# Reality and Real-World Data

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**Disclaimer**: This presentation contains my personal views only

# Overview

- Real-World Data: the by-now-fairly-familar story
- Reality and RWD: mind the gap?
- Research (on research)[1]

1 Hemkens et al, Routinely collected data and comparative effectiveness evidence: promises and limitations, CMAJ 2016, 188(8):E158-164

# What has been driving the focus on RWD?

## Significant changes in health care

| | | |
|---|---|---|
| SUPPLY | **Accelerated health care IT uptake** | Growing electronic health information infrastructure enabling routine collection of digital data at the point of patient care |
| DEMAND | **More challenging drug development** | Drug discovery and development is longer and more costly |
| DEMAND | **Calls for accelerated Regulatory approval** | Expectations from policy-makers and patient groups to shorten time to patients in some disease areas |
| DEMAND | **Changing Access expectations** | Payers focusing on value over volume and wanting to understand comparative effectiveness, not just benefit/risk |
| DEMAND | **Increasing patient engagement** | Patients are more involved than ever before in their own care decisions and the push for more personalized treatments |

# RWD quality and access are improving

## Claims

**Insurance Payer Data**

Disease diagnoses

Procedures

Medications

Costs

- Collected for insurance and reimbursement purposes
- Often include a number of health plans
- Often with >10million currently enrolled pts
- Often unable to validate outcome and case definition with chart

TRUVEN HEALTH ANALYTICS

KAISER PERMANENTE

OPTUM

JMDC

QuintilesIMS formerly known as IMS Health

## EMR

**Electronic Medical Records**

Disease diagnoses

Biomarker test results

Treatments

Clinical outcomes

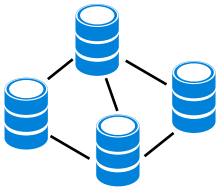
- Data collected for quality of care, performance measure, utilization, clinical research
- Some include all patient records from GP, specialty care visits, medications, in-patient stays, labs, etc.. But some only GP records
- Valuable details in unstructured data (notes)

GE Healthcare

MDV medical.data.vision

CPRD MORE DIMENSIONS TO DATA

FLATIRON



## Registries

**Linked from Multiple Sources**

Disease and/or geographic focus

Biomarker test results

Treatments

Clinical outcomes

- Can be disease-specific or product-specific
- Variable accessibility
- Essential to study rare conditions

