



# The Harvard-MIT CRS Regulatory Science Symposium

## Program Book

April 2, 2019 | 8:30am - 7pm  
American Academy Of Arts And Sciences | Cambridge, MA

# AGENDA

8:00 AM Registration and Breakfast

---

8:30 AM Welcome and Introduction to the Center for Regulatory Science (CRS)  
*Harvard-MIT CRS Leadership*

8:40 AM **Keynote: Richard Platt, Harvard Pilgrim Health Care Institute**

---

9:25 AM **Session 1: Digital Medicine**

*Chaired by Florence Bourgeois, Harvard-MIT CRS*

Safe, Effective, and Ethical Digital Medicine: Digital Biomarkers,  
Diagnostics and DTx

*Andy Coravos, Elektra Labs*

Digital Mental Health: New Opportunities and Challenges

*Liza Hoffman, Beth Israel Deaconess Medical Center*

Optimizing the Patient Journey with AI

*John Brownstein, Boston Children's Hospital*

10:40 AM Morning Coffee Break

---

10:55 AM **Session 2: Legal and Ethical Challenges in International Clinical Trials**

*Chaired by Barbara Bierer, Brigham and Women's Hospital*

Ethical Issues in International Clinical Trials

*Stephen Rosenfeld, Quorum Review IRB*

Impact of Data Privacy Legislation on Clinical Trials

*David Peloquin, Ropes & Gray LLP*

Evolution of Clinical Trial Regulations in India

*Barbara Bierer, Brigham and Women's Hospital*

12:00 PM **Panel 1: Towards an "Agile" Regulatory Framework**

*Chaired and moderated by Gigi Hirsch, Massachusetts Institute of Technology*

Panelists

*Anne-Virginie Eggimann, Bluebird Bio*

*John Ferguson, Genzyme*

*Paul Howard, Food and Drug Administration*

*Ed Pezalla, Enlightenment Bioconsult*

12:45 PM Lunch

---

**2:00 PM** **Session 3: Repurposing for Unmet Needs**

*Chaired by Artem Sokolov, Harvard Medical School*

Harnessing Diverse Informatics Approaches to Repurpose  
Drugs for Alzheimer's Disease

*Mark Albers, Massachusetts General Hospital*

Drug Repurposing, a Regulatory Perspective

*Joohee Sul, Food and Drug Administration*

Identifying and Targeting Vulnerabilities in Rare Brain Tumors

*Sandro Santagata, Brigham and Women's Hospital*

---

**3:05 PM** **Panel 2: Complex generics**

*Chaired and moderated by Michael Sinha, Harvard-MIT CRS*

Panelists

Rena Conti, Boston University

Wenlei Jiang, Food and Drug Administration

---

3:50 PM Afternoon Coffee Break

---

**4:05 PM** **Session 4: Real World Evidence and Regulatory Decision Making**

*Chaired by Sebastian Schneeweiss, Brigham and Women's Hospital*

Real World Evidence – The FDA's Program

*Jacqueline Corrigan-Curay, Food and Drug Administration*

Using Software to Generate Regulatory-Grade RWE

*Jeremy Rassen, Aetion*

Comparing Real World Data with Randomized Trial Results to Assess Validity:

Preliminary Insights from the RCT DUPLICATE Project

*Jessica Franklin, Brigham and Women's Hospital*

---

**5:20 PM** **Closing Remarks**

*Harvard-MIT CRS Leadership*

**5:30 PM** **Drinks Reception with Student and Trainee Poster Session**

**7:00 PM** **End of Symposium**

## SPEAKERS AND SESSION CHAIRS



### Mark Albers, MD, PhD

Frank Wilkens, Jr. and Family Endowed Scholar in AD Research,  
Massachusetts General Hospital  
Faculty Member, Laboratory of System Pharmacology, Harvard Medical School

Mark W. Albers is a neurologist specializing in memory and olfactory disorders. He earned a PhD in organic chemistry from Harvard University, working in the laboratory of Stuart Schreiber, and an MD degree from the H.S.T. program of Harvard Medical School and M.I.T. He was an internal medicine resident for two years at Massachusetts General Hospital and then trained in neurology at Mass General, and Brigham and Women's Hospital, where he was one of the first chief residents for the Partners neurology residency program. He completed a postdoctoral fellowship in the laboratory of Richard Axel while he practiced neurology at the Neurological Institute, Columbia University. In 2007, he returned to Mass General where he sees outpatients in the Memory Disorders Unit and attends on the inpatient neurologic wards. His clinical research is focused on developing sensitive probes of olfactory function as a biomarker for early neurodegenerative disease, including Alzheimer's and TBI. His laboratory research focuses on elucidating the mechanisms of neuro-degeneration, identifying novel drug targets that mediate neurodegeneration, and developing therapies to prevent neurodegeneration. He served as a member of the Translational Neuroscience committee of the American Academy of Neurology, is a faculty member of the Laboratory of Systems Pharmacology, and is the Assistant Director of the Massachusetts Center for Alzheimer's Therapeutic Science.



