Department of Health and Human Services
National Institutes of Health

National Center for Advancing Translational Sciences Advisory Council
and
Cures Acceleration Network Review Board

Minutes of Joint Meeting
September 27, 2018

The National Center for Advancing Translational Sciences (NCATS) Advisory Council and the Cures Acceleration Network (CAN) Review Board held a joint meeting in open session on September 27, 2018, convening at 8:30 a.m. ET in Conference Room 6, Building 31, on the National Institutes of Health (NIH) main campus. Christopher P. Austin, M.D., NCATS Advisory Council chair; and G. Lynn Marks, M.D., CAN Review Board chair, led the meeting. In accordance with Public Law 92-463, the session was open to the public.

Following the joint meeting, the NCATS Advisory Council met in closed session for the review and consideration of grant applications.

NCATS ADVISORY COUNCIL MEMBERS PRESENT

Chair

Christopher P. Austin, M.D., Director, NCATS

Executive Secretary

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

Council Members

Ronald J. Bartek, M.A. (by telephone)
Richard E. Kuntz, M.D.
G. Lynn Marks, M.D.
Valerie Montgomery Rice, M.D. (by telephone)
Megan O'Boyle
Alan D. Palkowitz, Ph.D.
Harry P. Selker, M.D., M.S.P.H.
Anantha Shekhar, M.D., Ph.D. (by telephone)

Representative Members

None present

***Ex Officio* Members**

Rachel Ramoni, D.M.D., Sc.D., U.S. Department of Veterans Affairs (VA)
York Tomita, Ph.D. (for Scott Gottlieb, M.D.), Food and Drug Administration (FDA)

CAN REVIEW BOARD MEMBERS PRESENT

Chair

G. Lynn Marks, M.D., Senior Research and Development (R&D) Advisor, Biomedical Advanced Research and Development Authority (BARDA), Office of the Assistant Secretary for Preparedness and Response (ASPR), U.S. Department of Health and Human Services (HHS); and Chair, CAN Review Board

Vice Chair

Ronald J. Bartek, M.A., Co-Founder and Founding President, Friedreich's Ataxia Research Alliance (by telephone)

Executive Secretary

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

Board Members

Valerie Montgomery Rice, M.D. (by telephone)
Megan O'Boyle
Alan D. Palkowitz, Ph.D.
Harry P. Selker, M.D., M.S.P.H.
Anantha Shekhar, M.D., Ph.D. (by telephone)

Representative Members

None present

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Richard E. Kuntz, M.D.
Rachel Ramoni, D.M.D., Sc.D., U.S. Department of Veterans Affairs (VA)
York Tomita, Ph.D. (for Scott Gottlieb., M.D.), Food and Drug Administration (FDA)

OTHERS PRESENT

Anne Berry, M.P.P., American Association of Medical Colleges
Paul Harris, Ph.D., Vanderbilt University
Consuelo H. Wilkins, M.D., M.S.C.I., Vanderbilt University Medical Center and Meharry Medical College
Robert Yates, SRI International
NCATS leadership and staff

I. CALL TO ORDER, OPEN SESSION

Christopher P. Austin, M.D., and G. Lynn Marks, M.D., called the meeting to order. Dr. Austin welcomed members and guests to the 19th meeting of the NCATS Advisory Council and the 24th meeting of the CAN Review Board. He reminded attendees that the open session was being videocast. Dr. Marks extended a welcome on behalf of the CAN Review Board, and Dr. Austin introduced the members of the Council and the Board and previewed the meeting agenda.

II. APPROVAL OF MINUTES: Anna L. Ramsey-Ewing, Ph.D., Executive Secretary, NCATS Advisory Council and CAN Review Board

Members approved the May 2018 minutes unanimously.

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

Anna L. Ramsey-Ewing, Ph.D., informed attendees that the NCATS Advisory Council and CAN Review Board will hold joint meetings on January 10, May 16 and September 19 in 2019. The 2020 joint meetings will take place on January 16, May 14 and September 17. The CAN Review Board will meet by teleconference on December 14, 2018; December 13, 2019; and December 11, 2020.

IV. DIRECTOR'S REPORT: Christopher P. Austin, M.D., Director, NCATS

Dr. Austin reviewed the agenda and began the director's report.

Helping to End Addiction Long-term (HEAL) Initiative

Congress appropriated to NIH $500 million in fiscal year (FY) 2018 for the HEAL Initiative to help improve prevention and treatment strategies for opioid misuse and addiction. The initiative is also meant to enhance pain management by researching the neurobiology of pain, developing nonaddictive treatments and developing shared treatment platforms.

NIH Director Francis S. Collins, M.D., Ph.D.; National Institute on Drug Abuse Director Nora Volkow, M.D.; and National Institute of Neurological Disorders and Stroke (NINDS) Director Walter Koroshetz, Ph.D., announced the HEAL research plan in July in a paper published in *JAMA*.

As part of the HEAL Initiative, NCATS is leading a project to engineer pre-clinical platforms to test new nonaddictive treatments. The platforms include induced pluripotent stem cell (iPSC)-derived neurons for pain and reward pathways, tissue chips and 3-D bioprinted tissue models.

