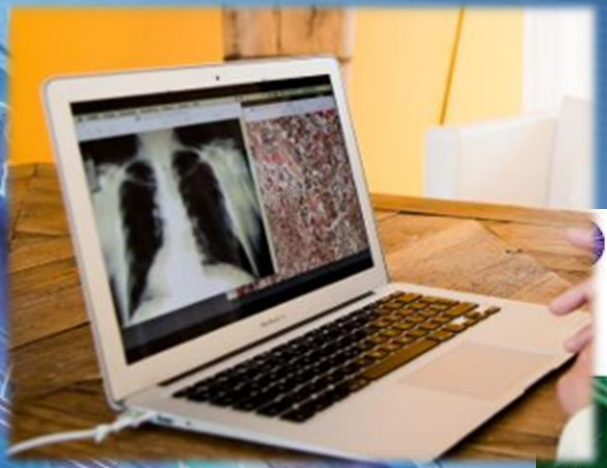
9th China International Medical Device Regulatory Forum

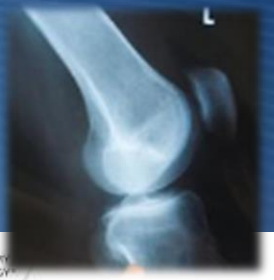
Real World Evidence:
Bringing Real World Opportunities for IVDs

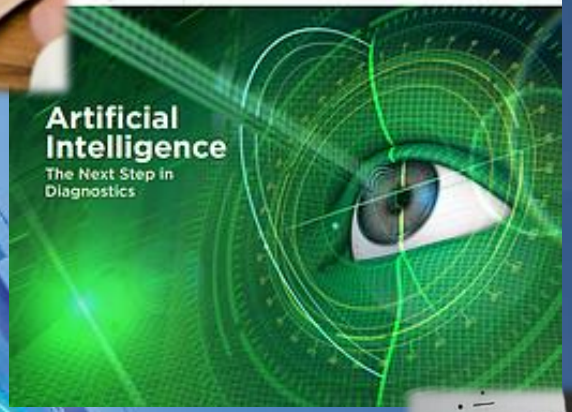
Tracy Bush for Lesley Maloney, Pharm.D., Head, U.S. Regulatory Policy

September 2018

Technology is transforming health care







Technology can help address challenges…

…..but only if regulatory approaches can keep pace

There is a need for scientific insight and knowledge, beyond the traditional clinical trial setting

Progress in science is outrunning the ability of using traditional clinical trials to generate the knowledge required to efficiently translate science into next-generation treatments, regulate drugs or to make informed reimbursement and treatment decisions

RWD: a “Hot Topic” all of a sudden?

- **1) RWD as a concept is not new (we have actually been using it for a long time in certain contexts)**
- **2) What is new:**
  - The ability to access RWD on new, deeper levels than before in addition to newer sources RWD
  - Availability of highly sophisticated and advanced electronic tools to analyze, integrate and link data sources
  - New possibilities to use RWD as an alternative data source in Healthcare sector is what is therefore really new
- **3) RCTs have considerable limitations which drive the need for alternative data sources:**
  - Only ~4% of all patients take part in clinical trials
  - RCT populations rarely reflect “real world” populations - conducted in highly controlled settings and do not reflect day to day realities of care outside of medical care system
  - Occur within a limited time frame and don’t allow insight into long-term clinical effects or effects of multiple Tx
  - Not large enough to detect rare treatment effects
  - May not be generating evidence on endpoints that are truly useful to patients, providers, or payers
  - Not always ethical to have patients on placebo or not enough patients to sufficiently power a trial (e.g. rare diseases)
  - Multitude of questions remain unanswered at the time of Regulatory approval
    - Optimal dosing regimens, long-term outcomes, outcomes in various subpopulations etc etc etc

Growing excitement for RWD, with promising developments

Excitement for RWD amongst the healthcare community has increased, triggered by several key developments.

Increasing availability and quality of RWD in electronic form

Emergence of tools for advanced analysis of large volumes of data

Increasing limitations of clinical trials, for example, due to feasibility, time and costs

Increasing appreciation of the potential value of RWD for patient health and healthcare systems

There is growing consensus across the healthcare ecosystem that PHC is the future.