### Barbara Bierer, MD

Professor of Medicine, Harvard Medical School  
Faculty Director, Multi-Regional Clinical Trials Center, Brigham and Women's Hospital and  
Harvard University

Barbara E. Bierer, M.D., a hematologist-oncologist, is Professor of Medicine at Harvard Medical School and the Brigham and Women's Hospital (BWH). Dr. Bierer co-founded and now leads the Multi-Regional Clinical Trials Center of BWH and Harvard (MRCT Center, [www.mrctcenter.org](http://www.mrctcenter.org)), a collaborative effort to improve standards for the planning and conduct of international clinical trials with a particular focus in emerging economies. In 2017, the MRCT Center launched the non-profit organization Vivli ([www.vivli.org](http://www.vivli.org)), a global clinical research data sharing platform. In addition, she is the Director of the Regulatory Foundations, Ethics, and the Law program at the Harvard Catalyst, the Harvard Clinical and Translational Science Award, working across the academic spectrum to enable the clinical trial enterprise from study planning through recruitment to data acquisition and dissemination. She is the Director of Regulatory Policy for SMART IRB ([www.SMARTIRB.org](http://www.SMARTIRB.org)), a national effort to align single site IRB review of multi-site trials. From 2003 – 2014, Dr. Bierer served as Senior Vice-President, Research at the Brigham and Women's Hospital (BWH). During her tenure, Dr. Bierer founded and served as Executive Sponsor of the Brigham Research Institute and the Brigham Innovation Hub (iHub), a focus for entrepreneurship and innovation in healthcare. In addition to her academic responsibilities, Dr. Bierer served as the Chair of the Secretary's Advisory Committee for Human Research Protections, HHS, and as a member of the National Academies of Sciences Committee on Science, Technology and the Law. She currently serves on the Board of Directors of Public Responsibility in Medicine and Research (PRIM&R), Management Sciences for Health (MSH), the Edward P. Evans Foundation, Clinithink, and Vivli. She has authored or co-authored over 210 publications.



## Florence Bourgeois, MD, MPH

Co-Director, Harvard-MIT Center for Regulatory Science  
Senior Associate Physician in Medicine, Boston Children's Hospital  
Associate Professor of Pediatrics, Harvard Medical School

Dr. Bourgeois, MD, MPH is Associate Professor of Pediatrics at Harvard Medical School and Director of the Initiative in Pediatric Therapeutics and Regulatory Science in the Computational Health Informatics Program at Boston Children's Hospital. Dr. Bourgeois' research is focused on the regulation and use of medications in children and the evaluation of gaps in pediatric drug evidence at the point of care. She has led studies investigating the development of drugs and devices in pediatric populations, the quality of pre-market pediatric safety and efficacy assessments, and the development of standardized metrics to assess the impact of FDA's regulatory programs on pediatric product information. She is the recipient of an Innovation in Regulatory Science Award from the Burroughs Wellcome Fund to evaluate the epidemiology of off-label drug and biologic use in children and improve provider access to benefit-risk information on FDA-regulated products. Most recently, Dr. Bourgeois served as an Expert Visitor to the European Medicines Agency to analyze the EU's pediatric drug legislation.



## John Brownstein, PhD

Chief Innovation Officer, Boston Children's Hospital  
Professor, Harvard Medical School

John Brownstein, PhD is Professor of Biomedical Informatics at Harvard Medical School and is the Chief Innovation Officer of Boston Children's Hospital. He directs the Computational Epidemiology Lab and the Innovation and Digital Health Accelerator both at Boston Children's. He was trained as an epidemiologist at Yale University. Dr. Brownstein is also Uber's healthcare advisor and co-founder of digital health companies Epidemico and Circulation.



## Rena Conti, PhD

Associate Professor, Boston University (BU) Questrom School of Business  
Associate Research Director, BU Institute For Health System Innovation and Policy

Rena M. Conti is the Associate Research Director of Biopharma & Public Policy for the Boston University Institute for Health System Innovation & Policy. She is also an Associate Professor at the Boston University Questrom School of Business. From 2006 through June 2018, Professor Conti was an Associate Professor of Health Economics and Policy at the University of Chicago Medical School and the Harris School of Public Policy. Dr. Conti is a health economist. Her research focuses on the organization, financing and regulation of medical care. She has written extensively on the pricing, demand and supply of prescription drugs.



## Andy Coravos

Chief Executive Officer, Elektra Labs  
Member, Harvard-MIT Center for Regulatory Science

Andy Coravos (@andreacoravos) is the CEO/co-founder of Elektra Labs, building a digital medicine platform with an initial focus on digital biomarkers for decentralized clinical trials, and a Member of the Harvard-MIT Center for Regulatory Science. Formerly, Andy was a Entrepreneur in Residence at the FDA working in the Digital Health Unit (DHU), focusing on the Pre-Cert program and policies around software and AI/ML. Previously, she worked as a software engineer at Akili Interactive Labs, a leading digital therapeutic company. Before grad school, Andy worked at KKR, a private equity firm, and at McKinsey & Company, a management consulting firm, where she focused on the healthcare industry. Andy writes about software/tech, digital medicine, data privacy and governance rights, and more on her blog. During her past few months as a CSR research collaborator, her work has been published in WIRED, Quartz, Nature npj Digital Medicine and JMIR.



