Forum on
DRUG DISCOVERY, DEVELOPMENT, and TRANSLATION

Innovation in Drug Research and Development for Prevalent Chronic Diseases

A Three-Part Virtual Workshop

February 22, March 1, and March 8, 2021

Main event page: https://www.nationalacademies.org/our-work/innovation-in-drug-research-and-development-for-prevalent-chronic-diseases-a-workshop

The National Academies of
SCIENCES • ENGINEERING • MEDICINE

Innovation in Drug Research and Development for Prevalent Chronic Diseases

A Three-Part Virtual Workshop

Table of Contents

The National Academies of | SCIENCES ENGINEERING MEDICINE

Forum on DRUG DISCOVERY, DEVELOPMENT, and TRANSLATION

Innovation in Drug Research and Development for Prevalent Chronic Diseases

A Virtual Workshop

February 22, March 1, and March 8, 2021

Statement of Task

Half of all Americans live with at least one chronic disease, such as heart disease, cancer, stroke, or diabetes. These and other chronic diseases are the leading cause of death and disability in the United States and are a leading driver of health care costs.[1] Yet investment in the leading causes of death and disability, other than cancer, has not kept pace with the public health need. Published data from BIO has shown that venture investment for drug development in areas such as psychiatric disorders, cardiovascular, diabetes, and respiratory diseases has declined over the last decade relative to the prevalence and health care cost of these diseases[2]. The recent outbreak of Coronavirus Disease 2019 (COVID-19) may further exacerbate the health disparities associated with highly prevalent chronic diseases. A case series on hospitalized COVID-19 patients in the New York City area showed that the most common comorbidities were hypertension, obesity, and diabetes.[3]

A planning committee of the National Academies of Sciences, Engineering, and Medicine, will organize and conduct a public workshop to examine the bottlenecks to innovation in drug research and development (R&D) for prevalent chronic diseases and highlight opportunities for spurring drug R&D in this space.

The public workshop will feature invited presentations and discussions to:

- Discuss the unique cross-cutting challenges to increased investment in early stage research and late stage drug development for prevalent chronic diseases (e.g. do we have promising targets?, are the regulatory requirements predictable?);
- Consider whether investment and attention enablers are in alignment for spurring the type of R&D that will address unmet need when it comes to prevalent chronic diseases (e.g., do we have the right business models in place?);
- Consider lessons learned from other disease areas (e.g., rare diseases) and/or use cases that could have cross-cutting applications for several prevalent chronic diseases; and
- Brainstorm and prioritize potential strategies to spur drug R&D innovation for several prevalent chronic diseases (i.e., highlight promising avenues forward that merit additional time/effort/funding/attention).

The planning committee will organize the workshop, develop the agenda, select and invite speakers and discussants, and moderate or identify moderators for the discussions. A proceedings of the presentations and discussions at the workshop will be prepared by a designated rapporteur in accordance with institutional guidelines.

[1] National Center for Chronic Disease Prevention and Promotion (https://www.cdc.gov/chronicdisease/index.htm).
[2] Thomas and Wessel, 2018 (https://www.bio.org/sites/default/files/legacy/bioorg/docs/BIO_HPCP_Series-Pain_Addiction_2018-02-08.pdf)
[3] Richardson et al, JAMA, 2020 (https://jamanetwork.com/journals/jama/fullarticle/2765184).

Planning Committee

Carlos Garner (co-chair), Eli Lilly and Co.

Anantha Shekhar (co-chair), University of Pittsburgh

Melinda Buntin, Vanderbilt School of Medicine

Grace Colón, InCarda Therapeutics

Bettina Drake, Washington University in St. Louis

Alyson Karesh, Center for Drug Evaluation and Research, FDA

Chronis Manolis, UPMC Health Plan

Phyllis Pettit Nassi, University of Utah

Howard Rosen, BonVelo Ventures/Stanford University

Susan Schaeffer, The Patients' Academy for Research Advocacy

Amir Tamiz, National Institute of Neurological Disorders and Stroke, NIH

The National Academies of SCIENCES ENGINEERING MEDICINE

Forum on DRUG DISCOVERY, DEVELOPMENT, and TRANSLATION

Innovation in Drug Research and Development for Prevalent Chronic Diseases — A 3-Part Virtual Workshop

February 22, March 1, and March 8, 2021

Half of all Americans live with at least one chronic disease, such as heart disease, cancer, stroke, or diabetes. These and other chronic diseases are the leading cause of death and disability in the United States and are a leading driver of health care costs. Yet investment in the leading causes of death and disability, other than cancer, has not kept pace with the public health need. This virtual public workshop will provide a venue for stakeholders to examine bottlenecks to innovation in drug research and development (R&D) for prevalent chronic diseases and highlight opportunities for spurring drug R&D in this space.

The virtual workshop will be conducted in three parts:

- Part One (February 22, 2021) will discuss key opportunities and challenges for increasing investment, broadening biospecimen collection and registry use, and supporting innovative discovery and preclinical research in prevalent chronic diseases.
- Part Two (March 1, 2021) will consider key aspects and opportunities related to development, translation, regulation, and support for innovative clinical research in prevalent chronic diseases.
- Part Three (March 8, 2021) will consider case studies in both discovery and clinical research related to prevalent chronic diseases, and discuss potential cross-cutting applications for other prevalent chronic diseases.

For additional information on this virtual workshop, please visit the main project page.

Access the Webinar for Part 1 of the Workshop

Part 1: February 22, 2021
Opportunities in Discovery and Preclinical Research for Prevalent Chronic Diseases
11:00 am – 3:00 pm ET

11:00 a.m. **Welcome and Opening Remarks**

CARLOS GARNER, *Workshop Co-chair*
Vice President, Global Regulatory Affairs
Eli Lilly and Company

ANANTHA SHEKHAR, *Workshop Co-chair*
Senior Vice Chancellor for Health Sciences and Dean of the School of Medicine
University of Pittsburgh

SESSION I OVERVIEW OF R&D FOR PREVALENT CHRONIC DISEASES

Session Objectives:

- Discuss the unique cross-cutting challenges facing preclinical research for prevalent chronic diseases; and
- Highlight opportunities to overcome those challenges and mobilize the R&D innovation engine.

11:10 am **A Patient's Perspective on Mobilizing the R&D Innovation Engine**
RUSS PAULSEN
Chief Operating Officer
US Against Alzheimer's

SESSION II FUNDING AND INVESTMENT DECISION-MAKING IN DISCOVERY RESEARCH

Session Objectives:

- Examine common causes of failures in discovery research for prevalent chronic diseases and how failures could be avoided or "go/no-go" decisions could be accelerated in the future
- Discuss whether investment and cultural incentives are in alignment for spurring the type of R&D that will address unmet need when it comes to prevalent chronic diseases; and
- Consider the factors that determine which research areas key decision-makers (e.g., investors, sponsors, researchers) decide to move forward.

11:25 am **Response and Overview**
SUSAN SCHAEFFER, *moderator*
President and Chief Executive Officer
The Patients' Academy for Research Advocacy

11:35 am **Funder Perspective**
JASON MELLAD
Chief Executive Officer and Founder
Start Codon

11:50 am **Public-private partnership investor perspective**
JOSEPH MENETSKI
Associate Vice President of Research Partnerships
Foundation for the National Institutes of Health

12:05 pm **Moderated Panel Discussion and Audience Q&A**

12:30 pm **BREAK** (*30 mins*)

SESSION III BIOSPECIMEN COLLECTION AND REGISTRY USE IN DISCOVERY RESEARCH

Session Objectives:

- Consider lessons learned from other disease areas that could have cross-cutting applications for prevalent chronic diseases; and
- Discuss the availability or need for high quality biospecimen repositories and datasets that represent the patient populations most impacted by prevalent chronic diseases.

1:05 pm **Introduction and Overview**
HOWARD B. ROSEN, *Moderator*
Managing Director, BonVelo Ventures
Lecturer, Stanford University

1:10 pm **Academic perspective**
ERICA WOODAHL
Associate Professor, Dept. of Biomedical and Pharmaceutical Sciences
University of Montana

SESSION IV NEW TECHNOLOGIES ENABLING DISCOVERY RESEARCH

Session Objectives:

- Discuss the unique cross-cutting challenges in pre-clinical research for prevalent chronic diseases and consider how new technologies could help researchers overcome these challenges; and
- Consider lessons learned from other disease areas for which new technologies have been a key driver of progress.

1:25 pm **Academic discovery science-technology perspective**
JOHN NGAI
Director
The BRAIN Initiative, NIH

1:40 pm **Artificial intelligence for discovery science**
ANDREW A. RADIN
Chief Executive Officer
twoXAR Pharmaceuticals

1:55 pm **Regulator perspective**
QI LIU
Senior Science Advisor, Office of Clinical Pharmacology & Translational Sciences
U.S. Food and Drug Administration

2:10 pm **Moderated Panel Discussion and Audience Q&A**

2:50 pm **Closing Remarks**

CARLOS GARNER, *Workshop Co-chair*
Vice President, Global Regulatory Affairs
Eli Lilly and Company

ANANTHA SHEKHAR, *Workshop Co-chair*
Senior Vice Chancellor for Health Sciences and Dean of the School of Medicine
University of Pittsburgh

3:00 pm **ADJOURN**

The National Academies of SCIENCES ENGINEERING MEDICINE

Forum on DRUG DISCOVERY, DEVELOPMENT, and TRANSLATION

Innovation in Drug Research and Development for Prevalent Chronic Diseases — A 3-Part Virtual Workshop

February 22, March 1, and March 8, 2021

Half of all Americans live with at least one chronic disease, such as heart disease, cancer, stroke, or diabetes. These and other chronic diseases are the leading cause of death and disability in the United States and are a leading driver of health care costs. Yet investment in the leading causes of death and disability, other than cancer, has not kept pace with the public health need. This virtual public workshop will provide a venue for stakeholders to examine bottlenecks to innovation in drug research and development (R&D) for prevalent chronic diseases and highlight opportunities for spurring drug R&D in this space.

The virtual workshop will be conducted in three parts:

- Part One (February 22, 2021) discussed key opportunities and challenges for increasing investment, broadening biospecimen collection and registry use, and supporting innovative discovery and preclinical research in prevalent chronic diseases.
- Part Two (March 1, 2021) will consider key aspects and opportunities related to development, translation, regulation, and support for innovative clinical research in prevalent chronic diseases.
- Part Three (March 8, 2021) will consider case studies in both discovery and clinical research related to prevalent chronic diseases, and discuss potential cross-cutting applications for other prevalent chronic diseases.

For additional information on this virtual workshop, please visit the main project page.

Access the Webinar for Part 2 of the Workshop

Part 2: March 1, 2021
Opportunities in Clinical Research for Prevalent Chronic Diseases
11:00 am – 3:00 pm ET

11:00 a.m. **Welcome and Opening Remarks**

CARLOS GARNER, *Workshop Co-chair*
Vice President, Global Regulatory Affairs
Eli Lilly and Company

ANANTHA SHEKHAR, *Workshop Co-chair*
Senior Vice Chancellor for Health Sciences and Dean of the School of Medicine
University of Pittsburgh

SESSION I OVERVIEW OF R&D FOR PREVALENT CHRONIC DISEASES

Session Objectives:

- Discuss the unique cross-cutting challenges facing clinical research for prevalent chronic diseases; and
- Highlight opportunities to overcome those challenges and mobilize the R&D innovation engine.

11:10 am **A Patient's Journey**
CHRISTIN VEASLEY
Co-founder and Director
Chronic Pain Research Alliance

11:25 am **Mobilizing the R&D Innovation Engine**
CHRONIS MANOLIS
Senior Vice President of Pharmacy
University of Pittsburgh Medical Center Health Plan

SESSION II INVESTMENT AND FUNDING DECISIONS IN CLINICAL RESEARCH

Session Objectives:

- Discuss whether investment and cultural incentives are in alignment for spurring the type of R&D that will address unmet need when it comes to prevalent chronic diseases; and
- Consider the factors that determine which clinical programs key decision-makers (e.g. investors, sponsors, and researchers) decide to move forward.

11:35 am **Economics perspective**
KIRSTEN AXELSEN
Visiting Fellow
American Enterprise Institute

11:50 am **A Payers Perspective: Pricing and Health Economic Drivers that Incentivize Development Investments**
KEN EHLERT
Chief Scientific Officer
United Health Group

12:05 pm **Moderated Panel Discussion and Audience Q&A**

12:25 pm **BREAK** (*30 mins*)

SESSION III INNOVATIVE APPROACHES TO EFFICIENT CLINICAL DEVELOPMENT

Session Objectives:

- Discuss the unique cross-cutting challenges in clinical trials for prevalent chronic diseases (e.g., are the regulatory requirements predictable?);
- Brainstorm and prioritize potential strategies to decrease costs and risks for development (i.e., highlight innovative ways to design clinical trials); and
- Discuss ways to meaningfully engage communities and patients in clinical trials.

1:00 pm **Introduction and overview**
BETTINA DRAKE, *Moderator*
Professor, Washington School of Medicine
Associate Director of Community Outreach and Engagement
Alvin J. Siteman Cancer Center

1:05 pm **Community health researcher perspective**
KAREN WINKFIELD
Executive Director
Meharry-Vanderbilt Alliance

1:15 pm **Industry (regulatory lead) perspective**
MICHELLE ROHRER
Senior Vice President, Global Head of Product Development Regulatory & Policy
Roche

1:30 pm **Regulatory perspective**
JAMES P. SMITH
Deputy Director, Division of Clinical Policy, Office of New Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

SESSION IV NEW TECHNOLOGIES ENABLING INNOVATIVE CLINICAL RESEARCH

Session Objectives:

- Discuss the unique cross-cutting challenges in clinical research for prevalent chronic diseases and consider how new technologies could help researchers overcome these challenges; and
- Consider lessons learned from other disease areas where new technologies have been a key driver of progress.

1:50 pm **Biotech perspective**
GRACE COLÓN
Chief Executive Officer
InCarda Therapeutics

2:05 pm **Regulatory perspective**
ELIZABETH KUNKOSKI
Clinical Methodology Team, Office of Medical Policy
U.S. Food and Drug Administration

2:20 pm **Moderated Panel Discussion and Audience Q&A**

2:50 pm **Closing Remarks**

CARLOS GARNER, *Workshop Co-chair*
Vice President, Global Regulatory Affairs
Eli Lilly and Company

ANANTHA SHEKHAR, *Workshop Co-chair*
Senior Vice Chancellor for Health Sciences and Dean of the School of Medicine
University of Pittsburgh

3:00 pm **ADJOURN**

The National Academies of SCIENCES ENGINEERING MEDICINE

Forum on DRUG DISCOVERY, DEVELOPMENT, and TRANSLATION

Innovation in Drug Research and Development for Prevalent Chronic Diseases — A 3-Part Virtual Workshop

February 22, March 1, and March 8, 2021

Half of all Americans live with at least one chronic disease, such as heart disease, cancer, stroke, or diabetes. These and other chronic diseases are the leading cause of death and disability in the United States and are a leading driver of health care costs. Yet investment in the leading causes of death and disability, other than cancer, has not kept pace with the public health need. This virtual public workshop will provide a venue for stakeholders to examine bottlenecks to innovation in drug research and development (R&D) for prevalent chronic diseases and highlight opportunities for spurring drug R&D in this space.

The virtual workshop will be conducted in three parts:

- Part One (February 22, 2021) discussed key opportunities and challenges for increasing investment, broadening biospecimen collection and registry use, and supporting innovative discovery and preclinical research in prevalent chronic diseases.
- Part Two (March 1, 2021) considered key aspects and opportunities related to development, translation, regulation, and support for innovative clinical research in prevalent chronic diseases.
- Part Three (March 8, 2021) will consider case studies in both discovery and clinical research related to prevalent chronic diseases, and discuss potential cross-cutting applications for other prevalent chronic diseases.

For additional information on this virtual workshop, please visit the main project page.

Access the Webinar for Part 3 of the Workshop

Part 3: March 8, 2021
Case Studies in Prevalent Chronic Disease Research

11:00 a.m. **Welcome and Opening Remarks**

CARLOS GARNER, *Workshop Co-chair*
Vice President, Global Regulatory Affairs
Eli Lilly and Company

ANANTHA SHEKHAR, *Workshop Co-chair*
Senior Vice Chancellor for Health Sciences and Dean of the School of Medicine
University of Pittsburgh

SESSION I Case Studies Across the R&D Lifecycle: Mobilizing Communities and Resources, Analyzing Past Success

Session Objectives:

- Consider lessons learned in research across the R&D lifecycle in several disease areas that could have cross-cutting applications for many prevalent chronic diseases.
    - Discuss how research and patient communities have been mobilized to address discovering treatments for some example diseases, and how those approaches led to success.
    - Discuss examples of successful development for prevalent chronic disease treatments and what aspects of those approaches led to success.
- Discuss potential strategies to spur drug R&D innovation for prevalent chronic diseases.

11:10 am **Introduction and overview**
GRACE COLÓN, *Moderator*
Chief Executive Officer
InCarda Therapeutics

11:20 am **Success story from cystic fibrosis**
ROBERT K. COUGHLIN
Managing Director, Life Sciences, JLL
Former President & CEO, MassBIo

11:35 am **Digital innovation for treating prevalent chronic diseases**
RAOLAT ABDULAI
Global Clinical Lead, Immunology & Inflammation
Sanofi

11:50 am **Investing in one treatment, applying to multiple diseases**
ROBERT HEINE
Distinguished Lilly Scholar
Eli Lilly and Company

12:05 pm **Moderated Panel Discussion and Audience Q&A**

Discussion Questions:

- *How can patient advocacy affect drug research and development?*
- *What can we learn from these examples about psychiatric disorders, cardiology, or other prevalent chronic diseases?*
- *How might success be replicated, and what might the investment look like for other prevalent chronic disease areas?*
- *What options exist for trials examining multiple indications?*
- *How might these successes be replicated or apply in the future, and what might the investment look like for other prevalent chronic disease areas?*
- *How have digital advancements changed approaches to developing treatments for prevalent chronic diseases, and how might they affect development in the future?*

12:45 pm **BREAK** (*30 mins*)

SESSION II Recap and Potential Future Strategies

Session Objectives:

- Reflect on approaches and potential strategies to spur drug R&D innovation for prevalent chronic diseases
- Brainstorm potential strategies to spur drug R&D innovation for prevalent chronic diseases (i.e., highlight promising avenues forward that merit additional time, effort, funding, or attention).

