RWE In Clinical Trial Development

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What is Real World Data (RWD)?

RWD typically meets two conditions:\(^1\):


- It reflects **actual experience of patients** during routine patient care
- It is gathered from sources **outside of randomized control trials**

**Examples of RWD**

<table>
<thead>
<tr>
<th>Switch Claims</th>
<th>Payer Claims</th>
<th>EHR</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Symphony Health Solutions" /></td>
<td><img src="image" alt="TRUVENT HEALTH ANALYTICS" /></td>
<td><img src="image" alt="HUMEDICA An Optum Company" /></td>
<td>- Disease registries</td>
</tr>
<tr>
<td><img src="image" alt="imshealth" /></td>
<td><img src="image" alt="OPTUMInsight" /></td>
<td><img src="image" alt="Cerner" /></td>
<td>- Patient chart reviews</td>
</tr>
<tr>
<td><img src="image" alt="IntrinsiQ" /></td>
<td><img src="image" alt="FLATIRON" /></td>
<td><img src="image" alt="practicefusion" /></td>
<td>- Patient &amp; population surveys</td>
</tr>
</tbody>
</table>

RWD has potential to address a number of key challenges faced by Pharma’s R&D organizations today

More than half of clinical trials have protocol amendments

Most trials are delayed by low speed of patient enrollment

Almost half of trial sites are unable to reach recruitment targets

Patient dropout remains very high

Value of using RWD and data-driven approaches to improve planning and execution of clinical trials:

1. Data-driven design and planning strategy to decrease clinical trials protocol and execution amendments
2. Accelerated site identification by analyzing patient concentration & site location
3. Improved patient access, referrals and recruitment; faster enrollment; patient engagement using tools and appropriate data
# Real World Data can support product lifecycle

<table>
<thead>
<tr>
<th>Early R&amp;D</th>
<th>Clinical trials</th>
<th>Commercial</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unmet Need Analysis</strong></td>
<td><strong>Trial/ Study Design &amp; Planning</strong></td>
<td><strong>HEOR</strong></td>
</tr>
<tr>
<td>• Natural progression of disease</td>
<td>• Study feasibility</td>
<td>• Comparative effectiveness</td>
</tr>
<tr>
<td>• Patient experience shortfalls</td>
<td>• Protocol design</td>
<td>• Economic value analysis</td>
</tr>
<tr>
<td>• Epidemiology</td>
<td>• Patient population, IC/EC development</td>
<td></td>
</tr>
<tr>
<td><strong>Understand disease</strong></td>
<td>• Treatment pathway and SoC</td>
<td><strong>Safety Evaluation</strong></td>
</tr>
<tr>
<td>• Genomic impact on disease</td>
<td>• Patient recruitment, PI/site selection</td>
<td>• Adverse event monitoring</td>
</tr>
<tr>
<td>• Patient behaviour</td>
<td>• Study representativeness</td>
<td>• Signal detection and validation</td>
</tr>
<tr>
<td>• Physician behaviour</td>
<td></td>
<td>• Treatment compliance</td>
</tr>
<tr>
<td><strong>Treatment pathways</strong></td>
<td><strong>Trial Management</strong></td>
<td><strong>Marketing</strong></td>
</tr>
<tr>
<td>• Treatment patterns and patient journey</td>
<td>• Innovative trial design (e.g. pragmatic trials, virtual control arms)</td>
<td>• Forecasting</td>
</tr>
<tr>
<td><strong>Portfolio management</strong></td>
<td>• Data collection and analysis</td>
<td>• Market sizing</td>
</tr>
<tr>
<td>• Asset prioritization</td>
<td>• Cross-study analysis</td>
<td>• Patient journey and segmentation</td>
</tr>
<tr>
<td>• Indication expansion</td>
<td></td>
<td></td>
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<tr>
<td>• Drug repositioning</td>
<td></td>
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</tbody>
</table>

**Trial Interpretation**

• Benchmark background rates
• Contextualise results and observations
# RWE Data Provider Market Is Growing

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples of Data Providers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacy LRx</td>
<td>IMS</td>
</tr>
<tr>
<td>Medical Switch</td>
<td>IMS</td>
</tr>
<tr>
<td>MD office EHR</td>
<td>GE Centricity</td>
</tr>
<tr>
<td>Integrated Delivery Network</td>
<td>Humedica (Optum), TriNetX, Oncology Research Information Exchange Network (ORIEN), InSite</td>
</tr>
<tr>
<td>Health Plan (Payer) Claims</td>
<td>Truven (now IBM), Optum (UnitedHealth Group)</td>
</tr>
<tr>
<td>Specialist EMR, Labs</td>
<td>FlatIron, Foundation Medicine, Tempus</td>
</tr>
<tr>
<td>Registries</td>
<td>American College of Cardiology</td>
</tr>
<tr>
<td>Diary Studies</td>
<td>IMS/IPSOS/Kantar</td>
</tr>
<tr>
<td>Data Marketplace</td>
<td>HealthVerity</td>
</tr>
</tbody>
</table>
New Emerging Model - Federated EHR platforms

