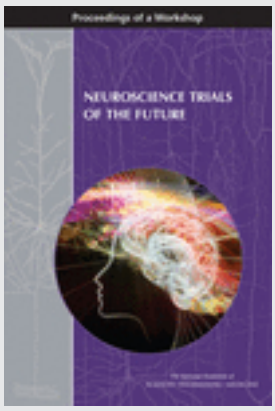

Neuroscience Trials of the Future: Proceedings of a Workshop

DETAILS

112 pages | 6 x 9 | PAPERBACK
ISBN 978-0-309-44255-8 | DOI: 10.17226/23502

AUTHORS

Sheena M. Posey Norris, Lisa Bain, and Clare Stroud, Rapporteurs; Forum on Neuroscience and Nervous System Disorders; Board on Health Sciences Policy; Health and Medicine Division; National Academies of Sciences, Engineering, and Medicine

NEUROSCIENCE TRIALS OF THE FUTURE

Proceedings of a Workshop

Sheena M. Posey Norris, Lisa Bain, and Clare Stroud, *Rapporteurs*

Forum on Neuroscience and
Nervous System Disorders

Board on Health Sciences Policy

Health and Medicine Division

The National Academies of
SCIENCES • ENGINEERING • MEDICINE

THE NATIONAL ACADEMIES PRESS
Washington, DC
www.nap.edu

PREPUBLICATION COPY: UNCORRECTED PROOFS

THE NATIONAL ACADEMIES PRESS • 500 Fifth Street, NW • Washington, DC 20001

This project was supported by contracts between the National Academies of Sciences and the Alzheimer's Association; Brain Canada Foundation; Cohen Veterans Bioscience; the Department of Health and Human Services' Food and Drug Administration and National Institutes of Health (NIH) (HHSN26300089 [Under Master Base # DHHS-10002880]) through the National Center for Complementary and Integrative Health, National Eye Institute, National Institute of Mental Health, National Institute of Neurological Disorders and Stroke, National Institute on Aging, National Institute on Alcohol Abuse and Alcoholism, National Institute on Drug Abuse, and NIH Blueprint for Neuroscience Research; Department of Veterans Affairs (VA240-14-C-0057); Eli Lilly and Company; Foundation for the National Institutes of Health; Gatsby Charitable Foundation; Janssen Research & Development, LLC; Lundbeck Research USA; Merck Research Laboratories; The Michael J. Fox Foundation for Parkinson's Research; National Multiple Sclerosis Society; National Science Foundation (BCS-1064270); One Mind for Research; Pfizer Inc.; Pharmaceutical Product Development, LLC; Sanofi; Society for Neuroscience; Takeda Pharmaceutical Company Limited; and Wellcome Trust. Any opinions, findings, conclusions, or recommendations expressed in this publication do not necessarily reflect the views of any organization or agency that provided support for this project.

International Standard Book Number-13: 978-0-309-XXXXX-X
International Standard Book Number-10: 0-309-XXXXX-X
Digital Object Identifier: 10.17226/23502

Additional copies of this publication are available from the National Academies Press, 500 Fifth Street, NW, Keck 360, Washington, DC 20001; (800) 624-6242 or (202) 334-3313; http://www.nap.edu.

Printed in the United States of America

Suggested citation: National Academies of Sciences, Engineering, and Medicine. 2016. *Neuroscience trials of the future: Proceedings of a workshop.* Washington, DC: The National Academies Press. doi: 10.17226/23502.

PREPUBLICATION COPY: UNCORRECTED PROOFS

The National Academies of
SCIENCES • ENGINEERING • MEDICINE

The **National Academy of Sciences** was established in 1863 by an Act of Congress, signed by President Lincoln, as a private, nongovernmental institution to advise the nation on issues related to science and technology. Members are elected by their peers for outstanding contributions to research. Dr. Marcia McNutt is president.

The **National Academy of Engineering** was established in 1964 under the charter of the National Academy of Sciences to bring the practices of engineering to advising the nation. Members are elected by their peers for extraordinary contributions to engineering. Dr. C. D. Mote, Jr., is president.

The **National Academy of Medicine** (formerly the Institute of Medicine) was established in 1970 under the charter of the National Academy of Sciences to advise the nation on medical and health issues. Members are elected by their peers for distinguished contributions to medicine and health. Dr. Victor J. Dzau is president.

The three Academies work together as the **National Academies of Sciences, Engineering, and Medicine** to provide independent, objective analysis and advice to the nation and conduct other activities to solve complex problems and inform public policy decisions. The Academies also encourage education and research, recognize outstanding contributions to knowledge, and increase public understanding in matters of science, engineering, and medicine.

Learn more about the National Academies of Sciences, Engineering, and Medicine at **www.national-academies.org.**

The National Academies of
SCIENCES • ENGINEERING • MEDICINE

Reports document the evidence-based consensus of an authoring committee of experts. Reports typically include findings, conclusions, and recommendations based on information gathered by the committee and committee deliberations. Reports are peer reviewed and are approved by the National Academies of Sciences, Engineering, and Medicine.

Proceedings chronicle the presentations and discussions at a workshop, symposium, or other convening event. The statements and opinions contained in proceedings are those of the participants and have not been endorsed by other participants, the planning committee, or the National Academies of Sciences, Engineering, and Medicine.

For information about other products and activities of the Academies, please visit nationalacademies.org/whatwedo.

PLANNING COMMITTEE ON NEUROSCIENCE TRIALS OF THE FUTURE[1]

RICHARD KEEFE (*Co-Chair*), Duke University Medical Center
ATUL PANDE (*Co-Chair*), Tal Medical
BRUCE BEBO, National Multiple Sclerosis Society
STEPHEN BRANNAN, FORUM Pharmaceuticals, Inc.
DANIEL BURCH, Pharmaceutical Product Development, LLC
TIMOTHY DENISON, Medtronic, Inc.
HANK GREELY, Stanford University
FRANCES JENSEN, University of Pennsylvania Perelman School of Medicine
AMIR KALALI, Quintiles, Inc.
PETRA KAUFMANN, National Center for Advancing Translational Sciences
THOMAS LAUGHREN, Laughren Psychopharm Consulting, LLC

HMD Staff

CLARE STROUD, Forum Director
SHEENA M. POSEY NORRIS, Program Officer
JOANNA ROBERTS, Senior Program Assistant (*from January 2016*)
ANNALYN WELP, Senior Program Assistant (*until December 2015*)
ANDREW M. POPE, Director, Board on Health Sciences Policy

[1]The National Academies of Sciences, Engineering, and Medicine's planning committees are solely responsible for organizing the workshop, identifying topics, and choosing speakers. The responsibility for the published Proceedings of a Workshop rests with the workshop rapporteurs and the institution.

FORUM ON NEUROSCIENCE AND NERVOUS SYSTEM DISORDERS[1]

[1]The National Academies of Sciences, Engineering, and Medicine's forums and round-tables do not issue, review, or approve individual documents. The responsibility for the published Proceedings of a Workshop rests with the workshop rapporteurs and the institution.

DAVID MICHELSON, Merck Research Laboratories
JAMES OLDS, National Science Foundation
ATUL PANDE, Tal Medical
STEVEN PAUL, Voyager Therapeutics, Inc.
EMILIANGELO RATTI, Takeda Pharmaceuticals International
TODD SHERER, The Michael J. Fox Foundation for Parkinson's Research
DAVID SHURTLEFF, National Center for Complementary and Integrative Health
PAUL SIEVING, National Eye Institute
NORA VOLKOW, National Institute on Drug Abuse
STEVIN ZORN, Lundbeck Research USA

HMD Staff

CLARE STROUD, Forum Director
SHEENA M. POSEY NORRIS, Program Officer
PAMELA REESE, Senior Program Assistant (*from May to July 2016*)
JOANNA ROBERTS, Senior Program Assistant (*from January to April 2016*)
ANDREW M. POPE, Director, Board on Health Sciences Policy

Reviewers

This Proceedings of a Workshop has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published Proceedings of a Workshop as sound as possible and to ensure that the Proceedings of a Workshop meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the process. We wish to thank the following individuals for their review of this Proceedings of a Workshop:

RAY DORSEY, University of Rochester Medical Center
DONALD JONES, Scripps Translational Science Institute
SALLY OKUN, PatientsLikeMe
WILLIAM POTTER, National Institute of Mental Health
STEVEN ROMANO, Mallinckrodt Pharmaceuticals

Although the reviewers listed above have provided many constructive comments and suggestions, they did not see the final draft of the Proceedings of a Workshop before its release. The review of this Proceedings of a Workshop was overseen by **JOSEPH T. COYLE,** Harvard Medical School. He was responsible for making certain that an independent examination of this Proceedings of a Workshop was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this Proceedings of a Workshop rests entirely with the rapporteurs and the institution.

Contents

1

Introduction[1]

Although major strides have been made over the past two decades in basic neurosciences, translation into more effective treatments has eluded the field (Kaitin, 2012). Among the many factors contributing to this reality are the standard clinical trial methods that have barely changed during this time, with the exception of increased use of electronic data acquisition and analysis.

Clinical trials for diseases of the central nervous system (CNS) suffer from high failure rates due, in part, to the limited understanding of disease pathophysiology and lack of well-validated targets (Pankevich et al., 2014; Wegener and Rujescu, 2013). In addition, even in the hands of experienced investigators, poor assay sensitivity[2]; the lack of reliable, validated, and clinically meaningful endpoints; high placebo or non-specific responses; high variability among participants and sites; poor treatment adherence; and inadequate recruitment and retention have adversely affected pharmaceutical and device development (Ereshefsky et al., 2016; Gupta, 2012; Silberman, 2009). One of the net effects of these challenges has been to simply increase the trial sample size in an attempt to control type II error (false-negative results) (Becker and Greig, 2009; Button, 2013). Yet, promising early clinical data are often not replicated in large registration trials, resulting in Phase III failure rates that are among the highest in medicine (Kesselheim et al., 2015). The apparent unsustainability of the current clinical development pipeline has driven many large pharmaceutical companies to significantly decrease investments in neuroscience (Abbott, 2011; Miller, 2010; Riordan and Cutler, 2011), alt-

[1]The planning committee's role was limited to planning the workshop, and the workshop summary has been prepared by the workshop rapporteur as a factual summary of what occurred at the workshop. Statements, recommendations, and opinions expressed are those of individual presenters and participants, and have not been endorsed or verified by the National Academies of Sciences, Engineering, and Medicine, and they should not be construed as reflecting any group consensus.

[2]For examples of recent terminated trials in Parkinson's disease and Huntington's disease due to futility, please go to: http://www.ninds.nih.gov/disorders/clinical_trials/2CARE-Early-Study-Closure.htm; https://nccih.nih.gov/research/extramural/crest-e; and https://parkinsontrial.ninds.nih.gov/netpd-LS1-study-termination.htm (accessed June 2, 2016).

hough, there is some evidence that this trend is reversing (Herper, 2015; Tracy, 2015). Of drug development projects started between 2000 and 2004, the number of new medical entities (NMEs)[3] generated each year was less than half the number of NMEs generated by projects started between 1990 and 1999. However, within each therapeutic area, the productivity was similar, indicating that lower productivity reflected a shift to areas where there is greater medical need, but higher risk, such as neuroscience and oncology (Pammolli, 2011). In comparison to oncology, there are far fewer clinical trials for nervous system disorders, yet in 2015 the Food and Drug Administration (FDA) approved 19 drugs in oncology and 9 in neuropsychiatry, suggesting greater efficiency in the neuroscience area, said Perry Nisen, chief executive officer of Sanford Burnham Prebys Medical Discovery Institute.

Quite apart from the business perspective, the fact that many early-stage clinical trials misleadingly provide a false-positive signal (a type I error) raises the question of whether volunteering for these trials is in the best interest of trial participants (Button et al., 2013; Cohen et al., 2007).

Better methods, from clinical study design through execution and evaluation, could help restore the integrity, feasibility, acceptability, efficiency, and economic viability of clinical neuropsychiatric drug development. However, in order to use innovative approaches to address these challenges, buy-in and acceptance from the regulatory community will be important (Parekh et al., 2015). For example, adaptive trials, in which trial parameters are modified based on interim data, could offer a more efficient means of addressing experimental questions involving multiple uncertainties, although they are often infrequently used (Wang et al., 2011). In addition, understanding the utility of wearable and patient monitoring devices (and the data generated) in neuroscience clinical trials is important (Capone, 2015; Desgrousilliers and Keet, 2015; Kumar et al., 2013).

WORKSHOP OBJECTIVES

On March 3–4, 2016, the National Academies of Sciences, Engineering, and Medicine's Forum on Neuroscience and Nervous System Disorders held a workshop in Washington, DC, bringing together key stakeholders to discuss opportunities for improving the integrity, effi-

[3]Drugs that containing an active moiety that has not been previously approved by the FDA.

ciency, and validity of clinical trials for nervous system disorders (see Box 1-1). Participants in the workshop represented a range of diverse perspectives, including individuals not normally associated with traditional clinical trials, added co-chair Atul Pande, chief medical officer and executive vice president of Tal Medical. The purpose of this workshop was to generate discussion about not only what is feasible now, but what may be possible with the implementation of cutting-edge technologies in the future, according to workshop co-chair Richard Keefe, professor of psychiatry and behavioral sciences at Duke University School of Medicine. Thus, workshop participants were asked to consider solutions that could be implemented immediately or over the short term, as well as innovations that will change the way clinical trials look over the next 10 years. Potential solutions offered by several participants addressed the need to simplify and decrease the costs of trials. Keefe noted that all innovations, whether technological or methodological, should be tested with empirical data, and such data should drive adoption. Robert Califf, Commissioner of Food and Drugs at the FDA, stated that the best medical outcomes occur when health care providers and patients are armed with high quality-based evidence to make medical decisions, which is most likely to happen when clinical trials are conducted in practice.

ORGANIZATION OF PROCEEDINGS

The following report summarizes the workshop presentations and discussion. Chapter 2 provides an overview of the challenges and opportunities for 21st-century neuroscience clinical trials noted by many workshop participants. Chapter 3 outlines novel research and clinical trial design approaches to address heterogeneity and expedite the development of biomarkers and other drug development tools, including clinically meaningful outcome measures. The potential impact of technological innovations on clinical trials is discussed in Chapter 4. Chapter 5 focuses on regulatory challenges with an international perspective and the potential implications for 21st-century clinical research innovations. Ethical considerations, including data protection and human subjects' protection, are addressed in Chapter 6. Finally, the evidence base for real-world use and reimbursement issues are discussed in Chapter 7.

BOX 1-1
Statement of Task

An ad hoc committee planned and conducted a 2-day public workshop to explore opportunities to improve the efficiency and validity of clinical trials for nervous system disorders. The workshop will bring together key stakeholders to consider ways to advance therapeutic development for nervous system disorders by using innovative clinical trial designs; improving patient selection, engagement, and retention; and enhancing clinical monitoring to help decrease the failure rate of drugs and devices in development.

Presentations and discussions will be designed to:

- Examine assay sensitivity challenges in clinical trials for nervous system disorders, including causes of poor signal detection and type II error.
- Explore opportunities to improve clinical trial methodology for nervous system disorders, including strategies for:
  - Guiding the selection of patient populations, such as using endophenotyping to increase the yield of responders and using genomics, proteomics, and imaging biomarkers to "stage" nervous system disorders.
  - Increasing patient engagement through all phases of the clinical trial (i.e., recruitment, screening, and posttrial) and improving adherence and retention.
  - Using patient-centric technologies (e.g., wearables) and integrating such real-world, real-time data with traditional clinical data.
  - Improving monitoring during clinical trials.
  - Leveraging recent advances in diagnostics, biomarkers, and endpoints to develop more efficient clinical trials. Using novel trial designs (e.g., adaptive, enrichment, and platform design studies) for nervous system disorders, including associated regulatory challenges and opportunities

2

Neuroscience Clinical Trials: An Overview of Challenges and Potential Opportunities

Drug development across all therapeutic areas is fraught with excessive risk, high costs, and low productivity, according to Steven Romano, senior vice president and chief science officer of Mallinckrodt Pharmaceuticals. In this challenging business climate, investment has been shifting to areas with a clear path forward; currently, there is no clear, rational path for many nervous system disorders. Although failed trials in the neuroscience space continue to plague the industry, Daniel Burch, vice president and global therapeutic area head for neuroscience at Pharmaceutical Product Development (PPD), stated that the ultimate failure is not learning from a negative trial the reasons for failure. Drew Schiller, chief technology officer and co-founder of Validic, suggested embracing failure and exploiting it as an avenue to find answers to questions that may not even have been asked. While some of the challenges, barriers, and opportunities discussed at the workshop were specific to neuroscience clinical trials, many were general to trials across therapeutic areas. These topics, listed on the next few pages, are expanded on in the succeeding chapters.

CHALLENGES AND BARRIERS TO NEUROSCIENCE CLINICAL TRIALS[1]

- **Limited Understanding of the Underlying Biology of Disease.** The inaccessibility of the brain makes it challenging to examine through traditional methods such as biopsy. Despite an explosion in basic neuroscience research, particularly in clinical biology and genetics, there are few validated molecular targets for most nervous system disorders. Those that have been identified—mostly for psychiatric diseases such as depression, psychosis, and anxiety—are decades old. The lack of novel and validated targets limits the development of innovative treatments. The lack of compelling biomarkers and new disease models limits investigators' ability to interrogate the pharmacology of investigational compounds across multiple dimensions (e.g., behavior, functional, electrophysiological, etc.) in proof of concept studies (Romano).
- **Understanding How Nosology May Be Constraining Innovation.** Several participants noted that progress towards identifying novel and effective treatments for psychiatric diseases may be constrained by reliance on the *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. (DSM-5) (American Psychiatric Association, 2013). Despite the perceived shortcomings of the DSM, it is an entrenched system widely used by drug developers, academic researchers, clinicians, regulators, and payers. Moving beyond the DSM will therefore be challenging, and regulators are open to alternatives, but lack efficient mechanisms to do so (Laughren).
- **Insufficient Sharing of Data, Knowledge, and Expertise.** Despite statements in support of data sharing from multiple sectors (e.g., IOM, 2015; Taichman et al., 2016), some academic and industry scientists continue to resist sharing their data (Rockhold). In addition, the research community is beginning to recognize that it may be time to review and revise the Health Insurance Portability and Accountability Act (HIPAA) restrictions as it continues to impede research (Koski).

[1]These lists highlight topics discussed throughout this workshop, but should not be construed as reflecting a consensus of workshop participants or any endorsement by the National Academies of Sciences, Engineering, and Medicine or the Forum on Neuroscience and Nervous System Disorders.

- **High Failure Rates of Clinical Trials.** During the drug development pipeline, thousands of compounds are screened through drug discovery efforts, with hundreds reaching the preclinical space. Of every 10 compounds that make it to human studies, approximately one will reach the marketplace. On average, this entire process takes between 10 and 15 years (DiMasi and Grabowski, 2007) (Romano). Clinical trial failures have increased across each phase of development, which continues to negatively impact research and development (R&D) productivity (Pammolli et al., 2011) (Romano).
- **High Cost of Clinical Trials Across Therapeutic Areas.** The cost of R&D for a new drug is now approaching $2.6 billion (direct cost plus the cost of failure) (TCSDD, 2014), with costs increasing across the entire spectrum of drug development activities. R&D spending from the early 1960s through 2013 has outpaced productivity across all therapeutic areas. These increased costs are attributed in part to the size of and complexity of clinical trials, which involve more stakeholders (Romano).
- **Operational Challenges Contributing to Variability Across Sites.** The large number of inexperienced investigators (e.g., first-time filers who often may not file again for another trial) conducting trials and the high turnover of even experienced investigators results in increased variability and poorer performance by clinical trial sites (TCSDD, 2015). In addition, protocol noncompliance has grown over the past decade, accounting for nearly half of all site deficiencies (TCSDD, 2015) (Romano).
- **Low Yield to Date in the Search for Biomarkers.** Several participants noted the lack of validated biomarkers for nervous system disorders; particularly those with predictive power.
- **Lack of Clarity on Regulatory Requirements.** A few participants stated that companies need more clarity from regulators on what information to collect as part of their clinical trial submissions. For example, data on non-serious adverse events or measures obtained as part of routine clinical care on every patient enrolled in a large pivotal trial are not useful to regulators and expensive to collect (Califf), yet sponsors collect many types of data out of concern that regulators will reject their applications if these data are not included.

OPPORTUNITIES TO IMPROVE NEUROSCIENCE CLINICAL TRIALS

Several workshop participants acknowledged that investigators are starting to address many of above challenges associated with neuroscience clinical trials. Moreover, Romano predicted that an explosion in neuroscience basic research, particularly in clinical biology and genetics, would drive more successful drug development paradigms. He noted that scientists are making progress in recognizing and deconstructing complex behavioral syndromes.