1:15 pm **Summary presentations by session moderators** *(10 mins each)*

GRACE COLÓN
Chief Executive Officer
InCarda Therapeutics

BETTINA DRAKE
Professor, Washington School of Medicine
Associate Director of Community Outreach and Engagement
Alvin J. Siteman Cancer Center

HOWARD B. ROSEN
Managing Director, BonVelo Ventures
Lecturer, Stanford University

SUSAN SCHAEFFER
President and Chief Executive Officer
The Patients' Academy for Research Advocacy

1:55 pm **Moderated Panel Discussion and Audience Q&A**

Discussion Questions:

- *Are there common characteristics of disease areas routinely more affected than others by either discovery and preclinical or clinical stage research barriers?*
- *What cross-cutting strategies could enable investment?*
- *How might overall risk for stakeholders innovating in prevalent chronic disease treatments be lowered, with an eye toward integrating policy with stimulus?*

2:50 pm **Closing Remarks**

CARLOS GARNER, *Workshop Co-chair*
Vice President, Global Regulatory Affairs
Eli Lilly and Company

ANANTHA SHEKHAR, *Workshop Co-chair*
Senior Vice Chancellor for Health Sciences and Dean of the School of Medicine
University of Pittsburgh

3:00 pm **ADJOURN**

Innovation in Drug Research and Development for Prevalent Chronic Diseases

A Three-Part Virtual Workshop

Planning Committee Biographies

CO-CHAIRS

CARLOS GARNER, PH.D
Vice President, Global Regulatory Affairs at Eli Lilly and Company

Carlos Garner joined Eli Lilly and Company in 1997 as a senior scientist where he led a laboratory investigating the drug metabolism, pharmacokinetics and pharmacodynamics of new chemical entities in animal models and humans. His work in these areas supported the advancement of many innovative molecules into human testing, late clinical development, and the commercialization of a unique long-acting form of a top selling anti-psychotic. Dr. Garner subsequently served as senior director of project management and research strategy overseeing the development of more than 50 programs in discovery and development and providing portfolio strategy and management to Lilly Research Laboratories.

Dr. Garner previously led the North American regulatory affairs support of Lilly's Biomedicines development and product portfolio across neuroscience, musculoskeletal, urology, men's health, cardiovascular, and immunology diseases, where his team brought a number of NMEs and NBE to market and supported the broad portfolio of marketed products. Dr. Garner currently leads the broader regulatory function for Eli Lilly and Company supporting all human health business units and global manufacturing. Dr. Garner has published many scientific articles on his research and has been invited to provide national and international lectures on his research, drug discovery, drug development and regulatory sciences. Dr. Garner holds a bachelor's degree in Chemistry from Auburn University and master's and doctorate degrees from Vanderbilt University.

ANANTHA SHEKHAR, PH.D.
Senior Vice Chancellor for Health Sciences and Dean of the School of Medicine, University of Pittsburgh

Anantha Shekhar is senior vice chancellor for the health sciences and John and Gertrude Petersen Dean of the School of Medicine at the University of Pittsburgh. He is a nationally recognized educator, researcher, and entrepreneur with major contributions in medicine and life sciences. Dr. Shekhar's career has spanned more than three decades at Indiana University School of Medicine (IUSM) and Indiana University Health before he began his leadership roles at the University of Pittsburgh in June 2020.

Dr. Shekhar's areas of expertise include basic and clinical research on the effects of stress, stress-induced psychiatric and medical conditions, and clinical psychopharmacology. His laboratory has developed some of the best translational models for panic and related anxiety disorders. His work focuses on the role of brain abnormalities that could lead to stress and psychiatric disorders and to the discovery of new treatments. He has directed phase I and phase II studies in healthy and diseased populations and biomarker studies using physiological and brain imaging methods. Dr. Shekhar has also initiated several Investigational New Drug applications; and he has conducted many pharmacokinetic, pharmacogenetic, and phase III studies of novel compounds in the treatment of anxiety, depression, schizophrenia, and bipolar disorders.

Dr. Shekhar, who was born in India, earned his medical degree at St. John's Medical College and Ph.D. in neuroscience at Indiana University.

MEMBERS

MELINDA BUNTIN, PH.D.
Mike Curb Professor and Chair of Health Policy, Vanderbilt School of Medicine

Melinda Buntin joined Vanderbilt School of Medicine in 2013 as professor and founding chair of the Department of Health Policy, and in March 2018 was appointed the Mike Curb Chair for Health Policy.

She was previously a Health Director at the Congressional Budget Office where she evaluated legislative proposals and directed studies related to health care financing, including reports on prescription drugs under Part D, beneficiaries dually eligible for Medicare and Medicaid, and care coordination demonstrations. Prior to that, Dr. Buntin was deputy director of RAND Health's Economics, Financing, and Organization Program, director of Public Sector Initiatives for RAND Health, and co-director of the Bing Center for Health Economics. Her research at RAND focused on insurance benefit design, health insurance markets, provider payment, and the care use and needs of the elderly.

Dr. Buntin's work at Vanderbilt is focused on health care delivery and costs, with an emphasis on improving the value created by the health care system. She is also co-leading the Vanderbilt Policies 4 Action Research Hub, which is conducting research on ways to improve the health and education outcomes of low-income children. Dr. Buntin is an elected member of the National Academy of Medicine for which she currently serves on the Board on Health Care Services, and of the National Academy of Social Insurance. She is also the deputy editor of the new JAMA Health Forum, which launched in January 2020.

Dr. Buntin has an AB from the Woodrow Wilson School at Princeton and a Ph.D. in Health Policy with a concentration in economics from Harvard.

GRACE E. COLÓN, PH.D.
Chief Executive Officer, InCarda Therapeutics, Inc.

Dr. Colón brings over 25 years of experience in biopharma, genomics, healthcare and industrial biotechnology. In addition to her role at InCarda, she is Executive Chairman (formerly CEO) of ProterixBio, and serves on the boards of CareDx (NASDAQ:CDNA) and Cocoon Biotech and on the Advisory Board of the Miller Center for Social Entrepreneurship at Santa Clara University. Formerly, she was a partner at New Science Ventures, a New York based venture capital firm with over $700M under management, and served on the boards of Paradigm Diagnostics and PerceptiMed.

Previously, she co-founded Pyranose Biotherapeutics, a biologics discovery platform company. She was also founding President of the Industrial Products Division at Intrexon Corporation, where she established a new division focused on leveraging synthetic biology for bioindustrial applications such as biofuels and renewable chemicals. Prior to Intrexon, she was head of Clinical Operations for Gilead Sciences, where she was responsible for global execution of clinical trials. She also created and led both the Alliance Management and Commercial Strategic Planning groups. Prior to Gilead, she was VP, Corporate Planning at Affymetrix, where she was responsible for strategic planning and project management and where she also served as COO for the International Genomics Consortium, a non-profit medical research organization focused on cancer genomics. Earlier in her career she was a consultant with McKinsey & Co., where she served clients in healthcare, biotech, high tech and venture capital. She was also an engineer with Merck & Co. in France and in Rahway, NJ.

Dr. Colón received her Ph.D. in chemical engineering from the Massachusetts Institute of Technology, where she was an NSF Fellow. She also holds a B.S. degree in chemical engineering from the University of Pennsylvania, where she was a Benjamin Franklin Scholar.

BETTINA F. DRAKE, PH.D., MPH.
Professor, Division of Public Health Sciences, Washington University School of Medicine
Associate Director of Community Outreach and Engagement, Alvin J. Siteman Cancer Center

Bettina F. Drake is a professor of surgery, at Washington University School of Medicine and Siteman Cancer Center. As an epidemiologist, her research has focused on identifying preventive strategies to reduce health disparities in cancer and other chronic disease outcomes. In addition, she co-leads the Prostate Cancer Community Partnership, a community partnership of PECaD, which seeks to reduce prostate cancer disparities in the region. She is most interested in how her community-

based work informs and strengthens her epidemiology findings. Information gained from community-based studies informs both study design and recruitment strategies. In turn, the results of the cancer prevention work can be disseminated in collaboration with community partners. Dr. Drake also teaches Intermediate Clinical Epidemiology in the Master of Population Health Sciences program.

Dr. Drake earned her PhD in epidemiology at the University of South Carolina Arnold School of Public Health and completed postdoctoral studies at the T.H. Chan Harvard School of Public Health.

ALYSON KARESH, M.D.
Director, Division of Clinical Trial Quality, Center for Drug Evaluation and Research, FDA

Alyson Karesh is a physician with twelve years of pharmaceutical lifecycle experience at the United States Food and Drug Administration. Her expertise includes clinical trials and observational studies which acquire real-world data and generate real-world evidence for decision making, quality management systems, good clinical practice requirements, pediatric and rare disease drug development, including regulatory requirements and practical strategies. Dr. Karesh earned her M.D. from the Virginia Commonwealth University School of Medicine and completed her residency in pediatrics at the Children's Hospital of Pittsburgh.

CHRONIS MANOLIS, RPH
Senior Vice President, Pharmacy; Chief Pharmacy Officer, UPMC Health Plan

Mr. Manolis oversees the pharmacy programs for the Health Plan's Medicare, Medical Assistance, and commercial products. Mr. Manolis has more than 30 years of experience in the pharmacy and managed care industry. He previously held management positions with Medco Health Solutions and Stadtlanders Specialty Pharmacy Services. Mr. Manolis is also an adjunct instructor at the University of Pittsburgh School of Pharmacy. He holds a bachelor's degree in pharmacy from the University of Pittsburgh.

PHYLLIS PETTIT NASSI, MSW
Associate Director Research & Science, Special Populations
Huntsman Cancer Institute, University of Utah

Ms. Nassi is enrolled in the Otoe-Missouri Tribe & a member of the Cherokee Nation Bear Clan & Red Paint Clan. Raised on the Navajo, Hopi & Zuni reservations, experienced in scientific research, outreach, development & implementation of research projects, she is well aware of the need for cultural humility & awareness & works with research teams to understand "how *complicated* it's going to be to get it right, & how *difficult* it will be for every researcher working with Native American people if they get it wrong." Formerly a Ph.D. student at the University of Utah's College of Social Work, Ms. Nassi's focus is on the health disparities of the medically underserved of rural & frontier populations, cancer research education, screening & early detection. She educates tribal populations about the future direction of cancer research (e.g. genomics, how data sharing will improve & bring equity to the research table, and the importance of participating in clinical trials). Ms. Nassi has studied cultural & social implications of underserved populations for more than 30 years. She has experience in strategic planning, and working with tribal governments & representatives of diverse groups, departments, & institutions; facilitating collaborations between tribes & institutions locally & from a distance. An Alliance for Clinical Trials in Oncology Patient Advocate serving on the Patient Advocate, Health Disparities & Pharmacogenetics & Population Pharmacology Committees; an Advocate in Science member for Susan G. Komen for the Cure; Co-Chair of the Southwest Region of the Intercultural Cancer Council Network, Ms. Nassi is also a member of the American Association for Cancer Researchers & a member of Subcommittee A - Cancer Centers National Cancer Institute Initial Review Group.

HOWARD B. ROSEN, MBA
Managing Director, BonVelo Ventures; Lecturer, Stanford University

Howie Rosen is an independent consultant and serves on the board of directors of AcelRx Pharmaceuticals, Inc. (NASDAQ: ACRX), ALCOBRA, LTD (NASDAQ: ADHD), where he has served as Chairman since 2014, ALDEA Pharmaceuticals, Inc., Entrega, Inc., Kala Pharmaceuticals, Inc., where he has served as Chairman since 2014 and PaxVax, Inc., where he has served as Chairman since 2011. From 2004 to 2008, he was Vice President, Commercial Strategy at Gilead Sciences, Inc. where his responsibilities included strategic marketing, global brand management, health economics, competitive intelligence, market research and Gilead's overall portfolio and business planning.

Prior to joining Gilead, Mr. Rosen was President of ALZA Corporation where he was responsible for all aspects of managing ALZA as an independent 1000-person operating company within the Johnson & Johnson Family of Companies. Previously at ALZA as Vice President, Product Development, he was responsible for product development activities, portfolio management and corporate and new product planning. Over his 10 years at ALZA, Mr. Rosen also had responsibilities for mergers and acquisitions, R&D planning, and technology ventures. Prior to joining ALZA, Mr. Rosen managed the west coast practice of Integral, Inc., was Director, Corporate Development at GenPharm International, Inc. and was a consultant in the San Francisco office of McKinsey & Co. Mr. Rosen was a member of the Stanford University Advisory Council on Interdisciplinary Biosciences from 2003 to 2011 and the Stanford School of
Engineering Advisory Council from 2004 to 2007. Mr. Rosen is a member of the Biomedical Engineering Advisory Board at City College of New York and the BOD of the MIT Club of Northern California. Previously he was a member of the BODs of CNS Therapeutics, Inc., CoTherix, Inc., NTF Therapeutics, Inc., Pearl Therapeutics, Inc., where he served as interim President and CEO from June 2010 to March 2011, and Pharsight Corporation.

Mr. Rosen is a Lecturer in the Department of Chemical Engineering at Stanford and a Lecturer in Management at the Stanford Graduate School of Business. He is also a member of the National Academy of Engineering (NAE), where he is Chair of the Bioengineering Section, and a Fellow of the American Institute for Medical and Biological Engineering (AIMBE). He is co-inventor on 7 US patents. Mr. Rosen received an MBA from the Stanford Graduate School of Business, where he graduated first in his class as the Henry Ford II Scholar. Mr. Rosen has an MS in Chemical Engineering from MIT and he graduated with distinction from Stanford University with a BS in Chemical Engineering.

SUSAN SCHAEFFER, BFA
President and CEO, The Patients' Academy for Research Advocacy

Susan Schaeffer founded The Patients' Academy for Research Advocacy in 2018 after spending 15 years informing and educating biopharma industry stakeholders on best practices and new thinking in clinical development, regulation, pricing, and market access.

In 2002 Ms. Schaeffer dedicated her career to learning about and improving drug development after the loss of a close friend to breast cancer at a very early age. She joined the biopharmaceutical industry journal *BioCentury* as a staff writer in 2003, with no background in science or the biopharmaceutical industry, learning about the business and science of developing drugs by interviewing CEOs and scientists about their work. Ms. Schaeffer became managing editor of *BioCentury* and the daily news digest *BioCentury Extra* in 2004, led *BioCentury*'s Product Discovery & Development coverage as senior editor from 2010 through 2012, and took the helm of the publication in 2012. As chief editor, Ms. Schaeffer became an early champion of patient-centered R&D as an essential practice for translating great science into medicines that patients really want and society will pay for. Her work has been cited in regulatory filings and has influenced global biopharmaceutical companies to begin working on pricing experiments that can improve access to healthcare innovation.

In January 2020, Ms. Schaeffer was appointed as member of the Forum on Drug Discovery, Development, and Translation, a group of leaders organized by the The National Academies of Sciences, Engineering, and Medicine to address issues related to drug R&D. She is a frequent speaker at private and public meetings, including the annual BIO International Convention, The Leaders in Global Health and Technology (LIGHT) Forum, the rEVOLUTION Symposium for CSOs, and the Milken Institute's Future of Health Summit. She holds a BFA in Painting from the San Francisco Art Institute.

AMIR TAMIZ, PH.D.
Director, Division of Translational Research, National Institute of Neurological Disorders and Stroke, National Institutes of Health

Amir Tamiz is the Director of the Division of Translational Research at the National Institute of Neurological Disorders and Stroke (NINDS). Prior to that he was a program director overseeing the NIH Blueprint Neurotherapeutics network (BPN) and Innovation Grants to Nurture Initial Translational Efforts (IGNITE). Blueprint Neurotherapeutics network is a collaborative effort among 15 of the agency's institutes and centers, leveraging their resources to offer neuroscience researchers grant funding for drug discovery and development activities to confront major, cross-cutting challenges in neuroscience. The program was established as a pipeline between academic and industry drug development research and offers neuroscience researchers a "virtual pharma" to develop promising hit compounds from chemical optimization through Phase I clinical testing. Principal Investigators receive grant funding and in kind discovery and development resources such

as medicinal chemistry, API synthesis and manufacture, formulation and drug product manufacture, IND enabling studies, and clinical trial capabilities. Launched in December 2014, IGNITE program is intended to create a more contiguous source of support from discovery to preclinical development. The first two programs include: 1) Assay Development and Therapeutic Agent Identification and Characterization to Support Therapeutic Discovery (PAR-15- 070) and 2) Pharmacodynamics and In vivo Efficacy Studies for Small Molecules and Biologics/Biotechnology Products (PAR-15-071). Prior to joining NIH in 2012, Dr. Tamiz had held scientific and management positions in research and development of therapeutic programs at Corvas International (acquired by Dendreon), CovX (now part of Pfizer), and Alba Therapeutics. Dr. Tamiz received his Ph.D. at University of Oregon and conducted postdoctoral research at the Department of Neuroscience at Georgetown University Medical Center.

The National Academies of SCIENCES ENGINEERING MEDICINE

Forum on DRUG DISCOVERY, DEVELOPMENT, and TRANSLATION

Innovation in Drug Research and Development for Prevalent Chronic Diseases

A Three-Part Virtual Workshop

Speaker Biographies

SPEAKERS

RAOLAT ABDULAI, M.D., M.M.SC., serves as a global clinical lead for the Immunology and Inflammation (I&I) division at Sanofi. In this position, she acts as the clinical strategic lead on projects with a focus of bringing transformational medicines to those with immune-driven diseases. In addition to her drug development role, she collaborates to advance technology that transforms the product life cycle for faster and more efficient clinical trials: integrating innovative tools and methods to disrupt traditional clinical research paradigms, using real world data to understand the patient journey for better decision making, and incorporating wearables and digital tools into clinical trials. She has been a featured panelist at several conferences including MassBio Digital Health Impact, BIO Digital 2020, and FierceAI week. In 2020, she was named by the Commonwealth Institute as one of the Extraordinary Women Advancing Healthcare.

