Examining the Impact of Real-World Evidence on Medical Product Development

A Workshop Series

WORKSHOP ONE: INCENTIVES

September 19–20, 2017
Washington, DC

#RealWorldEvidence
#DrugForum

The National Academies of SCIENCES ENGINEERING MEDICINE

Forum on DRUG DISCOVERY, DEVELOPMENT, and TRANSLATION

Examining the Impact of Real-World Evidence on Medical Product Development: A Workshop Series

Workshop 1: Incentives

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The National Academies of | SCIENCES ENGINEERING MEDICINE

Forum on DRUG DISCOVERY, DEVELOPMENT, and TRANSLATION

Examining the Impact of Real-World Evidence on Medical Product Development: A Three-Part Workshop Series

Workshop One: Incentives

September 19–20, 2017

National Academy of Sciences Building, Lecture Room
2101 Constitution Ave. NW, Washington, DC 20418

The National Academies of Sciences, Engineering, and Medicine (National Academies) is convening a three-part workshop series examining how real-world evidence development and uptake can enhance medical product development and evaluation. The workshops will advance discussions and common knowledge about complex issues relating to the generation and utilization of real-world evidence, including fostering development and implementation of the science and technology of real-world evidence generation and utilization.

This first workshop will include discussions, and background materials, that address:

- **Aligning incentives and addressing barriers to support collection and use of real-world evidence in health product review, payment, and delivery.**

Workshops TWO and THREE will foster discussions that will

- Illuminate what types of data are appropriate for what specific purposes and suggest approaches for data collection that match the right data to the right questions. (Q1 2018)
- Examine and suggest approaches for operationalizing the collection and use of real-world evidence. (Q3 2018)

DAY 1: SEPTEMBER 19, 2017

8:00 a.m. Breakfast Available Outside the Lecture Room

8:20 a.m. **Welcome and Opening Remarks**

GREG SIMON, *Workshop Series Co-Chair*
Investigator
Kaiser Permanente Washington Health Research Institute

KEYNOTE ADDRESS

8:30 a.m. **Vision and Goals of a Collaborative, Practical, and Sustainable Real-World Evidence Program**

SCOTT GOTTLIEB
Commissioner
U.S. Food and Drug Administration

8:50 a.m. **Discussion with Audience**

Moderator: Mark McClellan, Duke-Margolis Center for Health Policy

SESSION I SEEING OUR DESTINATION

Session Objectives:

- Explore what relevant facts the ultimate end-users of evidence need to know in order to make informed decisions about using medical products.
- Discuss possible approaches to generating such fit-for-purpose evidence.

Moderator: Andy Bindman, University of California, San Francisco

9:00 a.m. **A Payer perspective**

MICHAEL SHERMAN
Senior VP and Chief Medical Officer
Harvard Pilgrim Health Care

9:20 a.m. **Delivery System perspective: Integrated Care Model at Kaiser Permanente**

MICHAEL HORBERG
Executive Director, Research, Community Benefit, and Medicaid Strategy
Executive Director, Mid-Atlantic Permanente Research Institute
Kaiser Permanente Mid-Atlantic Permanente Medical Group

9:40 a.m. **Delivery System perspective: Academic health system**

DANIEL FORD
Director, Institute for Clinical and Translational Research
Johns Hopkins School of Medicine

10:00 a.m. **A Patient-focused perspective**

SHARON TERRY
President and Chief Executive Officer
Genetic Alliance

10:20 a.m. **Discussion with Audience**

Additional invited discussants:

JOANNE WALDSTREICHER
Chief Medical Officer
Johnson&Johnson

ELEANOR PERFETTO
Senior Vice President, Strategic Initiatives
National Health Council

11:10 a.m. **BREAK**

11:30 a.m. **Key Messages and Themes from the September 13th FDA/Duke-Margolis Workshop: Generating Fit-for Purpose Evidence**

MARK MCCLELLAN , *Workshop Series Co-Chair*
Director
Duke-Margolis Center for Health Policy

11:50 a.m. **Discussion with Audience**

12:00 pm **BREAK** (Lunch available Outside the Lecture Room)

SESSION II LEARNING FROM SUCCESS

Session Objectives:

- Highlight successful completed and ongoing initiatives that could potentially be examined for real-world evidence collection and use.
- Explore the features that led to the success in the given examples and how they could apply to future applications:
    - Conditions likely to make innovation successful; and
    - Potential ways to recreate those conditions to make real-world evidence use more routine.

Moderator: Greg Simon, Kaiser Permanente Washington Health Research Institute

1:00 p.m. **Generalizing and Scaling the Salford Lung Studies**

MARTIN GIBSON
Chief Executive Officer
Northwest EHealth

MARIE KANE
Chief Operating Officer
Northwest EHealth

1:30 p.m. **Using Sentinel to Evaluate Effectiveness or Efficacy**

RICH PLATT
Professor and Chair, Dept. of Population Medicine
Harvard Medical School

1:50 p.m. **Applying Lessons learned from Device Registries to Other Treatment Types**

RACHAEL FLEURENCE
Executive Director
NEST Coordinating Center

2:10 p.m. **Discussion with Audience**

Additional invited discussants:

JOHN GRAHAM
Head, Value Evidence and Outcomes
GlaxoSmithKline

RACHEL SHERMAN
Principal Deputy Commissioner
U.S. Food and Drug Administration

3:00 p.m. **BREAK**

SESSION III GETTING UNSTUCK: ALIGNING INCENTIVES

Session Objectives:

In a series of presentations, discuss with treatment developers and evidence generators:

- Incentives maintaining the current data generation process; and
- Disincentives and potential barriers to incorporation of real-world evidence.

Moderator: Petra Kaufmann, National Center for Advancing Translational Sciences, NIH

3:20 p.m. **Contract Research Organization Perspective**

JOHN DOYLE
Senior Vice President and Managing Director
QuintilesIMS

3:40 p.m. **A Product Developer Perspective**

ELLIOTT LEVY
Senior Vice President, Global Devlopment
Amgen

BRIAN D. BRADBURY
Executive Director, Center for Observational Research
Amgen

4:00 p.m. **An Academic Researcher Perspective**

DANIEL FORD
Director, Institute for Clinical and Translational Research
Johns Hopkins School of Medicine

4:20 p.m. **Data Stewards: Organizations with Large Data Sources**

MARCUS WILSON
President
HealthCore, Inc.

4:40 p.m. **Discussion with Audience**

Additional invited discussants:

MICHAEL HORBERG
Executive Director, Research Community Benefit, and Medicaid Strategy
Executive Director, Mid-Atlantic Permanente Research Institute
Kaiser Permanente

ANNA MCCOLLISTER-SLIPP
Chief Advocate for Participatory Research, Scripps Translational Science Institute
Co-founder, Galileo Analytics

5:30 p.m. **ADJOURN WORKSHOP DAY 1**

DAY 2: SEPTEMBER 20, 2017

8:00 a.m. Breakfast Available Outside the Lecture Room

8:30 a.m. **Recap Day One and Discussion with Workshop Participants**

GREG SIMON, *Workshop Series Co-Chair*
Investigator
Kaiser Permanente Washington Health Research Institute

KEYNOTE ADDRESS

9:00 a.m. **False Precision and Estimating the Reliability of Effects with the Traditional Evidence Generating Process**

ROB CALIFF
Vice Chancellor, Health Data Science, Duke University
Verily Life Sciences

SESSION IV GETTING UNSTUCK: MYTH-BUSTING

Session Objective: Examine ideas—and misconceptions—about the necessity and acceptability of established evidence-generation practices.

Moderator: Rob Califf, Duke University and Verily Life Sciences

9:30 a.m. **Moving from "One Study at a Time" to "All by All" Analyses**

PATRICK RYAN
Senior Director and Head, Epidemiology Analytics
Janssen Research and Development

9:50 a.m. **A Medical Product Developer Perspective**

JOHN GRAHAM
Head, Value Evidence and Outcomes
GlaxoSmithKline

10:10 a.m. **BREAK**

10:30 a.m. **Evolve or Die: The Urgent Need to Streamline Randomized Trials**

RORY COLLINS
Head of Nuffield Dept of Population Health
University of Oxford

10:50 a.m. **A Regulatory Perspective**

JANET WOODCOCK
Director
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

11:10 a.m. **Discussion with Audience**

Additional invited discussant:

DEVEN MCGRAW
Deputy Director, Health Information Privacy
Office for Civil Rights
U.S. Department of Health and Human Services

12:30 p.m. **ADJOURN WORKSHOP DAY 2**

Future Workshop Objectives

WORKSHOP TWO. Illuminate what types of data are appropriate for what specific purposes and suggest approaches for data collection that match the right data to the right questions. *(Q1 2018)*

- Precise language and nomenclature for describing data, data collection activities, and data sources.
- Sources of data that are curated, standardized, and analyzed to derive real-world evidence, such as safety surveillance, observational studies, registries, claims, or patient-centered outcomes research.
- Gaps in data collection activities, and priority areas and pilot opportunities that real-world evidence incorporation could address.
- Standards and methodologies for collecting and analyzing real-world evidence in support of new indications or postapproval studies, and the circumstances under which that evidence could be applied.

WORKSHOP THREE. Examine and suggest approaches for operationalizing the collection and use of real-world evidence. *(Q3 2018)*

- Applications for using real-world evidence to supplement traditional clinical trials, pragmatic/effectiveness trials, or routine clinical application.
- Mechanisms for determining which discrete types of real-world evidence could support regulatory decisions.
- Operational challenges and barriers for generating and incorporating real-world evidence in the context of a learning health system and how clinicians can best be involved in the collection and utilization of real-world evidence.

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PLANNING COMMITTEE BIOGRAPHIES

CO-CHAIRS:

Mark McClellan, M.D., P.H.D., is the Robert J. Margolis Professor of Business, Medicine, and Policy, and Director of the Duke-Margolis Center for Health Policy at Duke University with offices at Duke and in Washington DC. Dr. McClellan is a doctor and an economist, and his work has addressed a wide range of strategies and policy reforms to improve health care, including payment reforms to promote better outcomes and lower costs, methods for development and use of real-world evidence, and approaches for more effective drug and device innovation. Dr. McClellan is a former administrator of the Centers for Medicare & Medicaid Services (CMS) and former commissioner of the U.S. Food and Drug Administration (FDA), where he developed and implemented major reforms in health policy. He was also a Senior Fellow at the Brookings Institution and a professor of economics and medicine at Stanford University.

GREGORY SIMON, M.D., M.P.H., is an investigator at Group Health Research Institute and a psychiatrist in Group Health's Behavioral Health Service. He is also a Research Professor in the Department of Psychiatry and Behavioral Sciences at the University of Washington and chair of the national scientific advisory board of the Depression and Bipolar Support Alliance. Dr. Simon completed residency training in internal medicine at the University of Washington, residency training in psychiatry at the Massachusetts General Hospital, and fellowship training in the Robert Wood Johnson Clinical Scholars program at the University of Washington. Dr. Simon's research focuses on improving access to and quality of care for mood disorders, both unipolar depression and bipolar disorder. Specific areas of research include improving adherence to medication, increasing the availability of effective psychotherapy, evaluating peer support by and for people with mood disorders, suicide prevention, cost-effectiveness of treatment, and comorbidity of mood disorders with chronic medical conditions. Dr. Simon currently leads the Mental Health Research Network, an NIMH-funded cooperative agreement supporting population-based mental health research across 13 large health systems.

PLANNING COMMITTEE:

JEFF ALLEN, P.H.D., is President and CEO of Friends of Cancer Research (Friends). Friends is an advocacy organization based in Washington, DC that drives collaboration among partners from every healthcare sector to power advances in science, policy, and regulation that speed life-saving treatments to patients. During the past 20 years, Friends has been instrumental in the creation and implementation of policies ensuring patients receive the best treatments in the fastest and safest way possible. For over 10 years, Jeff has been a driving force in the growth and success of the organization. Under his leadership, Friends has evolved into a nimble, forward-thinking policy, public affairs, and research organization. As President and CEO, he leads the strategic development and implementation of Friends' scientific, policy, research, and legislative initiatives, as well as overseeing Board governance and organizational operations.

As a thought leader on many issues related to the Food and Drug Administration, regulatory strategy, and healthcare policy, he is regularly published in prestigious medical journals and policy publications. In addition to participating in major scientific and policy symposiums around the country each year, Jeff has had the honor to be called to testify before Congress on multiple occasions and regularly contributes his expertise to the legislative process. Recent Friends initiatives include the establishment of the Breakthrough Therapies designation and the development of the Lung Cancer Master Protocol (Lung-MAP), a unique partnership that will accelerate and optimize clinical trial conduct for new drugs. Jeff has the privilege to also serve on a

variety of influential committees, boards, and advisory councils including the Alliance for a Stronger FDA (Board Member, Past President), the Medical Evidence Development Consortium (MED-C; Board Chair), Lung-MAP Senior Leadership Team Member, and a participant on working groups convened by the National Academies of Medicine and President's Council of Advisors on Science and Technology (PCAST). Prior to joining Friends, Jeff was an endocrinology researcher at the National Institutes of Health. His background in cancer research focused upon molecular changes associated with cancer formation as well as treatments to prevent cancer progression. Jeff received his Ph.D. in cell and molecular biology from Georgetown University, and holds a Bachelor's of Science in Biology from Bowling Green State University.

ANDREW BINDMAN, M.D., was appointed as Director of AHRQ on May 2, 2016. Prior to his appointment, Dr. Bindman served as Professor of Medicine and Epidemiology & Biostatistics at the University of California, San Francisco (UCSF). He is a primary care physician with Federal and State health policy experience who has practiced, taught, and conducted health services research at San Francisco General Hospital, an urban safety-net hospital, for almost 30 years. During that time, he led the development of a nationally recognized academic division focused on improving the care of vulnerable populations and a State-university partnership with California's Medicaid program that promotes translating research into policy. Dr. Bindman has published more than 150 peer-reviewed scientific articles focused on primary care and on low-income individuals' access to and quality of care. Through his work, Dr. Bindman helped to establish the association between access to care and preventable hospitalizations for ambulatory care-sensitive conditions (what are now called Prevention Quality Indicators [PQIs]). Dr. Bindman has used PQIs to evaluate Medicaid programs and to design interventions to improve quality of care for low-income patients with chronic disease. He has also promoted a participatory research model with policymakers as a way to translate research into evidence-based policy. Dr. Bindman is a Senior Associate Editor of the journal Health Services Research and he was elected to the National Academy of Medicine in 2015.

At UCSF, Dr. Bindman contributed to the training of primary care physicians and the development of health services researchers. He has been the Director of UCSF's Primary Care Research Fellowship, the developer of a course on translating research into policy, and a co-editor of the textbook Medical Management of Vulnerable and Underserved Populations. In 2005, Dr. Bindman received an achievement award from the Health Resources and Services Administration in recognition of his contributions to research training in health care disparities and in improving the diversity of the Nation's health care workforce. He served on AHRQ's Health Care Research Training Study Section from 2005-2009. In 2009-2010, Dr. Bindman was a Robert Wood Johnson Health Policy Fellow who worked as a staff member on the Energy and Commerce Committee in the U.S. House of Representatives. From September 2011 until June 30, 2014, Dr. Bindman served as a senior advisor within the Assistant Secretary for Planning and Evaluation's Office of Health Policy, where he worked to establish new Medicare payment codes for transitional care and chronic care management. From July 2014 until November 2015, Dr. Bindman was a senior advisor to the Centers for Medicare & Medicaid Services, where he helped launch the Innovation Accelerator Program to support care transformation in State Medicaid programs.

ADAM HAIM, P.H.D., is the Chief of the Treatment and Preventive Intervention Research Branch within the Division of Services and Intervention Research at the National Institute of Mental Health (NIMH). Dr. Haim manages a broad portfolio of research focused on evaluating the efficacy and effectiveness of pharmacologic, psychosocial and combination interventions on mental and behavior disorders. He is also a thought leader in the development, evaluation and implementation of technology enhanced mental health interventions. Dr. Haim is a licensed clinical psychologist and earned his doctoral degree in clinical psychology from State University of New York at Albany and completed his research fellowship at the NIMH Intramural Program in the Division of Clinical Neuroendocrinology.

PETRA KAUFMANN, M.D., M.SC., is the director of both the Office of Rare Diseases Research and the Division of Clinical Innovation. Her work includes overseeing NCATS' Rare Diseases Clinical Research Network, Genetic and Rare Diseases Information Center, and Clinical and Translational Science Awards Program as well as the NIH/NCATS Global Rare Diseases Patient Registry Data Repository/GRDR® program. Kaufmann focuses on engaging a broad range of stakeholders to accelerate translation from discovery to health benefits through use of innovative methods and tools in translational research and training. Before joining NCATS, Kaufmann was the director of the Office of Clinical Research at the National Institute of Neurological Disorders and

Stroke (NINDS), where she worked with investigators to plan and execute a large portfolio of clinical research studies and trials in neurological disorders, including many in rare diseases. She established NeuroNEXT, a trial network for Phase II trials using a central institutional review board, streamlined contracting, active patient participation in all project phases, and a scientific and legal framework for partnership with industry. Kaufmann also promoted data sharing, working with multiple stakeholders from the academic, patient organization and industry sectors to develop data standards for more than 10 neurological diseases.

A native of Germany, Kaufmann earned her M.D. from the University of Bonn and her M.Sc. in biostatistics from Columbia University's Mailman School of Public Health. She completed an internship in medicine at St. Luke's/Roosevelt (now part of Mt. Sinai) in New York City, training in neurology and clinical neurophysiology at Columbia University, and a postdoctoral fellowship in the molecular biology of mitochondrial diseases at Columbia's H. Houston Merritt Clinical Research Center for Muscular Dystrophy and Related Diseases. Before joining NINDS, Kaufmann was a tenured associate professor of neurology at Columbia, where she worked as a researcher and clinician in the neuromuscular division, the electromyography laboratories and the pediatric neuromuscular clinic. She has served on scientific advisory committees for many rare disease organizations and is a member of the American Academy of Neurology Science Committee, the International Rare Disease Research Consortium Interdisciplinary Scientific Committee and the Clinical Trial Transformation Initiative Steering Committee. Kaufmann is board certified in neurology, neuromuscular medicine and electrodiagnostic medicine. Kaufmann's research focus is on the clinical investigation of rare diseases, such as spinal muscular atrophy, amyotrophic lateral sclerosis and mitochondrial diseases. She currently sees patients in the Muscular Dystrophy Association Clinic at Children's National Medical Center in Washington, D.C.

RICHARD KUNTZ, M.D., is Senior Vice President and Chief Scientific, Clinical and Regulatory Officer of Medtronic and serves as a member of the Company's Executive Committee. In this role, which he assumed in August 2009, Kuntz oversees the company's global regulatory affairs, health policy and reimbursement, clinical research activities, and corporate technology. Kuntz joined Medtronic in October 2005, as Senior Vice President and President of Medtronic Neuromodulation, which encompasses the company's products and therapies used in the treatment of chronic pain, movement disorders, spasticity, overactive bladder and urinary retention, benign prostatic hyperplasia, and gastroparesis. In this role he was responsible for the research, development, operations and product sales and marketing for each of these therapeutic areas worldwide.Kuntz brings to Medtronic a broad background and expertise in many different areas of healthcare. Prior to Medtronic he was the Founder and Chief Scientific Officer of the Harvard Clinical Research Institute (HCRI), a university-based contract research organization which coordinates National Institutes of Health (NIH) and industry clinical trials with the United States Food and Drug Administration (FDA). Kuntz has directed over 100 multicenter clinical trials and has authored more than 250 original publications. His major interests are traditional and alternative clinical trial design and biostatistics.

