Clinical Research Forum Annual Meeting  
April 9–10, 2014  
Washington, DC

Welcome and Overview of the Meeting  
Robert M. Califf, M.D., Chairman, Clinical Research Forum; Vice Chancellor, Clinical and Translational Research, Director, Duke Translational Medicine Institute, Duke University Medical Center

Dr. Califf welcomed members of the Clinical Research Forum to this meeting. The Forum’s current focus areas include advocacy and interventions related to policy, the work of the Forum’s Information Technology (IT) and Industry Roundtables, collaborations with patient advocacy groups and voluntary health organizations, and the Top 10 Clinical Research Achievement Awards. Some recent trends that the Forum is addressing are potential cuts to the National Institutes of Health (NIH) budget, the need to balance NIH funding for clinical and translational research, and new rules governing conflicts of interest in interactions between academia and industry.

Session 1: Intersection of NIH and Patient-Centered Outcomes Research Institute (PCORI) Clinical Trial Systems  
Chair: Robert M. Califf, M.D.

Joseph Selby, M.D., M.P.H., Executive Director of PCORI, described the National Patient-Centered Clinical Research Network (PCORnet), a large, highly representative, national clinical research network designed to improve the efficiency and timeliness of research. PCORnet consists of 11 Clinical Data Research Networks (CDRNs) based in health-care systems that collect health information during routine patient care, 18 Patient-Powered Research Networks (PPRNs) led by groups of patients and their partners that focus on common or rare conditions, and 1 coordinating center. The networks conduct multicenter comparative effectiveness research using standardized, interoperable electronic health record (EHR) data.

Rachael Fleurence, Ph.D., Program Director of PCORI’s CER Methods and Infrastructure Program stated that PCORnet’s development phase ends in 18 months. During this phase, objectives include making standardized data available for research in the network, initiating clinical trials and observational studies, developing the ability to capture longitudinal data on patients’ experiences, creating linkages to related initiatives, generating support for PCORnet from external funders, and establishing joint studies by CDRNs and PPRNs.

Elaine Collier, M.D., Acting Director of the Division of Clinical Innovation at the NIH National Center for Advancing Translational Sciences, explained that the NIH Clinical and Translational Science Award (CTSA) network addresses some PCORnet aims. Like PCORnet, the CTSA works closely with patient groups.

Josephine Briggs, M.D., Director of the National Center for Complementary and Alternative Medicine at NIH, described the NIH Health Care Systems Research Collaboratory as a new infrastructure for collaborative clinical research designed to ensure that health-care providers and
patients can make decisions based on good clinical evidence. The Collaboratory supports five high-impact pragmatic clinical trial demonstration projects on major public health issues.

During the discussion, the presenters explained that these networks will collaborate and share information with one another and their efforts will be complementary and not redundant. The new clinical trial infrastructures will answer many efficacy questions, and the networks will not conduct effectiveness studies without at least some promising efficacy data. Many clinicians do not want to participate in clinical trials because of the burdensome paperwork involved and the pressure to maximize their clinical revenue. To succeed, all of these programs must combat these disincentives by, for example, focusing on research questions that are important to clinicians. In addition, health professions training programs need to teach future clinicians that they have an obligation to participate in clinical research as part of the learning health system.

**Session 2: Efforts to Ensure Research Reproducibility**

*Chair: Robert M. Califf, M.D.*

Dr. Califf, reported that a Duke University cancer researcher initiated clinical trials in cancer patients based on erroneous claims that certain genomic markets could accurately identify which patients would benefit from certain cancer treatments. Statisticians from another institution identified serious problems with this research, including the inability to reproduce the results. As a result, the researcher’s articles were retracted from multiple journals and he resigned from his position. An IOM investigation provided a sentinel report (that extended far beyond this individual case and recommended significant changes in our fabric of reproducible research.