Dr. Abdulai has a Master of Medical Science in Biomedical Informatics from Harvard Medical School. She attended medical school at Howard University College of Medicine, completed internal medicine training at the Mayo Clinic in Rochester, MN and Pulmonary and Critical Care fellowship at Brigham and Women's Hospital in Boston, MA. She is triple board certified and continues to practice by volunteering at a Boston-based community health center where she treats patients with respiratory diseases. While in medical school, Dr. Abdulai co-founded the New Freedmen's clinic to provide free holistic care to the uninsured and underinsured local population. In 2009, Dr. Abdulai was featured in O! Oprah Magazine as one of 80 inspirational women entrepreneurs from around the country for the O! Oprah Magazine-White House Project Leadership Conference. Among her many other honors, Dr. Abdulai was invited to the White House for President Obama's Innovative Programs Summit which highlighted impactful social entrepreneurship programs across the country. Her passions include ensuring digital health equity and increasing access to clinical trials for women and people of color. Her personal project into this area was chosen for the Harvard iLab Venture Incubation Program.

KIRSTEN AXELSEN, M.S., works with leaders in healthcare and builds diverse and effective teams, helping to develop business practices that lead to affordable medicines, positive public perception and sustained investment in scientific advancement.

Ms. Axelsen was on the leadership team of Pfizer Inc's $30 billion global innovative pharmaceutical business, where she led Strategy and Business Evaluation. Previously, Ms. Axelsen led Pfizer's Global Policy team. She is currently a visiting scholar with the American Enterprise Institute, an Aspen Institute Health Innovator Fellow, and a consultant acting as a Senior Policy Advisor to DLA Piper and Charles River Associates. She is a founder and Executive Secretary of the Preparedness and Treatment Equity Coalition and organization focused on identifying metrics and reimbursement pathways to achieve greater equity in healthcare.

ROBERT K. COUGHLIN, is Managing Director of Life Sciences at JLL, Bob knows that for life science companies, solving complex human challenges is their top priority and that's why he is thrilled to make the transition into real estate. In this role, Bob will be a strong partner to life science companies to help them identify opportunities to optimize their portfolios, whether it's through site selection, tax incentives or operational efficiencies.

Most recently Bob served as the President and CEO at MassBio. In this role, Bob's mission was to advance Massachusetts' leadership in the life sciences to grow the industry, add value to the healthcare system and improve patient lives. Over the fourteen years, Bob truly became a champion for patients by ensuring innovative companies have the best environment possible to research, develop, and commercialize breakthrough therapies and cures for people around the world who need and deserve them. Bob played an integral role in making Massachusetts the best place in the world for the life science industry.

Bob has spent his career in both the public and private sectors. Before joining MassBio, he served as the Undersecretary of Economic Development within Governor Deval Patrick's administration, where he prioritized both healthcare and economic development issues and was a strong advocate for the life sciences industry in Massachusetts. Prior to that, he was elected as State Representative to the 11th Norfolk district for three terms. Bob has also held senior executive positions in the environmental services, capital management and venture capital industries.

In addition to his professional responsibilities, Bob is an active member in the community. He is a past board member of the Massachusetts Maritime Academy and Beth Israel Deaconess Hospital and is currently serving on the board of directors for The Schwartz Center for Compassionate Healthcare, Franciscan Children's Hospital and MassBio. He also serves on the board of directors of Synspira Therapeutics and Boston Analytical. Bob has served as the honorary chairman of the Great Strides Cystic Fibrosis Walk since 1996. In years past, he co-chaired the Children's Hospital Boston signature event, Champions for Children's and the Schwartz Center's Compassionate Healthcare Dinner.

He is a graduate of the Massachusetts Maritime Academy where he majored in Marine Engineering, and served as an officer in the United States Naval Reserve.

KEN EHLERT, is chief scientific officer, leading UnitedHealth Group's Research & Development function, an innovation engine intended to positively impact patient health on a global scale. UnitedHealth Group's R&D efforts are driven by math, data, and clinical science, but also focus on the human connections required to understand, manage, and prevent the chronic diseases that afflict nearly half of the world's population. Mr. Ehlert has worked with UnitedHealth Group since 2004 and became the chief scientific officer in 2017. Previously the co-founder and CEO of Savvysherpa, Mr. Ehlert has spent his career building products and businesses that improve the health care system.

ROBERT J. HEINE, M.D., PH.D., FRCP, joined Lilly Diabetes in January of 2008. He was the Vice President Global Medical Affairs for Lilly Diabetes until 2014. In his current position, he is responsible for the medical and scientific strategy, development of external research partnerships, and global medical education.

Before joining Lilly he was professor of Diabetology in the Department of Endocrinology and Director of the Diabetes Centre at the VU University Medical Center in Amsterdam. His main research areas included epidemiology and Type 2 diabetes pathophysiology.

Dr Heine has held several key positions within the EASD, including Honorary Treasurer and member of the Executive Committee, and was President of the Organizing Committee for the 2007 Meeting of the EASD, Amsterdam.

Dr Heine has served as Associate Editor of Diabetic Medicine, and has been a member of the editorial boards of several diabetes journals. To date, he has (co)authored more than 450 peer-reviewed papers and reviews.

ELIZABETH KUNKOSKI, M.S., currently works in the FDA's Center for Drug Evaluation and Research (CDER), Office of Medical Policy (OMP). She oversees several projects involving digital health technologies and electronic records and storage in clinical investigations. She worked for 15 years in the Center for Devices and Radiological Health (CDRH) in guidance document development and as a branch chief overseeing the review of orthopedic devices. She earned a Master's Degree in Biomedical Engineering and a Bachelor's Degree in Chemical Engineering from the University of Michigan.

QI LIU, PH.D., is a Senior Science Advisor in the Office of Clinical Pharmacology (OCP), FDA. At FDA, Dr. Liu contributed to the review of over 200 NDA/sNDA, 20 BLA/sBLA, and numerous IND. Dr. Liu co-authored about 40 manuscripts and presented on many topics at Advisory Committee meetings and scientific conferences. She worked on several working groups for FDA guidances and Manual of Policies & Procedures development. Dr. Liu is the lead of OCP's Innovative Data Analytics program and was the vice chair of the OCP Biologics Oversight Board. Dr. Liu is on the editorial board of CTS, CPT and the AAPS Journal. Before joining FDA, Dr. Liu was a senior pharmacokineticist at Merck. She obtained a Ph.D. in Pharmaceutics and a Master's degree in Statistics from the University of Florida.

JASON MELLAD, PH.D., is a scientist entrepreneur passionate about translating innovative technologies into more effective therapies and better patient outcomes. He founded Start Codon to identify and recruit high-potential and disruptive healthcare startups worldwide, seed fund them, and leverage the exceptional resources of the Cambridge (UK) Cluster with an aim to minimise risk and drive their success. Previously, Dr. Mellad was CEO of Cambridge Epigenetix which has developed a proprietary epigenetic biomarker discovery platform for the development of new diagnostic assays and the identification of novel drug targets.

While at Cambridge Epigenetix, he transformed the research tools company into a leading liquid biopsy player and led two successful fundraises (Series B and C) for a total of $49.8m. Dr. Mellad was awarded a Marshall Scholarship to obtain his PhD in Medicine from the University of Cambridge with a focus on the molecular mechanisms regulating vascular remodelling within coronary artery bypass grafts.

JOSEPH P. MENETSKI, PH.D., is Associate Vice President of Research Partnerships and Director of the Biomarkers Consortium at the Foundation for the National Institutes of Health. Dr. Menetski received his Ph.D. from Northwestern University Medical School with Dr. Stephen Kowalczykowski and completed his post-doctoral training at the Laboratory of Molecular Biology, National Institutes of Health (NIH/NIDDK) with Dr. Martin Gellert. He then started his career in industry in 1993 in the Immunopathology Department at Parke-Davis (later Pfizer), where he established a discovery research program in cellular inflammation that eventually transitioned to the molecular study of osteoarthritis. Joseph moved to Merck in 2004. His first position was in the department of Immunology where he was involved in the osteoarthritis new targets and biomarker program. While at Merck he was a member of the Molecular Profiling group, the Knowledge Discovery and Knowledge Management group and finally a Director in Global Competitive Intelligence. Over the years, he has been a key contributor to many basic research and clinical programs in the areas of arthritis, sarcopenia, osteoporosis and asthma. He has served as a core research team member on several external basic research projects for identification of new targets and molecular biomarkers. His industry research and development experiences include target identification, compound selection, translational biomarker identification, clinical study design and analysis, and external scientific collaborations. In the commercial space, he has been intimately involved in opportunity and asset identification and qualification, and in assessing the competitive landscape of disease areas that he is supporting. During this time, he has been recognized by multiple research and development awards for his contributions.

JOHN J. NGAI, PH.D., is the Director of the NIH's Brain Research through Advancing Innovative Neurotechnologies (BRAIN®) Initiative. Dr. Ngai earned his bachelor's degree in chemistry and biology from Pomona College, Claremont, California, and Ph.D. in biology from the California Institute of Technology (Caltech) in Pasadena. He was a postdoctoral researcher at Caltech and at the Columbia University College of Physicians and Surgeons before starting his faculty position at the University of California at Berkeley. During more than 25 years as a Berkeley faculty member, Dr. Ngai has trained 20 undergraduate students, 24 graduate students and 15 postdoctoral fellows in addition to teaching well over 1,000 students in the classroom. His work has led to the publication of more than 70 scientific articles in some of the field's most prestigious journals and 10 U.S. and international patents. Dr. Ngai has received many awards including from the Sloan Foundation, Pew Charitable Trusts, and McKnight Endowment Fund for Neuroscience. As a faculty member, Dr. Ngai has served as the director of Berkeley's Neuroscience Graduate Program and Helen Wills Neuroscience Institute. He has also provided extensive service on NIH study sections, councils and steering groups, including as previous co-chair of the NIH BRAIN® Initiative Cell Census Consortium Steering Group. Dr. Ngai will oversee the long-term strategy and day-to-day operations of the NIH BRAIN Initiative as it takes on the challenges of the next five year plan.

RUSS PAULSEN, M.A., is the Chief Operating Officer of UsAgainstAlzheimer's and UsAgainstAlzheimer's Action, which bring all of us together to win the fight against Alzheimer's disease and related dementias. As COO, Mr. Paulsen leads the program, fundraising, finance, and government relations and policy teams.

Before joining UsAgainstAlzheimer's, Mr. Paulsen held executive positions at the United Way and the American Red Cross, working on nationwide challenges in social service and public health. His team helped tens of thousands across the Gulf Coast and created the model for Red Cross long-term recovery programs when he headed up recovery after Hurricane Katrina. Then, the public health campaign his team created around reduction of deaths and injuries from home fires has saved more than 800 lives and made more than 870,000 American homes safer since 2014. An Illinois native, Mr. Paulsen currently lives with his family in suburban Washington, DC.

ANDREW RADIN, M.S., is chief executive officer and co-founder of twoXAR Pharmaceuticals. Prior to co-founding twoXAR, Mr. Radin held Chief Technology Officer roles at several early stage companies where he managed teams as large as a hundred technologists distributed around the world. Mr. Radin developed the company's proprietary algorithm and as

Chief Executive Officer is focused on overall company strategy, product development and fundraising. Mr. Radin studied biomedical informatics in Stanford University's SCPD graduate program and holds Master of Science and Bachelor of Science degrees in Computer Science from Rochester Institute of Technology.

MICHELLE ROHRER, PH.D., Michelle Rohrer, Ph.D., is Global Head of Product Development Regulatory at Roche. Dr. Rohrer joined Genentech, a member of the Roche group, 28 years ago as a Post-Doctoral Research Fellow and later became a Clinical Scientist before moving to Regulatory in 1999. Dr. Rohrer has held a number of leadership positions over the years within Product Development and Regulatory, including Head of US Regulatory and Site Head for Product Development at the South San Francisco Site. Prior to becoming the Global Head of Product Development Regulatory, she held the position of Global Head of Regulatory Regions and Policy. In her current position, Dr. Rohrer leads the global Regulatory organization overseeing Roche's regulatory development strategies and policy efforts worldwide. Dr. Rohrer is located in the California Bay Area.

In 2013, Dr. Rohrer was named by the SF Business Times as one of "The Most Influential Women in Bay Area Business." In 2014, she was selected by PharmaVOICE as one of the 100 most inspiring leaders in healthcare. Dr. Rohrer served on the Genentech Foundation Board for 3 years helping to oversee Genentech's charitable giving. Since 2014, she has served on the Science Advisory Board for the UCSF-Stanford Center for Excellence in Regulatory Science. In 2015 she was selected and served as one of the industry representatives to the FDA-industry team which negotiated the Prescription Drug User Fee Act VI draft agreement which is currently under legislative review. In 2016 she joined the Board of TransCelerate Biopharma and currently serves as Board Chairman. Dr. Rohrer received her PhD in Nutrition Science (1993) with a minor in Physiological Biochemistry from the University of California, Davis.

JAMES P. SMITH, M.D., M.S., is the deputy director of the Division of Clinical Policy, Office of New Drug Policy, in the Office of New Drugs (OND) at the FDA. In this capacity, he primarily works on clinical and scientific policy priorities of OND. He was previously responsible for overseeing development programs targeting lipid disorders and obesity as the deputy division director of the Division of Metabolism and Endocrinology Products. Prior to joining FDA in February 2011, he was a faculty member in the Division of Nephrology of the University of Michigan Health System. Dr. Smith is a graduate of the University of Michigan Medical School, and he completed his residency in Internal Medicine at the same institution. Subsequently, he completed fellowships in both nephrology and clinical pharmacology at Vanderbilt University Medical Center, as well as a master's degree in Clinical Research Design and Statistical Analysis at the University of Michigan School of Public Health.

CHRISTIN VEASLEY, B.S., is Co-founder and Director of the Chronic Pain Research Alliance. She has lived with chronic pain since surviving a near-fatal accident in her teens. Her health experiences led her to pursue a bachelor of science degree, time conducting neuroscience research at Johns Hopkins Medical School, and to the research advocacy community. Her life's work has been to advocate for the acceleration of rigorous multidisciplinary pain research and the translation of research findings into meaningful change for people with chronic pain – with a special emphasis on pain conditions that are common in women and frequently co-occur. She has been a passionate advocate at the Congressional and federal agency levels for bringing about public awareness of the profound impact of chronic pain, the urgent need for an increased federal research investment to address this public health crisis and the long-overlooked value of including patient perspectives in all aspects of the research continuum. For over twenty years, she has served in several nonprofit management and leadership positions. She holds advisory positions for numerous critical pain initiatives within federal agencies, such as the NIH, CDC and FDA; academic pain research studies; and various collaborative alliances and public-private partnerships working to promote pain research, treatment and education. Ms. Veasley has authored journal articles, op-eds, book chapters, continuing medical education programs for health care providers, patient tutorials and self-help guides. To promote awareness, she speaks openly about her experience with chronic pain and its profound impact on her life. Ms. Veasley has been a presenter at over 30 medical, research and policy conferences, as well as federal agency meetings, and has been interviewed for print, television and radio media.

KAREN WINKFIELD, M.D., PH.D., is the Executive Director of the Meharry-Vanderbilt Alliance, a strategic partnership between Meharry Medical College and Vanderbilt University Medical Center. Her primary responsibilities include working closely with Vanderbilt University Medical Center and Meharry Medical College to ensure their investigators have access to expert faculty collaborators, core resources and services to catalyze innovative research. She is a national expert in community engagement with research focused on the design and implementation of programming to reduce sociocultural and economic barriers that contribute to disparate health outcomes for racial/ethnic minorities and underserved populations.

Previously, Dr. Winkfield was an associate professor of Radiation Oncology at Wake Forest University, associate director for Community Outreach and Engagement and director of the Office of Cancer Health Equity at Wake Forest Baptist Comprehensive Cancer Center. Prior to joining Wake Forest in August 2016, Dr. Winkfield was a radiation oncologist at Massachusetts General Hospital Cancer Center. She specializes in the use of radiation therapy in the treatment of hematologic malignancies (lymphoma, leukemia, multiple myeloma, bone marrow transplantation) and breast cancer. She developed the first comprehensive clinical program focused on hematologic malignancies in the Department of Radiation Oncology at Massachusetts General Hospital. With support of collaborating oncologists, she also established the first multidisciplinary clinic for patients with hematologic disorders. While at Massachusetts General, Dr. Winkfield was a co-principal investigator of a $3 million grant that established the Lazarex-MGH Cancer Care Equity Program, a program designed to improve clinical trial access and enrollment in vulnerable populations. She was responsible for the community outreach and education component of the grant, and continued that work at Wake Forest.

ERICA WOODAHL, PH.D., is a Professor in the Department of Biomedical and Pharmaceutical Sciences in the Skaggs School of Pharmacy at the University of Montana. Dr. Woodahl received a B.S. in Biochemistry at the University of Notre Dame in 1998 and a Ph.D. from the Department of Pharmaceutics at the University of Washington in 2004. She completed a postdoctoral fellowship in clinical pharmacokinetics at the Fred Hutchinson Cancer Research Center in Seattle, Washington. She joined the faculty at the University of Montana in 2007 as an Assistant Professor, and was promoted to Associate Professor in 2012 and Professor in 2020. Dr. Woodahl teaches pharmacokinetics and pharmacogenomics and uses community-based participatory research to address complex and important challenges in conducting precision medicine research with underserved populations.