Kuntz also served as Associate Professor of Medicine at Harvard Medical School, Chief of the Division of Clinical Biometrics, and an interventional cardiologist in the division of cardiovascular diseases at the Brigham and Women's Hospital in Boston, MA. Kuntz has served as a member of the Board of Governors of PCORI (Patient Centered Outcomes Research Institute) since it was established in 2010 as part of the Affordable Care Act.Kuntz graduated from Miami University, and received his medical degree from Case Western Reserve University School of Medicine. He completed his residency and chief residency in internal medicine at the University of Texas Southwestern Medical School, and then completed fellowships in cardiovascular diseases and interventional cardiology at the Beth Israel Hospital and Harvard Medical School, Boston. Kuntz received his master's of science in biostatistics from the Harvard School of Public Health.

ELLIOTT LEVY, M.D., is senior vice president, Global Development, at Amgen. He is responsible for the clinical development of Amgen's investigative and marketed products. Before joining Amgen, Dr. Levy spent 17 years at Bristol-Myers Squibb (BMS) in clinical development and pharmacovigilance. He has contributed to the development and approval of numerous new therapies for cardiovascular, metabolic, inflammatory, and malignant diseases, and led large organizations through periods of transformative change. Dr. Levy is a graduate of the Yale School of Medicine, where he also trained in internal medicine and nephrology. Dr. Levy was also a member of the Renal Division at Brigham and Women's Hospital in Boston, Massachusetts, where he was an investigator in federally sponsored outcomes research as well as industry-sponsored clinical trials.

DAVID MADIGAN, P.H.D., received a bachelor's degree in Mathematical Sciences and a Ph.D. in Statistics, both from Trinity College Dublin. He has previously worked for AT&T Inc., Soliloquy Inc., the University of Washington, Rutgers University, and SkillSoft, Inc. He has over 100 publications in such areas as Bayesian statistics, text mining, Monte Carlo methods, pharmacovigilance and probabilistic graphical models. He is an elected Fellow of the American Statistical Association and of the Institute of Mathematical Statistics. He recently completed a term as Editor-in-Chief of Statistical Science.

DEVEN MCGRAW, JD, MPH, joined the HHS Office for Civil Rights (OCR) as the Deputy Director for Health Information Privacy on June 29, 2015. She is a well-respected expert on the HIPAA Rules, and comes to OCR with a wealth of experience in both the private sector and the non-profit advocacy world. Prior to joining OCR, she was a partner in the healthcare practice of Manatt, Phelps & Phillips, LLP. She previously served as the Director of the Health Privacy Project at the Center for Democracy & Technology, which is a leading consumer voice on health privacy and security policy issues, and as the Chief Operating Officer at the National Partnership for Women & Families, where she provided strategic leadership and substantive policy expertise for the Partnership's health policy agenda. Ms. McGraw spearheads OCR's policy, enforcement, and outreach efforts on the HIPAA Privacy, Security, and Breach Notification Rules; as well as lead OCR's work on Presidential and Departmental priorities on health privacy and security. Ms. McGraw graduated magna cum laude from the University of Maryland. She earned her J.D., magna cum laude, and her L.L.M. from Georgetown University Law Center and was Executive Editor of the Georgetown Law Journal. She has a Master of Public Health from Johns Hopkins School of Hygiene and Public Health.

JOHN DAVID NOLEN, M.D., P.H.D., MSPH, provides clinical strategic guidance for Cerner Corporation's solutions in precision medicine, laboratory medicine, behavioral health, and long-term post-acute care. Using his clinical knowledge, analytical skills and engineering talents, he is positioning Cerner's solutions and clients for the future of medicine. He represents Cerner on boards, working groups, and standards organizations, including HL7, IHE, DICOM, IOM, AMIA, and CLSI. Dr. Nolen joined Cerner in 2010 as the Director of Laboratory Strategy. Since then, he has been instrumental in guiding the incorporation of new solutions around genomics, automation, and technologies into Cerner solutions. He transitioned to the Managing Director of the laboratory business unit in 2013, and expanded his clinical strategic responsibilities in 2015 to solutions beyond laboratory medicine.

RICHARD PLATT, M.D., M.S., is Professor and Chair of the Department of Population Medicine at Harvard Pilgrim Health Care Institute. He has extensive experience in developing systems and capabilities for using routinely collected electronic health information to support public health surveillance, medical product safety assessments, comparative effectiveness and outcomes research, and quality improvement programs. Dr. Platt is Principal Investigator of the FDA Sentinel System. He co-leads the coordinating center of PCORI's National Patient Centered Clinical Research Network (PCORnet). He also co-leads the coordinating center of the NIH Health Care System Research Collaboratory, and he leads a CDC Prevention Epicenter. He is a member of the Institute of Medicine Roundtable on Value and Science Driven Healthcare and the Association of American Medical Colleges Advisory Panel on Research. Dr. Platt is a graduate of Harvard Medical School and the Harvard School of Public Health. He is clinically trained in internal medicine and infectious diseases.

PATRICK VALLANCE, M.D., is President of Research and Development at GlaxoSmithKline (GSK) and a member of the GSK Corporate Executive Team. Prior to joining GSK in 2006, Patrick Vallance was a clinical academic and as Professor of Medicine led the Division of Medicine at University College London and Consultant Physician at UCL. His academic work was in the field of cardiovascular biology and ranged from chemistry through to use of large electronic health records. Patrick Vallance is a Fellow of the Academy of Medical Sciences. He has been on the Board of the UK Office for Strategic Co-ordination of Health Research since 2009. He is also a director of Genome Research Limited.

JOANNE WALDSTREICHER, M.D., is Chief Medical Officer, Johnson & Johnson. In this role, she has oversight across pharmaceuticals, devices and consumer products for safety, epidemiology, clinical and regulatory operations transformation, internal and external partnerships and collaborations supporting development of the ethical science, technology and R&D policies, including those related to clinical trial transparency and

compassionate access. Joanne also chairs the Pharmaceuticals (Janssen) R&D Development Committee and supports the Device and Consumer Development Committees, which review late stage development programs in the pipeline. She also holds an appointment as a Faculty Affiliate of the Division of Medical Ethics, Department of Population Health, New York University School of Medicine.

Among her prior roles in Janssen, the pharmaceutical sector of Johnson & Johnson, Joanne was responsible for late-stage development spanning the areas of neuroscience, cardiovascular and metabolism including INVOKANA®, XARELTO®, INVEGA SUSTENNA®, and INVEGA TRINZA®. Before joining Johnson & Johnson in 2002, Joanne was head of the Endocrinology and Metabolism clinical research group at Merck Research Laboratories, and responsible for overseeing clinical development of MEVACOR®, ZOCOR®, PROSCAR® and PROPECIA®, and for clinical development programs in atherosclerosis, obesity, diabetes, urology and dermatology. During that time, she received numerous awards and distinctions, including the Merck Research Laboratory Key Innovator Award.

Joanne received both the Jonas Salk and Belle Zeller scholarships from the City University of New York and graduated Summa Cum Laude from Brooklyn College. Joanne graduated Cum Laude from Harvard Medical School in 1987, and completed her internship and residency at Beth Israel Hospital, and her endocrinology fellowship at MGH. She has won numerous awards and scholarships, and has authored numerous papers and abstracts. In December, 2016, Joanne was named Healthcare Champion of the Year for Women by the National Association of Female Executives. She has authored numerous papers and abstracts. In December, 2016, Joanne was named Healthcare Champion of the Year for Women by the National Association of Female Executives.

MARCUS WILSON, PHARM.D., is President of HealthCore, Anthem's wholly owned outcomes research subsidiary. HealthCore utilizes Anthem's rich data and extensive provider network to meet the evidence development needs of a broad array of healthcare stakeholders including Anthem, State and Federal agencies and the Life Sciences industry. He has been extensively involved in efforts to utilize electronic healthcare data environments to accelerate healthcare evidence development and to facilitate clinical decision support for more than 20 years. Prior to co-founding HealthCore in 1996, Dr Wilson spent seven years within an integrated delivery system owned by BCBS of Delaware where he oversaw the physician and patient clinical decision support, pharmacy policy and clinical trials programs.

Dr. Wilson is active on a number of boards and national committees including serving as chair of the Innovations in Medical Evidence Development (IMEDS) Steering Committee, Reagan-Udall Foundation for the FDA; chair of the Research Committee for the Academy of Managed Care Pharmacy (AMCP) & the AMCP Foundation; the FDA Mini-Sentinel Program's Project Operations Council; Board of Directors for the Center for Medical Technology Policy (CMTP); and the Dean's Roundtable, College of Science, Virginia Tech. He is a past member of the Board of Directors for the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) and is a reviewer for multiple journals. Dr. Wilson received his Bachelor of Science in Biochemistry from Virginia Tech and his Doctor of Pharmacy degree from the Medical College of Virginia. He completed a residency in Family Medicine at the Medical University of South Carolina prior to joining the faculty at the Philadelphia College of Pharmacy where he taught didactic and experiential courses in therapeutics and clinical decision support. His experiential site within the HMO of Delaware eventually served as the foundational assets for HealthCore. HealthCore was eventually acquired by WellPoint in 2003 just prior to the WellPoint-Anthem merger.

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SPEAKER BIOGRAPHIES

KEYNOTE SPEAKERS:

On September 19th, 2017:

SCOTT GOTTLIEB, M.D., was sworn in as the 23rd Commissioner of Food and Drugs on May 11, 2017. Dr. Gottlieb is a physician, medical policy expert, and public health advocate who previously served as the FDA's Deputy Commissioner for Medical and Scientific Affairs and before that, as a senior advisor to the FDA Commissioner. He also worked on implementation of the Medicare drug benefit as a senior advisor to the Administrator of the Centers for Medicare and Medicaid Services, where he supported policy work on quality improvement and the agency's coverage process, particularly as it related to new medical technologies.

In 2013 Dr. Gottlieb was appointed by the Senate to serve on the Federal Health Information Technology Policy Committee, which advises the Department of Health and Human Services on healthcare information technology. Dr. Gottlieb was previously a Resident Fellow at the American Enterprise Institute, and a Clinical Assistant Professor at the New York University School of Medicine in Manhattan, where he also practiced medicine as a hospitalist physician. He completed a residency in internal medicine at the Mount Sinai Medical Center in New York, New York and is a graduate of the Mount Sinai School of Medicine and of Wesleyan University, in Middletown, Connecticut, where he studied Economics.

On September 20th, 2017:

ROBERT M. CALIFF, M.D., MACC, is Professor of Medicine at Duke University. He was the Commissioner of Food and Drugs in 2016-2017 and Deputy Commissioner for Medical Products and Tobacco from February 2015 until his appointment as Commissioner in February 2016. Prior to joining the FDA, Dr. Califf was a professor of medicine and vice chancellor for clinical and translational research at Duke University. He also served as director of the Duke Translational Medicine Institute and founding director of the Duke Clinical Research Institute. A nationally and internationally recognized expert in cardiovascular medicine, health outcomes research, healthcare quality, and clinical research, Dr. Califf has led many landmark clinical trials and is one of the most frequently cited authors in biomedical science, with more than 1,200 publications in the peer-reviewed literature. Dr. Califf is a Member of the National Academy of Medicine (formerly known as the Institute of Medicine (IOM)) as of 2016, one of the highest honors in the fields of health and medicine. Dr. Califf has served on numerous IOM committees, and he has served as a member of the FDA Cardiorenal Advisory Panel and FDA Science Board's Subcommittee on Science and Technology. Dr. Califf has also served on the Board of Scientific Counselors for the National Library of Medicine, as well as on advisory committees for the National Cancer Institute, the National Heart, Lung, and Blood Institute, the National Institute of Environmental Health Sciences and the Council of the National Institute on Aging. He has led major initiatives aimed at improving methods and infrastructure for clinical research, including the Clinical Trials Transformation Initiative (CTTI), a public-private partnership co-founded by the FDA and Duke. He also served as the principal investigator for Duke's Clinical and Translational Science Award and the NIH Health Care Systems Research Collaboratory coordinating center and co-PI of the Patient Centered Outcomes Research Institute Network. Dr. Califf is a graduate of Duke University School of Medicine. He completed a residency in internal medicine at the University of California, San Francisco and a fellowship in cardiology at Duke.

SPEAKERS AND PANELISTS:

BRIAN D. BRADBURY, D.SC., is an Executive Director and Head of the Data and Analytic Center (DAC) within the Center for Observational Research (CfOR) at Amgen, Inc. As the Head of the DAC, he leads a team of epidemiologists, biostatisticians, and programmers who provide strategic and tactical support across the drug development lifecycle. The DAC has the responsibility of developing and maintaining Amgen's RWD platform, conducting epidemiologic research on the incidence and prevalence of target clinical indications, using RWD to support RCT design, conducting feasibility analysis for post-marketing commitments, and developing Amgen's Sentinel program, which can be used for comparative effectiveness and safety research, as well as quality of care evaluation. Brian received his DSc in Epidemiology from Boston University in 2004 and a MA in Education and Psychology from Pepperdine University in 1998. He has authored or co-authored over 70 peer-reviewed publications in the areas of pharmacoepidemiology, cancer and kidney disease epidemiology and methods for controlling confounding-by-indication in drug safety studies.

RORY COLLINS, M.D., FRS, FMEDSCI, studied Medicine at St Thomas's Hospital Medical School, London University (1974-1980), and Statistics at George Washington University (1976-7) and at Oxford University (1982-3). In 1985 he became co-director, with Professor Sir Richard Peto, of the University of Oxford's Clinical Trial Service Unit & Epidemiological Studies Unit (CTSU). In 1996, he was appointed Professor of Medicine and Epidemiology at Oxford, supported by the British Heart Foundation. He became Principal Investigator and Chief Executive of the UK Biobank prospective study of 500,000 people in September 2005. From July 2013, he became the Head of the Nuffield Department of Population Health at Oxford University. His work has been in the establishment of large-scale epidemiological studies of the causes, prevention and treatment of heart attacks, other vascular disease, and cancer. He was knighted in 2011 for his services to science.

JOHN DOYLE, DR.P.H., MPH, is Senior Vice President and Managing Director with Advisory Services at Quintiles. Dr. Doyle leads the Values & Outcomes Center of Excellence, working with Life Science companies to navigate the transformational changes in the health care marketplace from a population health perspective. As the global health care system migrates from volume to value and outcomes-based medicine, Dr. Doyle's team of strategists partners with clients to diagnose, strategize, and illuminate a product's benefit-risk and economic profile tailored to a myriad of market stakeholders to drive healthcare system performance in an increasingly evidence-based environment. Functional areas of expertise include pricing and reimbursement, health economic and outcomes research (HEOR), and medical affairs. Over the last two decades, Dr. Doyle has authored over 100 abstracts and original research articles in a variety of therapeutic areas, with special concentration in oncology. He has lectured for academic and commercial audiences in the U.S., Canada, Europe, Latin America, and Asia. Dr. Doyle received a Bachelor of Science degree in Applied Economics with a concentration in the Life Sciences from Cornell University. He received a Master of Public Health degree and a Doctor of Public Health degree in Epidemiology from the Mailman School of Public Health at Columbia University, where he maintains an adjunct faculty position.

RACHAEL FLEURENCE, P.H.D., is the newly appointed Executive Director for the NEST Coordinating Center. Previously she was with the Patient-Centered Outcomes Research Institute (PCORI) where she led PCORI's initiative to build the National Patient-Centered Clinical Research Network, or PCORnet, since 2012. PCORnet has been a transformational effort to engage patients and leverage electronic health data to improve the speed and efficiency of clinical research in the United-States. A 330 million dollar investment involving 130 health institutions across the country, 20 patient powered research networks and covering 110 Million patients, PCORnet has just launched as an independent foundation in March 2017. Dr. Fleurence has served on a number of Boards and Steering Committees, including most recently the National Medical Device Evaluation System Planning (NEST) Planning Board, the Medical Device Innovation Consortium (MDIC) Board and the SMART IRB Steering Committee, an effort to streamline IRB reviews across academic research institutions. She was the chair of the PCORnet Executive Committee, and vice-chair of the PCORnet Council.

A health economist and health services researcher by training, Dr. Fleurence previously worked in the private sector in health outcomes research and has authored multiple peer-reviewed publications. Dr. Fleurence received a BA from Cambridge University (United-Kingdom), a MA in business management from ESSEC-Paris (France), and a MSc and PhD in health economics from the University of York (United-Kingdom).

DANIEL FORD, M.D., MPH, is the David M Levine Professor of Medicine who came to Johns Hopkins in 1982 to complete the Osler Medicine residency. After completing a fellowship in Clinical Epidemiology at the National Institute for Mental Health and his Masters of Public Health at Johns Hopkins, he joined the faculty and developed his approach to research as a member of the Welch Center for Prevention, Epidemiology and Clinical Research. He has joint

appointments in Psychiatry, Epidemiology, Health Policy and Management and Nursing. In 2005 he was appointed to be the Vice Dean for Clinical Research in the Johns Hopkins School of Medicine. As part of this role, he is the Institutional Official in charge of protection of human subjects for Johns Hopkins Medicine and the IRB committees. In recognition of his commitment to supporting clinical and translational research across the institution he was chosen to be the Principal Investigator of the CTSA grant and the first Director of the Johns Hopkins Institute for Clinical and Translational Research. Many trainees are introduced to Dr. Ford as the Director of the 2 week Introduction to Clinical Research course held each July.

Dr. Ford's research has focused on understanding the relationships between depression and chronic medical conditions, particularly coronary artery disease, and how to improve care for patients with medical comorbidity. He was one of the first investigators to publish data documenting depression as a risk factor for myocardial infarction and stroke. In the spirit of translation, he has also sustained an interest in how to utilize Information Technology (IT) to improve care of patients with depression and tobacco abuse. Moving these interventions into the commercial world has been part of this process. Dr. Ford has broad interests and is always willing to work with research teams and patient groups to learn more about the challenges they face and how we can address barriers as efficiently and effectively as possible.

MARTIN GIBSON, M.D., FRCP, is Chief Executive Officer of NorthWest EHealth (NWEH), Director of the National Institute for Health Research Clinical Research Network for Greater Manchester and Research and Informatics Director for the Greater Manchester Academic Health Science Network. He is a consultant physician specialising in diabetes and lipid disorders at Salford Royal NHS Foundation Trust where he was formerly R&D Director of both the acute and primary care Trusts. Martin is an active clinical trialist and has had a long-term interest in the use of electronic clinical data systems to improve healthcare and facilitate research.

JOHN GRAHAM, PHARM.D., is a Vice President at GlaxoSmithKline and leads the Value Evidence and Outcomes (VEO) organization within GSK's R&D division. The VEO organization is accountable for providing strategic input into the progression of assets as well as ensuring the value demonstration through evidence generation of the assets that do progress. This evidence includes accountability for Real World Evidence across GSK products and across all regions globally. In addition, his organization is accountable for GSK's Patient Centered Outcomes and alignment with Patients in Partnership. His interests include Real World Evidence (RWE) particularly the integration of traditional clinical evidence with non-traditional RWE to answer questions from patients, providers as well as payers. John sits on various Advisory Boards relating to Real World Evidence including the National Academies of Science working group on RWE, OPERAND, as well as the RWE Forum. He has published scientific communications across cardiovascular and metabolic diseases and across both clinical as well as RWE areas. John joined GSK in 2014 as the Vice President, CV/Met, NS, Rare Disease VEO and then was promoted to his current role as the Head of the organization in November of 2015. He is located in the GSK R&D HUB in Collegeville, PA. Prior to GSK, John worked for over 16 years at Bristol-Myers Squibb where he was most recently the Head of the U.S. HEOR group and previously had roles across R&D and commercial with both Global and local accountabilities. Prior to Industry John worked in academia most recently as Assistant Professor of Clinical Pharmacy at St. Louis College of Pharmacy. John holds a Doctorate of Pharmacy degree from Idaho State University and completed a Primary Care Residency at the University of Nebraska Medical Center.