SEER

American Academy of Ophthalmology The Eye M.D. Association

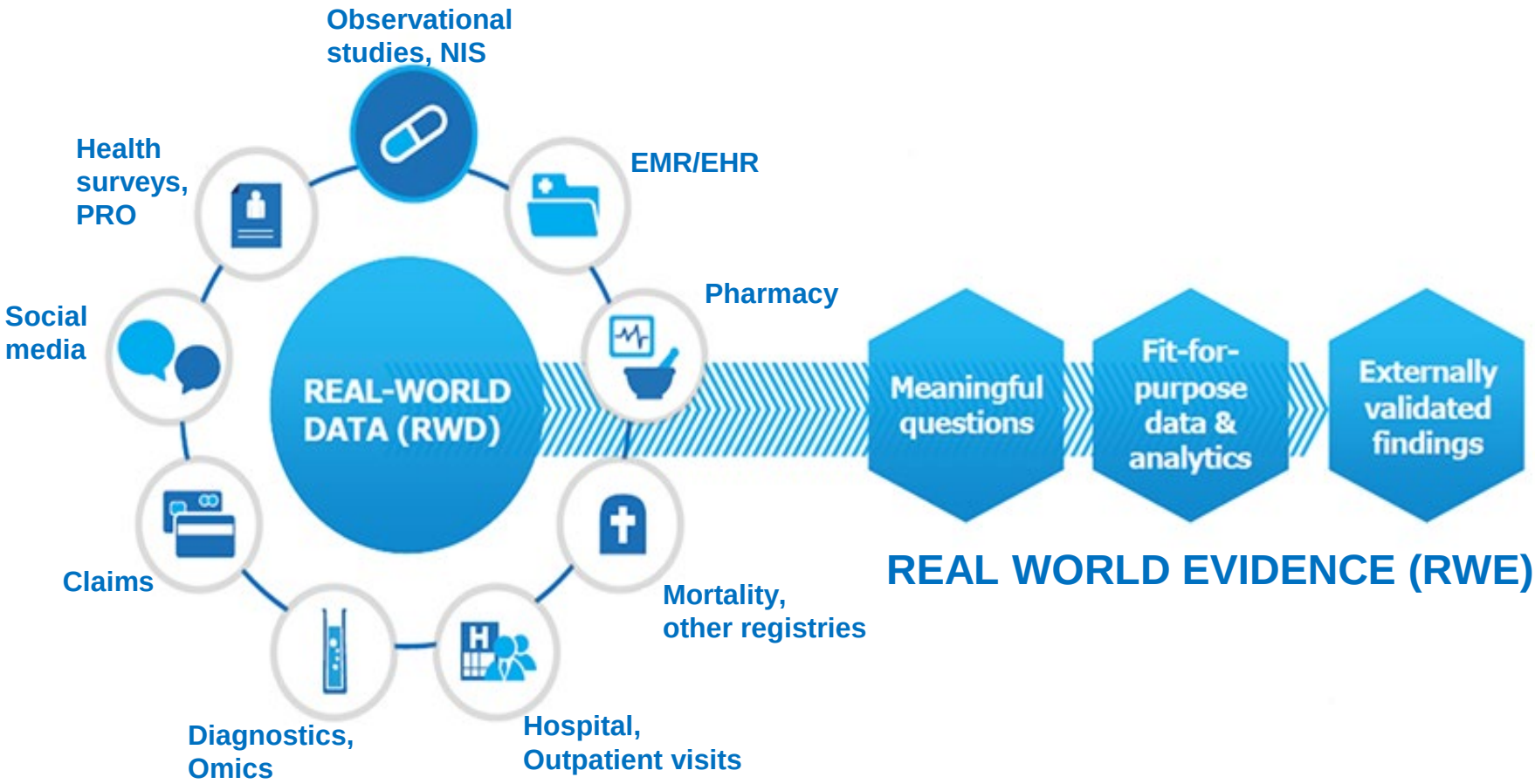
Enroll-HD

MSBase Multiple Sclerosis dataBase

eurIPFreg

**Real-World Data analysis enables quantification of clinical and health economic value of products in the real-world clinical settings.**

# Linkage has great potential to increase the value of RWD



# Methods and analytics are also promising to deliver from RWD

McKinsey&Company April 2013

## How big data can revolutionize pharmaceutical R&D

Sharpen focus on real-world evidence

Real-world outcomes are becoming more important to pharmaceutical companies as payors increasingly impose value-based pricing. These companies should respond to this cost-benefit pressure by pursuing drugs for which they can show differentiation through

## Observational Studies Analyzed Like Randomized Experiments

*An Application to Postmenopausal Hormone Therapy and Coronary Heart Disease*

*Miguel A. Hernán,[a,b] Alvaro Alonso,[c] Roger Logan,[a] Francine Grodstein,[a,d] Karin B. Michels,[a,d,e] Walter C. Willett,[a,d,f] JoAnn E. Manson,[a,d,g] and James M. Robins[a,h]*

*Epidemiology* • Volume 19, Number 6, November 2008

News room News releases

## MD Anderson Taps IBM Watson to Power "Moon Shots" Mission Aimed at Ending Cancer, Starting with Leukemia

**Big Data Insights to Help Accelerate Translation of Cancer-Fighting Knowledge to Cutting Edge Medical Practices**

**HOUSTON - 18 Oct 2013:** The University of Texas MD Anderson Cancer Center and IBM (NYSE: IBM) today an the IBM Watson cognitive computing system for its mission to eradicate cancer. Following a year-long collaboratic showcase a prototype of MD Anderson's Oncology Expert Advisor™ powered by IBM Watson. The organizations leverage Watson's cognitive computing power to help patients by enabling clinicians to uncover valuable insights and research databases.

## Using observational data to emulate a randomized trial of dynamic treatment-switching strategies: an application to antiretroviral therapy

**Writing committee: Lauren E Cain,[1]* Michael S Saag,[2] Maya Petersen,[3]**

*International Journal of Epidemiology*, 2016, 2038–2049
doi: 10.1093/ije/dyv295

DeepMind Health

University College London Hospital NHS Trust

**University College London Hospital** has one of the largest centres for head and neck cancers in England and is a world leader in oncology research.

