Perspectives on Real-World Data and How It Impacts the Current Healthcare Environment

With Real-World Examples

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Agenda

- What is RWD?
- Surge in the popularity of RWD
- Implications for pharma
- RWD Case studies
  - Pragmatic Trial
  - Patient and Site Identification
  - Novel Data Collection to replace/augment patient reports
  - Virtual Registry
  - Value Demonstration

My Favorite Big Data Quote

"Big Data is like teenage sex: everyone talks about it, nobody really knows how to do it, everyone thinks everyone else is doing it, so everyone claims they are doing it."

- Prof. Dan Ariely, Author of Predictably Irrational

What are RWD and RWE?

Real-World Data (RWD)

- Patient-level data *not* collected in conventional randomized controlled trials

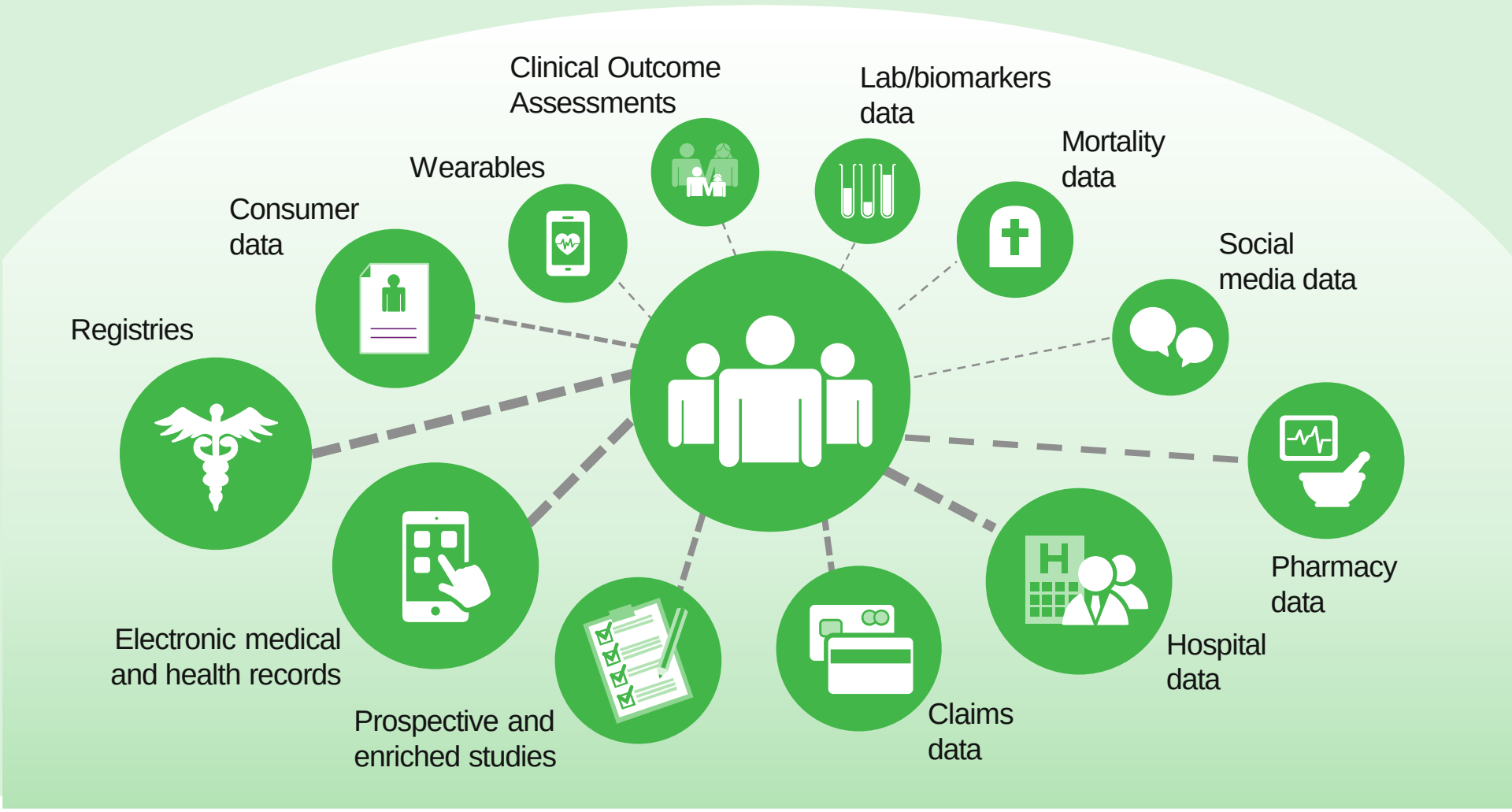
Real-World Insights (RWI)

- Insights generated from RWD using appropriate scientific and/or generated commercial analytics

Real-World Evidence (RWE)

- Insights generated from RWD using appropriate scientific and/or generated commercial analytics with the intention to support a claim or belief to produce evidence for multiple stakeholders