ABOUT THE FORUM

The Forum on Drug Discovery, Development, and Translation of the National Academies of Sciences, Engineering, and Medicine was created in 2005 by the Board on Health Sciences Policy to provide a unique platform for dialogue and collaboration among thought leaders and stakeholders in government, academia, industry, foundations, and patient advocacy with an interest in improving the system of drug discovery, development, and translation. The Forum brings together leaders from private sector sponsors of biomedical and clinical research, federal agencies sponsoring and regulating biomedical and clinical research, the academic community, and patients, and in doing so serves to educate the policy community about issues where science and policy intersect. The Forum convenes several times each year to identify, discuss, and act on key problems and strategies in the discovery, development, and translation of drugs. To supplement the perspectives and expertise of its members, the Forum also holds public workshops to engage a wide range of experts, members of the public, and the policy community. The Forum also fosters collaborations among its members and constituencies. The activities of the Forum are determined by its members, focusing on the major themes outlined below.

INNOVATION AND THE DRUG DEVELOPMENT ENTERPRISE

Despite exciting scientific advances, the pathway from basic science to new therapeutics faces challenges on many fronts. New paradigms for discovering and developing drugs are being sought to bridge the ever-widening gap between scientific discoveries and translation of those discoveries into life-changing medications. There is also increasing recognition of the need for new models and methods for drug development and translational science, and "precompetitive collaborations" and other partnerships, including public–private partnerships, are proliferating. The Forum offers a venue to discuss effective collaboration in the drug discovery and development enterprise and also hosts discussions that could help chart a course through the turbulent forces of disruptive innovation in the drug discovery and development "ecosystem."

Key gaps remain in our knowledge about science, technology, and methods needed to support drug discovery and development. Recent rapid advances in innovative drug development science present opportunity for revolution- ary developments of new scientific techniques, therapeu- tic products, and applications. The Forum provides a venue to focus ongoing attention and visibility to these important drug development needs and facilitates exploration of new approaches across the drug development lifecycle. The Forum has held workshops that have contributed to the defining and establishment of regulatory science and have helped inform aspects of drug regulatory evaluation.

CLINICAL TRIALS AND CLINICAL PRODUCT DEVELOPMENT

Clinical research is the critical link between bench and bedside in developing new therapeutics. Significant infrastructural, cultural, and regulatory impediments challenge efforts to integrate clinical trials into the health care delivery system. Collaborative, cross-sector approaches can help articulate and address these key challenges and foster systemic responses. The Forum has convened a multiyear initiative to examine the state of clinical trials in the United States, identify areas of strength and weakness in our current clinical trial enterprise, and consider transformative strategies for enhancing the ways in which clinical trials are organized and conducted. In addition to sponsoring multiple symposia and workshops, under this initiative, the Forum is fostering innovative, collaborative efforts to facilitate needed change in areas such as improvement of clinical trial site performance.

INFRASTRUCTURE AND WORKFORCE FOR DRUG DISCOVERY, DEVELOPMENT, AND TRANSLATION

Considerable opportunities remain for enhancement and improvement of the infrastructure that supports the drug development enterprise. That infrastructure, which includes the organizational structure, framework, systems, and resources that facilitate the conduct of biomedical science for drug development, faces significant challenges. The science of drug discovery and development, and its translation into clinical practice, is cross-cutting and multidisciplinary. Career paths can be opaque or lack incentives such as recognition, career advancement, or financial security. The Forum has considered workforce needs as foundational to the advancement of drug discovery, development, and translation. It has convened workshops examining these issues, including consideration of strategies for developing a discipline of innovative regulatory science through the development of a robust workforce. The Forum will also host an initiative that will address needs for a workforce across the translational science lifecycle.

Forum on Drug Discovery, Development, and Translation

Robert Califf (Co-Chair)
Verily Life Sciences and Google Health

Gregory Simon (Co-Chair)
Kaiser Permanente Washington Health Research Institute

Amy Abernethy
Office of the Commissioner, U.S. FDA

Christopher Austin
National Center for Advancing Translational Sciences, NIH

Linda Brady
National Institute of Mental Health, NIH

Barry Coller
The Rockefeller University

Thomas Curran
Children's Mercy, Kansas City

Richard Davey
National Institute of Allergy and Infectious Diseases, NIH

Katherine Dawson
Biogen

James Doroshow
National Cancer Institute, NIH

Jeffrey Drazen
New England Journal of Medicine

Steven Galson
Amgen Inc.

Carlos Garner
Eli Lilly and Company

Julie Gerberding
Merck & Co., Inc.

Deborah Hung
Harvard Medical School

Esther Krofah
FasterCures, Milken Institute

Lisa LaVange
University of North Carolina Gillings School of Global Public Health

Ross McKinney, Jr.
Association of American Medical Colleges

Joseph Menetski
Foundation for the NIH

Arti Rai
Duke University School of Law

Mark Rogge
Takeda Pharmaceuticals

Kelly Rose
Burroughs Wellcome Fund

Susan Schaeffer
The Patients' Academy for Research Advocacy

Joseph Scheeren
Critical Path Institute

Anantha Shekhar
University of Pittsburgh School of Medicine

Jay Siegel
Retired

Ellen Sigal
Friends of Cancer Research

Lana Skirboll
Sanofi

Amir Tamiz
National Institute of Neurological Disorders and Stroke, NIH

Ann Taylor
AstraZeneca

Pamela Tenaerts
Clinical Trials Transformation Initiative

Joanne Waldstreicher
Johnson & Johnson

Robert Walker
Biomedical Advanced Research and Development Authority

Jonathan Watanabe
University of California Irvine School of Pharmacy and Pharmaceutical Sciences

Carrie Wolinetz
Office of Science Policy, NIH

Alastair Wood
Vanderbilt University

Janet Woodcock
Center for Drug Evaluation and Research, U.S. FDA

Project Staff

Carolyn Shore, Ph.D.
Forum Director

Amanda Wagner Gee, M.S.
Program Officer

Leah Cairns, Ph.D.
Program Officer

Andrew March, M.P.H.
Associate Program Officer

Melvin Joppy
Senior Program Assistant

For more information, please visit:

NATIONALACADEMIES.ORG/DRUGFORUM

Health and Medicine Division
Boardon Health Sciences Policy

The National Academies of
SCIENCES · ENGINEERING · MEDICINE

Therapeutic Development in the Absence of Predictive Animal Models of Nervous System Disorders

Proceedings of a Workshop (2017)

Description

Compared with other disease areas, central nervous system (CNS) disorders have had the highest failure rate for new compounds in advanced clinical trials. Most CNS drugs fail because of efficacy, and the core issue underlying these problems is a poor understanding of disease biology. Concern about the poor productivity in neuroscience drug development has gained intensity over the past decade, amplified by a retraction in investment from the pharmaceutical industry. This retreat by industry has been fueled by the high failure rate of compounds in advanced clinical trials for nervous system disorders.

In response to the de-emphasis of CNS disorders in therapeutic development relative to other disease areas such as cancer, metabolism, and autoimmunity, the National Academies of Sciences, Engineering, and Medicine initiated a series of workshops in 2012 to address the challenges that have slowed drug development for nervous system disorders. Motivated by the notion that advances in genetics and other new technologies are beginning to bring forth new molecular targets and identify new biomarkers, the Academies hosted the third workshop in this series in September 2016. Participants discussed opportunities to accelerate early stages of drug development for nervous system disorders in the absence of animal models that reflect disease and predict efficacy. This publication summarizes the presentations and discussions from the workshop.

To access the full text of this workshop proceedings, see https://www.nap.edu/catalog/24672/therapeutic-development-in-the-absence-of-predictive-animal-models-of-nervous-system-disorders.

Financial Incentives to Encourage Development of Therapies That Address Unmet Medical Needs for Nervous System Disorders

Workshop Summary (2015)

Description

The Institute of Medicine (IOM) Forum on Neuroscience and Nervous System Disorders, in collaboration with the IOM Forum on Drug Discovery, Development, and Translation, convened a workshop on January 20-21, 2015, to explore policy changes that might increase private sector investment in research and development innovation that fills unmet medical needs for central nervous system (CNS) disorders. Workshop participants strategized about how to incentivize companies to fortify their CNS drug development programs, shrinking obstacles that currently deter ventures. Representatives from academia, government agencies, patient groups, and industry gathered to share information and viewpoints, and to brainstorm about budget-neutral policy changes that could help widen the pipeline toward drugs that address unmet needs for CNS disorders. This report summarizes the presentations and discussion of the workshop.

To access the full text of this workshop summary, see https://www.nap.edu/catalog/21732/financial-incentives-to-encourage-development-of-therapies-that-address-unmet-medical-needs-for-nervous-system-disorders.

Circulation: Cardiovascular Quality and Outcomes

FRONTIERS IN CARDIOVASCULAR QUALITY AND OUTCOMES

Improving Cardiovascular Drug and Device Development and Evidence Through Patient-Centered Research and Clinical Trials

A Call to Action From the Value in Healthcare Initiative's Partnering With Regulators Learning Collaborative

ABSTRACT: The pipeline of new cardiovascular drugs is relatively limited compared with many other clinical areas. Challenges causing lagging drug innovation include the duration and expense of cardiovascular clinical trials needed for regulatory evaluation and approvals, which generally must demonstrate noninferiority to existing standards of care and measure longer-term outcomes. By comparison, there has been substantial progress in cardiovascular device innovation. There has also been progress in cardiovascular trial participation equity in recent years, especially among women, due in part to important efforts by Food and Drug Administration, National Institutes of Health, American Heart Association, and others. Yet women and especially racial and ethnic minority populations remain underrepresented in cardiovascular trials, indicating much work ahead to continue recent success. Given these challenges and opportunities, the multistakeholder Partnering with Regulators Learning Collaborative of the Value in Healthcare Initiative, a collaboration of the American Heart Association and the Robert J. Margolis, MD, Center for Health Policy at Duke University, identified how to improve the evidence generation process for cardiovascular drugs and devices. Drawing on a series of meetings, literature reviews, and analyses of regulatory options, the Collaborative makes recommendations across four identified areas for improvement. First, we offer strategies to enhance patient engagement in trial design, convenient participation, and meaningful end points and outcomes to improve patient recruitment and retention (major expenses in clinical trials). Second, new digital technologies expand the potential for real-world evidence to streamline data collection and reduce cost and time of trials. However, technical challenges must be overcome to routinely leverage real-world data, including standardizing data, managing data quality, understanding data comparability, and ensuring real-world evidence does not worsen inequities. Third, as trials are driven by evidence needs of regulators and payers, we recommend ways to improve their collaboration in trial design to streamline and standardize efficient and innovative trials, reducing costs and delays. Finally, we discuss creative ways to expand the minuscule proportion of sites involved in cardiovascular evidence generation and medical product development. These actions, paired with continued policy research into better ways to pay for and equitably develop therapies, will help reduce the cost and complexity of drug and device research, development, and trials.

John J. Warner, MD, PhD
Hannah L. Crook, BSPH
Karley M. Whelan, BA
William K. Bleser, PhD, MSPH
Rachel A. Roiland, PhD, RN
Marianne Hamilton Lopez, PhD, MPA
Robert S. Saunders, PhD
Tracy Y. Wang, MD, MHS, MS
Adrian F. Hernandez, MD, MHS
Mark B. McClellan, MD, PhD
Robert M. Califf, MD
Nancy Brown, BS
and the American Heart Association Partnering with Regulators Learning Collaborative*

Key Words: American Heart Association ■ cardiovascular disease ■ health policy ■ risk ■ standard of care

https://www.ahajournals.org/journal/circoutcomes

Biomedical innovation in cardiovascular care is important given the significant burden of cardiovascular diseases (CVDs) in America. Over 18 million people have CVD; CVDs cause roughly a quarter of deaths nationally,[1,2] and unmet need remains in CVD care (especially risk reduction[3]). Furthermore, there are significant sociodemographic inequities, with older adults, those with lower education, racial or ethnic minority groups, and rural residents disproportionately affected. For example, individuals living in rural settings have higher age-adjusted CVD death rates relative to urban counterparts.[4–9]

The pipeline of new cardiovascular drugs in the United States is relatively limited compared with many other specialties, partially due to the complexity and cost of evidence generation.[10] There has been substantial growth in the pipeline for cardiovascular medical devices, however, with products for minimally invasive surgery, heart health tracking, interventional products for restoring heart rhythm and reviewing blockages, and wearables.

Although drugs and medical devices are approved under different regulatory regimes and face different evidence generation challenges, both could benefit from increased patient participation in clinical trials and patient engagement in clinical trial design and end point selection, better leveraging real-world evidence, ensuring clinical trial evidence meets the needs of regulators and payers, and expanding the number of health care organizations involved in clinical trials.

Many of these issues are broad-based challenges for all stages of drug and device research, development, and trials—but cardiology may be poised to address them with population health impact. First, given that CVD is the leading cause of death and significantly affects quality of life for years before death, cardiology is an impactful testbed for population-level improvements in drug and device research, development, and clinical trials. Second, cardiology is well-suited to capitalize on data generation capabilities of current digital technology. Smartphones, for example, are widely (and relatively equitably) available.[11] Although they have limited ability to generate clinically meaningful data in most medical fields, they can capture data relevant to cardiology (eg, physical activity tracking, heart rate, rhythm monitoring).

This article describes the efforts and vision for improving the cardiovascular medical product pipeline of the Partnering with Regulators Learning Collaborative of The Value in Healthcare Initiative,[10] a collaboration of the American Heart Association (AHA) and the Robert J. Margolis, MD, Center for Health Policy at Duke University. The Learning Collaborative is comprised of diverse stakeholders: patients, clinicians (including cardiologists), health systems, clinical research organizations, academia, government, professional associations, payers, and industry.

The Collaborative developed short- and long-term recommendations (summarized in Tables 1 and 2) to expand cardiovascular drug and device innovation by improving the clinical research and clinical trial process. To do so, they reviewed peer-reviewed and gray literature, analyses of regulatory options, and insights from the expert multistakeholder Collaborative. The recommendations center on improving patient engagement and patient-centeredness of trials; expanding use of real-world evidence (RWE), ensuring trial evidence meets the needs of multiple stakeholders, including regulators and payers; and expanding the network of health care organizations participating in cardiovascular clinical research.

UNEVEN STATE OF CARDIOVASCULAR DRUG AND DEVICE INNOVATION AND EVIDENCE GENERATION

The stark contrast between therapeutic development for CVD and cancer, the leading and second leading causes of death nationally, exemplifies CVD's lagging pipeline. Fewer than 8% of ≈7300 drugs in development in the United States in 2017 addressed cardiovascular conditions.[10,12] From 1996 to 2015, only 40 cardiovascular-related substances entered the market compared with 110 new oncological substances. Overall development of oncology-focused drugs or biologic products was nearly 7× greater.[10,13,14]

Lagging drug innovation is partially due to challenges in evidence generation. One estimate put the cost of a single, pivotal cardiovascular clinical trial at $157 million—6× most other disease areas.[15] Moreover, there is a high chance the product will not make it to market; one study estimated only 1 in 4 cardiovascular drugs that make it to phase 1 trials are approved by the Food and Drug Administration (FDA).[16]

Cardiovascular evidence generation is more expensive than other specialties for several reasons. Their clinical trials require longer timeframes, more substantial data collection, and a larger number of participants relative to most other fields.[10,17,18] Many promising intermediary cardiovascular outcomes and biomarkers have failed to accurately predict clinical outcomes (even validated biomarkers for blood pressure and cholesterol are not good predictors of treatment side effects).[19] Additionally, because in many cases there are beneficial treatments already on the market, trials must demonstrate noninferiority or superiority to current standards of care (often requiring longer, multi-arm trials) in addition to standard requirements of safety and efficacy compared with no treatment to qualify for additional payment. Some evidence suggests that cardiovascular trials are beginning to leverage more pragmatic trial methods,[20] but high costs are still normal.

In contrast to the drug pipeline, investment in medical devices for cardiovascular use has grown substantially.

Table 1. Short-Term Actions to Improve the Research and Trial Process for Cardiovascular Drugs and Devices

Establishing a more collaborative and inclusive research process
Conceptualizing and realizing opportunities for patient involvement. The FDA should recommend industry's pretrial Research and Development design include patients from a variety of backgrounds and perspectives.
Ensuring outcomes used in end points are meaningful to patients.
The FDA's PFDD should expand its reach to multiple cardiovascular conditions.
The AHA should build from PFDD infrastructure to create its own patient-centered cardiovascular therapy development forum.
Using new tools to enable convenient recruitment and participation. The AHA and FDA should focus their trial innovation convening efforts on how equitable use of technologies, including smartphones, wearables, and artificial intelligence, may streamline diverse participant recruitment and accessible "site-less" cardiovascular trials.
Expanding the research community network. The AHA should work to identify and actively connect community-based organizations, including patient advocacy groups, to the investigators, health systems, and hospitals participating in trials and expand their availability in underserved areas.
Developing a cardiovascular core outcome set. The AHA should work with FDA to build from the Clinical Outcome Assessment Compendium and develop a cardiovascular core outcome set.
Allowing patients to own, use, and share their trial data. The AHA and FDA should operationalize sharing trial data with patients, including bring your own device designs.
Leveraging real-world evidence and data to improve biomedical innovation
Using technology and real-world data to assess and improve currently licensed cardiovascular drugs and devices.
The AHA and FDA should focus their trial innovation convening efforts on how to use technology and patient data to streamline and enhance phase IV studies' patient-centricity.
The NHLBI should fund implementation science studies on cardiovascular therapy adherence, including strategies related to decision aids and communicating risks and benefits.
The FDA should provide guidance on equitable use of smart devices and other personal technologies in trials, which may include the direct provision of devices to patients.
Standardizing cardiovascular real-world data. The AHA and FDA should develop clear guidelines for obtaining and analyzing cardiovascular real-world data and transforming them into real-world evidence acceptable in cardiovascular clinical trials.
Ensuring clinical trials meet the evidence needs of regulators and payers
Including industry and researchers in trial design innovation.
The FDA/CDER should develop a forum similar to FDA/CDRH's Payor Communication Task Force where stakeholders can get feedback on a new drug submission.
The AHA should create a regular convening for industry, researchers, and other stakeholders to meet with the FDA and other regulators affecting research or implementation (eg, NIH, Centers for Medicare & Medicaid Services). This convening may focus on barriers to innovation and ideas for innovative design and may not be specific to a particular therapy application.
Creating cardiac research collaboratives of excellence
Better capturing trial successes by creating cardiac research collaboratives of excellence. The AHA should work with the NHLBI to create a program to recognize regional collaboratives of clinics, health systems, community-based organizations, and other relevant stakeholder groups with a demonstrated track record of successful cardiovascular trials.
Engaging a broader network of providers in research by creating a community cardiovascular research program. The AHA should create a research network to boost provider engagement in cardiovascular clinical trials, with a focus on community-based providers and underserved populations (similar to the National Cancer Institute's Community Oncology Research Program).

