

**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

January 15, 2015

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 January 15, 2015, 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 Freda C. Lewis-Hall, 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

Danilo A. Tagle, Ph.D., M.S., Associate Director for Special Initiatives, NCATS

Council Members

| | |
|---|--|
| Margaret A. Anderson, M.A. | Eric D. Kodish, M.D. (by telephone) |
| Pamela B. Davis, M.D., Ph.D. | Freda C. Lewis-Hall, M.D. |
| Jorge L. Contreras, J.D. | Bernard H. Munos, M.B.A. |
| Louis J. DeGennaro, Ph.D. (by telephone) | Harry P. Selker, M.D. |
| Mary L. Disis, M.D. | Anantha Shekhar, M.D., Ph.D. |
| Frank L. Douglas, Ph.D., M.D. | Scott J. Weir, Pharm.D., Ph.D. (by telephone) |
| Geoffrey S. Ginsburg, M.D., Ph.D. | |

Representative Members

Ankit A. Mahadevia, M.D., M.B.A., Atlas Venture (by telephone)
Robert I. Tepper, M.D., Third Rock Ventures, L.L.C.

Ad Hoc Member

Paul G. Yock, M.D., Stanford University (by telephone)

Ex Officio Member

David Atkins, M.D., M.P.H., Department of Veterans Affairs

CAN REVIEW BOARD MEMBERS PRESENT

Chair

Freda C. Lewis-Hall, M.D., Executive Vice President and Chief Medical Officer,
Pfizer

Vice Chair

Geoffrey S. Ginsburg, M.D., Ph.D., Director, Center for Applied Genomics &
Precision Medicine; and Professor of Medicine, Pathology and Biomedical
Engineering, Duke University Medical Center

Executive Secretary

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Robert J. Beall, Ph.D.

Jorge L. Contreras, J.D.

Louis J. DeGennaro, Ph.D. (by
telephone)

Mary L. Disis, M.D.

Frank L. Douglas, Ph.D., M.D.

Victoria G. Hale, Ph.D.

Eric D. Kodish, M.D. (by telephone)

Bernard H. Munos, M.B.A.

Myrl Weinberg, M.A.

Harry P. Selker, M.D.

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Ex Officio Members

David Atkins, M.D., M.P.H., Department of Veterans Affairs

Frank F. Weichold, M.D., Ph.D. (attending in place of Margaret A. Hamburg, M.D.),
U.S. Food and Drug Administration (FDA)

INVITED PRESENTERS

Michele Manion, Vice President, Executive Director, Founder, Primary Ciliary
Dyskinesia Foundation

Peter A. Merkel, M.D., M.P.H., Professor of Medicine and of Epidemiology, Chief of
Rheumatology, University of Pennsylvania

OTHERS PRESENT

Sarah Buchanan, Health and Medicine Counsel of Washington

Dale P. Dirks, Health and Medicine Counsel of Washington

William J. Heetderks, M.D., Ph.D., National Institute of Biomedical Imaging and
Bioengineering (NIBIB)

Aleek Kahramanian, KAI Research, Inc.

Mei Chun Lai, Physicians Committee for Responsible Medicine
Todd D. Merchak, NIBIB
Joan D. Nagel, M.D., NIH Office of Research on Women's Health
Yvette Seger, Ph.D., Federation of American Societies for Experimental Biology
York Tomita, FDA
Randi M. Williams, M.P.H., KAI Research, Inc.
NCATS leadership and staff

I. CALL TO ORDER AND WELCOME

Christopher P. Austin, M.D., welcomed members and guests to the eighth meeting of the NCATS Advisory Council and the 10th meeting of the CAN Review Board. He reminded attendees that the open session was being videocast.

Danilo A. Tagle, Ph.D., M.S., informed the group that the remaining 2015 joint meetings are slated for June 17 and 18 and September 3 and 4. In addition, the CAN Review Board will meet by teleconference on Dec. 11, 2015.

Dr. Austin welcomed Harry P. Selker, M.D., and Anantha Shekhar, M.D., Ph.D., as official members of the NCATS Advisory Council and CAN Review Board.

Since the last joint meeting, several new staff members have joined NCATS:

- **Peter John (P.J.) Brooks, Ph.D.**, has joined NCATS as a program director within NCATS' Division of Clinical Innovation. He previously was on a detail assignment in the NCATS Office of Rare Diseases Research (ORDR).
- **Kristin Wegner** has joined NCATS as a senior grants management specialist in the Office of Grants Management.
- **Stacy Fakinlede** has joined NCATS as a program specialist. She will coordinate future meetings of the NCATS Advisory Council and the CAN Review Board.

