# Department of Health and Human Services
# National Institutes of Health
# National Center for Advancing Translational Sciences

## 29th Meeting of the
## Advisory Council

## Minutes of Virtual Meeting
## January 20–21, 2022

The National Center for Advancing Translational Sciences (NCATS) Advisory Council held a meeting in open session on January 20, 2022, from 1:00 p.m. to 4:54 p.m. EST, and on January 21, 2022, from 1:03 p.m. to 3:54 p.m. EST via National Institutes of Health (NIH) Videocast. Joni L. Rutter, Ph.D., NCATS Advisory Council Chair, led the meeting. In accordance with Public Law 92-463, the session was open to the public.

Prior to the meeting, the NCATS Advisory Council met in closed session on January 20, 2022, from 11:01 a.m. to 12:18 p.m. EST for the review and consideration of grant applications.

**NCATS ADVISORY COUNCIL MEMBERS PRESENT**

**Chair**

Joni L. Rutter, Ph.D., Acting Director, NCATS

**Executive Secretary**

Anna L. Ramsey-Ewing, Ph.D., Director, Office of Grants Management and Scientific Review, NCATS

**Council Members**

Paul A. Harris, Ph.D.
Christina M. Hartman, M.P.H.
Theodore R. Holman, Ph.D.
Rebecca D. Jackson, M.D.
Annie M. Kennedy, B.S.
Matthias Kretzler, M.D.
Kelly Marie McVearry, Ph.D., Ed.M.
Keith J. Mueller, Ph.D.
Rajesh Ranganathan, Ph.D.
Paula K. Shireman, M.D., M.B.A.
Marshall L. Summar, M.D.

**Ad Hoc Council Members**

None present

**Ex Officio Members**

None present

**Others Present**

Tina M. Morrison, Ph.D., Director, Office of Regulatory Science and Innovation (proxy for Frank F. Weichold, M.D., Ph.D.), U.S. Food and Drug Administration (FDA)

Jill A. Morris, Ph.D., Program Director, Division of Neuroscience, National Institute of Neurological Disorders and Stroke (NINDS)
Tara A. Schwetz, Ph.D., Acting Principal Deputy Director, NIH
NCATS leadership and staff

## I. CLOSED SESSION OF THE NCATS ADVISORY COUNCIL

This portion of the Advisory Council meeting was closed to the public in accordance with the determination that it was concerned with matters exempt from mandatory disclosure under Sections 552b(c)(4) and 552b(c)(6), Title 5, U.S. Code, and Section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2).

Advisory Council members discussed procedures and policies regarding voting and the confidentiality of application materials, committee discussions, and recommendations. Members did not participate in the discussion of and voting on applications from their own institutions or other applications in which there was a potential conflict of interest, real or apparent.

## II. ADJOURNMENT OF CLOSED SESSION OF THE NCATS ADVISORY COUNCIL MEETING

Joni L. Rutter, Ph.D., adjourned the closed session of the NCATS Advisory Council meeting on January 20, 2022, at 12:18 p.m. EST.

# JANUARY 20, 2022

## III. CALL TO ORDER, OPEN SESSION DAY 1

Dr. Rutter called the meeting to order and welcomed members and guests to the 29th meeting of the NCATS Advisory Council. Anna L. Ramsey-Ewing, Ph.D., conducted the roll call, noted the meeting logistics, and reminded attendees that the open session was being videocast. Dr. Rutter reviewed the meeting agenda. She pointed out that the meeting will span two days: Day 1, January 20, 2022, from 1:00 p.m. to approximately 5:00 p.m. EST and Day 2, January 21, 2022, from 1:00 p.m. to approximately 4:00 p.m. EST.

APPROVAL OF MINUTES: Anna L. Ramsey-Ewing, Ph.D., Executive Secretary, NCATS Advisory Council and Cures Acceleration Network (CAN) Review Board

Members unanimously approved the minutes from the September 2021 Council meeting.

## IV. APPROVAL OF 2022 NCATS ADVISORY COUNCIL OPERATING PROCEDURES: Anna L. Ramsey-Ewing, Ph.D., Executive Secretary, NCATS Advisory Council and CAN Review Board

Members unanimously approved the 2022 NCATS Advisory Council Operating Procedures.

## V. CONFIRMATION OF DATES FOR FUTURE MEETINGS: Anna L. Ramsey-Ewing, Ph.D., Executive Secretary, NCATS Advisory Council and CAN Review Board

Dr. Ramsey-Ewing confirmed the schedule for the meetings of the NCATS Advisory Council for 2022 and 2023, noting that except for the virtual January sessions, other meetings are planned as in-person until further notice:

- May 19, 2022
- September 22, 2022
- January 26–27, 2023 (virtual meeting)
- May 25, 2023
- September 28, 2023

## VI. DIRECTOR'S REPORT: Joni L. Rutter, Ph.D., Acting Director, NCATS, Chair, NCATS Advisory Council

Dr. Rutter began by extending her appreciation to Council member, Christina M. Hartman, M.P.H., who no longer is with The Assistance Fund and is serving her last official day with NCATS. Dr. Rutter presented updates on leadership transitions, announcements, and events and reported on the NCATS fiscal year (FY) 2022 budget. She also discussed highlights on progress in some of the NCATS offices, divisions, and programs.

### NIH and NCATS Leadership Transitions

Dr. Rutter updated the Council on the NIH and NCATS leadership changes.

- **NIH.** On December 19, 2021, Francis S. Collins, M.D., Ph.D., stepped down as NIH director after more than 12 years. Dr. Collins, who has had the longest tenure of any NIH director (serving three U.S. Presidents), listed the founding of NCATS as one of his leading three NIH scientific accomplishments. NIH hosted a special tribute to Dr. Collins that included farewell messages from numerous fellow scientists, U.S. Presidents, and colleagues across multiple disciplines. Dr. Rutter explained that the NIH director is appointed by the President and approved by the Senate; no candidates have been presented. In the interim, President Joseph R. Biden appointed Lawrence A. Tabak, D.D.S., Ph.D., as NIH acting director. Tara A. Schwetz, Ph.D., was named NIH acting principal deputy director.

- **NCATS.** In November 2021, the NIH Office of the Director began a search for a new NCATS director, and applications are being accepted until the end of day, January 31, 2022. Anton Simeonov, Ph.D., scientific director, Division of Preclinical Innovation (DPI), will be transitioning to chief, Chemical Genomics Branch, NCATS Laboratories. A search for a new DPI scientific director soon will open, and Dr. Simeonov will continue in this position during the recruitment process. Anne R. Pariser, M.D., director, Office of Rare Diseases Research (ORDR), will be retiring in mid-February 2022. Dr. Rutter expressed appreciation to Dr. Pariser for her leadership in the ORDR to expand the Office and improve the understanding of the burden of rare diseases in the United States. Dr. Pariser and her team recently spearheaded the NCATS effort to achieve orphan drug status for one of the Platform Vector Gene Therapy (PaVe-GT) clinical trials. Dr. Rutter pointed out that Philip John (P.J.) Brooks, Ph.D., now deputy director, ORDR, will serve as acting director until a search is completed.

### NCATS Announcements and Events

Dr. Rutter congratulated leaders in NCATS research and in the Clinical Translational Science Awards (CTSA) Program on recent accomplishments.

- **NCATS-Funded Investigators.** In 2021, the following NCATS-funded investigators were elected to the National Academy of Sciences: Shari L. Barkin, M.D., M.S.H.S., Vanderbilt University Medical Center; Andrés J. García, Ph.D., Georgia Institute of Technology; Kenneth D. Mandl,

M.D., M.P.H., Harvard Medical School; Elizabeth M. McNally, M.D., Ph.D., Northwestern University Feinberg School of Medicine; Keith C. Norris, M.D., Ph.D. University of California, Los Angeles; and Marcella Nunez-Smith, M.D., M.H.S., Yale School of Medicine.

- **Clinical and Translational Science Awards (CTSA) Scholars, Trainees, and Community Engagement Leads**. Dr. Rutter noted recent Institutional Mentored Career Development Award (KL2) and Ruth L. Kirschstein National Research Service Award Training Award (TL1) scholars and trainee recognitions. Colleen Kelley, M.D., M.P.H., former KL2 scholar, Emory School of Medicine and Rollins School of Public Health, was awarded the HIV Medicine Association's 2021 Award for Excellence in HIV Research. Megha Ramaswamy, Ph.D., M.P.H., former KL2 scholar, University of Kansas School of Medicine, and Megan L. Srinivas, M.D., M.P.H., TL1 trainee, The University of North Carolina Institute for Global Health and Infectious Diseases, were recognized as 2021 National Minority Quality Forum's 40 Under 40 Leaders in Health. In addition, Dr. Rutter announced that Chao Yang, assistant director, Community Engagement to Advance Research and Community Health, University of Minnesota Clinical and Translational Science Institute, was selected as a de Beaumont Foundation's 40 under 40 in Public Health.

Dr. Rutter called attention to upcoming NCATS events and activities.

- **Rare Disease Day (RDD) at NIH.** In support of International RDD, NCATS sponsors the annual RDD at NIH, and this year's event will be held on February 28, 2022, and will be virtual. Dr. Rutter highlighted the RDD 2022 agenda featuring presentations on diversity in rare diseases research, equity of care, and personalized medicine. Members interested in attending can register via the NCATS 2022 RDD website.

- **Advanced Research Projects Agency for Health (ARPA-H) Presentation to Council.** Dr. Rutter noted that to continue the discussions and in response to Council's questions on ARPA-H, NCATS invited Dr. Schwetz, who was on a 6-month detail to the White House Office of Science and Technology Policy (OSTP), to present on this topic at today's meeting. Dr. Schwetz has been working with the OTSP in planning implementation of this initiative, details of which she will present later in the meeting.

- **Diversity, Equity, Inclusion, and Accessibility (DEIA) at NIH and NCATS.** The NIH **UNITE** (NIH's ending structural racism initiative) team is hosting a series of listening sessions through February 2022 on efforts addressing structural racism and health equity. In 2020, NCATS established an Inclusion, Diversity, Equity in Action Council to build and sustain a welcoming and inclusive environment and to ensure that the NCATS processes and operations are inclusive. CTSA investigators published in the January 20, 2022, issue *of The New England Journal of Medicine* their perspective on diversity, equity, and inclusion in terms of clinical and translational research. The authors highlight leadership, training, research, and clinical trials as efforts to advance and provide concrete goals that transform and build capacity. A Diversity, Equity, and Inclusion Task Force has been established within the CTSA Program Steering Committee to transition such efforts into measurable actions.

**FY 2022 Budget**

The fiscal year began on October 1, 2021, and the government is operating under a continuing resolution until February 18, 2022. The House Appropriations bill was approved on July 29, 2021, and includes a $42.4 million increase for NCATS above the FY 2021 enacted budget. The Senate Appropriation draft bill released on October 18, 2021, includes a $25.7 million increase for NCATS above the FY 2021 enacted budget. The President's FY 2023 Budget Request is anticipated to be released in early February 2022. Dr. Rutter briefly reviewed recently published funding opportunity announcements (FOAs) that span across NCATS programs, highlighting the depth and breadth of NCATS activities.

**NCATS COVID-19 Research Efforts**

Dr. Rutter remarked on the Center's ability to respond to public health emergencies, such as the COVID-19 pandemic, and focus on multiple disease–related research. She provided an update on NCATS' COVID-19 related activities and began with the Foundation for the NIH (FNIH)–led public–private partnership — Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) randomized controlled trials (RCTs). NCATS, in collaboration with the CTSA Program hubs, has been managing ACTIV trials.

