Improving clinical evidence generation with

Real World Evidence

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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

- 1747: James Lind’s scurvy trial
- 1800: Steam locomotives
- 1870: Gasoline powered combustion engine
- 1969: Man on the moon
- 1990: Internet & information age
- 1990: Human genome

“Controlled Empiricism”

Ethical conduct of research
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?

Data collected @ + research = clinical trial data

Data collected @ - research = real world data

Intended use of data at the time of collection
What is real world data?

Data collected @ - research = real world data
What is real world data?

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

Data collected @ + research = clinical trial data

Data collected @ + research = Prospective (i.e., pragmatic) clinical trial
False dichotomy

Data collected @ + research =

Prospective (i.e., pragmatic) clinical trial
Real world evidence key component in the expanding universe of big data

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.

<table>
<thead>
<tr>
<th>Intended use of data at the time of collection</th>
<th>Primary sources of data</th>
<th>Potential use cases</th>
<th>Challenges</th>
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</thead>
<tbody>
<tr>
<td>Delivery of routine health care services</td>
<td>EHRs and PHRs</td>
<td>Development of external control</td>
<td>Can primarily support retrospective analyses</td>
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<td></td>
<td>Insurance claims</td>
<td>Studying the natural history of disease</td>
<td>Limited availability of clinically relevant structured data elements in EHRs</td>
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<td>Patient registries</td>
<td>Postmarket pharmacovigilance</td>
<td>Extraction of data from unstructured content is resource intensive</td>
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<td></td>
<td>Digital health solutions</td>
<td>Hypothesis generation to support design of prospective clinical trials</td>
<td>Requires special procedures for assurance of data quality</td>
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<tr>
<td>Research</td>
<td>EHRs and PHRs</td>
<td>All of the above plus: Prospective pragmatic clinical trials that support randomization and other experimental design principles employed in conventional clinical trials</td>
<td>Creation of new incentives for capturing clinically relevant structured data elements at the point of care</td>
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<td>Digital health solutions</td>
<td></td>
<td>Providing appropriate training for community oncologists to ensure adherence to ethical, regulatory, and legal standards in conducting clinical research</td>
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*EHR = electronic health record; PHR = patient health record.*
Potential sources of bias in real-world studies threatening internal validity

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

*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.
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 Keelin O’Hare

Roger Pickar was diagnosed with a rare cancer in December 2014. A chef, comedian, husband and father of the Pickar family, he was successfully treated for more than a year with standard therapies. When the cancer eventually returned, his oncologist prescribed an experimental treatment—unlabeled—drug: one from the Food and Drug Administration had only approved for other types of cancer, but not the one that affected Roger. That would not 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 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 bring experimental treatments to the patients best suited for them. Typically, drug development is a long process that begins with a series of laboratory studies and culminates with human testing in controlled clinical trials. There is demand for access to experimental new treatments, 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—in which patients are randomly assigned to receive either experimental new treatments or a comparator therapy.

Despite the potential for direct health benefits, patients with cancer—especially sicker patients, those with rare cancer types, and elderly—enrol 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 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.

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 access timely and detailed data that can be used for exploring the safety and effectiveness of new treatments. This can help patients and providers respond more quickly to patients’ needs. Those records are becoming the technological building blocks of a new research model based on real-world evidence. This model aims to provide insights regarding the usage and potential benefits or risks of new treatments, thus providing patients and doctors with a more informed decision-making process.

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

It’s use. Researchers can, for example, search through anonymized data from patients taking a specific cancer drug to see whether those with a certain genetic mutation respond better or worse than other patients. Such information could help doctors personalize therapies based on the patient’s unique genomic makeup.

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 with their own patients, new uses of approved drugs could be carefully studied, potentially generating evidence supporting the approval of new uses. Real-world clinical trials could also limit disruptions to patients’ lives by reducing the need for long-distance travel.

The premise of real-world evidence obtained at the point of routine care comes with a responsibility to ensure data quality and patient safety, while maintaining ethical standards and compliance with good clinical practice guidelines. There are reasons why real-world evidence are not yet the norm. Lack of organizational and technical infrastructure at the point of care makes it difficult to meet the rigorous standards of 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 improved his condition. His story, gathered as real-world data, could have contributed to our collective knowledge about his disease. Dr. 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. Khojaz is an acting associate director in the FDA Food & Drug Administration’s Oncology Center of Excellence and founding director of the agency’s exchange and Data Transformation Center.
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
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