The Era of Precision Evidence: How RWE will Transform Clinical Research and Drug Development

WSMOS, Seattle WA
May 3, 2019
Our Topics Today

- Era of Precision Evidence
- RWE Research Approaches
- New Research Models
A New Regulatory Paradigm Sets a Context for Required and Desired Use

HITECH (2009)

21st Century Cures (2016)

FDA RWE Program (2018)

Use of Electronic Health Record Data in Clinical Investigations
Guidance for Industry

Food & Drug Administration
Work Plan and Proposed Funding Allocations
Required by Section 1002 of the 21st Century Cures Act (Public Law 114-255)
Scott Gottlieb, M.D.
Commissioner of Food and Drugs
June 6, 2017

Department of Health and Human Services
Food and Drug Administration
Use of Electronic Health Record Data in Clinical Investigations
Guidance for Industry
Increasingly, insights generated from ‘real world’ studies will be high influence sources of clinical evidence and the basis of regulatory decisions.

In many cases, these tools also help make prospective trials more efficient and more reflective of how care is delivered in the “real world”.

To take one example: Pragmatic and hybrid clinical trials, including decentralized trials that are conducted at the point of care – and that incorporate real world evidence (RWE) -- can help clinical trials become more agile and efficient by reducing administrative burdens on sponsors and those conducting trials, and can allow patients to receive treatments from community providers without compromising the quality of the trial or the integrity of the data that’s being collected.

Scott Gottlieb, M.D. -- January 28, 2019
1. **Strategies to decrease variability** — The decreased variability provided by these strategies would increase study power
2. **Prognostic enrichment strategies** — These strategies would increase the absolute effect difference between groups but would not be expected to alter relative effect.
3. **Predictive enrichment strategies** — These include choosing patients who are more likely to respond to the drug treatment than other patients with the condition being treated. Selection of patients could be based on a specific aspect of a patient’s physiology, a biomarker, or a disease characteristic that is related in some manner to the study drug’s mechanism.

*U.S. FDA – March 13, 2019*
A Tectonic Shift: From Data Collection to RWE-Driven Solutions

**RWD**
- Gen 1 RWD
  - E.g., Humedica, Explorys
  - Chart reviews, single-entity data sets, structured data
  - Insights into standard of care, understanding clinical decisions made, differences in care across settings

- Gen 2 RWD
  - E.g., Flatiron Oncology
  - Synthetic Control Arms
  - Pragmatic Trials
  - HEOR

- Gen 3 RWE
  - E.g., Concerto HealthAI
  - Value-centric Models
  - Prospective RWE
  - Smart AI Infrastructure

**RWE**
- 2017–2020
  - Support regulatory and market access decisions
  - Identify patients receiving greatest benefit; optimize precision in use; translate study results to full populations

**Value-centric**
- 2020–
  - RWE-driven innovations and care solutions
  - RWE solutions at scale and speed support intelligent next-best-action solutions for life sciences companies, payers, and providers

- 2005–2016
  - Disease Insights
Next Generation Approaches to Clinical Research

1. Synthetic / Hybrid Control Arms
1. Predictive Enrichment & AI
1. Prospective RWD/Pragmatic Studies
Traditional postmarket studies typically require years to design and complete and cost millions of dollars. By encouraging the use of RWD and RWE, we may be able to provide patients and providers with important answers much sooner by potentially identifying a broader range of safety signals more quickly.

Our work applying RWE to effectiveness decisions is also advancing. In the oncology setting, for example, we currently have new drug applications under review where RWD and RWE are helping to inform our ongoing evaluation as one component of the total complement of information on effectiveness that we’re evaluating.

In appropriate cases, we’ve also accepted RWE to support the evaluation of efficacy in product approvals – using data from registries, natural history studies and chart reviews – to establish a comparison arm in single arm trials in oncology and rare diseases.
Synthetic Control Arms (SCAs) for Rare Cancers and Priority Programs

SCAs are moving into broader use...

Approach to SCAs

- In depth feasibility to establish case eligibility through human review
- Pilot phase of work to establish data completeness, quality, and to finalize design
- Regulatory engagement to present research plan and receive regulatory feedback
- Finalize design, protocol and timeline in advance of data collection and in close alignment with external comparator cohort (endpoints, time origins, inclusion)
- Begin data collection following finalized Statistical Analysis Plan
- Continue with extensive quality control processes, including duplicate curation and programming in close collaboration with client and FDA, with regular check-ins
- Meet deliverable and consider follow-on work

... and are being held to a rigorous standard
Approaches to Synthetic Control Arms

Derived from Past RCT Controls

Use of a synthetic control arm drawn from historical clinical trial data could provide better information about a new investigational agent's safety and efficacy than single-arm studies and allow sponsors to conduct randomized trials that are smaller, or with more patients assigned to the investigational drug.