- **Convalescent Plasma to Limit COVID-19 Complications in Hospitalized Patients Trial (CONTAIN COVID-19).** This study, led by the New York University Langone Health CTSA, is evaluating the efficacy of convalescent plasma in hospitalized patients with COVID-19 and now is closed to enrollment. Findings revealed that the treatment did not meet the specified efficacy criteria based on the World Health Organization's 11-point ordinal scale for clinical improvement at 14 days, suggesting limited benefit to patients. Additional data are soon to be released.

- **Accelerating COVID-19 Therapeutic Interventions and Vaccines: ACTIV Master Protocol 1 of Immune Modulators (ACTIV-1 IM).** This international Phase 3 inpatient trial, led by the Washington University in Saint Louis CTSA and activated across an additional 35 CTSA hubs, was designed to investigate the effectiveness of three immune modulators — cenicriviroc, Orencia® (abatacept), and Remicade® — as add-on therapy to standard of care, including remdesivir. Enrollment was completed on December 30, 2021. Study participants were randomized to one of three treatments. Trialists predict finishing patient follow-ups in February to March 2022. The cenicriviroc treatment arm of the study ended early due to lack of efficacy. Data on the remaining treatments are anticipated in May 2022.

- **Accelerating COVID-19 Therapeutic Interventions and Vaccines: ACTIV-6.** This RCT is led by Duke Clinical Research Institute, Duke University, in collaboration with Vanderbilt University Medical Center. ACTIV-6 is an outpatient trial to evaluate the efficacy of repurposing existing medications (ivermectin, fluvoxamine, and fluticasone) for the reduction of COVID-19 symptoms and prevention of hospitalization. ACTIV-6 is unique in that medications are shipped directly to study participants, and follow-up (i.e., surveys) is performed remotely via telephone. Enrollment is ongoing until spring 2022, and reports will be forthcoming.

- **Antiviral Program for Pandemics.** The NCATS DPI Early Translation Branch is collaborating with the National Institute of Allergy and Infectious Diseases (NIAID) and the Biomedical Advanced

Research and Development Authority (BARDA) to increase efforts in the Antiviral Program for Pandemics. The goal is to develop a portfolio of direct-acting antiviral therapeutics against SARS-CoV-2 and other viruses of pandemic potential, thus creating Phase 2 trial–ready antivirals for rapid pandemic response. A survey of virus families revealed seven that are at high risk for a pandemic, including *Coronaviridae* (e.g., SARS-CoV-2). Because of the immediate public health crisis, most of the current studies have focused on this virus family. To date, four projects are in progress, and one candidate, papain-like protease inhibitor, developed by Clear Creek Bio, Inc., is advancing through the drug development pipeline.

- **COVID-19 OpenData Portal.** NCATS continues to ensure COVID-19 data are accessible to researchers through the DPI OpenData Portal, an online data resource and NCATS multidisciplinary and collaborative effort. Data on SARS-CoV-2 variants, including Omicron, have been shared in the portal, as well as assays and protocols of COVID-19 targets and approved drugs.

**National COVID Cohort Collaborative**

Dr. Rutter reminded the Council that the National COVID Cohort Collaborative (N3C), launched in 2020, is a partnership with the CTSA Program, the Center for Data to Health, the National Institute of General Medical Sciences Institutional Development Award (IDeA) Program, and OCHIN, Inc. The goals are to generate a secure national resource of electronic health record (EHR) data from COVID-19-tested patients and make available real-world clinical data for accelerating COVID-19 research and improving patient care. As of January 16, 2022, the N3C Data Enclave contained data from more than 10 million patients, 3.7 million of whom have received a COVID-19 diagnosis. These data span 12 billion rows and consist of 1.1 billion clinical observations. NIH clinical research networks and their partners are leveraging N3C's real-world EHR data to research COVID-19. NCATS has been working to augment EHR data, which tends to contain heterogeneous values and missing entries, to provide the most information possible. Dr. Rutter described updates and applications of N3C data.

- **External Data Sets: Privacy-Preserving Record Linkage (PPRL).** N3C is adopting PPRL techniques to maximize the potential of external data sets and those built from NIH-funded repositories, such as the Researching COVID to Enhance Recovery initiative that is co-led by the National Heart, Lung, and Blood Institute (NHLBI) and National Institute of Neurological Disorders and Stroke (NINDS). The data enclave recently began receiving data on mortality from sites. Data from the Centers for Medicare & Medicaid Services (CMS) (e.g., claims, prescriptions), and information on SARS-CoV-2 variants will be made available in February 2022. Intensive care unit waveform and imaging data are other targeted data sets that will be added in the future.

- **American Indian/Alaska Native (AI/AN) Data.** NCATS has been seeking input from tribal nations on the use of AI/AN data within N3C. These efforts give considerations to privacy and sovereignty of tribes. NCATS has been meeting with the NIH Tribal Health Research Office, Indian Health Services Tribal Epidemiology Centers, and NIH experts regarding these matters. Pending the Tribal Consultation, AI/AN data in N3C are aggregated, and ZIP codes overlapping tribal lands are not available. A virtual Tribal Consultation meeting is scheduled to be held on February 11, 2022. Tribal nations will have time to submit follow-up comments, and NCATS will prepare a report and action plan based on the tribal input.

- **COVID-19 Monoclonal Antibody (mAb) Colorado Project.** This real-world evidence study being led by University of Colorado Anschutz Medical Campus investigators Adit A. Ginde, M.D., M.P.H., and Tellen D. Bennett, M.D., M.S., is investigating the effectiveness of mAbs for treating COVID-19. NCATS-specific funds are supporting this study. The goal is to enroll 4,000 individuals who have received mAb treatment and those who have not. The outpatient follow-up is being conducted remotely. The EHRs are one component and will be used to monitor treatment effectiveness in preventing hospitalization, as well as long-term symptoms. Initial findings are promising in terms of averting hospitalizations and deaths. Pre-prints are available in *medRxiv*.

**NCATS' Anniversary Year 2021**

Dr. Rutter reported that the NCATS 10th Anniversary event — NCATS at 10: Improving Health for All Through Translational Science — was held on December 7, 2021. More than 700 people attended, including representatives from academia, government, patient advocacy groups, and rare diseases organizations. Topics focused on patient impact, diversity and inclusion, platform technologies, and data-driven solutions. The event provided NCATS the opportunity to showcase some of its programs and initiatives and to highlight the work of the Center.

**The Future of NCATS Today**

Dr. Rutter summarized that NCATS delivers an effective, efficient, and predictive preclinical pipeline and expands the repertoire of platform technologies for many diseases at a time; the Center promotes innovative clinical data science and transformative clinical research and trials. NCATS continues to revolutionize rare diseases diagnostics and treatments and prioritizes diversity, equity, inclusion, and access in all activities. The Center trains the next generation of translational scientists and engages old and new stakeholders, with the aim to build trust and nurture relationships. The primary goal remains to bring more treatments to all people more quickly. Translational science is, by definition, efficient, predictive, transformative, and revolutionary. In her remarks at the NCATS anniversary event, Dr. Rutter highlighted three overarching goals for the next decade of NCATS:

- **Goal 1: More Treatments.** Advance more treatments through the pipeline, increasing the percentage of rare diseases that have treatments from 5% to 25%. Enable the development and use of new platform technologies. Actively disseminate new initiatives. Democratize the technology. Enable the research. Continue collaborations.

- **Goal 2: All People.** Dramatically increase inclusivity in all areas. Address health disparities among racial and ethnic populations, sex/gender minority populations, and those in rural communities. Prioritize development of strong community engagement partnerships. Train the next generation of translational scientists. Emphasize DEIA in the workforce. Improve commercial interest and market incentives for rare diseases.

- **Goal 3. More Quickly.** Reduce by half the time required for treatments to reach the market. The need is for better predictive models, patient-centric designs, and many-diseases-at-a-time strategies. Train next-generation scientists to embrace team science. Streamline and

standardize administrative and operational processes. Employ master protocols in clinical trials to test multiple drugs concurrently. Continue drug repurposing.

***Discussion***

Regarding the agility and ability of NCATS to pivot activities in response to COVID-19, Annie M. Kennedy, B.S., noted that it is unclear how best to communicate NCATS' impact in addressing public health issues to immediate stakeholders and the public. Dr. Rutter noted public (e.g., published findings in peer-reviewed journals and press releases) and private (e.g., physician communications) channels to convey these messages about NCATS. She added that the OpenData Portal has been successful in communicating information to the scientific community about COVID-19 treatments.

Matthias Kretzler, M.D., encouraged NCATS to strongly pursue the goal of achieving treatments being developed for 25% of rare diseases. He continued that the field is constantly defining and redefining how research is performed and thus has the necessary instrumentation, and NCATS has the tools to identify shared common pathways of disease manifestation. Once determined, these commonalities can potentially prevent a lesion that would cause a phenotype in patients to remain subclinical. Dr. Rutter agreed that subclinical understanding of disease endpoints is important and pointed out that the *in vitro* assays being developed in the 3-D Tissue Bioprinting and Tissue Chip for Drug Screening programs are areas to begin to help identify clinical phenotypes and biomarkers.

Marshall L. Summar, M.D., commented on the emergence of a new type of field of medicine involving small patient-group populations, subdivided by molecular features in the rare diseases field, presenting with 11 new conditions a week. Linking of genetic variation to these groups does not fit the classic model, because the statistics and evidence are different. Dr. Summar remarked that NCATS, being disease-agnostic, is positioned to address these small groups of patients with rare diseases with appropriate clinical trial models; building new tools and engaging the FDA early will be necessary. Dr. Rutter noted that NCATS continues to work closely with the FDA regarding the framework and regulatory aspects beyond the science, particularly with new large-scale initiatives. Dr. Summar emphasized the need for online validated digital tools for testing outcomes designed for patients who are geographically separated (i.e., disparate).

Paul A. Harris, Ph.D., suggested investing in the workforce to ensure that upcoming translational scientists are data-proficient and are investing in efforts to pair data scientists with clinical experts and with community engagement experts. Dr. Rutter called attention to the N3C Data Enclave Domain Teams that are connecting researchers with data scientists and noted efforts to partner with the NIH Office of Data Science Strategy on their data proficiency–related initiatives, such as the Artificial Intelligence/Machine Learning Consortium to Advance Health Equity and Researcher Diversity (commonly called AIM-AHEAD).

Rebecca D. Jackson, M.D., asked what efforts will be made to address data equity, accessibility, and bias, particularly for community stakeholders, and whether NCATS will take a leadership role regarding rare diseases and translational science. Dr. Rutter explained that NCATS has taken a wide focus on data science and noted that Christine Cutillo, M.M.C.i., is leading this effort.

Ms. Hartman commented on NCATS' being a champion for rare diseases and asked how rare diseases would be prioritized in the NCATS budget. She called attention to a white paper authored by

organizations in the rare diseases community (e.g., EveryLife Foundation for Rare Diseases) detailing their recommendations for ARPA-H. Ms. Hartman suggested a review of the FDA risk calculation for children and engaging caregivers in the discussions.