II. CONSIDERATION OF MINUTES: Danilo A. Tagle, Ph.D., M.S., Associate Director for Special Initiatives, NCATS; Executive Secretary, NCATS Advisory Council and CAN Review Board

The minutes of the joint meeting held on Sept. 24, 2014, were approved as written.

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

Christopher P. Austin, M.D., introduced the participants to a new format for the director's report, which focuses on a few notable accomplishments rather than describing all of the Center's accomplishments since the last meeting so as to allow more time for discussion. Regarding the financial picture at NIH and NCATS, Dr. Austin noted that the fiscal year (FY) 2015 budget maintains NCATS funding at about the same level as last year (\$635 million, a 0.3 percent increase). NCATS staff are working now on the FY 2016 budget request, which is expected to be released on Feb. 2, 2015.

Since the last meeting of the Advisory Council and CAN Review Board, NCATS has taken advantage of several opportunities to brief members of Congress and their staffs and interact with them. For example:

- NCATS leadership participated in [21st Century Cures Initiative](#) roundtables.
- A Technology Transfer Caucus event titled “[Next-Generation R&D Partnerships: The NCATS Success Story](#)” was held.
- Visits were made to NCATS by the Senate Appropriations Subcommittee staff; Senate Health, Education, Labor and Pensions Committee staff; the House Technology Transfer Caucus and department of Energy staff; the House Energy and Commerce Subcommittee on Environment and the Economy; and the Senate Environment and Public Works Committee.

Austin also reported on Ebola Medicines Day, which was hosted by NCATS and the National Institute of Allergy and Infectious Diseases in November 2014. Attendees represented the biopharmaceutical industry, the Bill & Melinda Gates Foundation, the U.S. Army Medical Research Institute of Infectious Diseases, the Defense Threat Reduction Agency and other NIH Institutes and Centers (ICs). The purpose of the event was to present the most current information on the biology of the virus and host responses to this pathogen, along with a full enumeration of identified viral and host targets, in the hope that industry representatives would examine their investigational “medicine cabinets” to see what might be relevant.

Austin presented three examples of progress in early-, middle- and late-stage development along the translational science spectrum made possible through NCATS:

- **Early-stage translation:** To save money and reduce the waste stream, NCATS scientists developed a protocol to clean and reuse 1,536-well microtiter plates used in the high-throughput screening of chemicals. Thanks to the new technology, NCATS has kept nearly 50,000 microtiter plates out of landfills and saved nearly a half million dollars. [IonField Systems was awarded a Small Business Innovative Research \(SBIR\) contract](#) to develop the commercial potential of the cleaning system.
- **Middle-stage translation:** Niemann-Pick disease type C1 (NPC) is a rare lysosomal storage disease; such diseases often are fatal. Together with many patient groups, NCATS started an NPC project in 2006 that was based on the beneficial effects of cyclodextrin observed in animal models of the disease. Although cyclodextrin showed little activity in fibroblasts from affected children, induced pluripotent stem cells derived from fibroblasts showed excellent activity. The scientists also have found evidence of activity in other lysosomal storage diseases. Just a few weeks ago, [NCATS entered into an agreement with Vtesse, Inc.](#), to develop cyclodextrin as a treatment for NPC and explore its use in other lysosomal storage diseases. As Austin explained, this example illustrates several principles embraced by NCATS: First, because this effort involved more than 30 collaborators across 20 disciplines and 10 ICs, it shows that translation is a

“team sport.” Second, patients and advocacy groups provided the impetus for the project. Third, the results demonstrate how progress on treating multiple diseases can be accelerated by working on disease commonalities. Finally, the project demonstrates a successful handoff of a de-risked project to industry.

- **Late-stage translation:** NCATS’ Division of Clinical Innovation has completed a series of demonstration projects per the recommendations in the [Institute of Medicine's \(IOM's\) report on the Clinical and Translational Science Awards \(CTSA\) program](#) and is now releasing additional funding opportunity announcements (FOAs). The CTSA consortium will be testing innovative ways to reduce the inefficiencies of clinical translational studies through Trial Innovation Centers and Recruitment Innovation Centers. The Trial Innovation Centers will serve as a resource to the CTSA hubs by providing central institutional review boards (IRBs), contracting, budgeting and other support as needed. Recruitment Innovation Centers will promote innovation and efficiency in participant recruitment, building on the existing expertise at the CTSA hubs and on current CTSA consortium initiatives. The plan is to pilot these innovative trial components in a multisite study funded by an NIH IC or some other entity. Ultimately, these plug-and-play components could be applied in many trials across many Centers, increasing the efficiency of clinical research.