Real-World Data comes from a variety of sources



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RWD is PATIENT-level data

Real-World Data has been in use for certain applications

Clinical

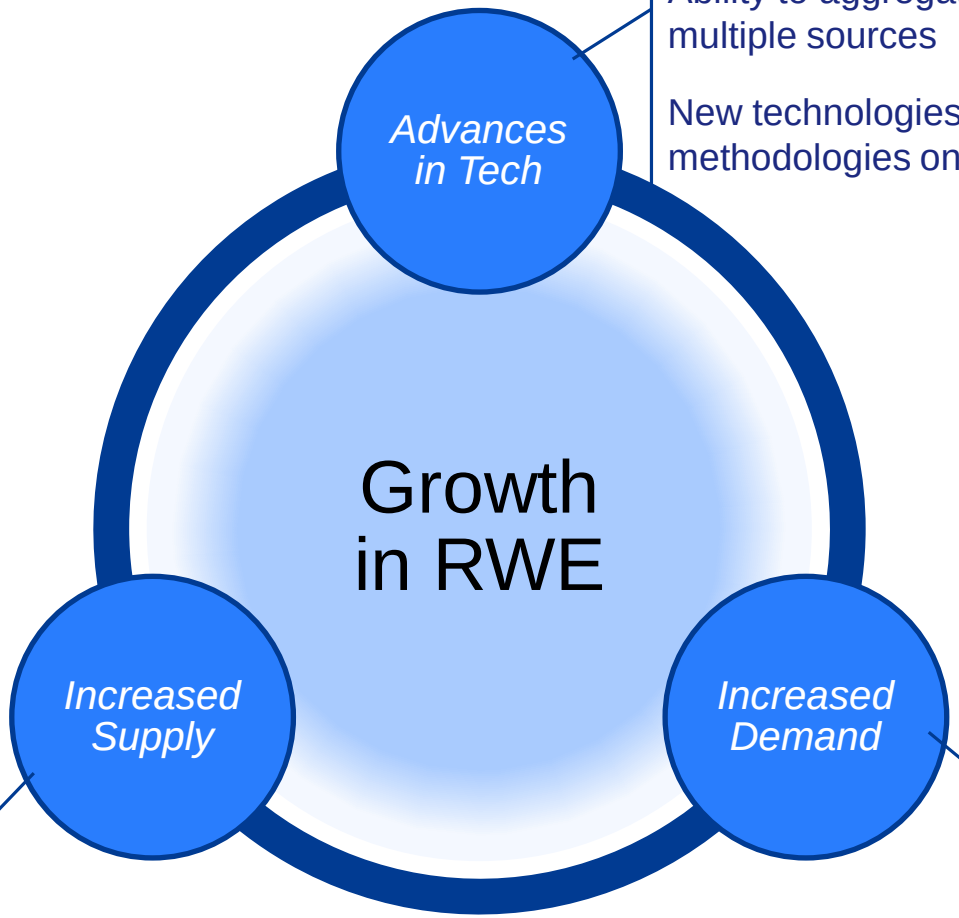
- Adverse event reporting / pharmacovigilance
- Drug / disease registries
- Health system studies / quality improvement efforts
- Epidemiological studies

Commercial

- Drug utilization
- Outcomes and comparative effectiveness research
- Cost and cost-effectiveness research
- Physician Targeting

Increasing interest in the use of RWE in these areas

Increased interest in RWE is driven both by supply and demand-side factors



Ability to aggregate data from multiple sources

New technologies and methodologies on data digitization

Explosion in volume of electronic patient data

Access to gold-standard data through various collaborators (e.g., biomarkers, imaging, etc.)

Move from volume-based to value-based payment

Adaptive licensing / increase in post-authorization regulatory requirements

Push to capture efficiencies in R&D and clinical trials

Evolution of personalized medicine

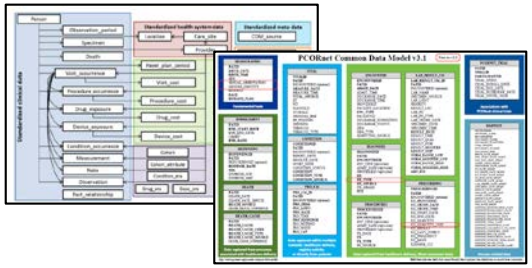
Increased Demand:
Stakeholders across the industry see innovative uses

Kaiser Permanente allocates >$1B spend	• *Kaiser Permanente spent >$1 billion developing data infrastructure and educating plan members on self-management*
Pharma / biotech is innovating in the space	• *Biogen entered into a collaboration with Imperial College on a 3-year project to develop and deploy tools to integrate brain scans, biomarker data and QoL measures*
FDA sponsored Mini-Sentinel initiative	• *The Mini-Sentinel project sponsored by the U.S. FDA intends to create a surveillance system to monitor the safety of FDA-regulated medical products, has over 125M patients*
Payers are evaluating their own data to determine effectiveness	• *Payers such as AIFA (Italy), Wellpoint (US) and others are seeking to control costs by monitoring the effectiveness of high cost drugs*

Advances in Technology: Common data models and linkages

Standardization

Common Data Models create the foundation upon which disparate data sources can be compared, aligned or combined

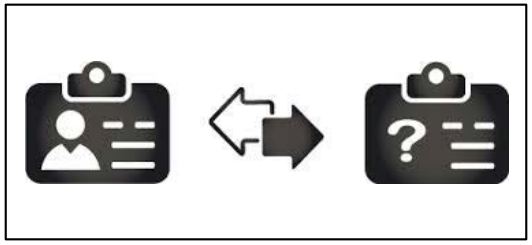


Linkage

Techniques and systems to match patient-level data across sources unlock insights greater than the sum of individual parts

Anonymization

Capabilities to ensure patient privacy whiie maintaining analytical utility of data



Evidence Platforms

Broad, Nationally Relevant Databases (e.g., IMS RWD Claims Data)

Augmented Datasets (e.g., Oncology EMR)

T-Shaped portfolio of Data Sources

Deep Clinical Data (e.g., Genomics Data)

Enriched Data (e.g., NLP, Linkage, Local Registry)

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Increases in Supply:
Increasing access to data and analytic technologies

Governments incentivizing data creation	• *In the US,* "Meaningful Use" and the HITECH act led to a *Proliferation of EMR systems driven by large vendors has increased the quantity and standardization of RWD*
Governments improving data quality	• *e.g. UK government are pushing the care data initiative to "drive economic growth by making England the default location for world-class health services research"*
Industry Partnerships for RWE	• *CROs and biopharma are extending their data business with collaborations with Lab & Diagnostic companies such as JVs between Quintiles & Quest and Covance & LabCorp*
New, novel data sources	• *First time collaborations are yielding access to data such as – biobanks, genomics, consumer and behavioral data– that were previously unavailable and disparate.*

2016 saw significant developments in US regulatory environment regarding RWE

March 2016

- Janet Woodcock, CDER Director, comments on potential of RWD in regulatory decision making

"The question on everyone's mind is: can we randomize people within the healthcare system to do a trial inside the healthcare system utilizing the data collection methods of the healthcare system?"

June 2016

- Bipartisan Policy Center issues report **calling on FDA to develop guidance on use of RWE** in regulatory context

"Neither definitions for 'adequate and well-controlled' investigations included in the law nor in the FDA's recent guidance preclude the use of real-world evidence for regulatory decision-making."