"There is an increasing drive **to improve collection, sharing and use of patients' data** in order to achieve better, more sustainable healthcare and advance health research. **The only way to do this in a meaningful and valuable way is together with patients**."

EPF European Patients Forum

Scripps Translational Science Institute

"**It's not the data, it's the analytics**. Up until three-to-five years ago, all that data was just sitting there. Now it's being analyzed and interpreted. **It's the most radical change happening in health care**."

"Use of **RWD** would give patients and providers the **access to near-real-time, post-market information that can better inform their decisions**. Such an enterprise can not only support our evaluation of **safety and benefit using data derived from real-world settings**, but it can also make the development of **new innovations more efficient**."

FDA

United States

- FDA **most advanced** Agency with respect to RWE
- Use of RWE as basis for Regulatory decision making initiated in field of **medical devices**
  - Guideline on use of RWE to support regulatory decision making for medical devices published 31 August 2017
  - Other guidance's in area of RWD exits e.g. use of EHR data
- Long and significant experience in post market safety with Sentinel System Network
- Key legislative drivers (21st Century Cures Act and PDUFA VI commitment) both direct FDA to engage with stakeholders, establish a working framework and **prepare draft guidance on RWE by 2021**
- New **FDA RWE Committee** available for informal discussions on RWE proposals
- New (Nov 2018) FDA released code & technical roadmap to allow researchers and app developers to use **agency's newly created RWD app** that helps link RWD with EHD

"*As the breadth and reliability of RWE increases, so do the opportunities for FDA to make use of this information……" "…. there's nothing in our statute or regulations that prevent FDA from using a broad range of informative sources of evidence*" **FDA Commissioner Scott Gottlieb, September 19, 2017**

21st Century Cures Act: Requires FDA to establish a program to evaluate potential use of RWE to:

- Help support the approval of new indications for an approved drug
- Help support or satisfy post approval study requirements
- **FDA must:** *develop framework for this program by end of 2018 and develop draft RWE guidance by end 2021*

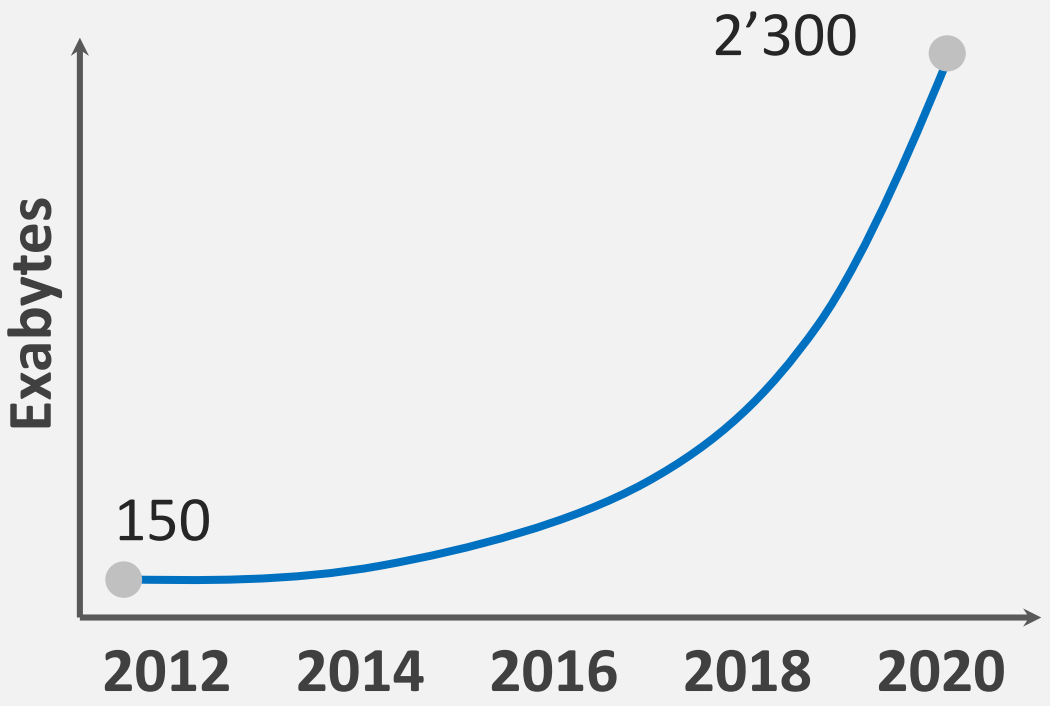
PDUFA VI Commitments: Requires FDA to Enhance use of RWE in regulatory decision making:

- **FDA must:** *Conduct a public workshop, initiate appropriate activities and issue draft guidance on use of RWE for regulatory decision making by end of 2021*

The New Data and Technology Environment are Creating new Opportunities for RWD

1 Exabyte = 1 billion Gigabyte!

HEALTHCARE DATA[1]



The number of **health & fitness tracker** sold worldwide has **more than tripled** from 26m in 2014 to **87 million in 2017**[4]

In the US, **EHR adoption in oncology** clinics has increased from ~10% **to >95%**[3]

Kaiser Permanente, … is believed to have **between 26.5 and 44 petabytes of […] rich data from EHRs**, including images and annotations[2]

1. International Data Corporation, US only; 2. Big data analytics in healthcare: promise and potential (Raghupathi and Raghupathi); 3. ONC/American Hospital Association (AHA), AHA Annual Survey Information Technology Supplement; 4. Statista.com

RWD has potential benefits for all healthcare stakeholders

All stakeholders in the healthcare system stand to gain from harnessing RWD's powerful potential.

- Patient and healthcare providers
- Payers/Health Technology Assessment (HTA) organisations
- Healthcare regulators
- Healthcare companies
- Policy makers

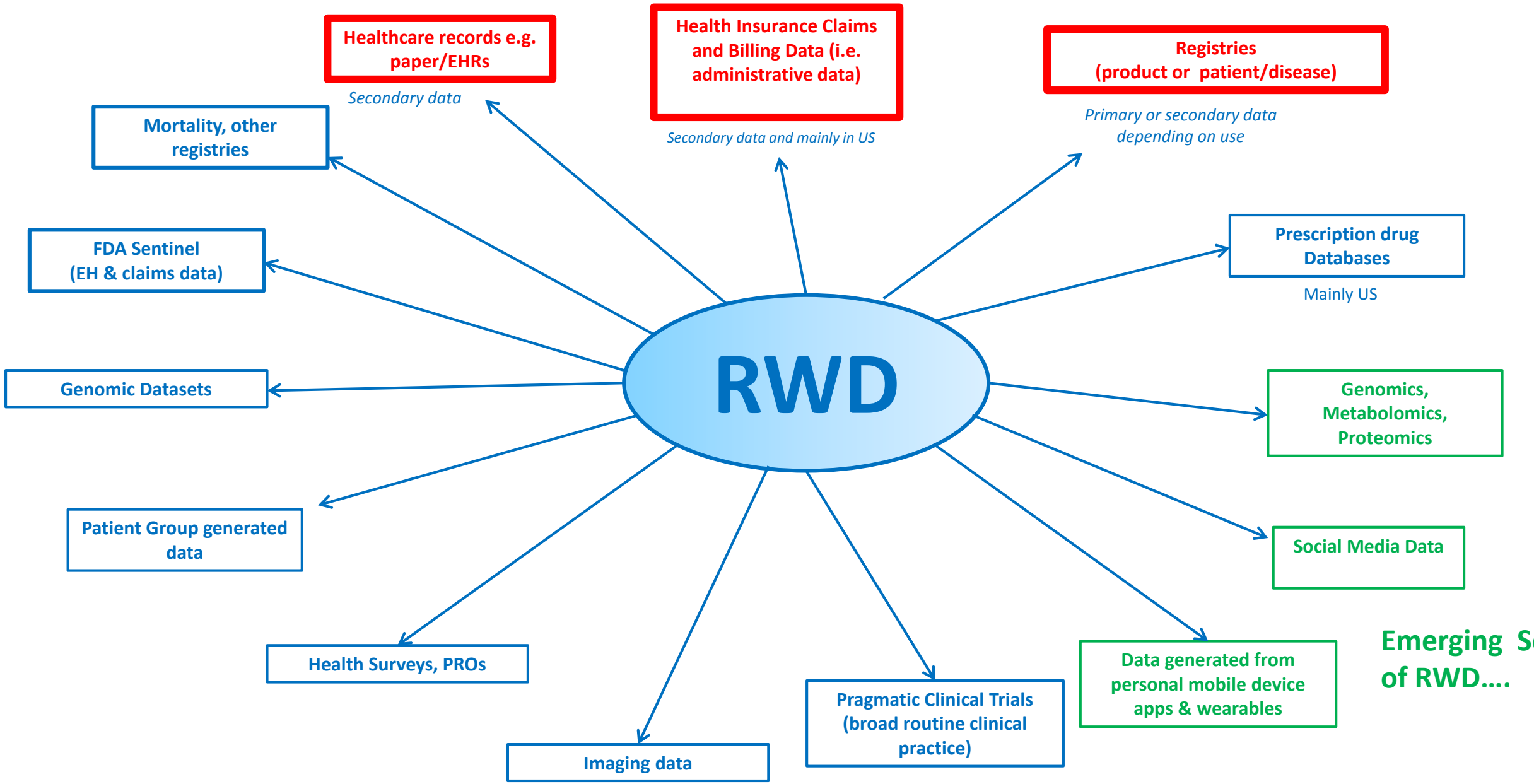
Real World Data (RWD)