MICHAEL HORBERG, M.D., MAS, FACP, is Executive Director Research and Community Benefit of Mid-Atlantic Permanente Medical Group (MAPMG) and the director of the Mid-Atlantic Permanente Research Institute (MAPRI). He is also director of HIV/AIDS for Kaiser Permanente. Dr. Horberg has been appointed to serve on the Presidential Advisory Council on HIV/AIDS (PACHA), and co-chairs the Access to Care and Improved Outcomes Committee of PACHA. Dr. Horberg is a Fellow of the American College of Physicians, and he presently serves as Vice-Chair of the Board of Directors of the HIV Medicine Association of the Infectious Disease Society of America. He has co-chaired the NCQA/AMA/HRSA/IDSA sponsored Expert Panel on HIV-related provider performance measures. He is Assistant Clinical Professor at Stanford University Medical School. Dr. Horberg is past-president of the national Gay and Lesbian Medical Association. His HIV research interests are health service outcomes for HIV-infected patients (including HIV quality measures and care improvement, and determinants of optimized multidisciplinary care for maximized HIV outcomes), medication adherence issues in these patients, and epidemiology of the disease. He graduated from Boston University's College of Liberal Arts and School of Medicine (with honors of Summa cum Laude and Phi Beta Kappa) and completed his internal medicine residency at Michael Reese Hospital in Chicago (University of Chicago affiliate). He received his Master of Advanced Studies (Clinical Research) from University of California San Francisco.

MARIE KANE is Chief Operating Office of NWEH, Marie has a wealth of experience in both Higher Education and the NHS having worked in web services, institutional change projects, knowledge management and research. Marie leads

on all aspects over the overall management of NWEH from the development and implementations of strategy, oversight of operational planning and the processes to ensure delivery, budget setting and team development.

ANNA MCCOLLISTER-SLIPP is Chief Advocate for Participatory Research for the Scripps Translational Science Institute (STSI). In addition, she is co-founder of Galileo Analytics, a visual data exploration and advanced data analytics company focused on democratizing access to and understanding of complex health data.
At Scripps, Anna works with STSI researchers to develop new ways of involving patients, caregivers and physicians in the design of clinical research using digital and genomic health tools. She is founder of VitalCrowd, a new platform she is developing with STSI to help facilitate, encourage and incentivize patients, caregivers, researchers and funders to work collaboratively in designing health research that will inform and improve care for health and disease. Anna's passion for innovation in health data analytics, participatory research and digital health tools is rooted in her personal experiences living with type 1 diabetes. In her professional and volunteer activities, Anna seeks to build platforms for better understanding of and engagement with the needs of patients. As a health IT entrepreneur and patient advocate, Anna has been appointed to and served on a number of government and private committees and boards aimed at promoting innovative ways to better understand, manage and treat complex chronic health conditions, such as diabetes. She speaks frequently about the promise of digital health, the need for innovation in medical device data and technology, promoting data standards, device interoperability and user platforms aimed at empowering patients to better manage their health. Anna's work as an advocate and entrepreneur has been featured in an array of publications and online media, including *Forbes, Huffington Post* and *US News & World Repor*t. She was named by XX In Health as a "Woman to Watch" at Health Datapalooza 2013, and as co-founder of Galileo Analytics, was one of a select group of innovators invited to participate in "The Hive" at TEDMED 2013. Prior to her work in digital health, Anna worked in global communications and public affairs, advising clients and working for organizations involved in array off issues, ranging from economic and foreign policy to global public health and pharmaceutical product launches.

ELEANOR PERFETTO, P.H.D., M.S., IS Senior Vice President of Strategic Initiatives for the National Health Council. Her policy work and research primarily focus on patient engagement in health care including comparative effectiveness and patient centered-outcomes research (CER-PCOR); medical product development; patient-reported outcome selection and development; health care quality; and value assessment. Dr. Perfetto also holds a part-time faculty appointment at the University of Maryland, Baltimore School of Pharmacy where she is Professor of Pharmaceutical Health Service Research. Dr. Perfetto was with Pfizer Inc for over seven years, most recently as Senior Director, Federal Government Relations; past positions were in Evidence-Based Strategies and Payment Policy Analysis. Dr. Perfetto currently serves as a board member for the Pharmacy Quality Alliance and Center for Medical Technology Policy, and on the Avalere/FasterCures Patient-Perspective Value Framework Advisory Panel. In the past, she served as: 2016 ISPOR Annual Meeting Co-chair; CMS MedCAC member ; co-chair of the National Quality Forum (NQF) Alzheimer's Disease and Related Dementias Project and member of the Patient-Reported Outcomes Expert Panel; Health Industry Council Board of Advisors member; Assistant Editor for the *Journal of Managed Care and Specialty Pharmacy*; and Drug Information Association Board of Directors member, of which she is a past President.

Dr. Perfetto holds BS and MS degrees in pharmacy from the University of Rhode Island, and a PhD from the University of North Carolina School of Public Health with concentrations in health policy and epidemiology. She served in the U.S. Public Health Service as senior pharmacoepidemiologist at the Agency for Health Care Policy & Research (now Agency for Healthcare Research & Quality), and began her government career by serving for 6 years as a pharmacist in the Indian Health Service in South Dakota and Oklahoma. Dr. Perfetto is serves as a peer reviewer for journals, the Patient-Centered Outcomes Research Institute, government granting agencies, and pharmacy professional organizations. She has spoken at many national and international conferences on patient-focused drug development, comparative effectiveness and patient-centered outcomes research, healthcare quality, and related policy and regulatory topics. She has contributed book chapters, published in professional journals, and presented at numerous scientific meetings. In 2009, Dr. Perfetto received the Distinguished Alumni award from the University of Rhode Island. As a caregiver for a spouse who suffered from dementia due to chronic traumatic encephalopathy, Dr. Perfetto is an advocate for patients with head-trauma-related dementias and their families. In May 2007, she received the Alzheimer's Association New York City Chapter Advocacy Leadership Award. In 2010, she received the Alzheimer's Association National Capital Area Chapter Award for Advocacy & Awareness. And in 2012, she received the Legacy Award from the Concussion Legacy Foundation, for which she is past board member and president.

PATRICK RYAN, P.H.D., is Senior Director of Epidemiology and the Head of Epidemiology Analytics at Janssen Research and Development, where he is leading efforts to develop and apply analysis methods to better understand the real-world effects of medical products. He is currently a collaborator in Observational Health Data Sciences and Informatics (OHDSI), a multi-stakeholder, interdisciplinary collaborative to create open-source solutions that bring out the value of observational health data through large-scale analytics. He served as a principal investigator of the

Observational Medical Outcomes Partnership (OMOP), a public-private partnership chaired by the Food and Drug Administration, where he led methodological research to assess the appropriate use of observational health care data to identify and evaluate drug safety issues.
Patrick received his undergraduate degrees in Computer Science and Operations Research at Cornell University, his Master of Engineering in Operations Research and Industrial Engineering at Cornell, and his PhD in Pharmaceutical Outcomes and Policy from University of North Carolina at Chapel Hill. Patrick has worked in various positions within the pharmaceutical industry at Pfizer and GlaxoSmithKline, and also in academia at the University of Arizona Arthritis Center.

MICHAEL SHERMAN, M.D., serves as Chief Medical Officer and Senior Vice President for Harvard Pilgrim Health Care. In this role, he is accountable for Harvard Pilgrim's medical trend management, provider engagement strategy, medical informatics, wellness and health promotion initiatives, care and disease management services, pharmacy services, NCQA accreditation and quality and utilization management programs. He also serves on the faculty of Harvard Medical School's Department of Population Medicine, as chair of the Board of Managers of the Harvard Pilgrim Health Care Institute and as a mentor for emerging physician executives enrolled in the AHIP Executive Leadership Program. Prior to joining Harvard Pilgrim, Dr. Sherman held leadership roles at Humana, UnitedHealth Group, and Thomson Medstat (now Truven). He holds a B.A. and an M.S. in Biomedical Anthropology from the University of Pennsylvania and received his M.D. from Yale and an M.B.A. from the Harvard Business School. Dr. Sherman is a diplomate of the American Board of Anesthesiology and American Board of Medical Management, and he practiced as a cardiac anesthesiologist prior to pursuing his MBA. A fellow of the American College of Physician Executives, Dr. Sherman was also appointed by Governor Deval Patrick to represent the health plan perspective on the Massachusetts Statewide Quality Advisory Committee. Dr. Sherman is a frequent speaker at national and regional conferences and has lectured as part of the Harvard Business School executive education program on value measurement in healthcare. He currently serves on the board of directors and as co-president of the Harvard Business School Healthcare Alumni Association, the board of advisors for the Harvard Business School Healthcare Initiative, and board of overseers for Boston's internationally renowned Museum of Science. Dr. Sherman also serves on the Advisory Board of the Institute for Clinical and Economic Review (ICER) and formerly served on the board of directors of Massachusetts Health Quality Partners.

RACHEL SHERMAN, M.D., MPH, is Principal Deputy Commissioner of the U.S. Food and Drug Administration (FDA). She oversees all FDA medical programs and initiatives that are agency cross cutting and clinical, scientific, regulatory, or operational. She also provides advice and counsel to the FDA Commissioner on medical product regulation and oversees on his behalf other high-priority agency initiatives and programs. Key focus areas include modernization of combination product review, orphan product development, the Oncology Center of Excellence, promoting the use of innovative trial designs, and standards for evidence development. Dr. Sherman has served FDA since 1989 in a variety of capacities, beginning as a primary reviewer in FDA's Center for Drug Evaluation and Research (CDER) during the height of the AIDS crisis. In 2005, Dr. Sherman moved to FDA's Office of the Commissioner, where she served until 2009 as Associate Commissioner for Clinical Programs and directed the agency's Critical Path Initiative. From 2009 to 2014, as CDER's Associate Center Director for Medical Policy and Director of CDER's Office of Medical Policy, Dr. Sherman led a large, multidisciplinary staff charged with developing and implementing high-priority policies and programs, including the Sentinel Initiative, FDA's program for regulating biosimilars, and the agency's expedited drug development and breakthrough therapy designation programs. She organized multi-stakeholder public private partnerships, oversaw development of regulations and guidance for industry, and played a key role in enhancing clinical trial quality and good clinical practice. Her achievements contributed directly to more effective prescription drug promotion and to the modernization of professional drug labeling, generic drug labeling, and medication information for patients.

In 2014, after 25 years of dedicated service to FDA and public health, Dr. Sherman retired. In 2015, she was asked to return to lead the Office of Medical Products and Tobacco, focusing on cross-center initiatives that foster efficient medical product development and facilitate patient access to new therapeutic products, work she will continue in her role as FDA Principal Deputy Commissioner. Dr. Sherman is an internist with a subspecialty in infectious diseases. She received her MPH from Johns Hopkins University, her MD from Mount Sinai School of Medicine, and her BA in mathematics from Washington University in St. Louis. She has served over the years as attending physician, Division of Infectious Diseases, at the Veterans Affairs Medical Center; clinical assistant professor of medicine (infectious diseases) at Georgetown University; and volunteer physician with Montgomery Mobile Health. Currently, Dr. Sherman is an adjunct assistant professor in the Division of Clinical Pharmacology in the Department of Medicine at Duke University.

SHARON F. TERRY, MA, is President and CEO of Genetic Alliance, a large network engaging individuals, families and communities to transform health. Genetic Alliance works to provide programs, products and tools for ordinary people to take charge of their health. As 'just a Mom' with a master's degree in Theology, she cofounded PXE International, a research advocacy organization for the genetic condition pseudoxanthoma elasticum (PXE), in response to the diagnosis of PXE in her two children in 1994. With her husband, she co-discovered the ABCC6 gene, patented it to ensure ethical stewardship in 2000, and assigned their rights to the foundation. She subsequently developed a diagnostic test and conducts clinical trials. She is the author of 140 peer-reviewed papers, of which 30 are clinical PXE studies.

In her focus at the forefront of consumer participation in genetics research, services and policy, she serves in a leadership role on many of the major international and national organizations, including the Precision Medicine Initiative Cohort Advisory Panel, Accelerating Medicines Partnership, Institute of Medicine (IOM) Science and Policy Board, the IOM Roundtable on Translating Genomic-Based Research for Health, the PubMed Central National Advisory Committee, the PhenX scientific advisory board, the Global Alliance for Genomics and Health, the International Rare Disease Research Consortium Executive Committee and as Founding President of EspeRare Foundation of Geneva, Switzerland. Terry is co-founder of the Genetic Alliance Registry and Biobank. She is on the editorial boards of several journals. She led the coalition that was instrumental in the passage of the Genetic Information Nondiscrimination Act. She received an honorary doctorate from Iona College for her community engagement work in 2006; the Research!America Distinguished Organization Advocacy Award in 2009; and the Clinical Research Forum and Foundation's Annual Award for Leadership in Public Advocacy in 2011. She was named one of FDA's "30 Heroes for the Thirtieth Anniversary of the Orphan Drug Act" in 2013. She is co-inventor of the Platform for Engaging Everyone Responsibly (PEER). PEER received $500,000 from the Robert Wood Johnson Foundation in 2014. PEER undergirds the Community Engaged Network for All (CENA), a PCORnet member funded in 2013 for Phase I and in 2015 for Phase II. She is Co-PI of the PCORnet Coordinating Center and Chair of the PCORnet Engagement Committee.

JANET WOODCOCK, M.D., is Director of the Center for Drug Evaluation and Research (CDER), at the Food and Drug Administration (FDA). In 2015, Dr. Woodcock also assumed the role of Acting Director of CDER's newly formed Office of Pharmaceutical Quality, (OPQ). Dr. Woodcock first joined CDER in 1994. For three years, from 2005 until 2008, she served FDA's Commissioner, holding several positions, including as Deputy Commissioner and Chief Medical Officer, Deputy Commissioner for Operations, and Chief Operating Officer. Her responsibilities involved oversight of various aspects of scientific and medical regulatory operations. Before joining CDER, Dr. Woodcock served as Director, Office of Therapeutics Research and Review, and Acting Deputy Director in FDA's Center for Biologics Evaluation and Research. Dr. Woodcock received her M.D. from Northwestern Medical School and completed further training and held teaching appointments at the Pennsylvania State University and the University of California in San Francisco. She joined FDA in 1986.

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RESPIRATORY RESEARCH

RESEARCH Open Access

The Salford Lung Study protocol: a pragmatic, randomised phase III real-world effectiveness trial in chronic obstructive pulmonary disease

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Abstract

Background: New treatments need to be evaluated in real-world clinical practice to account for co-morbidities, adherence and polypharmacy.

Methods: Patients with chronic obstructive pulmonary disease (COPD), ≥40 years old, with exacerbation in the previous 3 years are randomised 1:1 to once-daily fluticasone furoate 100 μg/vilanterol 25 μg in a novel dry-powder inhaler versus continuing their existing therapy. The primary endpoint is the mean annual rate of COPD exacerbations; an electronic medical record allows real-time collection and monitoring of endpoint and safety data.

Conclusions: The Salford Lung Study is the world's first pragmatic randomised controlled trial of a pre-licensed medication in COPD.

Trial registration: Clinicaltrials.gov identifier NCT01551758.

Introduction

Double-blind randomised controlled trials (RCTs) in chronic obstructive pulmonary disease (COPD) have indicated that inhaled corticosteroids (ICS) combined with a long-acting β_2-agonist (LABA) are more effective than the individual components in managing stable COPD, reducing exacerbations and improving lung function and health status [1]. However, double-blind RCTs differ from real life in having highly selective eligibility criteria, and enrolling participants who are not representative of patients in clinical practice and have much higher adherence [2]. The once-daily combination of the ICS fluticasone furoate (FF) and the novel LABA vilanterol (VI) (Relvar®) in a patient-friendly dry-powder inhaler (DPI) (Ellipta®) has the potential for improved adherence over the currently available twice-daily ICS/LABA combinations, with improved clinical effectiveness in a real-world setting [3].

The Salford Lung Study (SLS) is the world's first pragmatic RCT (pRCT) of an investigational medication. SLS will evaluate the effectiveness and safety of the FF/VI combination compared with existing maintenance therapy in a large, real-world population of patients with COPD in conditions of normal care. The study is being conducted in and around Salford, UK. Salford has a high prevalence of COPD in a community served by a single hospital and an established electronic medical record (EMR), connecting both primary and secondary care. Pharmacies also collaborate to allow patients to collect study medication from their usual community pharmacy.

Methods

Study design

SLS is a 12-month, open-label, phase III pRCT, evaluating the effectiveness and safety of FF/VI (Relvar®; 100 μg/25 μg once daily, delivered by a novel DPI, Ellipta®) in patients with COPD (clinicaltrials.gov identifier NCT01551758). The study is conducted in accordance with the International Conference on

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Harmonisation, Good Clinical Practice (GCP), all applicable data protection requirements and the ethical principles outlined in the Declaration of Helsinki 2008. The study was approved by the Ethics committee, National Research Ethics Service Committee North West, Greater Manchester South.

Patients

All patients with COPD at 66 primary care sites (at the time of manuscript preparation) in and around Salford and South Manchester are identified by their general practitioner (GP) from practice databases and invited to participate in the study.

Eligibility criteria include:

- aged ≥40 years
- documented GP diagnosis of COPD
- regular maintenance inhaler therapy (ICS alone or in combination with long-acting bronchodilator, one or more long-acting bronchodilators, or triple therapy [ICS/LABA plus long-acting muscarinic antagonist])
- at least one COPD exacerbation in the last 3 years.

Minimal exclusion criteria:

- an exacerbation within the previous 2 weeks
- chronic oral corticosteroid use.

At visit 1, patients are offered study participation through written informed consent (Fig. 1). At visit 2 (1–60 days after visit 1), patients are randomised (1:1) to receive either FF/VI or to continue their usual maintenance therapy. Patients randomised to FF/VI are instructed in the use of the Ellipta DPI. Patients randomised to their usual maintenance therapy are re-trained in the correct techniques and dosing. Baseline assessments are performed at visit 2, including quality of life and disease characteristics (e.g., disease duration, COPD maintenance therapy, smoking status, lung function, medical history). If at months 3, 6 and 9 the patient has had no contact with their GP practice within the previous 8 weeks, the patient is contacted by telephone to assess any serious adverse events (SAEs) or non-serious adverse drug reactions (ADRs) (visits 3, 4 and 5). There is no additional intervention at these assessments. At 12 months, the final visit (6) is a face-to-face meeting with the patient at which the final assessment of outcomes is conducted.

Participating sites

Primary care

To preserve the real-world nature of the study, the patient experience is as close to routine care as possible. The study's principal investigators are the GPs. They are ideally placed to facilitate recruitment, identify and report SAEs or serious ADRs and report study endpoints. GPs may make treatment adjustments according to their clinical opinion. Repeat prescriptions of study medication are issued by GPs as usual, and collected by patients from their usual pharmacy. As very few participating GPs had experience of clinical trial participation, all GPs have received training and support in GCP, patient recruitment, study protocol, coding of healthcare issues and general research procedures.

Pharmacy

Every pharmacy in Salford and others in South Manchester agreed to participate in the study. As with GPs, very few pharmacists had experience of clinical trial participation. All staff (>500) at participating pharmacies have received training in GCP and safety reporting and standard operating procedures were established. Initially, pharmacies faxed copies of study treatment prescriptions

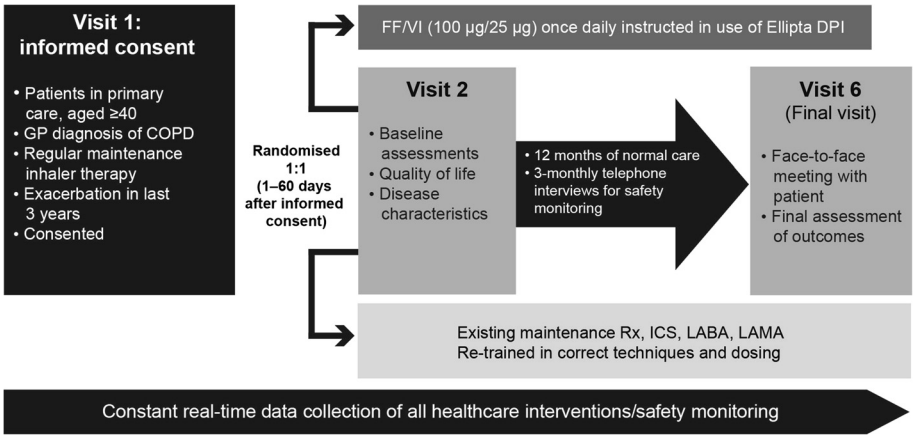

Fig. 1 Study design. COPD = chronic obstructive pulmonary disease; DPI = dry-powder inhaler; FF = fluticasone furoate; GP = general practitioner; ICS = inhaled corticosteroid; LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist; Rx = treatment; VI = vilanterol

to the study coordination centre, but these are now collected electronically. Prescription collection data are used to assess treatment adherence.