July 2016

- Draft FDA guidance published on RWE in medical device regulatory decisions

December 2016

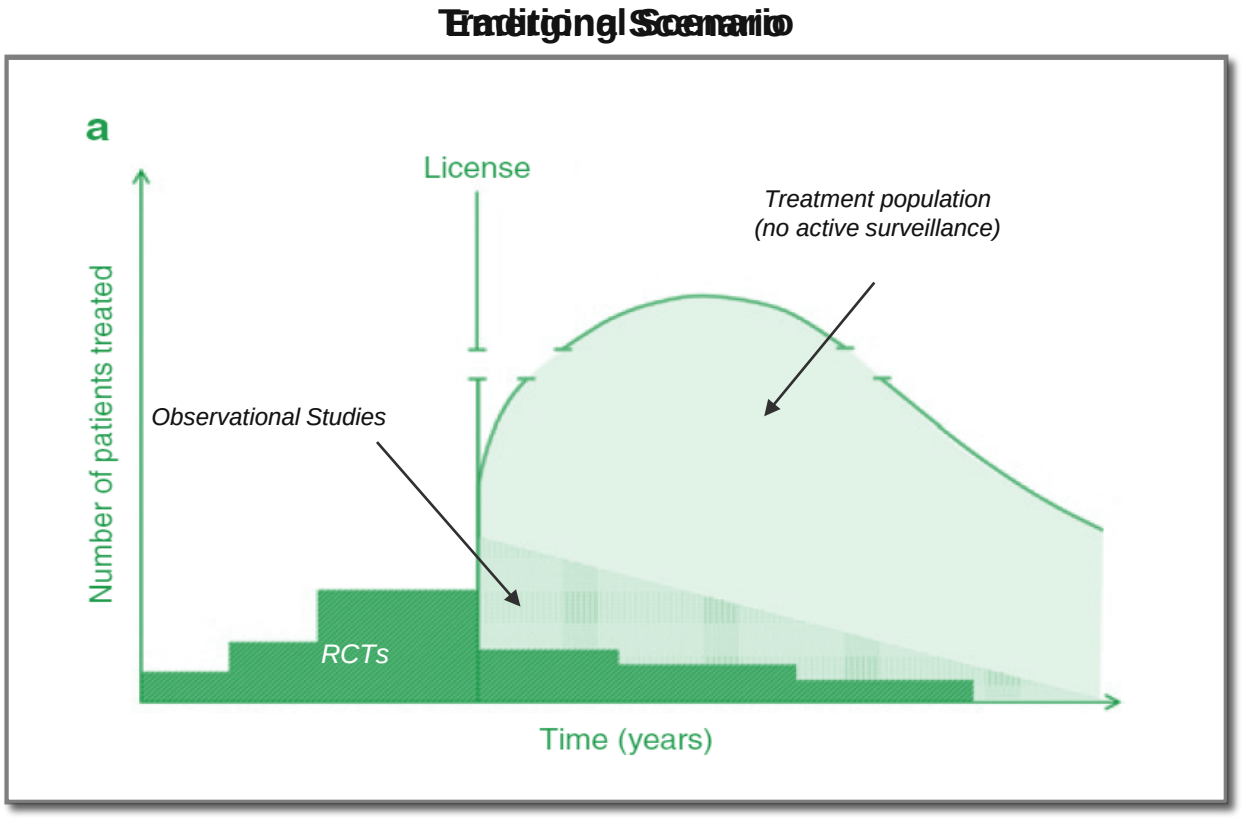
- *21st Century Cures Act* requires FDA to **establish a program to evaluate potential for RWE** in new indications for approved drugs and to help to support or satisfy post-approval study requirements

FDA has pledged to meet the following benchmarks with respect to RWE in regulatory decision-making:

- **FY 2018:** Convene one or more public workshops to gather input
- **FY 2019:** Initiate pilot studies or methodology development projects aimed at addressing key outstanding concerns and considerations
- **FY 2021:** Publish draft guidance on RWE in regulatory submissions, for example in the approval of new supplemental indications and for the fulfillment of post-marketing commitments and requirements

Emerging adaptive drug development scenario creates a need for data generation post-launch

- Earlier to market via FDA fast track / breakthrough or EMA prime status
- Collection of data for regulators continues past launch date
- Plan incorporates collection of **real-world evidence** after initial authorization
- Plan should address demands of **HTA (payers)** and ability to engage them should be demonstrated



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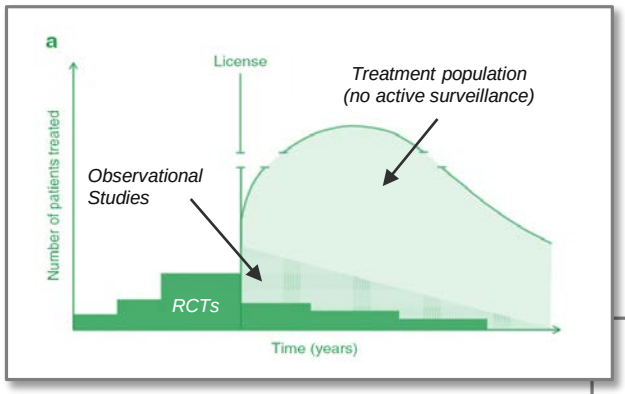
Source: Trustheim 2015: Adaptive Pathways: What's in it for Payers?; Eichler et al. 2012 CP&T 91(3)426:437

Emerging adaptive drug development scenario creates a need for data generation post-launch