Tina M. Morrison, Ph.D., called attention to a recent FDA Centers of Excellence in Regulatory Science and Innovation Summit that included discussions with past FDA commissioners and Acting Commissioner Janet Woodcock, M.D., on rare diseases and FDA's relationship with CMS regarding therapies. Dr. Morrison emphasized that aligning with NCATS' "more treatments to all patients" goals includes partnering with groups, such as health insurance payers, to deliver treatments to patients and identifying the information FDA and CMS needs to transition treatments.

**Additional comments/questions posted in the chat to all participants:**

13:47:36 From Marshall Summar to Everyone: To emphasize Joni's point, the rate of new genetic disease description (genetic change linked to clinical presentation) has been 11 per week since 2000. Requires new ways of thinking about disease informatics.

14:04:50 From Pj Brooks to Everyone: @Marshall we have and will continue to include explicit requirements to meet with the FDA as milestones in our FOAs

14:06:14 From Marshall Summar to Everyone: Thanks PJ! I'd love to see any clinical trial involving small patient size groups get some level of FDA input on how the generated data could be used for future trials.

14:09:30 From Annie Kennedy to Everyone: @PJ re: to milestones in FOAs, are there any requirements to involve stakeholders from the payer environment? As more and more rare approvals are met with complex access environments, we are learning from our extensive payer engagement that we are not involving payers early enough in discussions around how/why outcomes are being used within our trials and patient communities

14:15:58 From Tina Morrison to Everyone: Yes! CMS is critical to this effort as well. And thinking of ways FDA and CMS can work together to develop evaluation methods and data evidence needs that complement one another to help streamline getting treatments to all patients.

14:16:28 From Marshall Summar to Everyone: What Christina is saying is absolutely correct. We see age limits on rare disease trials for disease where the primary pathology is in the very young. So many issues. Would love to see an NCATS sponsored meet with FDA, NCATS, Medical Types, and Patients to come up with a statement around Risk etc. in Rare Disease Clinical trials.

## VII. INVITED PRESENTATION: The Advanced Research Projects Agency for Health (ARPA-H): A New Paradigm for Biomedical and Health Research, Tara A. Schwetz, Ph.D., Acting Principal Deputy Director, NIH

Dr. Schwetz provided an overview of the proposed structure of ARPA-H. The draft mission is to benefit the health of all Americans by catalyzing health breakthroughs not readily accomplished through traditional research or commercial activity. The approach will be to leverage the pioneering efforts of the Defense Advanced Research Projects Agency (commonly called DARPA) and what has been applied

in other research and development (R&D) areas, including Biomedical Advanced Research and Development Authority (BARDA) and Advanced Research Projects Agency (ARPA-Energy or ARPA-E). The Administration is proposing to establish a distinct entity within NIH that will have the autonomy, independence, resources, and authorities to tackle major challenges facing human health. Dr. Schwetz reviewed the ARPA model; its features include a program manager–centric approach; lean and nimble organizational structure; high-risk, high-reward approach; time-bound nature; mission-driven activities; independent and autonomous structure; active program management; and accountability.

- **Goals and Guiding Principles.** The goals will center on supporting transformative high-risk, high-reward research to speed application and implementation of health breakthroughs and foster them across various levels (i.e., molecular to the societal). APRA-H intends to build capabilities and platforms to revolutionize prevention, treatment, and cures in a range of diseases; convert use-driven ideas into tangible solutions for patients far more rapidly than previously believed possible; and overcome market failures through critical solutions or incentives. The Administration proposes that ARPA-H be linked to NIH to leverage the vast knowledge, expertise, and infrastructure but remain distinct, with a unique culture and organization. Five guiding principles will drive this culture: (1) Seek innovative ideas and collaborative, diverse people; (2) be nimble, urgent, and time-bound; (3) be open and transparent, and engage stakeholders; (4) be accountable, milestone-driven, yet independent; and (5) fail early and accept risk.

- **Authorities.** The authorities needed to accomplish the ARPA-H mission include rapid hiring outside the civil service system with competitive wages; recruitment of expert project managers for short terms (e.g., 3–5 years); broad, flexible funding authorities; and exemptions from traditional review processes. Idea generation will be informed by patients, academia, industry, government, philanthropy, and other scientific stakeholders, as well as ARPA-H program managers.

- **Outreach and Stakeholder Engagement.** To communicate and increase awareness of ARPA-H, the White House Office of Science and Technology Policy (OSTP) and NIH jointly published a commentary in *Science* outlining the mission, made several presentations, and held numerous informational sessions. To date, OTSP and the NIH leadership have held 15 listening sessions attended by more than 5,100 stakeholders representing 250 organizations. A *Listening Sessions for ARPA-H: Summary Report* was released in September 2021. Two key themes emerged, scientific portfolio and streamlined processes, both of which Dr. Schwetz elaborated further.

Regarding appropriations activities, Dr. Schwetz reminded the Council members that the President's FY 2022 budget proposal includes $6.5 billion to establish ARPA-H at NIH. The House Appropriations bill includes $3 billion, and the Senate Appropriations bill includes $2.4 billion. Two options for authorizing ARPA-H have been introduced in the House: a standalone bill and provisions in the 21st Century Cures 2.0 Act.

***Discussion***

Dr. Harris asked about the roles of the NIH Institute and Center (IC) directors in ARPA-H, measures in place to ensure no duplication of efforts, and ensuring that the focus is on the right problems.

Dr. Schwetz noted that the NIH director convened the IC directors to discuss coordinating and exchanging ideas. Two areas, the application review process and formal feedback loop, will leverage the expertise of the Institutes/Centers (ICs).

Rajesh Ranganathan, Ph.D., commented that the APRA-H model of recruiting workforce members for short terms is counter to the compensation scheme of the government and might not attract the most talented candidates. He asked whether adding ARPA-H would create a new NIH IC or an Office and pointed out that some of the proposed activities already are in practice in NCATS. Dr. Schwetz referred to the needed authorities for ARPA-H, described earlier, regarding flexibility in hiring and noted that the initiative will be on the level of — but will not be established as — an IC. Dr. Ranganathan also asked about possibly locating ARPA-H under the Department of Health and Human Services (HHS) directly. Dr. Schwetz reiterated three reasons for choosing NIH: the similar missions of NIH and ARPA-H, the ability to leverage expertise and knowledge, and the intent to capitalize on the existing infrastructure.

Kelly Marie McVearry, Ph.D., Ed.M., asked what would be unique to ARPA-H that is not being addressed in NCATS currently, particularly the breakthrough research infrastructure. Dr. Schwetz explained that ARPA-H would leverage the infrastructure across the federal government, in addition to that at NIH, to coordinate and improve operations; it would not duplicate networks but would act as a feedback loop for moving ideas forward. She pointed out that the proposed language presented today on ARPA-H implementation is in draft form and still is in the development phase.

**Additional comments/questions posted in the chat to all participants:**

14:29:21 From Pj Brooks to Everyone: @Annie, Tina, The FOAs I was referring to (e.g. https://grants.nih.gov/grants/guide/rfa-files/RFA-TR-20-031.html ) are very focused on how to start up a clinical trial for more than one disease at a time, including getting an IND. Because of that specific focus, we have not included a specific requirement to include payers. However, in response to a comment Annie made at last council, we do plan to engage payers in the BGTC program. Happy to discuss more tomorrow.

14:33:37 From Annie Kennedy to Everyone: @PJ - Thanks! Looking forward to hearing more! As for applicability to broader platforms, you may want to consider engagement with the PC-CIS Blueprint (if you haven't already). Partners have been working to develop Patient Centered Core Impacts Sets (building on the FDA PFDD efforts and existing measures for assessing core outcomes).

https://nationalhealthcouncil.org/pc-cis-blueprint/

14:37:58 From Christina Hartman to Everyone: See above for the document I mentioned earlier that TAF, ELF and others put together on the rare disease community priorities for ARPA-H

14:50:40 From Marshall Summar to Everyone: Such a cool project and will challenge the more conventional research groups by moving nimbly.

## VIII. PROGRAM UPDATE: Office of Strategic Alliances (OSA): Lili M. Portilla, M.P.A., Director, OSA, NCATS

Ms. Lili M. Portilla explained that the OSA is in charge of the scientific/research agreements and partnerships established across NCATS and manages the Center's Small Business Innovation Research

(SBIR)/Small Business Technology Transfer (STTR) program. She updated the Council and other attendees on the SBIR/STTR program, noting new initiatives and program changes and other activities. Congressionally mandated, SBIR and STTR programs represent one of the largest sources of early-stage financing across federal agencies; NIH allocated $1.035 billion in FY 2021 for the programs, supporting U.S. small businesses working in the biomedical field. NCATS is one of 24 grant-issuing Institutes/Centers (ICs) with budgets (3.65% set-aside) that support an SBIR/STTR program.

NCATS receives most (nearly 90%) of its applications through an Omnibus Solicitation (i.e., investigator-initiated grant funding) and supports a broad range of research priorities and topics. Other avenues include Grant Solicitations in Targeted Areas (i.e., grants to advance a particular technology or research area) or SBIR Contract Solicitations (i.e., contract opportunities to advance areas of high research interest).

The benefits of the SBIR and STTR programs include stability, predictability, non-dilutive funding, retention of intellectual property rights, and technical assistance for commercialization. Companies are provided the opportunity to participate in the innovation core training program at no cost. In addition, projects in this program undergo a rigorous scientific peer review process, and awards can be leveraged for other funding and collaborative opportunities.

NIH SBIR/STTR is a three-phase program structured by Congress. Phase I, a feasibility study, provides up to $300,000 for 6 months (SBIR) to 1 year (STTR). Phase II, full research and R&D, provides up to $2 million over 2 years. Fast-Track combines Phase I and Phase II. Direct-to-Phase II allows skipping Phase I. Phase IIB, competing renewal for Phase II/R&D, provides up to $1 million per year for up to 3 years. Phase III, commercialization, establishes a public–private partnership using non-SBIR/STTR funds. NIH is generally not the customer.

Ms. Portilla noted critical differences between SBIR and STTR regarding partnering, work, and principal investigator (PI). STTR requires a nonprofit research institution partner (e.g., university) and has minimum work requirements (e.g., 40% small business and 30% research institution partner). The PI may be employed by the research institution partner or the small business. Awards always are made to the small business.

**2021 Update on New NIH Initiatives and Program Changes**

Ms. Portilla explained that the NIH SBIR/STTR budget caps remained unchanged for a period of time. The Small Business Administration (SBA) has increased funding limits and adjusted budget limitations for inflation resulting in the current Phase I and Phase II caps described earlier. NIH has received a waiver from SBA, as authorized by statute, to exceed these total award amount hard caps for specific topics. The Phase I waiver is $325,000, and the Phase II waiver is $2 million. The current NCATS 2021 NIH Topics for Budget Waivers can be found in the Omnibus Solicitation or accessed from the NIH Small Business Education and Entrepreneurial Development (commonly known as SEED) website.

- **NCATS Additional Resources: Technical and Business Assistance (TABA) Program.** TABA helps small businesses identify and address their most pressing product development needs, and resources are available only for NIH SBIR/STTR award recipients. Applicants can request additional funding for assistance in marketing analysis, filing patents, and/or consulting services. Phase I has a cap of $6,500 per year. Phase II has a cap of $50,000 for the life of the project.

- **Administrative Supplements to Promote Diversity in R&D in Small Businesses.** NCATS provides administrative supplements to its Phase I and Phase II SBIR/STTR awardees to advance workforce diversity at all career levels. The supplements support individuals desiring to work and gain experience in a small business or performing research at a small business. NCATS is accepting applications on a rolling basis through September 2024.