Hospital

The majority of admissions are to the local hospitals: Salford Royal Hospital and University Hospital of South Manchester. Admissions are identified electronically and assessed by a separate secondary care team within 48 h.

Data monitoring

All hospital admissions, outpatient and emergency department visits are identified from the EMR database (whenever and wherever they occur). From primary care, all healthcare contacts, out-of-hours activity and prescriptions of antibiotics or oral steroids can be identified. These events are reviewed by the study research team and classified as COPD or non-COPD related. Furthermore, the EMRs capture suspected unexpected serious adverse reactions (e.g., reduced kidney function or elevated liver function tests) and, for the purposes of SLS, include data from external sources to identify, e.g., deaths or National Health Service (NHS) hospital admissions outside Salford. NorthWest EHealth (www.nweh.org.uk) manages the EMRs, enabling data on study endpoints and patient safety to be collected continuously and remotely in near-real time, without the need for face-to-face patient contact.

Endpoints

Effectiveness

The primary endpoint is the mean annual rate of moderate or severe exacerbations. Secondary endpoints include time to first exacerbation and healthcare utilisation. Other endpoints include hospitalisations, use of rescue medication, the COPD Assessment Test (CAT) [4] and EuroQoL-5 dimensions (EQ-5D) questionnaire, listed and defined in Table 1. EMR data for effectiveness endpoints are independently verified by the research team (GP, research nurse, research doctor).

Safety

Safety endpoints include death, pneumonia, frequency and type of SAEs, and ADRs. Investigators and site staff are responsible for detecting, documenting and reporting SAEs and ADRs on electronic case report forms (eCRFs), which are continuously monitored by a dedicated clinical safety team.

Withdrawals

Patients with COPD exacerbation during the treatment period may remain in the study and continue to take study medication at the discretion of their GP. Severe COPD exacerbations are reported as SAEs. Patients with worsening COPD status while on study treatment may have their medication adjusted at the GP's discretion or receive other permitted COPD therapies. If, in the investigator's opinion, the frequency or severity of exacerbations prevents ongoing participation, the patient can be withdrawn. The reason for withdrawal is recorded in the eCRF and patients are followed up for 12 months following randomisation, with their consent.

Table 1 Study endpoints

Endpoint	Definitions
Primary endpoint	
Mean annual rate of moderate or severe exacerbations	• Moderate exacerbation: patient receiving an exacerbation-related prescription of oral corticosteroids and/or antibiotic (with or without NHS contact) not requiring hospitalisation • Severe exacerbation: an exacerbation-related hospitalisation
Secondary endpoints	
• COPD-related secondary care contacts • COPD-related primary care contacts	• Respiratory-related contacts: contact where the most prominent signs and symptoms with which the patient presents are as a direct result of the patient's COPD
• All secondary care contacts • All primary care contacts • Time to discontinuation of initial therapy • Time to addition of a further COPD controller medication • Time to first moderate/severe exacerbation • Time to first severe exacerbation (i.e., hospitalisation)	• All contacts: any interaction between the patient and a doctor or nurse working as part of the NHS (including telephone calls), not including protocol-defined study-related visits
Other endpoints	
• Number of hospitalisations • Number of days in hospital • Total number of respiratory-related home visits (including out-of-hours calls) and telephone consultations • CAT: disease management, quality of life • EQ-5D • Adherence to study medication • Number of salbutamol inhalers collected by the patients from study-enrolled community pharmacies over the 12-month treatment period	• Adherence is assessed based on analysis of medications (prescribed, dispensed and collected) and use of the MARS-A at visit 2 and visit 6/early withdrawal visit

CAT COPD Assessment Test, *COPD* chronic obstructive pulmonary disease, *EQ-5D* EuroQol Questionnaire, *MARS-A* Medication Adherence Report Scale for Asthma, *NHS* National Health Service

Statistical analysis and rationale

The primary efficacy analysis population is intent-to-treat, defined as all randomised patients who have received at least one prescription of study medication.

Sample size calculations are based on the primary endpoint (mean annual rate of moderate and severe exacerbations) and primary efficacy analysis population. A total of 2238 patients (1119 patients per treatment group) are needed. The study has 80 % power to detect a relative reduction of 12 % in the mean annual moderate or severe exacerbation rate, assuming a mean exacerbation rate of 2.3 for the control group [5]. Calculations are based on a negative binomial regression with a dispersion rate of 0.7 and use a two-sided 5 % significance level.

To account for variation in treatment response between patient subgroups, randomisation is stratified by baseline maintenance therapy and by history of COPD exacerbation in the previous 12 months (yes/no) to ensure treatment balance for the primary efficacy analysis population. Analyses based on subgroups are also planned; subgroups will be defined on baseline medication, lung function, comorbidities and other factors.

Discussion

SLS is a unique pRCT and, to our knowledge, the first prospective real-world comparative effectiveness study of an investigational medicine, which commenced in March 2012, prior to UK regulatory approval (launch date January 2014). The pragmatic inclusion criteria in SLS represent the broad definition of a patient eligible for COPD maintenance therapy in the real world, irrespective of co-morbidities. Study accessibility is maximised by employing minimal exclusion criteria and requirements for additional GP visits. Medicine prescription and supply is achieved as usual, through the patient's own GP and pharmacy.

Real-world outcomes can be assessed by observational studies that provide high external validity but in contrast have low internal validity [6]. With the limitations in observational studies and those in double-blind RCTs [2] such studies alone may not fully reflect the true impact and value of treatments for COPD. As such, well-designed pRCTs may offer complementary data to these standard types of studies, representing true real-world effectiveness.

Performing a study of a pre-licence drug in a real-world setting has posed many new challenges in study design, operational planning and study support. Patient safety is a priority in studying a pre-licence medicine. Patient safety in SLS is monitored in almost real-time by a combination of remote surveillance of EMRs and clinical monitoring. This sets a new standard, in which safety signals can be seen more quickly than in conventional RCTs. The major challenge has been managing and assessing the relevance and importance of safety signals within the huge volume of healthcare data being generated.

The SLS has limitations. Patients are not blinded and although patients are far less selected than in a usual efficacy trial, some selection bias cannot be precluded. Also, the fact that patients are recruited on the basis of a diagnosis from an electronic medical record and not from a specialist clinic could raise concerns. However, our approach mirrors the real world and a recent study found that registered data had satisfactory validity [7].

Conclusions

SLS is an innovative project with the aim of evaluating the safety and effectiveness of an investigational medicine in a real-world setting. Data from SLS will allow a better understanding of the risk/benefit profile of the FF/VI combination in the wider COPD community. The study will likely be a role model for future evaluation of effectiveness of new therapies.

Abbreviations

ADR: Adverse drug reaction; CAT: COPD Assessment Test; COPD: Chronic obstructive pulmonary disease; DPI: Dry-powder inhaler; eCRF: Electronic case report form; EMR: Electronic medical record; EQ-5D: EuroQoL-5 dimensions (EQ-5D) questionnaire; FF: Fluticasone furoate; GCP: Good Clinical Practice; GP: General practitioner; ICS: Inhaled corticosteroid; LABA: Long-acting β_2-agonist; LAMA: Long-acting muscarinic antagonist; MARS-A: Medication Adherence Report Scale for Asthma; NHS: National Health Service; pRCT: Pragmatic randomised controlled trial; RCT: Randomised controlled trial; Rx: Treatment; SAE: Serious adverse event; SLS: Salford Lung Study; VI: Vilanterol.

Competing interests

NDB's employing organisation provides IT support to GlaxoSmithKline. He has received educational grants and speaker's fees from GlaxoSmithKline and Novartis, and support for attending educational conferences from Boehringer Ingelheim, GlaxoSmithKline and Novartis. AW has acted on advisory boards and provided consultancy for Almirall, Chiesi, Cytos and GlaxoSmithKline. He has received travel support to speak at international meetings from Boehringer Ingelheim and GlaxoSmithKline. He is an investigator on cough and asthma studies for Afferent and GlaxoSmithKline. JPN has received consulting and speaker's fees, and an educational grant from GlaxoSmithKline. JMG's institution has received funding from GlaxoSmithKline as the SLS study sponsor. WW is an employee of, and holds shares/stock options in, GlaxoSmithKline. DL is an employee of, and holds shares/stock options in, GlaxoSmithKline. JV has received travel support and consultancy fees from GlaxoSmithKline (related to the SLS study); in addition, he has received consultancy fees from Almirall, AstraZeneca, Bioxydyn, Boehringer-Ingelheim, Chiesi, GlaxoSmithKline (outside the SLS study), Novartis, Syntaxin and Takeda (Nycomed), and speaker's fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis and Takeda (Nycomed). His wife has previously worked for AstraZeneca, Ferring and GlaxoSmithKline (until 2009).

Authors' contributions

All authors are involved in the design and implementation of the Salford Lung Study and contributed equally to the preparation of this paper, including development of the outline, review of all drafts, final approval and decision to submit the manuscript to Respiratory Research.

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ORIGINAL ARTICLE

Effectiveness of Fluticasone Furoate–Vilanterol for COPD in Clinical Practice

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ABSTRACT

BACKGROUND

Evidence for the management of chronic obstructive pulmonary disease (COPD) comes from closely monitored efficacy trials involving groups of patients who were selected on the basis of restricted entry criteria. There is a need for randomized trials to be conducted in conditions that are closer to usual clinical practice.

METHODS

In a controlled effectiveness trial conducted in 75 general practices, we randomly assigned 2799 patients with COPD to a once-daily inhaled combination of fluticasone furoate at a dose of 100 μg and vilanterol at a dose of 25 μg (the fluticasone furoate–vilanterol group) or to usual care (the usual-care group). The primary outcome was the rate of moderate or severe exacerbations among patients who had had an exacerbation within 1 year before the trial. Secondary outcomes were the rates of primary care contact (contact with a general practitioner, nurse, or other health care professional) and secondary care contact (inpatient admission, outpatient visit with a specialist, or visit to the emergency department), modification of the initial trial treatment for COPD, and the rate of exacerbations among patients who had had an exacerbation within 3 years before the trial, as assessed in a time-to-event analysis.

RESULTS

The rate of moderate or severe exacerbations was significantly lower, by 8.4% (95% confidence interval, 1.1 to 15.2), with fluticasone furoate–vilanterol therapy than with usual care (P=0.02). There was no significant difference in the annual rate of COPD-related contacts to primary or secondary care. There were no significant between-group differences in the rates of the first moderate or severe exacerbation and the first severe exacerbation in the time-to-event analyses. There were no excess serious adverse events of pneumonia in the fluticasone furoate–vilanterol group. The numbers of other serious adverse events were similar in the two groups.

CONCLUSIONS

In patients with COPD and a history of exacerbations, a once-daily treatment regimen of combined fluticasone furoate and vilanterol was associated with a lower rate of exacerbations than usual care, without a greater risk of serious adverse events. (Funded by GlaxoSmithKline; Salford Lung Study ClinicalTrials.gov number, NCT01551758.)

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*A complete list of the investigators in the Salford Lung Study is provided in the Supplementary Appendix, available at NEJM.org.

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Guidelines on the management of chronic obstructive pulmonary disease (COPD) are based on numerous randomized, controlled trials of efficacy, which are usually generated for registration purposes.[1] However, these trials have included patients who were selected with the use of strict criteria and were closely monitored, and therefore the results have limited relevance to everyday clinical practice.[2] To counter this, it has been proposed that integrated comparative effectiveness trials involve more representative patients and be conducted in much less restricted environments.[3-5]

The Salford Lung Study was designed to evaluate the effectiveness and safety of the once-daily inhaled combination of fluticasone furoate and vilanterol (fluticasone furoate–vilanterol) as compared with existing maintenance therapy (usual care) in a large, real-world population of patients with COPD in conditions of normal care. The trial was initiated before the approval of fluticasone furoate–vilanterol in the United Kingdom and was conducted in and around Salford, United Kingdom, a community served mainly by a single hospital with an established electronic health record (EHR) system that connects primary and secondary care. This setting permits the unobtrusive observation of patients for effectiveness and safety monitoring, blended into routine clinical care.[6]

Methods

Patients

Between March 13, 2012, and October 23, 2014, we recruited patients who were 40 years of age or older, had received a documented diagnosis of COPD from a general practitioner, and had had one or more COPD exacerbations in the previous 3 years. Patients had to be taking regular maintenance inhaler therapy, defined as the use of one or more long-acting bronchodilators; inhaled glucocorticoids, alone or in combination with a long-acting bronchodilator; or a combination of inhaled glucocorticoids, a long-acting beta-agonist (LABA), and a long-acting muscarinic antagonist (LAMA). There were no restrictions regarding smoking history or spirometric values. Among the few exclusion criteria were an exacerbation within the previous 2 weeks and long-term use of oral glucocorticoids. Details of the trial design and the analysis approach have been published previously.[7,8]

Patients were recruited in primary care practices by the health care professionals who provided their normal, everyday care. All the patients provided written informed consent. The trial was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines and the provisions of the 2008 Declaration of Helsinki. The trial protocol was approved by the National Research Ethics Service Committee North West, Greater Manchester South. The protocol, including the statistical analysis plan, is available with the full text of this article at NEJM.org.

Trial Design

This prospective, 12-month, open-label, parallel-group, randomized trial was conducted in 75 general practices in Salford and South Manchester, United Kingdom. Randomization was performed by means of a centralized randomization service, with stratification according to baseline maintenance therapy and presence or absence of a COPD exacerbation in the previous 12 months. Participants were assigned, in a 1:1 ratio, to receive one of two treatments: combination therapy with 100 μg of fluticasone furoate and 25 μg of vilanterol (Relvar [in Europe] or Breo [in the United States], GlaxoSmithKline), administered once daily as a dry powder through an inhaler (Ellipta, GlaxoSmithKline) (the fluticasone furoate–vilanterol group); or the continuation of usual care as determined by the general practitioner (the usual-care group). Patients who were randomly assigned to fluticasone furoate–vilanterol and had been previously treated with two long-acting bronchodilators and an inhaled glucocorticoid were allowed to continue taking a LAMA in addition to fluticasone furoate–vilanterol.

At the first trial visit, patients were offered participation and provided written informed consent. Within 1 to 60 days after the first visit, patients were randomly assigned to receive fluticasone furoate–vilanterol or to continue their usual maintenance therapy. (The 2 full months was the result of being able to use planned appointments in order to make the trial as close to normal practice as possible.) Trial staff trained the patients in each treatment group in the correct inhaler techniques and dosing, obtained baseline information on disease duration, smoking status, lung function, and concomitant medical history, and performed baseline assessments

of COPD symptoms with the use of the COPD Assessment Test (CAT)[9] and of quality of life with the use of the European Quality of Life–5 Dimensions (EQ-5D) questionnaire.[10] Spirometric findings were evaluated according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD), with airflow limitation present when the ratio of the forced expiratory volume in 1 second (FEV_1) to forced vital capacity was less than 0.7. Severity was graded according to the level of FEV_1.

If at months 3, 6, and 9 patients had had no contact with their general practice within the previous 8 weeks, they were contacted by telephone by a trial team member to assess any serious adverse events or nonserious adverse drug reactions; there was no additional intervention at these assessments. At 12 months, trial staff met the patients to make a final assessment of outcomes. Thus, most patients had contact with trial staff only at recruitment, at the baseline visit, and at 12 months.

To preserve the real-world nature of the trial, the patients' experience was as close to everyday clinical practice care as possible. The key investigators in the trial were the general practitioners, who could choose the appropriate therapy according to their clinical opinion, and treatments were dispensed by community pharmacies in the usual way. Patients could switch from fluticasone furoate–vilanterol to usual care, but patients in the usual-care group were not permitted to switch to the fluticasone furoate–vilanterol group. All the general practitioners and pharmacy staff received training regarding Good Clinical Practice guidelines as well as training in trial procedures and trial medications as appropriate to their roles.[8]

OUTCOME MEASUREMENTS

The primary outcome was the mean annual rate of moderate or severe exacerbations, defined as any worsening of respiratory symptoms that led to treatment with antibiotic agents or systemic glucocorticoids (or both), to hospital admission, or to scheduled or unscheduled hospital visits. The primary outcome was assessed in the primary effectiveness analysis population, which was a subgroup of the entire trial population that included patients who had undergone randomization, received a prescription of the trial medication (e.g., fluticasone furoate–vilanterol or, in the usual-care group, a COPD-controller medication), and had had one or more exacerbations in the preceding year. All the secondary outcomes were analyzed in the entire trial population (i.e., all the patients who underwent randomization and received a prescription of the trial medication) and included the rate of first exacerbation, as assessed in a time-to-event analysis, and the annual rates of primary and secondary health care contacts. Other outcomes included the CAT score and the EQ-5D questionnaire results. Except for exacerbations, modification to trial medication, CAT score, EQ-5D questionnaire, and demographic characteristics, data were collected in real time with the use of an integrated primary and secondary care EHR that was developed by NorthWest EHealth (NWEH). EHR data for the primary outcome were independently verified by the research team (general practitioner, research nurse, or research doctor).

SAFETY EVALUATION

Safety outcomes included serious adverse events of pneumonia (defined as pneumonia, which was prespecified as an adverse event of special interest), the frequency and type of other serious adverse events, and adverse drug reactions. Adverse events of special interest were defined a priori as groups of events of interest that were considered to be possibly related to inhaled glucocorticoids or LABAs. Safety monitoring was performed by means of continuous real-time monitoring of the patients' EHRs with the use of the linked NWEH database system and by means of telephone contact every 3 months (unless another contact occurred). Investigators reported serious adverse events and adverse drug reactions on electronic case-report forms, which were continuously monitored by near–real-time data monitoring and a dedicated clinical safety team. Cause of death was not adjudicated but was assigned by the primary investigator for all fatal events.

TRIAL OVERSIGHT

The Salford Lung Study team sought scientific advice by means of a joint consultation process with the National Institute for Health and Care Excellence and the Medicines and Healthcare Products Regulatory Agency. Informal advice was sought from the National Research Ethics Service Committee North West, Greater Manchester South, United Kingdom, before the formal ethics application.

The trial was designed by the sponsor and the academic partners. The sponsor and NWEH collected the data. Statistical analyses were performed by a contract research organization on behalf of, and with oversight by, employees of the sponsor. All the authors had full access to the data and vouch for the accuracy and completeness of all the data and analyses and for the fidelity of the trial to the protocol. The first draft of the manuscript was written jointly by the primary academic and senior authors, and all the authors worked collaboratively to prepare the final content and made the decision to submit the manuscript for publication. Editorial support was provided by a medical writer, paid by the sponsor.

STATISTICAL ANALYSIS

Sample-size calculations were based on the primary outcome (mean annual rate of moderate or severe exacerbations). We calculated that 2238 patients would need to be enrolled for the trial to have 80% power to detect a relative change of 12% in the mean annual rate of moderate or severe exacerbations between the fluticasone furoate–vilanterol group and the usual-care group, assuming a mean rate of 2.3 exacerbations in the usual-care group, as estimated on the basis of a retrospective analysis of historical data from patients from the Salford area who underwent randomization at the time of the protocol amendment[11] that were collected from the linked NWEH database. Calculations were based on a negative binomial regression, with a dispersion rate of 0.7, and used a two-sided 5% significance level. All the analyses were conducted according to the intention-to-treat principle (see the Supplementary Appendix, available at NEJM.org).