AHA indicates American Heart Association; CDRH, Center for Devices and Radiological Health; FDA, Food and Drug Administration; NHLBI, National Heart, Lung, and Blood Institute; NIH, National Institutes of Health; and PFDD, Patient-Focused Drug Development.

The global market for cardiovascular devices is expected to expand from $42.4 billion in 2017 to $59.1 billion in 2022,[21] and[22] potentially $121 billion by 2024, driven primarily by surgical, diagnostic, and monitoring devices.[23] Hundreds of premarket approvals[21] and 510(k) clearances were filed in 2019. Continued innovation in minimally invasive surgery,[24] advances in electronic and digitally enabled devices, and smart wearable devices and other technologies to measure cardiac function[25] all drive development.

Additionally, significant evidence generation over the past decade has fueled the robust medical device pipeline. Data on clinicaltrials.gov as of early 2020 show a steady increase in cardiovascular device trials: 147 in 2010, 233 in 2015, and 253 in 2019. In 2015 alone, 115 randomized control trials investigating effects of therapeutic cardiovascular medical devices were published in academic journals.[26] Additionally, strong patient registries, most often funded privately by academic institutions,[27] contribute to the depth of opportunity for research and investment.

INNOVATION CHALLENGES FOR CARDIOVASCULAR DRUGS

Patient participation in cardiovascular trials is low.[28] One study found trial participation by eligible acute myocardial infarction patients in a national registry declined from 5.2% in 2008 to 3.4% in 2011,[29] and another of

Table 2. Long-Term Strategies to Improve the Cardiovascular Drug and Device Pipeline

Establishing a more collaborative and inclusive research process
Conceptualizing and realizing opportunities for patient involvement. The NIH (particularly NHLBI) should have a diverse committee of patients advise their grant offerings for patient-centric research.
Ensuring outcomes used in end points are meaningful to patients.
The NIH (especially NHLBI) and other funders should support research to develop patient-centered cardiovascular outcomes for use in trials.
Existing cardiovascular registries (eg, for hypertension) should capture patient-centered and patient-generated health data.
Leveraging real-world evidence and data to improve biomedical innovation
Using technology and real-world data to assess and improve currently licensed cardiovascular drugs and devices.
The NHLBI should dedicate research funding to learn how to use smartphones, wearables, artificial intelligence, and other technologies to improve medication adherence and uptake of current cardiovascular drugs and devices, especially in underserved populations.
The FDA should place a higher weight on patient-centered end points and quality of life metrics in all clinical trial phases.
Standardizing cardiovascular real-world data. The NHLBI should dedicate research funding for implementation science studies to learn to scale interventions directly importing cardiovascular data from patients' third-party apps into electronic health records for clinicians and into trial portals as evidence.
Developing innovative, affordable, and equitably available personal technologies for cardiovascular trial use. The AHA and FDA should focus longer-term trial innovation efforts on working with industry and technology companies to encourage production of inexpensive wearables/smartphones capable of biometric data collection.
Creating cardiac research collaboratives of excellence
Expanding the research community network.
The FDA should consider stronger and broader recommendations that women and racial and ethnic minorities be equitably included in trials.
The AHA and FDA should focus longer-term trial innovation convening efforts on how to make recruitment, participation, and retention more equitable and culturally competent, including how to build better trust in the medical and research establishment, and how to better include underserved rural and urban community settings.

AHA indicates American Heart Association; FDA, Food and Drug Administration; NHLBI, National Heart, Lung, and Blood Institute; and NIH, National Institutes of Health.

the same population has even lower estimates, most recently 0.8% participation through 2014.[30] Enrollment is especially limited for high-risk groups such as elderly and rural patients[31,32] because these groups face multiple logistical barriers to participating in trials.

Low patient participation can also lead to unmet enrollment targets, which can contribute to the failure of a trial, either from a lack of participants or the inability to demonstrate efficacy due to a small sample size.[33] For example, in the AleCardio trial (a large, international, phase III cardiovascular clinical trial), only 18.2% of sites met enrollment targets, and 10% closed before the end of recruitment, mostly because they failed to enroll a single patient.[34] The trial was ultimately terminated when a futility analysis showed it was subsequently unlikely to prove clinical efficacy.[35]

One explanation for low rates of patient participation may be limited clinician engagement. Another is lack of hospital and health system participation in clinical trials (only about 5% of acute care hospitals consistently participate in clinical trials[36]), with many hospitals not properly trained in conducting clinical research.[30]

Low patient participation may also reflect limited patient engagement in development of the trials themselves. For example, patients and families are often not involved in developing the trial operational plan to help ensure trial procedures are convenient for patients. Patients are often interested in how therapies may affect quality of life,[37] but this information is often not represented in trial end points.

ESTABLISHING A MORE COLLABORATIVE AND INCLUSIVE RESEARCH PROCESS

The current biomedical research paradigm is based on the need to prompt and answer questions of scientists, payers, clinicians, and regulators, among others. Patients are often less involved but have important perspectives and experiences that must be leveraged in the development and design of clinical trials to improve patient participation in trials and the meaningfulness of trial results. Patient perspectives can be captured on multiple topics, including informed consent, study procedures, end points and outcomes, publication, approval, and evaluation (summarized in the Figure). By identifying opportunities to improve patient recruitment and continued participation, overall trial costs may decline, as patient recruitment is a major expense. Below, we discuss challenges, barriers, and potential solutions to move the research enterprise to a multistakeholder, patient-centric research process.

Better Inclusion of Diverse Patient Populations in Clinical Trials

Opportunities exist to increase diversity of clinical trials, whether by sex, racial and ethnic minorities, rural residents, or other dimensions.[9,39–44] Sex diversity is especially important given that biological sex influences

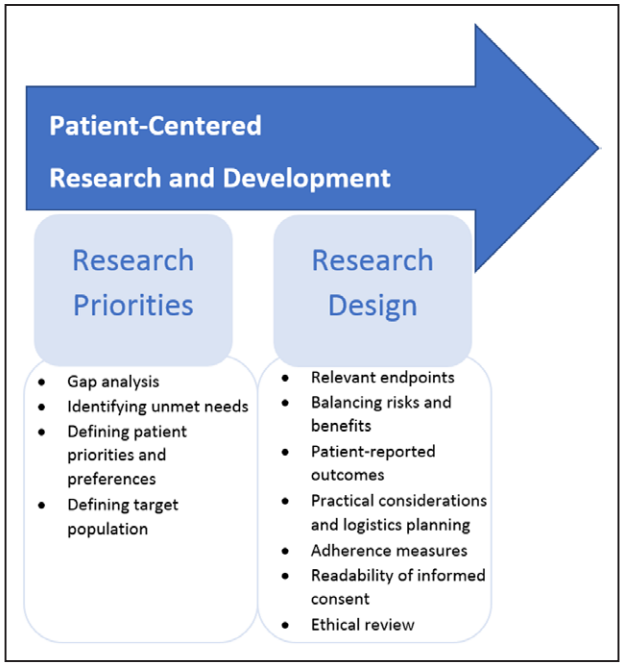

Figure. Areas for patient involvement in early-stage research of drugs and devices.
Guided by Geissler et al,[38] we highlight pretrial opportunities for patient involvement in the therapy research and development process. These opportunities were emphasized in Learning Collaborative discussions.

pharmacodynamics and pharmacokinetics, an emphasis reinforced by the National Institutes of Health (NIH) Revitalization Act of 1993.[45] Enrollment of women in cardiovascular trials has improved in recent years. For example, in 2018, 56% of the approved drug trial populations were women, although no cardiovascular indications were approved in this time period.[46] However, some research suggests clinical trial participation and analysis by sex could be improved. One study found that from 2011 to 2015 only one-third of cardiovascular trial participants were women,[47] and a review of clinical trials from 2005 to 2015 found women were significantly underrepresented in trials for heart failure, coronary artery disease, and acute coronary syndrome when compared with overall disease burden for women.[40] Of the 10 cardiovascular indications approved by FDA in 2015, 2 trials did not report efficacy statements on sex,[48] and 8 had study populations of <50% women.[49] Thirty percent of premarket approval supplement applications for high-risk medical devices do not report sex for all enrolled patients.[50] Of 11 cardiovascular devices approved by FDA's Center for Devices and Radiological Health (CDRH) in 2011, 10 had fewer than 50% female participation, with as little as 18% women in an endovascular occlusion device study.[51]

Several initiatives and groups, such as Research Goes Red, the FDA's Office on Women's Health, and the NIH's Office of Research on Women's Health, have greatly advanced women's representation in clinical cardiovascular research.[43] Research Goes Red empowers women to participate in clinical trial data collection by taking part in surveys, focus groups, and testing new tools and technologies.[52] Participants are also alerted when new studies open up meeting their preferences.[53]

Racial diversity in clinical trials has also significantly improved over time but racial and ethnic minorities are still underrepresented. In 2011, black patients, although 12% of the population, made up only 5% of participants[54–56] but has grown steadily to 7% in 2016 and 2017 to 11% in 2018.[46,49,57] Additionally, Hispanic representation over this time period increased from 4% in 2015 to a consistent 14% in 2017 and 2018.[46,49,57] Yet for some of these years, most or all of the studies for approved cardiovascular products still underrepresented black patients and did not report Hispanic representation.[49,51] There is still work to be done.

Cultural competency can greatly improve patients' trust in the medical establishment, interest in research participation, and retention in studies. For example, barbershop interventions have proven effective at increasing awareness and participation in members of black communities.[58] Studies in Hispanic communities have supported participation with Spanish-speaking investigators, advertising at churches, hair salons, and grocery stores, and speaking with families.[59] However, trust in the medical establishment and the research process, especially given the historical context of exploitative unethical studies, remains low.[60–62] Reconsiderations of patient motives and barriers to trial participation are needed, as well as a more robust suite of incentives to ethically encourage informed participation.

The AHA and the FDA should continue and expand their efforts to encourage equitable and culturally competent trial participation and recruitment opportunities. Engaging patients diverse in sex, race, and ethnic background in trial design may achieve the accessibility and cultural competency needed to draw a more diverse group of trial participants. The FDA should recommend industry's pretrial Research and Development designs to include patients from a variety of backgrounds and perspectives, especially those from underserved communities, as advisors at all points in the pretrial process.

Engaging Patients in Trial Design

Traditional approaches to clinical trial recruitment tend to be centered around convenience of the trial investigators and health institutions, not potential trial participants.[63] These approaches rely on identifying potential participants when those individuals come into contact with the health care environment (eg, during medical appointments) instead of reaching out directly to communities and neighborhoods of potential participants.

When patients and families are involved in developing a trial's operational plan, they can highlight potentially burdensome processes limiting enrollment, and

identify solutions ensuring people can take part in the trial's requirements. This is important as trial participation frequently requires individuals taking time away from their daily lives for various trial-related activities (eg, completing trial-related paperwork, gathering pertinent information on the potential therapy and trial, traveling to and from appointments for data collection). The frequent lack of support for transportation, appointment coordination, and child care limits who may participate and leads to smaller and less diverse study populations.

Although patient engagement can improve overall trial recruitment, it is especially important for improving diversity of recruited patients, which, in turn, generates evidence that can drive new treatments effective in underrepresented groups. For example, older adults' health status may make long trial-related activities uncomfortable and unfeasible. Many techniques for recruiting diverse study populations may also apply in reaching those willing to contribute to trial design. For example, engaging with patients at community centers like grocery stores and barbershops may reach patients from previously underrepresented groups that may contribute to defining study priorities and protocols.

Using New Tools to Enable Convenient Recruitment and Participation

Digital technologies can also enable less burdensome trial participation. For example, internet access enables flexibility for participants, which can reduce patient burden and inconvenience and increase trial retention. Recent technological advancements in the cardiology space, such as the ability to collect biometric data with smartphones, Amazon's Alexa having access to health information, targeted Facebook recruitment ads, and eCohort approaches offer unique routes for research recruitment and screening.[64–68] These improvements allow for site-less trial recruitment and participation that is convenient for patients and removes barriers to joining and completing a study. For geographies where internet access is limited or unavailable, trials should consider how to enhance access or develop alternative approaches to using these tools (eg, use smartphones for collecting and storing data, but data transfer to trial staff would occur at in-person appointments).

New technologies can also play a role in patient recruitment to trials. Artificial intelligence applied to clinical settings, especially in patient screening and participant enrollment, can help identify appropriate subjects and increase screening by almost 15% and enrollment by 11%.[69,70] Continuing to build these capabilities is important for identifying potential trial subjects and targeting direct outreach for recruitment. Of note, all strategies involving new technology and its data must be implemented alongside meaningful steps to address patient privacy and security of health information.

Beyond technology, patient recruitment can be improved by partnering with community-based organizations (including patient advocacy groups) to identify potential participants and by partnering with investigators to reach individuals who may not normally be accessed using traditional recruitment methods. Creative messaging approaches could inspire patients to be Clinical Trial Patient Heroes. The AHA may facilitate this work in conjunction with health systems, universities, and investigators conducting cardiovascular trials. This approach could help identify, leverage, and connect an existing base of activated and engaged patients to trials and provide supports that enable participation (eg, transportation, child care, peer network). Such supports would be particularly helpful in ensuring individuals from underrepresented, often high-risk, groups are able to participate.

Allowing Patients to Own, Use, and Share Trial Data

Participation in a clinical trial typically generates large amounts of patient data, yet sharing this data with patients is not standard practice. Communicating study results to participants alone is not sufficient, as valuable health information (such as lab or test results) are also generated through participation. Patients have expressed desire to record and save their data during and after a clinical trial.[71] Allowing for data-sharing back to patients may increase interest in trial participation and improve the patient experience.

Ensuring Trial End points Are Meaningful to Patients

Patient insights can improve products' value and usefulness to patients,[72] such as through outlining gaps in research, explaining perceptions of risks and benefits, and highlighting end points important to patients. Patients are uniquely qualified to describe their own experiences and can provide regulators and researchers with information that communicates the impact of conditions and treatment on their lives, goals, and priorities.[73] Patient-centered research also has practical value. If a drug or device does not address the problems most important to patients, they will be less likely to use it. For example, 92% of cardiovascular patients believe that medication adherence would improve if patients helped design clinical trials.[74]

Research has identified end points important to patients for cardiovascular conditions. For example, most cardiovascular patients prioritize heart attack as a more important end point than death by any cause

other than heart disease (a more common study end point) and perceive stroke as more detrimental than chest pain hospitalization or angioplasty (more common study end points).[74] Additional examples include prevention of a major stroke causing permanent disability was viewed as more important than prevention of death within 24 hours postintervention and redoing coronary artery bypass graft surgery was preferred over having recurrent angina.[75] Traditional end points (such as death and hospitalizations) are still important to both patients and clinicians, but additional end points can capture the range of outcomes meaningful to patients.

Patient-reported outcome measures may capture the most meaningful end points to patients. For example, to illustrate the meaningful effects of an intervention, heart failure trials could include the following patient-reported outcomes: physical interaction, social interaction, sexual activity, life dissatisfaction, somatic symptoms, self-efficacy, and psychological state.[76] Additional research should develop and validate more patient-reported outcome measures to be used in clinical trials.

A relevant example of how to systematically identify key end points important to patients comes FDA efforts related to patients with heart failure with preserved ejection fraction. Heart failure with preserved ejection fraction causes significant functional capacity impairment and quality of life impact far beyond the risk of traditional clinical end points of death and hospitalization. The FDA convened patients to develop patient-focused alternative end points for heart failure with preserved ejection fraction studies and identified more meaningful outcomes to include in trials, such as the 6-minute walk test.[77]

Patient convenings, organized by the FDA, AHA, or other key organizations, can identify patient-centered end points that may shape development of cardiovascular studies and products. Such convenings have been expanded as part of the FDA's Patient-Focused Drug Development effort, which seeks to provide a "systematic approach to help ensure that patients' experiences, perspectives, needs, and priorities are captured and meaningfully incorporated into drug development and evaluation."[78] Meetings convened under this initiative have focused on the impact of patients' conditions on their daily life, their most significant symptoms, and their current approaches to treatment.[73] To enhance the patient perspective, the AHA and other stakeholders may advocate for more cardiovascular conditions to be included in this formal infrastructure (thus far, pulmonary arterial hypertension has benefited from this type of structured inclusion in drug and device research and development).[73] Alternatively, the AHA may convene forums exclusively focused on patient-centered cardiovascular therapy development.

The routine and feasible collection of new patient-report end points in clinical trials is also critical. Ensuring consistent collection of these data may be achieved through multiple approaches. For example, FDA publishes a COA (Clinical Outcome Assessment) Compendium as a resource for identifying patient-focused outcomes for clinical trial design, which currently contains more than a dozen cardiovascular-related clinical outcomes.[79] Similarly, the COMET (Core Outcome Measures in Effectiveness Trials) Initiative is a collaborative effort to compile core outcome sets that could provide a backbone to cardiovascular trial design.[80]

In the short term, we recommend building on the Compendium and COMET Initiative to identify a core set of cardiovascular outcomes (including patient-reported outcomes, clinician-reported outcomes, observer-reported outcomes, and performance outcomes) meaningful to multiple stakeholders, especially patients. The FDA recently convened a public meeting in partnership with the American Society of Clinical Oncology for cancer clinical trials that built off of prior workshops to discuss core outcome sets[81]; the AHA could work with the FDA to develop a similar workshop focused on CVD. Such a core outcome set may standardize patient-centered cardiovascular information collected in clinical trials, and facilitate clear comparisons across therapies. Furthermore, if important patient-centered concepts are included in core outcome sets, it would make their collection more routine in clinical practice.

