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

Use of Real World Data (RWD) to Assess the Value of New Technology for Patients

Procedural

JNCI
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.

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

**Gen 1 RWD**
E.g., Humedica, Explorys

**Gen 2 RWD**
E.g., Flatiron Oncology

**Gen 3 RWE**
E.g., Concerto HealthAI

- Value-centric Models
- Prospective RWE
- Smart AI Infrastructure

**Disease Insights**
- Synthetic Control Arms
- Pragmatic Trials
- HEOR

**RWD**
- 2005–2016
- Chart reviews, single-entity data sets, structured data
- Insights into standard of care, understanding clinical decisions made, differences in care across settings

**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

**Superior Outcomes & Value**
Next Generation Approaches to Clinical Research

1. Synthetic / Hybrid Control Arms
2. Predictive Enrichment & AI
3. 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...

... and are being held to a rigorous standard

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
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.

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

Ruthie Davi

**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.


"... 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

**Abstract**

**Background:** Clinical trials of experimental drugs require controls. Concurrently randomized controls are the gold standard for judging drug effect. Historical controls are not ideal but are much more efficient and economical. Historical controls derived from a single clinical trial have the biases of that trial. Using many trials with comparable end points and eligibility minimizes such bias. Medidata’s archive contains ~4,000 trials with clinical data rights for identified aggregated analyses. We used this resource to develop a synthetic control arm (SCA) for a particular phase 2 single-arm trial in AML. We demonstrate the utility of this approach by addressing a different but equally important issue: establishing early end points as predictors of long-term clinical outcomes. Methods: We built an SCA from 1,320 retrospective RCT arms completed in last 5 yrs. They had similar eligibility criteria as a particular phase 2 trial for an investigational agent. We selected subsets for the SCA who had baseline covariates matching the subjects in the trial. Data cleaning and standardization ensured consistency of data fields. The primary outcomes were OS (complete remission) and CR (CR without hematologic recovery) at 56 days, and overall survival (OS) at subsequent 56 days. CR/Non-CR deaths before 56 days were set to OS. We used a landmark analysis to correlate CR and OS with OS, calculating the hazard ratios (HR) of OS CR and CR vs its comparison group. Results: The SCA included 340 subjects (median age 63 yrs, 52% male, 7% White Hispanic, 2% Black). Results are in this table. Conclusions: The Medidata archive is a resource for creating SCAs. The example SCA we created identified well-defined subjects for whom CR or OR is associated with longer OS. Investigations of SCAs for other drugs could aid in addressing the type of subjects and drug categories for which CR or OS can predict longer OS. Such information can help build more efficient and more informative adaptive clinical trials.
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 patient 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: alecitinib versus ceritinib

Jessica Davies*, 1, Michael Martinec1, Paul Delmar1, Mathieu Coudert1, Walter Bordignon2, Sophie Golding3, Reymaldo Martina4 & Gracy Crane1

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2 F Hoffmann-La Roche Ltd, Basel, Switzerland
3 F Hoffmann-La Roche Ltd, Bourgogne-Billancourt Cedex, France
4 Department of Biostatistics, University of Liverpool, Liverpool, UK

*Author for correspondence: Tel: +44 7584 587 927, jessica.davies@roche.com

Aim: To compare the overall survival of anaplastic lymphoma kinase positive non-small-cell lung cancer patients who received alecitinib with those who received ceritinib. Materials & methods: Two treatment arms (alecitinib [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. Alecitinib had a prolonged median overall survival (alecitinib = 24.3 months and ceritinib = 15.6 months) and lower risk of death (hazard ratio: 0.65; 95% CI: 0.48-0.88). Conclusion: Alecitinib was associated with prolonged overall survival versus ceritinib, which is consistent with efficacy evidence from clinical trials.
“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
"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

<table>
<thead>
<tr>
<th>Source evidence</th>
<th>rwRR</th>
<th>RECIST-defined RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>include various EHR unstructured/structured data ie: clinical case notes, radiology and pathology reports, laboratory data</td>
<td>Clinical assessment plus imaging</td>
<td></td>
</tr>
</tbody>
</table>

### Assessment interval
- Per clinical practice, recommend intervals to help interpretation of randomized data
- Predefined by protocol on assessment interval

### Target lesion/non-lesion
- NA
- Per investigator opinion that could reliably assess tumor response
  - Predefined, for example
    - At least longest dimension of lesion ≥1 cm by CT or MRI

### Imaging modalities
- Flexible and per standard of care
- Well defined mainly CT or MRI or CT portion of CT-PET

### Final determination
- Clinician’s overall assessment
- Predefined

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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.

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**Table:**

<table>
<thead>
<tr>
<th>Proposed Study</th>
<th>Conventional Study</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Data capture</strong></td>
<td>Point of care using EHR source data, minimal or no conventional CRF use</td>
</tr>
<tr>
<td><strong>SAE</strong></td>
<td>Investigators captures info in clinical notes, EHR system daily uploads to iCloud and then partner company facilitates the reporting via a secured email link between company and investigators/sites</td>
</tr>
<tr>
<td><strong>Laboratory based AE (such as neutropenia)</strong></td>
<td>Use structured data, grading by CTC AE criteria will occur automatically; EHR system will upload nightly and then partner company will send data to company Inform investigator in real time</td>
</tr>
<tr>
<td><strong>Non-laboratory based AE</strong></td>
<td>Investigators document in clinical notes types/severity of AE, FL exact data and send to company, collect Grade3</td>
</tr>
</tbody>
</table>

