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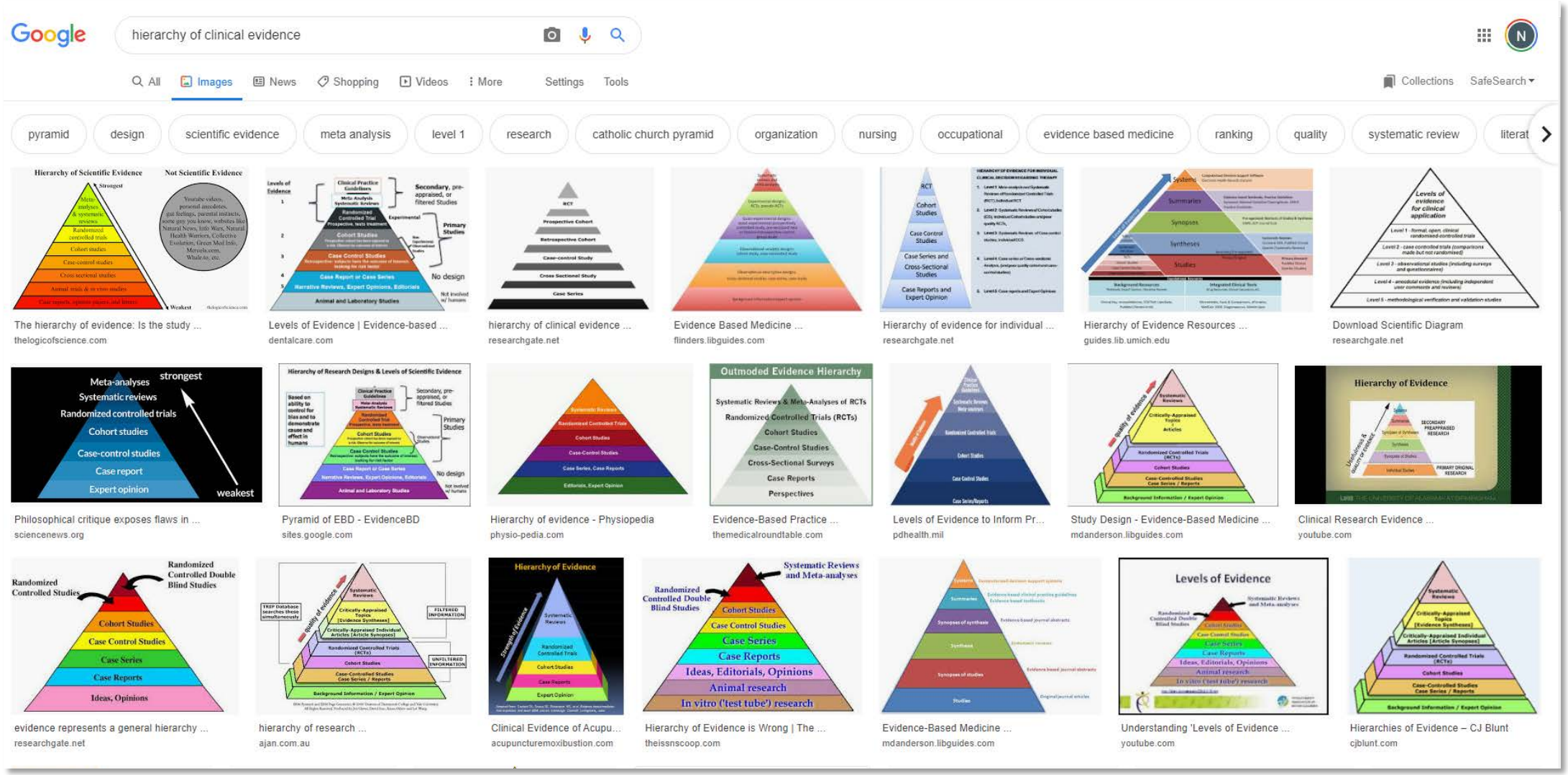
Enabling the Potential of Real World Data

Neil Corner, GM, IQVIA Canada
Nancy Dreyer, Chief Scientific Officer and SVP, IQVIA

Figuring out the correct hierarchy of evidence has refined researchers' PowerPoint skills – but remains locked in a paradigm which ignores the fact that we have been studying the perfect patient in the perfect setting