Lawrence Tabak D.D.S., Ph.D., Principal Deputy Director of NIH, described the NIH Reproducibility Initiative, which focuses on preclinical research, especially studies involving animal models. Many factors are impeding the checks and balances that ensure that research is reproducible. These factors include scientific misconduct, but the NIH initiative focuses instead on inadequate training that leads to poor experimental design, inadequate data provenance, poor statistical analysis methods, underreporting of important characteristics, difficulty of publishing negative findings, overemphasis on publishing “big, exciting” results in high-impact journals, and inadequate reporting of resources used or unexpected variability in resources. The NIH Reproducibility Initiative will include:

- Outreach to stakeholders, including professional societies, industry, academics, patient advocacy groups, study section chairs, and journal editors
- Development of an education module on research integrity for training programs
- Pilot projects, including development of a checklist to ensure more systematic evaluations of grant applications and support for replication studies
- PubMed Commons, which enables authors to share opinions and scientific publications

Story C. Landis, Ph.D., Director of the NIH National Institute of Neurological Disorders and Stroke (NINDS), described NINDS activities to enhance study replicability:

- Notice NOT-NS-11-023, which encourages applicants proposing preclinical studies or studies based on preclinical data to adequately describe the design, execution, and interpretation of their research and supporting data in their funding applications
- A checklist of “points to consider” regarding study design, potential for bias, and results
• Requirement that study sections evaluate the scientific rationale or support for each clinical study or translational project
• Attempts to replicate published results in the spinal cord injury field
• Meetings with publishers, scientists, and funders to call for more transparency in publishing to enhance the predictive value of preclinical research

Brian A. Nosek, Ph.D., Associate Professor of Psychology at the University of Virginia, said that the primary challenge to reproducibility is that researchers must publish as often as possible in the highest-impact journals to further their careers. The easiest results to publish are novel and positive and tell a great story. But such results do not accurately reflect most scientific findings. Researchers can make their results more publishable by analyzing data only from participants who have the desired effect, for example, or presenting exploratory research as confirmatory.

The Open Science Framework is helping change the scientific culture by facilitating open collaborations to independently replicate key results. Another approach is for researchers to send brief proposals to journals during the study design phase to explain why their research question is important and show that their design is effective to answer the question. Journals would conduct peer reviews of these proposals and, for studies with favorable reviews, conditionally agree to publish the results regardless of the outcomes. Researchers would then have an incentive to design their studies well and would have no incentive to make their data as clean as possible. This system would also make it easier for researchers to publish negative results.

Session 3: Implications of the Centers for Medicare and Medicaid Open Payments Program (“Sunshine Act”)

Chair: E. Albert Reece, M.D., Ph.D., M.B.A., Dean, School of Medicine, University of Maryland (UMD)

Dr. Reece explained that the Centers for Medicare and Medicaid Services (CMS) Open Payments Program (formerly known as the Physician Payment Sunshine Act) is part of the Affordable Care Act. The program requires annual reporting to CMS by drug and device manufacturers of all payments or other transfers of value to physicians and teaching hospitals as well as certain ownership or investment interests held by physicians. Initial reports from manufacturers are due to CMS between February and June 2014. Physicians may register with CMS in July or August 2014, and CMS will let registered physicians know of payments to them reported by manufacturers. CMS will give physicians 45 days to reconcile disputed data before publishing the aggregated information on a public website on September 30, 2014.

Lauren K. Roth, J.D., Assistant General Counsel at the Pharmaceutical Research and Manufacturers of America (PhRMA), reported that PhRMA members understand the importance of bringing more transparency to the kinds of interactions addressed by the Open Payments Program. Providing the detailed information that CMS now requires, as long as that information has the right context, can dispel public misunderstandings about the important collaborations between academic health centers (AHCs) and industry that speed up the availability of new treatments. Because the penalties for failing to comply are very steep, some companies appear to be overzealous in implementing the requirements. Industry knows that the new requirements will place physicians under heightened scrutiny and is committed to educating the public about the meaning of the data that CMS will publish and ensuring that these data are accurate.
Ann Bonham, Ph.D., Chief Scientific Officer at the Association of American Medical Colleges (AAMC), explained that AHCs need to determine when forming partnerships is and is not ethically appropriate. Relationships between AHCs and industry are not inherently problematic and being listed in the CMS database is not a penalty for a physician researcher. Clinicians will identify discrepancies in the data that companies report, but many of these will be easy to resolve. AAMC hopes to increase public awareness of the value of these partnerships for developing treatments that benefit patients and their small cost in relationship to amount of money spent on clinical research.