Research **Open Access**

## Comparison between logistic regression and neural networks to predict death in patients with suspected sepsis in the emergency room

Fabián Jaimes[1], Jorge Farbiarz[2], Diego Alvarez[3] and Carlos Martínez[4]

*Critical Care* 2005, **9**:R150-R156 (DOI 10.1186/cc3054)

# RWD will impact all stages and stakeholders in drug development

## R&D

**R&D targeted** towards areas of unmet need

Better, earlier, understanding of the potential **impact and long term outcomes of treatments**

**Faster, smaller trials** in better-targeted patient groups

## Regulator

Opportunity to support **early access schemes** and adaptive licensing

Enhanced post-marketing **surveillance of quality and safety**

## Payer

**More effective reimbursement** based on the value of medicines to patients, healthcare, and wider society

Enable **outcomes-based payments**

## Physician

**Treatment optimisation** (e.g. tailoring treatment for patient sub-groups and using the most appropriate dosage)

## Patient

**Access to most appropriate treatment** based on safety, convenience, clinical outcomes and patient preference

# Reality check: mind the gap?[1]


- Expectations >> delivery so far
- Decision-makers are cautious – perhaps not in principle, but certainly in practice
- Epidemiology still suffers from an image problem
- Methods progress has been impressive but we face a data bottleneck
- We risk being enamoured of tech and methods, at risk of not tackling the data problems
- Progress will be incremental, not disruptive
- Ultimately, this is a health-systems issue

1 Let me reiterate…a personal perspective.

# Regulators are still exploring...

## PDUFA VI (2018-2022)

As we participate in the current data revolution, it is important that **FDA consider the possibilities of using so-called "real world"** data as an important tool in evaluating not only the safety of medications but also their effectiveness.

To accomplish this will require an understanding of **what questions to ask**, including **how such data can be generated and used appropriately** in product evaluation, **what the challenges are** to appropriate generation and use of these data, and **how to address such challenges**."

## 21ST CENTURY CURES (2016)

**Utilizing Real World Evidence**
The Secretary shell establish a program to **evaluate the potential use of real world evidence**

- To help support the approval of a new indication for a drug approved under section 505(c);
- To help to support or satisfy post-approval study requirements

In this section, the term 'real world evidence' means data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than randomized clinical trials

## FINAL REPORT ON THE ADAPTIVE PATHWAYS PILOT (2016)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

The majority of the plans were vague in terms of the purpose of collection of real world data to supplement RCTs, and on the practical elements for implementation there was insufficient detail in the submitted proposals to explore the refinement of the safety profile, and even less about to what extent efficacy could be confirmed or augmented in the post-authorisation phase. A critical discussion on the quality, potential for bias, and reliability of the data acquired in the post authorisation setting, and their suitability for regulatory and HTA purpose, was lacking. The few submitted proposals relied mostly on a traditional registry paradigm, geared towards the confirmation of conditional marketing authorisation or the reimbursement/effectiveness link.

# Many RWD initiatives…with risk of overload and fragmentation


EMA 2016 (http://ec.europa.eu/health/files/committee/stamp/2016-03_stamp4/4_real_world_evidence_background_paper.pdf)

# Epidemiology's image problem

*Cartoons removed. Feel free to Google them (references / links left below).*

Cartoon by Jim Borgman, first published by the Cincinnati Inquirer and King Features Syndicate 1997 Apr 27; Forum section: 1 and reprinted in the New York Times, 27 April 1997, E4.

**The RCT paradigm:**

No RCT is perfect but **we all know and abide by the rules**

**The RWD paradigm:**

No RWD analysis is perfect and we all have **different opinions** on how to analyze it and different ways of analyzing it can give us **different results** so we can spend months **arguing about the findings** and **never really reach agreement**

https://xkcd.com/882/

# Epidemiology's image problem

## Evidence of heterogeneity of results across study designs, holding dataset constant

**Exposure to Oral Bisphosphonates and Risk of Esophageal Cancer**

Chris R. Cardwell, PhD
Christian C. Abnet, PhD
Marie M. Cantwell, PhD
Liam J. Murray, MD

JAMA, August 11, 2010—Vol 304, No. 6

- Cohort study in CPRD
- Study period 1996-2006
- **RR oesophageal cancer = 1.07 (0.74-1.25)**
- "The use of oral bisphosphonates was not significantly associated with incident esophageal…cancer "

