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 7, 2017

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 7, 2017, 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 acting 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

Daniel L. Hartman, M.D.
Megan O'Boyle
Alan D. Palkowitz, Ph.D. (by telephone)
Harry P. Selker, M.D., M.S.P.H.
Anantha Shekhar, M.D., Ph.D.

Representative Members

None present

Ad Hoc Members

Ronald J. Bartek, Friedreich's Ataxia Research Alliance
Katharine Ku, M.S., Stanford University
Richard Kuntz, M.D., Medtronic, Inc.
Geoffrey Shiu Fei Ling, M.D., Ph.D., Uniformed Services University of the Health Sciences
Kalpana M. Merchant, Ph.D., TransThera Consulting Company
Matthew Might, Ph.D., University of Utah
Valerie Montgomery Rice, M.D., Morehouse School of Medicine
Stephen P. Spielberg, M.D., Ph.D., Therapeutic Innovation & Regulatory Science (by telephone)
Sharon F. Terry, M.A., Genetic Alliance
Eric J. Topol, M.D., Scripps Translational Science Institute
Paul G. Yock, M.D., Stanford University (by telephone)

Ex Officio Members

Frank F. Weichold, M.D., Ph.D., Food and Drug Administration (representative)

CAN REVIEW BOARD MEMBERS PRESENT

Chair

G. Lynn Marks, M.D., Senior Vice President for Research and Development and Senior Clinical Advisor, GlaxoSmithKline

Vice Chair

Ronald J. Bartek, Co-Founder and Founding President, Friedreich's Ataxia Research Alliance

Executive Secretary

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

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Ex Officio Members

Christopher P. Austin, M.D., NCATS
Frank F. Weichold, M.D., Ph.D., Food and Drug Administration (representative)

OTHERS PRESENT

Stanley C. Ahalt, Ph.D., Professor, Director, Renaissance Computing Institute, University of North Carolina at Chapel Hill
Elizabeth Barksdale, Ph.D., Federation of American Societies for Experimental Biology
Gordon Bernard, M.D., Melinda Owen Bass Professor of Medicine, Associate Vice-Chancellor for Research, Vanderbilt University Medical Center
Barbara E. Bierer, M.D., Professor of Medicine, Harvard Medical School
Jeanine D'Armiento, M.D., Ph.D., Columbia University Medical School
Philip Goglas II, Health & Medicine Counsel of Washington
Joe Laakso, Ph.D., Endocrine Society
Lee Nadler, M.D., Virginia and D.K. Ludwig Professor of Medicine, Dean for Clinical and Translational Research, Dana Farber Cancer Institute, Harvard Medical School
NCATS leadership and staff

I. CALL TO ORDER

Christopher P. Austin, M.D., and Lynn Marks, M.D., called the meeting to order. Dr. Austin welcomed members and guests to the 15th meeting of the NCATS Advisory Council and the 19th meeting of the CAN Review Board. He reminded attendees that the open session was being videocast. Dr. Austin introduced the *ad hoc* members of the Advisory Council and the CAN Review Board.

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

The minutes of the joint meeting held on May 12, 2017, were approved as written.

Anna L. Ramsey-Ewing, Ph.D., informed the group that the NCATS Advisory Council and CAN Review Board will have joint meetings in 2018 on Jan. 11, May 10 and Sept. 27. The 2019 meetings will take place on Jan. 10, May 16 and Sept. 19. The CAN Review Board also will meet by teleconference on Dec. 15, 2017, Dec. 14, 2018 and Dec. 13, 2019.

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

Christopher P. Austin, M.D., shared recent advances in early, mid and late translational science.