Through its existing programs, NCATS can also help:

- Design and build new chemical structures to combat opioid misuse and addiction and treat pain through A Specialized Platform for Innovative Research Exploration (ASPIRE);
- Identify drug-like compounds that act on biological targets of opioids and pain and test them in cell and animal models; and
- Develop new therapies for clinical testing through the Bridging Interventional Development Gaps (BrIDGs) program.

The Stem Cell Translation Laboratory has developed a protocol to produce iPSC-derived sensory neurons that are physiologically active nociceptors. The protocol will allow investigators to generate nociceptors in large quantities to use for drug screening projects.

NCATS is actively soliciting collaborations with investigators inside and outside of NIH to work on HEAL initiatives related to pain, opioid overdose and opioid misuse. ASPIRE is planning to issue challenges for an integrated chemistry database, electronic synthetic chemistry portal, predictive algorithms, biological assays and integrated solutions.

Clinical and Translational Science Award (CTSA) Program Trainee Project Highlights

Researchers at the University of California, San Diego, a CTSA Program hub, have developed a wearable electronic device that is both stretchable and bendable and can control a robotic limb or monitor respiration, eye movement, and heart and brain activity.

Investigators at the University of Colorado developed a way to monitor hemodynamic vital signs, using machine learning techniques to detect changes in arterial pulse waveforms associated with progress to hemodynamic decompensation and fainting.

KL2 scholar Halima Amjad, M.D., M.P.H., found that 60 percent of adults with probable dementia were either undiagnosed or unaware of their diagnosis. KL2 scholar Adeyinka O. Laiyemo, M.D., M.P.H., developed an approach that uses social networks and paid patient navigators to increase the number of screening colonoscopies among African Americans. KL2 scholar David S. Auerbach, Ph.D., noting a link between long QT syndrome and seizure disorder, urged doctors to pay attention to the hearts and the brains of patients with long QT syndrome.

CTSA Program Supplements

The fiscal year (FY) 2018 budget, which Congress passed in March, contained an additional $26.6 million for the CTSA Program. NCATS issued a notice of the available supplements in April, received applications

by June 1 and completed reviews by July 1. Of the funding for projects, 48 percent went to research software applications, 16 percent to the opioid crisis, 13 percent to methods and processes, and 11 percent to education and training. Examples of projects include the following:

- Penn State University is developing a community engagement approach as a way to address diseases of despair such as suicide and chronic substance abuse.
- The University of Texas Medical Branch at Galveston is establishing a patient registry for analyzing opioid usage in burn and trauma patients.
- The Mayo Clinic is identifying "deep learning" solutions for classifying patient opioid use.
- The University of New Mexico, Tufts University and the University of Minnesota are conducting a pilot project to ensure that pharmacists can serve as independent naloxone providers.

The research software supplements will allow for more efficient tracking of clinical trial information and the assessment of accrual goals, as well as enhancing the ability to conduct multisite trials that adhere to the NIH single institutional review board (IRB) policy.

The Growing Promise of Gene Therapy

The Growing Promise of Gene Therapy Approaches to Rare Diseases meeting took place in August. Now that gene therapy has been in use for a while, it is receiving a more realistic assessment of its capabilities.

The Therapeutics for Rare and Neglected Diseases (TRND) program included a project to develop a gene therapy drug for aromatic L-amino acid decarboxylase (AADC) deficiency. Those with AADC have a life expectancy of about five years. The project goal was to develop reproducible and scalable viral vector production methods that would be open-access and applicable to many other rare diseases. The investigators successfully delivered a single AADC gene to the brain of a patient in Taiwan to restore critical levels of the neurotransmitters dopamine and serotonin. This trial has proven successful. NCATS developed the manufacturing process and completed safety evaluations. The FDA will allow the drug's entry into the market in 2019. Agilis Biotherapeutics and National Taiwan University collaborated on the project to transition the study to an approvable gene therapy drug.

BrIDGs Program. The NCATS BrIDGs program has worked with ReNetX Bio and Yale University to develop a new biologic to promote spinal cord regrowth after injury. In a study done on rats, AXER-204 blocked the three inhibitors of axon regrowth in the spine, allowing the axons to regrow. Developers expect to file AXER-204 as an investigational new drug (IND) by the end of the year. First-in-human studies may begin as early as 2019. NCATS helped develop a GMP-grade manufacturing process, complete the pharmacokinetic studies and complete the intrathecal safety evaluation.

Stimulating Peripheral Activity to Relieve Conditions (SPARC). In a project involving spinal cord stimulation for the treatment of gastroparesis, NCATS provided the template to expedite a collaboration between the Johns Hopkins investigator and Boston Scientific and has helped expedite the pre-clinical studies.

Extracellular RNA. NCATS helped fund a project by an investigator at the University of California, Los Angeles, who discovered and validated a biomarker for gastric cancer using salivary extracellular RNA.

Fiscal Year 2019 Budget. Congress combined the U.S. Department of Defense and the Labor, Health and Human Services, and Education appropriations into one spending bill and passed it on September 26. The bill provides a $2 billion increase to NIH, bringing the budget to a total of $39 billion. NCATS received $806 million, an increase of $64 million compared with FY 2018. The CTSA Program's budget

increased from $542.8 million to $559.8 million. CAN will be allowed to increase spending from $25.8 million up to a maximum of $80 million. However, the maximum of $80 million was not a line item to CAN but would come from within the NCATS budget.