## Jacqueline Corrigan-Curay, JD, MD

Director, Office of Medical Policy Center for Drug Evaluation and Research, US Food and Drug Administration

Jacqueline Corrigan-Curay, J.D., M.D., serves as Director of the Office of Medical Policy (OMP) in the Center for Drug Evaluation and Research, FDA. OMP is comprised of the Office of Prescription Drug Promotion (OPDP) and the Office of Medical Policy Initiatives (OMPI). Dr. Corrigan-Curay leads the development, coordination, and implementation of medical policy programs and strategic initiatives, including policy development on real world evidence, drug labeling, prescription drug promotion, clinical trial oversight and innovative trial design. She works collaboratively with other CDER program areas, FDA centers, and stakeholders on enhancing policies to improve drug development and regulatory review processes. Prior to joining FDA, she served as supervisory medical officer with the Immediate Office of the Director, National Heart, Lung and Blood Institute (NHLBI), at National Institute of Health's (NIH) where she focused on developing policies and procedures to enhance the clinical trial enterprise. She also served as the Director of the Office of Biotechnology Activities (OBA), Office of Science Policy at NIH, where she was executive secretary of the NIH Recombinant DNA Advisory Committee. She has held positions as an attending physician with the VA Medical Center, a policy analyst with the Congressional Office of Technology Assessment, and a practicing attorney in Washington, D.C. Dr. Corrigan-Curay earned her law degree from Harvard Law School, her medical degree from University of Maryland School of Medicine, and a bachelor's degree in history of science from Harvard/Radcliffe College in Cambridge, MA. She completed her training in internal medicine at Georgetown University Medical Center, where she also served as a clinical assistant professor of medicine. She continues to practice internal medicine part-time at the Veterans Affairs Medical Center in Washington, D.C.



## Anne-Virginie Eggimann, MSc

Vice President, Regulatory Science, Bluebird Bio

Anne-Virginie joined Bluebird Bio in 2011 to lead global regulatory strategy and create innovative pathways to accelerate the development of bluebird bio's gene therapy products. Previously, Anne-Virginie was an Executive Director at Voisin Consulting, leading rare diseases, oncology, and advanced therapies projects. Anne-Virginie holds a Master of Science from the UCLA School of Public Health, and a B.S. in Chemical Engineering from the California Institute of Technology.



## John Ferguson, MD

Head, Genzyme PV Unit  
Global Pharmacovigilance and Epidemiology, Sanofi US

Dr. Ferguson is a board certified Cardiologist and former co-principal NIH and the MRCC investigator. He received his training in Cardiology and Clinical Epidemiology at McGill University, McMaster University and Cedars-Sinai Medical Center. Prior to entering the pharmaceutical industry, his research focused on risk prediction in coronary artery disease and developing novel approaches to cerebrovascular disease, including carotid stenting and cerebral fibrinolysis. Dr. Ferguson has served as a panelist and benefit-risk key subject matter expert for the Institute of Medicine (IOM). His current work with industry groups, regulators and academic institutions focuses on structured benefit-risk optimization, real world evidence, patient preferences and adaptive product development.



## Jessica Franklin, PhD

Assistant Professor of Medicine, Division of Pharmacoepidemiology & Pharmacoeconomics, Brigham and Women's Hospital and Harvard Medical School

Jessica Franklin, PhD, is an Assistant Professor of Medicine at Harvard Medical School and biostatistician in the Division of Pharmacoepidemiology and Pharmacoeconomics at Brigham and Women's Hospital. Her research focuses on developing and applying statistical methods for the study of the comparative effectiveness, safety, and utilization of medicines based on large electronic healthcare databases, including insurance claims and electronic health records. Dr. Franklin has developed several novel approaches to evaluating the performance of causal inference methods in these data, including plasmode simulation. Currently, she is leading the RCT DUPLICATE project, which aims to build an empirical basis for causal inference methods applied to real world data analyses of medications through the large-scale replication of randomized trials in real world data. She received her Bachelor's degree in mathematics at the University of Georgia and her doctorate in biostatistics at the Johns Hopkins Bloomberg School of Public Health.



## Gigi Hirsch, MD

Executive Director, MIT Center for Biomedical Innovation

Dr. Hirsch is the Executive Director of the MIT Center for Biomedical Innovation (CBI) where she leads NEWDIGS, a "think and do tank" that is re-engineering pharmaceutical innovation to deliver more clinical value to patients faster, in ways that work for all stakeholders. NEWDIGS' flagship project on "Adaptive Biomedical Innovation" (ABI) helped inspire the successful EU-wide Adaptive Pathways pilot program led by the European Medicines Agency (2014-2016). Under Dr. Hirsch's leadership, NEWDIGS continues to channel multi-stakeholder thought leadership to advance other critical enablers of ABI such as "precision financing" models for durable, and potentially curative, therapies; structured evidence planning across the product lifecycle; and disease focused "learning ecosystems." Her current efforts are focused largely on the NEWDIGS LEAPS Project, applying a systems approach to the planning, generation, and use of evidence, now being prototyped for Rheumatoid Arthritis, with a pilot using Massachusetts as a statewide testbed planned for launch in 2020. Dr. Hirsch has held a number of leadership roles that leverage her broad clinical background (Internal Medicine, Emergency Medicine, and Psychiatry) both in industry (Millennium Pharmaceuticals) as well as academia (Harvard, Brown, and Tufts).