Clarifying the Underlying Biology of Nervous System Disorders

- Identifying endophenotypes—including neuroimaging, functional, neurocircuitry, biochemical, neuroendocrine, cognitive, and neuropsychological endophenotypes—has informed genetic analysis, resulting in a clarification of genetic determinants and identification of relevant targets. For example, in 2012, Buckholtz and Meyer-Lindenberg proposed that common symptoms arise from common circuit dysfunction, suggesting a different way of thinking about potential treatment targets that might be specific to a symptom, but not to a particular condition (2012). Developing more relevant animal models will facilitate translation of fundamental discoveries into effective treatments (Romano).

Achieving the Necessary Evidence Across All Phases of Drug Development

- Demonstrating proof of mechanism is essential to clarifying exposure at the target site and interaction with the pharmacological target, thus providing evidence of relevant and expected pharmacological activity (Romano).
- Demonstrating proof of concept enables optimization of signal detection, and may lead to representative clinical trials (Califf and Romano).
- Rigorously evaluating exposure and response in Phase IIb dose-finding studies is critical, and ensuring continuity between Phase II and Phase III pivotal trials with regard to population characteristics and outcome measures is necessary to allow translation of

the drug effect into a larger, more heterogeneous population, and to minimize placebo response and variability (Romano).

Developing Novel Tools, Endpoints, and Statistical Approaches to Improve the Efficiency of Clinical Studies

- Combining whole-genome sequencing and computerized, adaptive self-reports with item response theory and random forest models may enable more accurate assessment of dimensions of psychiatric conditions (Bilder).
- Using multilevel endpoints that enable assessment across multiple domains (e.g., symptoms, neuropsychological, cognitive) may improve linkage of these domains to disability (Bilder).
- Developing biomarkers using unbiased screening approaches and translating these endpoints into a clinical context through partnerships is needed for neuroscience trials (Chen-Plotkin).
- Eliminating silos in neurology and psychiatry, especially at the translational interface, is necessary in order to identify and validate common biomarkers or combinations of biomarkers across disease areas (Jensen).
- Aligning animal models and preclinical studies using common data elements may help to sync studies, allowing investigators to move efficiently from preclinical to clinical trials (Jensen).
- Incorporating causal and network models that demonstrate progression of symptoms over time may improve randomization, sample selection, and choice of interventions (Bilder).
- Standardizing measures, as well as how biospecimens are collected, as demonstrated by the Alzheimer's Disease Neuroimaging Initiative (ADNI) is important (S. Kapur and Pani).
- Testing novel treatments against comparators rather than placebos will be important to gain a better sense of their potential value in the marketplace compared with the current standard of care (Romano).
- Applying machine learning techniques to clinical trial data may help to identify fraudulent data, which are frequently introduced by underperforming clinical trial sites (de Vries).
- Exploiting innovative enabling technologies, such as virtual reality and the Internet of Things, may help to capture a greater array of data within clinical trials than traditional methods (Reites).

Implementing Operational Changes to Clinical Trials

- Improving the training and capabilities of investigators is critical, particularly for complicated trials that require a more sophisticated skill set among trialists (Koski and Romano).
- Generating data signatures before entry into a study and incorporating existing data streams help contextualize and validate in-trial data (Kieburtz).
- Removing administrative burdens on investigators and other site personnel may help to expand the number of studies that can be conducted without raising costs (Kieburtz).
- Building regionally powerful clinical trial centers in place of existing smaller trial sites would centralize expertise and provide economies of scale (Kieburtz).

Changing the Scope and Scale of Studies

- Using big data approaches—for example, studies that incorporate large genomics databases—has already become the dominant paradigm in some areas such as autism, and has the potential to transform other areas of neuroscience as well, leading to more targeted trials (S. Kapur). However, simple trials should not be overlooked as they may also provide value. The key is to design trials that meet specific and perhaps narrow objectives, with careful consideration of heterogeneity and methods of data analysis (Pencina).
- Recognizing the increasing role that patient advocacy organizations will likely play in trials of the future is important, particularly with regard to the creation of multisite data models and the involvement of technology companies (de Vries).

Building Innovative Research Programs

- Building a more agile research methodology may help to rapidly and efficiently test various technologies and conduct feasibility testing (Rodarte).
- Establishing an accelerator program with domain experts and scientists, where ideas are transformed into proof-of-concept studies, may reduce the length of study development and digital

health solutions from 12 to 18 months to approximately 90 days (Reites).
- Similar to oncology, integrating clinical trials into routine clinical care will be important for nervous system disorders (Kalali).
- Developing more collaborative programs between pharmaceutical and technology companies would tap into the strengths of both sectors to accelerate therapeutic development (Kalali).
- Adopting methodology from other therapeutic areas with regard to novel designs, recruitment, and assessment may be beneficial for neuroscience trials (Laughren).
- Establishing comprehensive neuroscience centers, akin to the National Cancer Institute's Comprehensive Cancer Centers, might improve integration between basic science and the clinical enterprise (Nisen).

Collaborating Across Disciplines and Countries

As the complexity of the drug development ecosystem has increased, collaboration among pharmaceutical companies, academia, regulators, patients, payers, and social and business entrepreneurs has increased.

- Facilitating cultural changes regarding how promotions are made and grants are awarded in academic institutions will be needed to facilitate increased collaboration and data sharing (S. Kapur).
- Building international consortia and public–private partnerships are needed to advance the development of new tools (Chen-Plotkin and S. Kapur).
- Identifying the pioneers who are testing novel paradigms in other fields, and bringing them together with neuroscientists, may help pivot those approaches to the clinical trials space (Reites).
- Creating an environment where innovative companies can come together and, within a rigorous scientific and regulatory framework, determine the best models, algorithms, and digital strategies, might optimally enable drug development and patient management (de Vries).
- Leveraging consumer engagement achieved by electronics companies that have created wearable devices and apps with new models of collecting information, as well as social media platforms that have been used to successfully recruit participants for clinical trials, will be important for trials of the future (Schiller).

Encouraging Increased Data Collection and Sharing to Maximize Learning from Clinical Trials

- Data mining using artificial intelligence algorithms and multivariate statistical techniques enables investigators to identify patterns in large datasets that can be useful for generating hypotheses (Koski).
- With regard to concerns about "phshing," that is, searching databases for personal information to be used for nefarious purposes, several workshop participants urged reasonableness and social responsibility, commenting that these concerns may be overblown and prevent valuable research (Chiauzzi, Koski, Rockhold, and Snowberg).
- Bringing various stakeholders in academia and industry together is needed to craft interoperable data-sharing mechanisms (Rockhold).
- Developing databases with clinical trial data across therapeutic areas, similar to the FDA's and Mortara Instruments' electrocardiogram (ECG) warehouse,[2] would be beneficial for investigators when assessing a potentially new therapeutic (Laughren).

Making Clinical Trials More Patient-Centric

- While statistical significance is important, it is not enough to determine if a therapeutic will be clinically meaningful to patients. Designing trials where clinical significance is at the forefront (e.g., measuring treatment effects against comparators and not just placebos) is imperative; however, several participants noted that the field needs to further define what it means for a therapeutic to be clinically significant (S. Kapur, Pencina, and Romano).
- Engaging in a sophisticated dialogue with patients about the value of different outcomes and the best way to measure and analyze these outcomes is needed (Kapur).
- Employing mobile and passive monitoring of motion, location, voice, app usage, facial affect, sleep, heart rate, and other characteristics may provide more patient-centric assessments of disease progression and response to treatment (Bilder).

[2]For more information, go to https://www.ecgwarehouse.com/index.php (accessed June 2, 2016).

- Building an open research environment, where participants have access to their own data, may help to increase patients' willingness to engage in a trial (Rodarte).
- When incorporating wearables into a clinical trial, it is important to consider at the design stage how devices will be allocated to participants and what will be done when device manufacturers introduce newer versions or implementations during a trial (Reites).
- Reinforcing to trial participants the nature of the social contract implicit in a clinical trial is critical in order to show that their value in the study is essential, not only for them, but to the broader patient population (Hernandez).
- Ensuring that protocols are simple both for the participants and the practitioners involved may help to decrease confusion and patient attrition (Hernandez).
- Implementing new technologies with a systems perspective helps to ensure they are inter-operable and connectable (Koski).
- Developing new paradigms that reduce patient burden, for example, by taking a sample collection to the participant rather than requiring the participant to come to a central location, may increase patient engagement and decrease attrition (Koski).
- It will be important to adapt our understanding of human subjects' protection to one that encourages more participation of patients and where the medical encounter becomes part of the research enterprise (Kaufmann).

Meeting Regulatory Requirements

- Innovative technologies may provide a novel approach for providing "substantial evidence" of effectiveness for regulators, if investigators can show that a device generates data that can be quantitatively linked to an element of disease progression (de Vries).
- When conducting trials internationally, consider different regulatory requirements, privacy and other regulations, cultural aspects, and digital enablement (e.g., access to different technologies and social media) (Reites).
- Investigators are encouraged to work with regulators to rethink the process for qualification of drug development tools, which present an obstacle to adoption of new methodologies (Laughren).

3

Clinical Trial Design

Highlights

- The National Institute of Mental Health (NIMH) established the Research Domain Criteria (RDoC) initiative to create a neurobiologically based research framework for addressing heterogeneity (which has been shown to confound signal detection in Phase II trials) across and within disease entities (Morris).
- There is a need to go beyond psychometric approaches and toward more causal modeling for nervous system disorders, using existing and new tools, in order to have more accurate endpoints in clinical trials (Bilder).
- Candidate biomarker approaches have worked well in identifying biomarkers for Alzheimer's disease that were later included in clinical trial enrollment criteria, but not as well for Parkinson's disease, where unbiased screening approaches have been more successful (Chen-Plotkin).
- Biorepositories with strict collection and storage protocols, data sharing, and partnerships are essential for promising biomarkers to reach clinical trials (Chen-Plotkin).
- Clinical as well as statistically significant evidence is important to establish safety and effectiveness for any given product; regulators and payers also look at clinical outcomes that are meaningful to patients (Bilder, Farchione, Hernandez, S. Kapur, Laughren, Pande, Pani, Peña, Pencina, Rockhold, and Romano).
- Trial designs should be fit-for-purpose, and employ appropriate statistical expertise in the planning stage (Pencina).

NOTE: These points were made by the individual speakers identified above; they are not intended to reflect a consensus among workshop participants.

Clinical trials are typically conducted in three phases prior to market approval: Phase I, to evaluate safety, determine a safe dose range, and identify side effects; Phase II, to further evaluate safety and assess efficacy; and Phase III, to confirm effectiveness, monitor side effects, and compare it to other treatments (U.S. National Library of Medicine, 2008). The goal of Phase II is "to obtain preliminary data on whether the drug works in people who have a certain disease or condition."[1] Failures in Phase II are also of substantial concern, said Steven Romano; approximately 80 percent of the compounds tested in Phase II fail. More than half of these fail for lack of efficacy (Arrowsmith and Miller, 2013), and another 30 percent because of a company's shift in strategic focus, which could reflect a company's concerns about comparative effectiveness and thus marketability. The fundamental challenge, according to Robert Bilder, professor-in-residence in the department of psychiatry and biobehavioral sciences at the University of California, Los Angeles, is the lack of validity for the "disease entities" associated with nervous system disorders, for which etiology and pathophysiology are mostly unknown. Both psychometric approaches and categorical approaches are insufficient for most disease entities, and heterogeneity within a syndrome and across syndromes is common, which could confound signal detection in Phase II trials. RDoC, described below, is one attempt to address these problems. In addition, several participants noted the need for better disease modeling—using both existing and new tools—and novel trial designs and statistical approaches.

ALTERNATIVES TO THE DSM

The DSM is a diagnostic tool that defines disorders as distinct entities and relies mainly on subjective measures—self-report from patients and clinicians' observations—rather than on an advanced understanding of the neurobiology of disease (Casey et al., 2013), said Steven Romano. In addition, the DSM fails to capture a number of disease domains such as volition, motivation, and speech (Kendler, 2016). Bilder added that categorical systems for defining disease are generally considered less valid than systems that capture the dimensionality of most psychiatric conditions (e.g., Haslam et al., 2012). He added that a dimension such as cognitive impairment may arise from different fundamental causes in

[1]See http://www.adaptimmune.com/patients-families/clinical-trial-faq (accessed June 23, 2016).

different disease states, such as cognitive dysfunction in major depressive disorder and schizophrenia. Nonetheless, it may be more valuable to assume that the dimensions are the same until they are shown to be different.

In recognition that drug development in psychiatry is significantly hampered by heterogeneity within diagnostic categories, NIMH established the RDoC initiative in 2009 to change how patients and nonpatients are identified and classified for research purposes, and to encourage researchers to think about and study psychopathology in different ways. RDoC became a more dominant paradigm in 2013, when then-Director of NIMH, Thomas Insel, posted a message on his blog, indicating that NIMH was reorienting its research away from DSM categorical syndromic diagnoses in favor of an approach that took into account heterogeneity in diagnosis—essentially the RDoC approach. For example, diagnosing a major depressive episode requires a patient to exhibit five of nine symptoms. Many of these symptoms, such as sleep disruptions or hallucinations, occur across multiple diagnostic categories. With 126 possible combinations of those 9 symptoms, there is substantial heterogeneity among those diagnosed with depression. Moreover, the occurrence of symptoms across multiple diagnoses supports the notion that these disorders are not fully distinct, said Sarah Morris, acting head of the NIMH RDoC unit and program chief for schizophrenia spectrum disorders research. The primacy of neurobiology over phenomenology is further supported by data from the Psychiatric Genomics Consortium, which showed high rates of shared heritability among diagnoses (Cross-Disorder Group of the Psychiatric Genomics, Consortium, 2013). In another example, there is evidence of shared patterns of gray matter loss among patients with schizophrenia, bipolar disorder, depression, addiction, obsessive-compulsive disorder, and anxiety (Goodkind et al., 2015).

Instead of grouping patients into heterogeneous diagnostic groups, RDoC provides a framework for classifying participants according to neurobehavioral constructs, based on what is known about the brain and behavior, rather than by heterogeneous diagnoses. Morris emphasized that the framework is a hypothesis, which assumes a developmental perspective from prenatal to late life as well as the ubiquitous impact of the environment across that developmental trajectory. It frames classification in terms of five domains and constructs associated with those domains (see Table 3-1). The list is dynamic and flexible enough to change over

TABLE 3-1 RDoC Domains and Constructs

Domains	Constructs
Cognitive systems	Attention
	Perception
	Declarative memory
	Language behavior
	Cognitive (effortful) control
	Working memory
Positive valence systems	Approach motivation
	Initial responsiveness to reward
	Sustained responsiveness to reward
	Reward learning
	Habit
Negative valence systems	Acute threat ("fear")
	Potential threat ("anxiety")
	Sustained threat
	Loss
	Frustrative non-reward
Arousal and regulatory systems	Arousal
	Circadian rhythms
	Sleep and wakefulness
Systems for social processes	Affiliation and attachment
	Social communication
	Perception and understanding of self
	Perception and understanding of others

SOURCE: Presented by Sarah Morris at the Workshop on Neuroscience Trials of the Future, March 3, 2016.

time. It assumes dimensionality among disorders and between illness and health, as well as interaction among constructs. Constructs can be measured at multiple units of analysis (genes, molecules, cells, circuits, physiology, behavior, and self-report), each of which informs and constrains the others.

NIMH encourages investigators to adopt RDoC principles in their clinical trials by focusing on functional domains or symptoms, thus increasing the probability that participants' disorders will share the same mechanism. Figure 3-1 illustrates NIMH's vision of this approach (Insel and Cuthbert, 2015). RDoC also has a database that is integrated with

other NIMH data- sharing resources, together providing data from more than 100,000 subjects who are available for hypothesis testing or hypothesis generation.

Morris also mentioned that using the RDoC framework will require creativity with regard to recruiting a sample that provides the strongest test of a hypothesis, given that the treatment focus is on functional domains or symptoms rather than unitary diagnostic categories. Enrollment criteria could be diagnostically agnostic; an example is recruiting based on presence of a symptom such as psychosis regardless of the particular diagnosis (e.g., schizophrenia or some other disorder), or perhaps in the future, expression of a particular gene related to a psychopathologic mechanism. Alternatively, diagnoses could be used as a proxy for a symptom such as psychoses.

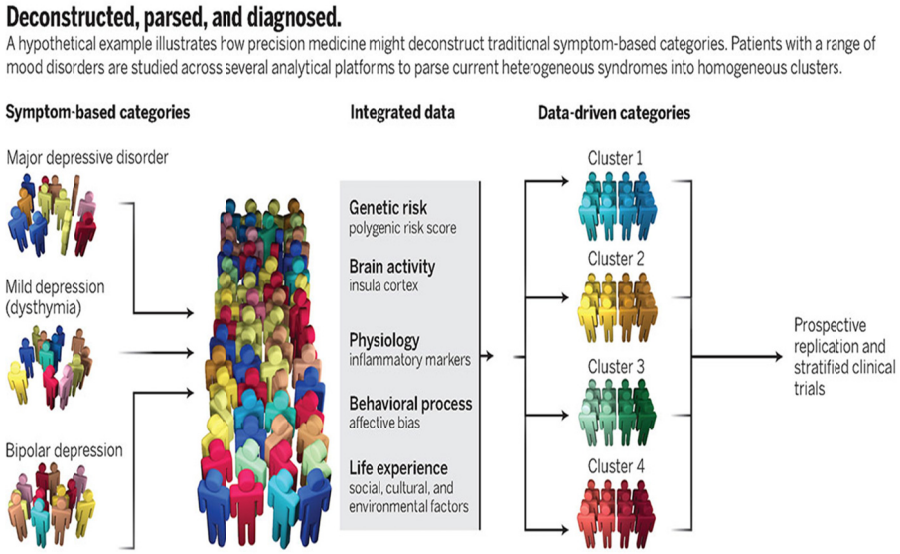

FIGURE 3-1 RDoC in neuroscience trials of the future.
SOURCES: Presented by Sarah Morris at the Workshop on Neuroscience Trials of the Future, March 3, 2016. From Insel, T. R., and B. N. Cuthbert. 2015. Brain disorders? Precisely. *Science* 348(6234):499–500. Reprinted with permission from American Association for the Advancement of Science.

BETTER DISEASE MODELS

Clinical trials in psychiatry are typically built around the DSM criteria, using neuropsychological tests as secondary outcome measures. Bilder suggested that classical psychometric tools (e.g., item response theory and computer adaptive testing) can be used in new ways. He suggested going beyond the psychometric model and for the field to consider causal models. For example, the classical psychometric explanation of depression assumes that there is an entity, major depression, which causes depressive symptoms, weight gain, sleep disturbances, etc. A network or causal modeling approach, by contrast, posits that depression results from the causal interplay among symptoms (Borsboom and Cramer, 2013). It also incorporates the concept of the progression of symptoms over time. Thus, chronic stress leads to depressed mood, which leads to self-reproach, which leads to insomnia, which leads to fatigue, which leads to problems with concentration. Bilder described a network model, built on data from more than 3,000 participants being treated for depression, that identified 28 interconnected nodes, including both DSM and non-DSM symptoms (Fried et al., 2016) (see Figure 3-2).

Biological validity is what Bilder called the "holy grail" of drug development, and viewing the multidimensionality of diseases is one step in that direction. Recent research has begun to demonstrate large genetic correlations where both diagnostic categories and dimensions, or symptoms within categories, have shared genetic contributions (see Kendler et al., 2011; Lahey et al., 2011). Population-based studies also show great overlap, implying shared genetic plus environmental contributions; this pattern of associations is not limited to psychiatric syndromes. An analysis of associations between psychiatric disorders with other medical conditions culled from 1.5 million patient records showed an increased risk of nearly every psychiatric disorder with every other medical disorder, suggesting significant shared genetic variation (Rzhetsky et al., 2007).

Thus, Bilder advocated for the use of dimensions and clusters of categories as treatment targets, as well as focusing on subgroups not only within disorders, but across syndromal boundaries. He pointed to a recent study investigating the genetic basis of major depressive disorder (MDD) in a population of Han Chinese women. By focusing on a subpopulation of women who had a particularly severe form of melancholic depression, the investigators were able to identify two genetic loci for MDD (Cai et al., 2015). Bilder also pointed to the need for validated biomarkers and explication of intermediate phenotypes to flesh out these cross-level links.

