cigarettes for the flavors, do they end up using them because of the nicotine/tobacco? The field doesn't know, because this is a new delivery system for making drugs appealing to adolescents. Observers don't think tobacco use is decreased because of e-cigarettes, but gains that have been made in smoking rates may be lost.

Dr. Eberwine asked Dr. Croyle about the percentage of funds for basic research in the Vice President's campaign. Dr. Croyle responded that the funding was not broken out that way in the budget request. There are themes, e.g., immunotherapy. There are components within that theme for basic research, translational research, biomarker research, genomic data, etc.

Dr. Marsch commented that it was exciting to see the collaboration across three ICs. Bearing in mind the prevalence of co-occurring disorders, she asked if the National Institute of Mental Health (NIMH) should be included. Dr. Koob responded that he and Dr. Volkow are having monthly meetings with the acting director of NIMH and making plans for extramural efforts. More collaboration might be possible once NIMH has a permanent director.

Dr. Molina inquired if future training grants will require both usual training and cross-training or if each Institute would add other substances to its training requirements. Dr. Weiss stated that the cross-training supplements reported on in the CRAN presentation was a one-time event. NIH is reviewing progress reports to see what worked, but does not anticipate this being a CRAN requirement in the future. If strong applications with cross-training components are received, co-funding might be an option. Currently, the focus is on helping reviewers to get a better sense of the full scope of training programs that are going on. Both NIDA and NIAAA review T32 applications in-house so this will be a full in-house training review with both NIDA and NIAAA on one panel.

Dr. Molina suggested having a joint session at meetings of the Research Society on Alcoholism (RSA) or the College on Problems of Drug Dependence (CPPD) with the intent of bringing scientists from different fields together. Dr. Weiss replied that this was a great idea that CRAN would consider. Dr. Koob suggested to Council members that those who sit on the committees for those meetings propose having them at the same time and place or adjoining dates to facilitate this type of interaction.

Dr. Gray commented that if there was a requirement in the training grant RFA to address cross-training that applicants would do so. Dr. DiClemente observed that he was on a committee in which members presented their work to one another so that committee members saw the gamut from animal to statistics research. He suggested doing that as a review group.

Dr. Carlos Blanco invited everyone present to attend a joint session at CPPD in which he and Dr. Joni Rutter will present the priorities of their respective divisions at NIDA, the Division of Epidemiology, Services, and Prevention Research; and the Division of Neuroscience and Behavior, respectively; and how they strive to integrate work across all domains.

In regard to the ABCD study, Ms. Dyak suggested that a family relocation could be a traumatic event for a child and should be factored into the study. Dr. Volkow thanked her for making the point, noting that the investigators need to balance such important issues with what is practical to address. Dr. Koob commented that NCANDA has had big problems with families moving. Dr. Pfefferbaum stated that the study has had people in one site move to another area; they were followed up with a nearby site at the new location. ABCD has even broader geographic coverage. The cost of paying for airfare to get people back may be worth the effort. In NCANDA, a retention rate of 100% at one year was achieved at one site. He commended Dr. Dowling for considering all the comments; Council members offered her a round of applause.

Adjournment

The meeting adjourned at 1:27 p.m.

CERTIFICATION

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

For NIAAA:

/s/

George Koob, Ph.D.
Director
National Institute on Alcohol Abuse and Alcoholism
and
Chairperson
National Advisory Council on Alcohol Abuse and Alcoholism

/s/

Abraham P. Bautista, Ph.D.
Executive Secretary
National Advisory Council on Alcohol Abuse and Alcoholism
National Institute on Alcohol Abuse and Alcoholism

For NIDA:

/s/

Nora Volkow, M.D.
Director
National Institute on Drug Abuse
and
Chairperson
National Advisory Council on Drug Abuse

/s/

Susan Weiss, Ph.D.
Executive Secretary
National Advisory Council on Alcohol Abuse
National Institute on Drug Abuse

For NCI:

/s/

Judy E. Garber, M.D., M.P.H.
Acting Chair
National Cancer Advisory Board
National Cancer Institute

/s/

Paulette S. Gray, Ph.D.
Executive Secretary
National Cancer Advisory Board
National Cancer Institute