Following Austin’s remarks, Frank L. Douglas, Ph.D., M.D., asked about embedding the components of training in clinical research within multisite studies. Austin responded that some CTSA hubs already are engaged in the training of clinical research professionals. Pamela B. Davis, M.D., Ph.D., mentioned that IRBs require some training for investigators.

Observing that some CTSA hubs have significant reach into their communities, Dr. Davis spoke of a movement to provide training for community members so that they can assume meaningful roles in clinical research. The education of patient participants is a key component of community engagement for the CTSA hubs.

Myrl Weinberg, M.A., inquired about ways to learn about the efforts of CTSA hubs to train community members and gauge the success of those efforts. According to Petra Kaufmann, M.D., M.Sc., some excellent local models exist for training individuals who are not traditional researchers. Dr. Kaufmann expressed interest in identifying success stories of partnerships with community members and creating reproducible models and metrics for training them in research.

Geoffrey S. Ginsburg, M.D., Ph.D., asked about next steps in the search for compounds effective against the Ebola virus. Dorit Zuk, Ph.D., suggested that the researchers would have some ideas about compounds to investigate within the next few weeks. A [collaboration](#) between NCATS and the Icahn School of Medicine at Mount Sinai already is in place to screen drugs approved for other indications. Sam Michael, NCATS director of automation and compound management, explained that the Mount Sinai researchers are generating two Ebola proteins, and NCATS is screening its collection of compounds for activity against the target proteins. Dr. Ginsburg asked about the sufficiency of the

intramural budget to cover unanticipated events, such as the Ebola outbreak. The budget can accommodate simple assay development and screening, but it could not cover expenditures such as biosafety level 4 experiments or facilities, Austin explained.

Eric D. Kodish, M.D., was curious about the relationship between NCATS and other NIH ICs. Austin said that since its inception, NCATS staff have worked closely with colleagues from the other ICs, and now all parts of NCATS have collaborative relationships with other ICs and their programs.

IV. THE RARE DISEASES CLINICAL RESEARCH NETWORK

Overview of the Network — *Rashmi Gopal-Srivastava, Ph.D., Director, Extramural Research Program, Office of Rare Diseases Research, NCATS*

Rashmi Gopal-Srivastava, Ph.D., provided an overview of the Rare Diseases Clinical Research Network (RDCRN), which currently is in its third funding cycle. RDCRN consists of 22 distinct multisite consortia and a central Data Management and Coordinating Center that supports all the consortia. The consortia are funded via U54 cooperative agreement awards, and each consortium receives no more than \$1.25 million total cost in support per year. This is a collaborative effort with 10 NIH ICs.

The consortia are required to engage patient advocacy groups (PAGs) as research partners, focus on a group of at least three related rare diseases, conduct clinical studies (including a longitudinal study) and provide training to young investigators. Nearly 100 PAGs are involved in the RDCRN; collectively, these groups constitute the RDCRN Coalition of Patient Advocacy Groups (CPAG).

Perspective from an RDCRN Consortium's PAG as Research Partner — *Michele Manion, Vice President, Executive Director and Founder, Primary Ciliary Dyskinesia Foundation*

Michele Manion spoke of her experience as founder and executive director of the Primary Ciliary Dyskinesia (PCD) Foundation, which she established in 2002. Initially, she worked with a single investigator at the University of North Carolina at Chapel Hill to create opportunities for PCD patients to participate in research, but since then more than 1,100 patients with PCD have been evaluated through the Genetic Disorders of Mucociliary Clearance Consortium (GDMCC).

GDMCC is a network of nine North American centers that are collaborating in diagnostic testing, genetic studies and clinical trials of patients with impaired [mucociliary clearance](#). Thanks to research on the natural history of the disease done through the consortium with the aid of some of the PAGs, researchers have elucidated the phenotype of PCD. The collaborative research has led to multiple publications in top-tier journals, a 32-gene diagnostic panel and diagnostic standards.

Some PAGs are simply small groups that meet around kitchen tables, but some others are well-established organizations with substantial resources. Regardless, all the PAGs are committed to making the network work; as members of CPAG, the individual PAGs

are also members of the RDCRN and, as such, must consider the needs of the RDCRN as a whole.