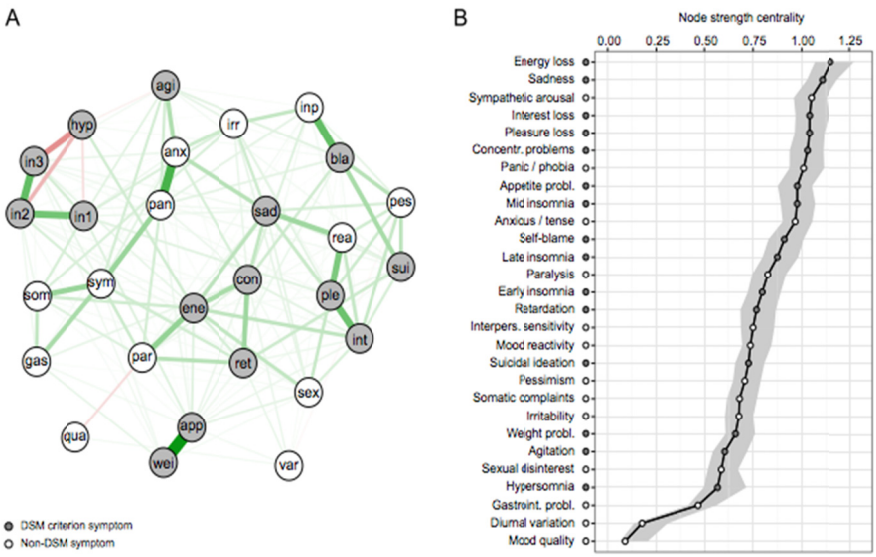

FIGURE 3-2 A network model of depression.
NOTE: A: Network containing 28 IDS-C depression symptoms. Green lines represent positive associations, red lines negative ones, and the thickness and brightness of an edge indicate the association strength. The layout is based on the Fruchterman–Reingold algorithm that places the nodes with stronger and/or more connections closer together and the most central nodes into the center. B: node strength centrality estimates of the 28 IDS-C depression symptoms, including 95% confidence intervals.

Short codes: Agi = psychomotor agitation; Anx = anxious/tense; App = appetite change; Bla = self-blame/worthless; Con = concentration/decisions; Ene = energy loss; Gas = gastrointestinal problems; Hyp = hypersomnia; In1 = early insomnia; In2 = mid insomnia; In3 = late insomnia; Int = interest loss; Inp = interpersonal sensitivity; Irr = irritability; Pan = panic/phobia; Par = paralysis; Pes = pessimism; Ple = pleasure loss; Qua = mood quality; Rea = mood reactivity; Ret = psychomotor retardation; Sad = sadness; Sex = loss of sexual interest; Som = somatic complaints; Sui = suicidal ideation; Sym = sympathetic arousal; Var = diurnal variation; Wei = weight change.

SOURCES: Presented by Robert Bilder at the Workshop on Neuroscience Trials of the Future, March 3, 2016. Reprinted from the *Journal of Affective Disorders*, 189, Fried, E. I., S. Epskamp, R. M. Nesse, F. Tuerlinckx, and D. Borsboom, What are "good" depression symptoms? Comparing the centrality of DSM and non-DSM symptoms of depression in a network analysis, 314–320, Copyright (2016), with permission from Elsevier.

There has also been a great deal of interest in leveraging and using genetic models to facilitate stratification of patients and validate targets, said Perry Nisen. However, he reminded workshop participants that association and causality are not the same; connecting a gene or mutation at a biological level to a disease process is critical. Similarly, he urged caution in interpreting cellular and animal models without a thorough understanding of the underlying biology of the disease.

BIOMARKERS

Biomarkers, defined as characteristics that can be objectively measured and evaluated as indicators of biological processes (Biomarkers Definitions Working Group, 2001), have become essential across different phases of drug development. They are typically categorized as diagnostic, prognostic, predictive, disease progression, or pharmacodynamic, according to their intended use. For example, pharmacodynamic biomarkers may be used in early-stage drug development to demonstrate target engagement, while in later stages, prognostic or predictive biomarkers may be used to stratify participants in a clinical trial or demonstrate treatment response.

Throughout the workshop, several participants expressed the need for more validated biomarkers in the field. In a recent systematic review examining published articles on biomarkers in psychosis since 2012, of 3,200 articles, the authors found that most of the biomarkers were diagnostic, with limited utility for precision medicine studies (Prata et al., 2014). Of the 257 potentially useful prognostic, predictive, or monitoring biomarkers studied, only one had both a reasonable effect size and high quality of evidence, yet even that one had sensitivity of only 21 percent, not enough to change clinical care. According to Shitij Kapur, this study illustrated several problems that plague the biomedical, including the neuroscience, literature: publication bias, lack of replication, or "approximate" replication (i.e., replication studies that use different measures and modalities [see Van Snellenberg et al., 2006]); insufficiently powered studies (Button et al., 2013); and insufficient attention to clinical significance (e.g., Levine et al., 2015).

Anil Malhotra, director of psychiatry research at Zucker Hillside Hospital and professor of molecular medicine and psychiatry at Hofstra North Shore—Long Island Jewish School of Medicine, illustrated the need for biomarkers using a recent trial that compared the efficacy of

acute treatment with aripiprazole[2] and risperidone[3] for first episode schizophrenia and related disorders (Robinson et al., 2015). The researchers examined the change in psychotic symptoms over 3 months, but despite the relatively large number of participants in the trial (198 patients), no difference was seen. Interestingly, however, there was significant variance in response. If it were possible to identify in advance who was likely to benefit from a specific treatment through the use of biomarkers, it might be possible to achieve greater power with smaller studies, said Malhotra.

He described some of the advantages and disadvantages of genetic and neuroimaging biomarkers for psychiatric disorders, noting, however, that there are many other types of biomarkers, including biochemical markers from the cerebrospinal fluid (CSF) and plasma, cognitive and neuropsychological measures, among others. With regard to plasma metabolites, although they are popular because of the relatively easy access, so far it has been very difficult to extrapolate from the plasma to the brain, said Malhotra.

Advantages of genetic biomarkers include the ease of access to DNA from blood or saliva and the stability of genotype over time, meaning you can collect samples after a trial for a prospective analysis. Disadvantages primarily relate to power: the sample sizes of most genetic studies are quite large. Neuroimaging biomarkers also have both advantages and disadvantages, said Malhotra. The most notable advantage is the ability to directly assess brain structure and function, including the ability to assess specific regions and circuits within the brain. Disadvantages include the difficulty of precise replication, potential confounds from environmental factors such as prior treatment, and subject acceptance. Moreover, it is not always clear what is being measured, he said. Many different neuroimaging modalities may yield potential biomarkers, including structural magnetic resonance imaging (MRI), diffusion tensor imaging (DTI), task-based functional MRI (fMRI), and resting-state fMRI (see Table 3-2).

Resting-state fMRI has shown particular promise in providing a good signal and also is one of the easier measures to access, said Malhotra. It provides a measure of brain activity in the absence of an externally prompted task as a means of defining functional networks. It also enables

[2]Aripiprazole is an atypical antipsychotic, used primarily to treat schizophrenia and bipolar disorder.

[3]Risperidone is an antipsychotic, used primarily to treat schizophrenia, bipolar disorder, and behavior problems.

TABLE 3-2 Neuroimaging Approaches to the Heterogeneity of Antipsychotic Response

Modality	Characteristic Measured
Structural CT or MRI	Assessment of morphology
Diffusion tensor imaging	Putative measure of white-matter integrity
Task-based fMRI	Change in BOLD signal during conduct of a cognitive/behavioral/emotional activation task
Resting-state fMRI	Correlation in BOLD signal during "rest"

NOTE: BOLD signal = blood-oxygen-level–dependent changes, induced by blood flow.

SOURCE: Presented by Anil Malhotra at the Workshop on Neuroscience Trials of the Future, March 3, 2016.

investigators to assess the functional connectivity among multiple regions of the brain. For example, Malhotra and colleagues showed that improvement in psychotic symptoms over 12 weeks in individuals with first episode schizophrenia correlated with increased connectivity in cortical striatal circuits, suggesting that increasing connectivity in these circuits could be used as a biomarker of antipsychotic efficacy (Sarpal et al., 2015). Indeed, in a more recent study, Malhotra's team used baseline striatal functional connectivity to predict antipsychotic drug response (Sarpal et al., 2016).

The SCI approach has also been applied to other clinical studies, including the aripiprazole and risperidone study mentioned at the beginning of this chapter, in which no difference in efficacy was seen. Among study participants who had undergone baseline resting- state fMRI scans, responders tended to have lower SCI than non-responders, further supporting its potential as a predictive biomarker.

Several participants highlighted that biomarkers for nervous system disorders are somewhat more developed in neurology than psychiatry. For example, Story Landis, former director of the National Institute of Neurological Disorders and Stroke (NINDS), commented that the identification of neuroimaging as a biomarker for immunological disturbances transformed drug development for multiple sclerosis (MS), where there are now drugs that slow progression of the disease. However, much remains to be learned with regard to how and why these drugs work as well as on other aspects of MS, such as the neurodegenerative component.

There has been a particularly substantial effort to develop biomarkers for Alzheimer's disease (AD), exemplified by ADNI. ADNI was launched in 2004 with the initial goal of developing imaging and bio-

chemical biomarkers for the early detection of AD, as well as for use in clinical trials. However, the impact of ADNI on the AD field and beyond has been far broader, said Alice Chen-Plotkin, assistant professor of neurology at the Perelman School of Medicine, University of Pennsylvania. It set a precedent for open data sharing in the neurodegenerative disease space and demonstrated the potential benefits of bringing together experts from industry, governmental agencies, academia, and private foundations to provide the funds required to address a monumental problem (Weiner et al., 2015).

The original ADNI cohort consisted of 200 normal controls, 200 people with overt AD, and 400 people with amnestic mild cognitive impairment (aMCI), which was thought to possibly represent prodromal AD. Study participants were assessed clinically and with biomarker studies at 6-month intervals for 4 years. Following the initial 5-year study, additional funding was obtained in 2009 with a Grand Opportunities grant (ADNI-GO) and in 2011 with a renewal (ADNI-2), enabling an additional 550 people to be enrolled and the focus to shift to earlier phases of the disease.

Since its inception, data from ADNI have resulted in more than 600 publications (Weiner et al., 2015) that have transformed the understanding of AD. Chen-Plotkin summarized some of the learnings from ADNI:

- Biochemical biomarkers in the CSF can discriminate individuals with aMCI who will go on to develop AD from those who will not (Shaw et al., 2009).
- Positron emission tomography (PET) scans using ligands that bind to beta amyloid (Aβ, the protein found in the amyloid plaques seen at autopsy) can demonstrate the deposition of amyloid in the brain *in vivo* (Clark et al., 2011).
- These measurements are meaningful if one knows the quantitation is accurate and can be reproduced in any lab that follows the standardized procedure.

ADNI has already led to changes in how AD trials are conducted, said Chen-Plotkin. Phase III trials are being conducted in preclinical stages of AD using amyloid imaging and CSF biomarkers as entry criteria to enrich for patients on the AD trajectory. Biomarkers are also currently being incorporated into diagnostic criteria in the research settings, but may be used for clinical diagnosis in the future (Sperling et al., 2011).

Identifying biomarkers to expedite clinical trials in Parkinson's disease (PD) has proved to be more difficult, said Chen-Plotkin. Although both AD and PD are characterized by misfolding and aggregation of a central culprit molecule—Aβ in AD and α-synuclein in PD—no specific imaging ligand for α-synuclein has been identified, and levels of α-synuclein in CSF are not predictive of disease progression (Kang et al., 2013). Chen-Plotkin, along with other PD researchers, think an unbiased screening approach, made possible by advances in genomics and proteomics, will be needed to identify predictive biomarkers for PD (Chen-Plotkin, 2014). The PD community (e.g., researchers and patient advocacy groups), like the AD community before it, now is organizing around a pipeline for discovery, replication, and further development of novel PD biomarkers. In 2012, the National Institute of Neurological Disorders and Stroke (NINDS) launched the Parkinson's Disease Biomarker Program (PDBP), which has collected biospecimens and clinical data from more than 1,000 people, stored them in a central repository, and made them available for discovery efforts by the neuroscience research community (Rosenthal et al., 2015). Meanwhile, the Parkinson's Progression Markers Initiative (PPMI), sponsored by the Michael J. Fox Foundation for Parkinson's Research, has collected samples along with clinical and behavioral assessments from multiple cohorts, including normal controls and individuals with PD, as well as those in the prodromal stage of PD. These samples and data are available to the research community.

Chen-Plotkin's group at the University of Pennsylvania was one of the first to use this pipeline. In 2013, they identified a candidate protein biomarker for PD using an unbiased screening approach on samples acquired at the university. They showed that higher plasma levels of Apolipoprotein A1 (ApoA1) were correlated with older age at PD onset and less severe PD (Qiang et al., 2013). Then, using samples from PPMI, they replicated the study, thus providing the first report of a plasma-based biomarker of disease progression in PD and suggesting that ApoA1 may represent a therapeutic target (Swanson et al., 2015).

Chen-Plotkin and colleagues were also interested in replicating a study that suggested that low levels of epidermal growth factor in the blood were predictive of which PD patients would become demented. However, they observed substantial site-to-site variability in the measurement of EGF at PPMI sites, highlighting the need for strict adherence to standardized protocols.

Moreover, there are gaps in our knowledge about biomarkers, which need to be overcome, said Bilder. For example, in a study of the associa-

tion of amyloid burden with disruption of the default mode network, neither of these measures were associated with cognitive impairment (Hedden et al., 2009). In addition, several participants noted that there is a great need for biomarkers with predictive power. This will likely require a multimodal approach rather than a single determinant biomarker, said Malhotra. Luca Pani, director general of the Italian Medicines Agency (AIFA), said biomarkers are also needed to show that a treatment makes sense in terms of value. For example, if a biomarker could predict that a specific treatment for hepatitis C reduces the need for transplantation in some patients, the savings could influence the approval decision. The predictive biomarkers (diagnostic) in oncology play a critical role in understanding molecular and cellular mechanisms, which drive tumor initiation, maintenance and progression. They help to optimize therapy decisions, as they provide information on the likelihood of response to a given chemotherapeutic. However, he noted that this would be more difficult for psychiatry and neurology area.

Chen-Plotkin and S.Kapur emphasized the need for building international consortia and public-private partnerships to advance the development of new tools. For example, an international consortium called Novel Methods leading to New Medications in Depression and Schizophrenia (NEWMEDS) has developed a tool called a clinical significance calculator to help investigators estimate whether a predictive biomarker for depression is likely to demonstrate clinical significance, shifting attention away from a focus on statistical significance, or p-values (Uher et al., 2012), said S. Kapur. In addition, Chen-Plotkin noted that biorepositories and sharing of biospecimens will enable the more efficient development of a wide range of biomarkers.

CLINICALLY MEANINGFUL OUTCOMES

In recent years, regulators and payers have increasingly required that clinical studies demonstrate not only statistical significance of an effect, but even more importantly, clinical significance (Ranganathan et al., 2015). This view was also reflected in comments from many workshop participants. The bottom line, said Romano, is that no payer will provide coverage for a product that does not show clinical relevance. Studies need to show that a difference is relevant not against placebo, but against comparators, he added. S. Kapur noted that effect size is not the same as clinical significance. He further proposed developing a framework for

assessing the clinical significance of potential innovative options that will make health care cheaper, not just "flashier" and stratified.

Clinically relevant endpoints are also important to promote clinical implementation. Publication in an appropriate peer-reviewed journal provides an avenue for acceptance by the community, yet an analysis of randomized clinical trials supported by the National Heart, Lung, and Blood Institute showed that only 57 percent of studies were published within 30 months of completion of the trial. However, those trials with clinical endpoints were published significantly sooner than those with surrogate endpoints (Gordon et al., 2013), noted Adrian Felipe Hernandez, professor of medicine at the Duke University School of Medicine.

NOVEL CLINICAL TRIAL DESIGNS

Statistical Approaches and Considerations

Many design and methodology approaches can increase trial efficiency, said Michael Pencina, director of biostatistics at the Duke Clinical Research Institute and professor of biostatistics and bioinformatics at Duke University. In general, he said, regulatory bodies are most open to innovative clinical trial designs in smaller studies and in earlier stages of drug development. The design has to be fit-for-purpose, and appropriate statistical expertise is needed in the planning stage. He gave a brief overview of the various design choices:

- **Event-driven trials** are appropriate if an outcome can be measured over time and the duration of the trial is sufficient to enable an adequate number of events to be observed. In contrast to more traditional studies where participants are followed for a specific period of time, time-to-event studies can be stopped when an adequate number of outcomes are achieved, and all follow-up is included in the analysis. Efficiency can be further maximized by blinded interim monitoring of event counts, followed by increasing or decreasing the planned study duration, or increasing the sample size.
- **Composite outcomes,** used extensively in cardiology studies, may also increase the efficiency of a study, particularly if there are multiple outcomes that are roughly similar in severity. The composite itself may provide increased power, while analysis of

individual components may bring added value. Hierarchical composites combine outcomes of varying severity. In this case, the most severe outcome (e.g., death) is used as the first comparator; if this outcome fails to materialize, the next most severe outcome (e.g., hospitalization) could be analyzed, etc. Continuous outcomes make this method more powerful.

- **Adaptive designs,** in which a key study feature, such as sample size, duration, or number of treatment arms, can be modified and adapted based on an interim analysis. One example is a "drop-the-losers" design, where treatment arms are dropped if they fail to meet a prescribed threshold, while those that meet this threshold are advanced to the next stage.
- **Enrichment designs** typically use biomarkers to ensure a more homogeneous and likely-to-respond study population. Adaptive enrichment designs adapt based on a biomarker. For example, different arms could include participants with different genetic markers. Following interim analysis those arms showing greater effect sizes could be enriched.
- **Sequential parallel comparison designs** are used to reduce the impact of the placebo response. In the first stage of such a design, participants may be randomized to receive treatment or placebo; in the second stage, placebo non-responders are re-randomized. The final summary statistic in this type of trial is then based on a weighted combination of effects from the two stages.
- **Controls** may sometimes be borrowed from historical information, using several different methods. The simplest, yet controversial, approach is to pool historical information with randomized controls. If there is enough homogeneity among the studies, this can substantially reduce sample size. Historical information may also be used to define performance criterion by enabling derivation of an estimated event rate that the treatment being tested must exceed. Another more sophisticated approach involves testing first to see if controls are sufficiently similar for pooling. Even more sophisticated approaches allow investigators to model variations between current and historical data to enable their use.

2×2 Blind Trial Design

Erik Snowberg, professor of economics and political science at the California Institute of Technology, proposed a novel design, which he developed with his colleague Sylvain Chassang, professor of economics and public affairs at Princeton University. Their design leverages the observation that dropouts decline when participants have a greater likelihood of receiving treatment, and capitalizes on the "placebo effect." In the biomedical world, placebo implies a sham treatment; however, economists equate placebo effects with behaviors, which can interact with treatment and affect the efficacy of a treatment. For example, participants who believe they are receiving treatment for depression may change their behavior with the thought that because they are being treated, they will be able to more successfully navigate social situations. Interacting with others may then help alleviate their depression, and the behavior thus influences the treatment effect.

Clinical trials that allocate participants equally to the treatment and placebo arms are typically suboptimally powered, said Snowberg, in part because of the high rate of dropouts. More power can be achieved by randomizing more participants to the treatment arm. This not only reduces dropouts, but changes behavior, because participants believe they have a higher likelihood of receiving treatment. Moreover, it allows investigators to assess the benefit from the interaction of behavior and treatment.

Snowberg and Chassang tested this theory using participant-level data collected by Fournier and colleagues (2010) in a meta-analysis of double-blind RCTs for depression. Data from six trials (three trials each for imipramine[4] and paroxetine[5]) were selected. Among the imipramine trials, two allocated participants equally and one allocated 70 percent to receive treatment. Among the paroxetine trials, one allocated equally and the other two allocated 65 percent and 67 percent to receive treatment. Their analysis showed that treatment probability affected participants' decision to drop out of a trial, and that for paroxetine, but not imipramine, there was an interaction between treatment and behavior that resulted in an improved treatment effect (Chassang et al., 2015).

With the 2×2 blind trial that Snowberg and Chassang propose (see Figure 3-3), the aggregate probability of treatment is 50 percent, but the

[4]Imipramine is a tricyclic antidepressant, used primarily to treat major depressive disorder.

[5]Paroxetine is a selective serotonin reuptake inhibitor (SSRI) used to treat major depressive disorder and other psychiatric disorders.

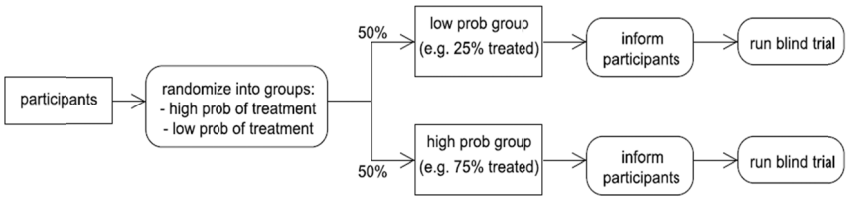

FIGURE 3-3 2×2 blind trial design.
SOURCES: Presented by Erik Snowberg at the Workshop on Neuroscience Trials of the Future, March 3, 2016, from Chassang et al., 2015.

different groups allow the investigator to decompose the treatment effect into three parts: the effect of behavior, the effect of the treatment itself, and the interaction of behavior and treatment. Participants are first randomized into two groups: a high probability (75 percent) of treatment group and a low probability (25 percent) of treatment group. Participants are informed of their probability of treatment, and the trials are run in a blinded fashion in the usual way, with a combined analysis of the two groups. Snowberg said this approach in Phase II provides investigators with information that will enable them to conduct more optimally powered Phase III studies.