## Liza Hoffman, MSW, LICSW

Clinical Director, Digital Psychiatry Division, Department of Psychiatry, Beth Israel Deaconess Medical Center

Liza Hoffman, MSW, LICSW is a clinical social worker and clinical director of the digital psychiatry division, in the Department of Psychiatry at Beth Israel Deaconess Medical Center, a Harvard Medical School affiliated teaching hospital. She attended the Simmons College School of Social Work and after completing her master's degree joined the Primary Care Behavioral Health Integration Program at Cambridge Health Alliance. Alongside her clinical work, Liza spearheaded a 3 year initiative to evaluate and disseminate mental health mobile apps for use within routine clinical care. As clinical director of the BIDMC digital psychiatry division, she is implementing evidence-based digital health interventions for both academic and community mental health systems, increasing access to services via innovative digital tools for diverse patient populations including those with serious mental illnesses, and creating new care delivery models for technology-supported psychiatric care.



## Paul Howard, PhD

Senior Advisor to the Commissioner & Chief Strategy Officer of the Information Exchange and Data Transformation Program (INFORMED), US Food and Drug Administration

Paul Howard is Senior Advisor to FDA Commissioner, where he works on matters relating to regulatory policy, strategic innovation initiatives, and promoting competition to efficiently advance public health and safety. Paul has nearly 20 years of public policy experience, and has written and researched extensively on FDA related matters while Director of Health Policy and Senior Fellow at the Manhattan Institute.



## Wenlei Jiang, PhD

Senior Science Advisor, Office of Research and Standards, Office of Generic Drugs, US Food and Drug Administration

Dr. Wenlei Jiang serves as a Senior Science Advisor in the Office of Research and Standards (ORS)/Office of Generic Drugs (OGD)/Center for Drug Evaluation and Research (CDER). Previously she served as the Acting Deputy Director of ORS, where she provided oversight on Generic Drug User Fee Act (GDUFA) regulatory science research programs. She has been championing regulatory research in the areas of generic nanomaterials, narrow therapeutic index drugs, and modified release products to support review standards development and ensure post-market safety and efficacy of these drug products. Currently she is leading efforts in complex drug product classification and research, promoting global bioequivalence harmonization, and developing opportunities for scientific outreach. She also serves as Vice Chair at Product Quality Research Institute (PQRI) Biopharmaceutical Technical Committee. Prior to joining FDA, she was at Novartis Pharmaceutical Corporation where her responsibilities included formulation development of conventional liquid and solid dosage forms, as well as advanced parenteral drug delivery systems. She received her PhD in Pharmaceutics and Pharmaceutical Chemistry from The Ohio State University in 2001.



## David Peloquin, JD

David Peloquin, Attorney, Ropes & Gray LLP

David Peloquin practices law at Ropes & Gray LLP where he is a member of the firm's health care group. He focuses his practice on advising academic medical centers, life sciences companies, and information technology companies on issues related to human subjects and animal research, data privacy, and Medicare/Medicaid and other third-party payor reimbursement issues. He frequently writes and speaks on topics related to each of these areas. He also serves as a community member of the Institutional Review Board at Partners Healthcare in Boston. David received his undergraduate degree from Carleton College, his law degree from the Yale Law School and clerked for Judge Diana E. Murphy of the United States Court of Appeals for the Eighth Circuit. Before attending law school, David worked as a project manager for Epic Systems, a manufacturer of electronic medical records.



## Edmund Pezalla, MD, MPH

Chief Executive Officer, Enlightenment Bioconsult, LLC

Dr. Pezalla is Founder and CEO of Enlightenment Bioconsult, LLC, a strategic payer consultancy advising biopharmaceutical firms on access, technology assessment, and drug evaluation in the US market. His clients include established pharmaceutical firms and emerging companies with innovative therapies. Dr. Pezalla served for nine years as VP for Pharmaceutical Policy and Strategy for Aetna, and four years as VP of Clinical Services for RxSolutions. In these roles he developed programs for drug evaluation, creation of clinical policy and formulary inclusion. Dr. Pezalla also served as the leading executive for Aetna on public policy issues related to drug approval, drug pricing and regulation. He is a member of the MIT Center for Biomedical Innovation NEWDIGS project and was a member of the inaugural class of Scholars-in-Residence at the Duke-Margolis Center for Health Policy. Dr. Pezalla received his BS and MD degrees with honors from Georgetown University and holds an MPH from the University of California at Berkeley. He was a Health Services Research Fellow and doctoral student at the University of Michigan Schools of Medicine and Public Health. Dr. Pezalla has published on a range of topics related to regulatory affairs/adaptive licensing and innovative healthcare financing models.



## Richard Platt, MD

Professor and Chair, Department of Population Medicine, Harvard Medical School  
Executive Director, Harvard Pilgrim Health Care Institute

Richard Platt, MD, MSc is Professor and Chair of the Harvard Medical School Department of Population Medicine at the Harvard Pilgrim Health Care Institute. He is principal investigator of the FDA's Sentinel System that studies the safety and effectiveness of marketed medical products. Dr. Platt is also co-principal investigator of the coordinating center of PCORI's Patient Centered Outcomes Research Network, leads the NIH Health Care Systems Research Collaboratory's Distributed Research Network, and is co-principal investigator of a CDC Prevention Epicenter. He is a member of the Association of American Medical Colleges' Advisory Panel on Research. He is a former chair of the FDA's Drug Safety and Risk Management Advisory Committee, and co-chair of the Board of Scientific Counselors of the CDC's Center for Infectious Diseases.



## Jeremy Rassen, ScD

President and Chief Science Officer, Aetion, Inc.