Source: Google image search October 2019, hierarchy of clinical evidence

Yet regulators are no longer tied to the old paradigm

Scott Gottlieb, Former FDA Commissioner

"Pre- and post market evaluations should be thought of as parts of a continuum rather than as two separate and distinct processes; in particular, he said, the "need for a point of regulatory accountability" should not preclude the possibility of evaluating products over their life cycle of use. RWE offers a way to better inform the benefit–risk profiles for medical products and is already used routinely by FDA to evaluate safety and emerging risk"

"FDA will uphold and promote the "gold standard" for evidence; however, the source of that evidence is not mandated"

Source: **Examining the Impact of Real-World Evidence on Medical Product Development**
I. Incentives *Proceedings of a Workshop—in Brief February 12, 2018*
http://nationalacademies.org/hmd/Activities/Research/DrugForum/2017-SEP-19.aspx.

Health Canada is embracing RWE in a structured logical way, challenging the traditional evidence generation paradigm

The Government of Canada is excited by the potential of using high-quality, real-world evidence to increase timely access to new treatment options for all Canadians, particularly special patient populations."

Ginette Petitpas Taylor, Minister of Health

- *"This project aims to improve our ability to assess and monitor the safety, efficacy, and effectiveness of drugs* ***across the drug life cycle****. It will do this by optimizing the use of RWE through* ***stakeholder engagement"***
- The project is expected to be **complete in 2022** and anticipated outcomes include:
  - Increased use of RWE to enhance regulatory decision making/risk communications through drug lifecycle
  - Improved use and sharing of RWE with health care system partners
  - Increased clarity for stakeholders on where and how RWE can support regulatory decision making
  - Improved access to drugs through the use of new sources of evidence to support drug applications

Sources: Health Canada "Increasing access to new treatments for special patient populations 16-Apr-2019
Health Canada "Strengthening the use of real world evidence for drugs 22-Aug-2018

As part of the initiative, Health Canada with CADTH and INESS has begun the project “optimizing the use of RWE to inform regulatory decision-making

Planned approach for implementation

1. **Developing Guidance for Industry and Data partners**
   - Publishing principles and guidance for industry and data partners on the key data elements needed for decision points across the product life cycle and how HC and industry can work together to optimize RWE use early on in submission discussion
2. **Developing and Implementing a Transparent Approach to Assessing Quality of Evidence**
   - Documenting the approach to assessing quality of evidence submitted across the life cycle
   - Aim to support data producers in collecting the right data of sufficient quality to inform regulatory decision making
3. **A Phased Approach to Implementation**
   - Health Canada already accepts RWE As part of submissions across life cycle, however with the guidance and quality of evidence (QoE) approach clarified, we will work with willing partners to phase in deliberate use of RWE starting with product lines for which use of RWE provides clear value-add to the health system and to Canadians. Lessons learned will be used to optimize the approach for future phases
4. **Working with Partners to Optimize Data Availability**
   - Collaborating with partners to support the development/sharing/optimization of sources with greatest return on investment for Canadians
   - Monitoring the safety and effectiveness ness of medical devices on the market requires data, both to identify signals and proactively assess for potential issues (regulatory/non regulatory solutions will be assessed)

Health Canada CADTH Evidence Driven. INESSS LE SAVOIR PREND FORME IHE INSTITUTE OF HEALTH ECONOMICS ALBERTA CANADA

Source: Adapted from **Defining decision-grade real-world evidence and its role in the Canadian context:** A design sprint
The workshop was held October 21, 2018 in Toronto, Ontario, as a satellite to the 2018 Annual Canadian Association for Population Therapeutics Conference.
The workshop was developed and delivered as a joint partnership between the Canadian Agency for Drugs and Technologies in Health (CADTH); Canadian Association for Population Therapeutics (CAPT), Health Canada, and the Institute of Health Economics (IHE). CADTH and Health Canada provided unrestricted grants to support the workshop; CAPT and the IHE provided in-kind support.