Data relating to patient health status and/or the delivery of health care **routinely collected** from a variety of sources.[1]

Sources can include EHRs, administrative and claims data, registries, and patient-generated data.

[1] Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices – Guidance for Industry and Food and Drug Administration Staff. Accessed July 11, 2018. https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm513027.pdf

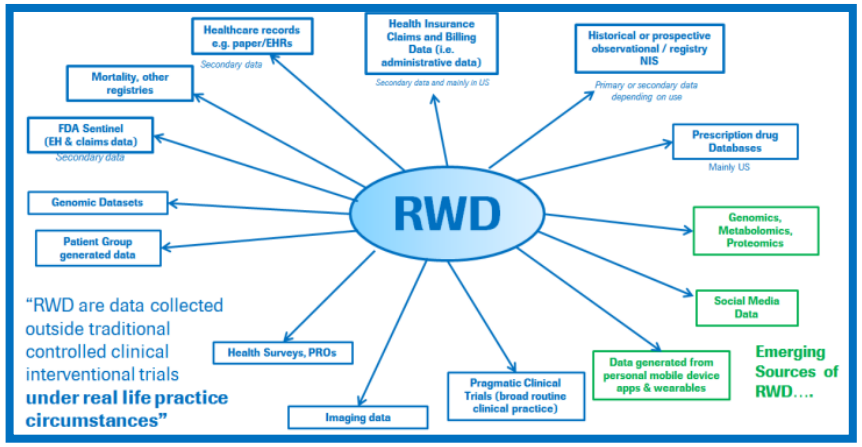
Sources of RWD



Real World Evidence (RWE)

RWE = Evidence derived from RWD (remember data on its own means nothing!)

FDA definition (Federal Food, Drug, and Cosmetic Act (FD&C Act): "*RWE is the clinical evidence regarding the usage and potential benefits or risks of a product derived from analysis of RWD*"



Analytics and Analysis of RWD through various methodologies addressing key research questions

RWE

To drive even greater insights from RWD – the key is to be able to **INTEGRATE and LINK various sources of RWD**

IMPORTANT TO KNOW!