Conventional Scenario



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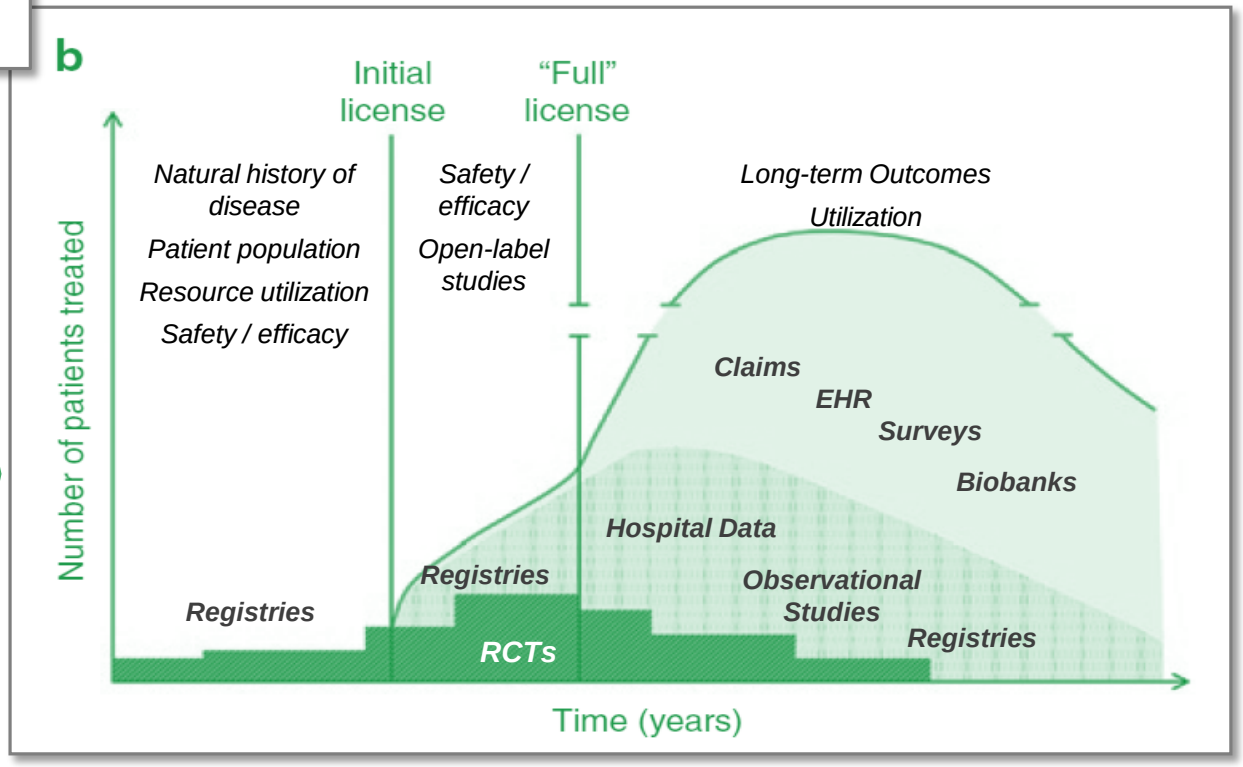
Emerging Scenario



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Use Case 1:

Pragmatic Clinical Trial: Salford Lung Study (GSK)

Prospective, randomized study of effectiveness of a licensed medicine

Specifically designed to compare the **real-world effectiveness** of Ellipta (Fluticasone Furoate / Vilanterol) to usual care treatments

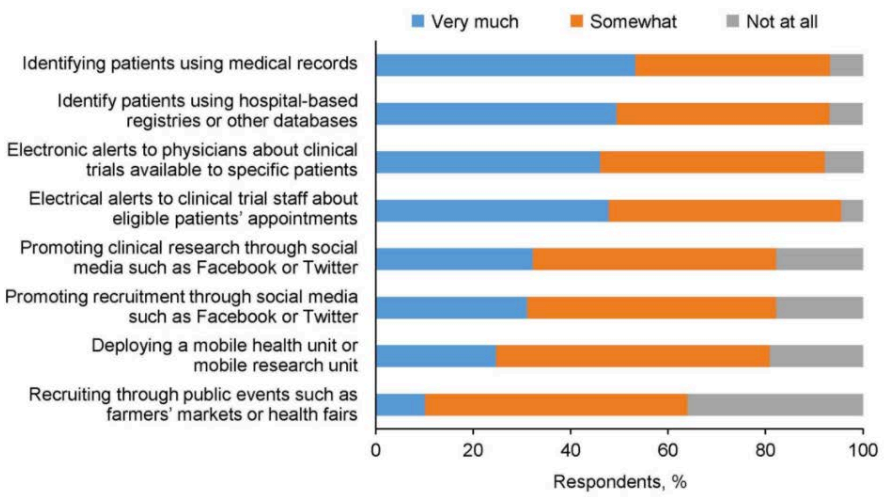
- **Minimal exclusion criteria**: *e.g. no restrictions regarding smoking history or spirometric values*
- Administered in **normal healthcare environments** (>80 primary care clinics, 130 community pharmacies, 2 hospitals)
- **Leveraged EHR records** infrastructure (Salford Integrated Record) to obtain a broad view of patients over 12 months on key metrics (e.g. hospital admissions, ED visits), combined with data from GSK feeds

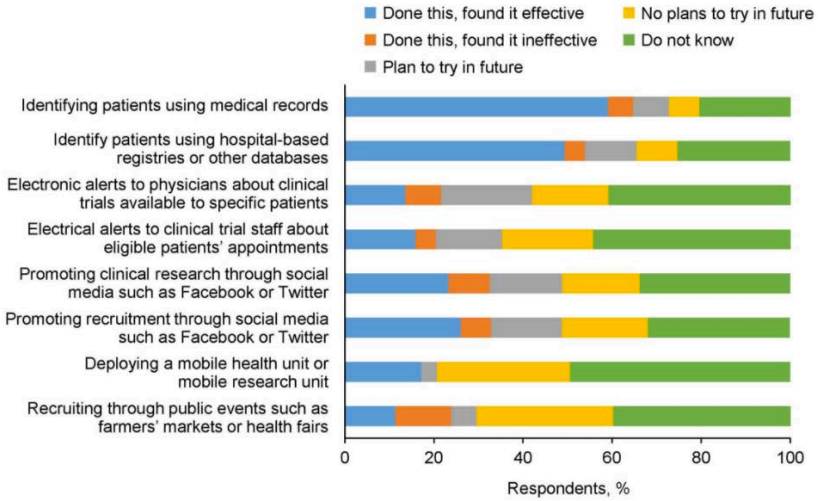
- Nearly 7,000 patients in study (2,800 COPD / 4,000 asthma), enrolled between March 2012 and October 2014
- **Result:** GSK demonstrated 8.41% decrease in severe exacerbations vs. standard of care in COPD

Use Case 2a & 2b:

Clinical Trial Recruitment (Multiple Companies)

- Recruiting for clinical trials can be time consuming and represents a significant portion of the effort in implementing a successful trial.
  - In 2011, 19% of trials failed to meet their goal of 85% patient recruitment
  - The average Ph-II Trial costs are approximately $10M - $20M. Ph-III $15M - $50M





- Two recent projects undertaken at QuintilesIMS successfully identified sites with a high number of patients for recruitment into a trials
  - Infection – Adolescent patients & COPD – Adult Patients

REF: http://www.appliedclinicaltrialsonline.com/barriers-clinical-trial-recruitment-and-possible-solutions-stakeholder-survey?pageID=4

COPD Trial Recruitment using RWD / RWI

Critical Client Need

- Client had a product in the COPD treatment space, with multiple competitor products
- Needed to quickly follow-up on a competitor's journal publication where competitor's product demonstrated superiority vs. ICS / LABA.