IQVIA®

Health Canada is calling for RWE submissions now for certain situations to develop regulatory RWE policy

Health Canada

Health Canada's Evolving Approach to Leveraging Real World Evidence (RWE) for Drug Regulatory Decisions

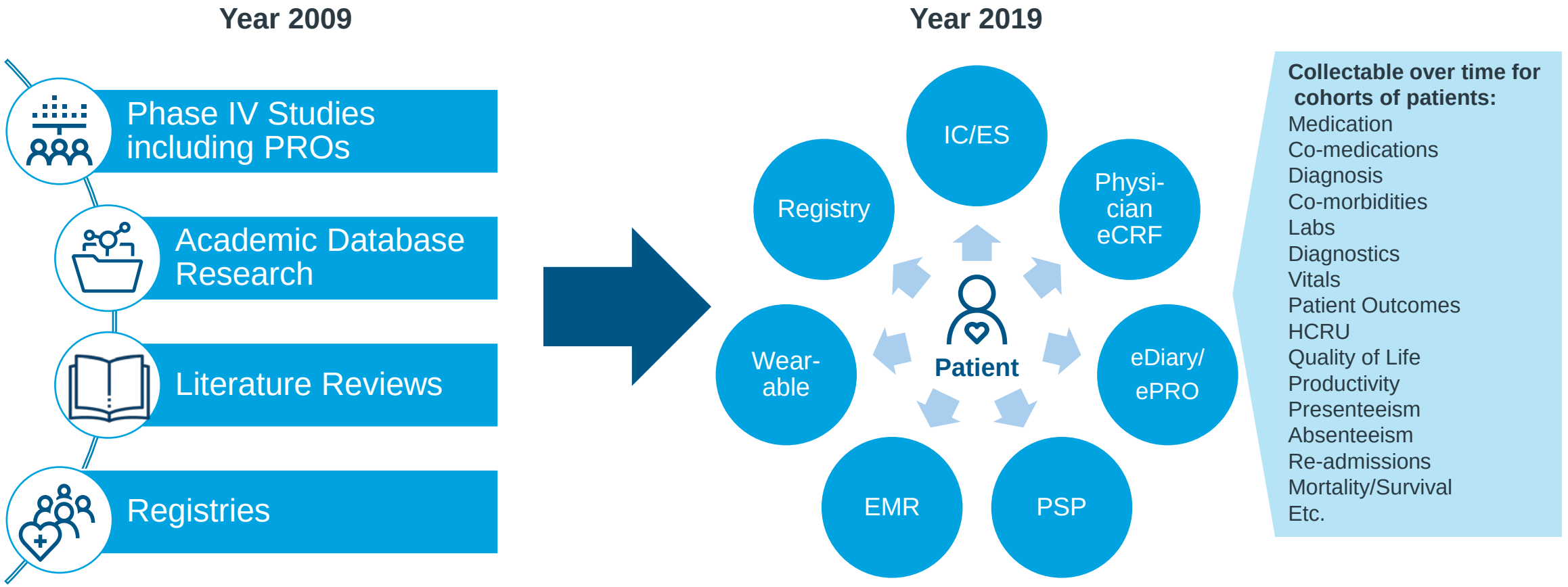
April 16, 2019

"We encourage RWE submissions:

1. That aim to expand evidence-based indications for populations often excluded from clinical trials (ex: children, seniors, and pregnant women)
2. For drugs/diseases where clinical trials are unfeasible such as may be the case with rare diseases
3. Where clinical trials are unethical, as may be the case during emergencies where dosages from animal studies may need to be extrapolated to treat humans potentially exposed to chemical or biological threats."

Source: **Optimizing the Use of Real World Evidence to Inform Regulatory Decision-Making Health Products and Food Branch Notice**
April 16, 2019

Real World Data sources are changing, today the model provides a detailed linked comprehensive view of the patient in the real world enabling regulatory standard data to support evidence generation



Nancy Dreyer, PhD, MPH

Chief Scientific Officer & Senior Vice President, Real-World & Analytic Solutions

Nancy Dreyer leads the Center for Advanced Evidence Generation, focusing on the use of real-world evidence using minimally interventional and non-interventional study designs. Her current interests focus on determining when real-world evidence is reliable enough for regulatory use and innovative study designs to advance understanding about treatment effectiveness and safety

She has worked with the FDA and the European Medicines Agency and was recently appointed to the Clinical Trials Advisory Committee of the Patient-Centered Outcomes Research Institute. She also serves on the Science Advisory Council for DIA and has been a Standing Consultant to the NFL Health and Safety Executive Committee since 2013. She is a Fellow of both the International Society of Pharmacoepidemiology and DIA.