- **Applicant Assistance Program.** NCATS participates with other ICs in the Applicant Assistance Program, an application preparation assistance program provided at no cost to the company. Applicants with strong technology and limited NIH experience are matched with an expert mentor who has a proven track record in grant success for companies. The applicant is thus provided the necessary tools and knowledge to be successful in gaining NIH funding. Companies that have not received an NIH SBIR/STTR award and do not have a current NIH SBIR/STTR application under review with the same scope of work are eligible to apply. NCATS ensures that an applicant's research area of interest aligns with the mission of the participating IC.

**Driving Awareness Through Social Media Channels and Webinars**

Ms. Portilla discussed NCATS SBIR/STTR outreach efforts and noted the objectives, including increasing (1) awareness of the programs, (2) the number of applications from women/minority-owned small businesses and those in Institutional Development Award (IDeA) states, (3) the number of quality applications, and (4) the number of applications in the SBIR/STTR budget line. In addition, the NCATS SBIR/STTR program aims to advance small businesses' innovation in drug development, discovery, research tools, and technologies to improve patient care.

- **Webinars.** In FY 2021, OSA partnered with various stakeholders, including state Biotechnology Innovation Organizations and academic technology transfer offices on joint outreach activities. The Office held 10 virtual events that spanned across 45 states and the District of Columbia and Puerto Rico, including 17 IDeA states.

- **Social Media.** OSA and the NCATS Communications Branch manage a social media engagement calendar for the SBIR/STTR program, in which information on funding, application tips, and upcoming events are announced. Other successful activities on NCATS social media platforms include generating social cards of quotes highlighting grantees, their companies, and milestones reached. OSA is using Salesforce, a customizable platform developed by the NCATS SBIR/STTR staff, for tracking early interactions with potential grantees through the project's closeout.

**SBIR/STTR FY 2021 Results**

Ms. Portilla reported that from FY 2015 to FY 2021, 75% to 80% of the SBIR/STTR budget supported grants, and the remainder was allotted to contracts. In FY 2021, funding was allocated across four topics: tools for drug discovery and development (45%), bioinformatic tools (21%), devices (21%), and gene therapy (13%). Applications received in any given year reflect consistent outreach efforts to increase awareness of the program. After a slight decrease in FY 2020 during the COVID-19 pandemic, applications increased in FY 2021. Approximately 30 new applications are funded each year, and the average priority score continues to improve.

**NCATS SBIR Success Stories**

In celebrating the NCATS 10th Anniversary, the SBIR/STTR program hosted a panel featuring three grantees to discuss the innovations and lessons learned in building their businesses using SBIR/STTR funding: Lena Wu, Ph.D., former CEO and president, Intabio, Inc.; Chris Gibson, co-founder and CEO, Recursion Pharmaceuticals; and Chang Hee Kim, Ph.D., CEO, GoDx, Inc.

- **Intabio, Inc.,** received funding to develop and market the Blaze System™, an automated instrument that combines mass spectrometry with a type of protein imaging. This system is improving manufacturing techniques to deliver high-quality biotherapeutics to the clinic faster.
- **Recursion Pharmaceuticals** reached a major milestone in April 2021 by raising $436 million after its initial public offering as the first drug-discovery company with an artificial intelligence approach. Since the NCATS SBIR Direct-to-Phase II award in 2014, the company has doubled the size of its venture rounds from a $60 million series B in 2017, to $121 million in financing in 2019, to a $239 million round last year.
- **GoDx, Inc.,** received funding to adapt a technology platform into a quick, simple, and inexpensive approach that could detect SARS-CoV-2 from nasopharyngeal or saliva samples in less than 30 minutes. This NCATS-supported test could provide faster diagnosis of COVID-19.

**Future Directions for the NCATS SBIR/STTR Program**

Ms. Portilla noted future directions and next steps. These include increasing outreach, increasing applications from women and minority-owned businesses and states with low success and application rates, identifying NCATS success stories, and providing potential applicants and grantees educational programming and resources about commercialization and partnering. The OSA is seeking Council input on outreach opportunities for the SBIR program and suggestions on leveraging SBIR in regard to existing NCATS initiatives and programs.

***Discussion***

Dr. Jackson suggested partnering with the CTSA Program on identifying mentors across both sectors, academia and business, which could help with sustainability of projects in the transition from a Phase I to a Phase II award.

Dr. Harris asked about targeted FOAs in the program and whether the end result needed to be a product or whether it could be a sustainable set of services. Ms. Portilla noted a targeted Request for Applications (RFA) successfully used by the Office of Rare Diseases Research to launch a basket trial leveraging the U44 mechanism on the SBIR as a complementary means to engage a small business. She continued that a product is the desired end result, but a sustainable service that is unique and innovative also could be considered.

**Additional comments/questions posted in the chat to all participants:**

15:35:04 From Kelly M McVearry to Everyone: Lili, these case studies are compelling. Thank you.

15:38:03 From Paula Shireman to Everyone: I watched that webinar, it was very interesting!

15:50:25 From Kelly M McVearry to Everyone: Lili, for outreach, I am happy to connect you with the leadership of early stage investing groups that work very closely with life science entrepreneur communities *and* have track records investing in NCATS-aligned ventures for SBIR/STTR Phase III. Please let me know if any of these are of interest: Life Science Angels in Palo Alto, CA; the director of the new Biomed commercialization program at Berkeley; and the Life Science Syndication group at the Angel Capital Association. Any one of these groups will gladly help support your outreach in well-stocked ponds.

## IX. CLEARANCE OF CONCEPTS

The Council received presentations on two new initiatives that NCATS is considering for funding. At the end of each presentation, the members discussed the concepts and voted on whether to approve moving forward with each concept.

**Introduction of the Office of Policy, Communications and Education (OPCE) Concept: Penny W. Burgoon, Ph.D., Director, OPCE, NCATS**

Dr. Penny W. Burgoon explained that the OPCE's three branches — Policy, Communications, and Education — provide guidance and support for NCATS activities on matters of communication, education and training, and science policy. The Education Branch, established in 2017 and made operational in 2019, has three main goals: (1) develop and disseminate evidence-based tools and best practices, (2) improve understanding of translational science, and (3) expand and diversify the translational science workforce. These goals are achieved by coordinating and providing central leadership for translational science education across NCATS, and developing new initiatives is one component of this activity. In addition, the Education Branch leads a Center-wide committee focused on translational science education.

Dr. Burgoon noted that the new concept being proposed leverages NCATS existing online courses (e.g., MEDI 501: Principles of Preclinical Translational Science), which are advancing understanding of translational science principles. The Education Branch is developing digital badges that communicate key messages of these principles: a focus on unmet needs, generalizable solutions, creativity and innovation, cross-disciplinary team science, efficiency and speed, boundary-crossing partnerships, and bold and rigorous approaches.

**Online Education Modules to Advance Understanding of Translational Science Principles: Jessica M. Faupel-Badger, Ph.D., M.P.H., Chief, Education Branch, OPCE, NCATS**

Jessica M. Faupel-Badger presented a new concept to develop online education modules to advance understanding of translational science principles. An extensive literature review that identified gaps in formal translational science education, experience with NCATS' internal training program, and feedback received from the community speak to the need for curricula and activities that disseminate effective practices in translational science. The Education Branch recently has developed and implemented two online courses that use examples of successful NCATS-led efforts to demonstrate how specific research advances can be examined to offer insight into the translational process and identify common challenges and solutions applicable to research initiatives across the translational science spectrum.

Those efforts have informed principles of effective translational science that have been incorporated into these initial courses.

Directly aligning with the NCATS strategic goals, this translational science initiative will increase the capacity of the Education Branch's teaching experience and educational research and will further develop and formalize core concepts, approaches, and strategies derived from the field's experience and knowledge. This concept also will increase broad access to translational science and advance innovative evidence-informed approaches to online education. New educational activities will supplement NCATS' current education and training programs, adding effective practices, and will make progress in establishing translational science as a distinct area of study.

Regarding objectives and areas of emphasis, NCATS proposes to develop a portfolio of extramural research education awards that would result in a suite of online education activities, focusing on teaching effective practices and core principles of translational science. Evaluation criteria of the modules include (but are not limited to) data fields on diversity of the participants across all areas (e.g., training and career) and adherence or scale of participation. NCATS anticipates that this concept will broaden and expand foundational translational science knowledge, maximize online learning, and catalyze development of new translational science curricula.

***Discussion***

Dr. Jackson expressed her enthusiasm at the prospect of leveraging the broader extramural community, including public–private partnerships, that can merge basic and advanced training in the underlying principles of translational science. She emphasized supporting the translational science spectrum — from discovery to dissemination to implementation science. Dr. Jackson suggested having a sustainability plan; investing in engaging, innovative curriculum approaches (e.g., gamification) for adult learners; and supporting other educational activities (e.g., discussion forums). She also noted supporting a community of practice as one way to expand the field, developing educational ontologies, and establishing formal translational science education consortia.

Dr. Ranganathan noted his experience with online educational programs focusing on drug discovery that had been less effective in adults. He expressed concerns that the NCATS model would not provide a better result than that effort and that an RFA would only attract proposals for developing lectures without adequate structure or normalization of principles. Dr. Ranganathan suggested leveraging game-based educational initiatives for this new series of online courses, such as PHARM GAME: Drug Discovery and Development or SCREENER.

Dr. Faupel-Badger responded that she appreciates the comments and understands the concerns. She explained that by starting with this traditional online course approach of teaching translational science, the Education Branch hopes to catalyze other methodologies (e.g., game-based) to reach a broader audience, including undergraduate students. Dr. Faupel-Badger continued that one objective is to expand translational science workforce diversity (i.e., getting translational science education to more people) and noted that many NIH funding mechanisms can be designed to fit the structure of this concept. Dr. Ranganathan further suggested extending beyond PIs to engage students (i.e., high school and college) to build these online courses and emphasized the need for precise expertise in educational methodology that works for the generation being taught.

Dr. Kretzler commented on how this concept is addressing an unmet need. He highlighted the Rare Diseases Research Training Program within the Rare Diseases Clinical Research Network (RDCRN), which — along with others in the Clinical and Translational Science Awards (CTSA) Program — can be cataloged and used as a framework for this initiative. Dr. Kretzler called attention to prize competitions that have worked to design molecular biology tools for software development that could potentially be adapted to translational science education. For example, a prize could be developed to address an educational problem and attract a large community of diverse stakeholders to compete, thereby establishing an effective, innovative benchmarking process.

Dr. McVearry emphasized that the concept's goal is to professionalize translational science and suggested thinking beyond the Web 2.0 environment to Web 3.0. Drs. McVearry and Ranganathan commended the content of the proposed online courses, and Dr. McVearry suggested investigating new content delivery approaches that would engage the younger generation.

Keith J. Mueller, Ph.D., commented on the evaluation component of this concept and underscored adopting innovative approaches and tailoring the methods of teaching to diverse audiences.

Dr. Jackson summarized that traditional lectures (i.e., with PowerPoint presentations) appear to be an ineffective strategy for this concept, but they can be used as background material. Other online approaches, such as gamification and computer applications, are more engaging. An integrated system will advance this effort to an available resource.