Other highlights include the following:

- NCATS will have open funding opportunities for the Rare Diseases Clinical Research Network, the Illuminating the Druggable Genome Program and the New Therapeutic Uses Program.
- Dr. Austin has been appointed to be the HHS liaison to the National Aeronautics and Space Administration (NASA) as part of the HHS-NASA Interagency Agreement.
- SpaceX is scheduled to launch on November 27, carrying tissue chips to the International Space Station. The tissue chips will be used to study senescence and immunosenescence.
- The search for a new NCATS deputy director to replace Pamela McInnes, D.D.S., M.Sc., should be completed soon.

Discussion

Dr. Marks asked for more detail about the CAN budget, which could receive "up to $80 million" in FY 2019. Dr. Austin said that the "up to" provision allows NCATS to designate some programs within the Center as CAN programs. CAN has matching authority that it can bring to its projects. Dr. Marks said that the CAN Review Board can work with Dr. Austin to prepare for this new approach.

Action Item: The CAN Review Board will discuss the CAN FY 2019 budget at its December meeting.

Rachel Ramoni, D.M.D., Sc.D., asked whether NCATS was working with electronic health record (EHR) companies to develop software that would provide clinical trial support. Michael Kurilla, M.D., Ph.D., said that Encore is the most popular EHR within the CTSA Program. NCATS has been working with the CTSA Program sites to remove the technical impediments to EHR systems interoperability. Dr. Ramoni said that the VA could request better interoperability of any new vendor it hires.

Action Item: Dr. Kurilla and Dr. Ramoni will discuss EHRs and EHR interoperability outside the meeting.

Richard E. Kuntz, M.D., said that neuromodulation has potential as a treatment but that the science must be developed to determine why some patients get relief and others do not. Danilo Tagle, Ph.D., M.S., said that SPARC is mapping the human peripheral nervous system. The HEAL Initiative will expand the mapping to the opioid circuitry in the brain and the peripheral nervous system. SPARC is also developing the next generation of neuromodulation devices that would use the mapping features to define what pathways will need to be stimulated and at what frequency.

V. CLEARANCE OF CONCEPTS

The Council and Board received presentations on seven new projects that NCATS is considering for funding. At the end of each presentation, the members discussed the proposal and voted on whether to approve NCATS' moving forward with the initiative.

Drug Development Collaboratory: Bobbie Ann Mount, Ph.D., Drug Development Partnership Programs

The proposed Drug Development Collaboratory would include the intramural Therapeutics Development Branch in the NCATS Division of Preclinical Innovation to conduct IND-enabling studies, develop regulatory strategy and allow changes in drug delivery and reformulation. The goals of the Collaboratory are to develop a strategic process for applicants to collaborate across multiple intramural and extramural NCATS programs; optimize drug delivery method, formulation, regulatory strategy and commercial viability for supported projects; and provide continuity of funding for projects that receive

in-kind resources from the Therapeutics Development Branch. The program will provide funding at a phase where some drugs under development struggle for funding.

Discussion

Dr. Kuntz asked whether the Collaboratory would include funding for drug discovery. Dr. Mount said that this program focuses on the pre-clinical development to early-stage clinical trials. NCATS de-risks projects that are not commercially viable so that companies can bring them to market.

Alan D. Palkowitz, Ph.D., said that this program could eliminate some of the gaps in drug development. It is built on NCATS' experience in developing a product that the private sector can bring to clinical use. The program will also provide the flexibility to reformulate drugs or use them in new ways.

Dr. Ramoni said that the VA is interested in collaborating with NCATS on de-risking compounds for companies to develop. The VA would also like to add arms to clinical studies so that veterans who have conditions that would exclude them from a study, such as traumatic brain injury, could be included.

Dr. Marks asked about NCATS' expertise to assess the commercial viability of products. Lili M. Portilla Weingarten, M.P.A., of the Office of Strategic Alliances, said that staff examine patents, strategic partnerships and market assessments to ensure there is commercial potential. Staff use experts from within and outside NCATS and consult outside databases to make these assessments.

Members unanimously approved the Drug Development Collaboratory concept.

Drug Screening of Biofabricated 3-D Disease Tissue Models: Dobrila D. Rudnicki, Ph.D., Office of Special Initiatives

Dobrila D. Rudnicki, Ph.D., said that less than 12 percent of the drugs that enter drug trials receive approval because the current 2-D testing models are too simplistic and are not good predictors of a drug's performance. This program will help develop better models for prediction by providing 3-D biofabricated disease tissue models that are physiologically relevant drug screening platforms.

NCATS has already established a 3-D bioprinting laboratory and is currently working on skin, retina, blood-brain barrier and cancer models. Skin tissue has a relatively simple laminar structure. The work with skin can be applied to produce other laminar structures, such as liver tissue, and other disease models. NCATS is working to develop 3-D bioprinting models of psoriasis with Columbia University and squamous cell carcinoma at The Rockefeller University. The next step is to incorporate the models in high-throughput drug screening platforms and extend the models to other tissue types.

This project has the potential to affect the drug discovery process and will facilitate the use of biofabricated 3-D tissue models for high-throughput drug screening for multiple diseases.