Highly noted publications include her work as co-editor of “Registries for Evaluating Patient Outcomes: a User Guide,” published by the US Agency for Research on Healthcare and Quality, and a highly downloaded 2018 publication on advancing a framework for regulatory use of real-world evidence. She is also know for creating the GRACE Checklist, the only validated checklist for measuring the quality of observational studies of comparative effectiveness.

She is an Adjunct Professor of Epidemiology at the UNC Gillings School of Global Public Health in North Carolina and a two-time recipient of *PharmaVOICE* magazine's annual list of the 100 most influential and inspiring individuals in life sciences. in 2019, she received DIA’s Global Inspire Award for Author of the Year for “Advancing a framework for regulatory use of real world evidence: When real is reliable,” the most downloaded publication in 2018 in Therapeutic Innovation & Regulatory Science.

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CAPT ACTP

Knowing when and how to use real-world data to support medical product approvals and use

Beyond the 1%

Nancy A Dreyer, Chief Scientific Officer
IQVIA Real-World Solutions

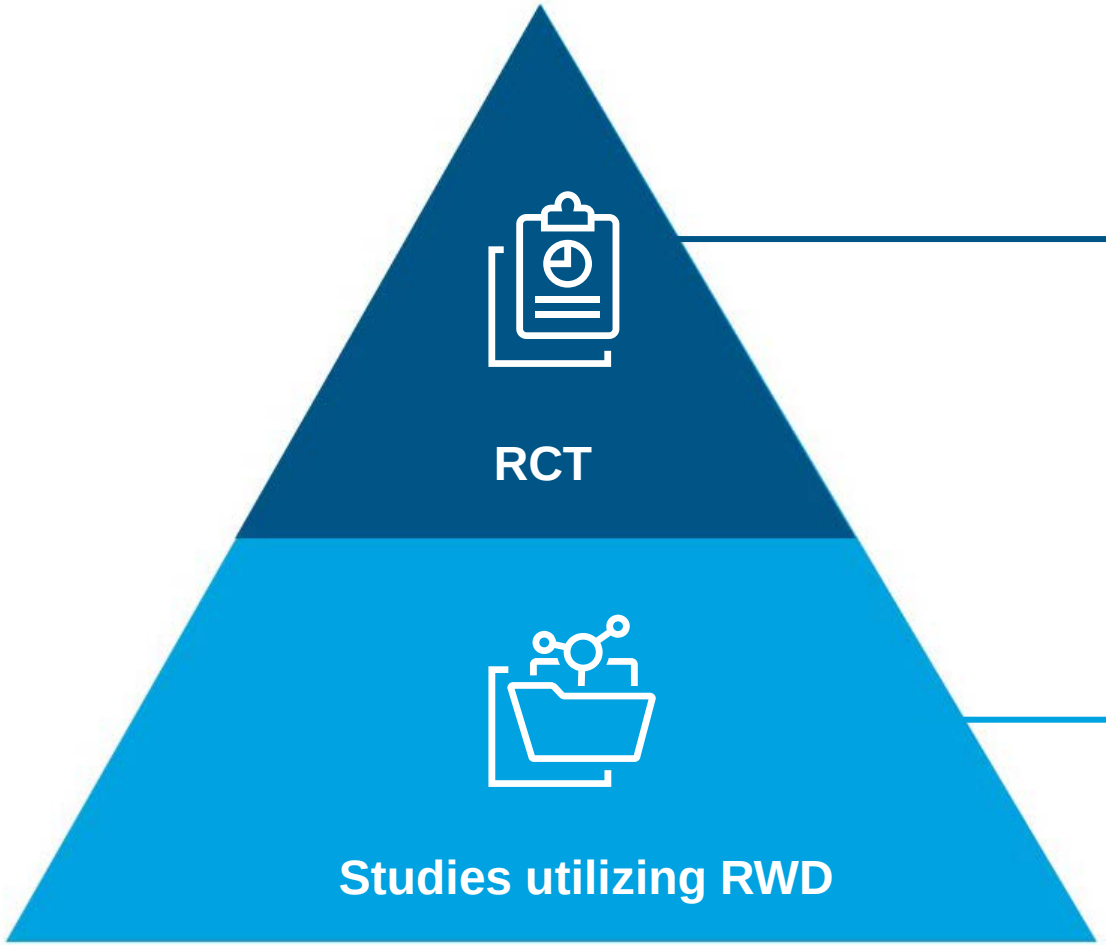
October 21, 2019

Toronto

<1% of the population participates in clinical trials

What does this mean for the rest of us?