LEVERAGING RWE AND DATA TO IMPROVE BIOMEDICAL INNOVATION

The traditional clinical research paradigm has advanced our understanding of cardiovascular conditions and effectiveness of various interventions. However, it is also time-consuming, expensive, and limited in ability to describe effects in real-world settings. RWE and real-world data (RWD) can help overcome these challenges, and using personal devices to do so is an exciting opportunity in the cardiovascular trial space.

There are practical issues in using RWE and RWD for regulatory decisions. Most wearable devices are designed for consumer use, not clinical trial data collection, raising questions about trial appropriateness, data validity, and data security.[82] One short-term opportunity to overcome these challenges is for AHA and FDA to convene stakeholders, especially clinical researchers, on how to use technology and patient-generated health data to simplify and improve existing postmarket surveillance requirements (stage IV clinical trials). In the longer term, the National Heart, Lung, and Blood Institute could dedicate funding for studies on how RWD and RWE may improve medication adherence and uptake of current cardiovascular drugs and devices. These studies should examine how enhanced adherence and uptake methods may need to be tailored to

be effective in high-risk groups or settings with limited resources (eg, rural health clinics or hospitals).

Potential Impact of RWE and Data

Understanding the real-world experience of patients using a drug or device, which may differ from the clinical trial context, is challenging. Patients often struggle to correctly use drugs currently on the market due to issues with adherence, costs, or side effects. For example, 40% to 50% of patients with a chronic condition are nonadherent to medications and cite costs and perceived usefulness of the drugs as barriers.[83,84] Real-world data and evidence may provide a better understanding of the less-than-ideal real-world use of products already on the market while monitoring safety and adverse effects of recently approved medical products.[85–87]

Smartphones, wearables, and other personal technologies may collect data in a convenient and potentially cost-effective way that can be translated into evidence used to improve patient-centeredness of current drugs and devices. As defined by FDA, RWD encompasses "data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources," and RWE includes "*clinical* evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD."[88]

Although there are different sources of RWD, there is particular interest in patient-generated health data. Technological advances, particularly in wearables and other personal technologies, offer new mechanisms to facilitate novel data collection and improve patient participation in pretrial Research and Development and clinical trials. Most importantly, these technologies offer unique abilities to improve cardiovascular drugs and devices relative to other medical fields. RWD, such as activity tracking and heart rate and rhythm monitoring, can be relatively easily captured on smartphones. There are opportunities for expanding existing registries by incorporating patient-generated health data. Moreover, new technology could be used to improve data quality in clinical trials, by making data collection more complete or filling in missing data.

Commercial activity trackers (such as FitBit, Apple Watch, etc) are becoming increasingly popular. The consumer-directed wearable technology market presents an opportunity for the use of technology in cardiovascular trials.[89] Cardiovascular care has some history of using wearable technologies in diagnosis and management of disease, although use of consumer-directed wearables in clinical trials is a relatively newer concept. However, innovation in this space is not entirely untested; for example, a recent systematic review identified 127 clinical trials across specialties and research areas that used consumer physical activity trackers.[90] Beyond generating data for trials, wearables-generated data may also be able to inform patients or caregivers of clinical status, adherence to medication, or effects of certain patient actions on health outcomes.[89]

Standardizing Cardiovascular RWD

To make meaningful use of patient-reported data collected by personal technologies, collection and analysis processes must be reliable. There is currently a lack of well-validated, standardized ways to collect and incorporate patient-generated data into drug and device outcomes assessments. The FDA could ameliorate this process by recommending research and development of clear guidelines for obtaining and analyzing cardiovascular data from nontraditional sources in clinical trials. Given the size of the technology market, it will be difficult for the entire technology industry to meet new standards (even minimal ones). Therefore, the FDA and the AHA should work with industry to ensure standards are implementable and identify practical strategies for overcoming limited standardization. Implementation science can be used in conjunction with this research to generate and employ a toolkit of best practices.

Streamlining the development and review process necessitates platforms that enable patients and their data to be brought together efficiently. Despite challenges, there are tools that use standard data formats (eg, Fast Healthcare Interoperability Resources) to directly import data from third-party apps (ie, on smartphones) into electronic medical records for clinicians to see.[91]

Data Quality, Completeness, and Comparability

Increasing usage of bring-your-own-device trial designs could allow for easier evidence generation by leveraging the increasingly prevalent ownership of smart devices. In these trials, patients use their phone, tablet, or other devices to enter data and retain access to their data after trial conclusion. Patients often prefer these methods, which may result in more complete data and lower costs.[92–94] However, data quality and comparability of technical data are challenges requiring additional research. Moreover, this trial design can limit the eligible patient population as patients are required to have a device meeting certain technical requirements.[95] Further guidelines are needed to ensure bring-your-own-device trials are conducted in ways that address data quality, comparability, and equity challenges.

Data completeness is another challenge when solely using smartphones to conduct clinical trials. For example, patients enrolled in the MyHeart Counts Cardiovascular Heart Study used a smartphone-based application to record physical activity, answer health question-

naires, and complete a 6-minute walk test.[96] Of those who consented, 18.3% uploaded no data, and 9.3% completed all 7 days of data collection. In total, only 2.7% completed enough data collection and health questionnaires to compute a 10-year risk score.[96]

Technology and Health Equity

Despite the widespread use of smartphones and other personal technologies, there remains concern that use of these technologies in clinical trials can worsen health inequalities.[97] Variations in access to the internet, smartphones, and other smart devices remain prevalent between age and income groups.[98,99] The use of technology in clinical trials may also provide fewer benefits for certain groups, which could in turn lead to health disparities. For example, underserved populations are more likely to experience challenges in accessing online resources and understanding health information.[100]

If smartphones or other smart device ownership are required for trials, there could be issues in equity as those who are unable to purchase such a device would effectively be barred from trial participation. Smartphones and wearables tend to be expensive; the average US cost of a new smartphone was $363 in 2018. Furthermore, differential ownership and understanding of smart devices by age is a concern.[99,101] Some surveys indicate that only half of those aged ≥65 years own a smartphone, which is particularly important considering the burden of CVD in this age group. Although the prevalence of smart device ownership in all age groups has steadily increased over time, trial designs that utilize these devices will need to ensure equitable representation across age groups. Still, the majority of Americans (81%) own a smartphone, with little difference in ownership between sex and racial groups.[11] Although almost all smartphones allow for patients to input data into apps, only more advanced smartphones include step counters or heart rate and rhythm monitors and can cost around $1000.[102] In addition, new technologies other than smartphones may be needed to maximize potential of using personal devices in cardiovascular clinical trials. The direct provision of devices to trial participants may be necessary in some cases to ensure equitable participation of underserved populations.

ENSURING CLINICAL TRIALS MEET THE EVIDENCE NEEDS OF REGULATORS AND PAYERS

This section focuses on distinct opportunities for how regulators and payers must work together to meet each others' evidence needs and move trial innovation conversations and process upstream.

Partnering With Regulators on New Trial Designs and Protocols

As the cost of trials pushes industry to revolutionize trial design and innovate on study protocols, regulators can partner with professional societies like the AHA to foster innovation in trial design. Regulators' flexibility, commitment to innovation, and willingness to support and accept novel trial designs will determine the extent to which industry can innovate on existing trial protocols.

The FDA encourages industry to interact with FDA early in the process (especially related to patient experience data collection[103]). Furthermore, both the FDA's Center for Drug Evaluation and Research and CDRH have recently released draft guidance or recommendations on how to interact with FDA about complex, innovative trial design, and early feedback on new drug or device submissions.[104,105] For device approvals, CDRH aims to engage device developers, especially small businesses or start-ups, and provide early regulatory assistance through informational meetings and The Q-Submission Program,[105,106] a presubmission program that allows developers to receive formal feedback on specific questions related to product development and the application process.[105] CDRH has also partnered with the National Heart, Lung, and Blood Institute to provide grants to device developers to receive additional regulatory support in the early stages of device development. Additional support can also be found in the FDA Innovation Challenge, which supports development of devices addressing urgent public health issues (eg, opioid use disorder).[107] It is unclear what cardiovascular focused device developers have leveraged these programs, but they represent promising pathways for encouraging greater innovation in device trials. These documents and efforts are helpful in laying out the ways for industry to approach the FDA about appropriate end points and new trial designs, and the guidance should be expanded.

These avenues are limited to new or potentially new applications, however, and industry and researchers are interested in broader, earlier, and more consistent feedback. Additionally, we understand that it will take more than guidance, recommendation, and a new forum to change current practice and encourage new interactions between FDA, payers, and industry. We recommend a systematic, standardized approach to facilitate clear communication between the regulatory and industry arms of cardiovascular Research and Development and trial innovation, independent of an individual case application. One approach could be a regular (1–2× a year) convening for industry, researchers, payers, and other stakeholders in the therapy pipeline ecosystem to meet with FDA and other regulators affecting cardiovascular research or implementation (eg, NIH, Centers for Medicare & Medicaid Services) about bar-

riers to innovation and ideas they are considering for innovative design. To avoid federal advisory committee limitations, the AHA could convene the meetings.

Partnering With Payers to Ensure Appropriate Evidence Is Collected

Traditionally, clinical trials are designed, and their end points selected, to provide detailed information related to safety and efficacy of a product for regulatory decisions and market entry. However, the ultimate use of a medical product will depend on whether it is covered by various public and private payers, and clinical trials often are not designed to provide evidence for coverage decisions. CDRH established a Payor Communication Task Force to help those interested in a new medical device submission get feedback on trial design.[108] This could be a useful vehicle on the drug side, and Center for Drug Evaluation and Research should investigate creating a similar structure.

EXPANDING THE RESEARCH COMMUNITY

This section focuses on creative opportunities for institutionalizing recognition for excellence in cardiac research and patient recruitment and retention.

Creating Cardiac Research Collaboratives of Excellence to Highlight Top Tier Investigators and Research Sites

To help identify and capitalize on best practices around recruitment and participation of diverse groups of trial participants, a designation program recognizing partnerships with a demonstrated track record of successful cardiovascular trials with a special title (eg, Cardiovascular Research Collaboratives of Excellence) would be a significant step. There are relevant examples to build from to accomplish this. First, the Heart Failure Society of America developed a collaborative research network to direct patients and providers to high-value clinical research opportunities.[109,110] In addition to their focus on patient education and engagement, the Heart Failure Society of America research network compiles a list of trials that are particularly patient-centered.[109,110] Second, the field of oncology's National Cancer Institute–Designated Cancer Centers offer a model of NIH engagement for recognizing clinical trial success in a specialty field.[111] The AHA could benefit from the structures, lessons learned, and successes from these initiatives. The AHA, potentially in collaboration with National Heart, Lung, and Blood Institute, could expand upon the National Cancer Institute professional distinction program and Heart Failure Society of America's compilation of high-value research opportunities to identify and highlight key investigators and sites in Cardiovascular Collaborative for Research Excellence (CVCREs) that are performing excellent cardiovascular clinical research.

Through such a designation program, information on best practices would be collected and spread to other facilities with the goal of expanding the network of facilities and institutions that are able to successfully recruit and retain trial participants from underrepresented groups. The CVCREs would send AHA data on recruitment and retention strategies and outcomes. In return, health systems and hospitals recognized in this program would gain access to a learning network of other successful regional collaboratives to disseminate and learn from successes, including knowledge of what strategies were successful.

Establish a Community Cardiovascular Research Program to Reach a Broader Network of Researchers and Patients

Though designating CVCREs may stimulate research and disseminate best practices across the research community, they may be concentrated within academic health centers and systems, missing patients who do not receive care at such centers and possibly exacerbating underrepresentation of minority groups. In light of this, we recommend AHA establish a Community Cardiovascular Research Program, modeled after the National Cancer Institute's Community Oncology Research Program, which brings clinical trials and research to patients in their communities.[112] The Community Cardiovascular Research Program network should include a diverse selection of community sites and research bases; the National Cancer Institute's Community Oncology Research Program network, for example, is comprised of 7 research bases and 46 community sites, 14 of which are designated as minority or underserved sites.[112]

Although provider-based research networks are believed to increase diversity and clinical trial participation by making clinical trials available in the community, provider incentives to participation are also critical.[113,114] Providers who have participated in the National Cancer Institute's Community Oncology Research Program have cited altruistic feelings of obligation to patients and desire to enhance accessibility of clinical research, a desire to enhance their reputation, and a need to better integrate and coordinate the complex oncology care of patients.[113] The Community Cardiovascular Research Program may learn from the National Cancer Institute's Community Oncology Research Program's experiences and work with provider groups in rural, urban, and suburban communities to encourage equitable and diverse provider and patient participation in research.

ENVISIONING A FUTURE CARDIOVASCULAR RESEARCH EXPERIENCE

Although many clinical trials are not yet incorporating strategies needed to improve the research and trial process, there are examples of progress. The ADAPTABLE [115] (Aspirin Dosing: A Patient-Centric Trial Assessing Benefits and Long-Term Effectiveness) and PREVENTABLE[116] (Pragmatic Evaluation of Events and Benefits of Lipid-Lowering in Older Adults) clinical trials are taking a pragmatic approach to patient-centered research. Both trials aim to enroll a large and diverse patient population and conduct the trial in the patient's usual care setting. In the ADAPTABLE trial, patients were involved in study design from the outset, collaborating with researchers to create the study protocol, consent form, and other materials. Notably, the PREVENTABLE trial is the first clinical trial evaluating statins with a noncardiovascular primary outcome. The study is instead focusing on the ability of statins to prevent dementia or physical disability, which are particularly patient-centered outcomes. Although it is too early to evaluate results of these trials (both are still ongoing), they represent a promising step forward in making cardiovascular clinical trials more patient-centered.

One focus of this work was an intentional exercise to envision an ideal hypothetical, future cardiovascular research experience from multiple perspectives (patient, clinician, industry, regulators). Based on the above recommendations, we sought to capture that potential future vision in narrative form in the text below. Tables 1 and 2 then summarize this paper's recommendations in the short and long term that could encourage better progress toward the vision.

Narrative Vision of a Future Cardiovascular Research Experience

Patient Brenda is involved with and supported by a local network of women with CVD and hears of an upcoming trial with open enrollment. She is eager to learn more and easily accesses information about the trial on a centralized, reputable website. She is immediately put in touch with a contact person who can better describe the trial and its purpose. She speaks with her cardiologist and the trial's clinical investigators to get a better sense of risks and benefits to herself and her loved ones and possible outcomes of participating in the trial. After completing a simple video-enabled consent process that includes a diverse group of participants, reflecting her own experiences as well as different perspectives, she enrolls in the trial.

Throughout the duration of the trial, she has a point of contact where she can ask questions and voice any concerns. Participation is convenient; data collection occurs mostly on her smartphone via a secure trial application, so she is able to participate from virtually anywhere and only very infrequently needs to schedule physical appointments, arrange transportation, take time off of work, or arrange childcare. Brenda receives frequent updates on emerging trial results as well as individualized reports of her data. Many of the trial's end points are of interest to Brenda, reflecting her quality of life with end points like 6-minute walking distance. She feels understood and validated when uploading data specifically related to those preferred end points and quality of life outcomes. Her social support is enhanced by the trial participant community, where she can message and share experiences with other trial participants beyond her typical support network.

Upon conclusion of the trial, Brenda is debriefed in an understandable way on the use of her data and the next steps of the research project beyond her participation, including on the therapy's progress in the evaluation process. If approved for marketing by the regulatory authority, she may receive expedited access to the treatment that her data helped advance, if clinically appropriate. Given her convenient and empowering experience with this clinical trial, she volunteers to be on a mailing list through which she can be notified of future research.

Brenda's home base for her participation in the trial is her local community health clinic, which belongs to a regional collaborative of clinics, hospital systems, and community-based organizations, including faith-based organizations and local senior or community centers. This collaborative is committed to working together to facilitate and support patient recruitment and participation in cardiovascular clinical trials. The collaborative recently received a renewal of its status as an AHA–National Heart, Lung, and Blood Institute–recognized CVCRE. This designation signals to the health care system, patient, and clinical trial communities that a regional group of stakeholders and organizations are committed to working together to actively engage in activities to achieve high quality and clinically impactful cardiovascular trials, and ensure their patients have rapid access to cutting edge diagnostics and therapeutics.

The CVCRE is required to share data with AHA on their recruitment efforts and effectiveness, including data on the number of potential patients within the collaborative, patient recruitment and retention rates, time to start up recruitment, and Institutional Review Board decision times. In return, the CVCRE participates in the CVCRE Learning Group where the CVCRE has access to other CVCREs' data and experiences. Through this, the CVCRE learns about new, innovative recruitment and retention strategies that worked in other regional collaboratives, such as communication tools that effectively communicate trial benefits and risks to potential participants, video-enabled consent pro-

cesses, web-based patient portals that provide patients with personalized trial-related information, and transportation services that can help trial participants travel to trial sites. The CVCRE has leveraged these resources to improve their trial participation numbers and lower their costs to conduct cardiovascular trials.

The cardiovascular drug and the FDA-approved trial to evaluate it was developed by Pharmaceutical Development Company (PDC). Two recent developments on the regulatory and industry side led PDC to invest in research resulting in this trial. First, since the FDA's Center for Drug Evaluation and Research released guidance indicating a range of new, innovative, and efficient trial design flexibility in the hypothetical future year of 20XX, PDC corporate leaders changed their minds about investing in Research and Development for this new cardiovascular drug. Previously, they were concerned that traditional trial designs would be so long, complicated, inefficient, and inconvenient for patients that developing this particular drug would take a decade, be very expensive, and would have a higher probability of failure; thus, they deemed it to be too risky. However, one of the trial designs mentioned in the 20XX guidance made sense for evaluating this drug and PDC greenlit the project. They worked with payers to help ensure that the outcomes of the trial, beyond being patient-centered, demonstrated care improvements that increased the payers' likelihood of rapidly adopting the new therapy. Second, the AHA, collaborating with FDA, began convening regular cardiovascular trial effectiveness, efficiency, and innovation forums twice a year. These meetings are attended by the eco-system of stakeholders—not just industry, but health systems, researchers, government (beyond FDA, also including relevant NIH, Centers for Disease Control and Prevention, and CMS representatives), patients, and others. At these meetings, PDC was able to discuss in general terms the new method they were considering and received feedback from other researchers and regulators at the meeting that allowed them to tweak their design. This increased their confidence in submitting an application to FDA, which they did.