Dr. Faupel-Badger and the Education Branch will explore Council members' suggestions to leverage existing efforts and nontraditional approaches for this concept — including game-based educational initiatives and prize competitions to teach drug discovery — and will consider establishing formal consortia.

Members approved the online education modules to advance understanding of translational science principles concept with 10 ayes, zero nays, and one abstention.

**Additional comments/questions posted in the chat to all participants:**

16:16:43 From Kelly M. McVearry to Everyone: Similarly, the curricula could be delivered in a gamified way in a Web3.0 environment (that could even simulate all the next-gen labs at NCATS)…good for the younger generation.

16:16:49 From Anna Ramsey-Ewing to Everyone: NCATS can hold prize competitions

16:17:43 From Kelly M. McVearry to Everyone: Would be very easy to tokenize learning milestones

16:26:10 From Marshall Summar to Everyone: We run the rare disease teaching course for RDCRN and the classic lecture model we dropped awhile back. Small group talk sessions and then content "packets" that have good info on a small bite have worked best. This course is at the fellow/junior faculty level.

16:26:54 From Matthias Kretzler to Everyone:
https://www.rarediseasesnetwork.org/researchers/training

16:28:22 From Marshall Summar to Everyone: We tracked the enrollees by retention in the field and alumni events. Deb Regier runs the course and has won almost every teaching award available at Children's (also NORD and NIH NHGRI ones). But we have an enriched audience of trainees working on rare disease projects.

**Introduction of the Office of Special Initiatives (OSI) Concept: Danilo A. Tagle, Ph.D., M.S., Associate Director, OSI, NCATS**

Dr. Danilo A. Tagle provided a brief overview of the OSI and noted the mission to address translational problems with innovative solutions through disruptive technologies and novel partnerships. He briefly displayed a list of the OSI's technologies and partnerships and introduced the new concept being proposed. The Exosome Therapeutics for Regenerative Medicine (ExTReMe) initiative leverages the NIH Common Fund investments in tools and resources to isolate exosomes, including the Extracellular RNA (ExRNA) Communication program, which focuses on secreted RNA for biomarker and therapy development.

Dr. Tagle explained that in the past decade, exosomes have been recognized as novel messengers for intercellular communication. Produced by endosomes and released into the extracellular matrix when multivesicular bodies fuse with the cell membrane, exosomes range from 40 to 150 nanometers in diameter and carry diverse bioactive cargo (i.e., molecules), including lipids, proteins, and messenger and regulatory RNA for signaling and other cellular functions. Exosomes also contain surface proteins for targeting and can be directly used to repair tissues or loaded with therapeutic cargo.

**Exosome Therapeutics for Regenerative Medicine (ExTReMe): Christine M. Happel, Ph.D., Program Officer, OSI, NCATS**

Dr. Christine M. Happel presented a new concept focusing on ExTReMe. Despite advances in regenerative medicine, major challenges remain. For example, stem cell transplantation is currently the main method for tissue regeneration, but progress is limited. Hurdles include ensuring a reliable cell source, tumor formation, inappropriate stem cell migration, immune rejection of transplanted stem cells, and complications during surgery and postoperative infection. To address these challenges, NCATS proposes a novel exosome-based therapeutics paradigm to catalyze regenerative medicine. In terms of the therapeutic potential, exosomes are endogenous, small membrane-enclosed carriers of bioactive molecules used for intercellular signaling. Exosome-based intercellular communication can occur bidirectionally during normal cell homeostasis or as a consequence of pathological development. In a diseased cell indicating distress, the stem cell responds by releasing specific repair exosomes.

This concept is a paradigm shift in that it will use non-living cellular products, rather than stem cells, to promote tissue regeneration. The exosome-based therapies can promote tissue repair and wound healing that can be better translated into the clinic. ExTReMe would expand knowledge and resources developed by the NIH Common Fund's ExRNA Communication Program, in which exosomes are being investigated as critical mediators of intercellular communication. In addition, the concept would extend the recently concluded NIH Common Fund Regenerative Medicine Program and leverage the expertise of the NCATS Stem Cell Translation Laboratory (SCTL).

The objective of this concept is to transform regenerative medicine through novel exosome-based therapeutics in tissue repair and wound healing, with emphasis on direct exosome therapy (stem cell–

isolated, stored as off-the-shelf), as well as designer exosomes (personalized to the individual patient's needs). This research, when implemented, would focus on investigational new drug (IND)–enabling therapeutics and would involve early engagement with the FDA toward regulatory approval. A milestone-driven approach will be used to ensure that these exosome-based therapeutics for productive regeneration are translated to the clinic. Research activities and results are expected to spur a number of commercial activities beyond the initial NCATS investment.

***Discussion***

Ms. Kennedy expressed her appreciation for the innovation and the focus on personalized medicine highlighted in this concept. Regarding the scope and ideas for partnering with other groups, she emphasized thinking beyond FDA regulatory approvals (e.g., IND-enabling) to aspects of access and the Centers for Medicare & Medicaid Services (CMS) decisions about reimbursements, particularly while this new therapeutic paradigm is being built. Ms. Kennedy also noted having a data-sharing component of this concept. Dr. Rutter agreed with thinking ahead to access for this proposed program. Dr. Happel added that these comments will be considered as the program moves forward.

Dr. Kretzler commented that this concept is timely for molecular biology and leverages the work of the ExRNA consortium to identify methodological constraints and develop assets applicable to clinical confirmation. Although this strategy (i.e., transferring of biological activity with minimal characterization into a disease state) can be successful, he expressed concern that much largely remains unknown, particularly in interpreting treatment responses. Building on advancements to design vesicles and predefine their content, Dr. Kretzler suggested expanding the scope to targeting barcoded vesicles toward a clinical implementation strategy, employing the use of new technologies to define the responders. More precisely, he pointed out the integration of the discovery component with the translational aspect and the incentivizing for these activities. Dr. Happel remarked that NCATS is positioned to advance improvements in regenerative medicine utilizing the expertise of SCTL to generate well-characterized stem cells, develop exosome isolation technologies through the ExRNA Communication Program, and leverage the resources from the Regenerative Medicine Program.

Because the mechanisms of action are not always well understood, Dr. Summar suggested partnering with other groups (e.g., National Science Foundation) on the basic science efforts to better interpret the bioactive properties and observed effects. Dr. Happel noted the tools developed in existing and prior NIH and NCATS programs, along with technologies that will be valuable for mechanistic studies.

Dr. Ranganathan expressed his support of this concept and called attention to a recent finding linking exosomes to the gut–brain axis, which could potentially be valuable to investigate as a source of exosomes that can be cultured and purified and could provide insight into underlying mechanisms for therapeutics.

Dr. Happel and the OSI will consider Council members' suggestions to expand the concept scope to include vesicle targeting and a clinical implementation strategy, explore opportunities to partner with other groups doing similar basic science, and investigate other sources of exosomes to support mechanistic studies.

Members unanimously approved the ExTReMe concept.

**Additional comments/questions posted in the chat to all participants:**

16:49:06 From Matthias Kretzler to Everyone: HubMAP is building both tools and maps of the relevant components in parallel as well and scaling down quickly to sub cellular levels.

## X. ADJOURNMENT DAY 1: Joni L. Rutter, Ph.D., Acting Director, NCATS, Chair, NCATS Advisory Council

Dr. Rutter adjourned Day 1 of the meeting at 4:54 p.m. EST.

# JANUARY 21, 2022

## XI. CALL TO ORDER, OPEN SESSION DAY 2

Dr. Rutter called the meeting to order at 1:03 p.m. EST and welcomed Council members and guests to the second day of the 29th meeting of the NCATS Advisory Council. Dr. Ramsey-Ewing reminded attendees that the open session is being videocast and reviewed the agenda.

## XII. PROGRAM UPDATE: Office of Rare Diseases Research (ORDR): Anne R. Pariser, M.D., Director, ORDR, NCATS; P.J. Brooks, Ph.D., Deputy Director, ORDR, NCATS

Dr. Pariser provided updates on the activities and ongoing programs in the ORDR, and she was joined by Dr. Brooks. Dr. Pariser acknowledged the ORDR team and reminded the Council of the ORDR mission: advancing rare diseases research to benefit patients. The underlying problem — a public health problem — the ORDR is trying to solve is that approximately 10,000 rare diseases are known, and this number increases by more than 200 new diseases annually. Although the field's ability to identify these diseases has improved, 90% are classified as ultra-rare, affecting only 1 in 1 million people. Diagnosis remains a challenge, with estimates of 5–10 years to obtain an accurate identification. Patients with rare diseases often are underrecognized, and many are not aware they have such a disease. Although the molecular basis for most of the 10,000 rare diseases is known, 95% have no approved therapy. Making the argument for a business model for developing a therapy for a rare disease with few patients remains challenging. To address its mission and these challenges, the ORDR directs programs in three areas: data and informatics, research programs, and collaborations.

**Data and Informatics**

- **Genetics and Rare Diseases (GARD) Information Center.** The GARD Information Center, a Congressionally-mandated (Rare Disease Act of 2002) information clearinghouse on rare and genetic diseases, was established in 2003. The original GARD website (GARD 1.0) launched in 2008 contains 6,500 disease pages, has more than 20 million users annually, and fields approximately 10,000 individual inquiries annually, providing support for people affected by rare diseases. Dr. Pariser explained that upgrades to a GARD 2.0 have required a 2-year effort to modernize the disease information by incorporating a machine learning, machine capture approach. Information is collected once and reused multiple times. These upgrades aim to improve health literacy of rare genetic disorders. The GARD 2.0 beta test version of the website has launched and can be accessed from any GARD 1.0 disease page; feedback is welcomed.

- **Impact of Rare Disease Patients and Healthcare Systems (IDeaS) Initiative: Pilot Study.** NCATS collaborated with the University of Colorado, Sanford Health, and Eversana Life Science Services, LLC, in a pilot study to quantify the burden of 14 representative rare diseases. Results reported in the October 2021 issue of *Orphanet Journal of Rare Diseases* concluded that rare diseases are

common, costly, and potentially actionable. Dr. Pariser detailed the key findings. Patients with rare diseases are difficult to identify — and thus quantify — within EHRs and health care system databases. Direct medical costs of rare diseases can be three to five times higher than for non-rare diseases. The journey to a diagnosis (i.e., diagnostic odyssey) is real and prolonged, resulting in irreversible complications of disease and ongoing high costs of care. Three groups (EveryLife Foundation for Rare Diseases, Advocate Aurora Health, and U.S. Government Accountability Office) also evaluating the burden of rare diseases published their results in 2021. The overall messages fit with the findings and conclusions of the IDeaS pilot study: Rare diseases are costly in both economic and human terms; patients and diseases are underrecognized in health care system databases; and rare diseases are actionable, but underprioritized, given their health care system impact.

**Research Programs**

- **Diagnostic Odyssey.** Dr. Pariser reported that the ORDR published a FOA — Multi-disciplinary, Machine-assisted, Genomic Analysis and Clinical Approaches to Shortening the Rare Diseases Diagnostic Odyssey — using the biphasic UG3/UH3 mechanism. Applicants were asked to develop three-pronged approaches (i.e., machine-assistance + genetics + clinical team) to accelerate rare diseases diagnosis. This one-time RFA will be awarded in FY 2022. In September 2021, the Council approved the Small Business Innovation Research (SBIR) mechanism, Machine-Assisted Approaches to Shortening the Diagnostic Odyssey for Rare Diseases. The next steps will be to use IDeaS and other rare diseases informatics approaches to shorten the time to diagnosis. One such approach is developing rare, novel methods (i.e., "zebra triggers") to solve this clinical problem. Medical records (or other databases) show potential zebra triggers (e.g., young age, high utilization, multiple consultations, imprecise diagnostic codes) that can provide benefit if further investigated.

