FDA U.S. FOOD & DRUG ADMINISTRATION

Improving clinical evidence generation with Real World Evidence

Sean Khozin, MD, MPH

Associate Director (Acting): *Oncology Center of Excellence*

Founding Director: *Information Exchange and Data Transformation (INFORMED)*

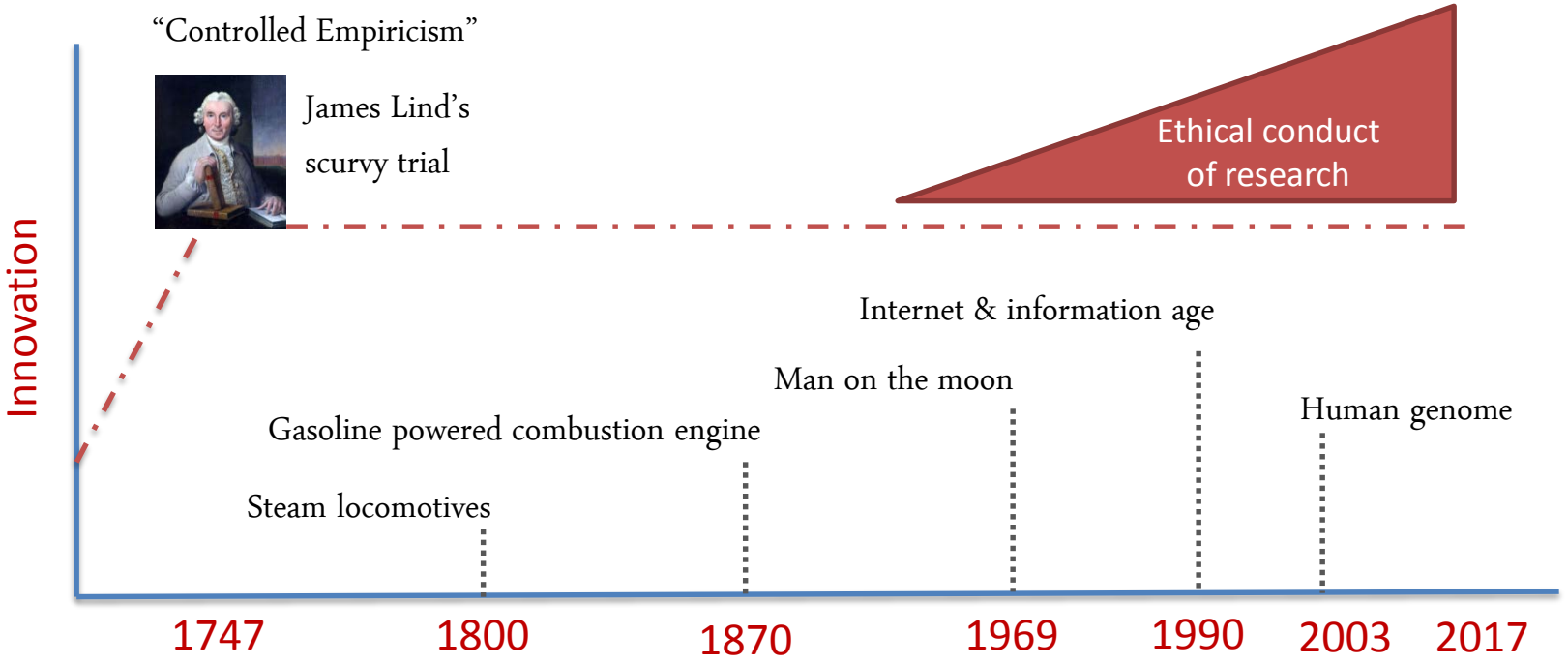
Food and Drug Administration

The views in this presentation do not necessarily represent the policies of FDA

Disclosures: None

A brief history of controlled clinical trials

1747 to 2017



Internal validity

Well-established methods to reduce bias and alternative explanations for treatment effect

