Real World Evidence for Clinical Evidence Generation

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The information in this presentation does not necessarily represent the view of the FDA
Disclosures: None
Real-World Data

- Real world data are the data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources, including:
  - Electronic health records (EHRs)
  - Claims and billing activities
  - Product and disease registries
  - Patient-related activities in out-patient or in-home use settings
  - Health-monitoring devices

Real-World Evidence

- Real world evidence is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of real-world data.

Source: FDA.gov
Information Exchange and Data Transformation (INFORMED)

An integrated approach to big data analytics

Input

• Clinical trials
• Electronic health records
• Biometrics
• Apps

Output
Information Exchange and Data Transformation (INFORMED)

An integrated approach to big data analytics

Input

• Clinical trials
• Electronic health records
• Biometrics
• Apps

Output

Collaborative partnerships
Information Exchange and Data Transformation (INFORMED)

An integrated approach to big data analytics

Launch of FDA’s New Digital Health Incubator

... to support the integration of data analytics into regulatory decision making, we’re taking another new step with the creation of an internal data science incubator called the Information Exchange and Data Transformation; or INFORMED

Remarks by Scott Gottlieb, M.D.
Commissioner of Food and Drugs
Academy Health’s 2018 Health Datapalooza
Washington, DC
April 26, 2018

https://www.fda.gov/NewsEvents/Speeches/ucm605697.htm
INFORMED

• Building technical and organizational capabilities for advanced analytics (artificial intelligence and machine learning)
• Digital biomarker development
• Digital Safety
• Real-world evidence
• Building technical and organizational capabilities for advanced analytics (artificial intelligence and machine learning)
• Digital biomarker development
• Digital Safety
• Real-world evidence
External Validity Deficit in Traditional Clinical Trials

- Differences in protocol-specified procedures and routine care
- Narrow eligibility criteria
- Sampling frame error
Sampling Frame

Sampling Frame: all eligible participants

Sample: Trial participants

Real-World Population

gefitinib

Effect Size Estimate

Total sampling error = error₁ + error₂ + error₃
Real-World Characteristics & Experience of Patients with Metastatic Non-Small Cell Lung Cancer (mNSCLC) Receiving Immune Checkpoint inhibitors

Real-World Characteristics & Experience of Patients with Metastatic Non-Small Cell Lung Cancer (mNSCLC) Receiving Immune Checkpoint inhibitors

Duration of treatment

Reported PD-L1 testing results among treated patients\(^1\,\,^2\)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Not tested on or before PD-1 start date (%)</th>
<th>PD-L1 positive (%)</th>
<th>PD-L1 negative/ not detected (%)</th>
<th>Unknown/ unsuccessful/ equivocal test result (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab (N = 1307)</td>
<td>1222 (93.5)</td>
<td>33 (2.5)</td>
<td>37 (2.8)</td>
<td>15 (1.1)</td>
</tr>
<tr>
<td>Pembrolizumab (N = 48)</td>
<td>18 (37.5)</td>
<td>25 (52.1)</td>
<td>0 (0)</td>
<td>5 (10.4)</td>
</tr>
</tbody>
</table>

\(^1\) For those patients with >1 PD-L1 test conducted before the start of their PD-1 inhibitor treatment, we chose the test and result that was closest to the start of the PD-1 inhibitor start date.

\(^2\) Patients receiving nivolumab and pembrolizumab in different metastatic line settings contributed to both strata.
Application of Diffusion of Innovation Theory (DOI) for Characterization of Real-World Adoption of Immuno-Oncology (IO) therapies in Patients with mNSCLC
Patterns of IO diffusion in mNSCLC (n=43,697; Jan 2011-Dec 2017)
Points are monthly rates of IO use

Application of Diffusion of Innovation Theory (DOI) for Characterization of Real-World Adoption of Immuno-Oncology (IO) therapies in Patients with mNSCLC
Real-World Characteristics & Experience of Patients with Metastatic Non-Small Cell Lung Cancer (mNSCLC) Receiving Immune Checkpoint inhibitors