Translational Science Advances: Selected Highlights

- **New Chemistry for Intractable Targets.** Several parasites and bacteria that cause disease in humans share a unique vulnerability in how they perform glycolysis, a basic function of cells. An enzyme called phosphoglycerate mutase functions quite differently in the disease-causing organisms than it does in humans, which makes it a good drug target. No known chemicals can interfere with the work of this enzyme. In this case, researchers at New England Biolabs, the University of Tokyo and the University of Kansas were able to produce a large number of noose-shaped peptides and test them against the enzyme. Their screens identified a particular peptide that is effective against the enzyme, and they have characterized its structure. This finding is particularly exciting because the method could be used on any target protein that can be expressed and purified as an immobilized "receptor" on a solid phase resin.
- **The NCATS Stem Cell Translational Laboratory (SCTL).** While stem cell science has made impressive advances in recent decades, this has not resulted in widely-available treatments. NCATS has opened the SCTL, with the goal of bringing induced pluripotent stem cells (iPSCs) closer to clinical applications by developing standards for characterizing the cells and better protocols for differentiating the cells. Differentiated cells are currently characterized by finding markers for certain types of cells. This is not good enough. The differentiation process currently requires products such as chicken embryo extract; SCTL will work on replacing this. SCTL has an ongoing solicitation to establish collaborations and welcomes researchers' problems related to differentiation. SCTL officially opened in July.
- **Gene Therapy in Therapeutics for Rare and Neglected Diseases (TRND) Program.** Gene therapy also needs translational work. Challenges include how to deliver a gene to the correct target and

how to scale up manufacturing. The first gene therapy, approved in Europe a few years ago, was so expensive that few people used it and the company eventually stopped making it. The TRND Program is building a diverse portfolio of gene therapy projects to identify bottlenecks and develop solutions. An example of this is aromatic L-amino acid decarboxylase (AADC) deficiency. A collaboration to build GMP-grade manufacturing production for a vector that delivers the gene to the brain had a successful end-of-phase-2 meeting at FDA in July, where a video showed a remarkable clinical response in a young girl with the disorder. Phase 1-2 clinical trial results for a project on Niemann-Pick Disease, type C1 (NPC1) were published in August, showing about a 70 percent decrease in progression. NPC1 currently has no FDA-approved therapy.

- **Clinical and Translational Science Awards (CTSA) Program: Common Metrics.** The Common Metrics Initiative is developing ways to measure the impact of the CTSA Program. These metrics could be useful for other large research programs. NCATS is approaching this experimentally and hoping to produce data that can be used for strategic management of the program. Metrics have already been implemented for Institutional Review Board (IRB) duration, pilot projects with publication and retaining under-represented and female scholars in research. Because of the IRB duration metric, one hub realized it was behind the curve and has improved. Metrics are being developed for accrual ratio and using standard formats for clinical research data. Potential future metrics could include community engagement, team science, innovation and integrating special populations.
- **Rare Diseases Toolkit:** The NCATS Toolkit for Patient-Focused Therapy Development launched in September. It provides patient groups with tools for advancing research on rare diseases, such as information on how to set up a patient registry.

Administrative, Policy, and Budget Updates

- **Fiscal Year (FY) 2017 and 2018 Budgets.** The FY 2017 budget included a $20 million increase, most of it to the CTSA Program. The FY 2018 budget is not known. In May, the president proposed a $5.8 billion reduction in NIH's budget and several changes across NIH organizations and activities. However, Congress makes the budget. The House passed a "minibus" bill on July 27, 2017, with four military-related appropriations bills. The current House and Senate spending plans exceed the spending caps set by the Budget Control Act of 2011, which means they would trigger the automatic across-the-board cuts known as "sequestration."
- **Executive Order: Reorganizing the Executive Branch.** A March 13, 2017, executive order gave the Office of Management and Budget 180 days to provide a plan with recommendations to reorganize departments and agencies. The only thing to do now is wait.
- **NCATS Day: Partnering with Patients for Smarter Science, June 30, 2017.** Participants included patients, family members, caregivers, researchers and representatives of dozens of patient and disease advocacy groups. NCATS heard ideas for improving communication between scientists and patients, meaningfully engaging patients in research and developing "on-ramps" for patient partnership with NCATS.

Discussion

Eric J. Topol, M.D., remarked that the T in NCATS should stand for "tough." He asked if NCATS envisions a facilitative role for iPSC therapies and about the combination of iPSCs plus genome editing. Dr. Austin said that the iPSC demonstration projects are meant to result in clinical use. He mentioned a macular degeneration project with a researcher at the National Eye Institute; the goals are both to provide an individual advance for that disease and to create generalizable protocols and differentiation methods. On the gene editing question, he said the combination of these technologies has great potential. SCTL will be working with another group at NCATS that studies *c*lustered regularly interspaced short palindromic repeats (CRISPR), a genome editing tool.

Kalpana M. Merchant, Ph.D., asked about the process for gene therapy with respect to industry. Dr. Austin said that companies come to NCATS, and that NCATS looks for projects on diseases that no one is working on, where the work is likely to lead to a generalizable approach. The program is intramural, but every project is done via peer review.