Internal validity

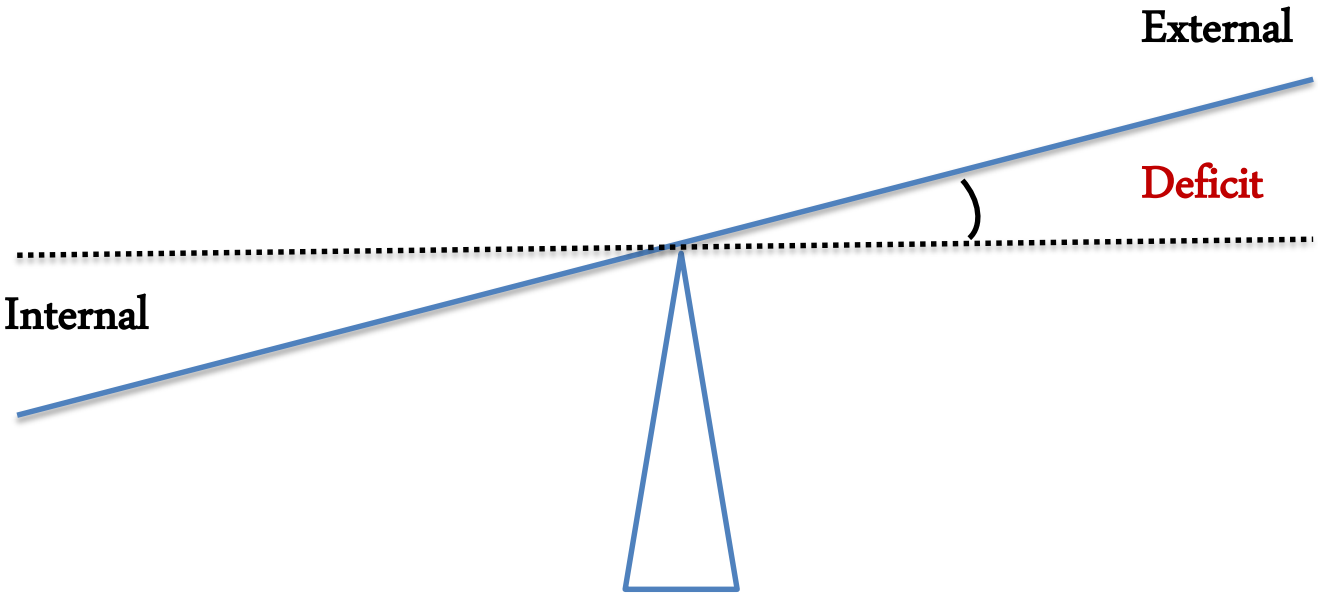
Well-established methods to reduce bias and alternative explanation of treatment effect

Procedural (vs statistical)

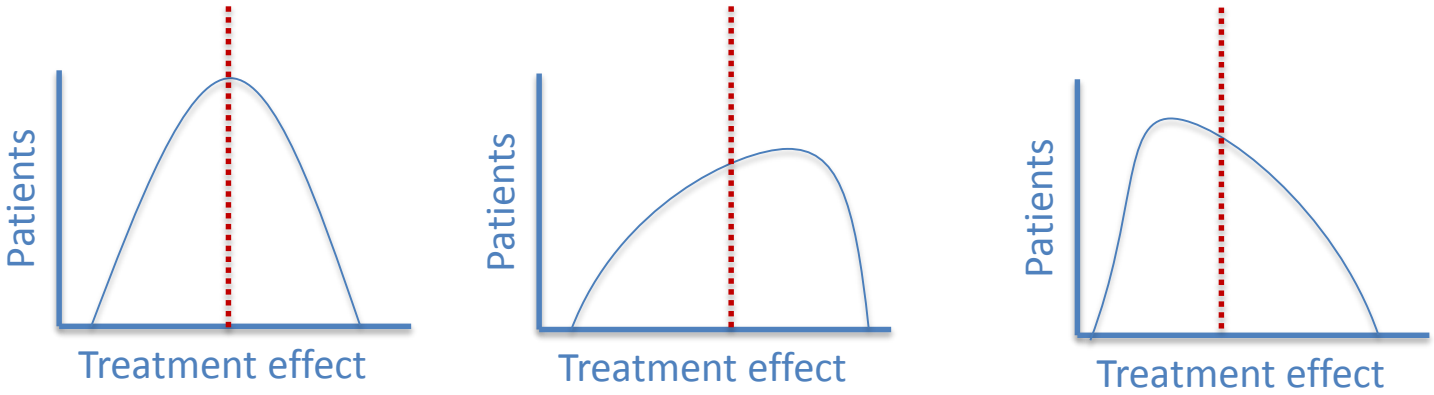
- Randomization
- Good clinical practice
- Strict eligibly criteria
- Audit trails