Traditional hierarchy of medical evidence ranks RCT as better than non-interventional study designs



Strengths

- **Only treatment varies**
- **Randomization is used to minimize influence of known and unknown confounders**

- Traditionally used for post-market safety/surveillance
- Measures **comparative effectiveness & safety** (no placebo)

Limitations

- Higher costs and resources
- Limited generalizability

- Less confidence in the data, design and analysis
- No guidance exists as yet

Studying treatment effects – time to move beyond study design

RANDOMIZED, CONTROLLED TRIALS, OBSERVATIONAL STUDIES, AND THE HIERARCHY OF RESEARCH DESIGNS

JOHN CONCATO, M.D., M.P.H., NIRAV SHAH, M.D., M.P.H., AND RALPH I. HORWITZ, M.D.

N Engl J Med 2000;342:1887-92

TABLE 2. TOTAL NUMBER OF SUBJECTS AND SUMMARY ESTIMATES FOR THE EFFECT OF FIVE INTERVENTIONS ACCORDING TO THE TYPE OF RESEARCH DESIGN.

CLINICAL TOPIC	TYPE OF STUDY	META-ANALYSIS*	TOTAL NO. OF SUBJECTS	SUMMARY ESTIMATE (95% CI)†
Bacille Calmette–Guérin vaccine and tuberculosis	13 Randomized, controlled	Colditz et al.[14]	359,922	0.49 (0.34–0.70)
	10 Case–control	Colditz et al.[14]	6,511	0.50 (0.39–0.65)
Mammography and mortality from breast cancer	8 Randomized, controlled	Kerlikowske et al.[15]	429,043	0.79 (0.71–0.88)
	4 Case–control	Kerlikowske et al.[15]	132,456	0.61 (0.49–0.77)
Cholesterol levels and death due to trauma	6 Randomized, controlled	Cummings and Psaty[16]	36,910	1.42 (0.94–2.15)
	14 Cohort	Jacobs et al.[17]	9,377	1.40 (1.14–1.66)
Treatment of hypertension and stroke	14 Randomized, controlled	Collins et al.[18]	36,894	0.58 (0.50–0.67)
	7 Cohort	MacMahon et al.[12]	405,511	0.62 (0.60–0.65)
Treatment of hypertension and coronary heart disease	14 Randomized, controlled	Collins et al.[18]	36,894	0.86 (0.78–0.96)
	9 Cohort	MacMahon et al.[12]	418,343	0.77 (0.75–0.80)

*Meta-analyses that included either randomized, controlled trials or observational studies are cited.

†CI denotes confidence interval.

The results of well-designed observational studies do not systematically overestimate the magnitude of the effects of treatment as compared with those in randomized, controlled trials on the same topic.

Cochrane Library

"Our results across all reviews (pooled ROR 1.08) are very similar to results reported by similarly conducted reviews. As such, we have reached similar conclusions; on average, there is little evidence for significant effect estimate differences between observational studies and RCTs…"