Harry Selker, M.D., M.S.P.H., suggested that NCATS measure the experience with the Rare Diseases Toolkit, learn from it how to engage the public and use this information for other problems.

Valerie Montgomery Rice, M.D., asked how NCATS disseminates its work on rare disease treatments. Dr. Austin said, in the case of NPC1, NCATS has published two papers on how the work was done and how to apply it to other diseases. Because parents usually do not have journal subscriptions, NCATS has discussed whether academic publishing is the best way to disseminate the work. NCATS also reaches out to other institute and center directors at NIH. The work can also be relevant to non-rare diseases, such as sickle cell disease.

Dr. Austin added that dissemination is more difficult because most of the translational world is committed to secrecy for business reasons; there are no well-developed ecosystems for sharing information on how to do translation better.

Sharon F. Terry, M.A., mentioned that metrics for engagement will be a requirement for the People-Centered Research Foundation (PCRF), the successor to PCORNet (the National Patient-Centered Clinical Research Network).

Anantha Shekhar, M.D., Ph.D., said that important challenges include community disengagement, health equity issues and the difficulty of implementing even common treatments. Dr. Austin thanked him for the suggestion and welcomed insights on how to do this work.

IV. CLEARANCE OF CONCEPTS

Christopher P. Austin, M.D., explained that NCATS is required to present ideas to this group for their approval. Questions to consider include whether the concept addresses an important problem and whether it is an appropriate focus for NCATS.

Rare Diseases Clinical Research Network (RDCRN): Anne R. Pariser, M.D., Deputy Director, Office of Rare Diseases Research, NCATS.

Anne R. Pariser, M.D., presented the fourth competition of the RDCRN. RDCRN's purpose is to facilitate rare disease research through the establishment and continuation of rare disease clinical research consortia. The RDCRN includes 21 research consortia, each consisting of physicians, scientists and their multidisciplinary teams that work together with patient advocacy groups to study rare diseases. Currently there is a cap of $1.25 million total funding per consortium. Funding comes from NCATS and from NIH institute and center partners. Each consortium must have at least two studies, one of which must be observational, such as a natural history study. Data are shared through the Data Management and Coordinating Center (DMCC). The 5-year funding cycle ends in the summer of 2019. For the re-competition, the goal is to make 5-year cooperative awards to approximately 20 consortia, including both established and new consortia. The DMCC award will also be re-competed.

The potential impact of the RDCRN is to accelerate rare disease research to benefit patients. RDCRN establishes and supports centers of excellence for rare diseases, as well as supporting infrastructure building, collaboration, training, patient involvement and funding studies, including clinical trials.

Automated Synthesis Platform for Innovative Research and Execution (ASPIRE): Dobrila D. Rudnicki, Ph.D., Office of Special Initiatives, Office of the Director, NCATS

The world of possible chemicals, known as chemical space, is vast. An estimated 10^{63} molecules have the potential to be pharmacologically active. By comparison, biological space is small, but 90 percent of biological space is currently undrugged. Finding chemicals that modulate that 90 percent is a core challenge for drug discovery and development, but existing chemical methods are quite limited. Additional chemistry-related translational roadblocks include limited ability to predict chemical reactions in advance and produce chemicals of desired structure cheaply and rapidly.

The goal of ASPIRE is to combine synthetic chemistry, robotic automation, high-throughput screening and machine learning in order to identify new chemical space with therapeutic potential. A workshop on automated chemical synthesis will be held in October 2017. The workshop will include a wide spectrum of experts from academia, government, pharma industry, professional societies and scientific journals who will discuss the challenges and opportunities of automated chemical synthesis as a tool to discover novel chemical methods and advance translation. Next, ASPIRE aims to develop and implement a highly collaborative, cross-disciplinary program in automated synthesis of novel biologically relevant chemical entities. Outcomes of ASPIRE include increased diversity of chemical libraries, better understanding of the relationship between chemical and biological space, rapid and widespread adoption of the developed tools/technologies and discovery and development of novel and more effective therapies.