Validity imbalance

"Over-Controlled Empiricism"



Results of all clinical trials on one page



..... Median ("average") patient is a statistical concept

Can translate poorly to making individualized treatment decisions at the point of care

What is real world data?

Intended use of data at the time of collection

Data collected @  *+ research = clinical trial data*

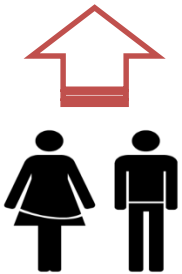
Data collected @  *- research = real world data*

What is real world data?

Intended use of data at the time of collection

Data collected @  *+ research = clinical trial data*

Data collected @  *- research = real world data*



What is real world data?

Data collected @  *- research = real world data*

What is real world data?

Retrospective

Data collected @  *- research = real world data*

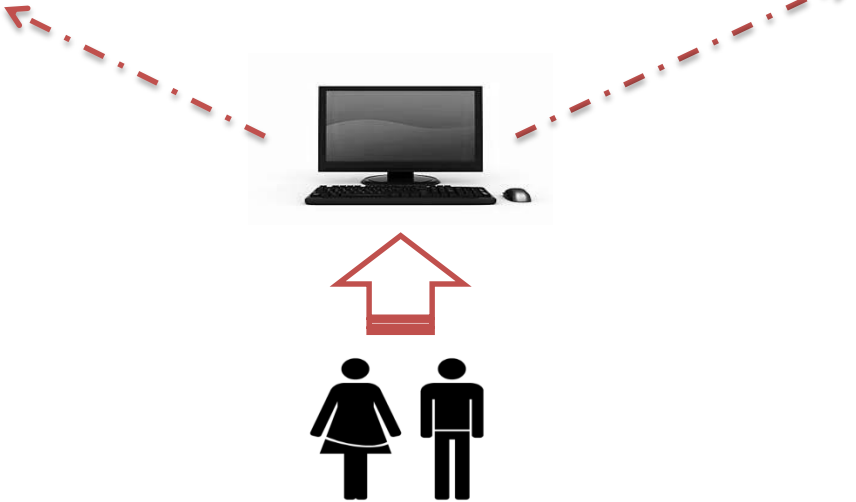
What is real world data?