Client Challenge

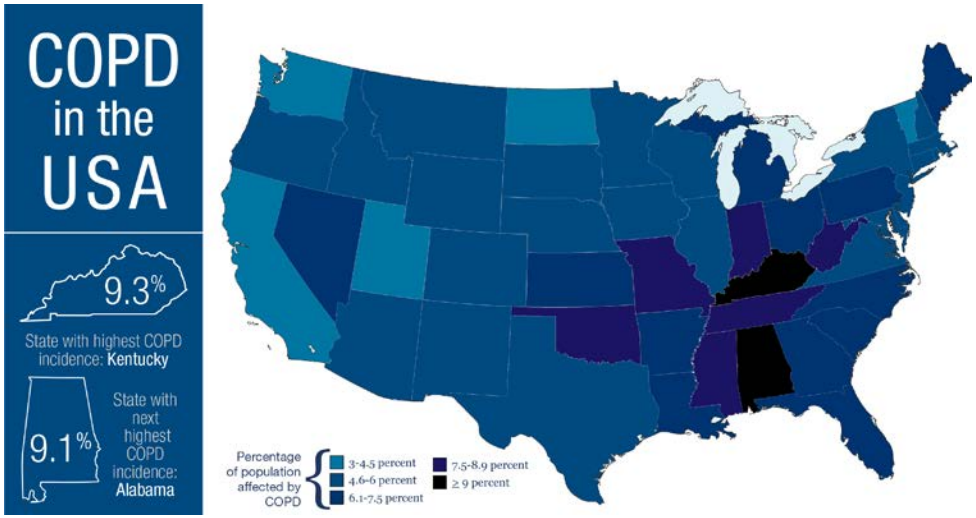
- Ensure an understanding of the clinical pathway and impact of intervention on disease progression to target the right sites.
- Short study start-up timelines to be able to respond rapidly to journal article

Differentiated Approach

- Utilize PharMetrics+ Real World Data to support Site Selection and ensure representativeness of patient population
- Utilize Bioresearch Monitoring Information Systems (BMIS) containing 1752 form information to evaluate investigator experience from Pharmetrics+ analysis.

Sites Geographic Distribution

Site and patient heatmap with geographic distribution input



Identified high COPD prevalence locations using EMR data to target patients meeting Inclusion/exclusion criteria

Matched these high prevalence locations with locations of >6,000 QuintilesIMS identified COPD investigators, using past trials conducted by Quintiles and within BMIS dataset

6085 US Investigators experienced in COPD trials with QuintilesIMS

Sites mapped against Pharmetrics+ & US Claims data incorporating patient level data

Identify recommended sites based on previous performance and Phase IV experience

Geographical distribution COPD prevalence in adults by US state

Ideal Trial Site Identified

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Use Case 2b:

Acute Infection Clinical Trial

Shifting practice patterns led to poor recruitment for initial attempt

Background

- Ph-III study of acute infection in adolescent patients. Study team selected sites based on performance of client's prior trial
  - Undertaken 4 years prior
  - Only pediatric patients in prior trial
  - Hospital-based investigators used
- After 1.5 years, no patients were enrolled in the US for the new adolescent trial. Study was at major risk of failure

RWD Solution

- Real-world data was leveraged (EMR) to
  - Identify patient pathway
  - suitable sites
- RWD suggested there was a difference and a change over the past 7 years in site of care.
  - More frequently ER and ambulatory
- New Strategy:
  - Adjusted site composition to include office settings as well as hospitals, leveraged EMR data to identify high-potential sites and retargeted
  - Provided resources for existing sites with considerable potential such that they could identify, screen and enroll patients in the ER

Case Study 3:

Evaluating RWD capture tools as a proxy for reporting

1. *Can consumer products provide enough insight to effectively replace or augment patient reports?*
2. *What works for which patients?*
3. *What data sources provide the best signal?*

Strategy

Researching across a population suffering with chronic intermittent pain to understand the best sources

- Leveraging the population currently under observation, we rendered daily information into interfaces to understand visual impact and accuracy of various connected consumer data sources

- We tested aggregated views and individual views

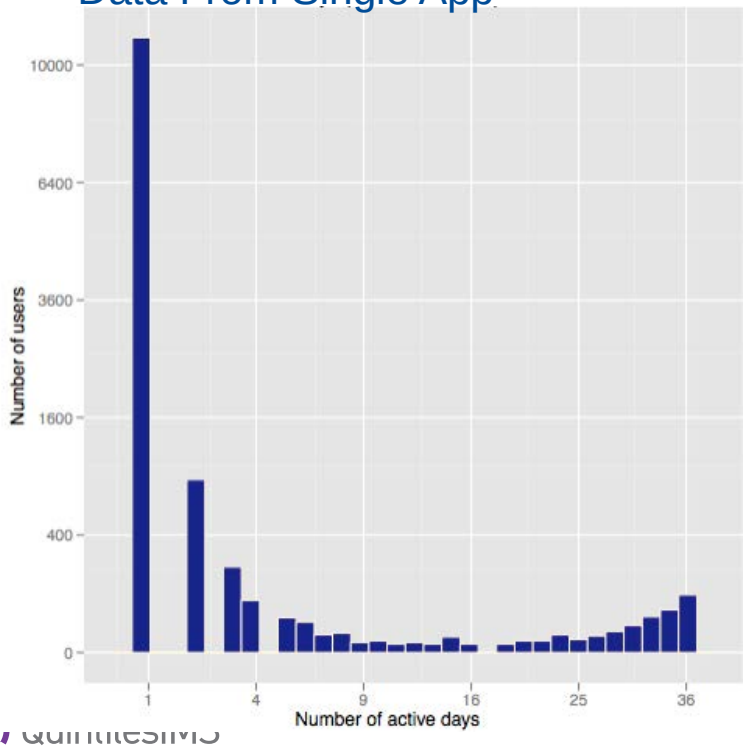
Results

- Sleep, steps & heart rate provide the most consistent signal, and have the capability of highlighting possible “events” confirmed by PROs
- What are they telling us though?