Stephen Davis, M.B.B.S., Professor and Chairman of the Department of Medicine at the UMD School of Medicine and Physician-in-Chief at the UMD Medical Center, reported that UMD faculty members embrace transparency but often believe that payments from the pharmaceutical industry are “dishonest,” lead to conflicts of interest, and result in patient coercion. No one believes that funding from NIH or a foundation taints a researcher’s results, and people need to be disabused of the notion that funding from the pharmaceutical industry has this effect. The pharmaceutical industry wants advice from academic experts on industry-sponsored trials, which is appropriate. Driving physicians away from industry will harm science and patients.

Forum members commented that the vast majority of collaborations between industry and clinicians are reasonable, but a handful of these relationships are “over the top.” AHCs need to publicly denounce these relationships and promote principled partnerships, such as those that follow the four principles of the National Dialogue for Healthcare Innovation for research collaborations between industry and physicians. The new CMS program could identify some payment inequities, resulting in physician demands to increase the value of their arrangements with industry. Therefore, guidelines from a credible organization, such as the Institute of Medicine, regarding reasonable payment levels for different activities are needed. AHCs should consider engaging legislators in modifying the Open Payments Program if it has unintended consequences.

Presentation of Top 10 Awards

Winners of the Top 10 Clinical Research Achievements Awards, which recognize outstanding clinical research published within the past year, gave presentations on their award-winning research. Details on all awardees and their research are available on the Forum’s website.

Session 4: IT Roundtable Follow-up and Use of EHRs in Clinical Research

Chair: Robert M. Califf, M.D.

Daniel Ford, M.D., Chair of the Forum’s IT Roundtable and Vice Dean for Clinical Investigation at the Johns Hopkins University School of Medicine, reported that the IT Roundtable met in October to develop recommendations regarding the use of EHRs in research. Dr. Ford and the meeting co-leaders, Dr. Peter Embi from Ohio State University and Dr. Peter Winkelstein from the University at Buffalo, drafted a white paper summarizing the more than 60 meeting recommendations.
Michael Becich, M.D., Chair of the Department of Biomedical Informatics at the University of Pittsburgh School of Medicine, described PaTH: Towards a Learning Health System in the Mid-Atlantic Region. The PaTH network, a PCORnet CDRN, includes four institutions that are sharing EHR data using a common data model to conduct research on idiopathic pulmonary fibrosis, atrial fibrillation, and obesity. The common data model is based on sets of common data elements for each of the three conditions, and all clinicians in participating institutions have agreed to use these common data elements in EHRs. The network has funding from the National Cancer Institute to develop an approach to extract useable data from text fields in EHRs using a natural language processing system. PaTH researchers will report on their activities in open-access journals and share their common data elements and raw data with other PCORnet members.

Session 5: The Future of Clinical Research in the EHR Era Using Genetic Tools
Chair: William F. Crowley, Jr., M.D., Founder and Past Chairman, Clinical Research Forum; Daniel K. Podolsky Professor of Medicine, Harvard Medical School

Nancy Cox, Ph.D., Professor and Chief of the Section of Genetic Medicine at the University of Chicago, explained that researchers are using large sets of genome-wide data on single nucleotide polymorphisms (SNPs) from thousands of patients to identify associations between common diseases or complex human traits and certain genomic variants. Genome-wide analyses can also assess the amount of heritability accounted for by different classes of variants. A recent study by Dr. Cox and colleagues based on more than 100,000 EHRs showed that Mendelian disease genes might contribute to common diseases that are not Mendelian.