Structured

- *Billing codes*
- *Laboratory*
- *Patient history*
- *Demographics*

Unstructured

- *Physician notes*
- *Diagnostic reports*



False dichotomy

Data collected @  ***+ research = clinical trial data***

Data collected @  ***- research = real world data***

False dichotomy

Data collected @  ***+ research = clinical trial data***

Data collected @  ***+ research = real world data***

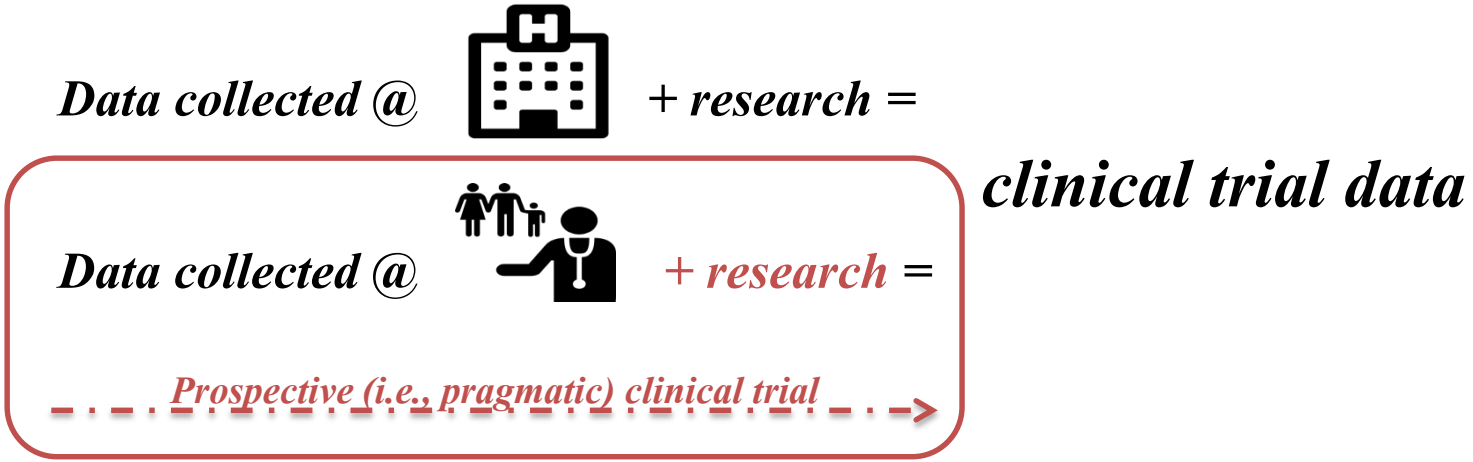
False dichotomy

Data collected @  ***+ research =***

clinical trial data

Data collected @  ***+ research =***

False dichotomy

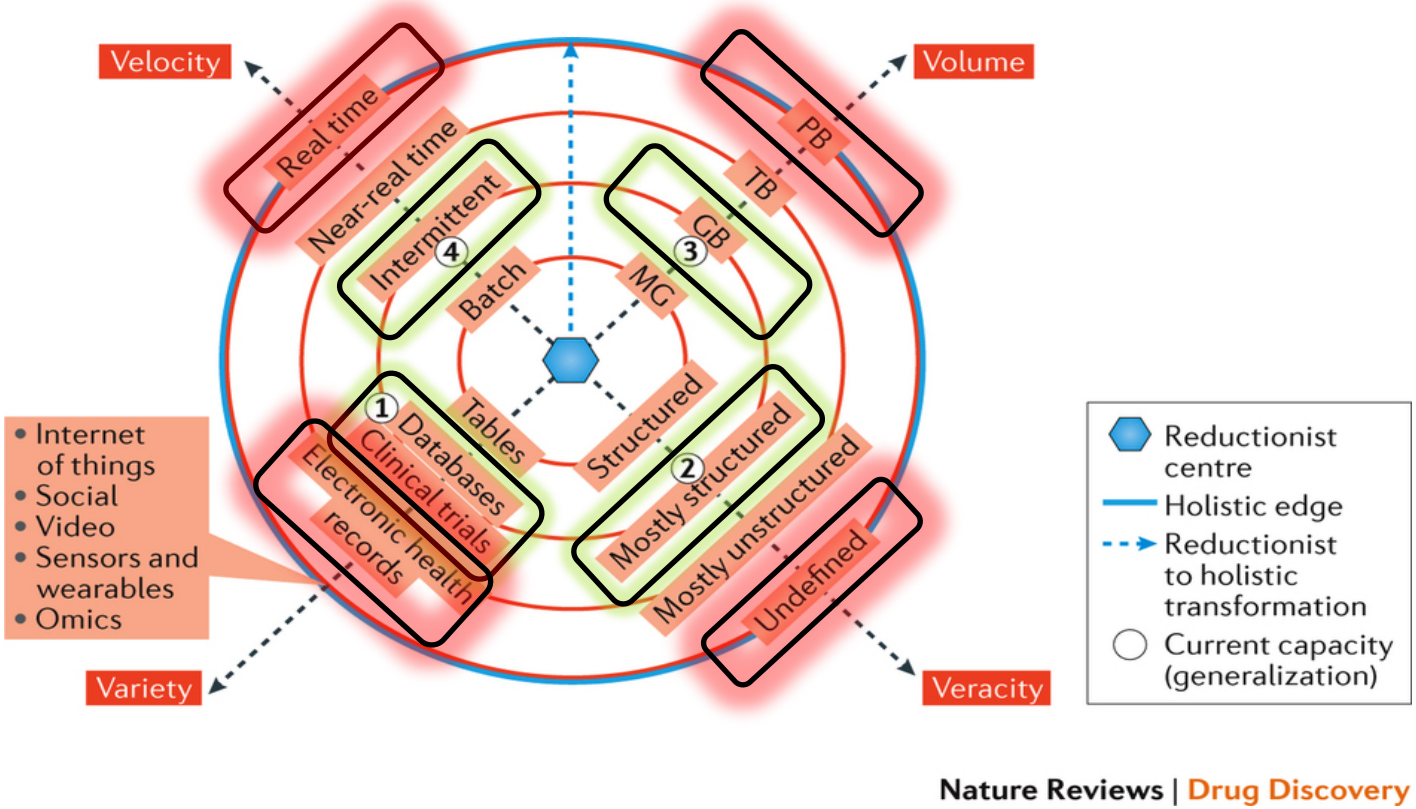


False dichotomy

+ research =

Prospective (i.e., pragmatic) clinical trial

Real world evidence key component in the expanding universe of big data



Khozin S, et al. Nat Rev Drug Discov. 2017.

Existing framework

- *Indication*
- *Study design*
- *Endpoints*

Review division

- *Data quality and integrity*
- *Source verification*

Office of Scientific Investigations

The intended use of point of care data at the time of collection is the primary feature informing potential use cases of real-world data for clinical evidence generation

Intended use of data at the time of collection	Primary sources of data	Potential use cases	Challenges
Delivery of routine health care services	EHRs and PHRs Insurance claims Patient registries Digital health solutions	Development of external control Studying the natural history of disease Postmarket pharmacovigilance Hypothesis generation to support design of prospective clinical trials	Can primarily support retrospective analyses Limited availability of clinically relevant structured data elements in EHRs Extraction of data from unstructured content (eg, physician notes and diagnostic reports) is resource intensive Requires special procedures for assurance of data quality
Research	EHRs and PHRs Digital health solutions	All of the above plus: Prospective pragmatic clinical trials that support randomization and other experimental design principles employed in conventional clinical trials	Creation of new incentives for capturing clinically relevant structured data elements at the point of care Providing appropriate training for community oncologists to ensure adherence to ethical, regulatory, and legal standards in conducting clinical research

*EHR = electronic health record; PHR = patient health record.

Khozin S, et al. JNCI. Vol. 109, No. 1