- Overall, we observed rapid and measurable adoption of IO agents for mNSCLC patients in US community oncology practices
  - Consistent with DOI theory, which predicts adoption will be faster when results from using the innovation are readily observable (e.g., rapidly fatal disease like mNSCLC)
- We’ve noted variability in the speed and extent of adoption
  - In the first year:
    - Slow adoption for treatment
    - Slow PD-L1 expression testing
    - 4 distinct groups of adoptors
  - According to DOI theory, such variability can be due to factors such as a) inherent characteristics of the practices and physicians regarding their tolerance for risk and attitude towards change, b) third party payment patterns, and c) patient preferences
- During the year following U.S. regulatory approval of immune checkpoint inhibitors for mNSCLC, real-world patients receiving nivolumab or pembrolizumab were older at treatment initiation and more had smoking history relative to clinical trial cohorts.
  - Median age at PD-1 inhibitor initiation was 69 years (interquartile range 61–75).
  - 88% smokers

Missing Data Elements in Traditional Electronic Health Records

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

**Missing**
- Data elements such as performance status

**Unstructured**
- Physician notes
- Diagnostic reports
Association of Baseline Body Mass Index (BMI) With Overall Survival in Patients With mNSCLC Treated With Nivolumab and Pembrolizumab

Precision Oncology is about capturing the experience of individual patients in the real-world:

The N of 1

There is no average/median patient
The N of 1: Real-World Clinicogenomic Database

- We identified sources of clinical and genomic data available at large scale:
  - **Clinical data**: Curated EHR data from a wide geographical distribution in the Flatiron Health network
  - **Genomic data**: Next-generation sequencing data produced by Foundation Medicine (>160K tumor samples from across the US)

- We linked these data in a HIPAA compliant, deidentified process that ensures security and privacy of protected health information
  - This enabled analysis of EHR and tumor genomics together

Real-World Clinicogenomic Database: Longitudinal N of 1 Experience

INFORMED: an incubator at the US FDA for driving innovations in data science and agile technology

Sean Khoozin, Richard Pazdur & Anand Shah

Information Exchange and Data Transformation (INFORMED), a multidisciplinary initiative anchored in the FDA Oncology Center of Excellence, is a decentralized science and technology incubator designed to harness the power of big data and advanced analytics to improve disease outcomes.

Regulatory watch: From big data to smart data: FDA's INFORMED initiative

Sean Khoozin, Geoffrey Kim & Richard Pazdur

Real-world evidence


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Commentary

Real-world Data for Clinical Evidence Generation in Oncology

Sean Khoozin, Gideon M. Blumenthal, Richard Pazdur

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Abstract

Conventional cancer clinical trials can be slow and costly, often produce results with limited external validity, and are difficult for patients to participate in. Recent technological advances and a dynamic policy landscape in the United States have created a fertile ground for the use of real-world data (RWD) to improve current methods of clinical evidence generation. Sources of RWD include electronic health records, insurance claims, patient registries, and digital health solutions outside of conventional clinical trials. A definition focused on the original intent of data collected at the point of care can distinguish RWD from conventional clinical trial data. When the intent of data collection at the point of care is research, RWD can be generated using experimental designs similar to those employed in conventional clinical trials, but with several advantages that include gains in efficient execution of studies with an appropriate balance between internal and external validity. RWD can support active pharmacovigilance, insights into the natural history of disease, and the development of external control arms. Prospective collection of RWD can enable evidence generation based on pragmatic clinical trials (PCTs) that support randomized study designs and expand clinical research to the point of care. PCTs may help address the growing demands for access to experimental therapies while increasing patient participation in cancer clinical trials. Conducting valid real-world studies requires data quality assurance through auditable data abstraction methods and new incentives to drive electronic capture of clinically relevant data at the point of care.
Big Data And The FDA: To Mine The Value, First Mind The Gaps

INFORMED is a new initiative at the FDA to incubate new ideas in applying big data to boost the scientific, economic and social returns from the regulation of drugs and medical devices, with a particular focus on cancer.

FDA’s INFORMED incubator seeks to emulate the entrepreneurial mind-set of a Silicon Valley start-up, applying data science approaches to drug development and regulatory decisions. Page 24
Thank you