But does this model actually work? Manion presented a timeline of progress in PCD research, demonstrating that shortly after the founding of the PCD Foundation in 2002 and the creation of the RDCRN and GDMCC, an explosion of research activity led to the identification of genes associated with PCDs, the establishment of PCD medical centers, the organization of professional meetings on PCD and the publication of papers on the topic.

Manion thanked NCATS and acknowledged the support of Dr. Gopal-Srivastava, Pamela McInnes, D.D.S., M.Sc.(Dent.), Stephen C. Groft, Pharm.D., and others at ORDR.

The Transformation of Clinical Research in Vasculitis Through the Rare Diseases Clinical Research Network — *Peter A. Merkel, M.D., M.P.H., Professor of Medicine and of Epidemiology, Chief of Rheumatology, University of Pennsylvania*

In his remarks, Peter A. Merkel, M.D., M.P.H., focused on the accomplishments of the Vasculitis Clinical Research Consortium (VCRC), which is part of the RDCRN. The international, multicenter VCRC is a research infrastructure for conducting clinical and translational investigation in various types of vasculitis. The consortium, which is in its third cycle of U54 funding (11th year), has transformed the landscape of vasculitis research.

Dr. Merkel is the principal investigator of the consortium, which consists of 16 sites in North America in addition to many partner sites in the European Union (EU), Asia and Australia. Merkel attributes the success of the VCRC in part to the fact that the investigators know and like each other and work collaboratively. The consortium has grown substantially, but in a cautious fashion. New sites are added on either a per-study or pan-study basis.

Six different longitudinal (natural history) studies are the heart of the VCRC's work; participants in clinical trials are recruited from these longitudinal studies. The VCRC maintains several patient registries as well as repositories for biomarkers and clinical data. Consortium researchers are carrying out a host of pilot studies, mechanistic studies, research in systems genetics and several randomized clinical trials, some of which are industry supported. Consortium researchers are just finishing the first-ever trial in Takayasu's arteritis.

All VCRC specimens are stored in one repository at the University of Pennsylvania. This resource currently houses more than 48,000 samples from more than 2,000 participants and that were obtained from 11,000 study visits. It is the largest such collection in the world, providing DNA, serum, plasma, urine and peripheral blood mononuclear cells for research.

VCRC investigators use reliance agreements to set up an IRB of record for each multisite trial, thereby reducing the time to initiate a study and related costs. The consortium also established a VCRC–National Institute of Arthritis and Musculoskeletal and Skin Diseases data safety and management board, which provides reviews by its expert members.

Patients with vasculitis may register with the online VCRC Patient Contact Registry to allow future contact regarding studies and to receive research updates. More than 4,000 patients already are registered and ready to enroll in trials and participate in surveys.

One goal of the VCRC is to develop outcome measures, including patient-reported outcomes, Merkel explained. The VCRC, along with the Vasculitis Foundation, secured funding from the Patient-Centered Outcomes Research Institute (PCORI) to form the Vasculitis Patient-Powered Research Network, which is part of PCORnet (the National Patient-Centered Clinical Research Network).

According to Merkel, the VCRC's genetic work is burgeoning now that a critical mass of patients has enrolled in the registry. A systems genetics approach is being applied to elucidate new targets for potential follow-up through NCATS' Therapeutics for Rare and Neglected Diseases program.

Merkel emphasized the importance of the VCRC's 10-year partnership with the Vasculitis Foundation, which co-funds fellowships for training fellows in the conduct of translational and clinical research in vasculitis. Some former fellows have been funded and are engaged in vasculitis research; some have even opened new vasculitis centers. All continue to see patients with vasculitis. In addition, the VCRC has been able to leverage support from the RDCRN to obtain other funding, making the VCRC the world's leading clinical research program in vasculitis.

Regarding the VCRC's randomized clinical trial enrolling patients with Takayasu's arteritis, Merkel explained that pharmaceutical companies have little financial incentive to conduct such a trial. But, once a trial has been organized, companies often are willing to provide compounds. Geoffrey S. Ginsburg, M.D., Ph.D., inquired about possibly involving companies earlier in the research continuum — before randomized clinical trials. Christopher P. Austin, M.D., suggested that the VCRC could identify targets and pull samples from its repositories to be tested against NCATS' library of compounds to look for signals of activity.

The vasculitides are not single-gene disorders, but there are clear genetic dispositions (racial/ethnic differences, genetic predispositions, association with human leukocyte antigen [HLA] types). Dr. Austin asked about what is involved in redefining this idiosyncratic group of variable eponymic disorders by using molecular/genetic bases. Merkel spoke of the VCRC's efforts to eliminate some of the names of the vasculitides, and he noted that more than one disease is probably nested in these disorders. A systems biology approach could reveal cross-cutting concepts and disease commonalities.