The Established Status Epilepticus Trial

Jaideep Kapur, Eugene Meyer III professor of neuroscience and neurology at the University of Virginia School of Medicine, described another novel trial design that is being used to identify the best way of treating benzodiazepine-refractory status epilepticus. The Established Status Epilepticus Trial (ESETT) was designed to identify the best treatment for the 35 to 45 percent of patients who do not respond to benzodiazepines, the standard first line agent for treatment of status epilepticus. There has been a lack of well-controlled studies for this indication, and treatment practices vary. In the United States, the most commonly used drug is fosphenytoin; however, a newer drug, levetiracetam , is easier to use and has fewer side effects, yet evidence from uncontrolled studies in Europe, India, and other places suggest that valproic acid is superior, said J. Kapur. The ESETT investigators have therefore designed a comparative efficacy trial to determine which drug is best (Bleck et al., 2013).

The trial, which is being conducted at 51 sites, has several unique characteristics. Recruitment is conducted by emergency department physicians from patients who are transported to the study sites and received benzodiazepines en route by emergency medical personnel. If a patient continues to seize and meets the inclusion criteria, the physician administers the study drug, which has been provided in prerandomized, blinded study boxes. The outcome is absence of seizures and regaining of consciousness at 60 minutes. J. Kapur noted that randomization will also be stratified into three age groups: 2–18 years, 19–65 years, and 66 years or older.

The second important feature of ESETT is a Bayesian adaptive design. In designing this trial, investigators ran thousands of simulations based on several different scenarios (e.g., different effect sizes and false-positive rates for the three compounds), which enabled them to select the optimal operating characteristics (e.g., timing of analyses, power, sample size, etc.) with adequate power and a minimum sample size (Connor et al., 2013). The design they selected will start by first enrolling 300 patients, allocated equally to each of the three drugs. After an interim analysis, allocation ratios will be modified based on performance, such that the best performing drug will get more patients and the worst performing drug will get fewer. This type of design ensures that the most effective drug will be given to the largest proportion of patients. J. Kapur noted that the trial will be stopped early for efficacy (one treatment clearly better) or futility (either all arms are bad or the trial appears unlikely to identify a best and worst treatment). He added that it will be finished and considered a success when the probability that one treatment is the most effective exceeds 0.975. The trial has been funded for 795 patients, but the investigators hope to have an answer and finish early.

LESSONS LEARNED FROM OTHER THERAPEUTIC AREAS

Successful drug development in other disease areas such as oncology and cardiology may provide insight for neurology and psychiatry. For example, a major advance in the treatment of melanoma required the development of a targeted regimen for melanomas resistant to therapy. This regimen uses two drugs that inhibit different cell-signaling molecules, and was made possible by leveraging genetic data to facilitate the stratification of patients, which enabled validation of targets, according to Nisen. Researchers had first discovered the mechanisms of resistance to one

type of inhibitor and then proceeded to design a study that demonstrated the efficacy of combined treatment with drugs that inhibit two different cell-signaling molecules (Flaherty et al., 2012; Wagle et al., 2011).

One of the important lessons from this effort, said Nisen, is that in addition to having a validated mechanism and a way of assessing an early signal, combining therapeutics at the earliest stages of drug development should be considered for disorders that are heterogeneous and multifactorial. In addition, while the conventional wisdom is that studies should be kept as simple as possible, Nisen said this study was extremely complicated and very adaptive, but enabled the investigators to answer fundamental questions about dose, drug–drug interactions, pharmacokinetics, safety and tolerability, and clinical activity.

Another important lesson from oncology relates to the establishment of Comprehensive Cancer Centers, which provide improved integration between basic science and the clinical enterprise. According to Nisen, about 90 percent of children with cancer participate in clinical trials at these centers, with high cure rates for certain types of cancer (e.g., most childhood acute lymphoblasic leukemia is cured). Adults with cancer are much less likely to be treated at one of these centers, and less than 5 percent participate in trials. The survival rate for all adults is much lower.

Cardiology provides additional lessons applicable to neuroscience trials of the future. The cardiology field has a relatively strong evidence base upon which treatment guidelines have been developed. Nonetheless, a cultural demand there remains within the cardiology community to fill in the knowledge gaps, according to Hernandez. Thus, networks of cardiologists have collaborated to develop large, multicenter randomized studies. For example, the Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO) study enrolled more than 40,000 patients at over 1,000 hospitals in 15 countries despite the required completion of a three-page case report form for each patient (GUSTO Investigators, 1993). Key to harnessing the community's interest is asking a relevant question, said Hernandez. For example, the drug neseritide was approved in 2001 for acute heart failure with a pivotal study of fewer than 500 patients. Widespread use, however, indicated that the drug was associated with acute adverse effects. This led to the creation of the Acute Study of Clinical Effectiveness of Nesiritide and Decompensated Heart Failure (Hernandez et al., 2009), a large pragmatic trial focused on understanding clinically meaningful outcomes in the context of real-world use. Despite the negative press about nesiritide, the cardiology community came together and successfully enrolled more

than 3,000 participants, exceeding its projected enrollment. Now, the cardiology community is moving forward with a large-scale (20,000 participants), pragmatic, adaptable, patient-centric, randomized controlled trial (RCT) using the National Patient-Centered Clinical Research Network (PCORnet). This study will leverage data from electronic health records and collect patient-reported information electronically through patient portals.

Another lesson learned from cardiology studies is the importance of making sure the background therapy is relevant to the market. For example, in a study of ticagrelor,[6] outcomes in North America were substantially poorer than those in other parts of the world (Wallentin et al., 2009). A post-hoc study identified the reason: A different dose of aspirin being used as an antiplatelet background therapy, said Hernandez. He added that selecting the appropriate outcome measure for the trial is also important.

In addition, a new paradigm that has emerged from cardiology is the registry-based randomized clinical trial (Lauer and D'Agostino, 2013), which the authors of the study called "the next disruptive technology in clinical research," said Hernandez. This approach leveraged clinical information collected by a preexisting observational registry to identify potential participants, which markedly accelerated enrollment and eliminated the need for lengthy case report forms (CRFs). Pencina noted that electronic health records and registry-enabled trials may also be useful in allowing investigators to run very large, simple trials for a fraction of the cost of more typical trials.

Finally, a few participants noted that value of trials in which patients serve as their control (also known as N of 1). Although not frequently used for trials for nervous system disorders, N of 1 trials may lead to more individualized treatment (Lillie et al., 2011).

DEVELOPING MORE EFFECTIVE THERAPEUTICS THROUGH PRECISION MEDICINE: IMPLICATIONS FOR CLINICAL TRIALS

Opportunities may also emerge from examination of success in other fields, said Shitij Kapur, executive dean and head of school at the Institute of Psychiatry, Psychology & Neuroscience, King's College London. In oncology, precision medicine has emerged as a valuable and innova-

[6]Ticagrelor is a platelet aggregate inhibitor used to prevent strokes and heart attacks.

tive approach for treating some of the most intractable types of cancer; many of the advances are found in the treatment of breast cancer. Today, nearly all newly diagnosed breast cancers are tested for the presence of the human epidermal growth factor receptor (HER2/neu).

These efforts in the breast cancer field highlight the need for patience and persistence, said S. Kapur. Two recent papers show that following the principles of personalized medicine double the chances of success (Cook et al., 2014; Nelson et al., 2015). However, the movement toward personalized medicine has not yet resulted in precision medicine trials in nervous system disorders despite a few promising leads (Liu et al., 2012; Volpi et al., 2009).

S. Kapur predicted that precision medicine in neurology and psychiatry will enrich and modify rather than replace current practice, presenting both challenges and opportunities for clinical trial design. Specifically, he noted that developing biomarkers that predict disease progression and treatment response longitudinally is needed for nervous system disorders. Several participants added that using multimodal approaches rather than a single approach may help to show which drugs or other intervention approaches work best for which patients. In addition, using big data approaches may help to identify correlations among diverse types of patient data and outcomes. Robert Califf emphasized that recruiting as many volunteers as possible to participate in research as a normal part of their patient care, through the Precision Medicine Initiative, will be important for therapeutic development (e.g., Slamon et al., 1987; Smith et al., 2007).

4

Transforming Clinical Trials with Technology

Highlights

- The traditional research model requires a substantial investment of upfront money and time to design a study, procure the technologies, identify clinical sites, and recruit patients, even before acquiring any feedback about the viability of the study (Rodarte).
- Technological innovations may improve the efficiency and productivity of neuroscience clinical trials through the use of novel outcomes, increased patient engagement, and reduced patient burden, but raise regulatory and operational concerns (Kalili).
- New technologies such as wearable devices, remote monitoring, and virtual clinical visits may help fulfill the goal of making clinical trials more patient focused (Kieburtz).
- Social media offers increased opportunities for patient engagement (Reites and Rodarte).

NOTE: These points were made by the individual speakers identified above; they are not intended to reflect a consensus among workshop participants.

New technologies are disrupting all industries, including health care and drug development, said Amir Kalali, head of the Neuroscience Center of Excellence at Quintiles. Although they have yet to make a major impact in clinical trials, technological innovations offer the potential to improve efficiency and productivity through the use of novel outcomes, increased patient engagement, reduced patient burden, and improved trial management. Indeed, Kalali said that he believes technology can enable the field's ethical duty to conduct efficient next-generation clinical trials. Yet the expanded use of new technologies also raises regulatory and operational concerns as well as barriers to implementation. Moreover,

Drew Schiller cautioned against replacing the entire human element of clinical trials with technology. Although there are some aspects of trial design where efficiencies can be gained by more rapidly enrolling and prequalifying large numbers of participants and gathering data that show whether a treatment works or not, humans are better at developing research objectives and analyzing data.

Exploiting new technologies in the design of clinical trials will require the drug development community to apply the lessons learned from other industries, including an increasing focus on the consumer, said Schiller. Most study participants today come into clinical trials with a high level of experience and comfort using technology in their personal life, said Kalali, and consumer technology companies have been built largely around the concept of improving the user experience. The R&D and business models upon which these companies have been built may be adaptable to pharmaceutical development, said Glen de Vries, president and co-founder of Medidata Solutions.

Kalali also mentioned other technologies that are likely to disrupt the drug development enterprise such as synthetic biology—so-called exponential technologies because they are developing at an exponential rate. Virtual reality and the Internet of Things are another two emerging paradigms that are transforming consumer-based technology development, said John Reites, head of Digital Health Acceleration at Quintiles. Given the rapid advancement of technology, William Potter, senior advisor to the director at NIMH, cautioned that companies may be reluctant to commit to a single technology for improved signal detection because future technologies may prove to be better.

PATIENT RECRUITMENT AND RETENTION IN CLINICAL TRIALS

Reites focused his remarks on direct-to-patient research, in which patient communities are built based on a clinical trial or study, but only later connected with the investigator. For example, if one is interested in evaluating prevention treatments for Alzheimer's disease (AD), one might establish a community of interested individuals who are invited to complete cognitive scales and contribute data from mobile health devices. Then, when a trial opportunity arises, they could be invited to contribute data to a trial, participate in the trial, or test a new drug or device.

This focus on patients in trials of the future was emphasized by many workshop participants. Bringing patients into the process—for example, understanding what matters to them and what the trial should measure—would help ensure that research is addressing clinically relevant questions, said Carlos Rodarte, chief executive officer of Health Rhythms. In addition, listening to what patients say about how they feel may provide clues about unexpected aspects of the treatment response, said Perry Nisen. He said the breakthrough in developing immunotherapy and checkpoint inhibitors in oncology came about when a patient reported feeling much better and was thus kept in the trial even though imaging studies suggested the therapy was not working. Only later were investigators able to develop new imaging techniques that visualized the immunological benefits.

Karl Kieburtz, Robert J. Joynt Professor in Neurology and director of the Clinical and Translational Science Institute at the University of Rochester Medical Center, said that regardless of the changes brought about by the introduction of new technologies, three aspects of traditional drug development will endure: (1) enabling the participation of patients and families in meaningful research opportunities, (2) generating robust data, and (3) drawing valid inferences. He predicted that the model of how clinical trials are conducted will change radically in the future, shifting from distributed loci to a central focus or single center, with investigators (academic, industry, or foundation based) starting off trials by directly reaching out to patients and families and with assessments carried out remotely or through telemedicine.

Kieburtz cited one Parkinson's disease (PD) study based solely on telemedicine versus live, in-person visits (Dorsey et al., 2015). Individuals from 39 states completed all visits in the trial and reported high levels of satisfaction. Moreover, people from 49 countries expressed interest in participating, highlighting the pent-up and entirely untapped demand for patients and families to participate in research. However, trials that capture participants from many sites must deal with the additional challenge of understanding how regional and cultural variability may impact outcomes. For example, if a trial is testing an intervention for mood disorders, patients and controls in sunny California may respond differently than those in the wintry Northeast, due to both differences in light exposure and physical activity, commented Rodarte.

The PD study also highlighted the important enabling role of social media. Volunteers for this study were solicited through Fox Trial Finder, an online tool that matches people with PD to trials for which they may

be eligible. One concern raised regarding social media is including people in a sample who have not been clinically diagnosed with a condition. Another concern is that individuals might falsely report data, or lend their wearable device to a friend. Rodarte, however, said that with a large enough sample size, it might be possible to identify the outliers; and Reites added that connecting directly with electronic medical records can provide added confirmation that participants are who they say they are.

Simple online assessments, data capture by wearable devices, remote monitoring, and virtual clinical visits offer additional advantages in terms of reducing patient burden, and this can have a substantial impact on recruitment and retention, said Schiller. For example, participants with child care and transportation needs may be able to remain in a study through the use of remote data capture technologies, he said. Indeed, added Rodarte, improving the patient experience in research studies is essential. The hospitality industry may provide lessons in this regard, he said.

NOVEL ASSESSMENT TOOLS

Continuous measurement of activity and behavior is one approach that enables collection of precise and frequent information at a relatively low cost, as well as new types of information that could not be measured in the past, said Atul Pande. Smaller and more sophisticated sensors are driving the increasing use of these technologies beyond the consumer market, added Rodarte. Thus, they could be used to develop digital signatures that characterize how different populations behave, such as people with schizophrenia or bipolar disease, he added. Continuous data capture of an individual enrolled in a trial can provide insight into that person's mental well-being and the stability of daily routines. Such measures could allow the reframing of behaviors beyond those included in the DSM-5 and could also enable the implementation of just-in-time interventions, said Rodarte.

Major challenges with regard to these devices include how to make sense of the enormous amounts of data that can be acquired, and how to leverage that data, including data about how an individual uses technology, to learn more about the disease itself and its progression, said Rodarte. Differentiating the signal from the noise presents yet another challenge, although de Vries suggested that digital measures allow investigators to embrace the noise by identifying interesting signals embedded

in noisy measures. However, while continuous monitoring such as this may be more objective than patient self-report measures, Thomas Laughren, director of Laughren Psychopharm Consulting, LLC, pointed out that conscious experience is an important component of psychiatric disease; this requires active measures such as self-report, in addition to more objective passive measures.

Other challenges for those hoping to use data from wearables and in-home monitoring devices are the standardization and normalization of data from many different types of devices and applications, noted Schiller. Standardization of measures is also very important, said S. Kapur, noting ADNI's success in this regard. According to Schiller, an association of large consumer technology companies has established a standards committee that is tasked with creating standards for consumer devices that assess activity, sleep, electroencephalogram (EEG), and other measures. Rodarte added that the underlying technology for these devices is often very similar, which should make standardization somewhat easier. There is also a trend toward "make-your-own" devices, he added. For example, Biogen has publicly stated it is developing a device with enhanced sensitivity to the multiple sclerosis patient experience.

However, Greg Koski, chief executive officer, president, and co-founder of the Alliance for Clinical Research Excellence and Safety (ACRES), noted that although implementation of Clinical Data Interchange Standards Consortium (CDISC) standards reduces the time from start-up to finish of a study by 60 percent, adoption of CDISC standards has been slow and has not penetrated the entire research ecosystem of stakeholders.

Integrating these data, along with physiologic, genotypic, and phenotypic data from other sources, presents an additional challenge, said de Vries. However, he posited that integrated disease models will enable creation of interesting multivariate models in neuroscience and other disease areas, and thus will become a preferred type of model.

Wearables and other types of sensors may also be useful as tools to assess compliance with a study protocol, said Stephen Brannan, vice president of clinical research and medical affairs at Forum Pharmaceuticals. de Vries added that models can be developed through machine learning to identify fraudulent sites and participants. In addition, Kieburtz suggested that objective data such as how many steps a person takes a day, or how many times he or she interacts with others, could provide good objective indicators of depression and other psychiatric conditions. Whatever novel treatment targets, endpoints, and trial designs

are used, what regulators are most interested in is clinical meaningfulness, according to Tiffany Farchione, deputy director of the Division of Psychiatry Products in the Center for Drug Evaluation and Research (CDER) at the FDA. To what extent does the treatment affect how the patient feels, functions or survives; how do you measure this?

5

The Regulatory Landscape: International Opportunities and Challenges

Highlights

- Regulators desire good proof-of-concept studies, leading to representative clinical trials that can then, in turn, result in appropriate clinical practice guidelines and performance measures (Califf).
- Regulators are also increasingly focused on sustainability, which may be achievable by simplifying trials and enrolling representative populations (Califf), and through the use of real-world data or drug-product monitoring registries (Pani). Another way to help sustainability is early health technology assessment (HTA) evaluation (Pani).
- Integrating clinical research networks is one way to ensure more efficient trials (Califf).
- The patient's voice in particular has become increasingly important to regulators in defining the value of a medicine, yet incorporating patients' viewpoints into clinical trials may further increase the complexity of those trials (Romano).
- Regulators have been pushing for increased data sharing to promote efficiency and ensure continued progress (Califf and Pani).
- There is a need for new regulatory approaches for combining passive and experimental data that would meet the needs of the 21st century (de Vries, Kieburtz, and Reitz).
- Drug-product monitoring registries enable tracking of longitudinal outcomes and adverse effects (Laughren and Pani).
- Randomization with a registry enables real-world testing of hypotheses (Califf).
- Randomization with a registry enables real-world testing of hypotheses (Califf).

NOTE: These points were made by the individual speakers identified above; they are not intended to reflect a consensus among workshop participants.

Many of the challenges raised in the previous chapters with regard to integrating novel tools, trial designs, and statistical approaches into neuroscience trials have regulatory implications. Regulatory agencies around the world have developed strategies to keep pace with the evolving product development in the context of each country's particular political, legal, economic, social, cultural climate. Yet despite their geopolitical differences, the goals of these countries remain essentially the same. As articulated by Carlos Peña, director of the Division of Neurological and Physical Medicine Devices in the Office of Device Evaluation at the FDA's Center for Devices and Radiological Health (CDRH), one central goal is to optimize trial design approaches to get products to patients who desperately need them while ensuring that these products undergo appropriate evaluation for safety and effectiveness.

REGULATORY PERSPECTIVES FROM THE UNITED STATES

Robert Califf, Commissioner of Food and Drugs, said that within the FDA, there is a shared view that the best medical outcomes occur when doctors and other health care providers and patients are armed with high-quality evidence to support what they do, and this is most likely to happen when the clinical trials and observational studies are actually done in practice. The FDA is tasked with providing instructions in the label on how to use the product in practice, not in theory, said Califf, so making an extrapolation from a rarified clinical trial to real practice does not make much sense. He acknowledged, however, the difficulty of collecting data from real-world situations, which has led to a "parallel universe" of data collected specifically for clinical trials. In addition, there is a disconnect between the instructions for use provided in the product label and actual use in clinical practice, such that, according to a recent study in Canada, more than 25 percent of drugs prescribed for CNS conditions were for "off-label" uses, and 21 percent were off label with no credible evidence of the drug's effectiveness for that condition (Eguale et al., 2016). For some CNS drugs, including clonazepam[1] and amitriptyline,[2] more than 70 percent of use was off-label. Interestingly, the adverse event rate for drugs used off label was twice as high as for drugs used on label, but when considering only drugs used off label but with good evidence of effectiveness, the rate was the same as the on-label rate.

[1]Clonazepam is used to treat seizures and panic disorder.
[2]Amitriptyline is a tricyclic antidepressant, used to treat symptoms of depression.

Califf offered a glimpse at what he thinks the system might look like. It begins with good proof-of-concept studies, which lead to representative clinical trials. The best knowledge from those trials is then used to craft clinical practice guidelines and performance measures. When what happens in practice deviates from what was expected, revisions may be needed in the clinical trials process. Underlying all of these steps, said Califf, is measurement and education both in the clinical trials arena and in clinical practice, which he described as a learning health care system (see Figure 5-1).