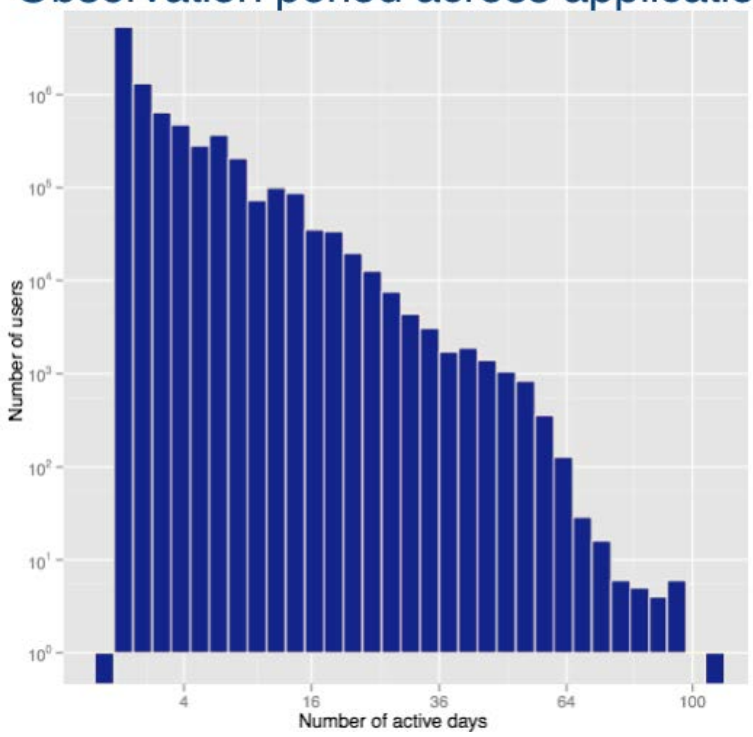
Study Sample

- ICD code 346* / G43 - Migraine
- 17,286 patients with connected with sensors and mobile applications
- 100 + Applications and devices including all commercially available Pedometers (Fitbit, Misfit, Garmin, Apple watch, Samsung, etc.) covering sleep, HR and steps/activity,
- Social network connections and wellness apps, **individuals matched to IMS data**