Anantha Shekhar, M.D., Ph.D., asked about lessons that could be applied to the CTSA network from experience with the VCRC. Austin said that the CTSA hubs provide access to a wide spectrum of clinical expertise as well as centralized processes, methods and resources. Certainly, there needs to be space for entrepreneurial experimentation, but centralization and standardization can make research more efficient.

Mary L. Disis, M.D., asked about interactions of the VCRC with the RDCRN. Merkel acknowledged that the VCRC probably would not have engaged in training to this extent without a mandate or guidance from the RDCRN; the provision of resources and tools, such as Research Electronic Data Capture (REDCap), can be a powerful motivator.

Pamela B. Davis, M.D., Ph.D., spoke of the energy generated by bringing families and patients together with researchers to take on the challenges of severe and rare diseases. Clearly, the VCRC illustrates the power of a mission shared by a number of groups (industry, patients and families, ICs, other federal agencies).

V. REPORT FROM THE MEDICAL TECHNOLOGIES SUBCOMMITTEE: Frank L. Douglas, Ph.D., M.D., President and CEO, Austen BioInnovation Institute in Akron

Frank L. Douglas, Ph.D., M.D., updated the group on recent activities of the Medical Technologies Subcommittee, which included a landscape review of devices and diagnostics. Much of this work built upon the efforts of Todd D. Merchak and William J. Heetderks, M.D., Ph.D., of NIBIB, who conducted an NIH portfolio analysis with regard to the development of medical devices.

Dr. Heetderks and Mr. Merchak found that no NIH Research, Condition and Disease Categorization system code for medical devices existed. They then drafted a classification system that included five subcategories (assistive, diagnostic, imaging, implant and surgical) and coded the NIH grant database using these subcategories.

Their analysis showed that diagnostic and imaging research accounted for 60 percent of grants for medical devices; the other three categories comprised 40 percent. Five Institutes (National Cancer Institute [NCI]; NIBIB; National Heart, Lung and Blood Institute; National Institute of General Medical Sciences; and National Institute of Neurological Disorders and Stroke [NINDS]) account for the vast majority of research activity related to device development. Medical technology accounts for about a third of all SBIR contracts.

Dr. Douglas highlighted several potential opportunities for NCATS with regard to medical technologies:

- Address systemic barriers to the development and implementation of medical devices for all applications, including diagnostics.
- Enhance collaboration and cooperation among stakeholders in research on medical devices.
- Provide education and training of the workforce.
- Define knowledge gaps and resource requirements.

The Medical Technologies Subcommittee offered two major recommendations for consideration by the Advisory Council and CAN Review Board:

- 1. Convene experts and stakeholders in workshops and conferences on specific challenges in medical devices.** Topics could include legal issues and intellectual

property, reimbursement, business plans, and market analysis. Stakeholders also could comment on clinical need and usability requirements. NCATS could encourage the use of team science and engage new communities in device development.

- 2. Engage all stakeholders in addressing gaps in knowledge and resources for investigators, clinicians, engineers and trainees to move products from discovery to patients.** Having a better understanding of the CTSA landscape with regard to training and educational resources in the development of medical devices could help define workforce needs and identify ways to meet those needs. Also, advisors, mentors and staff could benefit from access to expertise in regulatory requirements, reimbursement issues and other aspects of commercialization.

Harry P. Selker, M.D., said that the pathway for demonstrating the safety and efficacy of medical devices is not as well defined as it is for drug candidates. He asked about a potential role for NCATS in engaging patients as a constituency to push for a more balanced approach to evaluating tools and devices.

Paul G. Yock, M.D., referred to the FDA's [510\(k\) process](#), noting that it is a matter of fierce debate as to whether the approval process is effective. He agreed that greater emphasis on rigorous testing of devices should be a priority for NIH.

Louis J. DeGennaro, Ph.D., observed that the importance and value of laboratory-developed tests is changing dramatically. Is there a role for NCATS in the development of such tests?

Referring to the portfolio analysis, Christopher P. Austin, M.D., inquired about the proportion of the NIH budget that goes into medical technologies each year. Merchak explained that an analysis of the narrative sections of proposals revealed that the absolute amount is roughly \$300 million across NIH — about 1 percent of the total budget.