Discussion

Dr. Palkowitz asked about the process for validating the 3-D systems. What are investigators measuring in the psoriasis and carcinoma models? Dr. Rudnicki said that investigators are working to ensure that the models are robust and the responses to drugs are reproducible. One way to do that is to use known compounds and evaluate their effects on the model. The carcinoma model will be validated with imaging.

Dr. Kuntz asked whether this program could reduce the sample size when the drug is tested in humans and whether it would reduce the number of feasibility studies that fail. Dr. Rudnicki said that the 3-D model may be an intermediary step between the 2-D study and an animal study. It could confirm that a drug should be moved to the next stage of development. Dr. Austin said that until the researchers try

the 3-D approach, they will not know whether it is better than the 2-D approach. The 2-D approach may work better in certain circumstances.

Dr. Ramoni asked whether it is possible to include evaluation in this program. Dr. Austin said that testing usually begins with cell screening and then an animal model. The question is whether the 3-D model could substitute for either the cell screening or the animal model.

Dr. Ramoni asked whether NCATS will evaluate the model in terms of sensitivity and specificity by doing multiple passes with a drug to generate data about false positives and false negatives. Dr. Austin confirmed that this approach was part of the plan, but NCATS may not know which is a false positive and which is a false negative. Dr. Ramoni said that pharmaceutical companies will want to know that information and that it would be good to build in the information over the long term. Dr. Tagle said that NCATS has established independent testing centers as part of the tissue chip program. NCATS has been evaluating the physiological responses in the 2-D model versus the 3-D model, including responses for sensitivity and specificity, and has found that the 3-D model is better at predicting physiological outcomes.

Dr. Ramoni asked what standard the 3-D outcome is evaluated against. Dr. Tagle said that there is no gold standard for 3-D modeling because it cannot be benchmarked against the current gold standard, which is animal models. Dr. Ramoni said that companies ultimately want to know whether a drug can be approved for use in humans. Dr. Tagle agreed, saying that this is why NCATS consulted the FDA and the pharmaceutical industry when setting up the testing centers. The FDA and the companies advised NCATS on which assays, biomarkers and validation compounds to use. The 3-D models must be able to predict the toxicities that are not being predicted in the animal models. The tissue chips have been able to predict the toxicity that the 2-D models and the animal models were not able to predict.

Dr. Ramoni said that it is important that the method not screen out drugs that would work well in humans. Tests using existing compounds should be integrated into this concept to find false positives and false negatives.

Dr. Austin said that the difference between a tissue chip and a rat is that the rat can produce unexpected results. Investigators define the tissue chip in terms of an outcome. At the end of the experiment, the outcome is either achieved or not. Dr. Tagle described the multiple tissue chips that could help resolve some of the problems. Dr. Kuntz said that the retrospective analysis of approved drugs would be important to test. Dr. Palkowitz said that the chips are good at narrowing hypotheses and allowing the research to advance. There is a stepwise process that is more efficient and helps refine the drug developer's understanding.

Members unanimously approved the Drug Screening of Biofabricated 3-D Disease Tissue Models concept.

Biofabricated 3D Tissue Models of Nociception, Addiction and Overdose for Drug Screening: Dobrila D. Rudnicki, Ph.D., Office of Special Initiatives

Dr. Austin said that this concept is similar to the previous concept (Drug Screening of Biofabricated 3-D Disease Tissue Models). The HEAL Initiative will fund this program, while CAN will fund the previous concept.

Dr. Rudnicki said that the project aims to develop detection methods that are disease-relevant and compatible with 3-D high-throughput screening that can quickly screen up to 1,000 compounds. The models may include blood-brain barrier tissues, iPSC-derived sensory/pain neurons and neurons relevant to reward pathways. The goals are to develop morphologically and physiologically validated biofabricated 3-D models of pain, addiction and overdose; establish protocols to produce the iPSC cells

needed to biofabricate the tissue; and promote collaborations between the NCATS 3-D bioprinting laboratory and the scientific community.

Discussion

Dr. Marks said that it is important to note that the HEAL Initiative and CAN are working in the same field of inquiry. Drug screening is not in a good state, and this work is needed. Even compounds already on the market and successfully used in humans may have drawbacks that have not yet been discovered.

Dr. Ramoni asked whether it is possible to build genetic variability into the chip. This may be an opportunity to compare people who have been on opioids without a problem to people who became addicted to opioids the first time they tried them. Dr. Rudnicki said that it would not be possible to build in the genetic variability but that it would be possible to see individual differences by using patients' iPSCs.

Members unanimously approved the Biofabricated 3D Tissue Models of Nociception, Addiction and Overdose for Drug Screening concept.

Tissue Chips to Model Nociception, Addiction and Overdose: "Tissue Chips to HEAL": Lucie Low, Ph.D., Office of Special Initiatives

Lucie Low, Ph.D., said that NCATS is leading a trans-NIH collaborative to develop human-based screening platforms and novel drugs to treat pain and opioid use disorders. Tissue chips are part of the initiative. The goal is to create and test tissue chips that can model the mechanisms or effects of pain signaling, addiction or opioid use disorders using human tissues in physiologically relevant *in vitro* platforms.