Jeremy A. Rassen, MS, ScD is a pharmacoepidemiologist with nearly 25 years of academic and industry experience. He is Co-Founder, President and Chief Science Officer at Aetion, a health care technology company that delivers real-world evidence for life sciences companies, payers, providers, and regulatory agencies. Dr. Rassen leads Aetion's efforts to designing scale scientific products and methodologies for obtaining valid answers on treatments, costs, and outcomes from real-world data. Prior to Aetion, Dr. Rassen was Assistant Professor of Medicine at Harvard Medical School, where he focused on methods for improving the quality and validity of studies based on real-world data. Before coming to Harvard, Dr. Rassen worked in Silicon Valley in a variety of technology companies, focusing on high-performance software for the creation and analysis of large databases. Dr. Rassen received his bachelor's degree in Computer Science from Harvard College and his masters and doctorate degrees in Epidemiology from the Harvard T.H. Chan School of Public Health.



## Stephen Rosenfeld, MD

Board Chair, Advarra Chair, Secretary's Advisory Committee on Human Research Protections (SACHRP)

Dr. Stephen Rosenfeld is currently the Executive Chairperson of the Review Board at Quorum Review IRB, an Independent IRB located in Seattle. Dr. Rosenfeld is a hematologist who earned his medical degree from Cornell. He trained in internal medicine at Dartmouth and completed his hematology fellowship at the National Heart, Lung, and Blood Institute of the NIH. He spent 19 years at NIH, holding positions at NHLBI and the NIH Clinical Center, doing both basic and clinical research, and finally working in medical informatics and administration. He ended his time at the NIH as the Chief Information Officer of the Clinical Center. Dr. Rosenfeld moved from Bethesda, Maryland to Portland, Maine, where he was the CIO of MaineHealth, a large independent delivery network, before moving to Olympia, Washington as the CEO of the Western Institutional Review Board. In addition to his medical degree, he holds a Masters in Business Administration from Georgetown. Dr. Rosenfeld received the honor of Distinguished Professor of Medicine from Daegu Catholic University Medical Center in Korea in 2013. In July 2013, he was appointed to the Secretary's Advisory Committee on Human Research Protections (SACHRP) and in 2016 he was appointed Chair of SACHRP. In 2018 he was elected to the Board of Directors of Public Responsibility in Medicine and Research (PRIM&R) and in 2019 joined the Board of Directors of the Association for the Accreditation of Human Research Protection Programs (AAHRPP).



## Sandro Santagata, MD

Associate Professor, Brigham and Women's Hospital & Harvard Medical School

Sandro is an Associate Professor in Pathology at Harvard Medical School and practices Neuropathology at Brigham and Women's Hospital and Boston Children Hospital. He studied Neuroscience at Amherst College, and then entered the Medical Scientist Training Program at Mount Sinai School of Medicine (MSSM). He trained with Eugenia Spanopoulou and Stuart Aaronson and investigated the mechanism of genetic recombination in the immune system and how defects in this system result in immunodeficiency disorders. He subsequently trained in internal medicine at MSSM in 2003 and then joined the Anatomic Pathology Residency at Brigham and Women's Hospital, where he sub-specialized in Neuropathology. He is board certified in Anatomic Pathology and Neuropathology. He completed a research fellowship with Susan Lindquist at the Whitehead Institute/MIT studying stress responses in cancer and started his independent research laboratory in the BWH Department of Pathology in 2013. He is a member of the Ludwig Center at Harvard, the Harvard Program in Therapeutic Science and the HMS Laboratory for Systems Pharmacology. He is leading efforts to generate multi-dimensional tumor atlases as part of the Biden Moonshot Human Tumor Atlas Network (HTAN). His work focuses on identifying therapeutic vulnerabilities in brain tumors and in implementing new technologies for imaging tumors.



## Sebastian Schneeweiss, MD, ScD

Chief, Division of Pharmacoepidemiology & Pharmacoeconomics, Brigham and Women's Hospital

Professor of Medicine, Harvard Medical School

Professor in Epidemiology, Harvard TH Chan School of Public Health

Sebastian Schneeweiss, MD, ScD, is a Professor of Medicine and Epidemiology at Harvard Medical School and Chief of the Division of Pharmacoepidemiology, Department of Medicine, Brigham and Women's Hospital. His research focuses on the comparative effectiveness and safety of biopharmaceuticals. He has developed analytic methods to improve the scientific validity of epidemiologic analyses using complex longitudinal health-care databases for newly marketed medical products. The overarching theme of his research is applying advanced real-world data analytics for regulatory decision making transparently and in rapid cycles. His work is published in >400 articles. His work is funded by NIH, PCORI, Arnold Foundation, IMI, and FDA where he is also a voting consultant. Dr. Schneeweiss is Director of the Harvard-Brigham Drug Safety Research Center funded by FDA/CDER and Methods Lead of the FDA Sentinel program. He is Past President of the International Society for Pharmacoepidemiology and is Fellow of the American College of Epidemiology, the American College of Clinical Pharmacology, and the International Society for Pharmacoepidemiology. He received his medical training at the University of Munich Medical School and his doctoral degree in Pharmacoepidemiology from Harvard.