RESULTS

TRIAL POPULATION

Of 3161 patients with COPD who were screened, 2802 underwent randomization (see the Supplementary Appendix). Three patients in the fluticasone furoate–vilanterol group never took the trial medication, so the overall trial population consisted of 2799 patients. Of these, 2269 patients (81%) had one or more moderate or severe exacerbations in the year before the trial and made up the primary effectiveness analysis population (Table 1). In the overall trial population, 1291 patients in the fluticasone furoate–vilanterol group and 1309 in the usual-care group completed the trial; in the primary effectiveness analysis population, 1051 patients in the fluticasone furoate–vilanterol group and 1056 in the usual-care group completed the trial.

In the primary effectiveness analysis population, 276 patients (12%) were taking a LABA, a LAMA, or both (35 patients were taking both) at the time of randomization. A total of 762 patients (34%) were receiving inhaled glucocorticoids, a combination of inhaled glucocorticoids and a LABA, or a combination of inhaled glucocorticoids and a LAMA; 119 of these patients were using inhaled glucocorticoids as monotherapy. A total of 1231 patients (54%) were receiving combination triple therapy with inhaled glucocorticoids, a LABA, and a LAMA.

Overall, 47% of the patients reported having had two or more moderate COPD exacerbations in the year before entry; 7% reported having had one or more severe exacerbations. A total of 22% of the patients had a diagnosis of asthma recorded. More than three quarters of the patients (77%) had coexisting conditions (Table 1).

In the fluticasone furoate–vilanterol group, 342 patients (24%) modified their medication regimen; 302 of these patients (22%) switched back to their previous care, of whom 54 (4%) switched back because of a need for better control. In the usual-care group, 160 patients (11%) modified their medication regimen, including 114 (8%) who had a need for better control.

PRIMARY OUTCOME

In the primary effectiveness analysis population, the rate of moderate or severe exacerbations was 1.74 exacerbations per year in the fluticasone furoate–vilanterol group, as compared with 1.90 per year in the usual-care group, indicating an 8.4% (95% confidence interval [CI], 1.1 to 15.2) lower rate in the fluticasone furoate–vilanterol group (P=0.02) (Fig. 1A). This finding was confirmed in the entire trial population, in which the rate of moderate or severe exacerbations was 1.50 exacerbations per year in the fluticasone furoate–vilanterol group, as compared with 1.64 per year in the usual-care group, indicating an 8.4% (95% CI, 1.4 to 14.9) lower rate in the fluticasone furoate–vilanterol group (P=0.02). In patients with COPD of GOLD grade 1 or 2 at baseline (GOLD grade 1, indicating mild disease, is

Table 1. Characteristics of the Participants at Baseline.*

Characteristic	Entire Trial Population (N=2799)	Usual Care (N=1403)	Fluticasone Furoate–Vilanterol (N=1396)	Primary Effectiveness Analysis Population (N=2269)
Age — yr	67±10	67±10	67±10	67±10
Female sex — no. (%)	1369 (49)	671 (48)	698 (50)	1122 (49)
Body-mass index†	28±6	28±6	28±7	28±6
Current smoking — no. (%)	1289 (46)	666 (47)	623 (45)	1046 (46)
Postbronchodilator FEV_1 — liters	1.62±0.64	1.62±0.65	1.62±0.64	1.59±0.64
No. of exacerbations during the 12 mo before randomization	2.01±1.99	2.04±2.08	1.98±1.90	2.48±1.93
Coexisting condition — no. (%)				
Any	2145 (77)	1076 (77)	1069 (77)	1758 (77)
Cardiac condition	720 (26)	367 (26)	353 (25)	588 (26)
Vascular condition	1363 (49)	675 (48)	688 (49)	1095 (48)
Asthma	609 (22)	293 (21)	316 (23)	512 (23)
Diabetes	438 (16)	208 (15)	230 (16)	353 (16)

* Plus–minus values are means ±SD. There were no significant differences between the treatment groups in any of the baseline characteristics. The primary effectiveness analysis population was a subgroup of the entire trial population that included patients who had undergone randomization, received a prescription of the trial medication, and had had one or more exacerbations in the preceding year. Additional details on the baseline characteristics are provided in Table S1 in the Supplementary Appendix. FEV_1 denotes forced expiratory volume in 1 second.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.

defined as an FEV_1 ≥80% of the predicted value, and GOLD grade 2, indicating moderate disease, as an FEV_1 ≥50% and <80% of the predicted value, both in the presence of a ratio of FEV_1 to forced vital capacity of <0.7), the rate of exacerbations was 1.50 exacerbations per year in the fluticasone furoate–vilanterol group, as compared with 1.71 per year in the usual-care group, indicating a 12.1% (95% CI, 1.0 to 21.9) lower rate in the fluticasone furoate–vilanterol group.

Fig. 1B shows the percent change in the rate of moderate or severe exacerbations between the groups in the primary effectiveness analysis population, stratified according to prerandomization treatment; the interaction of treatment with strata was not significant (P=0.29). The treatment difference was significant among patients in the primary effectiveness population whose randomization stratum and prerandomization treatment included an inhaled glucocorticoid and a LABA (1.87 exacerbations per year among 927 patients in the fluticasone furoate–vilanterol group vs. 2.03 exacerbations per year among 908 patients in the usual-care group), with an 8.0% (95% CI, 0.11 to 15.4) lower rate in the fluticasone furoate–vilanterol group (P=0.047).

SECONDARY OUTCOMES

There was no significant difference in the rate of first moderate or severe exacerbation in the time-to-event analysis in the entire trial population (hazard ratio with fluticasone furoate–vilanterol vs. usual care, 0.93; 95% CI, 0.85 to 1.02). Similarly, there was no significant difference in the rate of severe exacerbations between the fluticasone furoate–vilanterol group and the usual-care group (0.09 and 0.08 exacerbations per year, respectively; the rate with fluticasone furoate–vilanterol was higher by 9.7% [95% CI, –16.9 to 44.7]; P=0.52) or in the rate of first severe exacerbation in the time-to-event analysis (hazard ratio, 1.27; 95% CI, 0.98 to 1.66; P=0.08).

There was no significant difference between the fluticasone furoate–vilanterol group and the usual-care group in the annual rate of COPD-related contact with primary care; the rate was 1.7% (95% CI, –5.1 to 8.0) lower in the fluticasone furoate–vilanterol group than in the usual-

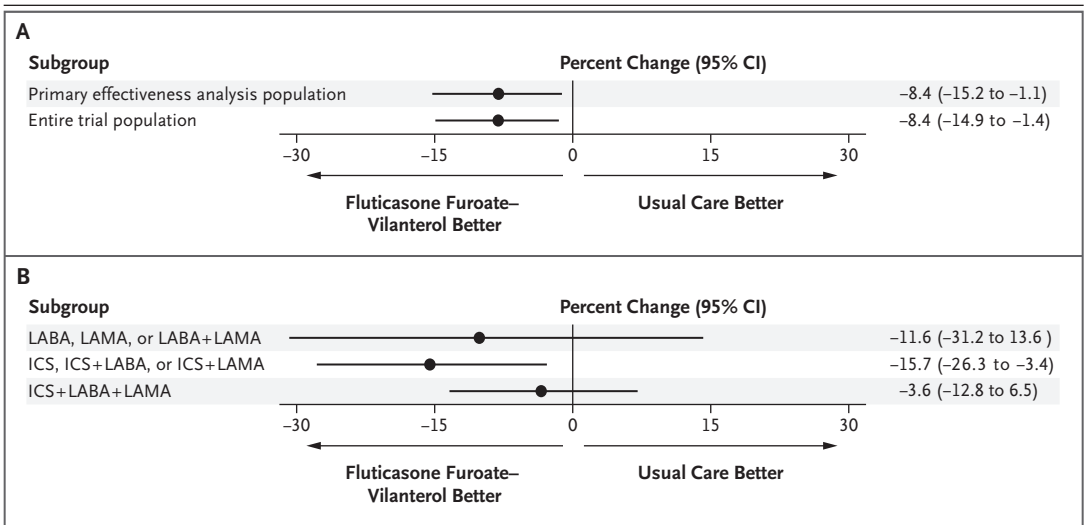

Figure 1. Treatment Effect on Moderate or Severe Exacerbations.

Shown is the effect of the combination of 100 μg of fluticasone furoate and 25 μg of vilanterol, as compared with usual care, on the rate of moderate or severe exacerbations. Percent-change estimates and 95% confidence intervals are shown. Panel A shows the primary-outcome analysis and the sensitivity analysis in the entire trial population. Panel B shows risk reductions stratified according to maintenance treatment at randomization for the primary effectiveness analysis population, which was a subgroup of the entire trial population that included patients who had undergone randomization, received a prescription of the trial medication, and had had one or more exacerbations in the preceding year. ICS denotes inhaled glucocorticoid, LABA long-acting beta-agonist, and LAMA long-acting muscarinic antagonist.

care group. The annual rate of all primary care contacts was slightly higher (12.3%; 95% CI, 5.4 to 19.6) in the fluticasone furoate–vilanterol group than in the usual-care group. There were no significant differences in the rate of secondary health care contacts.

In an analysis that was based on the entire trial population, 596 of 1317 patients (45%) in the fluticasone furoate–vilanterol group had a decrease in their CAT score by 2 or more points (indicating an improvement in COPD-related health status), as compared with 481 of 1325 patients (36%) in the usual-care group (odds ratio in favor of fluticasone furoate–vilanterol, 1.51; 95% CI, 1.28 to 1.77; P<0.001). There was no significant between-group difference in the change from baseline in the EQ-5D score. Results in the primary effectiveness analysis population were similar to those that were based on the entire trial population.

SAFETY

The incidence of serious adverse events during treatment was similar in the fluticasone furoate–vilanterol group and the usual-care group (with events occurring in 404 patients [29%] and 383 patients [27%], respectively). There was no notable difference between the two groups with regard to any adverse event of special interest (Table 2). A total of 94 patients (7%) in the fluticasone furoate–vilanterol group had one or more serious adverse events listed as pneumonia, as compared with 83 (6%) in the usual-care group (incidence ratio, 1.1; 95% CI, 0.9 to 1.5). For the comparison of the fluticasone furoate–vilanterol group with the usual-care group, there was a trend toward a higher mean number of serious adverse events of pneumonia in the stratum receiving a treatment regimen without an inhaled glucocorticoid at randomization (mean annual rate, 3.01 hospitalizations; 95% CI, 0.97 to 9.33) than in the strata receiving an inhaled glucocorticoid at randomization (P=0.10 for the interaction of treatment with baseline maintenance therapy in the analysis across the three strata). A total of 13 patients (1%) in each group had an event of pneumonia (adverse event of special interest) with a fatal outcome. A total of 45 patients in the fluticasone furoate–vilanterol group and 30 in the usual-care group died dur-

ing the trial; reported causes of fatal events are listed in the Supplementary Appendix. One patient in each group died from a serious adverse event that was recorded as being related to the trial medication (pneumonia in 1 patient in the usual-care group, and pulmonary embolism and deep-vein thrombosis in 1 in the fluticasone furoate–vilanterol group). No subgroups with a higher risk of a serious adverse event of pneumonia in the fluticasone furoate–vilanterol group than in the usual-care group were identified.

DISCUSSION

The Salford Lung Study on COPD was a large, randomized, comparative effectiveness trial conducted in a population that was intended to represent that seen in everyday clinical practice. We found that a simple, once-daily treatment with an inhaled combination of fluticasone furoate and vilanterol was superior to usual care by the patient's general practitioner with regard to the frequency of moderate or severe exacerbations and was not associated with a significantly higher risk of serious adverse events.

The combination of fluticasone furoate and vilanterol has been shown previously to result in lower rates of exacerbations of COPD than vilanterol alone in conventional randomized, controlled trials of efficacy.[12] However, this trial shows that broad populations of patients with COPD benefit from treatment with fluticasone furoate–vilanterol, and the findings differ from those of efficacy trials in which fluticasone furoate–vilanterol was associated with outcomes that were similar to those with the twice-daily combination of fluticasone propionate and salmeterol.[13] We found no excess number of serious adverse events of pneumonia in the overall comparisons, but as expected, we found a trend toward a greater number of serious adverse events of pneumonia with fluticasone furoate–vilanterol than with a treatment regimen consisting of bronchodilators only.[14] Also, we cannot rule out a higher incidence of mild pneumonia with fluticasone furoate–vilanterol than with usual care.

The strength of the trial derives from its innovative design. It took place in a single urban area, with primary and secondary care connected through an EHR, integrated with a new data recording system to enable the collection of a trial-relevant data set that contained more than 3 million lines of data for all the effectiveness and safety outcomes. After randomization, a patient was contacted by telephone only as a safety check on three occasions over a period of 12 months, and only then if there had been no health care contact within a 3-month period. All treatment was carried out by the usual caregivers, while patients were simultaneously monitored remotely with the use of the EHR for the early detection of safety events.

This comparative effectiveness trial needs careful interpretation. Although randomized, the trial was an open-label trial, which could potentially have introduced bias, although we made all efforts to have the treatment experience be similar for all the patients, by giving them similar initial training on the use of the inhaler, having them obtain their prescriptions from the general prac-

Table 2. Serious Adverse Events of Special Interest during Treatment in the Entire Trial Population.*

Event	Usual Care (N=1403)	Fluticasone Furoate–Vilanterol (N=1396)
	number (percent)	
Cardiovascular event		
Any event	107 (8)	108 (8)
Cardiac arrhythmia	54 (4)	52 (4)
Cardiac failure	28 (2)	28 (2)
Cardiac ischemia	33 (2)	34 (2)
Hypertension	1 (<1)	0
Stroke	25 (2)	21 (2)
Pneumonia	83 (6)	94 (7)
Lower respiratory tract infection, excluding pneumonia	58 (4)	64 (5)
Decreased bone mineral density and associated fracture	45 (3)	45 (3)
Effects on glucose level	16 (1)	23 (2)
Hypersensitivity	10 (1)	10 (1)
Effects on potassium level	2 (<1)	2 (<1)
Glucocorticoid-associated eye disease	2 (<1)	2 (<1)
Local effects from glucocorticoids	1 (<1)	0

* Serious adverse events of special interest during treatment that were associated with the known pharmacologic action of inhaled glucocorticoids or long-acting beta-agonists were identified with the use of standardized *Medical Dictionary for Regulatory Activities* (MedDRA), version 18.1, queries (SMQs) and sponsor-defined special interest terms when no SMQ was available. The grouping of events was defined according to standard MedDRA groups, if available.

titioner, having them collect the medication at their usual pharmacy, and so forth. However, the unblinded trial is the likely reason for the larger degree of switching of treatment over the first 3 months of the trial in the fluticasone furoate–vilanterol group than in the usual-care group. Patients switched to familiar treatment, despite fewer changes that were due to treatment failure in the fluticasone furoate–vilanterol group than in the usual-care group (i.e., need for better control). It should be noted that approximately 50% of the patients were taking triple therapy despite well-preserved lung function. A considerable proportion of patients had a diagnosis of asthma recorded. We do not believe that all these patients had an asthma–COPD overlap syndrome[15]; instead, the finding could indicate that some patients with COPD received a diagnosis of asthma early in the course of their COPD. This situation would usually have led to exclusion from COPD efficacy studies. Most of the general practitioners also took part in the Salford Lung Study involving patients with asthma[16] and thus had no incentive to include patients with current asthma in this trial.

Our findings challenge the automatic transfer of findings from efficacy studies to clinical guidelines or everyday clinical practice. For any new treatment, safety and efficacy randomized, controlled trials are essential, but they are carried out in carefully selected populations, from which patients with coexisting conditions are excluded, and represent less than 10% of patients with COPD.[2] Frequent face-to-face monitoring ensures high adherence to therapy and good inhaler technique. This comparative effectiveness trial that was conducted in a population of patients with COPD was largely unsupervised over the yearlong period, which allowed important factors in usual clinical care, such as adherence, frequency of dosing, and persistence of good inhaler technique, to come into play.

In conclusion, patients in general practice who had a diagnosis of COPD and a heightened risk of exacerbations had a benefit with simple, once-daily inhaled combination treatment with fluticasone furoate and vilanterol, without an additional risk of serious adverse events. Future effectiveness studies are likely to influence clinical guidelines, not only for COPD but for many other chronic diseases.

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Developing the Sentinel System — A National Resource for Evidence Development

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The Food and Drug Administration (FDA) now has the capacity to "query" the electronic health information of more than 60 million people, posing specific questions in order to monitor the safety of approved medical products. This pilot program, called Mini-Sentinel, uses a distributed data network (rather than a centralized database) that allows participating health plans and other organizations to create data files in a standard format and to maintain possession of those files. These organizations perform most analyses of their own data by running computer programs distributed by a coordinating center, and they provide consistent summarized results for the FDA's review.[1] The principles and practices involved in this effort to improve the safety of medical products can inform other uses of electronic health information to answer additional important questions about health and health care.

When the FDA announced the Sentinel Initiative in May 2008, it established a vision and objectives for the program, including the development of the Sentinel System, which will eventually be able to search the electronic health data of a minimum of 100 million patients.[2] Laying the groundwork for that system has required an extraordinary range of input from public and private organizations. Under a cooperative agreement with the FDA, the Engelberg Center for Health Care Reform at the Brookings Institution has been convening an ongoing series of discussions among stakeholders to address the near- and long-term challenges inherent in implementing the Sentinel System.[3] In 2009, the FDA gave the Harvard Pilgrim Health Care Institute the lead role in fulfilling a 5-year contract to establish a system — the Mini-Sentinel — for developing and testing approaches and methods that could be used to inform the structure and operations of the full Sentinel System. The institute is now leading a diverse partnership of approximately 200 epidemiologists, clinical content experts, statisticians, and data specialists from 27 institutions that are participating in this pilot system (www.minisentinel.org).

Through the Mini-Sentinel, capabilities are being developed for actively monitoring the safety of approved medical products using the electronic health information in claims systems, inpatient and outpatient medical records, and patient registries. The Mini-Sentinel builds on the work of the Vaccine Safety Datalink project (managed by the Centers for Disease Control and Prevention), the HMO Research Network, the Population Medicine Distributed Research Network (PopMedNet, funded by the Agency for Healthcare Research and Quality), and the Observational Medical Outcomes Partnership, among others.[4]

In the first year of the Mini-Sentinel project, its leaders established a network of data partners and a system with robust patient-privacy policies that could be used in querying the network's databases. The initiative's distributed data network allows each data partner to maintain physical and operational control over its own patient-level data, while providing the aggregated information needed to address the FDA's questions. Source data reside behind the data partners' institutional firewalls, where they are transformed into a standard format. This approach allows each data partner to answer the FDA's queries by executing standardized computer programs distributed by the Mini-Sentinel Operations Center. A typical result might include the number of new users of a product who experience a particular outcome, grouped according to age, sex, other treatments, and health status. This use of distributed analysis — whenever possible — eliminates or greatly reduces the exchange of protected health information. The data partners can obtain full-text medical records when necessary to confirm diagnoses or exposures and to determine the existence or severity of risk factors.

The initial focus of Mini-Sentinel has been on developing the ability to use claims data. In the next year, laboratory-test results and vital signs, derived from electronic health records and clinical laboratory records, will be added. The partnership is also evaluating procedures whereby Mini-Sentinel data partners will be able to link to data held by other organizations, such as state immunization registries and device registries.

The FDA will soon begin to actively monitor the data, seeking answers to specific questions about the performance of medical products, such as the frequency of myocardial infarction among users of oral hypoglycemic agents (a topic selected because it has

been difficult to identify drug-induced myocardial infarction through existing prospective surveillance mechanisms). The FDA will also monitor the occurrence of adverse events associated with select routinely administered vaccines. Using the Mini-Sentinel system, the FDA will also be able to obtain rapid responses to new questions about medical products and, eventually, to evaluate the health effects of its regulatory actions. This monitoring portfolio will expand as the FDA and its collaborators acquire experience and develop operational efficiencies and as additional data resources become available.