- **Rare Diseases Clinical Research Network (RDCRN).** NCATS' largest and longest-standing program, the RDCRN, was established in 2002 through the Rare Diseases Act. This Network of Centers of Excellence groups around rare diseases therapeutic areas. The purpose is to facilitate rare diseases research through the establishment or continuation of rare diseases clinical research consortia. Three or more related diseases or conditions are investigated within a consortium, and patients, researchers, and clinicians collaborate. The RDCRN comprises 20 consortia and a Data Management and Coordinating Center (DMCC); 10 NIH Institutes/Centers (ICs) collaborate in the network. The fourth award cycle (RDCRN4) cohort started in FY 2019, investigating roughly 175 rare diseases across more than 350 clinical sites and engaging more than 160 Coalition of Patient Advocacy Groups (CPAGs). More than 25,000 individual patients have enrolled in approximately 400 studies and trials. In terms of accomplishments, cumulatively RDCRN investigators have produced 1,500 publications and made nearly 2,500 presentations. The RDCRN has supported more than 300 early-stage investigators, conducted 87 natural history studies and activated 38 clinical trials, of which 26 are ongoing. Ninety studies have developed outcome measures, 76 have changed clinical practice, and 4 have resulted in FDA drug approvals.

- **Clinical Trial Readiness Grants.** NCATS released a 3-year Program Announcement with special review criteria and/or special receipt dates (PAR) for Exploratory/Developmental Research Grant (R21) awards and Small Research Grant (R03) awards to enable efficient and effective

movement of candidate therapeutics or diagnostics toward clinical trials, focusing on biomarkers and clinical outcomes. The final receipt date was October 2021, and more than 25 awards across a broad array of rare diseases have been issued in support of this PAR. The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) is a collaborator.

Dr. Brooks provided an update on the many-diseases-at-a-time projects.

- **Shared Molecular Etiologies (SaME).** Traditionally, diseases, including those that are rare, have been identified and treated based on clinical manifestations (e.g., phenotype). Many rare genetic diseases exist, but far fewer genetic etiologies (e.g., premature stop codons) have been described. Using SaME, patients with different diseases that are caused by the same underlying genetic abnormality can be treated with the same therapy in a basket clinical trial, a design successful in genomically-driven oncology basket trials. In FY 2021, the ORDR published two FOAs encouraging studies focusing on the treatment of SaME in non-oncology diseases. One FOA, the Basket Clinical Trials of Drugs Targeting SaME in Multiple Rare Diseases (UG3/UH3), is now closed, and two projects have been funded. The second FOA, Basket Clinical Trials of Drugs Targeting SaME in Multiple Rare Diseases (U44 Clinical Trial Required) uses the Small Business Innovation Research (SBIR) mechanism. In addition, the ORDR participates in the International Rare Diseases Research Consortium (IRDRC) and established a working group to focus on SaME.

- **Platform Vector Gene Therapy (PaVe-GT).** Three NCATS offices — ORDR, Office of Strategic Alliances (OSA), and the Therapeutic Development Branch — collaborated with the National Institute of Neurological Disorders and Stroke (NINDS) and the National Human Genome Research Institute (NHGRI) on the PaVe-GT. A research pilot through which four gene therapies for rare monogenic disorders are being developed simultaneously, PaVe-GT is using a platform design and adeno-associated virus (AAV) gene therapy vector. Multiple therapies for the same disease can thus be tested in the same clinical trial, a paradigm shift from a traditional one-at-a-time trial design. Dr. Brooks noted that all data, including FDA communications, will be made available to the public to share the lessons learned. Dr. Brooks explained that in contrast to the traditional clinical disease development paradigm of starting parallel trials in duplication for each disease using separate facilities, the PaVe-GT clinical development paradigm (a master protocol and basket trial) utilizes the same manufacturing facility and process, thus reducing the time to start a trial. The PaVe-GT is in its early stages of startup. In October 2021, a lead candidate drug for treating propionyl-CoA carboxylase deficiency, AAV9-rhPCCA, received FDA orphan-drug designation. The team is developing a white paper with the details of that process, and related documents will be publicly available. In July 2021, NCATS and the FDA Center for Biologics Evaluation and Research (CBER) held an INitial Targeted Engagement for Regulatory Advice on CBER producTs (commonly called INTERACT) meeting. A Rare Pediatric Disease Designation application is planned.

- **Bespoke Gene Therapy Consortium (BGTC).** NCATS, CBER, and FNIH organized the establishment of the BGTC, a major component of the FNIH Gene Therapy Accelerating Medicines Partnership (AMP). The goal is to identify and streamline the process of starting an AAV gene therapy trial. Many NIH ICs and private-sector partners are members of AMP, and the list is growing. The BGTC consists of two components. The basic science component focuses on AAV basic biology and translational implications to enhance vector generation and therapeutic gene expression. The larger clinical component seeks to advance access to AAV technologies and

vectors for Bespoke clinical applications. The aim is to create and build capacity, harmonize best practices, and streamline the regulatory pathway. The FNIH and NCATS are in the process of selecting rare diseases for the pilot projects in an open platform. Interested parties can submit a Disease Nomination Form for the BGTC clinical program until February 18, 2022.

- **Somatic Cell Genome Editing (SCGE) Program.** NCATS, in partnership with NINDS, is leading the SCGE, an NIH Common Fund program that began in 2017. The aim is to lower the barriers for new genome-editing therapies. Approaches include developing better animal models for testing genome editing, assessing unintended biological effects of genome editing, monitoring edited cells *in vivo*, improving *in vivo* delivery of genome-editing machinery, and expanding the human genome editing repertoire. A major component of the program is the dissemination and coordination system and a toolkit highlighting the technologies developed in the SCGE.
  Dr. Brooks acknowledged the NIH-wide SCGE Working Group that is co-chaired by Dr. Rutter and Walter Koroshetz, M.D., Director, NINDS. The SCGE Phase 2 was approved by the NIH Council of Councils in September 2021, and four initiatives were proposed, including platform clinical trials. The goal is to support gene-editing trials for multiple diseases at a time. The process and FDA requirements and interactions are similar to those of the PaVe-GT.

**Collaborations**

Dr. Brooks provided an update on ORDR collaborations and focused on meetings the Office is co-sponsoring. Dr. Rutter updated the Council on the 2022 NCATS Rare Disease Day (RDD) at NIH in the Director's Report.

- **Gene Therapy Meeting Series.** Dr. Brooks noted that in June 2021, the ORDR, NICHD, and NINDS collaborated to convene a series of three virtual meetings focusing on gene-targeted therapies in terms of early diagnosis and equitable delivery. Participants explored strategies for identification of all patients who might benefit from gene-targeted therapies, one disease at a time. More than 1,500 people attended, and the meeting archive can be accessed via the NIH VideoCast.

- **Regulatory Fitness and Rare Diseases Trials Workshop.** NCATS and the FDA Center for Drug Evaluation and Research (CDER) are co-sponsoring a virtual public workshop on regulatory fitness and rare diseases trials to be held on April 7–8, 2022. The purpose is to help rare diseases investigators develop the best regulatory-compatible INDs for their clinical trials. The intended audience is academic investigators and representatives from small pharmaceutical and biotechnology companies.

***Discussion***

Council members expressed appreciation to Dr. Pariser for her leadership of the ORDR and to the entire ORDR staff for their efforts. They also congratulated Dr. Pariser on her retirement.

Dr. Summar, who is a member of the Rare Disease Diversity Coalition Steering Committee for the Black Women's Health Imperative, called attention to a rare diseases initiative to collect baseline data on the participation of underrepresented minorities and ethnic groups in rare diseases research. The Steering Committee met with Rare Diseases Clinical Research Consortia (RDCRC) PIs of a large-scale, long-term

rare diseases study to obtain real-world data. The intent is to consolidate deidentified data from the annual reports of patient enrollment, representing 50,000 patients.

Dr. Summar asked about areas that need to be built to advance the rare diseases community and substantial opportunities for the future. Dr. Pariser highlighted advancing more of the many-diseases-at-a-time approaches for diagnostics and supporting studies in the 2- to 5-years old age group with rare diseases as two key areas to advance. Dr. Summar also asked whether interactions about diagnostics with the Global Commission on Rare Diseases (Global Commission) have occurred. Dr. Pariser noted that the ORDR and Global Commission have not had those discussions but agreed that doing so should be considered in the future. Dr. Brooks added that addressing diverse populations in clinical trials also would be an area in which the community could stand to advance.

Ms. Kennedy noted a resource that could be useful to the ORDR for planning of future initiatives, a soon-to-be published handbook detailing FDA guidance on patient experiences, data from across agencies, and information on the medical product life cycle. She inquired about plans to work with the Centers for Disease Control and Prevention, professional and medical societies, or the National Society of Genetic Counselors on data related to shortening the diagnostic odyssey. Dr. Pariser explained that the ORDR is working with a data analytics contractor to test some of the identified approaches and has funded grants to develop other strategies. Engaging these groups when more data become available, and approaches become actionable would be most beneficial.

Dr. Jackson pointed out that research shows that across the life span of children with a rare disease, the integrated systems of support accompanying a diagnosis are not sustained into the adult years. She reiterated addressing implementation across the entire translational science spectrum and supporting research to understand the best ways to live more effectively with a rare disease with no known cure. Dr. Pariser agreed and noted feedback from investigators and patients indicating that in some cases, certain diseases are victims of their own success; many patients who are living longer — and therefore are transitioning from pediatric to adult care — are without suitable clinics.

Ms. Hartman emphasized increasing awareness, education, and understanding on Capitol Hill about the diagnostic odyssey. Thanks to the advocacy efforts of EveryLife Foundation for Rare Diseases, The Assistance Fund, and other rare diseases organizations, Cures 2.0 contains language supporting the Centers for Medicare & Medicaid Services (CMS) coverage for genomic sequencing. She encouraged NCATS to take a leadership role in educating Congress about the issues regarding clinicians' access to the best available tests to diagnose a rare disease. Ms. Hartman also shared comments on the advantages of care coordination and complex care programs for families with children with rare diseases, of which she has firsthand experience.

Dr. McVearry agreed with the focus on diagnostics as a big opportunity for the ORDR and agreed with the comments on educating groups about the diagnostic journey. She also noted the need for industry incentives to recognize the commercial value of diagnostics. Dr. McVearry called attention to the Lupus Clinical Investigators Network (LuCIN). Although lupus is not a rare disease, LuCIN provides a rich resource that pharmaceutical companies and other organizations can activate to better manage care for patients with lupus; the network is underutilized because of limited diagnostic opportunities. Dr. Pariser commented that achieving a diagnosis is not a rare diseases issue; many common diseases, especially atypical presentations, are difficult to diagnose.

Dr. Kretzler encouraged continued interactions with the IRDRC, including engagement in leadership roles, and urged attendees not to allow the U.S.–international borders to inhibit progress in rare diseases research. He emphasized sending clear messages to scientists across the border that rare diseases are being addressed globally. Dr. Summar added that rare diseases research is a global exercise, noting the many ongoing international efforts, and knowledge gained from every patient with a rare disease, to advance the field.