Potential sources of bias in real-world studies threatening internal validity

Sources of bias	Individual	Technology	System
Arising from	Patient-provider dynamics and patient characteristics	EHRs	Trends and influences on the health care system
Primary type(s)	Information bias* influencing accuracy of data collection (recall, observer/ interviewer, and reporting bias)	Information bias* due to variations in EHR interfaces, data entry procedures, or data retrieval methods leading to compromising data quality	Selection bias due to variation in access to care affecting sampling frame
	Confounding bias† due to patient characteristics and comorbidities	Selection bias§ arising from selection of patients using EHR diagnostic and therapeutic codes	Confounding bias† due to regional variations in standards of care or available therapies due to third-party formularies
	Compliance bias‡ due to patient nonadherence to treatment		

*Information bias: erroneous or inaccurate capture of patient variables. EHR = electronic health record.
†Confounding bias: association between treatment and outcome being influenced by the presence of extraneous variables.
‡Compliance bias: variations in patient adherence to planned treatment affecting study outcomes.
§Selection bias: study population not representative of the true distributions in the overall population.

Khozin S, et al. JNCI. Vol. 109, No. 1

Overcoming bias and threats to internal validity

Randomization

Prospective (pragmatic) real world clinical trials

- Designed to produce results that uniquely support point of care clinical decisions
- EHRs as primary vehicles for prospective clinical research at the ***point of routine care***
- Can support randomization
- Patient-centered
- Provides access to experimental therapies
- May help bend the cost curve

Clinical Drug Trials May Be Coming to Your Doctor's Office

By Amy Abernethy
And Sean Khozin

Roger Pickar was diagnosed with a rare cancer in December 2014. A chef, comedian, husband, father and champion of the local arts community, he was successfully treated for more than a year with standard therapies. When the cancer eventually returned, his oncologist prescribed an "off label" drug—one the Food and Drug Administration had approved for other types of cancer, but not the one that afflicted Roger. That meant it wouldn't necessarily be covered by insurance.