**Oral bisphosphonates and risk of cancer of oesophagus, stomach, and colorectum: case-control analysis within a UK primary care cohort**

Jane Green, clinical epidemiologist,[1] Gabriela Czanner, statistician,[1] Gillian Reeves, statistical epidemiologist,[1] Joanna Watson, epidemiologist,[1] Lesley Wise, manager, Pharmacoepidemiology Research and Intelligence Unit,[2] Valerie Beral, professor of cancer epidemiology[1]

Cite this as: *BMJ* 2010;341:c4444
doi:10.1136/bmj.c4444

- Case-control study in CPRD
- Study period 1995-2005
- **OR oesophageal cancer = 1.30 (1.02-1.66)**
- "We found a significantly increased risk of oesophageal cancer in people with… prescriptions for oral bisphosphonates

# Epidemiology's image problem

## Evidence of heterogeneity of results across datasets, holding study design constant

**Evaluating the Impact of Database Heterogeneity on Observational Study Results**

David Madigan*, Patrick B. Ryan, Martijn Schuemie, Paul E. Stang, J. Marc Overhage, Abraham G. Hartzema, Marc A. Suchard, William DuMouchel, and Jesse A. Berlin

*Am J Epidemiol.* 2013;178(4):645–651

- **OMOP-led study**
- Looked at **53 drug-outcome pairs in 10 big observationa**l databases (2 to 90 million lives covered)
- Applied 2 classic study designs (cohort study, self-controlled case series)
- Statistically significant decreased risk and statistically significant increased risk in different datasets for 21% of drug-outcome pairs in cohort design and 36% in self-controlled case series design
- **"Attention is needed to consider how th**e choice of data source may be affecting results**"**

# D is the challenge...

## DATA QUALITY

- Primary use of most RWD still not research
- Limited incentives for the “data generator” to pay attention to quality

## DATA LINKAGE

- Fundamental issues with data ownership and governance
- Genuine concerns about data privacy
- Technical challenges to operationalize linkage
- Limited incentives to routinely link data

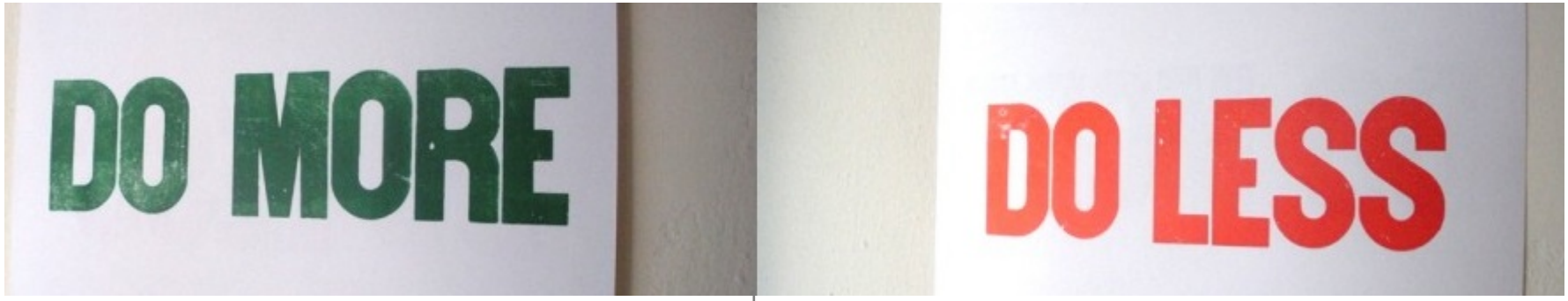
## DATA VOLUME

- Most health RWD so far is “small data”
- Applying new methods to understand heterogeneity, etc. needs truly big data

## BUT THERE ARE PROMISING DEVELOPMENTS

- Improving quality of patient/person-generated data
- Start-ups for patients to consent to linkage and control their own health data
- Emerging methods for managing data access  more effectively

# More research




- **Data quality assessments**
  - And share/publish
- **Behavioural research**
  - Patient & HCP willingness to share
  - Nudge policies
- **Individual-generated data**
  - Quality assessment
  - Analytics and reliable inference
- **Piloting incentive schemes**
  - Identify value of RWD for all actors, from patient to payor
- **Pilot evaluations**
  - Tackle as a health-systems research problem

- **Epidemiological methods research with marginal anticipated gain**
  - To refine existing methods AKA get another paper out