Dr. Harris asked when GARD 2.0 would be released. Dr. Pariser clarified that the test site (English version only) is live and available for examination and input. The exact date of the full launch of the upgrade will depend on the feedback received and the changes that will be made.

**Additional comments/questions posted in the chat to all participants:**

13:57:30 From Paul Harris to Everyone: Is there a projected date for release of GARD 2.0 website?

13:57:36 From Matthias Kretzler to Everyone: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/investigational-new-drug-application-submissions-individualized-antisense-oligonucleotide-drug-0

13:57:39 From Marshall Summar to Everyone: https://www.globalrarediseasecommission.com/

14:05:32 From Christina Hartman to Everyone: https://www.researchamerica.org/day-1-race-against-time

14:09:48 From Marshall Summar to Everyone: As Christina is saying the diagnosis is key but just the first step in a very long journey.

14:16:18 From Annie Kennedy to Everyone: Perhaps an example of how the Zebra Trigger initiative could move forward and partner with others to build algorithms and implementation tools for providers. This was an initiative funded by CDC to PPMD and we worked with AAP, NSGC, ACMG, and many others. https://childmuscleweakness.org/

14:17:07 From Marshall Summar to Everyone: https://www.foundation29.org/en/ Here is one of the international groups working on machine learning on dx for rare diseases.

## XIII. CLEARANCE OF CONCEPTS

The Council received presentations on two renewal initiatives that NCATS is considering for funding. At the end of each presentation, the members discussed the concepts and voted on whether to approve moving forward with each concept.

**Introduction of Office of Rare Diseases Research (ORDR) Concepts: Anne R. Pariser, M.D., Director, ORDR, NCATS**

Dr. Pariser noted the ORDR's mission and the main categories of focus, including research. The Rare Diseases Clinical Research Network (RDCRN) is the largest research effort of the Office and aligns with the overarching goal to improve the research environment for patients with rare diseases. Echoing her previous description of the RDCRN4 regarding the 20 consortia, she highlighted the diverse topics and collaborations. The ORDR is seeking approval of two renewal concepts of two components of the RDCRN, the Rare Disease Clinical Research Consortia (RDCRC) and Data Management and Coordinating

Center (DMCC). Dr. Pariser explained that the RDCRN goals and overview apply to both the RDCRC and DMCC concepts. If approved by the Council, each would have separate FOAs and RFAs.

**Rare Diseases Clinical Research Network (RDCRN) – Rare Disease Clinical Research Consortia: Tiina K. Urv, Ph.D., Program Director, ORDR, NCATS**

Tiina K. Urv, Ph.D., M.P.H., presented a renewal concept for the RDCRN Rare Disease Clinical Research Consortia (RDCRC). Established by the Rare Disease Act of 2002 to promote highly collaborative, multisite, patient-centric, translational, and clinical research in rare diseases research, the RDCRN, through the RDCRC, has always supported the study of three or more rare diseases at once. This renewal concept addresses several gaps in rare diseases research. The field lacks foundational and translational research that fully describes rare diseases and facilitates the movement of candidate treatments into the clinic. The cost (i.e., time and money) of one-disease-at-a-time approaches to rare diseases research remains high. Standardized, high-quality data and broad data sharing for rare diseases are needed.

NCATS proposes this renewal concept to advance the diagnosis, management, and treatment of rare diseases by focusing on unmet clinical trial readiness essentials that will advance the research by establishing, maintaining, and supporting Rare Disease Centers of Excellence. The objectives are threefold: (1) Lessen the risk of failure in clinical trials by being well prepared prior to starting a trial, (2) develop an effective and efficient research environment for rare diseases research, and (3) facilitate data sharing. The key areas of emphasis are to (1) conduct research studies that promote clinical trial readiness, such as natural history studies, biomarker identification, and outcome measures development; (2) provide a research environment that delivers support and opportunities for students and early-stage investigators and engages patient advocacy groups as full partners with RDCRN; and (3) develop and maintain a cloud-based research environment with shared tools and cross-network collaborations.

In terms of implementation and expected impact, the RDCRN currently supports 20 RDCRCs that study 165 different rare diseases and conducts research at 358 sites (144 co-located at Clinical and Translational Science Awards (CTSA) sites) in 12 countries. Currently, 166 Coalition of Patient Advocacy Groups (CPAGs) partner in the consortia. Within the RDCRN4 cohort, 10 will sunset and 10 will be eligible to recompete. The ORDR facilitates and coordinates rare diseases research at NIH, and the RDCRN plays a significant role. The RDCRN program partners with nine other NIH Institutes/Centers (ICs). The RDCRN is a one-of-a-kind translational research network at NIH, establishing partnerships to address multisystemic disorders, supporting research into very low prevalence rare diseases, and advancing the many-diseases-at-a-time approaches.

Success has been, and will continue to be, measured through progress in addressing consortia-specific gaps in clinical trial readiness; publications generated; initiation of longitudinal observational studies and accruals; participation of clinical sites and patient advocacy groups (PAGs) in the research; and the numbers and types of pilot studies and clinical trials conducted.

***Discussion***

Dr. Jackson commented that the RDCRN's natural history studies have identified the key issues in early diagnosis, treatment options, late ramifications, integration of health care, and social support. She pointed out the opportunity to think broadly across the entire translational research spectrum to

address these issues and build additional pilot studies that will be critical for people with rare diseases, a recurring theme among patients, clinicians, and caregivers. In terms of data equity and accessibility to all stakeholders, Dr. Jackson remarked that each individual who participates in a rare disease trial and donates his or her data should have the right to have equal access to the information to better understand results that are relevant, common, and emerging. Dr. Jackson encouraged thinking across pathways and broadening the scope to include studies that group by organ systems that could improve effectiveness around diagnosis and potentially in developing therapeutics. Dr. Urv pointed out that the definition of three rare diseases that must be studied by an RDCRC is broad to include rare disorders with similar pathways, or pathway-focused approaches. She added that data equity will be discussed in the next presentation.

Ms. Kennedy expressed her enthusiasm in the RDCRN, which has a lasting impact in the community and suggested updating the RDCRN website infographics. She also proposed including additional metrics to evaluate accomplishments, such as updates to the Recommended Uniform Screening Panel, nationally and internationally across the ORDR programs, as well as the resources generated to inform patient-focused drug development workshops or engagements with FDA or the Centers for Medicare & Medicaid Services (CMS). Ms. Kennedy asked about the percentage of consortia investigating ultra-rare diseases and how intentional NCATS is on evaluating the benefit the PAGs derive, beyond what aids the community. In addition, she commented that NCATS is well positioned to mentor new PAGs that join the RDCRC and that the NCATS Toolkit for Patient-Focused Therapy Development would be a place to start to identify capacities and resources. Dr. Urv explained that the DMCC supports the PAGs and that these groups have a presence in the RDCRN with a CPAG Steering Committee. She noted that mentors are assigned to work with new PAGs joining the consortia. Dr. Brooks added that the ORDR will continue to encourage investigators to propose alternative groupings that, to some extent, can redefine what a disease is and can address the ultra-rare disorders.

Dr. Summar commented on data collection and on the preservation and availability of these data beyond NIH funding. He suggested standardization of terms and data collection and engaging the FDA to review the RDCRN data structures for compatibility across systems. Dr. Summar also highlighted the need for ways to structure the RDCRC to increase patient participation, especially for patients living in remote areas from a consortium.

The ORDR will consider the Council members' suggestions to support additional pilot studies that will be critical for people with rare diseases, broaden the scope to include studies that group by organ systems, include additional metrics to evaluate accomplishments nationally and internationally, and develop data standards.

Members unanimously approved the RDCRN RDCRC renewal concept.

**Rare Disease Clinical Research Network (RDCRN) – Data Management and Coordinating Center: Tiina K. Urv, Ph.D., Program Director, ORDR, NCATS**

Dr. Urv presented a renewal concept for the RDCRN Data Management and Coordinating Center (DMCC). The objectives are to (1) provide administrative, clinical research, data management, and regulatory support to the individual RDCRCs and the RDCRN; (2) provide a centralized cloud-based research environment with shared resources for the network and participants; and (3) coordinate cross-network activities, such as working group or special interest group meetings. In addition, the DMCC

serves as a conduit of information related to the rare diseases research being conducted within the network to both the research community and the general public.

The DMCC has three key areas of emphasis: (1) Promote clinical trial readiness and support and facilitate cross-consortia collaboration; (2) establish and promote standards and good data practices, emphasizing scientific rigor, FAIR (Findable, Accessible, Interoperable, and Reusable) data principles, and data sharing; and (3) develop and maintain a cloud-based research environment with shared tools.

To date, the DMCC has provided services to more than 2,000 authenticated users across five continents and has developed 12 tools for shared network use (e.g., biospecimen tracking tool, pedigree drawing tool, Ambra Health, RStudio), 55 protocols in REDCap databases, several new and legacy forms, numerous new and legacy variables, and 1.5 terabytes of data in Box. The DMCC collaborated with the NCATS Information Technology Resources Branch to develop a two-pronged cloud-based workspace for RDCRN researchers.

The RDCRN is a one-of-a-kind translational research network at NIH. A successful program is one in which the investigators are working in the research environment established by the network and using the tools made available. Success also will be measured by the achievements of the individual RDCRCs and the use and acceptance of DMCC-hosted collaborative tools and activities.

***Discussion***

Dr. Jackson noted two points: (1) data accessibility for the research community should reflect a broad community of stakeholders and (2) the DMCC is bringing an additional data set that allows the field to utilize national data to better understand the rare diseases communities and natural history of disease. Dr. Urv called attention to the tools and data standards being developed in the DMCC to ensure data interoperability.

Ms. Kennedy commented on the copious data the rare diseases community collects that are stored in various sources. She emphasized the need for central data collection, with storage sustainability and to leverage major collaborative efforts of data collection groups, such as the Critical Path Institute, National Organization for Rare Disorders, or RARE-X.

Dr. Kretzler elaborated on how the RDCRN can align the knowledge streams in terms of available tools to rapidly target, recover, or eliminate functions of molecules in cells causing diseases. As new data fields continue to emerge from the studies, the value lies in the data sharing, not data isolation. He recommended incentivizing activities between RDCRCs, establishing data quality standards, and soliciting input from multiple stakeholders about data.

Jill Morris, Ph.D., the National Institute of Neurological Disorders and Stroke (NINDS) RDCRN liaison to NCATS, called attention to the establishment of four data standard working groups within this RDCRN4 cohort. The working groups meet regularly, and investigators, PAG representatives, and DMCC leadership attend. The groups will be establishing data standards that will be useful to advancing studies to the clinic.

Dr. Kretzler recommended providing incentives, establishing data quality standards, and engaging multiple stakeholders in the next phases of the DMCC.

Members unanimously approved the RDCRN DMCC renewal concept.

**Additional comments/questions posted in the chat to all participants:**

15:04:15 From Matthias Kretzler to Everyone: https://www.kpmp.org/opportunity-pool

15:05:26 From Matthias Kretzler to Everyone: https://www.nationalacademies.org/our-work/return-of-individual-specific-research-results-generated-in-research-laboratories

## XIV. NCATS Triennial Inclusions Report: Valery M. Gordon, Ph.D., M.P.H., Senior Advisor for Clinical Research and Inclusion Policy Officer, Office of Translational Medicine (OTM), NCATS

Dr. Valery M. Gordon presented the NCATS FY 2019–FY 2021 Triennial Report on Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities in Clinical Research. The Public Health Service Act requires NIH to include women and minorities in NIH-funded research in a manner appropriate to the scientific questions under study. NIH reports aggregate data to Congress in the NIH Triennial Report. As part of the report, each NIH IC presents the data to its Advisory Council. The NIH Office of Extramural Research (OER) requires certification by IC directors that data are acceptable for inclusion in the FY 2019–FY 2021 Triennial Report.