After the application was accepted, they worked with Brenda's local CVCRE to conduct the trial, a process that resulted in an effectively and efficiently run trial. They were eventually able to get the new drug to market at a cheaper price than previous comparable cardiovascular therapies they had developed, and because the payers had been involved in the process, approval for the new therapy was more likely and more timely—ultimately benefiting Brenda.

CONCLUSIONS AND NEXT STEPS

CVD continues to be the leading cause of death and disability and remains highly costly, complicated, and burdensome. Despite this, drug innovation is lagging and US enrollment in drug and device trials is limited. New strategies are needed to streamline and reduce the costs of clinical trials, all the while placing greater emphasis on the patient voice and experience. New technologies offer a promising path forward and can help improve upon current patient participation, generate high-quality evidence in real-world settings, and ensure evidence meets the needs of all stakeholders. Industry and regulators must also commit to partnering in upstream discussions of trial innovation. We offer short- and long-terms recommendations related to all of these areas. Adopting these recommendations would help achieve the hypothetical narrative vision, potentially lowering the costs for evidence generation of new cardiovascular therapies downstream, especially when paired with continued policy research on better ways to pay for and equitably develop drugs and devices. Ultimately, these strategies could improve the cardiovascular pipeline while making cardiovascular therapies more effective, meaningful, and equitable to patients.

ARTICLE INFORMATION

*A list of all American Heart Association Partnering with Regulators Learning Collaborative is given in the Data Supplement

The Data Supplement is available at https://www.ahajournals.org/doi/suppl/10.1161/CIRCOUTCOMES.120.006606.

Correspondence

William K. Bleser, PhD, MSPH, Payment Reform and Population Health, Robert J. Margolis, MD, Center for Health Policy, Duke University, Washington, DC. Email william.bleser@duke.edu

Affiliations

University of Texas Southwestern Medical Center, Dallas (J.J.W.). Robert J. Margolis, MD, Center for Health Policy, Duke University, Washington, DC and Durham, NC (H.L.C., K.M.W., W.K.B., R.A.R., M.H.L., R.S.S., M.B.M.). Duke University School of Medicine, Duke University, Durham, NC (T.Y.W., A.F.H.). Verily Life Sciences, South San Francisco, CA (R.M.C.). Google Life Sciences, Palo Alto, CA (R.M.C.). American Heart Association, Dallas, TX (N.B.).

Acknowledgments

We formally recognize Adam Kroetsch, Madeleine Konig, Mathew Alexander, and Nirosha Mahendraratnam Lederer for their important contributions to this work.

Sources of Funding

The American Heart Association Partnering with Regulators Learning Collaborative is part of the broader Value in Healthcare Initiative, a collaboration of the American Heart Association and the Robert J. Margolis, MD, Center for Health Policy at Duke University. The broader Value in Healthcare Initiative is supported in part by the American Heart Association and industry partners (Amgen, Bristol-Myers Squibb, the Bristol-Myers Squibb-Pfizer Alliance, and the Sanofi-Regeneron Alliance). American Heart Association volunteers (clinicians, patient representatives, and other experts) received reimbursement for travel to project meetings, but no other compensation was provided to Learning Collaborative members. The views of this article do not necessarily represent the views of the Learning Collaborative members or the organizations that they represent. Learning Collaborative members provided feedback on the content of this article, but the content of the article was independently determined by the Duke-Margolis Center, which is part of Duke University, and as such honors the tradition of academic independence on the part of its faculty and scholars. Neither Duke nor the Margolis Center takes partisan positions, but the individual members are free to speak their minds and express their opinions

regarding important issues. The Duke-Margolis Center received funding from the American Heart Association for this work.

Disclosures

Dr Bleser has previously received consulting fees from Merck on vaccine litigation unrelated to this work and serves as Board Vice President (uncompensated) for Shepherd's Clinic, a clinic providing free healthcare to the uninsured in Baltimore, MD. Dr Saunders has a Consulting Agreement with Yale–New Haven Health System for development of measures and development of quality measurement strategies for Center for Medicare & Medicaid Innovation Alternative Payment Models under Centers for Medicare & Medicaid Services Contract Number 75FCMC18D0042/Task Order Number 75FCMC19F0003, Quality Measure Development, and Analytic Support, Base Period. Dr Wang reports receiving research grants to the Duke Clinical Research Institute from AstraZeneca, Bristol-Myers Squibb, Cryolife, Chiesi, Merck, Portola, and Regeneron and receiving honoraria from AstraZeneca, Cryolife, and Sanofi. Dr Hernandez reports receiving research funding from American Regent, AstraZeneca, Merck, Novartis, and Verily and receiving consulting fees from Amgen, AstraZeneca, Bayer, Boston Scientific, Merck, Novartis, and Relypsa. Dr McClellan is an independent board member on the boards of Johnson & Johnson, Cigna, Alignment Healthcare, and Seer; co-chairs the Accountable Care Learning Collaborative and the Guiding Committee for the Health Care Payment Learning and Action Network; and receives fees for serving as an advisor for Cota and MITRE. Dr Califf is an employee of Verily Life Sciences and Google Life Sciences and is a board member of Cytokinetics. The other authors report no conflicts.

REFERENCES

1. Centers for Disease Control and Prevention. Heart Disease Facts & Statistics. 2018. Available at: https://www.cdc.gov/heartdisease/facts.htm. Accessed November 14, 2019.
2. Fryar CD, Chen T-C, Li X. Prevalence of uncontrolled risk factors for cardiovascular disease: United States, 1999-2010. *NCHS Data Brief*. 2012;1–8.
3. AJMC Participating Faculty. Unmet Needs in Cardiovascular Risk Reduction [Internet]. Cranbury, NJ: AJMC; 2017. [Cited 2020 February 17]. Available at: https://ajmc.s3.amazonaws.com/_media/_pdf/A709_03_2017_CV_Whitepaper.pdf.
4. Heart Disease Facts & Statistics cdc.gov. 2019. Available at: https://healthmetrics.heart.org/wp-content/uploads/2019/02/At-A-Glance-Heart-Disease-and-Stroke-Statistics-%E2%80%93-2019.pdf. Accessed June 21, 2019.
5. Avinainder S, Jiang Nona M, Michael B, Ron B, Khurram N. Abstract 135: Urban-Rural Differences in Coronary Heart Disease Mortality in the United States in 2010-2015. *Circ Cardiovasc Qual Outcomes*. 2020;12:A135. doi: 10.1161/hcq.12.suppl_1.135
6. Kubota Y, Heiss G, MacLehose RF, Roetker NS, Folsom AR. Association of educational attainment with lifetime risk of cardiovascular disease: the Atherosclerosis Risk in Communities Study. *JAMA Intern Med*. 2017;177:1165–1172. doi: 10.1001/jamainternmed.2017.1877
7. Curtis AB, Karki R, Hattoum A, Sharma UC. Arrhythmias in patients ≥80 years of age: pathophysiology, management, and outcomes. *J Am Coll Cardiol*. 2018;71:2041–2057. doi: 10.1016/j.jacc.2018.03.019
8. Dhingra R, Vasan RS. Age as a risk factor. *Med Clin North Am*. 2012;96:87–91. doi: 10.1016/j.mcna.2011.11.003
9. Harrington RA, Califf RM, Balamurugan A, Brown N, Benjamin RM, Braund WE, Hipp J, Konig M, Sanchez E, Joynt Maddox KE. Call to action: rural health: a presidential advisory from the American Heart Association and American Stroke Association. *Circulation*. 2020;141:e615–e644. doi: 10.1161/CIR.0000000000000753
10. McClellan M, Brown N, Califf RM, Warner JJ. Call to action: urgent challenges in cardiovascular disease: a presidential advisory from the American Heart Association. *Circulation*. 2019;139:e44–e54. doi: 10.1161/CIR.0000000000000652
11. Demographics of Mobile Device Ownership and Adoption in the United States. Pew Research Center; 2019. Available at: https://www.pewresearch.org/internet/fact-sheet/mobile/. Accessed November 5, 2019.
12. International Federation of Pharmaceutical Manufacturers & Associations. The Pharmaceutical Industry and Global Health. 2017. Available at: https://www.ifpma.org/wp-content/uploads/2017/02/IFPMA-Facts-And-Figures-2017.pdf. Accessed November 26, 2019.
13. IQVIA Institute for Human Data Science. Medicine Use and Spending in the US: A Review of 2017 and Outlook to 2022. Available at: https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/medicine-use-and-spending-in-the-us-a-review-of-2017-and-outlook-to-2022.pdf. Accessed October 31, 2018.
14. IQVIA. Lifetime Trends in Biopharmaceutical Innovation. 2017. Available at: https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/lifetime-trends-in-biopharmaceutical-innovation.pdf?_=1535640647050. Accessed September 17, 2018.
15. Moore TJ, Zhang H, Anderson G, Alexander GC. Estimated costs of pivotal trials for novel therapeutic agents approved by the US Food and Drug Administration, 2015-2016. *JAMA Intern Med*. 2018;178:1451–1457. doi: 10.1001/jamainternmed.2018.3931
16. Wong CH, Siah KW, Lo AW. Estimation of clinical trial success rates and related parameters. *Biostatistics*. 2019;20:273–286. doi: 10.1093/biostatistics/kxx069
17. Prashant A. Global challenges in cardiovascular drug discovery and clinical trials. *Mol Biol Open Access*. 2017;6:1–4. doi: 10.4172/2168-9547.1000193
18. Pocock SJ, Clayton TC, Stone GW. Challenging issues in clinical trial design: part 4 of a 4-part series on statistics for clinical trials. *J Am Coll Cardiol*. 2015;66:2886–2898. doi: 10.1016/j.jacc.2015.10.051
19. Weintraub WS, Lüscher TF, Pocock S. The perils of surrogate endpoints. *Eur Heart J*. 2015;36:2212–2218. doi: 10.1093/eurheartj/ehv164
20. Sepehrvand N, Alemayehu W, Das D, Gupta AK, Gouda P, Ghimire A, Du AX, Hatami S, Babadagli HE, Verma S, Kashour Z, Ezekowitz JA. Trends in the explanatory or pragmatic nature of cardiovascular clinical trials over 2 decades. *JAMA Cardiol*. 2019;4:1122–1128. doi: 10.1001/jamacardio.2019.3604
21. BCC Research. Cardiovascular Devices: Global Markets to 2022: Report Highlights. 2018. Available at: https://secure.livechatinc.com/. Accessed February 6, 2020.
22. Food and Drug Administration. Premarket Approval (PMA) Database. 2020. Available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm. Accessed February 6, 2020.
23. Grand View Research. Cardiovascular Devices Market To Reach $121 Billion By 2024. 2016. Available at: https://www.grandviewresearch.com/press-release/global-cardiovascular-devices-market. Accessed February 6, 2020.
24. Market Reports World. Global United States European Union And China Cardiovascular Device Market – Market Reports World. 2019. Available at: https://www.marketreportsworld.com/global-united-states-european-union-and-china-cardiovascular-device-market-13791842. Accessed February 6, 2020.
25. Grand View Research. Portable Medical Devices Market Size, Share & Trends Analysis Report By Product (Diagnostic, Monitoring, Therapeutics, Smart Wearable Devices), By Application, By Region, And Segment Forecast, 2018 - 2025. 2018. Available at: https://www.grandviewresearch.com/industry-analysis/portable-medical-devices-market. Accessed February 6, 2020.
26. Chen W, Yu J, Zhang L, Su G, Wang W, Kwong J, Sun X, Li Y. Quality of reporting in randomized controlled trials of therapeutic cardiovascular medical devices. *Surgery*. 2019;165:965–969. doi: 10.1016/j.surg.2018.09.010
27. Rajan PV, Holtzman JN, Kesselheim AS, Yeh RW, Kramer DB. Landscape of cardiovascular device registries in the United States. *J Am Heart Assoc*. 2019;8:e012756. doi: 10.1161/JAHA.119.012756
28. Martin SS, Ou FS, Newby LK, Sutton V, Adams P, Felker GM, Wang TY. Patient- and trial-specific barriers to participation in cardiovascular randomized clinical trials. *J Am Coll Cardiol*. 2013;61:762–769. doi: 10.1016/j.jacc.2012.10.046
29. Udell JA, Wang TY, Li S, Kohli P, Roe MT, de Lemos JA, Wiviott SD. Clinical trial participation after myocardial infarction in a national cardiovascular data registry. *JAMA*. 2014;312:841–843. doi: 10.1001/jama.2014.6217
30. Fanaroff AC, Vora AN, Chen AY, Mathews R, Udell JA, Roe MT, Thomas LE, Wang TY. Hospital participation in clinical trials for patients with acute myocardial infarction: results from the National Cardiovascular Data Registry. *Am Heart J*. 2019;214:184–193. doi: 10.1016/j.ahj.2019.05.011
31. Cherubini A, Oristrell J, Pla X, Ruggiero C, Ferretti R, Diestre G, Clarfield AM, Crome P, Hertogh C, Lesauskaite V, Prada GI, Szczerbinska K, Topinkova E, Sinclair-Cohen J, Edbrooke D, Mills GH. The persistent exclusion of older patients from ongoing clinical trials regarding heart failure. *Arch Intern Med*. 2011;171:550–556. doi: 10.1001/archinternmed.2011.31
32. Kim SH, Tanner A, Friedman DB, Foster C, Bergeron CD. Barriers to clinical trial participation: a comparison of rural and urban communities in South Carolina. *J Community Health*. 2014;39:562–571. doi: 10.1007/s10900-013-9798-2