Data From Single App

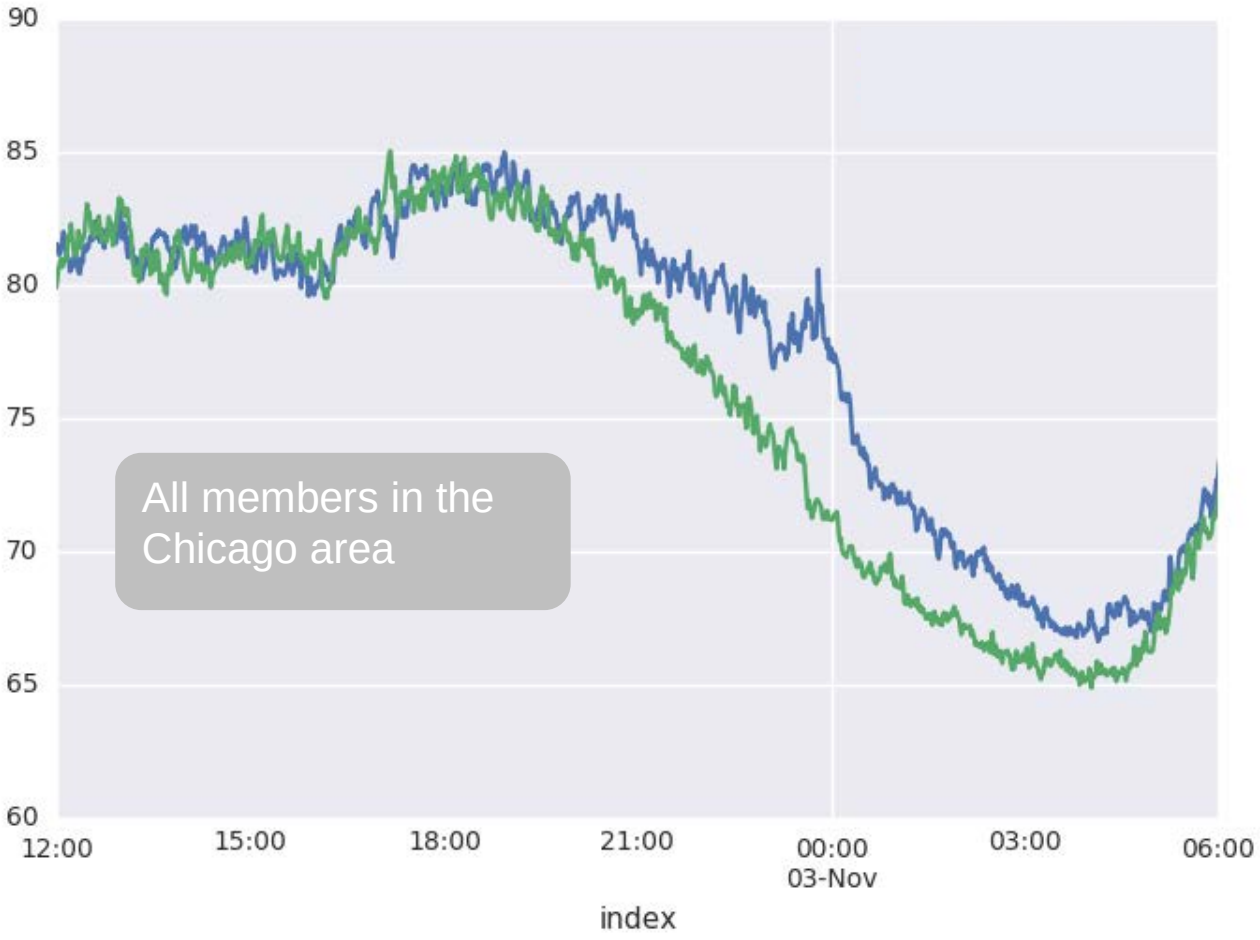


Observation period across applications

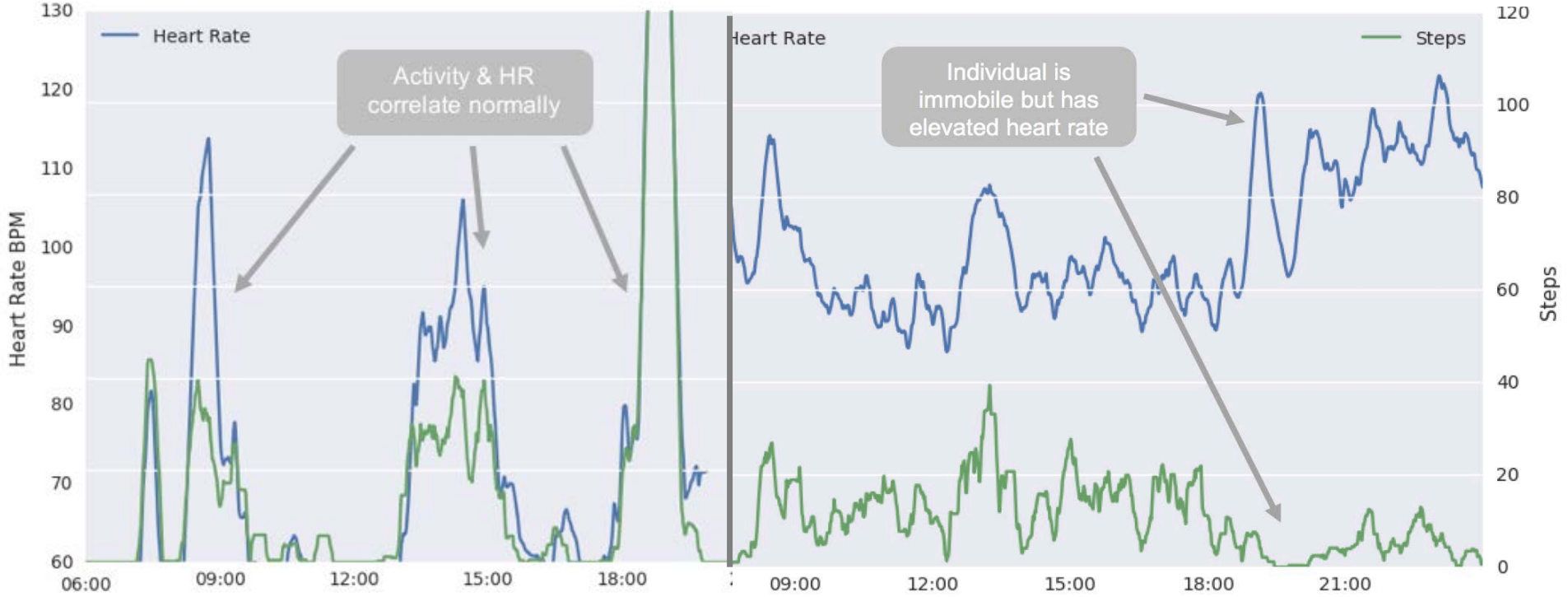


Can the data detect differences?

We observed avg. heart rates in Chicago on 10/19 and 11/2

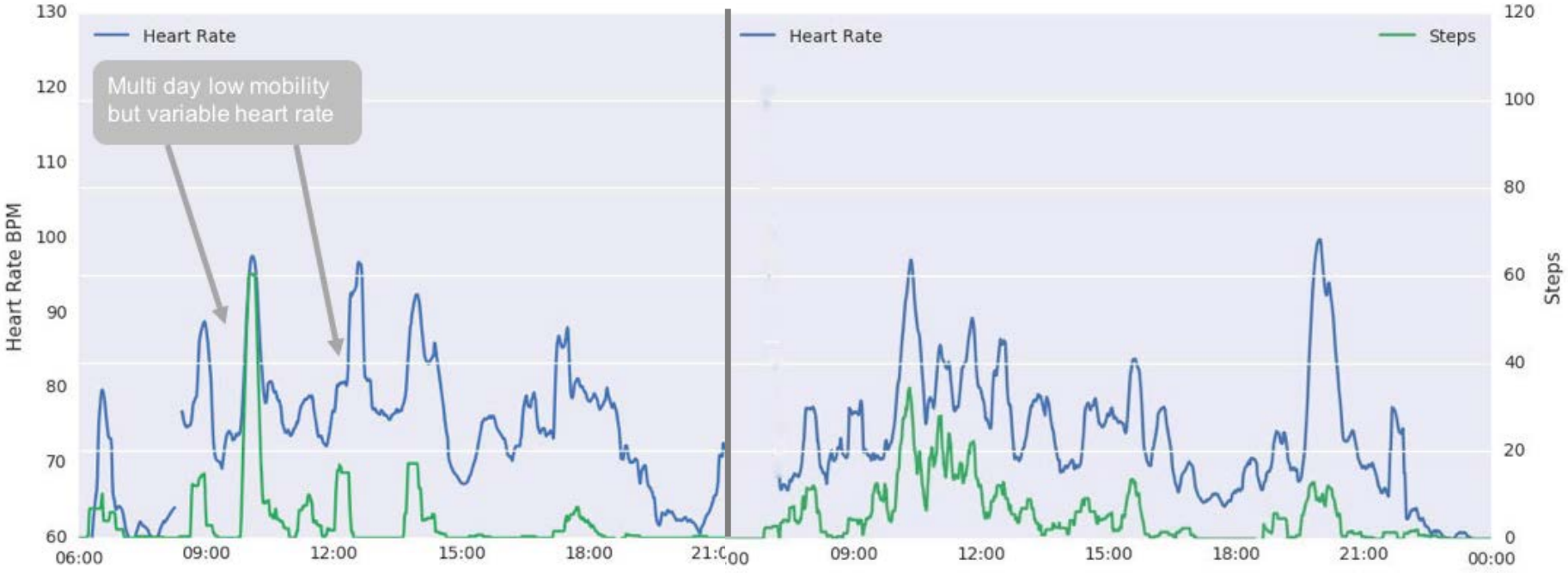


Patient 1: “Normal Day” and “Bad Day”?