The initiative could help to reveal the mechanisms underlying an individual's response to pain, related opioid use and potential overdose. It could also provide insights into the impact of physiological comorbidities, therapeutic responses and addiction treatment outcomes.

Criteria for success include the appropriate modeling of a pain/addiction/overdose-relevant organ system, a chip that provides a more useful readout than those already available, and end points that can be demonstrated to correlate with clinical measures of pain, addiction and overdose. Another criterion of success would be having the iPSCs or commercially available cell lines as the cell source.

The program must find quantitative end points that correlate with clinical measures of pain, addiction and overdose; use mature human-derived tissues for central and peripheral nervous system tissues and non-nervous system tissues; and identify pain experts as collaborators.

NCATS made seven supplemental awards to members of the Tissue Chip Consortium to develop chips to model pain, opioid addiction and overdose. NCATS is planning to reissue the notice in 2019 to expand tissue chip development beyond the consortium.

Discussion

Dr. Marks asked how the 3-D biofabricated model and the tissue chip model will work together. Dr. Rudnicki said that the Tissue Chip program is more advanced, but anything that the Tissue Chip program experiences with human cells is relevant to the 3-D program. Both programs focus on testing efficacy and safety. Dr. Low said that the Tissue Chip program will be working with experts in pain and addiction and can link those experts to the 3-D program.

Dr. Marks, noting the integrated models of peripheral and central nervous system tissues, asked how the program will communicate the diversity of approaches to applicants. Dr. Low said that the Tissue Chip program staff will write a funding opportunity announcement (FOA) that will encourage

researchers to think creatively about the body's systems. Applicants will be asked to drill down to something that is needed in this research area.

Dr. Kuntz asked whether it is possible to develop a surrogate measure of pain. Dr. Low said that pain can be subjective but that there are also some end points that correlate with phenomenological measures of pain such as synaptic density, changes in RNA or electrophysiological responses. The field is looking for biomarkers, and NCATS is looking for new ways to model physiological responses.

Megan O'Boyle asked whether there is a role for diseases in which patients do not experience pain appropriately. Dr. Low said that tissue chips can provide a way to model these conditions and show how such patients are different from those with more typical responses to pain.

Members unanimously approved the Tissue Chips to HEAL concept.

"Clinical Trials on a Chip": Tissue Chips to Inform Clinical Trials for Rare Diseases: Lucie Low, Ph.D., Office of Special Initiatives

Both rare and common diseases are represented on the tissue chips developed so far. NCATS will focus on rare diseases as the first priority, in part because there is little commercial investment in rare diseases and in part because chips help overcome the difficulty of having few patients to study. The tissue chip also allows for research without harming patients.

The goal of this program is to move from populating chips with small numbers of donor iPSC-derived commercially available cell sources to cell sources that represent much larger patient populations. Tissue chips can help streamline clinical trials by helping to select and stratify subgroups in pre-clinical and early clinical trial stages and by providing safety and efficacy data.

Among the criteria for success is the production of tissue chips that allow physicians and patients to make informed decisions about appropriate treatment regimens. Success will also be measured by the partnerships formed with clinical and patient groups who will be the end users, having sufficient enrollment numbers of tissue donors, and having useful and relevant readouts. The project will have broad and significant impact by validating the usefulness of tissue chip platforms in a clinical setting, and will be disease-relevant.

There is very little published data about clinical trials in a dish. This project will produce more trials in this area. Dr. Low and Dr. Tagle have held meetings with stakeholders to ensure that the appropriate variables are considered and that NCATS is forming appropriate partnerships.

Discussion

Ms. O'Boyle asked at what stage the patient groups would be involved. Dr. Low said that applicants would be encouraged to contact the patient groups even before applying for funding. Ms. O'Boyle asked whether NCATS would require including a patient group as a co-investigator, and Dr. Low said NCATS could consider making that a requirement.

Ms. O'Boyle said some rare disease groups have iPSC banks and registry data. Would NCATS link up with those groups? Dr. Low said that it would make sense for investigators to use existing data from registries and biobanks. If those data are not available, NCATS would encourage the investigator to create the resource as part of their project.

Ms. O'Boyle asked whether NCATS would target specific diseases or whether the targeting is investigator initiated. Dr. Low said that the critical need is in rare diseases but that NCATS would not require modeling particular diseases. Ms. O'Boyle asked whether NCATS would encourage work in

conditions caused by a single gene. Dr. Low said that NCATS could do that and that doing so may be desirable because it is easier to control for some of the variability.

Ms. O'Boyle suggested informing patient advocacy groups of this opportunity. Those groups may seek out researchers who would be interested.

Dr. Ramoni said that the VA would be interested in funding a study on Gulf War illness to evaluate the veterans' exposures to toxins. The VA is currently working with NINDS to phenotype Gulf War veterans with the illness. The VA could collect the cells for the tissue on a chip at the same time.

Action Item: Dr. Low and Dr. Ramoni will discuss VA participation in the Clinical Trials on a Chip initiative.

Anantha Shekhar, M.D., Ph.D., said that the proposed concept is a great step, particularly for rare disease. The biggest challenge will be defining the organ chip and the outcome. A tissue on a chip may include brain cells, but the disease under study may also affect the liver, for example. The study should target pharmacodynamic questions and complex end points.