The physician mentioned another possibility: Roger could apply to be considered for experimental treatment as part of a special program or a clinical trial at a medical center thousands of miles away. Roger decided to stay close to family and in the care of his own oncologist.

Like countless other cancer patients, he faced difficult choices. He died at 73, two years after his diagnosis.

Roger's story illustrates the challenges facing patients, their oncologists and the cancer researchers who aim to match experimental treatments to the patients best suited for them. Typically, drug development is a multiyear process that begins with a series of laboratory studies and culminates with human testing in controlled clinical trials. There is strong demand for access to experimental therapies in clinical trials, but only an estimated 3% to 5% of adult cancer patients in the U.S. end up participating.

Traditionally, the safety and effectiveness of new cancer therapies is demonstrated through randomized clinical trials—studies in which patients are randomly assigned to receive either an experimental new treatment or a comparator therapy. Despite the potential for direct health benefits, patients with cancer—especially sicker patients, those in rural areas, minorities and the elderly—enroll at lower rates than those with other diseases.

That's often because of strict eligibility requirements, combined with logistical challenges. Conventional clinical trials are usually conducted at large medical centers, far from where most cancer patients live and get treatment. The trials can also be difficult to find, require time away from work and family, and present complicated insurance challenges.

The good news is that technology innovations are moving us toward modern clinical trial designs. Electronic health records, now common in U.S. medical practices, allow physicians to collect timely and detailed data that could be used for exploring ways of bringing clinical research directly to patients. Those records are becoming the technological building blocks of a new research model based on real-world evidence, which aims to provide insights regarding the usage and potential benefits or risks of a drug by analyzing patient data collected as part of routine delivery of care.

Real-world evidence captures the experience of real-world patients, who are generally more diverse than the selective cohorts enrolled in clinical trials. Additionally, real-world data from electronic health records may be used after a drug's approval to answer important questions about its use. Researchers can, for example, search through anonymized data from patients taking a specific cancer drug to see whether those with a certain tumor mutation respond better or worse than other patients. Such information could help doctors personalize therapies based on the patient's genomic makeup.

> Electronic medical records make possible a new research model based on real-world evidence.

Moving clinical research to a doctor's office, the point of routine care, may also address the difficulties patients and doctors face with off-label drugs. If local physicians can participate in conducting real-world randomized clinical trials in their own practices, new uses of approved drugs could be carefully studied, potentially generating evidence supporting approval of a new use. Real-world clinical trials could also limit disruptions to patients' lives by reducing the need for long-distance travel.

The promise of real-world evidence obtained at the point of routine care comes with a responsibility to ensure data quality, privacy and safety, while maintaining ethical standards and compliance with good clinical-practice guidelines. There are reasons why real-world trials are not yet the norm: lack of organizational and technical infrastructure at the point of care makes it difficult to meet the rigorous standards conventional clinical trials are required to meet. Addressing these and other challenges will take a thoughtful, well-coordinated approach involving all stakeholders.

As for Roger Pickar, evidence specific to treatments for his disease could have informed more-individualized treatment decisions—and his experience, gathered as real-world data, could have contributed to our collective knowledge about his disease. He was the father of Amy Abernethy, one of the authors of this article, and he would have wanted others to learn from his experience to help patients like him in the future.