NextGen Tissue Chip Testing Centers (TCTCs): Danilo A. Tagle, Ph.D., Associate Director for Special Initiatives, Office of the Director, NCATS

This will be a re-issue for the TCTCs that will continue NCATS' ongoing efforts on making tissue chips available and useful for drug discovery and development through independent validation. Tissue chips are microphysiological systems (MPS) that mimic human organ functions. The next iteration for this program aims to expand the number of compounds being tested on MPS disease models for safety and efficacy and to fully use tissue chip technology to address unmet medical needs, such as coming up with

definitive battery of assays for cardiotoxicity. There is now a greater need from the scientific community to use these testing centers for validating the tissue chips to gain better confidence in the technology. Through the TCTCs, NCATS is helping to bring standardization and uniformity to the field and achieve its mission of creating and developing novel and innovative technologies for drug development. Success would be represented by the widespread use and adoption of tissue chips as tools for assessing safety and efficacy of candidate therapeutics.

NIH-Center for Advancement of Science in Space (CASIS) Coordinated Program in Tissue Chip Systems for Translational Research in Space: Danilo A. Tagle, Ph.D., Associate Director for Special Initiatives, Office of the Director, NCATS

This concept is a re-issue of an existing program which is a collaboration between NCATS, NASA and CASIS that takes advantage of the unique research environment provided by the International Space Station – National Laboratory (ISS-NL). The physiological changes that occur under microgravity are akin to the changes associated with aging. Goals of the program include further developing tissue chip technology — particularly taking advantage of the space program's expertise to rapidly evolve the tissue chip in terms of automation and decreased footprint. This research should provide insight into muscle wasting, osteoporosis and other aging-related changes, and identify targets for disease intervention whose process is accelerated under microgravity conditions. The project would take a multidisciplinary approach, bringing together experts in space engineering, bioengineering, microfluidics, material science, computational biology and other fields.

Discussion

Ronald J. Bartek, Megan O'Boyle, and Anantha Shekhar, M.D., Ph.D., were the three assigned discussants for RDCRN4.

Mr. Bartek mentioned that he serves on the RDCRN Data Safety and Monitoring Committee. He said that the RDCRN4 is a reasonable use of NCATS resources. It could be a model clinical network that is truly collaborative, with true data sharing, conducting the natural history studies that are essential to rare diseases. The work of the consortia also represents a model of true patient engagement. The current funding levels for the consortia are low, and they could accomplish more with more funding.

Ms. O'Boyle noted that her daughter participates in a natural history study. She agreed that $1.25 million, shared among three diseases over five years at multiple sites, is not much money. She noted that her daughter's natural history study had also led to biomarkers and had gone far beyond the initial description. The RDCRN has been a success from the point of view of both families and researchers.

Dr. Shekhar said that the RDCRN is a gem that does a lot of work with very little funding. He said it would make sense for the CTSA Program to make its funding and infrastructure available for the study of rare diseases.

Richard E. Kuntz, M.D., asked for clarification of NCATS's role in moving from the knowledge development phase on rare diseases to the translation phase, and the translational strategy. Mr. Bartek

said that natural history studies are a valuable part of translational science, and are a necessary step before industry will work on rare diseases. Dr. Pariser said that translation includes engaging patients and centers in the clinical research project. NCATS is also looking at the data collected through RDCRN to see how to translate this work to other rare diseases.

Valerie Montgomery Rice, M.D., asked if RDCRN could be recruiting people from Medicaid databases and insurance company claim forms, and whether geographical diversity is part of the criteria for funding pilot studies. Dr. Pariser said that this is not a specific requirement. Rare diseases often only have a few specialists, and the network makes it easier to reach patients around the country. Rashmi Gopal-Srivastava, M.Sc., Ph.D., said that some of the consortia of RDCRN hold travel clinics. Mr. Bartek pointed out that patient advocacy organizations are very engaged in the program, and these groups are dedicated to finding every person with their disease. Petra Kaufmann, M.D., M.Sc., noted that the CTSA Program hubs could also expand the reach of the RDCRN.

Sharon F. Terry, M.A., said that her encounters with investigators working in the RDCRN has been typical: They do not want to share data. If NCATS required data sharing, this would be progress for these diseases and for all science. On the topic of engagement, she does not see anything unusual from the RDCRN; NCATS needs to work harder to change the culture.

Kalpana M. Merchant, Ph.D., asked if there is potential for coordination between RDCRN and other NCATS programs — for example, using patient-derived materials to create iPSC-derived cell types. Dr. Pariser noted that RDCRN consortia are working with the tissue chip program.