The majority of NCATS-supported clinical research is structured within formal partnerships with other NIH Institutes/Centers (ICs). To avoid duplication of reporting, the partnering IC, not NCATS, reports the inclusion enrollment data. Examples of NIH and NCATS programs for which other ICs report enrollment data include the NIH Community Engagement Alliance (CEAL) Against COVID-19 Disparities, NIH Helping to End Addiction Long-term℠ (HEAL) Initiative, NCATS Trial Innovation Network (TIN), and Rare Diseases Clinical Research Network (RDCRN). Examples of NCATS programs for which NCATS reports the enrollment data include Clinical and Translational Science Awards (CTSA) Program Collaborative Innovation Awards, Small Business Innovation Research (SBIR)/Small Business Technology Transfer (STTR) awards, and CTSA pilot studies, of which more than 300 were conducted in FY 2021. Dr. Gordon explained that the NCATS intramural program did not support any clinical research involving human subjects directly during this reporting period but is planning research projects through Division of Preclinical Innovation for FY 2022.

### NCATS FY 2019–2021 Inclusion Efforts

NCATS applied the innovative translational science paradigm to address health disparities in underserved and vulnerable populations. The Center leveraged the CTSAs to participate in NIH-wide efforts (e.g., CEAL) to explore ways to increase inclusion of rural, underserved, and vulnerable populations. NCATS published a notice (NOT-TR-19-015) to promote expansion of CTSA efforts to accelerate clinical and translational research to address health disparities and the significant burden of conditions that disproportionately affect rural, minority, and other underserved populations. In 2021, NCATS enhanced CTSA Program goals to address health disparities and deliver the benefits of translational science to all. Dr. Gordon noted that NCATS had a lower number of awards involving human subjects research in FY 2021 due to coordinated efforts related to the COVID-19 pandemic.

### NCATS FY 2019–2021 Inclusion Enrollment Data

Dr. Gordon explained that the tables show interim and cumulative data. Interim data reflect the information collected by OER for studies that may continue beyond FY 2021. Cumulative data are enrollment data for studies that may have started prior to FY 2021. The FY 2019 and FY 2020 data are

provided as a benchmark for the FY 2021 data. All studies involving secondary data analysis are excluded. The data shown in the tables are standardized and represent responses to specific requests to NIH. Inclusion enrollment data by Research Condition and Disease Categorization (commonly referred to as RCDC) category are available on the NIH website.

Dr. Gordon highlighted the major points of the following NCATS data tables: Domestic vs. Foreign Inclusion Enrollment Reports (IERs); NIH-Defined Phase 3 Clinical Trials; Enrollment by Sex/Gender; Enrollment by Sex/Gender and Race/Ethnicity; U.S. Site Minority Enrollment; Enrollment by Minority and Race; and U.S. Site Enrollment by Ethnicity. Those data show that significantly more studies were conducted in the United States than internationally, and the number of FY 2021 IERs was similar to FY 2019. Enrollment was delayed at some clinical sites because of COVID-19, and those IERs are yet to be reported. NCATS reported no NIH-defined Phase 3 clinical trial IERs in FY 2021, which was a decrease from prior years. The number of total females enrolled in FY 2021 is similar to the number of males enrolled. The percentage of unknown enrollees decreased significantly in FY 2021 and now approaches the NIH level of 3%, all to the credit of a focused effort by the NCATS Division of Clinical Innovation (DCI). For all NCATS NIH-defined clinical research, the numbers of female and male minority enrollees were similar each fiscal year. Most enrollees in FY 2021 were white and non-Hispanic. The percent minority enrollment in the United States was similar across the last three fiscal years. The percentage of minority enrollees in the United States was lower in FY 2021 than the previous fiscal year. FY 2021 shows increasing percentages of white and more than one race enrollees (self-reported data). The percentage of enrollees indicating more one race increased over the last three years, and the percentage of enrollees with unknown race decreased. The percentage of Hispanic enrollees decreased between FY 2019 and FY 2021.

**Future Plans and Next Steps**

Dr. Gordon informed the Council that NCATS has three major approaches to adhering to the NIH Policy on the Inclusion of Women and Minorities in Clinical Research. First, support efforts to increase minority participation and diversity in NCATS-specific programs and other NIH programs that leverage the Center's programs and resources. Second, strengthen partnerships with collaborators to ensure that equity, diversity, and inclusion are meaningfully addressed in all NCATS initiatives. Third, provide public transparency on the equity, diversity, and inclusion goals, actions, and metrics of NCATS research projects and activities, including grants.

***Discussion***

Paula K. Shireman, M.D., M.B.A., commented that she was amazed that Hispanic enrollment decreased, particularly because this population is one of the most rapidly growing in the United States. She noted the challenge to interpret data when values are missing, inaccurate, and/or conflicting and asked about plans to improve these data issues so that the unknown category is not inflated for any specific race or ethnicity. Dr. Shireman also asked how variables related to low economic status, low resources, and rural health would be accounted for in this already complex area. Dr. Gordon conveyed that NCATS is closely monitoring minority enrollment and noted that the small numbers (i.e., sample size) have magnified the differences. Any data issues that will be corrected later will still show in the report, because the data presented at today's meeting reflect the information collected as of the date the report was obtained, which, in this case, was in November 2021.

Dr. Rutter explained that these data are dynamic — and can be challenging to interpret — but highlight issues NCATS needs to address. She noted discussions with the National Institute on Minority Health and Health Disparities about coordinating and/or collaborating efforts with their Research Centers in Minority Institutions Specialized Centers program. Dr. Rutter also called attention to ongoing efforts in the CTSA Program and interactions across NIH ICs to address diversity, equity, and inclusion. Michael G. Kurilla M.D., Ph.D., Director, DCI, NCATS reminded the Council that major efforts in which NCATS is involved — such as CEAL and large clinical trials in the TIN — are reported by partnering ICs and are not included in this report presented at today's meeting.

Dr. Harris appreciated Dr. Rutter's further elaborating on NCATS' remediation plan regarding minority enrollment. He requested an update at the next Council meeting on the ongoing strategies and approaches on this topic, to which Dr. Rutter agreed. Dr. Gordon added that OTM generates an internal report annually that could be made available to the Council.

Regarding minority enrollment in trials, Dr. Summar observed a trend in self-reporting more than one race that is frequent among families but does not necessarily reflect who the patients are. He also observed that people from non-English-speaking communities, including the Hispanic population, who choose not to participate in clinical research report feeling overwhelmed by the institutional review board consent process.

Dr. Kretzler called attention to the challenges that are consequences of external forces, such as the COVID-19 pandemic, that likely are reflected in these recent data. In addressing minority engagement in trials, he encouraged closely monitoring how minority populations recover from the COVID-19 pandemic.

**Action Item:** NCATS OTM, at a future meeting, will update the Council on strategies to improve minority enrollment in NIH-defined Phase 3 clinical trials that the Center reports.

## XV. Public Hearing of Proposed Organizational Change – Division of Extramural Activities and Division of Rare Diseases Innovation: Keith R. Lamirande, M.B.A., Associate Director for Administration and Executive Officer, NCATS

Keith R. Lamirande, M.B.A., reminded Council members of the requirement of the NIH Reform Act of 2006 for public hearings and NIH director approval of any organizational changes within the NIH Institutes/Centers (ICs). Mr. Lamirande announced that NCATS proposes the following organizational changes: the Office of Grants Management and Scientific Review (OGMSR) would be elevated to the Division of Extramural Activities (DEA), and the Office of Rare Diseases Research (ORDR) would become the new Division of Rare Diseases Research Innovation (DRDRI). Of the 24 grant-issuing ICs, 15 have a DEA to conduct grants management and scientific review functions and to coordinate extramural policy and operations. This proposal seeks to align NCATS accordingly. The current OGMSR structure within the Office of the Director includes the Office of Grants Management and Office of Scientific Review. The proposed structure will establish an Office of the DEA Director, Grants Management Branch, and Scientific Review Branch.

Mr. Lamirande explained that the ORDR has been a part of NCATS since inception. The ORDR director is responsible for advising the NIH director and NCATS director on rare diseases. NCATS now seeks to elevate this Office to a Division to reflect the importance of rare diseases research to the Center. This

proposal will establish two subcomponents as operating branches: Advanced Therapeutics and Research Branch and Collaborative Research, Informatics, and Special Programs Branch.

Regarding the Delegations of Authority, approval of reorganizing the OGMSR to the DEA is made by the NIH Deputy Director for Management. Approval of reorganizing the ORDR to a Division is made by the Department of Health and Human Services (HHS) Secretary. Conforming legislation is to be passed following approval of the organizational change.

Mr. Lamirande informed the Council that comments can be sent via email to NCATSCouncilInput@mail.nih.gov until February 5, 2022. Public comment also is invited on NCATS' Proposed Organizational Changes at NCATS website. Comments from the website will be reviewed the week of January 31, 2022 to February 4, 2022, and will be summarized for the respective organizational change packages.

***Discussion***

Ms. Kennedy asked whether the use of "research" in the proposed Division of Rare Diseases Research Innovation would be restrictive. She explained that NCATS is the central location of rare diseases research, including innovation for NIH, which also encompasses aspects of data, diagnostics, and screening, among others. Mr. Lamirande stated that discussions were held within NCATS to address this point, but concerns were raised about the overall acronym. Dr. Rutter added that NCATS welcomes Council input. Members made some suggestions that NCATS will address.

NCATS will consider Council input on the naming for the proposed offices and divisions in the organizational changes. Council members will send comments on the proposed NCATS organizational changes by February 5, 2022.

**Additional comments/questions posted in the chat to all participants:**

15:48:49 From Marshall Summar to Everyone: Annie is making a great point. Like the title without research.

15:51:20 From Marshall Summar to Everyone: Division of Rare Advancement DORA,

15:51:30 From Christina Hartman to Everyone: Love that!!!

15:53:28 From Paula Shireman to Everyone: Division of Rare Disease Advancement and Innovation DORDAI?

## XVI. PUBLIC COMMENTS

Comments from the public were accepted until February 5, 2022 (15 days after the meeting) and will be appended to the minutes.

## XVII. ADJOURNMENT OF THE OPEN MEETING

Dr. Rutter thanked the participants for their input. The next meeting is scheduled for May 19, 2022 and is planned as an in-person assembly. Dr. Rutter adjourned the meeting on January 21, 2022, at 3:54 p.m. EST.

**CERTIFICATIONS**

We hereby certify that, to the best of our knowledge, the foregoing minutes and supplements are accurate and complete.

Joni Rutter, Ph.D. Date
Chair, NCATS Advisory Council
Acting Director, National Center for Advancing Translational Sciences, NIH

Anna L. Ramsey-Ewing, Ph.D. Date
Executive Secretary, NCATS Advisory Council
Executive Secretary, Cures Acceleration Network Review Board
Director, Office of Grants Management and Scientific Review, NCATS