Dr. Abernethy is chief medical officer and chief scientific officer at Flatiron Health. Dr. Khozin is an acting associate director in the U.S. Food & Drug Administration's Oncology Center of Excellence and founding director of the agency's Information Exchange and Data Transformation

THE WALL STREET JOURNAL.
PUBLISHED SINCE 1889 BY DOW JONES & COMPANY

Rupert Murdoch, *Executive Chairman, News Corp*
Robert Thomson, *Chief Executive Officer, News Corp*
Gerard Baker, *Editor in Chief*
William Lewis, *Chief Executive Officer and Publisher*

Matthew J. Murray, *Deputy Editor in Chief*

DEPUTY MANAGING EDITORS:
Michael W. Miller, *Senior Deputy;* Thorold Barker, *Europe;* Paul Beckett, *Washington;* Andrew Dowell, *Asia;* Christine Glancey, *Operations;* Jennifer J. Hicks, *Digital;* Neal Lipschutz, *Standards;* Alex Martin, *News;* Shazna Nessa, *Visuals;* Ann Podd, *Initiatives;* Matthew Rose, *Enterprise;* Stephen Wisnefski, *Professional News*

Paul A. Gigot, *Editor of the Editorial Page;* Daniel Henninger, *Deputy Editor, Editorial Page*

WALL STREET JOURNAL MANAGEMENT:
Suzi Watford, *Marketing and Circulation;* Joseph B. Vincent, *Operations;* Larry L. Hoffman, *Production*

DOW JONES MANAGEMENT:
Mark Musgrave, *Chief People Officer;* Edward Roussel, *Innovation & Communications;* Anna Sedgley, *Chief Operating Officer & CFO;* Katie Vanneck-Smith, *President*

OPERATING EXECUTIVES:
Ramin Beheshti, *Product & Technology;* Jason P. Conti, *General Counsel;* Frank Filippo, *Print Products & Services;* Steve Grycuk, *Customer Service;* Kristin Heitmann, *Transformation;* Nancy McNeill, *Advertising & Corporate Sales;* Jonathan Wright, *International*
DJ Media Group:
Almar Latour, *Publisher;* Kenneth Breen, *Commercial*
Professional Information Business:
Christopher Lloyd, *Head;* Ingrid Verschuren, *Deputy Head*

EDITORIAL AND CORPORATE HEADQUARTERS:
1211 Avenue of the Americas, New York, N.Y., 10036

DOW JONES

Notable & Quotable: Energy

Mark Mills writing in the Spring issue of the New Atlantis:

While a barrel's worth of oil weighs just over 300 pounds and can be stored in a $40 tank, to store the equivalen[t] the kind of b[attery] Tesla car com[pany] tons of batte[ries] more than se[ven] sand dollars. Even if engineers were able to double or quadruple battery efficacy, that still would not come between energy from wind and energy from liquid hydrocarbons for transportation.

These stark facts often elicit the response that the alternative technologies will get better with time [than] they will. But [a] significant scale bene[fit] [in] the underlying ma[terials] steel, fiberglass, [etc.]) are already in mass production. Nor are there big gains possible in the underlying technologies given the physics we

Electronic medical records make possible a new research model based on real-world evidence.

FDA's demonstration projects

Real World Evidence Benefits, Limits Explored In US FDA Demonstrations

29 Oct 2017 | **ANALYSIS**

by Cathy Kelly

Catherine.Kelly@informa.com

Executive Summary

FDA's Jacqueline Corrigan-Curay lists three demonstrations now underway that are aimed at looking at different aspects of generating real world evidence and may inform the agency's evaluation of the data and methods.

- FDA Oncology Center for Excellence, Information Exchange and Data Transformation Initiative
  - Flatiron Health
  - CancerLinQ
- Cross-network directory service using Sentinel and the Patient-Centered Outcomes Research Institute's (PCORI's) National Patient-Centered Clinical Research Network to address barriers in working across networks
  - Intended to create an open source interoperable service that allows data partners to participate in multiple data research networks, query across networks, and share analytic capabilities and knowledge

Challenges

Data quality

&

Incentives


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Pharmacovigilance

- Traditionally passive
  - Voluntarily reports of adverse events
  - FDA Adverse Event Reporting System (FAERS)
- Real world data can power an active pharmacovigilance system
  - Sentinel (indirect)
  - Direct EHR abstraction

External control arms

- To inform clinical trial design
- When early clinical evidence in a single arm trial suggests significant clinically activity
- Can potentially provide a reliable assessment of the safety and effectiveness of available therapies
- Breakthrough therapy designated products especially appropriate candidates
  - Allow alternative trial designs such as real world-derived historical control data to support regulatory decisions