The distributed-database-and-analysis model and the infrastructure of the Mini-Sentinel data network can be extended to other forms of evidence development. Provisions in the economic stimulus and health care reform legislation, and a recent report from the President's Council of Advisors on Science and Technology,[5] envision expanded use of electronic health information for other types of public health surveillance, quality measurement, comparative effectiveness research, and biomedical research — all of which are essential to improving the country's health and health care delivery system.

Issues relevant to other secondary uses of electronic health information include recruitment of appropriate data partners, development and refinement of analytic methods, implementation of standards to ensure that analytic methods are consistent across the data sources, and above all, protection for the rights and privacy of patients. Data privacy and security are top priorities that were key considerations in the decision to build Mini-Sentinel as a system that uses a distributed data system and distributed analysis whenever possible. The committed collaboration among representatives of patients and consumers, health care professionals, Mini-Sentinel's data partners and safety scientists, and the medical-products industry has been essential to the Sentinel Initiative's progress.

It is particularly challenging to establish appropriate governance for a distributed data network that can support multiple secondary uses for health information. The current infrastructure is supported by a single federal agency, the FDA, and all the data are provided by private organizations, yet potential users of such a system reside not only broadly in government but also in academia, the private sector, and other user communities. To facilitate the development of this infrastructure into a national resource, this distributed system may ultimately be best managed by a consortium of interested parties operating as a public–private partnership. For example, specialized network-coordinating centers might rely on a consistent infrastructure to use the same sources of health information for various purposes, including public health uses, effectiveness research, quality measurement, and health services research.

The envisioned Sentinel System will build on the knowledge, partnerships, data resources, privacy protections, and technical capabilities that are being developed in the Mini-Sentinel program. Success in the form of improved safety of medical products will depend on the continued engagement of all concerned stakeholders and on ensuring that patients, consumers, and health care providers understand that all medical products pose risks and that postmarketing surveillance is critical to expanding the limited evidence base that exists when products are approved. Success also depends on the continued development of surveillance methods and on increasing the workforce of scientists who are trained to develop and interpret this evidence effectively.

Health care data represent a precious resource that must be used to the fullest possible extent to promote the public health, while the rights of patients and consumers are protected. As an early working model for secondary uses of data produced in the routine delivery of health care, the Sentinel System can and should become a national resource for evidence development and a cornerstone of a learning health care system.

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meaningfulness of inferences made from massive amounts of data, and approaches to interpreting results for decision-making. However, there is still a strong need for data scientists with thorough training in the conduct of principled analyses that minimize bias. Although a new generation of software products will support this effort, a deep understanding of the source data and how it was generated will remain critical to the success of big healthcare data analytics.

CONFLICT OF INTEREST
Dr. Schneeweiss is consultant to WHISCON, LLC, and to Aetion, a software company in which he also owns equity. He is principal investigator of investigator-initiated grants to the Brigham and Women's Hospital from Novartis, Genentech, Boehringer Ingelheim, and Genentech unrelated to the topic of this study.

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The FDA's Sentinel Initiative—A Comprehensive Approach to Medical Product Surveillance

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In May 2008, the Department of Health and Human Services announced the launch of the Sentinel Initiative by the US Food and Drug Administration (FDA) to create the Sentinel System, a national electronic system for medical product safety surveillance.[1,2] This system complements existing FDA surveillance capabilities that track adverse events reported after the use of FDA regulated products by allowing the FDA to proactively assess the safety of these products.

The Sentinel System includes the Active Postmarket Risk Identification and Analysis (ARIA) system mandated by Congress in the US Food and Drug Administration (FDA) Amendments Act (FDAAA) of 2007. In addition, the Sentinel Initiative created focused surveillance efforts around vaccine safety using the Postmarket Rapid Immunization Safety Monitoring (PRISM) system,[3] and supports regulatory review of blood and blood products with its Blood Surveillance Continuous Active Network (BloodSCAN).

One of the first stages of the development of the Sentinel System included Mini-Sentinel, a pilot program launched in 2009 to test the feasibility of and develop the scientific approaches needed for creating such a national system.[2] In 2014, the FDA began transitioning from the Mini-Sentinel pilot to the fully operational Sentinel System. The Sentinel System will build upon the successes of the Mini-Sentinel pilot[4] and leverage the Sentinel Infrastructure, a distributed database with a Common Data Model to enable the creation of analytical programs to be run remotely in participating data partner's secure data environment for analysis. The FDA is also seeking to develop the use of the Sentinel Infrastructure for questions outside of safety surveillance, but of importance to the FDA in the protection and promotion of public health. All these elements are defined in **Table 1**.

Assessment of the Sentinel System's current capabilities

The Sentinel Program Interim Assessment mandated by the Prescription Drug User Fee Act (PDUFA) V concluded that "In the implementation and execution of Mini-Sentinel, FDA has met or exceeded the requirements of FDAAA and . . .PDUFA."[5] The report highlights several additional accomplishments: (1) the establishment of the Mini-Sentinel Operations Center; (2) creation of a common data model and distributed-data approach; (3) successful development of processes for turning safety concerns into queries of the Mini-Sentinel data; and (4) making good progress toward building a mature data analytics system.[5] Other major accomplishments included exceeding the FDAAA 2007 milestones

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Table 1 Glossary of Sentinel Initiative terminology

1.	Sentinel Initiative—A long-term effort to create a national electronic system for monitoring FDA-regulated medical products.
2.	Mini-Sentinel—A pilot project, now complete, sponsored by the FDA to create an active surveillance system - the Sentinel System - to monitor the safety of FDA-regulated medical products.
3.	Sentinel System—A system being developed and implemented in stages, to expand FDA's existing postmarket safety surveillance capabilities by enabling the FDA to actively gather information about the safety of its regulated medical products once they reach the market. Includes ARIA, PRISM, and BloodSCAN (see below).
4.	ARIA – The Active postmarket Risk Identification and Analysis system—A subcomponent of the Sentinel System mandated in the Food and Drug Administration Amendments Act (FDAAA) of 2007 that is comprised of pretested, validated, and parameterized analytic programs and the Sentinel Common Data Model. The FDAAA requires the FDA to develop, in collaboration with public, academic, and private entities, methods to obtain access to disparate data sources and validated methods for the establishment of a system to link and analyze safety data from multiple sources.
5.	PRISM – Postlicensure Rapid Immunization Safety Monitoring program—A subcomponent of the Sentinel System focusing on immunization safety surveillance that is fully integrated into CBER's regulatory review process of vaccines and has been deployed for refinement and evaluation of potential safety signals identified during premarket and postmarket reviews.
6.	BloodSCAN – Blood Safety Surveillance Continuous Active Network—A subcomponent of the Sentinel System focusing on blood and blood product safety surveillance.
7.	Sentinel Infrastructure — The underlying data infrastructure created to enable analysis within the Sentinel System. The Sentinel Infrastructure involves: (1) a distributed data approach in which Data Partners maintain physical and operational control over electronic data in their existing environments; and (2) a Common Data Model consisting of standardized administrative and clinical information across Data Partners. The Sentinel Infrastructure has the potential to allow analysis of the data for other purposes besides safety for the FDA or those outside the FDA.
8.	Guardian System — A system being developed to use the Sentinel Infrastructure to expand the FDA's ability to actively gather information about the performance of its regulated medical products once they reach the market. This system relies on the Sentinel infrastructure to conduct analysis, but unlike the Sentinel System, its activities are not limited to the assessment of safety.

ARIA, Active postmarket Risk Identification and Analysis; BloodSCAN, Blood Safety Surveillance Continuous Active Network; CBER, Center for Biologics Evaluation and Research; FDA, US Food and Drug Administration; PRISM, Postlicensure Rapid Immunization Safety Monitoring.

with over 300 million person-years of high quality, unduplicated, curated data and recruiting a broad group of scientific collaborators who regularly provide the FDA with valuable technical support in evaluating electronic health data.[6] The report also points out that although the FDA has reported using Mini-Sentinel information in only a few cases (**Table 2**), Mini-Sentinel information has provided supporting information in many other situations, including when the information shows that existing FDA labels and communications are accurately describing risks of a medical product.[5] An example of this use of Mini-Sentinel data is the recent finding of no evidence of an association between human papillomavirus vaccination and venous thromboembolism.[7] The continued expansion of the use of modular analysis programs with common data model elements in ARIA will make the use of the Sentinel System a regular part of the FDA evaluations.

Table 2 Mini-Sentinel medical product and outcome assessments that led to FDA action

Dabigatran and bleeding
The FDA ascertained that bleeding rates associated with dabigatran, a new drug, were not significantly higher than bleeding rates associated with warfarin, an older drug, despite the large number of postmarket adverse event reports of serious and fatal bleeding events.
Olmesartan and sprue-like enteropathy
The FDA confirmed results of case studies that demonstrated increased risk of sprue-like enteropathy (intestinal problems, including severe chronic diarrhea with substantial weight loss) with long-term olmesartan use, but it did not find class effects.
Rotavirus vaccine and intussusception
The FDA identified that administration of rotavirus vaccine (Rotateq) led to an increased risk of intussusception (a serious intestinal condition), which was not detected during clinical trials before approval.
Influenza vaccine and febrile seizures
The FDA found no increase in risk of febrile seizures in children after receiving vaccination with Fluzone.

FDA, US Food and Drug Administration.

Despite these successes, others have criticized the current state of the Sentinel System. Some authors noted that consumer advocates would like to see the FDA use the Sentinel System as an "early warning system"[8] and others have identified similar limitations but have pointed out that "such modest results did not appear to flow from problems unique to the project itself but rather resulted primarily from drawbacks of electronic health data."[9]

The Interim Sentinel System Assessment implicitly acknowledges some of these criticisms and recommends several steps to improve the Sentinel System. In particular, the report recommends expanding the system's data sources and core capabilities,

implementing new processes for performance measurement, and improving the skills and training of key FDA personnel to enable more systematic and consistent use of the Sentinel System by the FDA.[5]

A fully mature Sentinel System

Transitioning to the full Sentinel System provides the FDA the opportunity to address many of these concerns and continue the development of this novel surveillance tool toward a fully mature Sentinel System outlined in the Interim Sentinel System Assessment.[6] Continued investment in the science that supports the use of the vast amounts of health care data currently available, and growing exponentially, is critically needed.

Expanding data sources and core capabilities

First and foremost, the FDA has continued to support the growth of the Sentinel Infrastructure to improve the Sentinel System and ARIA capabilities. Currently, the Sentinel Infrastructure is comprised largely of administrative and claims data. Some contributing data partners are able to utilize clinical data (e.g., vital signs, laboratory results) for analysis, although the size of this cohort is limited. Although administrative and claims data provide defined populations for assessment and can therefore more definitively indicate the absence of an event is more likely attributed to the lack of an occurrence rather than data incompleteness, it is known to have shortcomings related to data granularity when compared to data contained within an electronic health record. These reasons illustrate the continued focus on evaluating the opportunities to expand access to new populations and types of data. Plans are underway to expand the Sentinel Infrastructure to include data from the Medicare Virtual Research Data Center and Hospital Corporation of America. These data sources represent more data in patients over age 65 (Medicare covers at least 94% of the US elderly) and in hospitalized patients (the Hospital Corporation of America represents 5% of hospitalizations in the United States), and will fill current gaps in Sentinel System capabilities. Along with broadening data sources, an additional focus will be on better understanding data characteristics and how this data can improve the quality of surveillance (e.g., incorporating additional data into algorithms to identify health outcomes of interest and obtaining data on confounding variables).

Integrating the Sentinel System into the FDA's regulatory programs

The FDA continues to work to better integrate Sentinel into the FDA's regulatory programs. Sentinel is becoming incorporated into the FDA's pharmacovigilance and surveillance toolbox. PRISM and BloodSCAN programs are integrated into the regulatory decision-making processes of Center for Biologics Evaluation and Research (CBER). The ARIA system leverages existing modular analysis methods and the Sentinel Infrastructure to evaluate safety signals identified during the premarketing phase and in the postmarket setting and is a key component for integration of Sentinel into the FDA's regulatory programs. Integral to Sentinel's success is further training on the appropriate application of these capabilities to address more safety questions.

Early warning system

The FDA is focusing on projects to refine existing methodologies and develop new and innovative approaches to support safety surveillance. For example, several projects are underway to test methods of identifying unexpected safety concerns. CBER conducted a pilot study on a vaccine to evaluate one statistical approach, TreeScan, and has launched another pilot study, a prospective evaluation of a recently licensed vaccine to further evaluate the tool in conducting general safety studies.[10]

Supporting the development of a national resource

Although the FDA has focused much of its efforts on developing Sentinel to serve as a tool for safety surveillance, the underlying Sentinel Infrastructure has the potential for much broader uses. Such an infrastructure has the potential to generate evidence for other purposes besides safety for the FDA (e.g., product performance) or even those outside the FDA (e.g., those interested in public health surveillance or clinical decision-making). In principle, the Sentinel Infrastructure could also be used to study the role of genomic data in the safety and effectiveness of medical products, especially as such data is integrated into electronic health records. The FDA is actively engaged in promoting synergies and identifying opportunities for these enhanced capabilities. In particular, the FDA is seeking to develop the use of the Sentinel Infrastructure for questions outside of safety surveillance, but of importance to the FDA in the protection and promotion of public health. CBER has launched a pilot project to evaluate the feasibility and possible approaches for conducting vaccine effectiveness studies. This could also serve as a model for developing the needed infrastructure and governance that could allow for other uses of the Sentinel Infrastructure. For example, the National Institutes of Health Collaboratory Distributed Research Network (www. nihcollaboratory.org/Pages/distributed-research-network.aspx) allows the National Institutes of Health and other investigators to engage with Sentinel data partners and use the Sentinel Infrastructure. The Patient Centered Outcomes Research Network (PCORnet www.pcornet.org), the Patient Centered Outcomes Research Initiative's electronic health records-based comparative effectiveness research network, has adopted a common data model that is nearly identical to Sentinel's to facilitate use of Sentinel's library and analytical programs and linkage of the two resources when the respective network partners choose to do so.

SUMMARY

The Mini-Sentinel pilot has demonstrated the important contributions that the Sentinel System can make to the FDA's safety surveillance. However, we must continue to better utilize and understand the areas where it can further contribute to regulatory purposes, and ultimately inform patients and providers on the safe use of medical products. Enhancements in the Sentinel Infrastructure, methods, and staff expertise will continue to broaden the impact and breadth of safety questions a fully mature Sentinel System can address. Equally important is planning for sustained growth of the Sentinel System through aligning our efforts

with others toward a national resource that can support broad evidence generation to inform public health through the use of these rich data sources.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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Big Data and Adverse Drug Reaction Detection

R Harpaz[1], W DuMochel[1] and NH Shah[2]

Big Data holds the promise of fundamentally transforming the manner in which adverse drug reactions can be identified and evaluated. This commentary discusses new data sources that are envisioned to form a Big Data-enabled pharmacovigilance system and the role of these data in powering the future of adverse drug reactions detection.

Many unintended side effects of drugs become evident only after the drugs reach the market and are used by much larger and diverse populations. Such unintended side effects, also termed adverse drug reactions (ADRs), are a significant cause of morbidity and mortality, and present a major challenge to health systems worldwide, making effective postmarketing safety surveillance (pharmacovigilance) a crucial necessity.

Pharmacovigilance presently relies on the collection and analysis of spontaneous reports of adverse events obtained from drug manufacturers, healthcare professionals, and consumers. With the exclusion of manufacturers, reporting into this system is voluntary, which is why the process is often characterized as passive. Spontaneous reporting systems (SRS) have proven vital to postmarketing surveillance, and are effective at detecting many types of ADRs, especially rare ones. However, the significant delays in detecting other types of ADRs, and the realization that a substantial number of ADRs remain unreported, have led to the search of complementary approaches for ADR detection.

Big Data refers to large volumes of diverse, distributed, and dynamic data, whose size, content, and complexity pose both challenges and opportunities to its holders. A confluence of recent developments has made new kinds of observational, experimental, and knowledge-based data available for pharmacovigilance applications. Collectively labeled Big Data, these new data provide unique opportunities to improve pharmacovigilance, including mechanisms by which ADRs can be identified and evaluated. We begin this commentary with a brief discussion of these new data, and follow it with a broader view of Big Data's role in powering future ADR detection.

THE BIG FOUR

A major catalyst to fuel future pharmacovigilance is electronic medical records (EMR), which include any data generated during routine clinical care. Amassing rich data about large populations of patients, which include drug usage and outcomes, EMRs offer an ideal medium to complement existing surveillance approaches. Importantly, EMRs offer the potential for a more proactive approach to surveillance, as well as the ability to quantify the magnitude of problems.

A reflection of the state of the art for the use of EMR data is the US Food and Drug Administration (FDA) Sentinel Initiative,[1] which aims to establish a national network of medical databases to proactively monitor the safety of medical products and rapidly respond to emerging risks. The sentinel system is currently comprised of 18 data partners and contains data on ~178 million patients. However, it is currently used only for confirmatory analysis, and has not yet fulfilled its role as the rapid tool for safety assessments it was envisioned to be.[2] EMRs were thought to embody all the ingredients needed for effective drug

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NEWS FROM THE ACC

The STS-ACC Transcatheter Valve Therapy National Registry

A New Partnership and Infrastructure for the Introduction and Surveillance of Medical Devices and Therapies

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The Society of Thoracic Surgeons (STS) and American College of Cardiology (ACC) transcatheter valve therapy (TVT) registry is a novel, national registry for all new TVT devices created through a partnership of the STS and the ACC in close collaboration with the Food and Drug Administration, the Center for Medicare and Medicaid Services, and the Duke Clinical Research Institute. The registry will serve as an objective, comprehensive, and scientifically based resource to improve the quality of patient care, to monitor the safety and effectiveness of TVT devices, to serve as an analytic resource for TVT research, and to enhance communication among key stakeholders. (J Am Coll Cardiol 2013;62:1026–34) © 2013 by the American College of Cardiology Foundation

A novel, national clinical registry program for new transcatheter valve therapy (TVT) devices has been created through a partnership of The Society of Thoracic Surgeons (STS) and the American College of Cardiology (ACC). The STS/ACC TVT registry (NCT01737528) was developed in close collaboration with the Food and Drug Administration (FDA), the Center for Medicare and Medicaid Services (CMS), and the Duke Clinical Research Institute. The TVT registry will have multiple unique characteristics, partnerships, and applications that represent a paradigm shift in the introduction and on-going evaluation of new medical device technology (Table 1).

The first embedded post-approval study (PAS) using the TVT registry was developed in collaboration with the FDA and the industry sponsor of the first FDA-approved transcatheter aortic valve, Edwards Lifesciences. The first embedded investigational device exemption (IDE) study sponsored by professional societies was recently approved by the FDA and CMS with the 3 goals of providing access to TAVR treatment for inoperable patients unable to undergo transfemoral valve delivery, conducting a scientifically rigorous study for consideration of expanded indications, and gathering data to guide clinical decision making.

The intent of the TVT registry is to provide a data repository and reporting infrastructure to monitor the safety and effectiveness of TVT devices. Importantly, it will also be an objective, comprehensive, and scientifically based resource to measure and improve the quality of patient care, to serve

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as an analytic resource for TVT research, and to enhance communication among key stakeholders.

The TVT registry was publicly proposed by professional society leadership with the endorsement of the FDA and panel members at the FDA Cardiovascular Circulatory Device Expert Panel meeting in July 2011. It became operational on December 1, 2011.

Why We Need a TVT Registry

The FDA is the primary authority in the United States to regulate medical devices and is required by law to provide "reasonable assurance of safety and effectiveness." Once regulatory approval of a medical device has been granted, post-market surveillance is performed to ensure that safe and effective use of the device continues in the general population. However, the infrastructure for gathering and analyzing device use in the U.S population has been problematic and inadequate. There have been calls for the "professional societies, the medical device industry, and the FDA to mobilize available resources to improve post-market surveillance" (1,2).