Califf also addressed concerns about sustainability, citing a recent study showing that the cost of clinical trials is rising twice as fast as the rest of the American economy (Berndt and Cockburn, 2014). He noted that the driver of this unsustainable growth in the cost of conducting clinical trials is complexity, which also drives a reduction in the number of people who enroll in trials—a trend that is worsening in the United

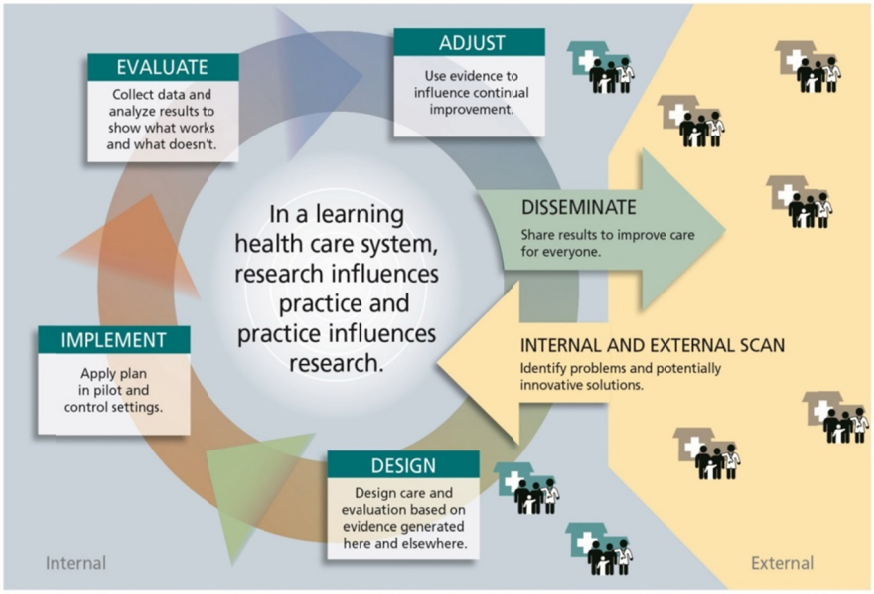

FIGURE 5-1 Learning health care system.
SOURCES: Presented by Robert Califf at the Workshop on Neuroscience Trials of the Future, March 4, 2016. From *Annals of Internal Medicine*, Greene, S. M., R. J. Reid, and E. B. Larson. Implementing the learning health system: From concept to action, 157, 3, 207–210. Copyright © [2012] American College of Physicians. All Rights Reserved. Reprinted with permission of American College of Physicians, Inc.

States and is leading to increased inefficiency. His FDA colleagues in the CNS space reiterated many suggestions raised throughout the workshop, to include the need to: simplify and enroll relevant, not rarified, populations; make trials more inclusive; stop the collection of non-serious adverse events for every patient; reduce the number of clinic visits required for research studies; and invest in technologies that provide the clearest answers to critical questions.

The FDA continues to optimize trial design approaches to achieve its goals, according to Peña. CDRH uses a risk-based approach, requiring increased oversight for products deemed to present a greater possible risk. The drug and biologic divisions of the FDA, CDER, and the Center for Biologics Evaluation and Research (CBER) use similar approaches. The FDA has published numerous guidance documents to clarify the considerations that should be taken into account by sponsors through the approval process, beginning with presubmissions. They also strongly encourage sponsors to initiate dialog with them at the earliest stages, so that the agency can provide feedback and suggestions on the anticipated designs before a study is initiated and data collection has begun.

REGULATORY PERSPECTIVES FROM ITALY

Luca Pani, director general of the Italian Medicines Agency (AIFA), also addressed sustainability. Because AIFA functions as a regulatory, payer, and HTA institution, it must grapple with all its roles to achieve better outcomes and controlling costs, he said. Sustainability and real-world effectiveness are thus central tenets of the Italian regulatory system. To meet these challenges, AIFA has invested more than €22 million (about $25 million) in information technology and the development of drug-product monitoring registries in the past 5 years. Given the importance of the investments made in this space, the National Health Service Information Technology Law was passed in Italy in 2012. It mandated the implementation of Web-based registries after marketing authorization to measure drug safety and effectiveness for approved therapeutic indications and some selected off-label uses (Montilla et al., 2015). As of February 2016, data from 850,000 patients have been captured by the registries.

A second key aspect of the AIFA system that addresses sustainability is pricing and reimbursement, said Pani. He described a range of possible reimbursement outcomes that await Market Authorization Holder who

seek registration by AIFA, ranging from a refusal to reimburse, reimbursement without particular conditions, reimbursement with a control on prescription (adherence to an optimized therapeutic plan) to a Managed Entry Agreement (MEA). MEAs are a heterogeneous group of instruments that are being increasingly implemented to guarantee sustainability of innovative and expensive medicines. MEAs can be purely financial based (price/volume agreements) or health-outcome based (Ferrario and Kanavos, 2015). Most frequently a combination of the two may be applied. For example, AIFA has signed contracts with pharmaceutical companies that set payment based on treatment effectiveness (performance-based risk sharing agreements), with companies refunding costs if the medication fails, said Pani.

Pani described how the AIFA strategy was applied to the approval of new treatments for hepatitis C (HCV), which are highly effective, but extremely expensive. Like the United States, Italy has a high incidence of HCV, and the cost of treating them all would be prohibitive. Thus, AIFA created a permanent national working group to develop a strategy for providing HCV drugs. After developing seven prioritization criteria that would provide the drug to patients with the greatest clinical need, AIFA used data from their registries to calculate the total number of treatments needed, and thus to negotiate a price/volume discount with the manufacturer.

AIFA also used earlier versions of the registries to determine how best to use new diabetes therapies (incretins) most effectively. In 2008, they approved the reimbursement of three drugs—exenatide, sitagliptin, and vildagliptin—in which patients were subject to enrollment in the real-world data. Data from the post-marketing registry revealed substantial off-label use, little adherence, as well as inconsistent effectiveness. However, the data also showed that when used appropriately in combination with exercise, the effectiveness of the drugs was consistent with the results seen in the registration trials (Montilla et al., 2014).

In the area of psychiatry, AIFA used the national drug utilization database (Osmed Health-DB) to study treatment-resistant depression. They developed an antidepressant usage index, which revealed that the higher the degree of "resistance" along a continuum, the higher the cost of both depression-related and depression-unrelated resources for the National Health System said Pani.

POTENTIAL REGULATORY IMPLICATIONS FOR CLINICAL RESEARCH INNOVATIONS

Recognizing the inefficiencies of the historical model of clinical research, where a single coordinating center manages a trial with top-down decision making with independently operated sites, Califf proposed a different model of interoperable networks that share sites and data. Integrating clinical research networks not only ensures more efficient trials, but also enables patients, physicians, and scientists to form true "communities of research."

Indeed, such systems are already being built. The FDA's Sentinel Initiative,[3] launched in 2008, is a national electronic system that will enable postmarket safety monitoring of FDA-approved drugs by providing access to claims data from more than 100 million people. Linked to Sentinel is the National Institutes of Health (NIH) Health Care Systems Research Collaboratory,[4] which has initiated 10 demonstration projects spanning 12 NIH institutes and centers to reduce the cost of clinical trials by capturing electronic health record data. Another network, the National Patient-Centered Clinical Research Network (PCORnet),[5] brings patients into the process as full partners. With the support of user fees from the Prescription Drug User Fee Act (PDUFA), a national evidence generation system is being built to combine data from different networks through collaborations with industry, academia, and integrated health systems.

The culmination of all of this, said Califf, is the Precision Medicine Initiative.[6] The FDA is integrally involved in this NIH-led effort to get volunteers to participate in research as a normal part of their patient care. He noted that this initiative was fueled by a recognition by the U.S. President and Vice President that what is holding the country back from exploiting the computational power currently available is culture, not technology, which has resulted in people hoarding rather than sharing data.

[3]For more information, go to http://www.fda.gov/Safety/FDAsSentine/Initiative/ucm2007250.htm (accessed June 3, 2016).

[4]For more information, go to https://www.nihcollaboratory.org/about-us/Pages/default.aspx (accessed June 3, 2016).

[5]For more information, go to http://www.pcornet.org (accessed June 3, 2016).

[6]For more information, go to https://www.whitehouse.gov/precision-medicine (accessed June 3, 2016).

Encouraging Data Sharing

A potential roadblock to these efforts is the privacy protections on data, particularly mental health data, noted Robert Bilder. Califf said the expert community and patients would need to push for solutions that enable data sharing with appropriate protections. In Italy, said Pani, there has been a push for sharing data from control arms (which is often the standard-of-care treatment) in clinical trials; in the United States, the FDA is close to publishing the Final Rule for www.ClinicalTrials.gov, which will require sponsors to share results from clinical trials or potentially face fines of up to $10,000 per day, according to Califf. While several potential barriers exist to sharing clinical trial data, several participants acknowledged the many benefits. For example, sharing clinical trial data:

- "has great potential to accelerate scientific progress and ultimately improve public health by generating better evidence on the safety and effectiveness of therapies for patients;
- increases patients' contributions to generalizable knowledge about human health by potentially facilitating additional findings beyond the original, prespecified clinical trial outcomes;
- could provide a more comprehensive picture of the benefits and risks of an intervention and allow health care professionals and patients to make more informed decisions about clinical care; and
- could potentially improve public health and patient outcomes, reduce the incidence of adverse effects from therapies, and decrease expenditures for medical interventions that are ineffective or less effective than alternatives" (IOM, 2015, pp. 31–32).

No company has the power (or desire) to implement universal data sharing by itself; it will more likely come from legislation, said Pani. Other possible solutions include having the FDA serve as an honest broker to manage shared data, or forming a consortium that hosts a clinical data repository. A model for this in Europe could be the Innovative Medicines Initiative (IMI) called Novel Methods leading to NEWMEDS,[7] an international public–private partnership that encourages data sharing

[7]For more information, go to http://www.newmeds-europe.com (accessed June 3, 2016).

from companies and investigators with the goal of identifying new methods for drug development for depression and schizophrenia. Califf said ECG data were shared in this way years ago, after overcoming legal hurdles. This resulted in a much better understanding of cardiac events associated with prolonged QT interval[8] issues. Califf added that part of the solution has to be a firewall and an audit trail to protect data that are contributed to such initiatives.

A New Regulatory Framework for Combining Passive and Experiential Data

In 1962, the U.S. Congress passed the Kefauver-Harris Amendments to the Federal Food, Drug, and Cosmetics Act, for the first time requiring trials to demonstrate substantial evidence of effectiveness prior to market approval. With the passage of the Orphan Drug Act in 1983, the FDA recognized the need for a different regulatory framework around rare disease entities. Since then, the identification of specific genetic mutations that could predict prognosis or response to the therapy, as well as the emergence of the Internet and the digital revolution, have highlighted the need for a new regulatory framework appropriate for the 21st century, according to Karl Kieburtz.

Thomas Laughren cited some of the 21st-century approaches that present challenges to be addressed in this new framework:

- Incorporating novel designs and methods into clinical studies, and how sponsors can gain regulatory guidance on the adoption of new methodologies in a drug development program;
- Using the Internet and social media for patient recruitment and assessment;
- Conducting trials at geographically dispersed sites; and
- Incorporating more clinically meaningful endpoints into trials.

Pani added that the shifting classification boundaries for therapeutics present a challenge for regulators with respect to considerations of both efficacy and safety. A drug may first be developed for the treatment of psoriasis, for example, and then be used to treat arthritis, Crohn's dis-

[8]The QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. A long QT interval is a risk factor for sudden death, while a short QT interval indicates a genetic condition (http://www.tga.gov.au/file/1140/download, accessed June 23, 2016).

ease, or even cancer, said Pani. In addition, particularly for precision medicine, but for other drugs in development as well, variability in response needs to be better understood. Thus, rather than striving for homogeneity in clinical trials to reduce variability, it may be more advantageous to enroll very large heterogeneous populations and then use analytics to discover commonalities and differences. However, the enrollment of large heterogeneous populations in the RCTs is the opposite approach of the adaptive pathway, said Pani. He added that enrolling large population from an academic point of view is acceptable, but on the other hand, is very expensive and it may delay the access of new drugs.

As the range of treatment targets expands, there will be an increasing need for collaboration among regulators, other governmental agencies, and the research community, added Tiffany Farchione.

Drug Product Registries

Registries are an enormously useful source of information that could generate many hypotheses that might lead to randomized trials, according to Laughren. For example, a registry was required for the clozapine[9] registration trials, which enabled generating data regarding the hazard curve for the potentially fatal adverse event agranulocytosis, in which the level of white blood cells called neutrophils drops to dangerous levels, causing suppression of the immune system (Alvir et al., 1993). It also suggested that clozapine reduced suicides in patients with schizophrenia.

Italy also has established registries for many medications, including the treatment- resistant depression registry mentioned earlier. These registries provide information about the effectiveness and safety of a treatment. In addition, because registries collect fairly rigorous data, they are an ideal place to embed randomization, said Califf. For example, Sweden is doing a series of registry trials where everyone gets randomized as part of routine care. As a result, they were able to conduct a trial of a thrombectomy device, which removes a clot from a blood vessel, for a tiny fraction of what it would have cost to run such a trial in the United States. Randomization with real-world data is done every day in the business world, but has encountered roadblocks in medicine, said Pani.

However, Laughren cautioned that many registries which have been set up are failing to generate useful data because they were poorly designed. Italy has addressed this by requiring that registry databases meet

[9]Clozapine is an atypical antipsychotic agent.

International Organization for Standardization standards and by continuously and randomly checking the data, according to Pani. One challenge is the quality of data; the data must be well structured but the quality may depend by other factors, he added. Califf commented that there are excellent models in the United States, such as one developed by the Society of Thoracic Surgeons, where data are checked and audited. They were designed that way because surgeons realized they would not be reimbursed unless they produced reliable outcome data. Several health systems are investing heavily in integrated data warehouses; there are also efforts to enable these data warehouses to communicate with each other while retaining local control.

6

Ethical Considerations

Highlights

- As clinical trials continue to transform, ethical considerations that need to be addressed include respecting the autonomy and privacy of patients, protecting and securing patient data, and balancing the risks and benefits of individuals against the risks and benefits to the community of patients at-large (Kaufmann).
- Patient engagement, improved communication, and transparency are key to encouraging patients to agree to share their data, despite the risk of re-identification (Rockhold).
- Data should be thought of as something patients donate rather than something that is collected (Chiauzzi).
- PatientsLikeMe's Clinical Trial Awareness tool is one example of a patient recruitment tool in which patients are matched with clinical trials for which they may be eligible (Chiauzzi).

NOTE: These points were made by the individual speakers identified above; they are not intended to reflect a consensus among workshop participants.

Petra Kaufmann, director of the Office of Rare Diseases Research and Division of Clinical Innovation at the National Center for Advancing Translational Sciences (NCATS), began with the admonition that the field has a moral obligation in neuroscience trials to explore change, given the stagnant drug development environment for some disorders. Changes are coming, she continued, as a result of technological advances

as well as the changing landscape in health care, where electronic medical records are enabling novel ways of using data. Yet as the field explores changing how clinical trials are conducted, several participants noted that a number of ethical considerations need to be addressed, including respect for the autonomy and privacy of patients, ensuring that they are safe from the risk of exposure of their data, and balancing the risks and benefits of the individual against the risks and benefits to overall patient community. In addition, she suggested that as opposed to parallel systems of data collection in the context of clinical care, research, and regulatory approval, it would be more ethically sound to have better alignment of these data streams in order to maximize the usefulness of those data. This would call for more attention to both data protection and human subjects protection, yet while there appears to be momentum across the field for more data sharing, cultural barriers remain. Indeed, the technology to share data is available, but incentives are not yet aligned with that goal, said Kaufmann.

DATA PROTECTION

Throughout the workshop, several participants highlighted the need for data sharing in a variety of contexts. In the context of ethics, data privacy and data protection are particularly important. Frank Rockhold, senior vice president of Global Clinical Safety and Pharmacovigilance at GlaxoSmithKline (GSK) at the time of the meeting, and now professor of biostatistics and bioinformatics at Duke University School of Medicine, noted that large datasets are already available and accessible, even as guidelines for data protection are still evolving. For example, www.clinicalstudydatarequest.com (CSDR) is an independent custodian of anonymized patient-level data from clinical trials that has amassed data from more than 1 million patients. The Wellcome Trust, Multi-Regional Clinical Trials Center at Brigham and Women's Hospital, Harvard University, along with others, have launched an initiative to support this effort by creating and implementing a sustainable, centralized international data-sharing platform. According to Rockhold, one of the central issues of large databanks is how to safely share information. CSDR established an independent review panel to determine whether researchers should be granted access to these data, based on the scientific rationale and significance of the proposed research as well as the qualifications of the investigators and other criteria (Strom et al., 2014).

In addition, the Institute of Medicine conducted a study on *Sharing Clinical Trial Data: Maximizing Benefits, Minimizing Risk* addressing these issues (IOM, 2015).

Rockhold posited that data privacy should be thought of as a probability issue. Despite several different levels of de-identification before data are incorporated into a shared database, the risk of re-identification will never be zero unless the data are stripped of so much information that their value is essentially zero. Moreover, the patient's perception of risk and harm from re-identification, and thus the patient's benefit–risk assessment, may be very different from the perception of sponsors, clinicians, and other stakeholders, said Rockhold. In addition, the potential benefits for the patient contributing the data may be vastly different from the potential benefits to future patients. Thus, the appropriate balance between providing valuable data and protecting the privacy of those who donated those data will shift with different studies, populations, and over time.

Statisticians have created complex probability models to assess the risk of re-identification under different scenarios (Dankar et al., 2012; Wan et al., 2015). Yet communicating what these probabilities mean in real life to patients remains a challenge. Adding to the complexity, laws regarding data privacy can differ among countries, as well as variations in individuals' perception and fear of exposure, make it especially challenging to establish a workable worldwide system, said Rockhold.

Despite these challenges, he said most patients are willing to accept some small level of risk if it means their information can be reused to help somebody in the future. In addition, Rockhold argued that by not reusing data, we are violating our commitment to patients to search for better treatments. Recently, GSK added a statement to their informed consent documents indicating that as a condition of enrolling in trials, patients had to accept that their data would be shared publicly despite the small risk of re-identification; little resistance to this requirement was encountered. For studies conducted before this statement was added to the informed consent, the company enlisted the help of data privacy and legal experts to estimate the probability that patients would have agreed to share their data, although in a few cases the informed consent explicitly precluded sharing of information.

Ironically, said Rockhold—although for rare diseases it is especially difficult to de-identify information and thus, these data are frequently not shared—many rare disease patient groups have indicated support for data sharing. There are also certain data, such as the name of the investigator,

that are typically not shared because they increase the risk of re-identification. Other approaches to lessen the risk of re-identification include the use of a trusted third party to carry out the de-identification process, encrypting information, and anonymizing the information and then discarding the key. This latter approach, however, precludes the possibility of going back to the dataset to answer new questions. Indeed, each of these steps to protect data may diminish their usefulness.

Greg Koski proposed another model, which he called the "Fidelity" model for patient engagement. It allows patients to place their personal health information, genomic information, among others, in a secure personal account, which they control and can invest in ways they choose to support research. This approach, he said, truly empowers patients and equalizes the power differential between those who do the research and those who depend on it.

HUMAN SUBJECTS PROTECTION

Koski said he and many others believe the current approach to human subjects protection is dysfunctional and inappropriate for our current environment and needs to be fundamentally reconsidered. For example, he said that the research community is beginning to recognize that including research use under HIPAA restrictions has impeded research and that it may be time to review and revise these restrictions. Furthermore, he argued for moving to a model based on a paradigm of professionalism rather than protectionism, built on the assumption that well-trained, committed individuals will do what's right according to general standards of responsible behavior. This model would also create an environment that aligns physicians and others for doing things properly. Moreover, he and others argued for more patient-centric approaches that recognize patients as more than clinical trial participants.

Emil Chiauzzi, research director for PatientsLikeMe, offered a different perspective on a truly patient-centered approach as it might apply to clinical trials with regard to data sharing and privacy. The PatientsLikeMe[1] platform operates in the service of patients rather than patients serving to provide the research community with data. This includes considering the patient experience over a long period of time, and thinking of data as something patients donate rather than something that is collected.

[1]For more information, go to https://www.patientslikeme.com (accessed June 3, 2016).

At the time of the workshop, approximately 400,000 patients were registered to use the PatientsLikeMe platform. Approximately 2,500 diseases are represented with varying levels of data density across those diseases. Both structured data from validated measures and unstructured, qualitative data are captured; in both cases these are real-world longitudinal data provided by patient report. The site allows people to track their diseases, monitor symptoms and reactions to medication, and share their information with people who have similar conditions. These data are also used by research partners who seek to gain insight into disease processes, medication adherence, and other aspects of the patient experience. The data-sharing agreements for these studies typically remove identifiers such as name, address, and e-mail address. Qualitative data are less frequently shared because they are difficult to de-identify, said Chiauzzi.

Patients are informed through the user agreement that there are no guarantees with regard to data privacy. Moreover, Chiauzzi noted that people who join PatientsLikeMe have already bought into the social media concept and thus have somewhat different views compared to the general population with regard to privacy. Yet there is still a need to explore privacy in a more nuanced way in terms of conditional and personal factors; thus, PatientsLikeMe is working with research partners to develop measures to assess individual affinity for different aspects of privacy, protection, and data sharing.