The Advisory Council unanimously approved this concept.

Alan D. Palkowitz, Ph.D., and G. Lynn Marks, M.D., were the assigned discussants for ASPIRE.

Dr. Palkowitz noted that Eli Lilly and Company has been working on automation, and the technology has evolved. ASPIRE could advance the mission of NCATS and of NIH by creating a forward-looking resource to expand access to chemical diversity, advance interrogation of biological targets and bring more innovation to the process, while also bringing in collaborators from many fields. Because the system will be accessible remotely from anywhere in the world, it will be easy for collaborations to arise. It will have synergies with many initiatives of NCATS, such as rare disease research. This will work has great potential for the future and for the NCATS mission.

Dr. Marks started by noting that NCATS should have more funding, because its work helps enable the agendas of all of the institutes and centers of NIH. On the topic of ASPIRE, he noted that there have been great advances in large molecules and monoclonal antibodies. ASPIRE makes it possible to address more disease areas. While most of the information presented was about efficacy, he notes that safety could also be a factor in choosing chemicals from iterative loops of assays.

Geoffrey Shiu Fei Ling, M.D., Ph.D., applauded NCATS for thinking beyond biology to work in the field of chemistry. ASPIRE is wonderful because it is outside of NIH's comfort zone.

Daniel L. Hartman, M.D., said that ASPIRE addresses chemical diversity, an important issue. He recommended that NCATS consider whether this is the most efficient way to address the problem. Based on the natural history of a disease, it could be possible to come up with effective chemicals through other mechanisms. NCATS should record metrics as part of ASPIRE.

Dr. Shekhar said that this technology represents the democratization of medicinal chemistry. Medicinal chemistry is a high-end enterprise often run in large corporations. With a system like this, any organic chemist with a disease of interest could have the equivalent of the resources of a major pharmaceutical company.

The Advisory Council unanimously approved this concept.

Dr. Palkowitz and Dr. Marks were the assigned discussants for the tissue chip concepts.

Dr. Palkowitz has followed this area closely. This technology has growing importance for addressing a translational gap in drug discovery: Linking pre-clinical observations to the clinical setting. Tissue chip technology can help reduce the time it takes to go from a concept to more effective and predictive human testing. NCATS's work will continue to bring more validation to the tissue chips and other systems that are being developed. This technology could be used to identify therapies or help model different disease populations. The connection with the National Aeronautics and Space Administration will be a catalyst for looking at miniaturization and making the systems accessible to primary users. Industry response to the tissue chip program has been favorable. With the FDA partnership, tissue chips could get new therapies to patients more quickly and efficiently.

Dr. Marks noted that future generations will be shocked that animal testing was used to predict toxicology. Animal testing is poorly predictive and poorly reproducible. The expansion of tissue chips is an important initiative for NCATS and shows how some efforts need to be centralized, and not spread across NIH. This is also something that industry would struggle to do without help from NCATS.

Dr. Ling said that the tissue chip work is exciting and should be pushed forward in every way possible.

Dr. Tagle noted that industry has been engaged with this project since the beginning, and the program has agreements with several pharmaceutical companies to provide compounds for testing.

Dr. Weichold said that it was smart to involve FDA early, because industry will not get involved with an initiative if they do not already know that FDA will accept it. In a few years, he predicted, FDA will have defined and specific conditions under which it will accept information based on chips from sponsors.

Dr. Tagle said that FDA is working with a company studying bioavailability of supplements with a gastrointestinal chip. The chips could also be used to study toxins, and discussions are going on with the National Institute of Environmental Health Sciences and the Environmental Protection Agency.

Dr. Marks suggested that the multi-company consortium Bioaccelerate could be a partner for advancing tissue chips.

The Advisory Council unanimously approved the two tissue-chip-related concepts.

V. NCATS BIOMEDICAL DATA TRANSLATOR PROGRAM UPDATE: Christine M. Colvis, Ph.D., Director, New Therapeutics Uses Program, NCATS, and Noel T. Southall, Ph.D., Director, Informatics, Division of Pre-clinical Innovation, NCATS

The goal of the Biomedical Data Translator program is to reveal new connections among existing data and find new insights, research opportunities, intervention opportunities, more success in clinical trials, and possibly new patient populations. The translator will integrate clinical and pre-clinical data from many sources to answer a wide range of translational questions by providing a dossier of information that helps an investigator focus their search and points them to sources with answers.