Patients who have rare diseases will come from a broad range of genetic backgrounds. Dr. Shekhar asked whether the cell lines will be diverse enough to generalize the findings. He also said that rare disease groups should be included in the research from the very beginning of any project.

Dr. Tagle said that NCATS would include mutations that come from different ethnicities in isogenic iPSC lines to prevent confounding the phenotype. NCATS would also obtain endogenous material from patients to look at other contributing factors to disease manifestation. Dr. Shekhar said that gender would be important as well.

Ronald J. Bartek, M.A., said that many rare diseases are neurological and progressive. At some stage, a disease may have progressed too far for a drug to have an effect. Dr. Low said that NCATS is working to model amyotrophic lateral sclerosis and taking individual variability and disease progression into account.

Dr. Kuntz asked how disease progression could be incorporated into work that involves iPSCs. Dr. Tagle said that it could be done by maturing the cells. The pharmaceutical industry is interested in the developmental response to treatment with drugs. There is a critical need to test drugs on pediatric populations as well as pathogenic progression.

Members unanimously approved the Tissue Chips to HEAL concept.

HEAL Pain Effectiveness Research Network (HEAL Pain-ERN): Jane C. Atkinson, D.D.S., Director, Trial Innovation Network (TIN), Division of Clinical Innovation

The evidence for optimal pain management, such as long-term opioid use for management of chronic pain, is often insufficient. The HEAL Pain-ERN would conduct clinical trials and studies to establish interventions or programs to manage, reduce or prevent acute and chronic pain and provide evidence to inform practice-based guidelines. The HEAL Pain-ERN will leverage the existing CTSA Trial Innovation Network (TIN) to implement studies of interest to multiple NIH Institutes and Centers (ICs).

Jane C. Atkinson, D.D.S., described the proposed infrastructure that would include TIN Clinical and Data Coordinating Centers and also outlined a Pain Leadership Group that would report to entities within NIH, including the Pain IC Councils and the NIH Pain IC Directors. NINDS will provide the repositories for clinical data and biosamples.

A trans-NIH group will write the FOAs. The trials and studies will use standard outcome measures whenever possible, and all data will be stored centrally to ensure data sharing. The initiative will help

break down pain research silos separating disciplines, help resolve the problem of having limited outcome measures for pain and provide more functional pain measures.

Discussion

Harry P. Selker, M.D., M.S.P.H., advised that investigators be required to engage patients and other stakeholders, including professional societies, from the time that the investigator is writing the grant application. He also advised that studies produce useful effectiveness data. Dr. Selker said that this initiative is likely to attract public attention. It will be important to use innovative approaches and to establish useful outcome measures.

Dr. Austin agreed that this is a high-profile project and that it is very important that the project succeed.

Dr. Shekhar said that it is a good idea to start with effectiveness trials and trials that strengthen guidelines. He also suggested conducting studies on how providers perceive the guidelines and whether they implement them. The other need is to find ways to measure pain in reproducible and reliable ways.

The members unanimously approved the HEAL Pain-ERN concept.

CTSA Program: Competitive Supplement Applications to Develop, Demonstrate and Disseminate Translational Science Advances: Michael G. Kurilla, M.D., Ph.D., Director, Division of Clinical Innovation

Dr. Kurilla said that this program would provide supplements to translational science projects that address the goals of the CTSA Program. These are peer-reviewed competitive supplements that could extend beyond the scope of the parent grant.

The supplements will allow projects to respond to emerging scientific opportunities, stimulate high-priority translational science areas and provide the opportunity to extend new projects, activities and collaborations across the CTSA Program consortium. The supplements will allow the development of new approaches, the demonstration of their efficacy and the dissemination of the findings. Success will be measured in terms of the ability of the proposed activities to advance translational science and increase and broaden the overall impact of the CTSA Program.

Discussion

Dr. Marks asked whether NCATS could urge greater outreach and collaboration as part of the supplements. Dr. Austin said that NCATS would signal that outreach and diversity are areas of particular interest. Congress has also signaled through its budget language that outreach and diversity are important.

Ms. O'Boyle asked for an example of how the supplements would work. Dr. Kurilla gave the example of a current award in which a limited number of CTSA Program hubs are generating iPSC lines that they will share. With additional funding, the CTSA Program hubs could share the iPSC lines across the entire CTSA Program consortium.

Dr. Selker said that the CTSA Program sites work on projects to help others do research. The supplements are about expanding the CTSA Program sites' research services. Dr. Shekhar said that the CTSA Program sites have produced novel techniques, tools and technologies, but they have not been disseminated widely because of lack of funding. The peer review supplements will be helpful to get some of the CTSA Program's products and ideas into much wider use.

Valerie Montgomery Rice, M.D., asked how much funding would be set aside for the supplements. Dr. Kurilla said that NCATS would assess funding in conjunction with other CTSA Program funding initiatives.

The members unanimously approved the CTSA Program Competitive Supplement concept.