PatientsLikeMe also includes a Clinical Trial Awareness tool that matches patients with clinical trials for which they may be eligible. As noted in previous chapters, the use of social media for recruitment in clinical trials raises some concerns about blinding and sharing different kinds of medical advice (Glickman, 2012). Chiauzzi suggested that there may be a way to leverage that kind of patient-to-patient communication in a positive way. PatientsLikeMe is now involved in an oncology study in which they are providing a collection point for people to have conversations as a way to encourage retention. This site also provides a mechanism for investigators to communicate with study participants.

7

Improving the Evidence Base for Real-World Use

Highlights

- Specialty medications account for one-fourth of health care costs. To make reimbursement decisions, payers require comparative effectiveness data in addition to data regarding the feasibility of implementation (Robinson Beale), which can be increasingly difficult for sponsors to show given the high cost of drug development (Romano).
- Pragmatic trials provide regulators, payers, sponsors, providers, and patients with real-world data about treatment effectiveness, safety, and use (Cziraky and Robinson Beale).
- Observational studies have been shown in a number of publications to approximate the effects of treatment as well as randomized controlled trials (Stang).
- Data environments that contain core administrative claim databases and networks of providers offer the capability of data generation through the implementation of pragmatic trials (Cziraky).
- Administrative claim databases with the ability to connect to clinical data elements maintained by health plans offer a rich source of mineable data for development of pragmatic trials (Cziraky).

NOTE: These points were made by the individual speakers identified above; they are not intended to reflect a consensus among workshop participants.

PERSPECTIVES FROM PAYERS

According to several participants, the tension between the rising cost and complexity of clinical trials for innovative treatments for nervous system disorders and the desire to make these treatments accessible for patients reaches its zenith in the reimbursement space. For payers, the dilemma of unsustainability revolves around the expansion and delivery of new technologies and treatments, and how those treatments are paid for, according to Rhonda Robinson Beale, senior vice president and chief medical officer at Blue Cross of Idaho. She noted that in the specialty drug area, new drugs may cost more than $100,000 per year over the lifetime of the patient. As a result, the 3.6 percent of patients who use specialty medications account for 25 percent of health care costs (Milliman, Inc., 2013).

The type of information needed by payers to facilitate adoption and coverage may be very different from that needed by regulators. It may, for example, include the feasibility of implementing a new technology with fidelity, said Robinson Beale. Moreover, different types of payers—health plans, employers, accountable care organizations (ACOs), and individual patients—require different information. For example, ACOs consider not only cost, but also the practicality of implementing a new treatment to achieve the outcomes seen in a clinical trial and whether the treatment is more efficacious compared to existing treatments. Should a new treatment be covered if it only provides incremental improvement over existing treatment? Should off-label use be covered? Ethical choices may also be necessary, said Robinson Beale, for example, if a costly new treatment is to be covered, will something else lose coverage? How does one balance cost with extension of life decisions?

Historically, payers have made decisions based on medical necessity with evidence obtained from peer-reviewed articles, technology reviews, and practice guidelines from credible organizations, said Robinson Beale. She added that payers typically look not only at RCTs, but pragmatic trials as well in order to gain a real-world understanding of the efficacy and practicality of the treatment over a longer period of time than the duration of a clinical trial. Comparative effectiveness studies and a comparative cost–benefit analysis may also be required.

For very expensive treatments, payers may also ask for definitive evidence that a standard treatment is not effective in a particular patient. For example, said Robinson Beale, transcranial magnetic stimulation has been shown to be effective as a treatment for depression, but is far more

expensive than antidepressant medications; thus it is typically reserved only for those who receive no benefit from medications. In the precision medicine world, some treatments, including expensive specialty drugs, also work only on subsets of the population. Studies to identify responsive subgroups would thus also be extremely helpful for payers, said Robinson Beale.

In Italy, there is a different approach to reimbursement, as described by Luca Pani in Chapter 5. Outcome-based reimbursement requires companies to refund money if a treatment did not work. This model is particularly challenging in the CNS field, which has a particularly high failure rates. For example, sponsors are developing drugs to treat AD presymptomatically; in addition to the lack of measures for such trials, healthy patients may be exposed to drugs that have some side effects. Studies would need to show some real-life advantages for these patients, which is particularly challenging, said Pani.

PERSPECTIVES FROM THE PHARMACEUTICAL INDUSTRY

Several participants highlighted the importance of payer concerns and how they are factored into pharmaceutical companies' drug development programs. They noted that this requires generating credible evidence of value in the real world from both observational studies, including registry studies, and randomized trials in real-world settings, also known as pragmatic trials. Steven Romano said that drug developers are now talking with payers and health technology assessment groups even before initiating a Phase II study. This requires investigators to assess the value proposition for a new medicine, including functional outcomes and health economic outcomes.

According to Paul Stang, vice president of global epidemiology for Janssen Research and Development, payers want to understand the performance of products in the specific population they serve. Selecting the appropriate comparator and relevant populations for studies thus may vary, depending on the payer. For example, the population served by the Department of Veterans Affairs may have unique characteristics that influence their use of a treatment and they may also receive care according to a different model than a population served by a commercial insurer. Additionally, patients in the United States frequently change health plans, complicating the value proposition because a payer may question

the merit of paying for a treatment that may only provide a benefit in the future when the patient is no longer in the plan. Different payers also value indirect benefits differently, such as loss of productivity, family impact, or the effect of a treatment on quality of life. Finally, Stang said, both sponsors and payers must grapple with the question of what constitutes a meaningful difference.

METHODOLOGY FOR OBSERVATIONAL STUDIES

While RCTs are considered the "gold standard," a few participants stated that well-designed observational studies have been shown to approximate the effects of treatment as well as RCTs (Anglemyer et al., 2014; Benson and Hartz, 2000; Concato et al., 2000). Compared to pivotal RCTs, Stang noted that observational trials tend to follow people for a longer period of time, may include much larger and more diverse populations, and may incorporate existing data collection infrastructure such as electronic medical records. They also involve a more diverse group of investigators with varying levels of experience in conducting trials, increasing variability. Hybrid studies have recently emerged as another alternative, said Stang. These trials randomize patients and use electronic health records as the data collection tool.

METHODOLOGY FOR PRAGMATIC TRIALS

Demand is growing from regulators, payers, providers, and patients for pragmatic trials, according to Mark Cziraky, co-founder and vice president of research at HealthCore, Inc. These trials are designed to evaluate the risk and benefits of interventions in real-world, naturalistic community settings. In addition to testing in a real-world population and comparing a treatment to the standard of care rather than a placebo because pragmatic trials are typically conducted by practitioners, they provide a window into the effectiveness and value of a treatment when used as intended. They also provide regulators with real-world evidence around safety, and payers with real-world data about use. Figure 7-1 summarizes some characteristics of pragmatic trials.

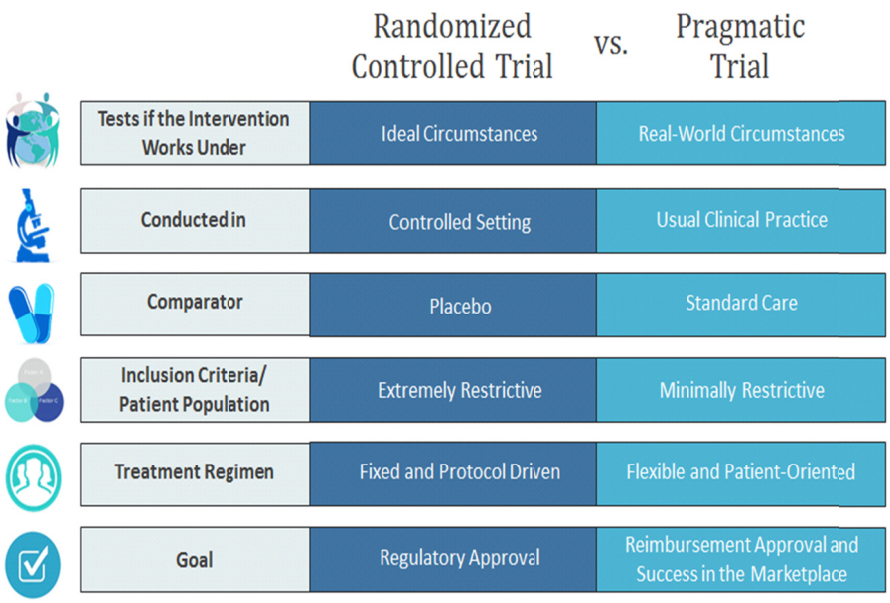

FIGURE 7-1 Pragmatic trials versus randomized controlled trials.
SOURCE: Presented by Mark Cziraky at the Workshop on Neuroscience Trials of the Future, March 4, 2016.

In a search of www.ClinicalTrials.gov, Cziraky examined 367 studies identified as pragmatic trials, 11 percent of which were in the neurosciences—primarily in psychiatry (Purgato et al., 2015) and psychopharmacology (Vitiello, 2015). Many of the studies use cluster randomization, where population groups (e.g., in nursing homes, inpatient facilities, or physician practices) rather than individuals were randomized. This approach lessens the burden on practitioners and avoids contamination across interventions, but introduces a loss of statistical efficiency (Meurer and Lewis, 2015). However, in psychiatry, there is the potential for spillover effects in clusters, for example, if many individuals in the cluster received effective antidepressants, suggested Erik Snowberg. While this might be a good thing for the patients involved, it could at the same time make interpretation of results difficult.

One of the challenges with pragmatic trials is selecting the comparator. The standard of care may be well established throughout the field, or may be selected individually by the provider. In the neurosciences, the standard of care is often not obvious, said Stang, making these pragmatic

trials noisier than those done on other fields such as cardiology, where standards of care are more widely recognized. Even in cardiology, however, standard treatments such as statins for lowering cholesterol are widely underused, said Cziraky, adding even more complexity to the trial. An additional question related to the standard of care is whether the experimental treatment is given in addition to, or instead of, the standard treatment, noted Frank Rockhold. In the neuropsychiatry there are even more complications, he said, because the comparator may be psychotherapy, which may be problematic or unethical to withhold. On the device side, additional variability in the standard of care arises because of variability in the skill of the operators (i.e., surgeons), said Stang.

According to a few participants, real-world trials add other complexities, including variability around diagnoses, whether patients are taking medications as directed, and what other treatments are being taken concurrently. Daniel Burch and Michael Pollock, vice president of real-world outcomes at PPD, cited other differences between explanatory (efficacy) and pragmatic (effectiveness) trials. Explanatory trials try to set ideal conditions to achieve a well-controlled study, yet result in questionable external validity and generalizability. They also may be affected by non-adherence. Burch added that while placebo responses and variability complicate explanatory trials, they are essential parts of the real world that patients, clinicians, and payers live in.

New technologies are increasingly being employed in real-world trials, including automated reminder systems to maximize compliance and biomeasures (such as those using smartphones) to help further identify patients who are likely to benefit or be harmed by a treatment, said Stang.

DATA SOURCES FOR REAL-WORLD TRIALS

The databases maintained by health plans and large provider networks offer a rich source of minable data for pragmatic trials, according to several participants. For example, HealthCore maintains an integrated research database[1] that captures 10 years of data from about 65 million individuals, including data from administrative claims, physician and facility claims, prescriptions, and laboratory tests, said Cziraky. Together, these data can provide a picture of a patient's exposure to the health

[1]For more information, go to https://www.healthcore.com/database (accessed June 3, 2016).

care system, including procedures and tests performed, treatments, hospitalizations, and costs, he added. For about 30 percent of their population, results from laboratory tests are also included, providing a proxy for diagnosis. Moreover, Cziraky stated that working through providers, these data can be connected with clinical data in the trial setting to create an integrated dataset for analysis.

Burch commented that the workshop discussions suggest that distinctions between regulatory and pragmatic trials may become blurred, which raises concerns because of the potential for real-world trials to impede assay sensitivity. However, Robert Califf used the example of opioid use and abuse to illustrate why pragmatic trials are needed. Although there is good evidence that opioids provide much-needed pain relief for 2 months, there has never been a study to show that there is a benefit beyond 3 months. Yet patients often take these drugs for extended periods of time, resulting in many overdose deaths. Part of the FDA's postmarketing requirement now for opioids is a randomized withdrawal study out to a year to provide doctors with prescribing guidance.

Similarly, said Pani, there is virtually no evidence of what will happen if disease-modifying drugs for a disease like AD are given for an extended period of time and outcomes needed for registration may different from health-outcomes needed for price negotiation pointing again to the need of early scientific and HTA advice. Califf commented that tools like Sentinel should provide an inexpensive way to collect long-term data for these types of follow-up studies. Moreover, he thinks these very large databases will provide a self-correcting system to prevent the reporting of false-positive results of a problem when, in fact, a drug is quite safe. Thomas Laughren added that most of these databases have committees that review analysis plans before sharing data to ensure that the study being proposed is legitimate and rigorous. A workshop participant said this problem is being addressed by the National Center for Health Statistics and other federal agencies by a process called a research data center, where people can submit a research design, which, if deemed worthwhile by a group of experts, is turned over to a team of technologists and statisticians who will execute the research plan for a fee.

Story Landis relayed an experience with PatientsLikeMe, that while not a pragmatic trial per se, further illustrates the value of the patient experience. After a paper published in a reputable journal suggested that lithium delayed the progression of amyotrophic lateral sclerosis (ALS) (Fornai et al., 2008), many ALS patients obtained off-label prescriptions and began taking the drug. As NINDS and partners were conducting a

multi-center, double-blind, placebo controlled trial, PatientsLikeMe and its ALS patient community using lithium off-label found that there was no effect on disease progression (Wicks et al., 2011). Consistent with their conclusion, NINDS halted their trial early based on futility (Aggarwal et al., 2010).

FINAL REMARKS

At the start of the workshop, Romano argued that the field was reaching an inflection point. According to Romano, "Neuroscience basic research is exploding. The knowledge is exploding for clinical biology and genetics. Human experimental biology platforms are being refined and incorporated into development paradigms, which will help us going forward. Clarification of functional domains and relevant neurocircuitry should allow for more effective de-risking in the early phase of development. Enhancements in clinical trial methodology and trial execution should increase the probability of success in late-phase development." Throughout the workshop, several participants highlight potential near- and long-term opportunities for clinical trial improvement for nervous system disorders. According to Thomas Laughren and a few other participants, advances in methodology continues to progress offering novel designs, assessments, recruitment tools, among others, to be used in the near term. Stephen Brannan noted that collaborative efforts are increasing and the field may begin to see more ADNI-like initiatives and public-private partnerships to address complex problems (e.g., biomarker identification and validation). Petra Kaufmann added that part of these collaborations include increasing data sharing which might improve the efficiency of trials and decrease duplicative efforts.

Many workshop participants highlighted the increased focus on patients and real-life outcomes in neuroscience trials of the future. Enabling technologies discussed include mobile health, remote monitoring, and wearable devices as well as other technologies that have yet to be developed, said Atul Pande. A few participants noted the need for increased interaction and communication between pharmaceutical and technology companies to better understand the application and use of these technologies in clinical trials. Given the fact that disruptive innovation requires a process of change, several participants recognized that this will be an ongoing process and will not happen overnight. Opportunities that are further down in the pipeline, according to some participants, include un-

derstanding how to capitalize on biomarkers as a way of teasing out subgroups within targeted populations. In addition, understanding how new technologies might be used for trialists to recruit participants more globally.

Highlighting the collective effort that is needed to address the challenges in the field, Pande stated that in order to see the ideas discussed at the workshop come to fruition, someone is going to have to take the first step. Quoting Kurt Vonnegut (2013), Pande ended by saying, "Sometimes we just have to jump off a cliff and grow our wings on the way down."

A

References

Abbott, A. 2011. Novartis to shut brain research facility. *Nature* 480(7376):161-162.

Aggarwal, S.P., L. Zinman, E. Simpson, J. McKinley, K. E. Jackson, H. Pinto, R. A. Conwit, D. Schoenfeld, J. Shefner, and M. Cudkowicz. 2010. Clinical trial testing lithium in ALS terminates early for futility. *Lancet Neurology* 9(5):481.

Alvir, J. M., J. A. Lieberman, A. Z. Safferman, J. L. Schwimmer, and J. A. Schaaf. 1993. Clozapine-induced agranulocytosis. Incidence and risk factors in the United States. *New England Journal of Medicine* 329(3):162-167.

American Psychiatric Association. 2013. *Diagnostic and statistical manual of mental disorders*, 5th ed. Washington, DC: American Psychiatric Publishing.

Anglemyer, A., H. T. Horvath, and L. Bero. 2014. Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials. *Cochrane Database of Systematic Reviews* 4:MR000034.

Arrowsmith, J., and P. Miller. 2013. Trial watch: Phase II and Phase III attrition rates 2011-2012. *Nature Reviews Drug Discovery* 12(8):569.

Becker, R. E., and N. H. Greig. 2009. Neuropsychiatric clinical trials: Should they accommodate real-world practices or set standards for clinical practices? *Journal of Clinical Psychopharmacology* 29(1):56-64.

Benson, K., and A. J. Hartz. 2000. A comparison of observational studies and randomized, controlled trials. *New England Journal of Medicine* 342(25):1878-1886.

Berndt, E. R., and I. M. Cockburn. 2014. Price indexes for clinical trial research: A feasibility study. No. w18918. *Monthly Labor Review: U.S. Bureau of Labor Statistics.*

Biomarkers Definitions Working Group. 2001. Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. *Clinical Pharmacology & Therapeutics* 69(3):89-95.

Bleck, T., H. Cock, J. Chamberlain, J. Cloyd, J. Connor, J. Elm, N. Fountain, E. Jones, D. Lowenstein, S. Shinnar, R. Silbergleit, D. Treiman, E. Trinka, and J. Kapur. 2013. The established status epilepticus trial 2013. *Epilepsia* 5(s6):89-92.

Borsboom, D., and A. O. Cramer. 2013. Network analysis: An integrative approach to the structure of psychopathology. *Annual Review of Clinical Psychology* 9:91-121.

Buckholtz, J. W., and A. Meyer-Lindenberg. 2012. Psychopathology and the human connectome: Toward a transdiagnostic model of risk for mental illness. *Neuron* 74(6):990-1004.

Button, K. S., J. P. Ioannidis, C. Mokrysz, B. A. Nosek, J. Flint, E. S. Robinson, and M. R. Munafo. 2013. Power failure: Why small sample size undermines the reliability of neuroscience. *Nature Reviews Neuroscience* 14(5):365-376.

Cai, N., T. B. Bigdeli, W. Kretzschmar, Y. Li, J. Liang, L. Song, J. Hu, Q. Li, W. Jin, Z. Hu, and G. Wang. 2015. Sparse whole-genome sequencing identifies two loci for major depressive disorder. *Nature* 523(7562):588-591.

Capone, M. 2015. How wearables and mobile health tech are reshaping clinical trials. *Venture Beat* http://venturebeat.com/2015/04/17/how-wearables-and-mobile-health-tech-are-reshaping-clinic (accessed June 3, 2016).

Casey, B. J., N. Craddock, B. N. Cuthbert, S. E. Hyman, F. S. Lee, and K. J. Ressler. 2013. DSM-5 and RDoC: Progress in psychiatry research? *Nature Reviews Neuroscience* 14(11):810-814.

Chassang, S., E. Snowberg, B. Seymour, and C. Bowles. 2015. Accounting for behavior in treatment effects: New applications for blind trials. *PLoS ONE* 10(6):e0127227.

Chen-Plotkin, A. S. 2014. Unbiased approaches to biomarker discovery in neurodegenerative diseases. *Neuron* 84(3):594-607.

Clark, C.M., J. A. Schneider, B. J. Bedell, T. G. Beach, W. B. Bilker, M. A. Mintun, M. J. Pontecorvo, F. Hefti, A. P. Carpenter, M. L. Flitter, and M. J. Krautkramer. 2011. Use of florbetapir-PET for imaging β-

amyloid pathology. *Journal of the American Medical Association* 305(3):275-283.

Cohen, P. D., L. Herman, S. Jedlinski, P. Willocks, and P. Wittekind. 2007. Ethical issues in clinical neuroscience research: A patient's perspective. *Neurotherapeutics*, *4*(3):537-544.

Concato, J., N. Shah, and R. I. Horwitz. 2000. Randomized, controlled trials, observational studies, and the hierarchy of research designs. *New England Journal of Medicine* 342(25):1887-1892.

Connor, J. T., J. J. Elm, K. R. Broglio, ESETT, and Adapt-It Investigators. 2013. Bayesian adaptive trials offer advantages in comparative effectiveness trials: An example in status epilepticus. *Journal of Clinical Epidemiology* 66(8):S130-S137.

Cook, D., D. Brown, R. Alexander, R. March, P. Morgan, G. Satterthwaite, and M. N. Pangalos. 2014. Lessons learned from the fate of AstraZeneca's drug pipeline: A five-dimensional framework. *Nature Reviews Drug Discovery* 13(6):419-431.