In January it was decided to use a blackboard architecture. This is made up of three components: A blackboard where a question is posed; knowledge sources that look at the question and respond to it, either immediately or based on responses from other knowledge bases; and a reasoning tool.

The reasoning tool is the brain of the software. A notice of the funding opportunity announcement (FOA) for building the reasoning tool was posted the morning of this meeting. The application process is unique. Only by completing a series of computational tasks can prospective applicants access the FOA and instructions for the concept letter submission. The concept letter must be submitted by September 22, 2017, and successful teams will receive written notification with instructions for the full proposal and presentation. This process is designed to find people, including individual U.S. citizens, who have the skills to develop a reasoning tool and the capacity to do so quickly.

Biomedical Data Translator: A Perspective from the Trenches: Stanley C. Ahalt, Ph.D., Professor, Director, Renaissance Computing Institute, University of North Carolina at Chapel Hill

Stanley C. Ahalt, Ph.D., introduced the work of the Translator Teams. He said that this is the most exciting project he has worked on in his career. It will democratize biomedical and health science data and create a new approach and framework for understanding disease.

- **Defining disease.** The program is trying to move past phenotype and endotype by integrating data from different knowledge sources. For example, the asthma-like phenotype includes wheezing, reduced lung function and shortness of breath. It can be associated with many endotypes. Distinguishing them is important for clinicians and researchers. Queries for a translator could include the relationship between particulate matter, ozone and responsiveness to treatment, or the mechanisms that link perinatal pollution exposure to chronic lung disease later in childhood. Data sources include national air quality and allergen exposure data, North Carolina patient data and census data. In a preliminary review of the data, a link has emerged between pollen counts and emergency room admissions.
- **The power and challenge of data.** It is difficult to integrate knowledge sources because there has been no incentive for harmonizing datasets. Both Duke and the University of North Carolina use Epic, for example, but bringing together the data for one patient can be difficult because the

data is recorded differently and access to patient data is highly regulated. The researchers have generated imitation data to help develop the translator.

- **Key drivers of success.** The project has worked well because it involves well-organized team science facilitated by NCATS. Involvement of NCATS leadership in regular meetings and calls has helped team members feel engaged and excited. Timing has also been part of success; the data, tools, networks and more have become available in recent years. Use cases such as the asthma example above have been a good way to organize.

Discussion

Christopher Austin, M.D., expressed amazement at the progress the teams have made.

Valerie Montgomery Rice, M.D., asked if there are plans to use other databases, such as insurance databases or Medicaid. Dr. Ahalt said that 44 knowledge sources are connected so far. The researchers would like to include more, but there are licensing issues and the data should be open source if possible.

Frank Weichold, M.D., Ph.D., agreed that health data needs to be accessible, not just for each person's benefit but for the greater good. This work could lead to data brokers that can receive data from patients, then organize the data so they are compatible, accessible and exchangeable.

Anantha Shekhar, M.D., Ph.D., noted that electronic health record data can be unreliable, and that data reliability in general is a challenge. Also, there are many regulatory barriers to this kind of work, which means engagement with local and state governments is needed. Dr. Ahalt said that some of the curation is currently done manually, and he hopes to develop automated tools. He said that municipalities and state governments must see that the work is leading to benefits.

Geoffrey Shiu Fei Ling, M.D., Ph.D., noted the unusual process for accessing the FOA and said this kind of project would be perfect for a prize.

Daniel L. Hartman, M.D., asked how the researchers are determining whether a data source will be useful. Dr. Ahalt said the group is discussing data quality and considering software that can look at data sources. Some databases are dumping grounds; people add data because they are required to, but do not clean up and document the data so they could be useful to someone else.

Dr. Austin led attendees in a round of applause for the two speakers. He said that the project is trying to change the terms of the conversation, in the true NCATS spirit.