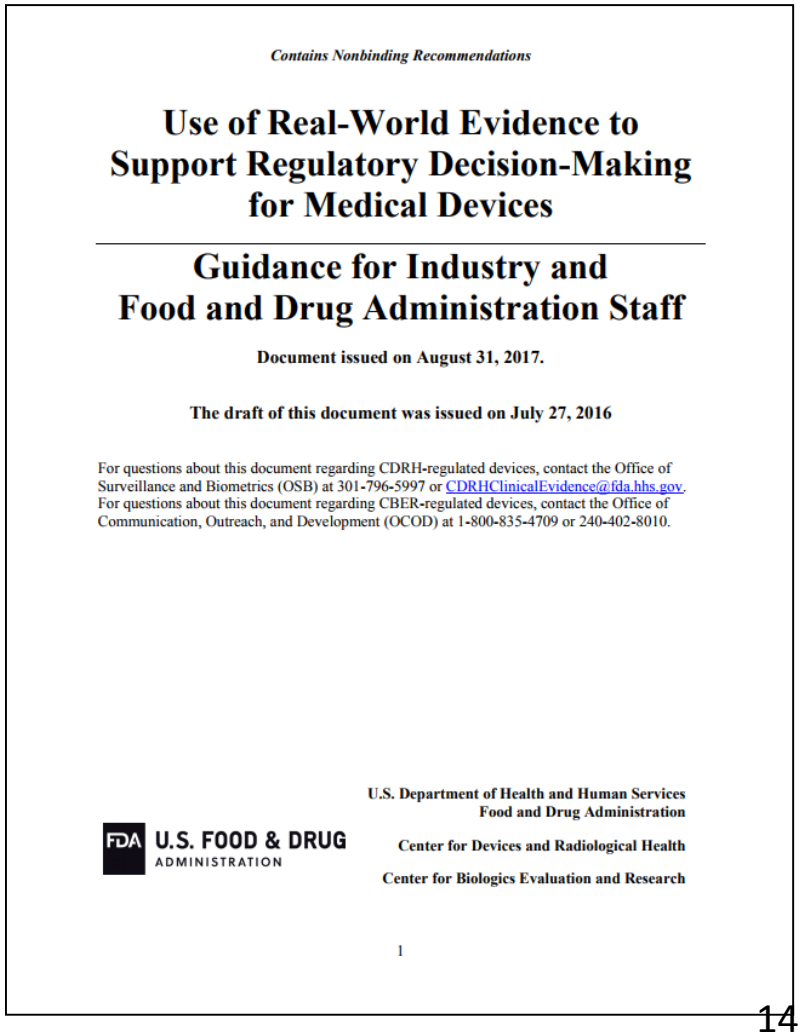
Up to **50% of EHR data is "unstructured"**… and in most healthcare systems, a majority of the core clinical data is buried in unstructured text notes

- **Multitude of EHR sources** and **entry variations** cause unstructured data:
  - Each hospital, healthcare provider, physician and nurse may have **own style** to describe the patient's condition and development
  - Regional specifics in healthcare systems, **languages and dialects**
  - Many hospitals use **multiple** EHR systems (16 in a recent study*)
- Even if data is structured it isn't **necessarily standardised** (i.e. has a common format)
- Given EHRs are common source of RWD – there is a need to work on **methods to standardise and structure data** (Flatiron, common data model discussions, IMI projects etc)

**Source: HIMSS Analytics*

Current Status of RWE in U.S.
U.S. FDA Final Guidance

- Real World Evidence (RWE)
  - Clinical evidence regarding the usage and potential benefits or risks of a medical product **derived from analysis of RWD**
- Key points
  - RWE **doesn't change evidentiary standard** for U.S. FDA regulatory decision-making
  - U.S. FDA evaluates whether RWE is **sufficient quality to address specific regulatory decision** being considered
    - Quality threshold depends on specific regulatory use
    - "Relevant and reliable"
  - U.S. FDA open to engagement with industry



Contains Nonbinding Recommendations

Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices

Guidance for Industry and Food and Drug Administration Staff

Document issued on August 31, 2017.

The draft of this document was issued on July 27, 2016

For questions about this document regarding CDRH-regulated devices, contact the Office of Surveillance and Biometrics (OSB) at 301-796-5997 or CDRHClinicalEvidence@fda.hhs.gov. For questions about this document regarding CBER-regulated devices, contact the Office of Communication, Outreach, and Development (OCOD) at 1-800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration

FDA U.S. FOOD & DRUG ADMINISTRATION

Center for Devices and Radiological Health

Center for Biologics Evaluation and Research

1

RWD Quality and Relevance

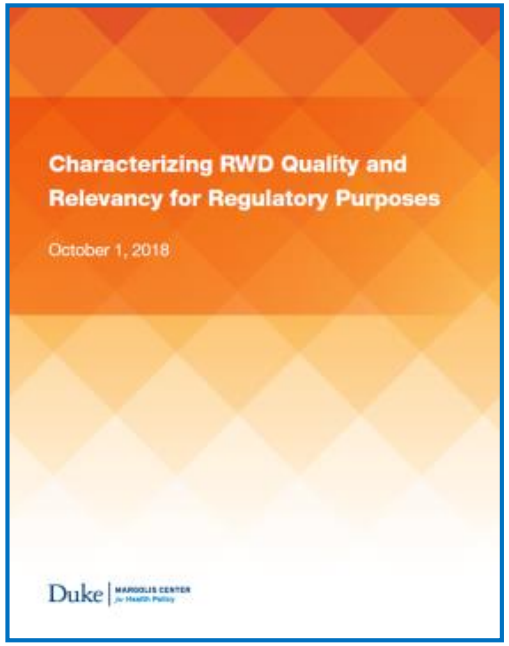
- One of the regulators **top concerns** is the **quality of the data** from is derived