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Source: Real World Pragmatic Studies: Pharma Perspective and a Recent Example; Cynthia Huang Bartlett, MD
Senior Medical Director, Breast Cancer Portfolio Pfizer Oncology
https://www.fda.gov/media/108510/download
Redefining Quality in RWD for RWE-based Research

Differences in Methodology For Determining PFS can affect Median Survival by at least 6 Months

Product-Limit Survival Estimates
With Number of Subjects at Risk

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

Clinical Pharmacology & Therapeutics, Volume: 103, Issue: 2, Pages: 202-205, First published: 06 December 2017, DOI: (10.1002/cpt.946)

Electronically Signed by: RADIOLOGIST, ADMIN on MRI OF THE BRAIN WITHOUT CONTRAST 06/05/2010 3:45:15 PM

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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**
  - $7.5M vs. $2.25M
  - Accelerated Time-to-Patient

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

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

Source: 2018 Concerto HealthAI analyses
Summary: Oncology Clinical Development & Outcomes Studies

Clinical Development & Post-Approval Studies are an approx. $30B+ Market

Between 20% and 80% of spend is Addressable by RWE-complemented Solutions

Total Spend

<table>
<thead>
<tr>
<th>Year</th>
<th>Total Spend</th>
<th>External Spend</th>
</tr>
</thead>
<tbody>
<tr>
<td>2018</td>
<td>$28.5B</td>
<td></td>
</tr>
<tr>
<td>2019</td>
<td>$30B</td>
<td></td>
</tr>
<tr>
<td>2020</td>
<td>$32.1B</td>
<td></td>
</tr>
</tbody>
</table>

Per Study Costs

<table>
<thead>
<tr>
<th>Phase</th>
<th>Total Spend</th>
<th>RWD Addressable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph I</td>
<td>$4.5M</td>
<td></td>
</tr>
<tr>
<td>Ph II</td>
<td>$11.2M</td>
<td></td>
</tr>
<tr>
<td>Ph III</td>
<td>$22.1M</td>
<td></td>
</tr>
<tr>
<td>Ph IV/RWD</td>
<td>$5.0M</td>
<td></td>
</tr>
</tbody>
</table>

Source: 2019 CHAI Estimates
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

**Key Challenges**

**Availability of High-Quality Data**
A central challenge in building a machine-learning model is assembling a representative, diverse data set. It is ideal to train a model with data that most closely resemble the exact format and quality of data expected during use. For instance, for a model that is intended to be used at the point of care, it is preferable to use the same data that are available in the EHR at that particular moment, even if they are known to be unreliable or subject to unwanted variability.

**Training**

1. Example is run through the model
2. Predicted label is compared with ground-truth label

**Label for example**

**Prediction for example**

**Evaluation**

Test examples → Machine-Learning Model → Predictions for test set → Labels for test set
By integrating AI models with RWD we are seeing improved accuracy from the reference models and improvements from new ML approaches.

Retrospective cohort of 14,603 breast cancer patients from the ASCO CancerLinQ Discovery™ dataset
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**

- **AI Enabled Approach**
  - 119 Unknown
  - 751 Not Eligible
  - **120 Potential Recruits**

**Inclusion/Exclusion Criteria**

- **Onco Surg Only**
  - 10
- **Onco Surg + Onco Stage**
  - 21
- **Onco Surg + Onco Stage + Onco Met**
  - 42
- **Onco Surg + Onco Stage + Onco Met + Onco NLP**
  - 0

**Cumulative effect of AI models**

- **4 Potential Recruits**
  - Standard
  - Onco Surg Only
  - Onco Surg + Onco Stage
  - Onco Surg + Onco Stage + Onco Met
  - Onco Surg + Onco Stage + Onco Met + Onco NLP
  - **120 Potential Recruits**
Next Generation RWE Research Solutions Integrate into Clinical Site Workflows and Drive Speed, Productivity and Cost Improvements

<table>
<thead>
<tr>
<th>Standard</th>
<th>Criteria</th>
<th>EMR-EDC Direct</th>
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<tbody>
<tr>
<td>Custom Integration once/study</td>
<td>Adoption, set up and validation</td>
<td>Easy install, one time set-up and validation</td>
</tr>
<tr>
<td>0%</td>
<td>Percent eCRF data transfer</td>
<td>40–70%</td>
</tr>
<tr>
<td>9 days</td>
<td>Data entry delay</td>
<td>No delay</td>
</tr>
<tr>
<td>Slow/not scalable</td>
<td>Site productivity</td>
<td>50% improvement</td>
</tr>
<tr>
<td>9%</td>
<td>Error rate</td>
<td>0%</td>
</tr>
<tr>
<td>Central labs or heavy operational burden</td>
<td>Labs</td>
<td>Local labs</td>
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An Emerging Next Generation Digital Clinical Research Infrastructure

**Explore**
- RWE-derived study concept definition and cohort modeling for clinical study design

**eProtocol**
- Automated protocol deployment and modifications

**Randomize**
- Randomize from within eCRF; multiple methods
- Blinded or unblinded; stratify; unlimited treatment groups

**Operational Oversight**
- Operational and clinical data
- Queries; adverse event identification
- Data Visualization

**Identify**
- AI-driven patient identification for study eligibility within clinical workflows, securely

**eSite Management**

**eData Management**

**Monitor**

**Sponsor Reporting**
“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”
THANK YOU!