VI. CTSA PROGRAM UPDATE: Streamlined, Multisite, Accelerated Resources For Trials IRB (SMART IRB)

Accelerating the Path from Discovery to Health Benefit: One IRB For Multi-Site Studies: Petra Kaufmann, M.D., M.Sc., Director, Division of Clinical Innovation; Director, Office of Rare Diseases Research, NCATS and Michelle A. Culp, M.P.H., Director of Clinical Operations, Division of Clinical Innovation, NCATS

Petra Kaufmann, M.D., M.Sc., introduced single IRBs. Using single IRBs for multisite studies will help decrease the time it takes for clinical trials to start and get treatments to patients. It may also be safer to have accountability centralized in one IRB rather than spread out. NIH will soon require use of a single IRB for multisite studies. The CTSA Program can play a unique role in the transition. The culture has changed, with increased acceptance of single IRBs. IRB approval time is only one factor in start-up time delays for trials. Other local reviews, such as radiation safety, can also cause delays. The process needs to be harmonized; it is burdensome for one institution to have to deal with many models of IRB reliance. Institutions and investigators need training and education.

Michelle A. Culp, M.P.H., introduced the NIH single IRB policy. The policy was announced earlier this year after approximately three years of development. NIH has found overwhelming support from investigators for single IRB review of multisite research. IRB administrators are less positive, because of administrative challenges. The policy takes effect in January for new grant applications and contract proposals. The policy applies to domestic sites of multi-site studies conducting non-exempt human subjects research. A *single* IRB is selected on a study-by-study basis. A *central* IRB does reviews for all sites in a particular network, consortium or program.

The NCATS Streamlined, Multisite, Accelerated Resources for Trials (SMART) IRB Reliance Platform is a way to streamline the single IRB process. It offers a single national reliance agreement. It can handle large and small studies and has electronic systems for documentation. It leverages expertise from the CTSA Program hubs and the Trial Innovation Network to support a developing IRB reliance network. By joining SMART IRB, institutions reduce negotiations. Institutions that join SMART IRB can work together to inform, enable and harmonize single IRB practices.

How the SMART IRB Exchange Web Portal Facilitates Implementation of the Central IRB Process: Gordon R. Bernard, M.D., Melinda Owen Bass Professor of Medicine, Associate Vice-Chancellor for Research, Vanderbilt University Medical Center

IRBexchange tracks all reliance relationships in a central, easy-to-use portal that captures and stores static local context. It also captures information such as what ancillary reviews are needed for a particular study for a particular site, and information about the site and Principal Investigator (PI). The software automates tracking, stores site-specific approval documents and centralizes approval information. It also automates communications from the central IRB, such as reminders about upcoming deadlines. Ninety institutions have signed the both the SMART IRB agreement and the IRBexchange agreement, including 41 CTSA Program sites.

SMART IRB: Supporting Single IRB Review – Advancing Collaborative Research: Lee M. Nadler, M.D., Virginia and D.K. Ludwig Professor of Medicine, Dean for Clinical and Translational Research, Dana Farber Cancer Institute, Harvard Medical School, and Barbara E. Bierer, M.D., Professor of Medicine, Harvard Medical School

Lee M. Nadler, M.D., shared some of the history of SMART IRB. It used to take months to start a trial involving multiple Harvard medical centers, because they were independent. When Harvard was writing its CTSA Program application, the researchers built in a reliance agreement. They shared the idea with

other parts of the CTSA Program and it spread. The structure of academic health care systems and their lawyers make IRB reliance agreements difficult to set up; the partnership with NCATS was very important. SMART IRB required an authorization agreement, which is signed once and implemented. Most of the work was getting those signatures. To date, 271 institutions have joined SMART IRB.

Barbara E. Bierer, M.D., noted that there can be many trivial differences between institutions; one might allow a child to assent at 12, while another only allows assent starting at age 13. This is the sort of challenge encountered in multisite studies. SMART IRB offers educational resources, including a webinar series on how to use SMART IRB and a growing library of collaboratively-developed resources. Consultations with IRB experts are also available. Many institutions do not have experience with reliance agreements. The group is working on some of the ongoing problems created by different groups and federal agencies with different requirements for IRBs, such as particular requirements from the department of Veterans Affairs (VA). The Harmonization Steering Committee is working to promote a more strategic, effective, efficient and cooperative approach to policies, processes and procedures related to single IRB review of multi-site studies. Committee members, which represent many different organizations, were surveyed about policies that can be changed. The group has prioritized the issues and subcommittees are working on the details — such as sorting out what policies are institutional and which are state-level requirements. Moving forward, it is important to have one information technology infrastructure that supports the work flow. In the future, the hope is for industry to sign on.