Transcatheter aortic valve replacement (TAVR) for aortic stenosis using the Sapien valve from Edwards Lifesciences, Inc., has received FDA approval for patients considered inoperable for surgery. On June 13, 2012, an FDA Advisory Panel voted in favor of extending approval of the Sapien technology to high-risk patients including the use of the transapical approach in addition to the transfemoral route of vascular access for device delivery (3). Full FDA approval was subsequently announced (4).

Other transcatheter therapies for valvular heart disease are being developed and the TVT registry has been designed to facilitate their incorporation. The process of adding new technologies, such as transcatheter mitral repair technology, involves significant planning including identifying data elements that must be captured in a fashion that is standardized, well-defined, and harmonized with the clinical trials leading to regulatory approval.

The introduction of new treatment options presents challenges that are magnified when the therapy represents a substantial transformation of both patient care and the process of care to deliver the new therapy. Rational dispersion of TAVR into centers with sufficient experience and patient volume may maintain the reported results of the PARTNER trial in inoperable and/or high-risk patients with aortic stenosis (5). An expert consensus document on transcatheter valve therapy has outlined the initial technology, the targeted patient population, the multidisciplinary heart team, the specialized facilities needed, and the critical need for a new type of device registry (6). Some of the proposed uses of the registry are described in Table 2.

The Center for Devices and Radiological Health at the FDA has embarked on a substantial effort to strengthen post-market device surveillance. They and others have encouraged the use of professional clinical registries for post-approval studies (7,8). The TVT registry will provide the data gathering and analysis infrastructure to enable comprehensive monitoring of device safety and performance throughout the device life cycle in all patients being treated with this technology. The TVT registry will also incorporate "unique device identifiers" being introduced in 2013 by the FDA as another effort to improve the safe and effective use of medical devices (9).

When new and potentially high-risk technologies come to market, the FDA mandates the medical device companies to carry out PAS. Traditionally, manufacturers have devoted considerable effort and expense to develop a registry to fulfill PAS requirements that is often created as a stand-alone project, uses separate data elements and endpoints, and has little coordination with other registry efforts. This has led to predictable inconsistencies in cardiovascular data reporting and safety surveillance efforts. Furthermore, industry studies have typically not been open to independent data analysis, and potential conflicts of interest exist when a manufacturer conducts studies of its own device.

Abbreviations and Acronyms

ACC = American College of Cardiology
CMS = Center for Medicare and Medicaid Services
FDA = Food and Drug Administration
IDE = investigational device exemption
NCD = national coverage decision
NCDR = National Cardiovascular Data Registry
PAS = post-approval study
RCT = randomized clinical trial
STS = Society of Thoracic Surgeons
TAVR = transcatheter aortic valve replacement
TVT = transcatheter valve therapy

The TVT registry represents a new model combining the needs of the medical device industry, regulatory and reimbursement agencies, clinicians, hospitals, patients, researchers, and professional societies. The STS National Database and the ACC's National Cardiovascular Data Registry (NCDR) have the ability to coordinate the development and execution of this national registry and have developed other mature national registries with well-defined protocols for data collection and audits to ensure high quality.

Unique and Innovative Aspects of the TVT Registry

The TVT registry will have multiple innovations.

Immediate focus on critical issues. Initial TAVR clinical trials and FDA panel experts have identified the risk of stroke, paravalvular regurgitation, outcomes differences between sexes, vascular complications, and device durability as key issues. The TVT registry has been designed to further clarify these issues.

Long-term and quality-of-life outcomes. The TVT registry will be linked to CMS claims data to evaluate longitudinal patient outcomes, including hospitalizations and survival. This strategy has been successfully used by the STS and NCDR registries to examine long-term coronary revascularization outcomes (10–12). Moreover, after the

Table 1 Transcatheter Valve Therapy Registry Overview

Composition and enrollment
• Prospective enrollment of all patients in the United States receiving FDA-approved transcatheter heart valve devices
Registry data elements, analysis, and reporting
• Standardized and comprehensive data elements: indications, patient characteristics, periprocedural results and complications, in-hospital, 30-day, and subsequent yearly outcomes, and patient health status measures
• Harmonization of elements and definitions with national and international registries, pivotal trials, and consensus groups (e.g., VARC) whenever possible
• Unique device identification
• Long-term outcomes with linkages to CMS administrative claims data with adjudication of pre-specified adverse outcomes relevant to individual devices
• Implantation hospitals responsible for data entry using web-based data entry interface from the NCDR
• Completeness and accuracy of data entry monitored and audited both internally (NCDR-STS) and externally (FDA)
• Protection of confidential health care information and utilization of patient-informed consent when appropriate
• Quarterly benchmarking reports for hospitals to compare the institution's performance with that of volume-based peer groups and the national experience
Governance and structure
• Steering committee
• Research and publications subcommittee
• Stakeholders advisory group
Analytic centers and research
• Contracted analytic center: Duke Clinical Research Institute
• FDA-mandated PAS nested within the Registry with the ability of industry to use this infrastructure to meet their condition of approval requirements
• IDE studies sponsored by professional societies
• Future linkages with other professional society registries and other national registries
• Other substudies nested within the TVT registry
Funding
• STS, ACC, TVT registry site fees, medical device industry, FDA, and research grants

ACC = American College of Cardiology; CMS = Center for Medicare and Medicaid Services; FDA = Food and Drug Administration; IDE = investigational device exemption; NCDR = National Cardiovascular Data Registry; PAS = post-approval study; STS = The Society of Thoracic Surgeons; TVT = transcatheter valve therapy; VARC = Valve Academic Research Consortium.

Table 2 Major Questions and Applications Potentially Addressed by the Transcatheter Valve Therapy Registry

Patient selection and outcomes in different groups
• Evolving patient selection criteria. Will these closely match those enrolled in pivotal randomized clinical trials?
• The impact of defined "off-label" applications on patient outcomes and can "coverage with evidence development" be the model applied to these patient groups?
• The balance of risks and benefits in different patient groups. What are the major patient predictors of early and late outcomes?
• What patients are optimally suited for TVT versus traditional surgical versus medical management?
Device performance and safety
• How well will the technology perform in broad clinical use, i.e., "real-world" use?
• Will there be new safety issues that arise when the therapy is used in large numbers of patients over extended periods of time; will new device failure modes be identified?
• How do newer device iterations compare with prior ones?
Procedure performance
• In what sort of facility is the procedure optimally performed, by whom, and associated with what type of learning curves?
• How do acute and long-term TVT outcomes vary among sites? Is there a volume threshold for optimal outcomes?
• How will performance standards be defined, the TVT registry be used to quantify performance, and methods be distributed to improve performance of the systems delivering the therapy?
Registry performance
• What are the lessons learned in building and executing a national device registry?
• How well does it serve as an effective tool for conducting PAS, tracking off-label use, and so forth?
• Can it be adapted in the future as an alternative mechanism for pre-IDE studies by providing the infrastructure for coverage with evidence development?

Abbreviations as in Table 1.

CMS coverage criteria, the TVT registry also includes collection of quality-of-life measures. The primary measure will be the Kansas City Cardiomyopathy Questionnaire (KCCQ), a valid and reliable measure of patient-reported symptom burden, functional status, and quality of life that is sensitive to clinical change and has been used in TAVR patients (13).

Risk models tailored for the TVT population. Models of outcomes will be developed and validated using TVT registry data that will be used for benchmark comparisons of risk-adjusted outcomes among centers, and can potentially provide personalized risk estimates to support informed decisions by patients and clinicians regarding the likelihood of benefits and complications.

Appropriateness of use. Data collected over years can be analyzed for the appropriateness of the procedure correlating patient characteristics with post-procedural outcomes. With the procedure indications thus defined, it will then be possible to effectively monitor for potentially appropriate or inappropriate "indication creep."

Expansion of indications for use. The TVT registry will gather data on device use in ways not originally intended using clinical research protocols imbedded in the registry. "Valve-in-valve" (the placement of TVT valves in degenerated surgical bioprostheses) and alternative vascular access (i.e., transapical, transaortic, trans-subclavian, and transiliac) are uses of TAVR technology not part of FDA-approved indications from November 2011 and not covered by the CMS national coverage decision (NCD) from May 2012 for the Sapien valve use in inoperable patients. Part B of the CMS NCD provides reimbursement of procedures performed as part of a CMS-approved research study (14). After months of developing a new model for a TVT registry-based IDE study, the STS and ACC submitted to CMS and FDA a research proposal to study alternative access for inoperable patients. The FDA has recently approved the IDE study (G120291); the clinical trial number has been issued (NCT01787084); CMS has approved the research proposal; and the study will soon be initiated and be open to all qualifying and compliant TAVR sites in the United States. This unique study is also constructed so that the scientific evidence developed can be used by the FDA to expand indications.

Nested PAS studies. Data for FDA-mandated PAS will be nested within the TVT registry and will satisfy the FDA requirements placed on the sponsor. The registry design can accommodate differences in the scope of data collection and operation as requested by the FDA for the sponsor. The

entire TVT registry population may be used for future PAS studies.

Linkages to Other Registries and Relationship to Randomized Clinical Trials

The TVT registry is a registry focused on new transcatheter technologies, is not a comprehensive disease-based registry, and, by itself, cannot be used to compare treatment alternatives or to establish appropriateness or one treatment versus another. Links can and will be made to the STS Adult Cardiac Surgery Database to compare open surgical techniques to TVT techniques. For other patients who have neither surgery nor TVT, there will be the need to gather data on medical management from PINNACLE (Practice Innovation and Clinical Excellence), a NCDR registry of out-patient quality improvement, or other sources.

Registries, such as the TVT registry, can support observational studies but are not a substitute for randomized clinical trials (RCT) when needed to control for selection bias. However, the network of hospitals involved in the TVT registry may be useful for the recruitment and conduct of RCTs. Data from the TVT registry may be helpful in planning RCTs, and/or may be useful within an RCT conducted using the TVT registry sites/infrastructure, leading to a more efficient clinical trial.

The TVT Registry Defined

The TVT registry is placed in the context of the FDA's medical device regulatory process (Fig. 1) and is a next generation of prospective registries implemented with the introduction of new technologies into real-world practice. Initially, the registry will contain data on only 1 TAVR device but it eventually can include all future approved technologies in the TVT domain.

The TVT registry is a national registry in the United States. More than 50,000 TAVR procedures have been completed after commercial release in 46 countries worldwide. Reports in 2011 from registries in Canada (15), Italy (16), Germany (17), France (18), and the United Kingdom (19) included 2,817 patients. Subsequently, in 2012, the German Registry (GARY) has been described in detail with >15,000 datasets entered (20). Most recently, the Transcatheter Valve Treatment Sentinel Pilot Registry, a prospective independent consecutive registry, reported 4,571 patients undergoing TAVI between January 2011 and May 2012 in 137 medical centers of 10 European countries (21) The groundwork for TVT worldwide registries has been laid.

In a paradigm shifting approach to surveillance, the FDA has recently initiated efforts to facilitate and promote the development of international registry consortia with the goal to augment the infrastructure for evidence generation,

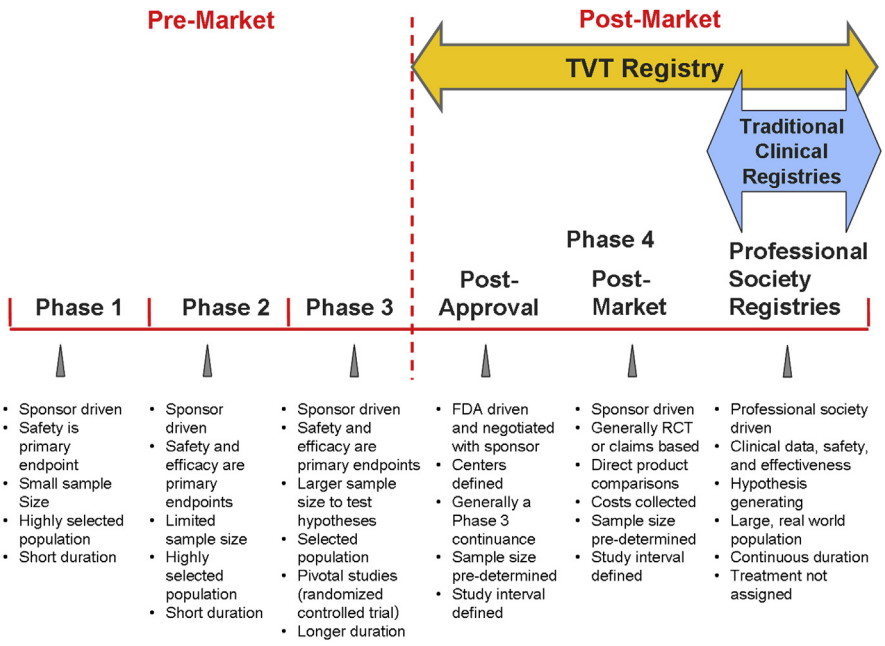

Figure 1 TVT Registry Is Placed in Context of Process of Device Evaluation Leading to and After FDA Approval

The **dotted vertical line** represents the time when Food and Drug Administration (FDA) approval occurs. Previous clinical registries run by professional societies have been developed to monitor results of established procedures. The transcatheter valve therapy (TVT) registry will prospectively capture patients immediately after device approval. There are plans to potentially expand the TVT registry into the pre-PMA period to further bring data element standardization and efficient transitions from the pre-approval to post-approval phases of device evaluation. PMA = premarket approval; RCT = randomized clinical trial.

synthesis and appraisal of device performance, and clinical outcomes throughout the product life cycle. Notably, in 2011, the International Consortium of Orthopedic Registries was created, consisting of 29 orthopedic registries from 14 nations and capturing 3.5 million procedures involving orthopedic implants worldwide (22). The FDA also initiated efforts to develop an international consortia of cardiovascular registries (23).

The TVT registry is listed in the U.S. National Institutes of Health clinicaltrials.gov (NCT01737528) as part of this database of clinical studies conducted worldwide.

Patient Composition and Enrollment in the TVT Registry

In the past, studies reported from some registries were difficult to interpret because of potential selection bias and lack of knowledge of the overall population. The TVT registry with its expected inclusion of most, if not all, treated patients in the United States should eliminate this concern.

Several factors will likely result in a high rate of enrollment. The CMS NCD includes a requirement that TAVR will be covered for Medicare beneficiaries only if the patient is enrolled in a prospective national registry (14). Furthermore, institutions need a site-specific analysis of their programs compared to benchmarks from a nationwide experience. PAS studies may be required to use a national registry. Figure 2 shows the growth of formal participation of the TVT registry, and Figure 3 shows the number of patient records submitted from the initial TAVR procedure. As of August 7, 2013 there have been 245 sites in the United States formally enrolled in the TVT registry.

Clinical registry data collection is considered a part of an institution's quality assessment and improvement process and therefore does not require specific written informed patient consent. The TVT registry complies with the relevant regulations relating to the protection of human research subjects, and this protocol is part of the TVT registry that has undergone and had been given approval by an independent institutional review board review from Chesapeake Research Review Inc. There is no added procedural risk to patients through involvement in the TVT registry. Patient data used in potentially CMS-approved studies on such topics as valve-in-valve and alternative access approaches are collected using only data elements included in the original TVT registry and undergoing variations in the use of TAVR as decided by the clinicians caring for the patients. No risk or procedures beyond those required for routine care will be imposed. Conversely, if the goal of such studies is to expand a device's indication, then a formal IDE may be necessary; and this carries additional responsibilities and compliance issues that have been the subject of extensive discussions between the TVT registry and the FDA. Finally, participation in a specific prospective, FDA-regulated PAS may

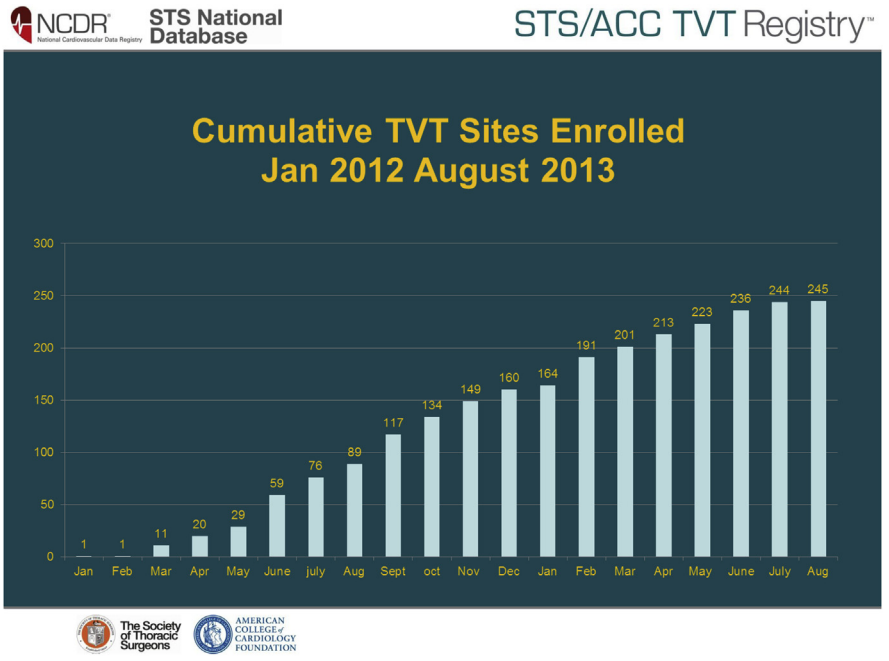

Figure 2 Cumulative TVT Registry Sites Enrolled From January 2012 to Beginning August 2013

The graph depicts the number of hospitals enrolled in the transcatheter valve therapy (TVT) registry during 2012 plus mid 2013 and represents nearly all active transcatheter aortic valve replacement sites in the United States. The process of enrollment can take some time for hospitals to complete, and the few remaining sites are expected to complete the process soon. ACC = American College of Cardiology; NCDR = National Cardiovascular Data Registry; STS = The Society of Thoracic Surgeons.

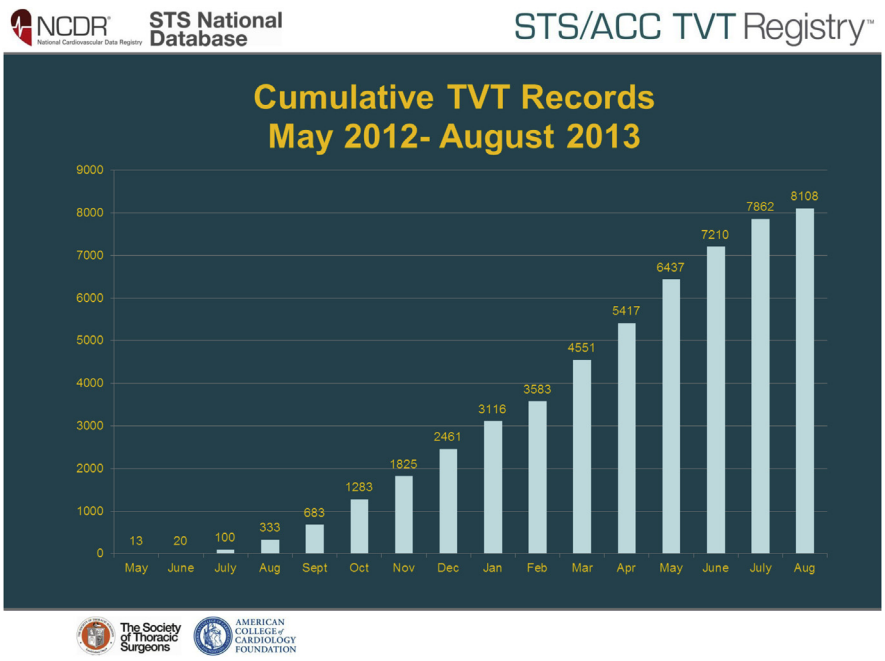

Figure 3 **Cumulative TVT Records May 2012 to Beginning August 2013**

Patients who have undergone transcatheter aortic valve replacement and have had their data entered into the transcatheter valve therapy (TVT) registry during 2012 plus mid 2013 are plotted as a function of month of data submission for their procedure. Acceleration of entries occurred after the national coverage decision from the Center for Medicare and Medicaid Services announced the reimbursement requirements that included registry participation. Sites are still entering their backlog of completed cases. As of August 7, 2013 there were 8,108 patient records entered. Abbreviations as in Figure 2.

require both institutional review board approval and written informed consent if the PAS involves collecting specific elements of personal health information or data for research purposes.