Cross-Disorder Group of the Psychiatric Genomics Consortium. 2013. Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. *Nature Genetics* 45(9):984-994.

Dankar, F. K., K. El Emam, A. Neisa, and T. Roffey. 2012. Estimating the re-identification risk of clinical data sets. *BMC Medical Informatics and Decision Making* 12(1):66.

Desgrousilliers, M., and G. Keet. 2015. How wearable electronics will change clinical trials. *Clinical Leader*. http://www.clinicalleader.com/doc/how-wearable-electronics-will-change-clinical-trials-0001 (accessed July 27, 2016).

DiMasi, J. A., and H. G. Grabowski. 2007. The cost of biopharmaceutical R&D: Is biotech different? *Managerial and Decision Economics* 28(4-5):469-479.

Dorsey, E. R., J. D. Wagner, M. T. Bull, A. Rizzieri, J. Grischkan, M. A. Achey, T. Sherer, S. Chowdhury, C. Meunier, L. Cappelletti, C. Rocker, I. H. Richard, H. Schwarz, G. Kang, S. H. Ahmad, R. A. Biemiller, and K. M. Biglan. 2015. Feasibility of virtual research visits in Fox Trial Finder. *Journal of Parkinson's Disease* 5(3):505-515.

Eguale, T., D. L. Buckeridge, A. Verma, N. E. Winslade, A. Benedetti, J. A. Hanley, and R. Tamblyn. 2016. Association of off-label drug use and adverse drug events in an adult population. *Journal of the American Medical Association Internal Medicine* 176(1):55-63.

Ereshefsky, L., R. Evans, R. Sood, D. Williamson, and B. A. English. 2016. *Venturing into a new era of CNS drug development to improve*

success. Waltham, MA: Parexel. https://www.parexel.com/files/4314/4113/4032/Venturing_Into_a_New_Era_of_CNS_Drug_Development_to_Improve_Success.pdf (accessed June 22, 2016).

Ferrario, A., and Kanavos, P. 2015. Dealing with uncertainty and high prices of new medicines: A comparative analysis of the use of managed entry agreements in Belgium, England, the Netherlands and Sweden. *Social Science & Medicine* 124:39-47.

Flaherty, K. T., J. R. Infante, A. Daud, R. Gonzalez, R. F. Kefford, J. Sosman, O. Hamid, L. Schuchter, J. Cebon, N. Ibrahim, R. Kudchadkar, H. A. Burris, 3rd, G. Falchook, A. Algazi, K. Lewis, G. V. Long, I. Puzanov, P. Lebowitz, A. Singh, S. Little, P. Sun, A. Allred, D. Ouellet, K. B. Kim, K. Patel, and J. Weber. 2012. Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. *New England Journal of Medicine* 367(18):1694-1703.

Fornai, F., P. Longone, L. Cafaro, O. Kastsiuchenka, M. Ferrucci, M. L. Manca, G. Lazzeri, A. Spalloni, N. Bellio, P. Lenzi, N. Modugno, G. Siciliano, C. Isidoro, L. Murri, S. Ruggieri, and A. Paparelli. 2008. Lithium delays progression of amyotrophic lateral sclerosis. *Proceedings of the National Academy of Sciences of the United States of America* 105(6):2052-2057.

Fournier, J. C., R. J. DeRubeis, S. D. Hollon, S. Dimidjian, J. D. Amsterdam, R. C. Shelton, and J. Fawcett. 2010. Antidepressant drug effects and depression severity: A patient-level meta-analysis. *Journal of the American Medical Association* 303(1):47-53.

Fried, E. I., S. Epskamp, R. M. Nesse, F. Tuerlinckx, and D. Borsboom. 2016. What are "good" depression symptoms? Comparing the centrality of DSM and non-DSM symptoms of depression in a network analysis. *Journal of Affective Disorders* 189:314-320.

Glickman, S.W., S. Galhenage, L. McNair, Z. Barber, K. Patel, K. A. Schulman, and J. G. McHutchison. 2012. The potential influence of internet-based social networking on the conduct of clinical research studies. *Journal of Empirical Research on Human Research Ethics* 7(1):71-80.

Goodkind, M., S. B. Eickhoff, D. J. Oathes, Y. Jiang, A. Chang, L. B. Jones-Hagata, B. N. Ortega, Y. V. Zaiko, E. L. Roach, M. S. Korgaonkar, S. M. Grieve, I. Galatzer-Levy, P. T. Fox, and A. Etkin. 2015. Identification of a common neurobiological substrate for mental illness. *Journal of the American Medical Association Psychiatry* 72(4):305-315.

Gordon, D., W. Taddei-Peters, A. Mascette, M. Antman, P. G. Kaufmann, and M. S. Lauer. 2013. Publication of trials funded by the National Heart, Lung, and Blood Institute. *New England Journal of Medicine* 369(20):1926-1934.

Greene, S. M., R. J. Reid, and E. B. Larson. 2012. Implementing the learning health system: From concept to action. *Annals of Internal Medicine*, 157(3):207-210.

Gupta, S. 2012. Patient recruitment and retention are major challenges for clinical trials in CNS. *Applied Clinical Trials* 21(1). http://www.appliedclinicaltrialsonline.com/patient-recruitment-and-retention-are-major-challenges-clinical-trials-cns (accessed July 27, 2016).

GUSTO Investigators. 1993. The effects of tissue plasminogen activator, streptokinase, or both on coronary-artery patency, ventricular function, and survival after acute myocardial infarction. The GUSTO Angiographic Investigators. *New England Journal of Medicine* 329(22):1615-1622.

Haslam, N., E. Holland, and P. Kuppens. 2012. Categories versus dimensions in personality and psychopathology: A quantitative review of taxometric research. *Psychological Medicine* 42(5):903-920.

Hedden, T., K. R. Van Dijk, J. A. Becker, A. Mehta, R. A. Sperling, K. A. Johnson, and R. L. Buckner. 2009. Disruption of functional connectivity in clinically normal older adults harboring amyloid burden. *The Journal of Neuroscience* 29(40):12686-12694.

Hernandez, A.F., C. M. O'Connor, R. C. Starling, C. J. Reist, P. W. Armstrong, K. Dickstein, T. J. Lorenz, W. B. Gibler, V. Hasselblad, M. Komajda, and B. Massie. 2009. Rationale and design of the acute study of clinical effectiveness of nesiritide in decompensated heart failure trial (ASCEND-HF). *American Heart Journal*, 157(2):271-277.

Herper, M. 2015. The coming boom in brain medicines. Forbes, February 11. http://www.forbes.com/sites/matthewherper/2015/02/11/brain-boom-the-drug-companies-bringing-neuroscience-back-from-the-brink/#7247c0d352a2 (accessed June 22, 2016).

Insel, T. R., and B. N. Cuthbert. 2015. Brain disorders? Precisely. *Science* 348(6234):499-500.

IOM (Institute of Medicine). 2015. *Sharing clinical trial data: Maximizing benefits, minimizing risk.* Washington, DC: The National Academies Press.

Kaitin, K. I. 2012. Pace of CNS drug development and FDA approvals lags other drug classes. *Tufts Center for the Study of Drug Development Impact Report* 14(2).

Kang, J. H., D. J. Irwin, A. S. Chen-Plotkin, A. Siderowf, C. Caspell, C. S. Coffey, T. Waligorska, P. Taylor, S. Pan, M. Frasier, K. Marek, K. Kieburtz, D. Jennings, T. Simuni, C. M. Tanner, A. Singleton, A. W. Toga, S. Chowdhury, B. Mollenhauer, J. Q. Trojanowski, L. M. Shaw, and Parkinson's Progression Markers Initiative. 2013. Association of cerebrospinal fluid beta-amyloid 1-42, T-tau, P-tau181, and alpha-synuclein levels with clinical features of drug-naive patients with early Parkinson disease. *Journal of the American Medical Association Neurology* 70(10):1277-1287.

Kendler, K. S. 2016. The phenomenology of major depression and the representativeness and nature of DSM criteria. *American Journal of Psychiatry* 173(8):771-780.

Kendler, K. S., S. H. Aggen, G. P. Knudsen, E. Roysamb, M. C. Neale, and T. Reichborn-Kjennerud. 2011. The structure of genetic and environmental risk factors for syndromal and subsyndromal common DSM-IV axis I and all axis II disorders. *American Journal of Psychiatry* 168(1):29-39.

Kesselheim, A. S., T. J. Hwang, and J. M. Franklin. 2015. Two decades of new drug development for central nervous system disorders. *Nature Reviews Drug Discovery* 14(12):815-816.

Kumar, S., W. J. Nilsen, A. Abernethy, A. Atienza, K. Patrick, M. Pavel, W. T. Riley, A. Shar, B. Spring, D. Spruijt-Metz, D. Hedeker, V. Honavar, R. Kravitz, R. C. Lefebvre, D. C. Mohr, S. A. Murphy, C. Quinn, V. Shusterman, and D. Swendeman. 2013. Mobile health technology evaluation: The mHealth evidence workshop. *American Journal of Preventative Medicine* 45(2):228-236.

Lahey, B. B., C. A. Van Hulle, A. L. Singh, I. D. Waldman, and P. J. Rathouz. 2011. Higher-order genetic and environmental structure of prevalent forms of child and adolescent psychopathology. *Archives of General Psychiatry* 68(2):181-189.

Lauer, M. S., and R. B. D'Agostino, Sr. 2013. The randomized registry trial—the next disruptive technology in clinical research? *New England Journal of Medicine* 369(17):1579-1581.

Levine, S. Z., J. Rabinowitz, R. Uher, and S. Kapur. 2015. Biomarkers of treatment outcome in schizophrenia: Defining a benchmark for clinical significance. *European Neuropsychopharmacology* 25(10):1578-1585.

Lillie, E.O., B. Patay, J. Diamant, B. Issell, E. J. Topol, and N. J. Schork. 2011. The n-of-1 clinical trial: The ultimate strategy for individualizing medicine? *Personalized Medicine* 8(2):161-173.

Liu, Q., M. Jamba, C. Patrick, 3rd, S. Padmanabhan, and M. D. Brennan. 2012. Targeted pharmacogenetic analysis of antipsychotic response in the CATIE study. *Pharmacogenomics* 13(11):1227-1237.

Meurer, W. J., and R. J. Lewis. 2015. Cluster randomized trials: Evaluating treatments applied to groups. *Journal of the American Medical Association* 313(20):2068-2069.

Miller, G. 2010. Is pharma running out of brainy ideas? *Science* 329(5991):502-504.

Milliman, Inc. 2013. *Milliman Specialty Medication Benchmark Study, 2013 analysis of 2011 data.* Brookfield, WI. Millman, Inc.

Montilla, S., G. Marchesini, A. Sammarco, M. P. Trotta, P. D. Siviero, C. Tomino, D. Melchiorri, L. Pani, and AIFA Anti-diabetics Monitoring Group. 2014. Drug utilization, safety, and effectiveness of exenatide, sitagliptin, and vildagliptin for type 2 diabetes in the real world: Data from the Italian AIFA Anti-diabetics Monitoring Registry. *Nutrition, Metabolism and Cardiovascular Diseases* 24(12):1346-1353.

Montilla, S., E. Xoxi, P. Russo, A. Cicchetti, and L. Pani. 2015. Monitoring registries at Italian Medicines Agency: Fostering access, guaranteeing sustainability. *International Journal of Technology Assessment in Health Care* 31(4):210-213.

Nelson, M. R., H. Tipney, J. L. Painter, J. Shen, P. Nicoletti, Y. Shen, A. Floratos, P. C. Sham, M. J. Li, J. Wang, L. R. Cardon, J. C. Whittaker, and P. Sanseau. 2015. The support of human genetic evidence for approved drug indications. *Nature Genetics* 47(8):856-860.

Pammolli, F., L. Magazzini, and M. Riccaboni. 2011. The productivity crisis in pharmaceutical R&D. *Nature Reviews Drug Discovery* 10(6):428-438.

Pankevich, D.E., B. M. Altevogt, J. Dunlop, F. H. Gage, and S. E. Hyman. 2014. Improving and accelerating drug development for nervous system disorders. *Neuron* 84(3):546-553.

Parekh, A., S. Buckman-Garner, S. McCune, O. Neill R, M. Geanacopoulos, S. Amur, C. Clingman, R. Barratt, M. Rocca, I. Hills, and J. Woodcock. 2015. Catalyzing the Critical Path Initiative: FDA's progress in drug development activities. *Clinical Pharmacology & Therapeutics* 97(3):221-233.

Prata, D., A. Mechelli, and S. Kapur. 2014. Clinically meaningful biomarkers for psychosis: A systematic and quantitative review. *Neuroscience and Biobehavioral Reviews* 45:134-141.

Purgato, M., C. Barbui, S. Stroup, and C. Adams. 2015. Pragmatic design in randomized controlled trials. *Psychological Medicine* 45(2):225-230.

Qiang, J. K., Y. C. Wong, A. Siderowf, H. I. Hurtig, S. X. Xie, V. M. Lee, J. Q. Trojanowski, D. Yearout, B. Leverenz J, T. J. Montine, M. Stern, S. Mendick, D. Jennings, C. Zabetian, K. Marek, and A. S. Chen-Plotkin. 2013. Plasma apolipoprotein A1 as a biomarker for Parkinson disease. *Annals of Neurology* 74(1):119-127.

Ranganathan, P., C. S. Pramesh, and M. Buyse. 2015. Common pitfalls in statistical analysis: Clinical versus statistical significance. *Perspectives in Clinical Research* 6(3):169-170.

Riordan, H., and N. Cutler. 2011. The death of CNS drug development: Overstatement or omen. *Journal of Clinical Studies* 3(6):12-15.

Rosenthal, L. S., D. Drake, R. N. Alcalay, D. Babcock, F. D. Bowman, A. Chen-Plotkin, T. M. Dawson, R. B. Dewey, Jr., D. C. German, X. Huang, B. Landin, M. McAuliffe, V. A. Petyuk, C. R. Scherzer, C. S. Hillaire-Clarke, B. A. Sieber, M. Sutherland, C. Tarn, A. West, D. Vaillancourt, J. Zhang, K. Gwinn, and PDBP Consortium. 2015. The NINDS Parkinson's disease biomarkers program. *Movement Disorders* 31:915-923.

Rzhetsky, A., D. Wajngurt, N. Park, and T. Zheng. 2007. Probing genetic overlap among complex human phenotypes. *Proceedings of the National Academy of Sciences of the United States of America* 104(28):11694-11699.

Sarpal, D. K., D. G. Robinson, T. Lencz, M. Argyelan, T. Ikuta, K. Karlsgodt, J. A. Gallego, J. M. Kane, P. R. Szeszko, and A. K. Malhotra. 2015. Antipsychotic treatment and functional connectivity of the striatum in first-episode schizophrenia. *Journal of the American Medical Association Psychiatry* 72(1):5-13.

Sarpal, D. K., M. Argyelan, D. G. Robinson, P. R. Szeszko, K. H. Karlsgodt, M. John, N. Weissman, J. A. Gallego, J. M. Kane, T. Lencz, and A. K. Malhotra. 2016. Baseline striatal functional connectivity as a predictor of response to antipsychotic drug treatment. *American Journal of Psychiatry* 173(1):69-77.

Shaw, L. M., H. Vanderstichele, M. Knapik-Czajka, C. M. Clark, P. S. Aisen, R. C. Petersen, K. Blennow, H. Soares, A. Simon, P. Lewczuk, R. Dean, E. Siemers, W. Potter, V. M. Lee, J. Q. Trojanowski,

and Alzheimer's Disease Neuroimaging Initiative. 2009. Cerebrospinal fluid biomarker signature in Alzheimer's Disease Neuroimaging Initiative subjects. *Annals of Neurology* 65(4):403-413.

Silberman, S. 2009. Placebos are getting more effective. Drugmakers are desperate to know why. *Wired* Magazine. http://archive.wired.com/medtech/drugs/magazine/17-09/ff_placebo_effect?currentPage=all (accessed July 27, 2009).

Slamon, D. J., G. M. Clark, S. G. Wong, W. J. Levin, A. Ullrich, and W. L. McGuire. 1987. Human breast cancer: Correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science* 235(4785):177-182.

Smith, I., M. Procter, R. D. Gelber, S. Guillaume, A. Feyereislova, M. Dowsett, A. Goldhirsch, M. Untch, G. Mariani, J. Baselga, M. Kaufmann, D. Cameron, R. Bell, J. Bergh, R. Coleman, A. Wardley, N. Harbeck, R. I. Lopez, P. Mallmann, K. Gelmon, N. Wilcken, E. Wist, P. Sanchez Rovira, M. J. Piccart-Gebhart, and Hera study team. 2007. 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: A randomised controlled trial. *Lancet* 369(9555):29-36.

Sperling, R. A., P. S. Aisen, L. A. Beckett, D. A. Bennett, S. Craft, A. M. Fagan, T. Iwatsubo, C. R. Jack, Jr., J. Kaye, T. J. Montine, D. C. Park, E. M. Reiman, C. C. Rowe, E. Siemers, Y. Stern, K. Yaffe, M. C. Carrillo, B. Thies, M. Morrison-Bogorad, M. V. Wagster, and C. H. Phelps. 2011. Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging–Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia* 7(3):280-292.

Strom, B. L., M. Buyse, J. Hughes, and B. M. Knoppers. 2014. Data sharing, year 1—access to data from industry-sponsored clinical trials. *New England Journal of Medicine* 371(22):2052-2054.

Swanson, C. R., Y. Berlyand, S. X. Xie, R. N. Alcalay, L. M. Chahine, and A. S. Chen-Plotkin. 2015. Plasma apolipoprotein A1 associates with age at onset and motor severity in early Parkinson's disease patients. *Movement Disorders* 30(12):1648-1656.

Taichman, D. B., J. Backus, C. Baethge, H. Bauchner, P. W. de Leeuw, J. M. Drazen, J. Fletcher, F. A. Frizelle, T. Groves, A. Haileamlak, A. James, C. Laine, L. Peiperl, A. Pinborg, P. Sahni, and S. Wu. 2016. Sharing clinical trial data--a proposal from the International Committee of Medical Journal Editors. *New England Journal of Medicine* 374(4):384-386.

TCSDD (Tufts Center for the Study of Drug Development). 2014. *Cost of developing a new drug.* http://csdd.tufts.edu/files/uploads/Tufts_CSDD_briefing_on_RD_cost_study_-_Nov_18,_2014..pdf (accessed June 3, 2016).

TCSDD. 2015. High turnover, protocol noncompliance plaque the global site landscape. *Tufts Center for the Study of Drug Development Impact Report* 17(1).

Tracy, H. 2015. CNS funds raised 2014. *NeuroPerspective* 230/231:4

Uher, R., K. E. Tansey, K. Malki, and R. H. Perlis. 2012. Biomarkers predicting treatment outcome in depression: What is clinically significant? *Pharmacogenomics* 13(2):233-240.

U.S. National Library of Medicine. 2008. *FAQ ClinicalTrials.gov—clinical trial phases.* https://www.nlm.nih.gov/services/ctphases.html (accessed June 6, 2016).

Van Snellenberg, J. X., I. J. Torres, and A. E. Thornton. 2006. Functional neuroimaging of working memory in schizophrenia: Task performance as a moderating variable. *Neuropsychology* 20(5):497-510.

Vitiello, B. 2015. Practical clinical trials in psychopharmacology: A systematic review. *Journal of Clinical Psychopharmacology* 35(2):178-183.

Volpi, S., S. G. Potkin, A. K. Malhotra, L. Licamele, and C. Lavedan. 2009. Applicability of a genetic signature for enhanced iloperidone efficacy in the treatment of schizophrenia. *Journal of Clinical Psychiatry* 70(6):801-809.

Vonnegut, K. 2013. *If this isn't nice, what is? Advice to the youn*g. New York: Seven Stories Press.

Wagle, N., C. Emery, M. F. Berger, M. J. Davis, A. Sawyer, P. Pochanard, S. M. Kehoe, C. M. Johannessen, L. E. Macconaill, W. C. Hahn, M. Meyerson, and L. A. Garraway. 2011. Dissecting therapeutic resistance to RAF inhibition in melanoma by tumor genomic profiling. *Journal of Clinical Oncology* 29(22):3085-3096.

Wallentin, L., R. C. Becker, A. Budaj, C. P. Cannon, H. Emanuelsson, C. Held, J. Horrow, S. Husted, S. James, H. Katus, K. W. Mahaffey, B. M. Scirica, A. Skene, P. G. Steg, R. F. Storey, R. A. Harrington, Plato Investigators, A. Freij, and M. Thorsen. 2009. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *New England Journal of Medicine* 361(11):1045-1057.

Wan, Z., Y. Vorobeychik, W. Xia, E. W. Clayton, M. Kantarcioglu, R. Ganta, R. Heatherly, and B. A. Malin. 2015. A game theoretic

framework for analyzing re-identification risk. *PLoS ONE* 10(3):e0120592.