- They want to know:
  - how data are captured
  - whether data points are captured as part of routine clinical practice
  - how consistently they are captured
  - if we can capture in multiple databases to have more confidence as patients move between provider etc

- 2 papers worth reading:
  - Duke Margolis *"Characterizing RWD Quality and Relevancy for Regulatory Purposes"*
  - *"Harnessing the Power of Real-World Evidence (RWE): A Checklist to Ensure "Regulatory-Grade Data Quality"*

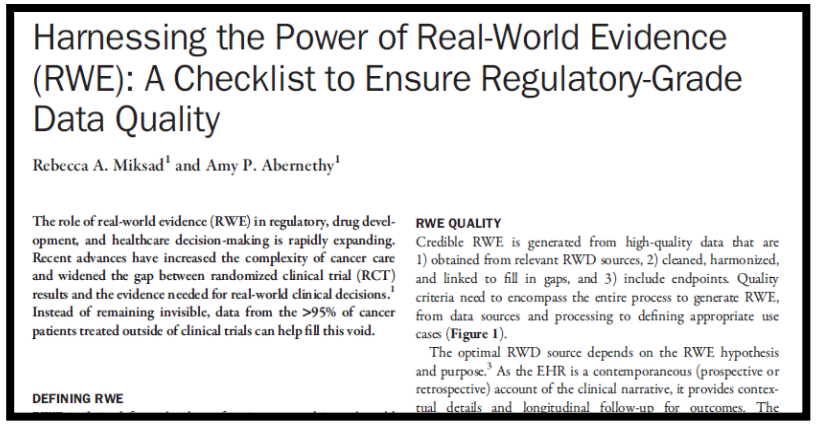
1. Duke Margolis “Characterizing RWD Quality and Relevancy for Regulatory Purposes”

- **Quality**
  - Accuracy (validity of data elements and algorithms used to transform the data)
  - Completeness (extent of missingness)
  - Transparency (of data processing)
- **Relevance**
  - Representative (how representative of the population of interest are the patients in the dataset)
  - Linking (If more than one data source is required, are data fields present that permit accurate linking at the patient-level?)



2. “Regulatory Grade” RWE

- **“Harnessing the Power of Real-World Evidence (RWE): A Checklist to Ensure “Regulatory-Grade Data Quality”**
- Credible RWE is generated from high-quality data that are 1) obtained from relevant RWD sources, 2) cleaned, harmonized, and linked to fill in gaps, and 3) include endpoints
- RWD must be:
  - Of high quality (provenance)
  - Complete (structured and unstructured)
  - Generalizable (as opposed to clinical trials)
  - Timely (especially critical in oncology)
  - Scalable (as data needs increase, system must scale)
  - Transparent (in terms of study and analysis design)



Harnessing the Power of Real-World Evidence (RWE): A Checklist to Ensure Regulatory-Grade Data Quality

Rebecca A. Miksad[1] and Amy P. Abernethy[1]

The role of real-world evidence (RWE) in regulatory, drug development, and healthcare decision-making is rapidly expanding. Recent advances have increased the complexity of cancer care and widened the gap between randomized clinical trial (RCT) results and the evidence needed for real-world clinical decisions.[1] Instead of remaining invisible, data from the >95% of cancer patients treated outside of clinical trials can help fill this void.