During the discussion, Dr. Cox explained that obtaining complete genomic information on every patient is very costly compared to obtaining biospecimen bank information. Instead of waiting until complete genomic information is available, researchers should use the data that are available now to identify rare variants associated with common diseases. Identifying people in large biospecimen banks who are at high risk of a common disease but do not develop that disease can help detect rare variants with strong protective effects. Examining people with low polygenic risk who develop a disease early is also useful.

Josh C. Denny, M.D., M.S., Associate Professor of Biomedical Informatics and Medicine at Vanderbilt University, reported that more than 1,200 published genome-wide association studies have identified associations between genetic variants and more than 500 diseases and traits. As part of the Electronic Medical Records & Genomics (eMERGE) Network funded by the National Human Genome Research Institute, Vanderbilt University is using large sets of DNA samples and EHR data to rapidly identify and validate genetic predictors of phenotypes of interest. EHR-linked biospecimen banks are allowing for rapid interrogation of biology and can be used for non-genetic research (including studies on drug repurposing, detection of adverse events, and disease correlations). All eMERGE algorithms use billing codes and most have natural language processing elements that are specific to the phenotype of interest. Linkages of large biospecimen banks and EHR data can help find patients with unusual conditions who should undergo more intensive genomic sequencing to probe the relationship between their phenotype and genotype.
Session 6: Why Networking with Patients and Their Advocates is Critical to Future Research Funding

Chairs: Enriqueta Bond, Ph.D., and Elaine Gallin, Ph.D., Partners, Q/E Philanthropic Advisors

Bray Patrick-Lake, M.F.S., Director of Stakeholder Engagement at the Clinical Trials Transformation Initiative (CTTI), described CTTI as a public-private partnership created by Duke University and the Food and Drug Administration. CTTI’s mission is to identify and promote practices that increase the quality and efficiency of clinical trials. Patients serve on CTTI’s steering committee and executive committee and participate in all CTTI workshops, expert meetings, and projects. CTTI’s Patient Leadership Council provides a collective voice for patient advocacy organizations and voluntary health agencies to systemically improve the clinical trials enterprise. The CTTI transformation Initiative is developing best practices for effective engagement with patient groups around clinical trials. Patient advocates are effective voices calling for funding for their diseases on Capitol Hill, and AHC researchers need to partner with these groups.

Robert McBurney, Ph.D., President and CEO of the Accelerated Cure Project for MS, commented that clinical trials do not always measure variables of interest to patients. For example, clinical trials in multiple sclerosis (MS) tend to focus on ambulation, even though fatigue and mood are more important to patients. The foundation has a repository of data and specimens from more than 3,200 people with multiple sclerosis and healthy people that are available to researchers. The foundation’s non-financial resources have supported approximately 80 research projects around the world. The OPT-UP Program is a large-scale, real world treatment outcomes clinical study and collaborative research program to optimize treatment of MS and understand the progressive disability associated with MS.

Sharon Terry, M.A., President and CEO of the Genetic Alliance and PXE International, reported that most people are willing to share at least some of their health data for health research, but they have different views on how much of their data to share and under what conditions. The Genetic Alliance created Reg4All for patients to store their health information and share it with the medical and research community to the extent that patients feel comfortable doing so. The Genetic Alliance’s Platform for Engagement Everyone Responsibly (PEER) is an intuitive, consumer-centric, privacy-assured, and customizable portal of clinical information and biospecimens. Participants can choose to make their health information available for research and set up individual permissions for access to and use of this information.

During the discussion, participants stated that patient groups are reluctant to collaborate with AHCs because of burdensome contracting processes and high indirect cost rates. Engagement of patients throughout the research process helps ensure that patients do not drop out of studies. The clinical research experience needs to be so enriching and valuable that almost all patients want to participate in a clinical study. Patients need to be asked to join a trial and researchers need to share understandable status updates and results with them. Schools should teach students about the benefits of clinical trials. Physicians and patients need to educate lawmakers about the value of clinical research, and they should be cautious about asking for earmarked funds for specific diseases because this approach detracts from the common cause to fund biomedical research.