Wang, S. J., H. M. Hung, and R. O'Neill. 2011. Adaptive design clinical trials and trial logistics models in CNS drug development. *European Neuropsychopharmacology* 21(2):159-166.

Wegener, G. and Rujescu, D., 2013. The current development of CNS drug research. *International Journal of Neuropsychopharmacology* 16(7):1687-1693.

Weiner, M. W., D. P. Veitch, P. S. Aisen, L. A. Beckett, N. J. Cairns, J. Cedarbaum, M. C. Donohue, R. C. Green, D. Harvey, C. R. Jack, Jr., W. Jagust, J. C. Morris, R. C. Petersen, A. J. Saykin, L. Shaw, P. M. Thompson, A. W. Toga, J. Q. Trojanowski, and Alzheimer's Disease Neuroimaging Initiative. 2015. Impact of the Alzheimer's Disease Neuroimaging Initiative, 2004 to 2014. *Alzheimer's & Dementia* 11(7):865-884.

Wicks, P., T. E. Vaughan, M. P. Massagli, and J. Heywood. 2011. Accelerated clinical discovery using self-reported patient data collected online and a patient-matching algorithm. *Nature Biotechnology* 29(5):411-414.

B

Workshop Agenda

NEUROSCIENCE TRIALS OF THE FUTURE: A WORKSHOP

March 3–4, 2016

Keck Center
500 Fifth Street, NW Room 100
Washington, DC 20001

Background: Although major strides have been made over the past two decades in basic neurosciences, the pace of translation into more effective treatments has eluded the field. Among the many factors contributing to this reality are the standard clinical trial methods that have barely changed, perhaps with the exception of increased use of electronic data acquisition and analysis.

Clinical trials in neuropsychiatric disorders continue to suffer from high failure rates even with biological targets that are well validated. Even in the hands of experienced investigators, the now commonplace problem of poor assay sensitivity, and attendant trial failure, have adversely affected pharmaceutical and device development. Signal detection in central nervous system trials is regularly beset by high placebo or non-specific response, intrasubject variability of endpoints, intersubject and intersite variability in multicenter trials, poor treatment adherence, and weak patient engagement and retention. The net effect of these challenges has been to simply increase the trial sample size in an attempt to control type II error. Yet, promising early clinical data often are not replicated in larger registration trials, and Phase III failure rates in

neuroscience randomized controlled trials remain among the highest in medicine. The apparent unsustainability of the current clinical development scenario has driven many large pharmaceutical companies entirely out of investment in neurosciences.

Quite apart from the business perspective, the fact that many early-stage clinical trials misleadingly provide a signal (a type I error) raises the question of whether volunteering for these trials is in the best interest of trial subjects, in particular, and for the patients with that particular disorder in general.

Better methods, from clinical study design through execution and evaluation, could help restore the integrity, feasibility, acceptability, efficiency, and economic viability of clinical neuropsychiatric development. However, in order to use innovative approaches to address these challenges, buy-in and acceptance from the regulatory community will be important. For example, adaptive trials could offer a more efficient means of addressing experimental questions involving multiple uncertainties, although they are often infrequently used. In addition, understanding the utility of wearable and patient monitoring devices (and the data generated) in neuroscience clinical trials is needed. Given the current challenges in neuroscience clinical trials, this public workshop will bring together key stakeholders to discuss opportunities to improve the integrity, efficiency, and validity of clinical trials for nervous system disorders (focusing specifically on Phase II and Phase III trials).

Meeting Objectives:

- Examine assay sensitivity challenges in clinical trials for nervous system disorders, including causes of type I error in early trials and poor signal detection and type II error in later stage trials.
- Explore opportunities to improve clinical trial methodology for nervous system disorders, including strategies for:
  - Guiding the selection of patient populations, such as using endophenotyping to increase the yield of responders and using genomics, proteomics, and imaging biomarkers to "stage" nervous system disorders.
  - Increasing patient engagement through all phases of the clinical trial (i.e., recruitment, screening, and posttrial) and improving adherence and retention.

- Using patient-centric technologies (e.g., wearables) and integrating such real-world, real-time data with traditional clinical data.
- Improving monitoring during clinical trials.
- Leveraging recent advances in diagnostics, biomarkers, and endpoints to develop more efficient clinical trials.
- Using novel trial designs (e.g., adaptive, enrichment, and platform design studies) for nervous system disorders, including associated regulatory challenges and opportunities.

March 3, 2016

8:30 a.m. Opening Remarks

ATUL PANDE, *workshop co-chair*
Chief Medical Officer and Executive Vice President
Tal Medical

RICHARD KEEFE, *workshop co-chair*
Professor of Psychiatry and Behavioral Sciences
Duke University School of Medicine

Neuroscience Clinical Trials: Challenges and Opportunities

8:45 a.m. STEVEN ROMANO
Senior Vice President and Chief Science Officer
Mallinckrodt Pharmaceuticals

9:05 a.m. SHITIJ KAPUR
Executive Dean and Head of School
Institute of Psychiatry, Psychology & Neuroscience
King's College London

9:30 a.m. Discussion Among Speakers and Workshop Participants

9:45 a.m. BREAK

SESSION I: CLINICAL TRIAL DESIGN

Session Objectives: Discuss current challenges to clinical trial design for nervous system disorders. Explore elements of clinical trial protocols that might be improved and lead to more efficient trials. Discuss how novel trial designs (e.g., adaptive, enrichment, and platform design studies) might be used for nervous system disorders.

10:00 a.m. Session Overview and Objectives

STEPHEN BRANNAN, *session moderator*
Vice President of Clinical Research and Medical Affairs
Forum Pharmaceuticals

Biomarkers

10:10 a.m. ANIL MALHOTRA
Director, Psychiatry Research, Zucker Hillside Hospital
Professor, Molecular Medicine and Psychiatry
Hofstra North Shore–Long Island Jewish School of Medicine

10:25 a.m. ALICE CHEN-PLOTKIN
Assistant Professor of Neurology
Perelman School of Medicine, University of Pennsylvania

Diagnosis and Patient Identification

- Discuss alternatives to the *Diagnostic and Statistical Manual of Psychiatric Disorders* (DSM).

10:40 a.m. SARAH MORRIS
Acting Head, NIMH RDoC Unit
Program Officer, Schizophrenia Spectrum Disorders Research Program
National Institute of Mental Health

10:55 a.m. ROBERT BILDER
Professor-in-Residence, Department of Psychiatry and Biobehavioral Sciences,
University of California, Los Angeles
Editor-in-Chief, *Diagnostics in Neuropsychiatry*

11:10 a.m. **Statistical Approaches and Considerations**

MICHAEL PENCINA
Director of Biostatistics, Duke Clinical Research Institute
Professor of Biostatistics and Bioinformatics
Duke University

Novel Clinical Trial Designs

11:25 a.m. ERIK SNOWBERG
Professor of Economics and Political Science
California Institute of Technology

SYLVAIN CHASSANG
Professor of Economics and Public Affairs
Princeton University

11:45 a.m. JAIDEEP KAPUR
Study Chair, Established Status Epilepticus Treatment Trial (ESETT)
Eugene Meyer III Professor of Neuroscience, Neurology
University of Virginia School of Medicine

12:00 p.m. Panel Remarks

Additional Panelists:

TIFFANY FARCHIONE
Deputy Director, Division of Psychiatry Products
Center for Drug Evaluation and Research

Food and Drug Administration
CARLOS PEÑA

Director, Division of Neurological and Physical Medicine Devices
Office of Device Evaluation
Center for Devices and Radiological Health
Food and Drug Administration

12:30 p.m. Discussion Among Speakers and Workshop Participants

1:00 p.m. LUNCH

SESSION II: CLINICAL TRIAL METHODOLOGY

Session Objectives: Explore opportunities to improve clinical trial methodology for nervous system disorders, including strategies for patient selection, engagement, and retention. Examine the extent to which current diagnostic methods contribute to the inherent variability in study populations. Discuss the utility of patient-centric technologies (e.g., wearables) and how such real-world, real-time data might be integrated with traditional clinical data to improve the integrity and efficiency of trials. Consider lessons learned and best practices from other therapeutic areas that might be applied to neuroscience clinical trials.

1:45 p.m. Session Overview and Objectives

AMIR KALALI, *session moderator*
Head, Neuroscience Center of Excellence
Quintiles

2:00 p.m. **Transforming Clinical Trials with Technology (guided panel discussion)**

- Discuss opportunities to improve patient engagement and retention.
- Discuss how to improve patient adherence to assigned treatment.

- Discuss opportunities to improve patient assessments.
- Consider the potential applications of emerging technologies (e.g., wearables) for clinical trials.
  - What are common clinical applications of these technologies?
  - What are the known benefits and risks associated with use? What are the scientific controversies behind this evidence?

CARLOS RODARTE
Chief Executive Officer
Health Rhythms

JOHN REITES
Head, Digital Health Acceleration
Qunitiles

DREW SCHILLER
Chief Technology Officer and Co-Founder
Validic

GLEN DE VRIES
President and Co-Founder
Medidata Solutions, Inc.

KARL KIEBURTZ
Robert J. Joynt Professor in Neurology
Senior Associate Dean for Clinical Research
Director of the Clinical & Translational Science Institute
University of Rochester Medical Center

3:15 p.m. BREAK

Lessons Learned from Other Therapeutic Areas

3:30 p.m. *Oncology*

PERRY NISEN
Chief Executive Officer
Sanford Burnham Prebys Medical Discovery Institute

3:45 p.m. *Cardiology*

ADRIAN FELIPE HERNANDEZ
Professor of Medicine
Duke Clinical Research Institute
Duke University School of Medicine

4:00 p.m. Discussion Among Speakers and Workshop Participants

4:45 p.m. Day One Wrap-Up

Workshop Co-Chairs

5:00 p.m. ADJOURN DAY ONE

March 4, 2016

8:30 a.m. Day Two Opening

ATUL PANDE, *workshop co-chair*
Chief Medical Officer
Tal Medical

RICHARD KEEFE, *workshop co-chair*
Professor of Psychiatry and Behavioral Sciences
Duke University School of Medicine

KEYNOTE SESSION III: INTERNATIONAL REGULATORY LANDSCAPE

Session Objectives: Consider the regulatory landscape for neuroscience clinical trials. Explore differences in regulatory pathways among countries and consider the impact.

8:50 a.m. Session Overview and Objectives

THOMAS LAUGHREN, *session moderator*
Director
Laughren Psychopharm Consulting, LLC

Key Regulatory Opportunities for Neuroscience Clinical Trials

9:00 a.m. Regulatory Opportunities and Challenges in the United States

ROBERT CALIFF
Commissioner of Food and Drugs
Food and Drug Administration

9:20 a.m. Regulatory Opportunities and Challenges in Europe

LUCA PANI
Director General
Italian Medicines Agency (AIFA)

9:40 a.m. Discussion Among Speakers and Workshop Participants

10:45 a.m. BREAK

SESSION IV: ETHICAL CONSIDERATIONS

Session Objectives: Examine ethical, legal, and social questions about neuroscience clinical trials. Consider potential data protection and human subjects' issues that might arise as clinical trials continue to transform.

11:00 a.m. Session Overview and Objectives

PETRA KAUFMANN
Director, Office of Rare Diseases Research and Division of Clinical Innovation
National Center for Advancing Translational Sciences

11:10 a.m. **Data Protection**

FRANK ROCKHOLD
Senior Vice President, Global Clinical Safety and Pharmacovigilance
GlaxoSmithKline
Professor of Biostatistics and Bioinformatics (*starting March 2016*)
Duke University School of Medicine

Human Subjects Protection

11:25 a.m. GREG KOSKI
President and Co-Founder
Alliance for Clinical Research Excellence and Safety (ACRES)

11:40 a.m. EMIL CHIAUZZI
Research Director
PatientsLikeMe

12:00 p.m. Discussion Among Speakers and Workshop Participants

12:30 p.m. LUNCH

SESSION V: REIMBURSEMENT

Session Objectives: Consider how data collected by payers are used to inform reimbursement decisions and influence the long-term translation of products in the marketplace. Consider economic outcome measures used to determine payer practices. How will and should these measures be worked into future clinical trials?

1:15 p.m. Session Overview and Objectives

DANIEL BURCH, *session co-moderator*
Vice President and Global Therapeutic Area Head for Neuroscience
Pharmaceutical Product Development (PPD)

MICHAEL POLLOCK, *session co-moderator*
Vice President, Real World Outcomes
Pharmaceutical Product Development (PPD)

1:25 p.m. **Improving the Evidence Base for Reimbursement**
What evidence is needed from research to align with insurance policies and evidence criteria?

RHONDA ROBINSON BEALE *via teleconference*
Senior Vice President and Medical Officer
Blue Cross of Idaho

1:40 p.m. **Challenges of Generating the Required Evidence: An Industry Perspective**

PAUL STANG
Vice President, Global R&D Epidemiology
Janssen Research and Development

1:55 p.m. **Pragmatic Trials: Challenges and Opportunities for Neuroscience Trials**

MARK CZIRAKY
Co-Founder and Vice President of Research
HealthCore, Inc.

2:10 p.m. Discussion Among Speakers and Workshop Participants

2:45 p.m. BREAK

SESSION VI: MOVING FORWARD

Session Objectives: A panel will synthesize and discuss key highlights from the workshop presentations and discussions, including identifying next steps and promising areas for future action and research.

3:00 p.m. Panel Discussion: Session Moderators

ATUL PANDE, *workshop co-chair*
RICHARD KEEFE, *workshop co-chair*
STEPHEN BRANNAN, *session I moderator*
AMIR KALALI, *session II moderator*
THOMAS LAUGHREN, *session III moderator*
PETRA KAUFMANN, *session IV moderator*
DANIEL BURCH AND MICHAEL POLLOCK, *session V moderators*

3:45 p.m. Discussion Among Session Moderators and Workshop Participants

4:15 p.m. Closing Remarks from the Workshop Co-Chairs

4:30 p.m. ADJOURN WORKSHOP

C

Registered Attendees

Kathleen Anderson
National Institute of Mental Health

Alexandra Atkins
NeuroCog Trials

Erika Augustine
University of Rochester Medical Center

Shelli Avenevoli
National Institute of Mental Health

Farah Bader
National Institutes of Health

Joana Balardin
Albert Einstein Hospital

Bruce Baron
Sanofi

Steven Becker
National Eye Institute

Martin Bednar
Pfizer Inc.

Dawn Beraud
National Institute on Aging

Sangeeta Bhargava
National Eye Institute

Brendon Binneman
Pfizer Inc.

Carlos Blanco
National Institute on Drug Abuse

Susan Borja
National Institute of Mental Health

Lizbet Boroughs
Association of American Universities

Linda Brady
National Institute of Mental Health

Stephen Brannan
FORUM Pharmaceuticals, Inc.

Zachary Brennan
Regulatory Affairs Professionals Society

Timothy Brindle
Department of Veterans Affairs

Kristin Bullok
Eli Lilly and Company

James Burke
National Academy of Medicine

Gregory Busse
Takeda Pharmaceuticals

Rosa Canet-Aviles
Foundation for the National Institutes of Health

Charlie (Gouliang) Cao
Takeda Pharmaceuticals

Monique Carter
Pfizer Inc.

Shailesh Chavan
Biotest Pharmaceuticals

Cássia Coelhoso
Hospital Israelita Albert Einstein

Robert Conley
Eli Lilly and Company

Albert Covelli
Medidata Solutions, Inc.

Michelle Crouthamel
GlaxoSmithKline

Cyrus Davani
National Institute of Mental Health

Kimberly del Carmen
U.S. Army Medical Materiel Development Activity

Nicholas DeMartinis
Pfizer Inc.

Robert DiCicco
GlaxoSmithKline

Ellen Donnelly
Pfizer Inc.

Kristin D'Onofrio
Takeda Pharmaceuticals

Ray Dorsey
University of Rochester

Rebecca Evans
Parexel

Scott Fogerty
Thermo Fisher Scientific

Lisa Ford
Janssen Research & Development, LLC

Terence Fullerton
Pfizer Inc.

Marjorie Garvey
National Institute of Mental Health

Alex Gilbert
Assurex Health

Sharon Gilbert
U.S. Army Medical Materiel Development Activity

Lisa Gilotty
National Institute of Mental Health

Margaret Grabb
National Institutes of Health

Marlene Guzman
National Institute of Mental Health

Shwe Gyaw
National Institute on Drug Abuse

Magali Haas
Cohen Veterans Bioscience

Adam Haim
National Institute of Mental Health

Jennifer Hart
Duke Clinical Research Institute

Mi Hillefors
National Institute of Mental Health

Debbie Indyk
Icahn School of Medicine at Mount Sinai

Frances Jensen
University of Pennsylvania Perelman School of Medicine

Liliana Jorge
Albert Einstein Hospital

Petra Kaufmann
National Center of Advancing Translational Sciences

David Keller
Pfizer Inc.

Noam Keren
The National Academies of Sciences, Engineering, and Medicine

Walter Koroshetz
National Institute of Neurological Disorders and Stroke

Elena Koustova
National Institute on Drug Abuse

Vasudha Kowtha
University of Maryland

Victor Krauthamer
Food and Drug Administration

James Kupiec
Pfizer Inc.

Audrey Kusiak
Department of Veterans Affairs

Story Landis
National Institute of Neurological Disorders and Stroke (Director Emeritus)

Patroski Lawson
Lundbeck, LLC

Mark Lee
Genentech

Judith Lelchook
Paving the Way Multi Service Institute

Alyson Levitz-Jones
Medidata Solutions

Honglan Li
Janssen Research & Development, LLC

Jim Li
Assurex Health

Sarah Lisanby
National Institute of Mental Health

Eva Loth
King's College London

Jennifer Madsen
Arnold & Porter, LLP

Kathryn Martin
The National Academies of Sciences, Engineering, and Medicine

Anna Mazzucco
National Eye Institute

Cathy McDermott
U.S. Army Medical Materiel Development Activity

Lauren McLaughlin
The Michael J. Fox Foundation for Parkinson's Research

Emilio Merlo Pich
Takeda Pharmaceuticals

Karen Mowrer
National Institute of Mental Health

Claudia Moy
National Institute of Neurological Disorders and Stroke

Declan Murphy
King's College London

Gretchen Murphy
Medidata Solutions

Venkatesha Murthy
Takeda Pharmaceuticals

Barbara Myklebust
Food and Drug Administration

George Niederehe
National Institute of Mental Health

Jean Noronha
National Institute of Mental Health

Peter Ogbuoji
Federal Ministry of Labour and Employment

Mark Opler
ProPhase

Anna Ordonez
National Institutes of Health

Alexandre Paim Diaz
Columbia University

Joselisa Paiva
Hospital Israelita Albert Einstein

Nicole Pariser
Medidata Solutions

Michele Pearson
National Institute of Mental Health

William Potter
National Institute of Mental Health

Tanya Ramey
National Institute on Drug Abuse

Khara Ramos
National Institute of Neurological Disorders and Stroke

Diane Robertson
Peterson Wilmarth and Robertson, LLP

Erica Rosemond
National Center for Advancing Translational Sciences

Jonathan Rubin
Alcobra

Judith Rumsey
National Institute of Mental Health

Erik Runko
National Science Foundation

Andrea Samdahl
Medidata Solutions

Liana Sanches
Albert Einstein Hospital

Brian Saxby
NeuroCog Trials

Rachel Scheinert
National Institute of Mental Health

Pamela Shell
National Institute of Mental Health

Ira Shoulson
Georgetown University

David Shurtleff
National Center for Complementary and Integrative Health

Phil Skolnick
National Institute on Drug Abuse

Richard Smith
National Alliance on Mental Illness

Joshua Spiegel
NeuroCog Trials

Ioan Stroescu
NeuroCog Trials

Mary Tobin
Alliance for Clinical Research Excellence and Safety

Gary Tong
Lundbeck, LLC

Farris Tuma
National Institute of Mental Health

Nicole Turner
Pharmaceutical Product Development, Inc.

Maria Uria-Nickelsen
Pfizer Inc.

Abhi Vase
Minnetronix

Srikanth Vasudevan
Food and Drug Administration

Ann Wagner
National Institute of Mental Health

Amanda Wagner Gee
The National Academies of Sciences, Engineering, and Medicine

Tracy Waldeck
National Institute of Mental Health

Jennifer Watson
National Institute on Aging

Jill Wechsler
Applied Clinical Trials Magazine

Cole Werble
Prevision Policy

Matthew Whalen
Alliance for Clinical Research Excellence and Safety

Paul Wilburn
Department of Justice (Retired)

Kenneth Wilmarth
Peterson Wilmarth and Robertson, LLP

Ling Wong
National Institute of Neurological Disorders and Stroke

Winifred Wu
Strategic Regulatory Partners, LLC

Jerry Yang
Uniformed Services University of the Health Sciences

Meijun Ye
Food and Drug Administration

Sally Young
Lundbeck, LLC

Steven Zalcman
National Institute of Mental Health

Silvia Zaragoza
CogState and Psyncro

Danna Zimmer
University of Maryland School of Medicine