Derived from RWD Sources

FDA's real-world evidence (RWE) framework released Dec. 6 discusses the potential use of single-arm trials with an external RWD control to support new effectiveness claims and the limitations of such an approach. “Collection of RWD on patients currently receiving other treatments, together with statistical methods, such as propensity scoring, could improve the quality of the external control data that are used when randomization may not be feasible or ethical, provided there is adequate detail to capture relevant covariates,” the framework states.

…”we create something that looks a lot like a randomized control for a setting where randomization is problematic”

Ruthie Davi

“… when you use a synthetic arm ... where it's a kind of a molecular defined disease, you might have a better handle to control the homogeneity and really mitigate against the heterogeneity of the potential differences in these populations”

Rick Pazdur with Amy Aberthany

Approaches to Synthetic Control Arms: Use of Past RCT Controls

- Past RCT study control arm patient populations are being used as the basis for new prospective RCT study control arms
- Results to date reflect reasonable conformance to randomized controls
- Concerns about this approach are several fold
  - RCTs are disproportionately run at Academic Medical Centers and may not be reflective of community care
  - RCT controls are monitored in ways that typical patients in community clinical setting are not
  - Active arm study designs are moving towards being ‘more practice relevant’ and therefore RCT controls may not appropriately complement new active treatment arm designs
Increasingly, however, studies are preferring EMR or RWD derived Synthetic Control areas for their relevance to the current standard of care.

Hybrid study designs, where patients are prospectively followed after a retrospective analysis, will drive the industry further towards EMR derived data as the source.

“This is the first time EHR data have been used for a first-line approval in oncology. The trial was really challenged in recruiting, and if they had had to go by standard clinical trial practice to recruit both arms, it was probably never going to get done.”

Sarah Alwardt, PhD, McKesson, HEOR

Use of Synthetic Controls is accelerating, especially in Oncology

Although randomization may always be the gold standard, Big Data is breathing new life into clinical trial design.

“When we’re looking at tumors, the response rate for untreated patients is known to be essentially zero, reflecting that tumors do not shrink on their own. As a result, if all patients in a trial are given a treatment, tumor reduction of sufficient magnitude and duration is believed to indicate treatment effect and can support approval,” Pulkstenis explains. “In this case the ‘control’ group is based on what we know historically about the course of untreated disease and the lack of placebo effect in this setting.”

Comparative effectiveness from a single-arm trial and real-world data: alectinib versus ceritinib

Jessica Davies1, Michael Martinec2, Paul Delmar2, Mathieu Coudert3, Walter Bordignon2, Sophie Golding3, Reynaldo Martina4 & Gracy Crane2

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4Roche Products Ltd, 6 Rocin Way, Shire Park, Welwyn Garden City, AL7 1TW, UK

Aim: To compare the overall survival of anaplastic lymphoma kinase-positive non-small-cell lung cancer patients who received alectinib with those who received ceritinib. Materials & methods: Two treatment arms (alectinib [n = 183] and ceritinib [n = 67]) were extracted from clinical trials and an electronic health record database, respectively. Propensity scores were applied to balance baseline characteristics. Kaplan-Meier and multivariate Cox regression were conducted. Results: After propensity score adjustment, baseline characteristics were balanced. Alectinib had a prolonged median overall survival (alectinib = 24.3 months and ceritinib = 15.6 months) and lower risk of death (hazard ratio: 0.65; 95% CI: 0.48–0.88). Conclusion: Alectinib was associated with prolonged overall survival versus ceritinib, which is consistent with efficacy evidence from clinical trials.
RWE Solutions are Replacing Traditional Registries and Phase IV Studies

**Concerto HealthAI, Astellas partner on RWE in acute myeloid leukemia**

The partnership will focus on using real-world evidence to improve understanding of responses among patients with acute myeloid leukemia whose disease carries mutations in the FLT3 gene. Astellas markets a drug for FLT3-positive AML, Xospata, approved in November.


“As treatment options expand for AML, it’s more important than ever to understand how alternative approaches impact outcomes and how they might be improved. Identifying the real-world impact of existing treatments is an important complement to our work developing innovative new cancer medicines for patients with urgent, unmet needs.”

Halit Bander
The FDA’s Oncology Center of Excellence (OCE) is also working with Friends of Cancer Research, the National Cancer Institute, and other stakeholders to harmonize reference standards for assessing tumor mutational burden (TMB), -- as determined by multiple proprietary assays -- to help identify cancer patients who are more likely to respond to immunotherapy.

“Our Framework for Real-World Evidence Program will apply a consistent strategy for harnessing these tools across our drug and biologic review programs.”