Emerging federated on-line EHR technologies combined with expanding networks to include larger databases collected from multiple healthcare organizations will transform the entire biomedical research enterprise, making innovation faster, more powerful and radically cheaper. The technology is disruptive to the current Business Models by collaborating directly with HCOs. Key impact areas are:

- **Real time access at source** (Digitized Centric & Continuous Data Flow Capabilities)
- **Stronger collaboration and trust with health care/hospitals** (Streamlining operations)
- **Gateway for cost effective data exchange services at sites** (e.g. direct data capture into EDC (Clinical Trial, Genomics and RWE capabilities)
- **Emerging vehicle for conducting PCTs**
Two examples of EHR network service providers

Two mature service providers are using this technology: InSite network (Europe) and TriNetX network (US) allowing trustworthy re-use of on-line EHR data in almost real time.

During 2018 expected combined access of +100 M EHRs in +20 countries

Europe

InSite

- European based (depl. from IMI/EHR4CR)
- Live on platform: +20 M EHRs from 13 HCOs/29 sites in six countries
- Expected to open 10-20 HCOs by Q2 2018 (add. +37 signed LOIs).

US+, America and Asia

TriNetX

- US based. Live on platform: +50 M EHR from 34 US HCOs/80 sites.
- Expected soon to open sites in Americas, EMEA and Asia (now 5 non-US institutions), incl. >5 paediatric centers.
THE NETWORK – IN NUMBERS

- **95M** patients
- **44M** live on network
- **21** industry clients
- **9.8B** clinical facts

- **68** HCOs
- **37** live on network
- **11** countries

- **5,941** protocols analyzed
- **115** clinical trials

**Clinical Facts:**
- **4.7B** labs
- **2B** diagnoses
- **1.7B** medications
- **1.4B** procedures
- **32M** tumor facts
- **361K** genomics

**Opportunities for HCOs:**
- **224** average facts per patient
- **361K** opportunities for HCOs

Statistics as of January 12, 2018
HEALTHCARE ORGANIZATION MEMBERS
PATIENT DATA

Constantly Updated

7 Years of History on Average

FACTS

9.7B Clinical Facts

Types of Data

- Demographics
- Diagnoses
- Procedures
- Medications
- Lab Results
- Vitals
- Oncology
- Molecular Genomics
- Cardiology
- Pulmonology

Data Depth

Clinical Facts:
- 2015: 2
- 2016: 4
- 2017: 8

Billions
Federated EHR platforms - What can the technology do?

Global Hospital networks (US, Europe beyond)

Pharma user interface

On-line Federated EHR central platform services

Provides a new gateway to PCTs. Capture data directly at source. Managed and controlled at site. Secure data transfer to through ICF at site, or pseudo anonymised mechanisms at site via central platform transfer. E.g. reducing SDV and site burden

S4: emerging services: allowing remote data analytics on large hospital sites. facilitate bi-lateral cooperation between pharma & hospitals to enable direct data access.

Services in place – were EHR data stays in site

Individual & clusters of hospitals

@site level

S1: Enabling protocol testing with real world data in potential trial sites rather than with guestimates.

S2: Speeding up recruitment by making EHR data searchable for investigators and establishing a unified communication path between sponsors and sites.

S3: Facilitating EHR data extraction for applications used during trial execution (e.g. prefilling of CRFs and of SAE reporting).

Services in development – data transfer in a controlled environment
EHR enabled patient population funnel analysis

Various and Disparate Data
- Demographics
- Lab Results
- Diagnoses
- Oncology
- Procedures
- Genomics
- Medications
- NLP

Mapped to Industry Standard Terminologies
- HL7
- ICD-10, ICD-9
- CPT
- RxNorm, NDF-RT
- LOINC
- NAACCR, ICD-O
- HGNC, HGVS, ClinVar, dbSNP

Master Terminology / Intelligent Synonym Search
- MUST Have
  - HbA1c
- CANNOT Have
  - Search Term...