With regard to the timeline for development and approval of new devices, it can take a long time, depending on whether the 510(k) process applies. If there is a predicate — a proven device — the 510(k) approval process would apply to a similar device that can be compared to the predicate. Heetderks explained further: Basic research for a new device might involve 10 percent of the total development costs, while the remaining 90 percent would be required to take the results and move them into a product. The time from showing feasibility to having an approved device can be as long as 10 to 15 years, which was the case for cochlear implants, for example. The cost of entry as the predicate device is extremely high, but for second and subsequent devices, costs are dramatically lower.

If one looks across the spectrum of devices, on average the time cycle is quite a bit shorter (in the range of several years) for devices than it is for drugs, and the costs tend to be lower, according to Dr. Yock. Roughly speaking, the cost can be in the high hundreds of thousands of dollars for a complex premarket approval for a medical device.

Several participants pointed out that technology development is much easier in the EU than in the United States. The group compared the FDA's Investigational Device Exemption and the EU's CE-marking process (the CE designation, which translates to "European conformity," indicates that a device can be marketed). Developers say that they prefer to obtain the CE mark in the EU and then go through the approval process in the United States. Douglas thought that this would be a topic for the Medical Technologies Subcommittee to take up.

Dr. Selker remarked on the importance of involving the Centers for Medicare & Medicaid Services (CMS) because developers need to be assured of reimbursement. Heetderks suggested that integrating research on devices with FDA and CMS requirements would be an opportunity for NCATS.

Some participants recommended working on signal processing as a common need across the subcategories of devices.

Dr. Austin thanked the subcommittee for its service to the Council, and he acknowledged the contributions of Heetderks and Merchak.

VI. CTSA UPDATE: Petra Kaufmann, M.D., M.Sc., Director, Division of Clinical Innovation, NCATS

After reviewing the strategic goals of the Division of Clinical Innovation, Petra Kaufmann, M.D., M.Sc., showcased four demonstration projects being undertaken by the CTSA Consortium:

- **Transforming Multisite Trials: Central IRBs for the CTSA Program:** To help streamline multisite trials, NCATS is funding an initiative to build national trial support centers that centralize IRB review through [reliance agreements](#). The aim is to move toward a single IRB for multisite trials undertaken by the CTSA consortium to speed up the initiation of these trials. In December 2014, NIH issued a [draft policy](#) to promote the use of a single IRB in multisite clinical research studies. Dr. Kaufmann pointed out that NCI and the NINDS NeuroNEXT network have demonstrated the feasibility of relying on a central IRB. For the NCATS demonstration project, the CTSA investigators are drafting a national IRB reliance agreement and setting up an informatics infrastructure to support a reliant IRB model for a pilot project. As an example of the value of IRB reliance, Kaufmann explained how clinicians at Massachusetts Eye and Ear Infirmary realized that they could learn more about blast-related ear injuries by studying victims of the 2013 Boston Marathon bombing. The [Harvard CTSA already had an IRB reliance system](#) in place, enabling researchers to rapidly enroll victims at eight hospitals to learn about ear injuries and healing.
- **Innovating Research Participant Recruitment:** NCATS is funding an initiative to improve recruitment capacity using data from electronic health records to identify potential trial participants. The Accrual to Clinical Trials (ACT) project is starting with 13 initial sites and will add eight more to test a data system called

[i2b2/SHRINE](#). Using pilot queries, ACT investigators will evaluate how many patients with a given condition are being seen at the study sites and assess whether the patients meet the study entry criteria. The goal is to include all of the CTSA hubs eventually. As of December 2014, the NCATS milestones for this project were met.

- **Enhancing Clinical Research Professionals’ Training and Qualifications:** As Kaufmann explained, good clinical research training can minimize errors and help protect research participants. Variations in training standards can decrease data quality and cause delays when research funders have to redundantly evaluate training levels each time. This demonstration project, which involves all 62 CTSA hubs, aims to: (1) create standards for research workforce training, using Good Clinical Practice (GCP) certification as a “floor”; and (2) develop a competency-based, clinical research professionals’ training curriculum. Regarding the GCP training component, a face-to-face meeting with representatives of all 62 CTSA hubs took place in November 2014. To develop a training curriculum, the investigators are examining existing competency frameworks in terms of their suitability for the CTSA consortium. A meeting is slated for February 2015 to identify key competencies and explore possible evaluation metrics. Kaufmann pointed out that this demonstration project is the first national CTSA initiative to include all the hubs.
- **Innovating Scientific Review for the CTSA Program:** Scientific review of research on human subjects ensures scientific validity and the operational feasibility of protocols. A stakeholder committee, which met in December 2014, prepared a draft consensus document including review standards, recommendations on an information technology (IT) infrastructure, and an evaluation plan.