Registry Data Elements

The TVT registry data collection form and dictionary are available at the TVT registry website (www.tvtregistry.org). Version 1.1 has online data entry that became active in July 2012.

Although TAVR technology has led to some unique data elements, most elements and definitions are commonly included in other clinical registries. In the design of the TVT registry, particular attention was given to data elements and definitions that are harmonized with TAVR trials. The Valve Academic Research Consortium is a multiple stake holder group that has created consistent endpoint definitions and consensus recommendations for TAVR clinical research programs (24–26). These efforts have been valuable to the TVT registry focused on use of these technologies in real-world settings.

Echocardiographic data post-TAVR are also important parameters that will be captured in the TVT registry to assess prosthetic durability, but are currently not incorporated in clinical management guidelines (27).

Data Entry, Monitoring, and Auditing

Participating sites will submit complete periprocedural and short-term follow-up data on all patients who undergo a TAVR procedure. Outcomes beyond the first year will be captured through linkage with the CMS database.

The TVT registry will have an extensive data quality program including multiple mechanisms to monitor completeness and accuracy. These include site training and support by TVT registry staff, data "cleaning" by data integrity checks utilizing range validation and other measures, auditing at the site level portions of data, and adjudication of selected 30-day and 1-year outcomes. Collection of source documents and verification of pre-specified key events can be added specifically for PAS studies. Audit strategies will be executed by the FDA for the TVT registry. The Duke Clinical Research Institute will also provide event adjudication services for pre-specified events and other operational support.

Reporting

The TVT registry will provide feedback to sites including quarterly quality national benchmarking. Participants will have access to a repository of their own data and tools to evaluate their local practice and conduct user-specified local data queries. Heart teams will be encouraged to review

outcome reports for opportunities for improvement (28). The TVT registry will also issue annual reports at professional meetings of TAVR and future TVT technology that will include volume and outcomes. CMS-approved studies as described in part B of the NCD will be reported as specified in the protocol. The PAS studies will be reported as determined by its research and publications committee.

Funding

The investment to enable the creation of the TVT registry began 2 decades ago as STS and ACC founded their respective national clinical databases. The development of the TVT registry has been funded by STS and ACC. The on-going funding must maintain the independence of the governance and day-to-day activities of the registry.

Funding for operational expenses associated with TVT registry will predominantly be from site fees, namely, paid for by institutions with TVT programs. The FDA will provide some resources for monitoring the quality of data entered by sites through audits, particularly associated with PAS studies. Device PAS studies that are nested within the TVT registry will be appropriately funded by the sponsor. Investigator-initiated research will be able to access the data in the TVT registry with funding from private and public agencies. Funding for IDE studies may include support from industry, but strict firewalls have been placed to maintain the independence, impartiality, and scientific credibility of the professional societies in designing, conducting, and reporting trials. Both ACC and STS have formal rules for engagement with industry involving data use, scientific integrity, governance, marketing, and promotion (29–32).

Governance

The primary independent governing body is a steering committee of representatives from STS and ACC. Representatives from the Duke Clinical Research Institute, the National Heart, Lung, and Blood Institute, the FDA, and the CMS are nonvoting ex-officio members of the steering committee. The steering committee shall provide strategic direction for the TVT registry, monitor all activities, and have ultimate authority and responsibility for the scientific integrity and appropriate use of the TVT registry data for research and publications.

The research and publications subcommittee will oversee all activities related to research and publications using TVT registry data. Industry-sponsored PAS will have a separate research and publications committee. All committee members are required to submit relationship with industry information.

The stakeholder advisory group will provide input, guidance, and feedback to the steering committee on pertinent clinical and scientific topics. Members selected by the steering committee will represent stakeholders, including government entities, patient advocates, device manufacturers, and insurers.

Challenges for the TVT Registry

The principle challenges of the TVT registry include demonstration of its added value versus maintaining the status quo, justifying the burden of data collection, validating the completeness and quality of data, and being a professional "good shepherd" of using these data for objective, bias-free, and scientifically based reports. Furthermore, the TVT registry must be linked to other professional registries to enhance the efficiency of data entry, reduce redundancies, and to enable comparative effectiveness research and regulatory decision making.

National clinical registries are becoming part of the cost to offer high-end therapies such as ventricular assist devices, implantable defibrillators, and now TAVR. The burdens associated with entering high-quality data from hospitals are recognized and potentially will be reduced with medical information technology infrastructure improvements.

The costs of the TVT registry will need to be periodically assessed with transparency of the expenses and demonstration of the value of the deliverables. For industry, the transition from the prior PAS model to the use of the TVT registry must also have an on-going evaluation and process of improvement. The structure and governance of the TVT registry provides for this process and involvement of industry.

The quality of the data in the TVT registry is a top priority, and the means to monitor, audit, and adjudicate have been outlined. The reliance on CMS administrative data for longitudinal outcomes must be further studied. The implementation of novel and potentially more efficient means of event adjudication must be assessed in peer-reviewed scientific publications. New challenges are expected in implementing and optimizing the new pathway for clinical protocols that will provide CMS reimbursement and gather data for potential FDA decisions to expand indications for use of an approved device. This replaces the prior system of "off-label" use of devices with no pre-specified data collection and analysis, no pathway to potential expansion of indications, and challenges to the reimbursement and regulatory systems.

While a rational dispersion of new technology is appropriate, there are many unexplored and potentially unintended consequences of this new model of novel technology dispersion and centrally based control. For example, the need for a CMS-approved research protocol to allow use of an alternative access site to place an approved TAVR device starts to cross into the traditional realm of clinician control of procedural techniques. The CMS and FDA controlled research protocol pathway for the use of new approved technologies in narrowly defined off-label uses may result in more frequent appropriate use with a better understanding of these applications from registry-based data collection and analysis, but

the bureaucratic burdens, costs, and time delays need to be minimized. Finally, there will always be outliers not covered by research protocols for common off-label uses. The challenge is significant to refine this new model to optimize rational device dispersion, appropriate reimbursement, and effective regulation without compromising the need for clinicians and patients to individualize care within the broad context of scientific evidence presented in guidelines derived from population-based recommendations.

Future Perspective

The TVT registry is an ambitious undertaking with a potential to have a major impact on patient health care and safety, clinical research, evaluation throughout the device life cycle , and informed decision making by clinicians, patients, policy makers, payers, and regulators. Successful implementation of this model can be replicated broadly in other medical specialties and other areas of medical care. The TVT registry has been developed and implemented in the midst of on-going developments in the FDA's vision for the novel approaches to medical device evidence generation, synthesis, and evaluation, CMS's deliberations on national coverage decisions, and the medical device industry's adaptation to these changes (33,34). The data infrastructure created offers the ability to catalyze the joint initiatives of CMS and FDA (35). The professional societies have also embraced a new level of responsibility in coordinating and implementing these changes as well as being the voice and advocate of patients and clinicians. The launch of the TVT registry is only the beginning of a new model that will be refined and improved in the years to come.

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Key Words: aortic stenosis ■ mitral regurgitation ■ registry ■ valves.

VIEWPOINT

Need for a National Evaluation System for Health Technology

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Federal regulatory frameworks governing medical products are designed to (1) provide evidence that a product benefits patients when used as intended and should be available despite accompanying risks and (2) ensure timely access to needed therapies and diagnostics. Historically, policy makers and product developers have viewed these objectives as being in tension. However, ensuring safety, expediting patient access, and enabling innovation can be complementary goals within a regulatory framework for medical devices.

The US standard for marketing a medical device is "reasonable assurance of safety and effectiveness" (RASE).[1] Generally, clinical studies must be conducted to demonstrate RASE for both high-risk and innovative lower-risk devices and US patients and clinicians have greater assurances that the benefits of devices outweigh the potential risks. In contrast, other countries apply a standard of safety and performance with limited clinical data. The greater evidentiary burden of RASE may create disincentives for manufacturers to bring important medical devices to the United States or may delay access to devices. For example, the first transcatheter aortic valve replacement device was available for clinical use in Europe several years before it was available in the United States. However, there are examples of unsafe and ineffective devices that never made it to the US market; these can be found in a report[2] from the US Food and Drug Administration (FDA).

A key dilemma for device regulation is how to ensure timely access while also providing evidence to guide safe and appropriate use. When a device is approved for the US market, residual uncertainty about benefit and risk is typically addressed through postmarket evaluation. Premarket studies often do not fully reflect how a device will be used in practice, and participants enrolled in such studies may not represent the entire spectrum of patients likely to receive the device. The effects of operator experience, user learning curves, or skill level of the individual who implants the device and the supporting team also cannot be assessed until the device is in wider use. However, current approaches to postmarket evaluation have limitations. Even though the FDA can require device makers to perform postmarket studies, patients have few incentives to enroll in a study once a device is marketed, and many FDA-mandated postmarket studies for devices have been delayed, scaled back, or never finished. Generally, if the company makes a good-faith effort in performing postmarket studies, there are no penalties.

Furthermore, reporting of adverse events and device malfunctions currently depends on clinicians identifying and reporting a possible association; therefore, underreporting is likely common. Spontaneous reporting also fails to capture numerators and denominators that allow reliable risk estimation. Safety issues are therefore often not identified until many patients have been exposed to risks, leading to greater potential for avoidable harm as well as greater liability and loss of consumer confidence in the manufacturer. Spontaneous reporting is not systematic and can be biased by extraneous factors such as news reports. Other safety issues also depend on companies appropriately assimilating and reporting data.

However, a strategic approach to linking and using clinically based data sources, such as registries, electronic health records (EHRs), and claims data, could potentially reduce the burdens of obtaining appropriate evidence across the life cycle of a device. By leveraging clinical data and applying advanced analytics and flexible regulatory approaches tailored to the unique data needs and innovation cycles of specific device types, a more comprehensive and accurate framework could be created for assessing the risks and benefits of devices.

Harnessing New Technologies and Methods

Recent empirical work[3] has demonstrated the value of balancing rigorous premarket trials and effective postmarket evaluation. Raising premarket standards too high may lead device development and access to other countries with lower barriers and reduce investment in new technology.[4] Conversely, an ineffective postmarket system perpetuates uncertainty about appropriate device use. An ideal approach would match the degree of premarket evaluation with the degree of probable risk and benefit posed by the device, while emphasizing rigorous postmarket evaluation in conjunction with carefully planned premarket clinical studies.[3]

In 2012, the FDA took the first steps toward establishing a National Evaluation System for Health Technology (NEST) that could quickly identify problematic devices, accurately and transparently characterize and disseminate information about device performance in clinical practice, and efficiently generate data to support premarket clearance or approval of new devices and new uses of currently marketed devices. Recent multistakeholder reports[5] recommended developing a federated virtual system for evidence generation by creating strategic alliances among data sources including registries, EHRs, payer claims, and other sources; incorporating unique device identifiers (UDIs) over time; and activating multiple linkages among data sources to address specific questions. NEST should be operated by an independent coordinating center with governance comprising ecosystem stakeholders such as patients, health care professionals, health care organizations, payers, the medical device and digital health industries, and the government. Essentially, NEST should be of, by, and for the medical device ecosystem and configured to provide

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maximal value to stakeholders, including the critical data needed by the FDA to make decisions that currently must be made with less comprehensive information.

Building on Current Efforts

Professional societies have developed device registries focused on quality of care that include detailed information about clinical circumstances, procedures, and outcomes. When linked with projects leveraging EHRs and complementary sources, such as claims databases, device registries can provide rich data on long-term outcomes. In addition, the FDA's Sentinel Initiative[6] collects detailed claims data on the clinical outcomes of more than 100 million individuals in the US system. If the Sentinel Initiative would incorporate UDIs, it could provide a strong component of NEST.[5] In addition, efforts such as the National Patient-Centered Clinical Research Network and the National Institutes of Health Collaboratory are building on the experience of the Sentinel Initiative. The 2015 certification criteria[7] require that EHRs be capable of capturing UDIs for implantable devices in a standardized way. Accelerating incorporation of UDIs could further enhance the utility of EHRs for this purpose because current EHRs often do not identify the specific device used.

However, better evidence requires more than just improved infrastructure. A more strategic approach is needed for collecting data, establishing core data sets, using common definitions, facilitating transfer and linking among interoperable data sources, and efficiently embedding research data collection into routine clinical workflow and participating patients' daily activities. Public and private sectors must share data, expertise, and funding, and the end result must provide value to all stakeholders. Importantly, the national system would not create its own evidence repository from clinical practices, but instead could provide the governance, transparency, consistency, coordination, and standardization necessary to reduce costs and the time required to generate evidence while expanding appropriate access to and use of data sources from clinical practice.

All stakeholders in the medical device ecosystem have strong incentives for engaging with NEST. Patients could benefit from a systematic, transparent approach to device evaluation and access to better information about appropriate device use. Physicians, hospitals, health systems, and practices could benefit from information about quality of care related to device selection, procedural outcomes, and follow-up; they may also see a reduction in multiple reporting requirements. Device manufacturers could provide high-quality data to support informed decisions about when devices should be used in particular patients and how to mitigate risk across the life cycle of the device. NEST also could highlight opportunities for adding value through device enhancements and suggest development pathways for innovative technologies.

NEST also could reduce the time and cost associated with developing evidence to support premarket approval, clearance, payer coverage, and reimbursement decisions. For cases in which the potential public health value of the device is high, data otherwise collected in the premarket setting could be responsibly collected after the device enters the market, given appropriate assurances. NEST also could potentially reduce the cost of or even the need for some postmarket studies and adverse event reporting because relevant data are already being gathered. In addition, NEST may obviate the need for FDA premarket review of some device modifications because more timely and informative evaluations could occur during routine data collection, which is an approach already being piloted for a handful of device types.

Conclusions

A national evaluation system that engages all stakeholders could enable the FDA to focus efforts on facilitating the development and interpretation of more informative data essential for policy making and clinical decisions for individuals and populations. When issues with medical technologies arise, they could potentially be quickly detected and understood within the appropriate context. Ultimately, these changes could contribute to a much more efficient system that rewards innovation that leads to better health outcomes, creating powerful incentives for continuous improvement and accelerating access to technologies that patients and physicians can use with the assurance of safety, efficacy, and a well-characterized balance of benefit and risk.

ARTICLE INFORMATION

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Forum on
DRUG DISCOVERY, DEVELOPMENT,
and TRANSLATION

MEMORANDUM

TO: Drug Forum Members

FROM: Jonathan Phillips, Associate Program Officer

DATE: September 11, 2017

SUBJECT: Real-World Evidence Public Workshop #1, September 19-20

Date/Time: **Tuesday, September 19, 2017** Public Workshop: 8:00 am–5:30 pm
Tuesday, September 19, 2017 Dinner, 6:30 pm–8:30 pm at Rasika West End, 1190 New Hampshire Ave NW, Washington, DC 20037
Wednesday, September 20, 2017 Public Workshop: 8:00 am–12:30 pm

Meeting: National Academy of Sciences Building, Lecture Room
2101 Constitution Avenue NW, Washington, DC 20418

Workshop Objectives:

- This workshop will focus on how to align incentives to support collection and use of real-world evidence in health product review, payment, and delivery. Incentives need to address barriers impeding the uptake of real-world evidence, including barriers to transparency.

Meals: On Tuesday, September 19 a breakfast (8:00 am) and lunch will be provided during the public workshop. A working dinner will be hosted at that evening at 6:30 pm (**Rasika West End**, 1190 New Hampshire Ave NW, Washington, DC 20037). On Wednesday, September 20 a breakfast (8:00 am) will be provided.

Travel: **We request that all guests book their transportation arrangements by calling Kentlands Travel at 1-800-552-6425 or by sending an email to NAS@UniglobeKentlands.com.** Refer to **Travel Code HMD170204** when making travel arrangements. Note: Any travel not booked through Kentlands must be pre-approved by NASEM staff.

Hotel: A block of rooms has been reserved at the **State Plaza Hotel, 2117 E Street, Washington, DC 20037**. Contact Jonathan Phillips (jphillips@nas.edu) to reserve a room (or use **this link**). The cost of your room will be billed directly to the National Academies; however, any incidental expenses will need to be settled during checkout. **Please note: if you choose not to use our accommodations and book with another hotel, we will be generally unable to reimburse your hotel stay.** Hotel confirmations will be emailed prior to the meeting.

NOTE: Federal employees are asked to pay for their own travel expenses and lodging.

Travel Policies:

- **Making your own travel arrangements:** If for some reason you must make your own travel arrangements, **please note that all travel not booked through Kentlands must be pre-approved by National Academies staff in order to be reimbursed.** Please contact Jonathan Phillips with your proposed travel details for review.
- **Making a stop en route:** If you need to make an additional stop(s) en route to or from the meeting, please inform Jonathan Phillips in advance so that comparative ("constructive") costs, upon which reimbursement is based, may be obtained. You will be reimbursed for the cost of a direct round trip ticket between your permanent place of business and the National Academies' meeting place or the face value of the ticket, whichever is less.
- **Ticket changes:** It is National Academies policy that no changes in tickets will be paid for by the National Academies except in the cases of a documented emergency. Therefore, any changes to your tickets will need to be accompanied by an explanation of the emergency necessitating the change. Kentlands will then contact the National Academies to approve the requested change. Please understand that we will not be able to pay for changes due to scheduling issues.
- **Reimbursement:** The National Academies will reimburse for coach-class travel on U.S. flag carriers only. All booking methods will require you to submit the airline bill for reimbursement after the event. **Reimbursement instructions will be released following the meeting.**

Reimbursement information:

The National Academies will reimburse you after the meeting via an electronic Travel Expense Report (eTER) voucher for reasonable travel expenses, including:

- Economy coach fare on American-owned carriers
- Ground transportation: personal cars, taxi cabs, shuttles, and public transportation expenses
    - Sedan services are only reimbursable if the cost is comparable to a taxi fare.
    - Car rental is not an allowable expense in the DC area.
- Hotel lodging cost up to the maximum lodging rate and as part of our hotel room block
- Meal costs

The maximum daily reimbursement amount for meals, tips, and other incidentals is $69/day. The current rate for reimbursement of mileage for use of a personal vehicle is 51.0 cents per mile.

Please retain all receipts for any expenses over $75 incurred during travel on Academy business, including original airline receipts, even if they were direct billed to NAS. No charges over $75 can be reimbursed without an accompanying receipt. This includes items such as airfare, parking, taxi charges, and meals as described above.

TERs should be submitted within 15 days of completion of travel.

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Directions from the State Plaza Hotel to the National Academy of Sciences

NOTE: The National Academy of Sciences is 0.2 miles from the hotel

By Walking:

Start: 2117 E Street NW

1. Head east on E Street NW toward 21st Street NW
2. Turn right onto 21st Street NW (0.2 miles)

End: 2101 Constitution Avenue NW

Getting to the National Academy of Sciences (NAS) Building

2101 Constitution Avenue, Washington DC 20418

Airports: The meeting site is approximately 5 miles from Washington National Airport (a 20-minute cab ride depending on the time of day) and approximately 25 miles from Dulles International Airport (a 45-minute cab ride).

Metro: The Foggy Bottom metro stop (Orange/Blue Line) is located at 23rd and I Streets NW. Walking from the metro to the NAS building takes approximately 15 minutes. The *C Street Entrance* to the NAS building is the closest entrance to Metro. A map is located below. **(A is the NAS Bldg.; B is the State Plaza; C is the Foggy Bottom Metro station)**.

Parking: The parking lot for the National Academy of Sciences is located on 21st Street NW, between Constitution Avenue and C Street. However, space is very limited, so you may want to use an alternate mode of transportation. If the lot is full, there is a Colonial Parking garage near G and 18th Streets, NW (cash only). It is about 15 minutes walking distance from the NAS building.