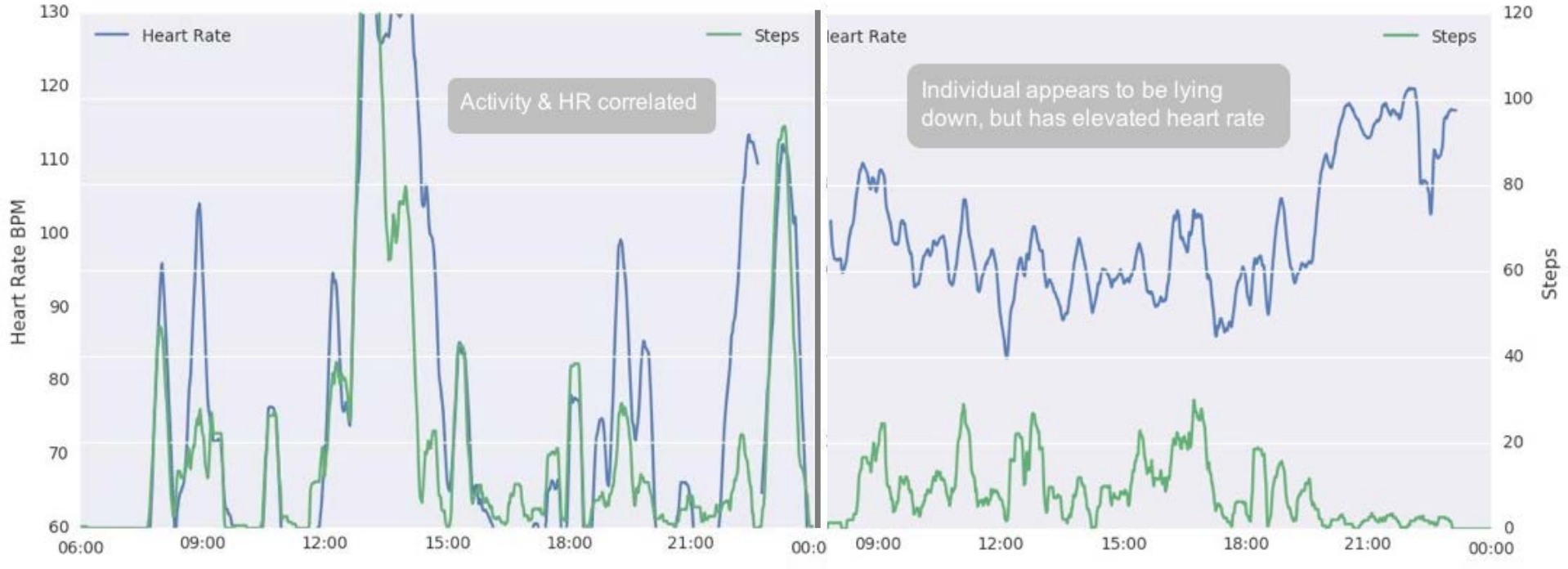
Day 1: **Day 2:**

Patient 2: Two “Normal” Days?



Day 1: **Day 2:**

Patient: “Normal Day” and “Bad Day”



Day 1:

Day 2:

Case Study 4:

PASS / PAES and Disease Registry Alternative

Situation

- As a condition of approval, the FDA required a client to monitor and report the occurrence of a specific type of cancer in patients exposed to their drug.
- The client pharma was unable to get a sufficient number of their patients enrolled in a drug-specific registry to monitor this cancer occurrence

Approach

- QuintilesIMS implemented an alternate approach leveraging State Cancer Registries.
- Solution involved linking up to 40 State Cancer Registry patients to IMS's real world data reporting on the client's drug.
- The linked patients' incidence of cancer will be compared to a control population in the RWD for reporting to the FDA

Results

- IMS has received IRB approval and FDA acceptance of the approach, and is in the process of linking the State Cancer Registry data to enable the protocol execution in 2017.

Case Study 5:
Product Value Demonstration

United States

Conceptual framework – American Society of Clinical Oncology (ASCO)

DrugAbacus – Memorial Sloan Kettering Cancer Center (MSKCC)

Building blocks – National Comprehensive Cancer Network (NCCN)

Value Assessment Project – Institute for Clinical and Economic Review (ICER)

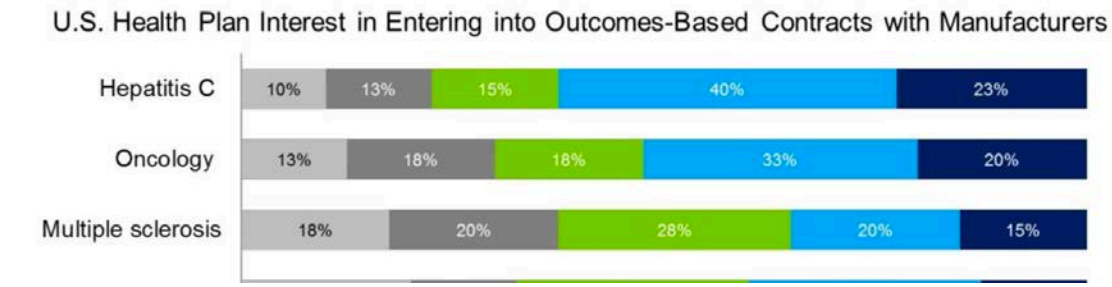
Europe

PASKWIL criteria – Nederlandse Vereniging voor Medische Oncologie (NVMO; Netherlands)

Prioritisation Tool – National Cancer Drugs Fund (NHS, England) VBP / VBA Failure

Magnitude of Clinical Benefit Scale – European Society for Medical Oncology (ESMO-MCBS)

Case Study 5:
Product Value Demonstration



Cigna inks outcome-based payment contracts with makers of Praluent, Repatha

Under the contracts, if Cigna patients don't see cholesterol reduction in-line with numbers seen in clinical trials, the manufacturers will discount the cost of the drugs. If the treatments deliver, the original negotiated price will remain in place.

Inovalon Announces Agreement with Bristol-Myers Squibb to Focus on Real World Outcomes & Value-Based Contracting Initiatives

BOWIE, M.D. – May 19, 2016 – Inovalon (Nasdaq: INOV), a leading technology company providing advanced, cloud-based analytics and data-driven intervention platforms to the healthcare industry, today announced that it has entered into an agreement with Bristol-Myers Squibb (NYSE: BMY), a global BioPharma company, to bring Inovalon and Avalere's combined capabilities to bear on supporting real-world outcomes and value-based contracting initiatives.

The engagement will leverage the capabilities of Inovalon's data platforms and Avalere's extensive industry experience, to support Bristol-Myers Squibb's real-world outcomes and value-based contracting initiatives. The application of advanced predictive analytics modeling and large scale real-world outcomes analyses will support consideration of value-based contracts with innovative payers. Inovalon's national-scale clinical and quality outcomes platforms will allow for real-world insight into the monitoring, reporting, administration, and improvement of outcomes.

Parting Thought

"In God we trust. All others must bring data."

- *W. Edwards Deming, Statistician*