Kaufmann highlighted progress in transforming the CTSA program per the [recommendations of the IOM](#) and a [report issued by a working group](#) of the NCATS Advisory Council. A new, streamlined CTSA communication structure is being rolled out. Guided by the CTSA Consortium Steering Committee, a series of discussion groups was set up according to various domains of interest to the CTSA program: workforce development, collaboration engagement, integration across the life span, methods and processes, and informatics. The structure of discussion groups is outcome-driven and involves a limited number of groups and voluntary participants. Each group will have a timeline and outcome; they all report to the Steering Committee.

On the topic of evaluation, Kaufmann underscored the importance of selecting the most relevant metrics in order to minimize burden on investigators. The evaluation framework should build upon existing metrics, be concise and be capable of discerning trends.

Applications for the CTSA FOA have been received, Kaufmann announced. The applications will be discussed in closed session during the next meeting of the Advisory Council.

Kaufmann offered two take-home messages. First, the opportunities in translational science are huge and systematic and, therefore, require systematic solutions. Second, the transformation of the CTSA program will allow it to seize opportunities for the benefit of patients.

Following Kaufmann's remarks, Robert J. Beall, Ph.D., asked about how the CTSA institutions and Congress are receiving the program's strategic goals and overall transformation. Kaufmann said that the CTSA investigators are demonstrating leadership by recognizing the need for improvement as well as the importance of shared goals.

Frank F. Weichold, M.D., Ph.D., explained that the FDA needs metrics to assess the quality of clinical trials. He recommended working with the FDA and other stakeholders to identify "low-hanging fruit" and to build confidence in the research, data and competencies of the CTSA hubs. Could the CTSA end up becoming somewhat of a contract research organization (CRO)? Kaufmann clarified that the CTSA are not CROs; the CTSA program will remain a strong academic endeavor that builds on the intellectual capacity of hub investigators.

Frank L. Douglas, Ph.D., M.D., asked whether the program changes came from the top down or from the bottom up. Clearly a great deal of collaboration is going on among the hubs, but how likely are these changes to be adopted if they are seen as coming from the top? Kaufmann said that the CTSA principal investigators are leaders and that every academician is an entrepreneur. If NCATS would like the hubs to function more as a network, as advised by the IOM, they will have to come together like an orchestra instead of being soloists. Furthermore, Kaufmann explained, the IOM report reflects the need for the program to maintain a balance between being a "bottom up" (institution and investigator) entity and being a national network. The CTSA program as a whole should cover the entire spectrum of translational research.

David Atkins, M.D., M.P.H., spoke of the potential of the informatics domain to be transformative and engage all stakeholders. Electronic health records are an excellent source of both clinical and research data, and this is an area of interest at the Department of Veterans Affairs. Kaufmann responded that the CTSA Consortium recently launched [a new task force on informatics](#), and she encouraged Atkins to participate.

Pamela B. Davis, M.D., Ph.D., remarked on the Ohio Clinical Trials Collaborative, noting that it has a reliant IRB model, common budget and contract forms, and a system to prospectively identify patient populations to recruit for participation in trials. Anantha Shekhar, M.D., Ph.D., spoke about a similar effort to connect six CTSA hubs across four states through a central mechanism. Each institution contributed \$50,000 to create a central office, and multiple trials were carried out through the network. The i2b2 platform was used for cohort discovery.

Dr. Shekhar pointed out that setting up FDA-compliant databases would be a very large task. Dr. Douglas expressed concern that in about two years, the FDA may start

requiring the submission of electronic databases and disallow paper submissions. Harry P. Selker, M.D., recommended that NCATS call on the other ICs to pull together and encourage hospitals to use electronic health records to create data warehouses.

The meeting participants discussed commercial IRBs; it was noted that investigators often prefer IRBs to be embedded in the research community rather than elsewhere. Christopher P. Austin, M.D., explained that the pilot projects, including the one on IRB reliance, are all funded by NCATS. Dr. Davis observed that the local sites need to have personnel to manage the IT aspects of the projects. Mary L. Disis, M.D., speculated that if the reliant IRB model is adopted across the CTSA hubs, eventually the individual institutions will have to underwrite the costs.

Myrl Weinberg, M.A., inquired about establishing a national group of external stakeholders to recommend metrics for evaluating training. Kaufmann mentioned convening a working group of the Advisory Council to provide recommendations.