33. Fogel DB. Factors associated with clinical trials that fail and opportunities for improving the likelihood of success: a review. *Contemp Clin Trials Commun.* 2018;11:156–164. doi: 10.1016/j.conctc.2018.08.001
34. van den Bor RM, Grobbee DE, Oosterman BJ, Vaessen PWJ, Roes KCB. Predicting enrollment performance of investigational centers in phase III multi-center clinical trials. *Contemp Clin Trials Commun.* 2017;7:208–216. doi: 10.1016/j.conctc.2017.07.004
35. Lincoff AM, Tardif JC, Schwartz GG, Nicholls SJ, Rydén L, Neal B, Malmberg K, Wedel H, Buse JB, Henry RR, Weichert A, Cannata R, Svensson A, Volz D, Grobbee DE; AleCardio Investigators. Effect of aleglitazar on cardiovascular outcomes after acute coronary syndrome in patients with type 2 diabetes mellitus: the AleCardio randomized clinical trial. *JAMA.* 2014;311:1515–1525. doi: 10.1001/jama.2014.3321
36. Califf RM, Harrington RA. American industry and the U.S. Cardiovascular Clinical Research Enterprise an appropriate analogy? *J Am Coll Cardiol.* 2011;58:677–680. doi: 10.1016/j.jacc.2011.03.048
37. Heo S, Lennie TA, Okoli C, Moser DK. Quality of life in patients with heart failure: ask the patients. *Heart Lung.* 2009;38:100–108. doi: 10.1016/j.hrtlng.2008.04.002
38. Geissler J, Ryll B, di Priolo SL, Uhlenhopp M. Improving patient involvement in medicines research and development:: a practical roadmap. *Ther Innov Regul Sci.* 2017;51:612–619. doi: 10.1177/2168479017706405
39. Kim ES, Menon V. Status of women in cardiovascular clinical trials. *Arterioscler Thromb Vasc Biol.* 2009;29:279–283. doi: 10.1161/ATVBAHA.108.179796
40. Scott PE, Unger EF, Jenkins MR, Southworth MR, McDowell TY, Geller RJ, Elahi M, Temple RJ, Woodcock J. Participation of women in clinical trials supporting FDA approval of cardiovascular drugs. *J Am Coll Cardiol.* 2018;71:1960–1969. doi: 10.1016/j.jacc.2018.02.070
41. Mazure CM, Jones DP. Twenty years and still counting: including women as participants and studying sex and gender in biomedical research. *BMC Womens Health.* 2015;15:94. doi: 10.1186/s12905-015-0251-9
42. Ramasubbu K, Gurm H, Litaker D. Gender bias in clinical trials: do double standards still apply? *J Womens Health Gend Based Med.* 2001;10:757–764. doi: 10.1089/15246090152636514
43. National Institutes of Health. Review of the Literature: Primary Barriers and Facilitators to Participation in Clinical Research. Bethesda, MD: National Institutes of Health: Office of Research on Women's Health. Available at: https://orwh.od.nih.gov/sites/orwh/files/docs/orwh_outreach_toolkit_litreview.pdf. Accessed November 26, 2019.
44. American College of Cardiology. Increasing Diversity in Clinical Trials. 2017. Available at: https://www.cardiosmart.org/Heart-Conditions/The-Research/Clinical-Trial-Diversity. Accessed November 26, 2019.
45. Yoon DY, Mansukhani NA, Stubbs VC, Helenowski IB, Woodruff TK, Kibbe MR. Sex bias exists in basic science and translational surgical research. *Surgery.* 2014;156:508–516. doi: 10.1016/j.surg.2014.07.001
46. Food and Drug Administration. 2018 Drug Trials Snapshots and Summary Report. 2019. Available at: https://www.fda.gov/media/120253/download. Accessed February 6, 2020.
47. Gong IY, Tan NS, Ali SH, Lebovic G, Mamdani M, Goodman SG, Ko DT, Laupacis A, Yan AT. Temporal trends of women enrollment in major cardiovascular randomized clinical trials. *Can J Cardiol.* 2019;35:653–660. doi: 10.1016/j.cjca.2019.01.010
48. Whyte J, Woodcock J, Wang J. Review of the drug trials snapshots program of the US Food and Drug Administration: women in cardiovascular drug trials. *JAMA Intern Med.* 2017;177:724–727. doi: 10.1001/jamainternmed.2017.0033
49. Food and Drug Administration. 2015-2016 Drug Trials Snapshots and Summary Report. 2017. Available at: https://www.fda.gov/media/103160/download. Accessed February 6, 2020.
50. Zheng SY, Dhruva SS, Redberg RF. Characteristics of clinical studies used for US Food and Drug Administration approval of high-risk medical device supplements. *JAMA.* 2017;318:619–625. doi: 10.1001/jama.2017.9414
51. Food and Drug Administration. Collection, Analysis, and Availability of Demographic Subgroup Data for FDA-Approved Medical Products. 2013. Available at: https://www.fda.gov/media/86561/download. Accessed February 6, 2020.
52. Karimi T. Project Baseline and the American Heart Association's Go Red For Women movement collaborate to include more women in research. Verily Blog; 2019. Available at: https://blog.verily.com/2019/02/project-baseline-and-american-heart.html. Accessed September 9, 2019.
53. American Heart Association, Verily Life Sciences. Go Red. 2019. Available at: https://www.projectbaseline.com/gored/. Accessed September 9, 2020.
54. Hamel LM, Penner LA, Albrecht TL, Heath E, Gwede CK, Eggly S. Barriers to clinical trial enrollment in racial and ethnic minority patients with cancer. *Cancer Control.* 2016;23:327–337. doi: 10.1177/107327481602300404
55. Coakley M, Fadiran EO, Parrish LJ, Griffith RA, Weiss E, Carter C. Dialogues on diversifying clinical trials: successful strategies for engaging women and minorities in clinical trials. *J Womens Health (Larchmt).* 2012;21:713–716. doi: 10.1089/jwh.2012.3733
56. Bransford T. Charting the Course for Better Cardiovascular Health in African-American Communities. Worldwide Clinical Trials; 2018. Available at: https://www.worldwide.com/blog/2018/02/equity-cardiovascular-health-charting-course-better-cardiovascular-health-african-american-communities/. Accessed August 13, 2019.
57. Food and Drug Administration. 2017 Drug Trials Snapshots and Summary Report. 2018. Available at: https://www.fda.gov/media/112373/download. Accessed February 6, 2020.
58. Victor RG, Lynch K, Li N, Blyler C, Muhammad E, Handler J, Brettler J, Rashid M, Hsu B, Foxx-Drew D, Moy N, Reid AE, Elashoff RM. A cluster-randomized trial of blood-pressure reduction in black barbershops. *N Engl J Med.* 2018;378:1291–1301. doi: 10.1056/NEJMoa1717250
59. Zupancic B. Patient Engagement in Clinical Trials: Motivation and Influence, Pt. 2. Worldwide Clinical Trials. 2018. Available at: https://www.worldwide.com/blog/2018/03/comes-patient-engagement-clinical-trials-think-motivation-influence-part-2/. Accessed August 13, 2019.
60. Burke CW. The Importance of Diversity in Clinical Trials (Because Right Now, It's Lacking). BioSpace. 2018. Available at: https://www.biospace.com/article/the-importance-of-diversity-in-clinical-trials-because-right-now-it-s-lacking-/. Accessed August 21, 2019.
61. Burgess LJ, Sulzer NU, Hoosain F, Leverton N, Bliganut S, Emanuel S. Patients' motivations for participating in cardiovascular clinical trials: a local perspective. *Cardiovasc J Afr.* 2009;20:220–223.
62. Zupancic B. Patient Engagement in Clinical Trials: Motivation and Influence, Pt. 1. Worldwide Clinical Trials. 2018. Available at: https://www.worldwide.com/blog/2018/03/patient-engagement-in-clinical-trials/. Accessed August 13, 2019.
63. Institute of Medicine (US) Forum on Drug Discovery, Development, and Translation. Challenges in Clinical Research. National Academies Press (US); 2010. Available at: https://www.ncbi.nlm.nih.gov/books/NBK50888/. Accessed November 6, 2019.
64. Luo H, Yang D, Barszczyk A, Vempala N, Wei J, Wu SJ, Zheng PP, Fu G, Lee K, Feng ZP. Smartphone-based blood pressure measurement using transdermal optical imaging technology. *Circ Cardiovasc Imaging.* 2019;12:e008857. doi: 10.1161/CIRCIMAGING.119.008857
65. Rae-Dupree J. Doctor Alexa Will See You Now: Is Amazon Primed To Come To Your Rescue? Kaiser Health News. 2019. Available at: https://khn.org/news/amazon-alexa-health-care-medical-diagnostic-skills-artificial-intelligence/. Accessed August 14, 2019.
66. Jones R, Lacroix LJ, Porcher E. Facebook advertising to recruit young, urban women into an HIV prevention clinical trial. *AIDS Behav.* 2017;21:3141–3153. doi: 10.1007/s10461-017-1797-3
67. Guo X, Vittinghoff E, Olgin JE, Marcus GM, Pletcher MJ. Volunteer participation in the Health Eheart Study: a comparison with the US population. *Sci Rep.* 2017;7:1956. doi: 10.1038/s41598-017-02232-y
68. Perez MV, Mahaffey KW, Hedlin H, Rumsfeld JS, Garcia A, Ferris T, Balasubramanian V, Russo AM, Rajmane A, Cheung L, Hung G, Lee J, Kowey P, Talati N, Nag D, Gummidipundi SE, Beatty A, Hills MT, Desai S, Granger CB, Desai M, Turakhia MP; Apple Heart Study Investigators. Large-scale assessment of a smartwatch to identify atrial fibrillation. *N Engl J Med.* 2019;381:1909–1917. doi: 10.1056/NEJMoa1901183
69. Artificial Intelligence Solution Improves Clinical Trial Recruitment. DAIC. 2019. Available at: https://www.dicardiology.com/content/artificial-intelligence-solution-improves-clinical-trial-recruitment. Accessed August 14, 2019.
70. Standley C. eClinical Technology Trends Reshape Future of Cardiovascular Outcome Trials. Worldwide Clinical Trials. 2018. Available at: https://www.worldwide.com/blog/2018/02/eclinical-technology-trends-reshape-future-of-cardiovascular-outcome-trials/. Accessed August 14, 2019.
71. TransCelerate Biopharma Inc. What do Clinical Trial Participants Want? Patient Preferences for Clinical Trial Information. 2017. Available at: https://transceleratebiopharmainc.com/wp-content/uploads/2017/11/What-do-Patients-Want-Visualization.pdf. Accessed November 5, 2019.

72. Smietana K, Siatkowski M, Møller M. Trends in clinical success rates. *Nat Rev Drug Discov.* 2016;15:379–380. doi: 10.1038/nrd.2016.85
73. Chalasani M, Vaidya P, Mullin T. Enhancing the incorporation of the patient's voice in drug development and evaluation. *Res Involv Engagem.* 2018;4:10. doi: 10.1186/s40900-018-0093-3
74. Chow RD, Wankhedkar KP, Mete M. Patients' preferences for selection of endpoints in cardiovascular clinical trials. *J Community Hosp Intern Med Perspect*. 2014;4:10.3402/jchimp.v4.22643. doi: 10.3402/jchimp.v4.22643
75. Vaanholt MCW, Kok MM, von Birgelen C, Weernink MGM, van Til JA. Are component endpoints equal? A preference study into the practice of composite endpoints in clinical trials. *Health Expect.* 2018;21:1046–1055. doi: 10.1111/hex.12798
76. Anker SD, Agewall S, Borggrefe M, Calvert M, Jaime Caro J, Cowie MR, Ford I, Paty JA, Riley JP, Swedberg K, Tavazzi L, Wiklund I, Kirchhof P. The importance of patient-reported outcomes: a call for their comprehensive integration in cardiovascular clinical trials. *Eur Heart J.* 2014;35:2001–2009. doi: 10.1093/eurheartj/ehu205
77. Butler J, Hamo CE, Udelson JE, Pitt B, Yancy C, Shah SJ, Desvigne-Nickens P, Bernstein HS, Clark RL, Depre C, Dinh W, Hamer A, Kay-Mugford P, Kramer F, Lefkowitz M, Lewis K, Maya J, Maybaum S, Patel MJ, Pollack PS, Roessig L, Rotman S, Salsali A, Sims JJ, Senni M, Rosano G, Dunnmon P, Stockbridge N, Anker SD, Zile MR, Gheorghiade M. Exploring new endpoints for patients with heart failure with preserved ejection fraction. *Circ Heart Fail.* 2016;9:e003358. doi: 10.1161/CIRCHEARTFAILURE.116.003358
78. Food and Drug Administration. CDER Patient-Focused Drug Development. 2018. Available at: http://www.fda.gov/drugs/development-approval-process-drugs/cder-patient-focused-drug-development. Accessed June 21, 2019.
79. Food and Drug Administration. Clinical Outcome Assessment Compendium. 2019. Available at: http://www.fda.gov/drugs/development-resources/clinical-outcome-assessment-compendium. Accessed August 15, 2019.
80. COMET Initiative. Overview: Core Outcome Measures in Effectiveness Trials Initiative (COMET). 2019. Available at: http://www.comet-initiative.org/about/overview. Accessed November 20, 2019.
81. Food and Drug Administration. FDA-ASCO Public Workshop: 2019 Clinical Outcome Assessments in Cancer Clinical Trials Fourth Annual Workshop. 2019. Available at: http://www.fda.gov/drugs/news-events-human-drugs/fda-asco-public-workshop-2019-clinical-outcome-assessments-cancer-clinical-trials-fourth-annual. Accessed November 20, 2019.
82. Izmailova ES, Wagner JA, Perakslis ED. Wearable devices in clinical trials: hype and hypothesis. *Clin Pharmacol Ther.* 2018;104:42–52. doi: 10.1002/cpt.966
83. Kleinsinger F. The unmet challenge of medication nonadherence. *Perm J.* 2018;22:18–033. doi: 10.7812/TPP/18-033
84. Gadkari AS, McHorney CA. Unintentional non-adherence to chronic prescription medications: how unintentional is it really? *BMC Health Serv Res.* 2012;12:98. doi: 10.1186/1472-6963-12-98
85. Food and Drug Administration. MedWatch: The FDA Safety Information and Adverse Event Reporting Program. 2019. Available at: http://www.fda.gov/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program. Accessed November 5, 2019.
86. Food and Drug Administration. Questions and Answers on FDA's Adverse Event Reporting System (FAERS). 2018. Available at: http://www.fda.gov/drugs/surveillance/questions-and-answers-fdas-adverse-event-reporting-system-faers. Accessed November 5, 2019.
87. Food and Drug Administration. Postmarket Requirements (Devices). 2018. Available at: http://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/postmarket-requirements-devices. Accessed November 5, 2019.
88. Food and Drug Administration. Framework for FDA's Real-World Evidence Program. 2018. Available at: https://www.fda.gov/media/120060/download. Accessed November 21, 2019.
89. Pevnick JM, Birkeland K, Zimmer R, Elad Y, Kedan I. Wearable technology for cardiology: An update and framework for the future. *Trends Cardiovasc Med.* 2018;28:144–150. doi: 10.1016/j.tcm.2017.08.003
90. Wright SP, Collier SR, Brown TS, Sandberg K. An analysis of how consumer physical activity monitors are used in biomedical research. *FASEB J.* 2017;31:1020.24–1020.24.
91. Abedin Z, Hoerner R, Kawamoto K, Habboushe J, Lu Y, Warner PB, Shields DE, Shah RU. Abstract 13: Evaluation of a FHIR-based clinical decision support tool for calculating CHA2DS2-VASc scores. *Cardiovasc Qual Outcomes*. 2019;12:A13. doi: 10.1161/hcq.12.suppl_1.13
92. Glimcher P. Bring-Your-Own-Device In Clinical Trials: Achieving High Quality Data At Lower Cost. Clinical Research News. 2019. Available at: http://www.clinicalinformaticsnews.com/2019/02/21/bring-your-own-device-in-clinical-trials-achieving-high-quality-data-at-lower-cost.aspx. Accessed November 5, 2019.
93. Gwaltney C, Coons SJ, O'Donohoe P, O'Gorman H, Denomey M, Howry C, Ross J. "Bring Your Own Device" (BYOD): the future of field-based patient-reported outcome data collection in clinical trials? *Ther Innov Regul Sci.* 2015;49:783–791. doi: 10.1177/2168479015609104
94. Pugliese L, Woodriff M, Crowley O, Lam V, Sohn J, Bradley S. Feasibility of the "Bring Your Own Device" model in clinical research: results from a randomized controlled pilot study of a mobile patient engagement tool. *Cureus.* 2016;8:e535. doi: 10.7759/cureus.535
95. Bring-Your-Own-Device: The Benefits, Risks and Practicalities of its Implementation in Clinical Trials. Clinical Trials Arena. Available at: https://www.clinicaltrialsarena.com/comment/bring-your-own-device-the-benefits-risks-and-practicalities-of-its-implementation-in-clinical-trials-6074078-2/. Accessed January 15, 2020.
96. McConnell MV, Shcherbina A, Pavlovic A, Homburger JR, Goldfeder RL, Waggot D, Cho MK, Rosenberger ME, Haskell WL, Myers J, Champagne MA, Mignot E, Landray M, Tarassenko L, Harrington RA, Yeung AC, Ashley EA. Feasibility of obtaining measures of lifestyle from a smartphone app: the MyHeart Counts Cardiovascular Health Study. *JAMA Cardiol.* 2017;2:67–76. doi: 10.1001/jamacardio.2016.4395
97. Brodie M, Flournoy RE, Altman DE, Blendon RJ, Benson JM, Rosenbaum MD. Health information, the Internet, and the digital divide. *Health Aff (Millwood).* 2000;19:255–265. doi: 10.1377/hlthaff.19.6.255
98. Pew Research Center. Internet/Broadband Fact Sheet. 2019. Available at: https://www.pewresearch.org/internet/fact-sheet/internet-broadband/. Accessed May 12, 2020.
99. Pew Research Center. Mobile Fact Sheet. 2019. Available at: https://www.pewresearch.org/internet/fact-sheet/mobile/. Accessed May 12, 2020.
100. Banerjee A. Digital health interventions and inequalities: the case for a new paradigm [published ahead of print November 21, 2019]. *BMJ Evid Based Med.* 2019. doi: 10.1136/bmjebm-2019-111282
101. Statista. Share of adults in the United States who owned a smartphone from 2015 to 2018, by age group. Statista. 2020. Available at: https://www.statista.com/statistics/489255/percentage-of-us-smartphone-owners-by-age-group/. Accessed May 12, 2020.
102. Molla R. Why people are buying more expensive smartphones than they have in years. Vox. 2018. Available at: https://www.vox.com/2018/1/23/16923832/global-smartphone-prices-grew-faster-iphone-quarter. Accessed November 5, 2019.
103. Food and Drug Administration. Patient-Focused Drug Development: Methods to Identify What Is Important to Patients: Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders: Draft Guidance. 2019. Available at: https://www.fda.gov/media/131230/download. Accessed November 18, 2019.
104. Food and Drug Administration. Interacting with the FDA on Complex Innovative Trial Designs for Drugs and Biological Products: Draft Guidance for Industry. 2019. Available at: https://www.fda.gov/media/130897/download. Accessed November 18, 2019.
105. Food and Drug Administration. Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program: Guidance for Industry and Food and Drug Administration Staff. 2019. Available at: https://www.fda.gov/media/114034/download. Accessed November 18, 2019.
106. Food and Drug Administration. Activities to Support Medical Device Innovators. 2019. Available at: http://www.fda.gov/about-fda/cdrh-innovation/activities-support-medical-device-innovators. Accessed February 6, 2020.
107. Food and Drug Administration. FDA Innovation Challenge: Devices to Prevent and Treat Opioid Use Disorder. 2019. Available at: http://www.fda.gov/about-fda/cdrh-innovation/fda-innovation-challenge-devices-prevent-and-treat-opioid-use-disorder. Accessed February 6, 2020.
108. Food and Drug Administration. Payor Communication Task Force. 2019. Available at: http://www.fda.gov/about-fda/cdrh-innovation/payor-communication-task-force. Accessed November 18, 2019.
109. Heart Failure Society of America. HFSA Research Network. 2020. Available at: https://www.hfsa.org/hfsa-research-network/. Accessed January 15, 2020.
110. Heart Failure Society of America. HFSA Research Network Overview Flyer. 2018. Available at: https://www.hfsa.org/wp-content/uploads/2018/10/2018-Research-Network-Overview-Flyer-5.21.2018-001.pdf. Accessed January 16, 2020.

111. National Cancer Institute. NCI-Designated Cancer Centers. 2019. Available at: https://www.cancer.gov/research/nci-role/cancer-centers. Accessed November 19, 2019.
112. National Cancer Institute, National Institutes of Health. The NCI Community Oncology Research Program (NCORP). Available at: https://ncorp.cancer.gov/. Accessed April 23, 2020.
113. McAlearney AS, Song PH, Reiter KL. Why providers participate in clinical trials: considering the National Cancer Institute's Community Clinical Oncology Program. *Contemp Clin Trials.* 2012;33:1143–1149. doi: 10.1016/j.cct.2012.08.008
114. Song PH, Reiter KL, Weiner BJ, Minasian L, McAlearney AS. The business case for provider participation in clinical trials research: an application to the National Cancer Institute's community clinical oncology program. *Health Care Manage Rev.* 2013;38:284–294. doi: 10.1097/HMR.0b013e31827292fc
115. ADAPTABLE. ADAPTABLE: The Aspirin Study. 2020. Available at: https://theaspirinstudy.org/. Accessed February 6, 2020.
116. Duke Clinical Research Institute. DCRI to Lead Pragmatic Study to Assess Effectiveness of Statins in Older Adults. 2019. Available at: https://dcri.org/preventable/. Accessed February 6, 2020.