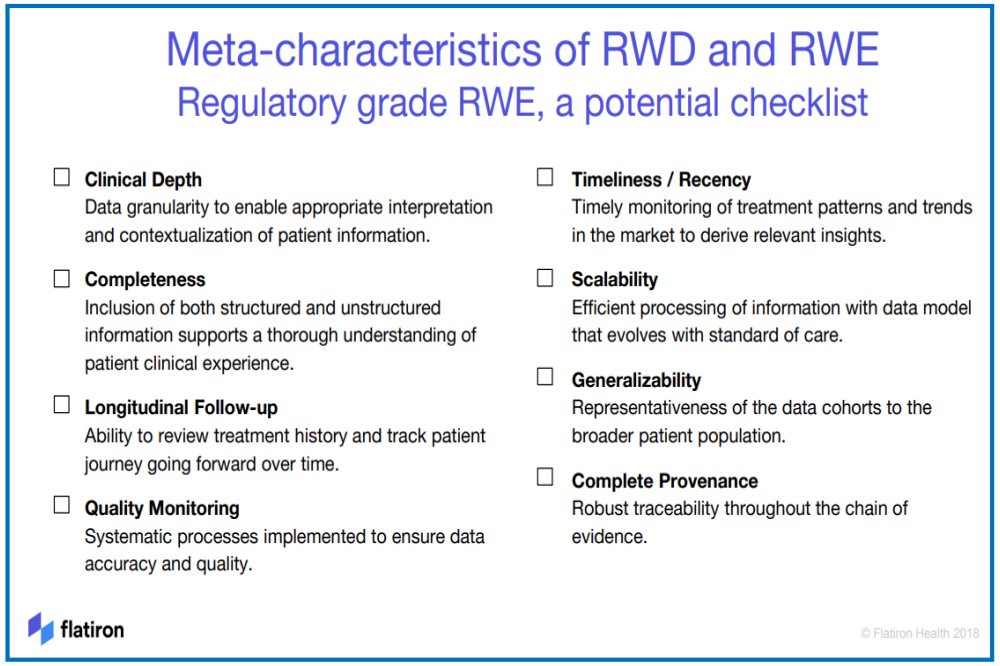
DEFINING RWE

RWE QUALITY

Credible RWE is generated from high-quality data that are 1) obtained from relevant RWD sources, 2) cleaned, harmonized, and linked to fill in gaps, and 3) include endpoints. Quality criteria need to encompass the entire process to generate RWE, from data sources and processing to defining appropriate use cases (**Figure 1**).

The optimal RWD source depends on the RWE hypothesis and purpose.[3] As the EHR is a contemporaneous (prospective or retrospective) account of the clinical narrative, it provides contextual details and longitudinal follow-up for outcomes. The

Miksad and Abernethy. Harnessing the Power of Real-World Evidence (RWE): A Checklist to Ensure Regulatory-Grade Data Quality. Clin Pharmacol Ther. 2018 Feb: 103(2): 202-205.



Meta-characteristics of RWD and RWE

Regulatory grade RWE, a potential checklist

- ☐ **Clinical Depth**
  Data granularity to enable appropriate interpretation and contextualization of patient information.
- ☐ **Completeness**
  Inclusion of both structured and unstructured information supports a thorough understanding of patient clinical experience.
- ☐ **Longitudinal Follow-up**
  Ability to review treatment history and track patient journey going forward over time.
- ☐ **Quality Monitoring**
  Systematic processes implemented to ensure data accuracy and quality.
- ☐ **Timeliness / Recency**
  Timely monitoring of treatment patterns and trends in the market to derive relevant insights.
- ☐ **Scalability**
  Efficient processing of information with data model that evolves with standard of care.
- ☐ **Generalizability**
  Representativeness of the data cohorts to the broader patient population.
- ☐ **Complete Provenance**
  Robust traceability throughout the chain of evidence.

flatiron

Building a Framework for IVDs
Medical Device Innovation Consortium (MDIC)

National Evaluation System for Health Technology (NEST)	IVD RWE Framework
• All medical devices • Focused on **access to RWD** • Demonstration projects	• IVDs • Focused on use of RWD/RWE to support **IVD development and regulatory submissions** • Common terminology and scientific support

Rigorous data analysis techniques are essential for quality and reliability

Concerns exist surrounding the quality and reliability of RWD, as well as the aggregation and analysis of data.

Quality and reliability

- RWD originates from multiple, diverse, non-standardised sources
- Comes in structured and unstructured formats

Data aggregation and analysis

- Link/aggregate/integrate data on a larger scale for analysis
- Significant costs for curation of data
- Non-randomised nature of RWD studies mean they may be subject to potential bias/subjective study design and interpretation

For RWD to be credible, it must meet fundamental criteria

Roche views RWD as a credible source of scientific information and evidence, provided two fundamental criteria are met.