Code
TNX:LAB:903
Term Description
Hemoglobin a1c/hemoglobin.total in blood
Patients
3,294,500

ADD TO QUERY
- D Demographics
- M Medications
- P Procedures
- G Genomics
# EHR enabled patient population funnel analysis

<table>
<thead>
<tr>
<th>Event</th>
<th>Patients</th>
<th>HCOs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event 15A</td>
<td>57,432,760</td>
<td>42</td>
</tr>
<tr>
<td>Event 8A</td>
<td>286,890</td>
<td>39</td>
</tr>
<tr>
<td>Event 5A</td>
<td>271,590</td>
<td>39</td>
</tr>
<tr>
<td>Event 10A</td>
<td>179,630</td>
<td>39</td>
</tr>
<tr>
<td>Event 4A</td>
<td>151,000</td>
<td>39</td>
</tr>
<tr>
<td>Event 9A</td>
<td>138,550</td>
<td>39</td>
</tr>
<tr>
<td>Event 1A</td>
<td>129,190</td>
<td>39</td>
</tr>
<tr>
<td>Event 8A</td>
<td>121,480</td>
<td>39</td>
</tr>
<tr>
<td>Event 5A</td>
<td>116,750</td>
<td>39</td>
</tr>
<tr>
<td>Event 4A</td>
<td>113,740</td>
<td>39</td>
</tr>
<tr>
<td>Event 1A</td>
<td>111,620</td>
<td>39</td>
</tr>
</tbody>
</table>
Real-time data driven study design & feasibility

Launch query

Analyze Results

Formalize Clinical Questions

Turn around time of minutes

www.insiteplatform.com
Recruitment support

Hospital Software

Patient Recruitment

- Participate in clinical studies published on the InSite platform
- Computer-assisted candidate patient selection enables efficient screening
- Receive up-to-date information and feedback from sponsors

Now piloted for two AZ studies with promising results
Comparing normal practice and InSite enabled recruitment.
AZ InSite recruitment pilot

Summary: In March 2018, the first patient ever recruited into AZ clinical trial using this EHR platform support. After 8 months of recruitment the participating InSite hospital is recruiting **five times faster** compared to other sites in the study showing promising potential of this new technology.

Background:

- Opportunity to compare InSite recruitment service versus “traditional practice” for one site into a AZ oncology sponsored trial
- InSite platform improve workflow by comparing InSite’s performance to the traditional method of patient recruitment in an open trial
- From the total population of 71,600 patients, InSite suggested 67 potential candidates of which 33 were found to be eligible after manual verification
- Candidate patients corresponded exactly to the population that was found using the traditional approach, confirming platform accuracy and completeness
- This traditional method already includes an initial query of EHR data. However, with the InSite platform the same result was obtained with more than 2x less effort spent by the investigators (8 vs 16 hours)
Case study: Quantification of patient treatment flow in NSCLC using WebMD claims data

1L Maintenance therapy (n=1.6k)  
Avg. Duration – 116 days  
Avg. visits – 13

2nd Line of therapy (n=11.9k)  
Avg. Duration – 78 days  
Avg. visits – 13

3rd Line of therapy (n=5.2k)  
Avg. Duration – 80 days  
Avg. visits – 12

1st Line of therapy (n=29.5k)  
Avg. Duration – 80 days  
Avg. visits – 18

Total Metastasized NSCLC patients (n = 29.5k)

De novo N = 28.1K

Stage III localized NSCLC patients (n = 1.3k)

Surgery N = 2.7K

Neo-adjuvant therapy (n = 172)  
Avg. Duration – 30 days  
Avg. visits – 8

Patients progressing to L1 post surgery (N = 1.4k)

Thoracotomy/Surgical Thoracoscopy

Adjuvant therapy (n = 1.3k)  
Avg. Duration – 77 days  
Avg. visits – 16

Therapy (top 10 regimens)  
- Carbo + Paclitaxel  
- Carbo  
- Alimta + Carbo  
- Cis

Specialty  
- Hematology & Oncology  
- Medical Oncology

Biomarker tests: EGFR, Fish, PD-L1 tests
Case study: Flatiron NSCLC Clinico Genomic Dataset Analysis

Background
• Generate hypotheses regarding biomarkers of IO response and other exploratory hypotheses requiring genomic data.

Results and Impact
• Results of the TMB analysis are feeding into trial designs. These analyses are helping to determine if TMB should be used to stratify patients and what cut-off should be used for TMB High.
Forward looking - PCT is more pragmatic approach to RCT

“Pragmatic clinical trials are research investigations embedded in health care settings designed to increase the efficiency of research and its relevance to clinical practice”
Richesson et al. 2017 NIH perspective, JAMIA

- Clinical research is more than just traditional RCTs
- **Pragmatic research** is designed with input from health systems—and produces evidence that can be readily used to improve care
- By engaging health systems, providers, and patients as partners, pragmatic research accelerates the integration of research, policy, and practice
Summary of RWE In Clinical Trial Development

- Incidence trends and statistically validated projections
- Identify matching patients & sites
- Protocol execution assessment

- Molecular/TA specific biomarker breakdown
  Survival trends and high level capture of outcomes within current Standards of Care

- Drug patterns & longitudinal uptake
- Brand switching & disease onset
- Patient level costing
Thank You!

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