## Michael Sinha, MD, JD, MPH

Regulatory Science Fellow, Harvard-MIT Center for Regulatory Science, Harvard Medical School

Affiliated Researcher, Program On Regulation, Therapeutics, And Law (PORTAL), Brigham and Women's Hospital

Michael S. Sinha, MD, JD, MPH is a Regulatory Science Fellow in the Harvard-MIT Center for Regulatory Science, within the Harvard Program in Therapeutic Science (HiTS) at Harvard Medical School. He is also affiliated with the Program On Regulation, Therapeutics, And Law (PORTAL), within the Division of Pharmacoeconomics and Pharmacoepidemiology, Department of Medicine at Brigham and Women's Hospital. He graduated from Dartmouth College and earned MD and JD degrees from Southern Illinois University in 2012 and an MPH degree in Law and Public Health from the Harvard T.H. Chan School of Public Health in 2015. Legal scholarship includes articles in the American Journal of Legal Medicine, the American Journal of Law and Medicine, the Harvard Law & Policy Review, the Food and Drug Law Journal, and the Stanford Law and Policy Review (forthcoming). Medical publications have appeared in JAMA, JAMA Internal Medicine, CHEST, PLOS Medicine, the American Journal of Bioethics, Mayo Clinic Proceedings (forthcoming), and the Health Affairs Blog.



## Artem Sokolov, PhD

Director of Informatics and Modeling, Laboratory of Systems Pharmacology  
Instructor, Department of Biomedical Informatics, Harvard Medical School

Artem completed a PhD in Bioinformatics at Colorado State University, under the supervision of Asa Ben-Hur, and a postdoc at UC Santa Cruz, working closely with Josh Stuart on cancer genomics projects. As Director of Informatics and Modeling at the Laboratory of Systems Pharmacology (LSP), Artem leads a group of computational biologists and software engineers who model pre-clinical, translational and clinical data using a wide range of machine learning and artificial intelligence approaches. He plays a key role in training and mentoring a diverse group of students and postdocs and in managing the lab's collaborations with academic and industrial groups across a wide spectrum of projects.



## Johee Sul, MD

Clinical Reviewer, Brain and CNS Malignancies Scientific Liaison, Office of Hematology and Oncology Products, US Food and Drug Administration

Dr. Joohee Sul is Medical Officer and Scientific Liaison for Brain and CNS Malignancies in the Office of Hematology and Oncology Products (OHOP) at the FDA. Dr. Sul completed her fellowship in neuro-oncology at Memorial Sloan-Kettering Cancer Center in 2007. Prior to joining the FDA, Dr. Sul was a Staff Clinician at the National Cancer Institute (NCI). Dr. Sul has worked with multiple stakeholders, including advocacy groups, to support development of products for CNS malignancies.

# POSTERS

1

## Bayesian optimality of testing procedures for survival data in the non-proportional hazards setting

Andrea Arfé

PhD Student in Statistics, Program in Regulatory Sciences, Dana-Farber Cancer Institute

Most statistical tests for treatment effects used in randomized clinical trials with survival outcomes are based on the proportional hazards assumption, which often fails in practice. Data from early exploratory studies may provide evidence of non-proportional hazards which can guide the choice of alternative tests in the design of practice-changing confirmatory trials. We study a test to detect treatment effects in a late-stage trial which accounts for the deviations from proportional hazards suggested by early-stage data. Conditional on early-stage data, among all tests which control the frequentist Type I error rate at a fixed level, our testing procedure maximizes the Bayesian prediction of the finite-sample power. Hence, the proposed test provides a useful benchmark for other tests commonly used in presence of non-proportional hazards, for example weighted log-rank tests. We illustrate the approach in a simulation based on data from a published cancer immunotherapy phase III trial.

2

## Heterogeneous large datasets integration using Bayesian factor regression

Alejandra Avalos Pacheco

Research Scientist, Harvard Medical School

Two key challenges in modern statistical applications are the large amount of information recorded per individual, and that such data are often not collected all at once but in batches. These batch effects can be complex, causing distortions in both mean and variance. We propose a novel sparse latent factor regression model to integrate such heterogeneous data. The model provides a tool for data exploration via dimensionality reduction while correcting for a range of batch effects. We study the use of several sparse priors (local and non-local) to learn the dimension of the latent factors. Our model is fitted in a deterministic fashion by means of an EM algorithm for which we derive closed-form updates, contributing a novel scalable algorithm for non-local priors of interest beyond the immediate scope of this paper. We present several examples, with a focus on bioinformatics applications. Our results show an increase in the accuracy of the dimensionality reduction, with non-local priors substantially improving the reconstruction of factor cardinality, as well as the need to account for batch effects to obtain reliable results. Our model provides a novel approach to latent factor

3

## Advances in International Clinical Trials

Geetha Godlove

Candidate for MS Regulatory Affairs, Northeastern University

In 2018 the FDA's Center for Drug Evaluation and Research (CDER) alone approved 59 novel drugs and the number of NDA submitted has increased considerably over the years. Due to the increasing cost of drug development and a shortage of suitable human subjects for clinical trials, the number of clinical trials conducted outside the US has increased greatly. Clinical trials conducted outside the United States comes with many challenges such as statistical, clinical, operational, regulatory and ethical. Despite these challenges, tremendous progress has been made for the more efficient conduct of international clinical trials. The FDA has very stringent requirements for the conduct of clinical trials in the United States. However, Developing countries have less stringent regulatory requirements compared to developed countries. Harmonizing these regulatory requirements is a major step towards the successful completion of international clinical trials. Harmonization ensures that clinical studies are conducted according to good clinical practices and the quality of data collected. The International Council for Harmonization (ICH) has proposed a Multi-regional clinical trial (MRCT). It has widely been conducted by many global pharmaceutical companies to accelerate drug launch in key markets and improve patient access to innovative drugs. Data collected for the MRCT can be submitted to multiple regulatory agencies around the world. The MRCT has its own challenges and each country should have its own guidance to implement the MRCT to see real progress in international clinical research.