VI. WHEN DOES A PATIENT BECOME A RESEARCH PARTICIPANT?: Valery M. Gordon, Ph.D., M.P.H., Senior Advisor for Human Subjects Protection, Division of Clinical Innovation

Valery M. Gordon, Ph.D., M.P.H., said that this presentation grew out of the Council's discussion in May regarding the TARGET (Treatments Against Rheumatoid Arthritis and the Effect on FDG-PET/CT) Trial's request to the Recruitment Innovation Center (RIC) to help enhance its enrollment. The RIC designed a smartphone app to help clinicians describe the TARGET Trial to eligible patients. The Council and Board members raised the following questions about the TARGET Trial:

- Did clinicians enter identifiable private information about their patients into the app? If so, did the IRB approve the process, and did the patients consent?
- Did patients consent for clinicians to enter their EHR information into the app? Did the IRB approve a waiver of some or all of the elements of consent?

Clinicians did not enter private information about their patients. Instead, the app provided information about the study procedures, inclusion and exclusion criteria and research contacts for interested patients. This answer meant that the second set of questions was not applicable.

Council and Board members also asked other questions, including when a patient becomes a research participant and how patients' and participants' rights are protected.

Dr. Gordon said that patients become research participants when they sign an informed consent to participate in a study, but they also remain patients. Patients and participants are protected by federal laws such as the Health Insurance Portability and Accountability Act of 1996 (HIPAA) Privacy Rule and by state laws. Research participants are also protected by HHS regulations.

Discussion

Dr. Austin asked about the General Data Protection Regulation (GDPR). Dr. Gordon said that the GDPR is a European rule that applies to human data. The regulation is new, and it is not yet clear how it will be interpreted. There has been some fear that the GDPR could make collaborations between U.S. and European researchers more difficult. Dr. Austin said that the GDPR was meant to regulate the selling of data among private entities, but there is concern that it could stop some kinds of research, such as research involving meta-analysis. Most therapeutic development trials and rare disease trials include international sites. The European Union is aware of the problems and may take steps to address them. Ms. O'Boyle added that the GDPR affects nonprofits that have a donor base with European contacts and nonprofit registries that have data from Europeans.

VII. CTSA PROGRAM UPDATE: INTEGRATING NOVEL INFORMATICS TOOLS AND COMMUNITY ENGAGEMENT INCREASES PARTICIPANT RECRUITMENT AND RETENTION

Overview of Operation Challenges in Clinical Trials: Patricia Jones, Dr.P.H., M.P.H., Common Metrics Initiative Program, Division of Clinical Innovation, NCATS

Patricia Jones, Dr.P.H., M.P.H., said that NIH has a substantial investment in clinical trials: about $3.2 billion in FY 2015. Congress, the General Accounting Office and NIH leadership have called for enhanced stewardship of NIH-funded clinical trials. To address clinical trial operational challenges, NCATS funded three Trial Innovation Centers (TICs) and the Recruitment Innovation Center (RIC). The TICs, the RIC and the CTSA Program hubs make up the TIN.

The TIN develops and disseminates scientific and operational innovations to increase the efficiency and effectiveness of clinical trials. The goal is to create a national platform that focuses on new approaches to operationalize clinical trials and help studies finish on time and within budget. The TIN addresses

scientific translational problems, including patient recruitment, using EHRs in research, clinical diagnostic criteria, adaptive clinical trial designs and harmonized IRBs. The TIN, which began two years ago, has built the TIC and RIC teams and launched the network. To date, TIN has received 144 proposals for funding.

Recruitment Innovation Center (RIC): Consuelo H. Wilkins, M.D., M.S.C.I., RIC, Vanderbilt University Medical Center and Meharry Medical College

The RIC is based at the Vanderbilt University Medical Center but works collaboratively with five partners: Columbia University Irving Medical Center, Regenstrief Institute, The Ohio State University Wexner Medical Center, University of Utah Health Sciences and The Rockefeller University.

The goal is to improve enrollment and retention in multicenter trials. Achieving the goal will require informatics-based recruitment tools and new engagement approaches. The RIC develops tools and strategies that can be used in thousands of trials and incorporates continuous learning into its process so that it is always improving enrollment and retention in clinical trials. It aims to become a national storefront for recruitment and retention best practices, enhance patients' awareness of research and conduct studies on methods to enhance recruitment efficiency.

The RIC supports many studies with a light-touch consultation but provides comprehensive consultations and services to a few. Each consultation produces four or five recommendations specifically tailored to the study.

The RIC's services include recruitment planning and feasibility assessments, recruitment materials, Community Engagement Studios and EHR cohort assessment. It is as well developing an EHR workflow assessment and a competing trials assessment, and a participant compensation assessment is also available.

The RIC has a Community Advisory Board (CAB), whose members represent patients, caregivers, clinicians and advocates. The CAB also includes racial and ethnic minorities and clinical trial participants, and one member represents the Vanderbilt Institute for Clinical and Translational Research Community Advisory Council.

The Community Engagement Studio is an approach to engagement that involves a onetime small-group meeting involving the investigator and patients or interested community members. The meeting lasts two hours and includes a neutral facilitator, and discussion is bidirectional. The objective is to decrease or even eliminate the power differential between the community members and the investigator. For those interested in running their own Community Engagement Studio, the RIC has created a toolkit and videos to help them get started.

The RIC conducted two studios for the Molecular Transducers of Physical Activity Consortium (MoTrPAC) Study. The investigators found the studios so helpful that they organized a studio engagement implementation training for CTSA Program site staff and the entire MoTrPAC research team.