VII. COUNCIL AND CAN REVIEW BOARD—INITIATED DISCUSSION: Advisory Council and CAN Review Board Members

Robert J. Beall, Ph.D., inquired about the status of the CAN budget, and Christopher P. Austin, M.D., said the FY 2015 budget is the same as last year's (\$9.835 million). Although this situation is frustrating, it seems that many members of Congress favor the CAN mission. Dr. Austin said that NCATS staff are working to heighten awareness of CAN's activities and its special authorities. Freda Lewis-Hall, M.D., encouraged the Review Board to explore other options, such as matching funds and novel collaborations, to carry out its mission. She recommended further discussion at the joint meeting in June.

Geoffrey S. Ginsburg, M.D., Ph.D., suggested inviting someone from the National Human Genome Research Institute (NHGRI) to speak at a joint meeting to discuss possible synergies between NCATS and NHGRI's translational genomics programs, namely:

- **Electronic Medical Records and Genomics:** This [network](#) is developing, disseminating and applying approaches that combine DNA biorepositories with electronic health record systems for large-scale, high-throughput genetic research. A network of 15 to 20 sites already is in place.
- **Clinical Sequencing Exploratory Research:** This [program](#) supports methods development as well as the ethical, legal and psychosocial research necessary to responsibly apply personal genomic sequence data to clinical care. About a half-dozen sites are sequencing individuals and working through the placement of the information. A single-page report to present all the significant genetic findings could be used in clinical care.
- **Implementing Genomics in Practice (IGNITE):** This new [translational consortium](#) of NHGRI is enhancing the use of genomic medicine by supporting the development of methods for incorporating genomic information into clinical care and exploration of the method for use in diverse clinical settings. IGNITE

researchers are working on a family history tool to help make decisions about diagnostic and genetic testing.

Each of the three programs has the aim of being incorporated into the clinical space. They are designed to demonstrate the value proposition of genomics in terms of process and clinical and economic measures. Myrl Weinberg, M.A., recommended involving PCORI, some companies and other agencies, including those in the EU. She suggested mapping those activities that are ongoing to figure out where NCATS can plug in.

Regarding the use of technologies in research, Pamela B. Davis, M.D., Ph.D., suggested that the CTSA hubs could run technology-enabled pilots. Technology could reduce the need for follow-up visits in certain clinical trials, for example.

Anantha Shekhar, M.D., Ph.D., commented on a possible role for the CTSA hubs in identifying actionable types of genetic tests done in laboratories certified for Clinical Laboratory Improvement Amendments and then arranging for medical providers to access and use the information in clinical practice. The CTSA network could take on that challenge.

According to Frank F. Weichold, M.D., Ph.D., most CROs are oriented toward overseas trials, and that means that the United States is losing expertise in clinical trials. The CTSA program is not funded sufficiently to make a meaningful difference, and thus Dr. Weichold recommended that the CTSA hubs partner with large payer and hospital networks and leverage the position of NIH and the FDA within the Department of Health and Human Services to accrue enough resources to carry out well-run trials. Petra Kaufmann, M.D., M.Sc., spoke about the importance of giving patients in this country access to research. Dr. Kaufmann also said that high-level academic institutions likely would not be interested in trials that do not require their intellectual input. As Frank L. Douglas, Ph.D., M.D., pointed out, CROs are good at collecting statistical evidence of safety.

Dr. Lewis-Hall suggested thinking further about tools for clinical trials: “What would clinical trials look like if we started with what we needed to accomplish and ignored the existing systems?” In other words, the exercise should start with desired outcomes and work backward to see what sort of clinical trials enterprise would achieve those outcomes.

For the June meeting, Dr. Shekhar recommended having a wrap-up session to summarize discrete components and action items.

ADJOURNMENT OF JOINT MEETING

Danilo A. Tagle, Ph.D., M.S., adjourned the meeting at 3:09 p.m. ET.

CLOSED SESSION OF NCATS ADVISORY COUNCIL

This portion of the 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).

Council members discussed procedures and policies regarding voting and confidentiality of application materials, committee discussions, and recommendations. Members absented themselves from the meeting during 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.

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 4:00 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

Danilo A. Tagle, M.S., Ph.D. Date
Executive Secretary, NCATS Advisory Council
Executive Secretary, Cures Acceleration Network Review Board
and
Associate Director for Special Initiatives, NCATS

Freda C. Lewis-Hall, M.D. Date
Chair, Cures Acceleration Network Review Board
and
Executive Vice President and Chief Medical Officer, Pfizer