4

## Phase II and III trials for less money: harnessing variability

Daniel Goldenholz

Instructor, Beth Israel Deaconess Medical Center

**BACKGROUND:** Like other diseases, the costs of randomized clinical trials (RCTs) in epilepsy have been rising exponentially. Simultaneously, people with epilepsy continue to require newer therapies, because 1 in 3 are not seizure free in spite of any medication combination used. Recent work has shown that natural variation in seizure frequency may be sufficient to produce realistic placebo response values in epilepsy RCTs. The present study evaluated a new approach to control for variability. **METHODS:** Two trial outcome metrics were assessed: the traditional 50%-responder rate (RR50), and the proposed variability-corrected score,  $Z_v$ . Each predicted seizure frequency upper and lower limits using prior seizures. Accuracy was defined as percentage of time-intervals when the observed seizure frequencies were within the predicted limits. First, we tested the  $Z_v$  method on three datasets (SeizureTracker:  $n = 3016$ , Human Epilepsy Project:  $n = 107$ , and NeuroVista:  $n = 15$ ). An additional independent SeizureTracker validation dataset was used to generate a set of 200 simulated trials each for 5 different sample sizes (total  $N = 100, 200, 300, 400$ , and  $500$ ), assuming 20% dropout and 30% drug efficacy. “Power” was determined as the percentage of trials successfully distinguishing placebo from drug ( $p < 0.05$ ). **RESULTS:** Prediction accuracy across datasets was,  $Z_v$ : 91–100%, RR50: 42–80%. Simulated RCT  $Z_v$  analysis achieved  $> 90\%$  power at  $N = 100$  per arm while RR50 required  $N = 200$  per arm. **CONCLUSION:** Accounting for variability in seizure frequency may increase the statistical power of an RCT relative to the traditional outcome methods. With this higher power, less patients and therefore cheaper RCTs become possible.

5

## Discovery of functionally redundant gene units through small molecule polypharmacology

Nienke Moret

Fellow, Harvard Medical School

Polypharmacology – the ability of small molecule compounds to bind to multiple gene-targets—has been a challenge for drug discovery since the onset of targeted therapy discoveries. Classically, polypharmacology has been implicated in both desirable and undesirable properties of drugs, depending on the targets engaged. More recently, after several studies found that polypharmacology was necessary for efficacy, an interest in the relation between functional gene redundancy and polypharmacology of therapeutic drugs has emerged. In our study we ask whether polypharmacologic drugs are efficacious because they target multiple (functionally redundant) proteins, or whether this secondary binding is irrelevant to efficacy. To answer this question, we compare small molecule efficacy and target binding data to hypothesize which gene-sets are redundant in function. We then confirm this redundancy by mapping of siRNA off-targets and the consequently observed epistasis.

**6**

## **Multiplexed Imaging of Biomarkers in Human Tissue Resection Samples**

Rumana Rashid

Biomedical Informatics Student, Harvard Medical School

Tissue cyclic immunofluorescence (t-CyCIF) is a method for multiplexed immunofluorescence imaging and single cell quantification of formalin fixed paraffin embedded (FFPE) clinical samples. The method uses multiple cycles of staining with fluorescently tagged antibodies, imaging on conventional microscopes, and fluorophore inactivation to construct high-dimensional images from single tissue sections that can be extended to at least 60 antigens. In the Lab for System Pharmacology (LSP), we are using t-CyCIF to characterize tumor cells states and the immune cells within the tumor microenvironment. We are also using the method to characterize various subcellular structures in cancer cells including stress foci, primary cilia, and ruptures of the primary nuclear envelope and of micronuclei. We have used the CyCIF method in multiple settings including cultured cells, tissue sections, and tissue microarrays. By using CyCIF, we aim to generate a more quantitative, granular, and spatially resolved understanding of a broad range of phenotypes that are integral to the process of oncogenesis and to use this information to better inform cancer diagnostics and the development and implementation of new anti-cancer therapeutics.

**7**

## **Optimizing Macrophage Regulation Therapy: Single Cell Characterization of Macrophage States in Disease Models**

Kela Roberts

Graduate Student/Data Scientist, Harvard Medical School

The understanding of the heterogeneity of macrophages states and their tissue resident immune function has long been incomplete. In vivo, tissue resident macrophages are known to have make definitive changes when exposed to a broad range of stimuli whose integration eventually determines a continuum of distinct transcriptional and functional outputs. The emergence of single cell RNA-seq has enabled de novo discovery of immune cell types and states, and the development of new mechanistic hypotheses. Here we investigate changes in macrophage states as a result of disease or in response to treatment to test the hypothesis that there are unique expression profile characteristics in macrophages related specifically to disease state. This multiphase project is unique in the analysis of macrophages in both infectious and autoimmune diseases. This work focuses on characterizing macrophage states in chronic hepatitis C virus (HCV) infection and other systems of disease. The main result this work has been to make quantitative comparisons between the transcription profiles of patients with chronic Hepatitis C Virus (HCV) infection, before and after treatment, the changes in macrophages during HCV disease have been illustrated. By extracting, sorting and sequencing, filtering, aligning, quantifying, and clustering the single cell transcriptome data, we can gain insight about macrophage activity in chronically infected HCV patients and how this could influence more current macrophage treatment regimens.