The RIC has developed a recruitment and retention plan template to help research teams assess feasibility, risk, cost, time and resources needed for recruitment and retention. The template consists of 10 parts. Consuelo H. Wilkins, M.D., M.S.C.I., noted that when investigators complete a recruitment plan, the last four items on the list (a communications plan, a recruitment and retention timeline, an evaluation plan and a budget) are often missing. The template therefore prompts study teams to think more realistically about what is required to recruit, engage and retain participants.

Faster Together is a program that focuses on accelerating minority recruitment by co-designing recruitment plans with stakeholders from diverse populations and providing culturally tailored

recruitment messaging. For example, in working with Duke University to meet the goal of 20 percent minority participation in one study, the RIC tailored the email, phone scripts and flyers to the target population, reducing the reading grade level from 11.9 to 7.3. Research teams interested in Faster Together training can access an online course, available through Coursera.

Returning value to participants is an important part of engagement and retention. The RIC surveyed more than 2,500 people, 62 percent of them minorities, and found that the participants rated pharmacodynamics information as having the highest value to them, with genetic and lifestyle-associated risk for medical conditions ranked second and third highest, respectively. By contrast, monetary compensation was ranked seventh highest out of a list of 12.

Collaborative Webinars Recruitment and Retention Toolkit: Paul Harris, Ph.D., Vanderbilt University

The TIN began collaborative webinars to provide a forum for sharing expertise and best practices to improve the conduct of clinical trials, inform researchers of new recruitment and retention initiatives and establish a collaboration with the CTSA Recruitment and Retention Working Group. There have been about 40 webinars so far, with as many as 142 attendees. Fourteen institutions have presented at least one webinar so far this year.

The TIN has an online resource-sharing site for members. Contributors to the site include the RIC, advocacy organizations, academic institutions, government, nonprofit organizations and the private sector. One of the resources on the site is the RIC Download, a biweekly publication with the latest recruitment and retention news. There is also a "Community of Practice" page, where individuals can share information, and a Recruitment and Retention Toolkit, which has been either downloaded or viewed nearly 5,400 times.

The RIC also has an online registry, ResearchMatch, for individuals interested in participating in research. Through the site, those who express interest in a particular study are put in contact with the researcher. Thus far, nearly 29,000 people have volunteered for studies through the registry. RIC has also translated the application into Spanish. ResearchMatch offers another option, Trials Today, for those who want to join a trial immediately, and the platform can also match participants who want to participate in studies at particular institutions.

Vanderbilt University developed the Research Electronic Data Capture (REDCap) data management platform, which now has 800,000 users. REDCap recently developed both an eConsent module and a platform to pull EHR data for use in research.

The RIC has also developed MyCap, a mobile app that is a participant-centered data capture tool focused on participant engagement and return of value. The Community Advisory Board is now working to further develop MyCap. Meanwhile, the RIC has also been working on an EHR cohort assessment tool and an EHR recruitment toolbox to get into the EHR workflow in a way that helps with recruitment. The RIC has created a website template that studies can quickly adapt for their own use and a clinician's app to help recruit study participants.

Discussion

Dr. Austin said that Dr. Wilkins made an important point when she noted that many investigators plan a clinical trial without including specifics for recruitment. Without a comprehensive plan, a clinical trial may fail or finish over time and over budget. With more extensive planning up front to recruit and engage participants, many potential problems can be addressed.

Dr. Kuntz asked how to deal with primary care physicians who are obstacles to patient recruitment. Dr. Wilkins said that it is necessary to engage physicians early and understand that recruiting subjects is a

burden to physicians. It is important to ask them what they need and to keep providers in the loop so that they know what information their patients receive and what the information means for their patients.

Dr. Ramoni asked how the VA could work on this project with the RIC and TIN. Dr. Harris said that the RIC has already begun working with the VA through the Network of Dedicated Enrollment Sites (NODES). The next step might be to work together on a demonstration project.

Dr. Selker stated that it is important to respect clinicians and engage them by providing value to them and their patients. Dr. Wilkins said that the RIC published a paper about the provider's barriers to engagement, including workflow disruption. It would be helpful to find a way to obtain providers' input concerning the types of studies that interest them.

Ms. O'Boyle added that foundations are trusted entities that are good at patient recruitment. Researchers should ensure that their studies contain the right key words so that foundations can find them on sites such as ClinicalTrials.gov. She provided the example of a researcher who is doing six studies on Friedreich's ataxia, but only one study shows up in searches.

VIII. ADJOURNMENT OF THE OPEN MEETING

Dr. Austin thanked all participants for their input. He and Dr. Marks adjourned the open portion of the meeting at 3:22 p.m. ET.

IX. 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.

X. ADJOURNMENT OF CLOSED SESSION OF THE NCATS ADVISORY COUNCIL MEETING

Dr. Austin adjourned the closed session of the NCATS Advisory Council meeting at 4:23 p.m. ET.

CERTIFICATION

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

Christopher P. Austin, M.D. Date
Chair, NCATS Advisory Council;
and
Director, National Center for Advancing Translational Sciences, NIH

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

Date

G. Lynn Marks, M.D.
Chair, Cures Acceleration Network Review Board;
and
Senior R&D Advisor, Biomedical Advanced Research and Development Authority (BARDA), ASPR/HHS

Date