1 The data is of high, fit-for-purpose quality

2 The analysis is subjected to scientifically rigorous study design and analytical methodologies

There is a need to preserve and protect patient privacy

Data anonymisation and pseudonymisation protects privacy, but allows patients to be informed of their insights if desirable.

Anonymisation of RWD

Removes the ability to identify an individual, alleviating concerns around violation of patients' privacy rights

Pseudonymisation of RWD

Enables the anonymisation of data to be reversible in instances where it is appropriate to contact the patient

Data and security challenges during collection, transfer, storage and retrieval of RWD

De-identification, anonymisation and pseudonymisation

Key patient concerns

MDIC IVD RWE Framework
Study Design

- Fit for Purpose Study Design (clinical and regulatory context)
  - Study objectives and specific research questions determine the choice of study design
- Additional considerations
  - Bias
    - Selection
    - Inform (misclassification)
    - Measurement error
  - Confounding
  - Missing data

Roche’s commitment to advancing the field of RWD

Translating RWD into actionable information is an obligation for society as a whole.

Roche is committed to playing its role to advance this field, applying the highest standards and acknowledging that the outcome also may not be favourable for its products

Individual ownership of data should not extend beyond de-identification

Extending individuals' reach over their data beyond de-identification of data would stifle scientific, clinical and health economic research.

An individual's right to exert control over his or her personal health data extends to the rights under the respective privacy laws, but not beyond (unless otherwise agreed)

An individual's right to privacy has been fully respected once the data has been properly de-identified (i.e. anonymised or pseudonymised) – *for more information, see Appendix on slide 40*

Common frameworks are needed for legal and regulatory alignment on RWD

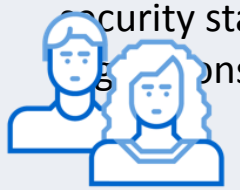
Realising common frameworks will take some time; in the meantime Roche will work with the relevant authorities.

Complexity, diversity and historic development of healthcare systems have led to diverse legal and regulatory frameworks across the globe, pertaining to different aspects of RWD (e.g. data privacy, access and sharing)

The overall success of the RWD promise hinges on a collective effort

Roche strives to build trust by being transparent and forthcoming about its motives and systematic efforts in RWD and working with stakeholders to shape the RWD debate and to foster acceptance .

Working together with industry trade associations and health policy organisations to drive adoption of high quality and ecurity standards/ ons



A pragmatic approach to the use of RWD is essential to allow development of new technologies and products to foster vation

Anticipating policy stakeholder concerns will be critical to effective engagement.

Potential Concern	Mitigation Strategy*
Data Privacy/Security (e.g. patient data not properly anonymized)	• Highlight Roche's/industry's long history of anonymizing, pseudonymizing and controlling access to sensitive patient data.
Data Sharing (e.g. who owns the data; sharing of sensitive data)	• Acknowledge complexity of multi-party data sharing and the need for key stakeholders to co-create appropriate models.
Data Quality (e.g. reluctance to accept RWE as it's not considered "decision grade")	• Share Roche's initial thinking on establishing appropriate standards for the use of RWE in decision-making and our obligation to do so for the betterment of society.
Higher Drug Prices (i.e. PHC has the potential to "create" pricier "super orphan" drugs)	• Highlight the risks and rewards that all stakeholders must consider as we adopt value-based medicine and Roche's desire to co-create a system that unlocks the promise of PHC.

**High-level overview of approach. Please visit supporting documents for details on Roche's position, specific messaging and supporting evidence.*

Policy Ask

A PHC future—that harnesses the power of data to drive health system efficiency and improved patient outcomes—can only be achieved by co-creation of innovative policies and infrastructure.

Roche is excited to leverage its deep healthcare expertise and commitment to PHC and work with governments to establish:

- Legal and regulatory frameworks that support the capture, aggregation, and sharing of meaningful healthcare data;
- Interoperable systems that allow seamless flow of meaningful healthcare data across organizations, institutions and geographies;
- Regulatory pathways and guidance that accept novel types and sources of evidence for timely approval of innovative PHC solutions; and
- Reimbursement pathways and funding models that enable access to advanced diagnostic and personalized treatment options, powered by real world evidence.

**High-level overview of approach. Please visit supporting documents for details on Roche's position, specific messaging and supporting evidence.*

Doing now what patients need next