Scott Gottlieb, M.D.
Industry Leaders and Translating Former Research Approaches to RWE

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<thead>
<tr>
<th>rwRR</th>
<th>RECIST-defined RR</th>
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<tr>
<td>Source evidence</td>
<td>include various EHR unstructured/structured data ie: clinical case notes, radiology and pathology reports, laboratory data</td>
</tr>
<tr>
<td>Assessment interval</td>
<td>Per clinical practice, recommend intervals to help interpretation of randomized data</td>
</tr>
<tr>
<td>Target lesion/non-lesion</td>
<td>NA Per investigator opinion that could reliably assess tumor response</td>
</tr>
<tr>
<td>Imaging modalities</td>
<td>Flexible and per standard of care</td>
</tr>
<tr>
<td>Final determination</td>
<td>Clinician’s overall assessment</td>
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"...traditional on-site monitoring of each clinical site to evaluate study conduct and perform 100% source data verification is highly resource intensive. It accounts for up to a third of the total clinical trial cost. But traditional on-site monitoring doesn’t guarantee data quality."

Scott Gottlieb, M.D.
Differences in Methodology For Determining PFS can affect Median Survival by at least 6 Months.

Product-Limit Survival Estimates

- Median 12.2 months with direct observation of PFS
- Median 9.2 months using time to next treatment as proxy
- Median 7.6 months using treatment discontinuation as proxy
Next Generation RWE Studies Reduce Costs and Time 50 to 75%

**Use Case #1:** Hybrid Studies
Replacing Prospective Phase IV Registries

- **Current Cost vs. RWE-Centric:**
  - Current Cost: $7.5M
  - RWE-Centric: $2.25M
  - Accelerated Time-to-Patient: + Months

**Use Case #2:** Synthetic Control Arm with U.S. FDA

- **Current Cost vs. RWE-Centric:**
  - Current Cost: $3.0M
  - RWE-Centric: $1.0M
  - Accelerated Time-to-Patient: + Months

Source: 2018 Concerto HealthAI analyses
Current Applications of Synthetic Controls and Hybrid Studies

- Market Access Decisions
- Control for Small Population Cancers
- Post-approval Label Modification and Expansion
“As the volume, velocity, and variety of real world data reaching the agency increases, we have an opportunity to use new software-based machine learning algorithms – like natural language processing or deep learning – to help develop regulatory science tools like surrogate endpoints or digital biomarkers that can be used to guide more efficient development programs.”
With Changes in FDA Guidance, Predictive Enrichment, and Software-as-a-Medical Device (SAMD) A.I. will come into broad use
By integrating AI models with RWD we are seeing improved accuracy from the reference models and improvements from new ML approaches.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Female</th>
<th>99%</th>
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<tbody>
<tr>
<td>Mean Age (years)</td>
<td>59</td>
<td></td>
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<tr>
<td>Eastern Cooperative Oncology Group (ECOG) Score</td>
<td>&lt; 2</td>
<td>91%</td>
</tr>
<tr>
<td></td>
<td>≥ 2</td>
<td>9%</td>
</tr>
<tr>
<td>Race</td>
<td>White</td>
<td>62%</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>24%</td>
</tr>
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Retrospective cohort of 14,603 breast cancer patients from the ASCO CancerLinQ Discovery™ dataset

Chemotherapy Induced Neutropenia

- Lyman 2011 Lin Reg
- Concerto Un Reg
- Concerto Neural Net

Clinically validated AI/ML Rapidly Advancing into Clinical Research

Concerto AI Models meet or exceed accuracy of reference literature models

Collaborations with ASCO and the FDA led to 6 Major Research Projects Submitted to Major Symposia
AI Models Enable up to 30x Higher Patient Match Rates by Completing Missing Information with a Known Accuracy

1,000 Non-Curated Oncology Patients EMR

- 617 Unknown
- 359 Not Eligible
- 4 Potential Recruits

1,000 Non-Curated Oncology Patients EMR

- 119 Unknown
- 751 Not Eligible
- 120 Potential Recruits

Inclusion/Exclusion Criteria

- Standard
- Onco Surg Only
- Onco Surg + Onco Stage
- Onco Surg + Onco Stage + Onco Met
- Onco Surg + Onco Stage + Onco Met + Onco NLP

Cumulative effect of AI models

- 4 Potential Recruits
- 10 Potential Recruits
- 21 Potential Recruits
- 42 Potential Recruits
- 120 Potential Recruits

120 Potential Recruits
We are now in the Era of Precision Evidence

“Pragmatic and hybrid clinical trials, including decentralized trials that are conducted at the point of care – and that incorporate real world evidence (RWE) -- can help clinical trials become more agile and efficient by reducing administrative burdens on sponsors and those conducting trials, and can allow patients to receive treatments from community providers without compromising the quality of the trial or the integrity of the data that’s being collected”
F.D.A. April 17, 2019: Ned Sharpless, Acting F.D.A. Commissioner

“And let me dispel any misconceptions that the change in leadership reflects some desire of the president or the secretary for the FDA to go in a different direction from the Gottlieb era. That is not the case, Secretary Azar and the White House have been very clear with me that they have been impressed with the FDA’s efforts and would like to see this strong progress continue”
THANK YOU!