Discussion

Christopher P. Austin, M.D., said that SMART IRB is the most important thing NCATS has accomplished during his tenure as director. He noted that the group did not have power or authority, and yet it was able to bring about change. He mentioned that the advisory council includes members from the VA and the Department of Defense (DOD) who might be able to help.

Eric J. Topol, M.D., said that the work is based on an old model in which people go to a certain place to consent and participate; he asked how it could be used for digital end-to-end trials. Dr. Nadler said it takes time to build respect and trust. Patients build trust with their doctor and accrual to clinical trials requires that trust. Dr. Bernard said that the Recruitment Innovation Network has created a tool for sending an electronic consent that can be signed on a participant's phone. Sharon F. Terry, M.A., said that PCORNet has been working with digital communities where patients control their own information.

Harry Selker, M.D., M.S.P.H., asked about institutional versus IRB responsibility for scientific feasibility, including ability to recruit, and how SMART IRB handles the problem that exceptions to informed consent have to be decided locally. Dr. Bierer said SMART IRB needs to work with the Office for Human Research Protections and the DOD on how to handle emergency consent, because this requires a community process. She said feasibility assessment is handled well in industry, but poorly in academia. In academia, many trials terminate early because they cannot recruit. This is an ethical issue because no risk is worthwhile if no generalizable knowledge is created. Dr. Nadler agreed that this problem must be solved and mentioned that cancer centers carry out many futile trials. Dr. Kaufmann mentioned that having access to more data should make it easier to tackle this problem. Dr. Nadler said it was individual CTSA Program PIs that made SMART IRB happen.

Megan O'Boyle said, as a parent of a sick child, she was very frustrated by the delay created by the IRB.

Dr. Kaufmann said she would like to hear discussion on whether the SMART IRB system is scalable, or whether there will be multiple approaches. Dr. Bernard noted that, with a rare disease, if a patient appears in a remote location, they can be enrolled quickly if the institution is already taking part in SMART IRB and IRBexchange. Dr. Topol said the person could be enrolled virtually. Dr. Bierer said sometimes the drug has to be dispensed at a particular place.

G. Lynn Marks, M.D., asked if the network can be a resource for difficult topics, such as introducing tissue chip data to IRBs that are more familiar with animal data. He also asked how SMART IRB will expand internationally. Dr. Bierer said that some international institutions have signed. Dr. Marks recommended working with TransCelerate BioPharma Inc. on international collaborations. Dr. Nadler said that one of the advantages of central IRBs is that they could specialize in topics such as tissue chips.

Daniel L. Hartman, M.D., expressed reservations about running trials in developing countries; he said there are more efficient ways to move quickly and safely. On the topic of SMART IRB, he encouraged NCATS to think about explaining its case for change in IRBs in terms of time, money and people. Also, sponsorship by people with authority, such as the NIH Director, can help.

Dr. Bierer said that an IRB that is reviewing on behalf of dozens of sites will be in a lot of trouble if it makes a mistake, and NCATS needs to be prepared for this. She said NCATS can also have a leadership role in setting of data standards and return of results to participants.

Dr. Kaufmann asked the panelists to speak briefly about the future and next steps. Dr. Bernard said the goal is to get patients into studies right away, and that is easier if sites sign up for SMART IRB and IRBexchange. Dr. Nadler said researchers needed one infrastructure system that everyone uses and harmonized processes. Dr. Bierer said a more creative, strategic group should be created to think about how to enable new kinds of studies, and more education and engagement are needed. Valerie Montgomery Rice, M.D., mentioned that the Research Centers in Minority Institutions Program is advancing training for its central IRB.

VII. ADJOURNMENT OF OPEN MEETING

Christopher P. Austin, M.D., thanked all participants for their input. He and G. Lynn Marks, M.D., adjourned the open portion of the meeting at 3:05 p.m.

VIII. CLOSED SESSION OF 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.

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

Christopher P. Austin, M.D., adjourned the closed session of the NCATS Advisory Council meeting at 3:55 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. Date
Executive Secretary, NCATS Advisory Council
Executive Secretary, Cures Acceleration Network Review Board
and
Director, Office of Grants Management and Scientific Review, NCATS

G. Lynn Marks, M.D. Date
Chair, Cures Acceleration Network Review Board
and
Senior Vice President for Research and Development and Senior Clinical Advisor, GlaxoSmithKline