**8**

## Model of natural variability in seizure count data

Juan Romero

Research Assistant, Beth Israel Deaconess Medical Center

Introduction: Randomized controlled trials (RCT) of devices and drugs meant to treat patients with epilepsy use efficacy endpoints that rely on seizure count data, but reported endpoints in the literature often show a large placebo response. The objective of this project is to understand the role of naturally occurring fluctuations in seizure count data in the placebo response of RCTs. Methods: A statistical model of daily seizure count data was designed such that statistical properties seen in multiple heterogeneous patient populations matched the properties of the synthetic population of patients generated by the statistical model. The RR50 (50% responder rate) and MPC (median percent change) were calculated for 5000 trials consisting of synthetic patients under typical RCT parameters using a drug 20% more effective than placebo. A meta-analysis of 23 historical RCTs was compared to the simulations. Results: The placebo RR50 was  $27.3 \pm 3.6\%$  (simulated) and  $21.1 \pm 10.0\%$  (historical). The placebo MPC was  $22.0 \pm 6.0\%$  (simulated) and  $16.7 \pm 10.3\%$  (historical). A typical patient diary demonstrated apparent seizure clustering, despite the temporal independence of seizures in the synthetic model. Conclusion: The model suggests that the majority of the placebo response in RCTs for drugs and devices meant to treat epilepsy is due to natural fluctuations in the seizure count data which obscure the true drug efficacy. Also, the model indicates that the phenomena of 'seizure clustering' may simply be due to seizures randomly occurring in close proximity to each other.

**9**

## An interactive web tool to explore comparative toxicology

Kenichi Shimada

Postdoctoral Fellow, Harvard Medical School

The liver and kidneys in mammals play central roles in protecting the organism from xenobiotics and are at high risk of xenobiotic-induced injury. Xenobiotic-induced tissue injury has been extensively studied from both classical histopathological and biochemical perspectives. Previously, we used a machine-learning approach to analyze toxicological response to discover concurrent physiological and histological changes induced by chemical administrations in a large toxicogenomic dataset revealed nine discrete toxin-induced disease states, some of which correspond to known pathology, but others were novel. However, since a scientific publication requires a succinct story to tell and it has to focus only on a major discovery, detailed changes upon each chemical exposure cannot be covered. On the other hand, researchers in experimental toxicology tend to have a very specific interest in one or a few molecules. To satisfy such demands from the community, here we introduce a web tool that lets researchers explore toxicologic response in rats interactively. This will be of particular use for those who want to understand physiological, histopathological, and transcriptomic changes that a specific compound of interest induces in rats, and desire to compare them with the changes induced by 160 other compounds in rats.

**10**

## Investing in a biotech revolution: analysis of clinical trials and financial investments in CAR-T and TCR therapies for the treatment of cancer

Jonathan Thomas

Technical Research Associate, MIT Center for Biomedical Innovation

Chimeric antigen receptor and T-cell receptor (CAR-T/TCR) cellular immunotherapies have shown remarkable success in the treatment of refractory B-cell malignancies. This has, in turn, served to reinforce the widely held belief in their potential to provide durable clinical response for other types of cancer. In this paper, we look at all available FDA CAR-T/TCR clinical trials for the treatment of cancer, and analyze them with respect to different disease tissues, targeted antigens, products, and trial locations. Our analysis suggests that the rapid increase in the number of clinical trials has been, at least partially, driven by the development of different CAR-T/TCR products that use a similar therapeutic approach. We also provide insights on the level and type of financial investment that has under-pinned the development of those CAR-T/TCR products that are either already approved or currently in clinical trials. Overall our results suggest that a driving feature of the CAR-T/TCR industry has been a robust response to success and failure of competitor products.

## About this meeting

The Harvard-MIT CRS Regulatory Science Symposium is an annual meeting of the Boston area regulatory science community. This is a scientific meeting open to the entire community that aims to promote open, multi-stakeholder dialogue about important regulatory science challenges and advances. In addition to participation from members of the Harvard-MIT Center for Regulatory Science, this symposium welcomes broader participation from academia, regulatory agencies, industry, and patient advocates.



## About the Harvard-MIT Center for Regulatory Science

Harvard, MIT, and the FDA have partnered to create a center focused on innovative approaches for the development and evaluation of medical products. Working across academia, industry, and government institutions, the Center promotes regulatory science through research and education programs, uniting stakeholders under a common mission: promoting optimal patient health outcomes by enabling biomedical innovation and the availability of safe and effective diagnostics and treatments. The Center is part of the Harvard Program in Therapeutic Science at Harvard Medical School.

### Get in touch

 [hits.harvard.edu/regsci](https://hits.harvard.edu/regsci)

 [@HarvardMIT\\_CRS](https://twitter.com/HarvardMIT_CRS)

 [hits\\_regsci@hms.harvard.edu](mailto:hits_regsci@hms.harvard.edu)

 Harvard-MIT Center for Regulatory Science  
200 Longwood Ave  
Armenise Building Rm 109  
Boston, MA 02115