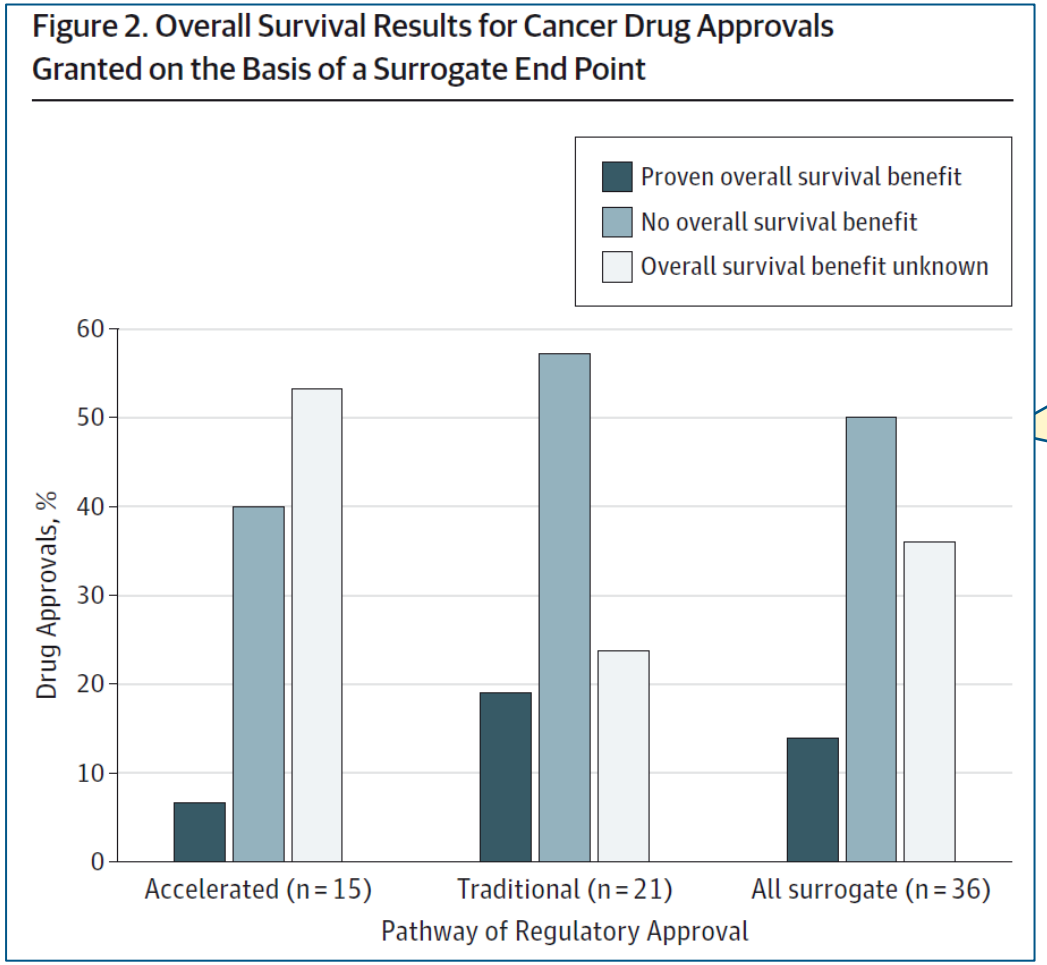
Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials (Review)

Anglemyer A, Horvath HT, Bero L 2014

The problem…is that only some observational studies are misleading (just as some RCT are misleading), but that no one has devised a foolproof method for distinguishing those that are useful from those that are misleading.

Sacks, H. Letter to Editor, NEJM Volume 343 Number 16 · 1195, 2000

Oncology drugs are often approved using surrogate endpoints but few show any survival benefit



50% of all cancer drugs approved with surrogate endpoints showed no overall survival benefit

FDA approvals for oncology drugs from 1/2008 to 12/2012

Source: Kim C, Prasad V. Cancer drugs approved on the basis of a surrogate end point and subsequent overall survival: an analysis of 5 years of US FDA approvals. JAMA Internal Med 2015; 175(12):1992-1994

Why push for expanding use of RWD/RWE?

Digitization of health care provides new opportunities to close the divide between research and clinical care

- Improve efficiency of clinical research -- capitalize on data that is being captured every day by getting information from more diverse settings and populations
- Big data – potential for detection of infrequent events, long-term but infrequent outcomes
- Lower resource intensity – more questions answered

Sources: Adapted from Jacqueline Corrigan-Curay, FDA, presented August 26, 2019 at Int'l; Conf of Pharmacoepidemiology

Table of Contents

IMS Health & Quintiles are now

When are RWD good enough?

21st Century Cures Act is intended to enable rapid modernization

FDA published Real-World Evidence Framework in December, 2018. ***Draft guidance due in 2021***

Amy Abernethy, MD, PhD
Principal Deputy Commission, FDA

Current scope of 21st Century Cures Act is to formalize and systematically expand use of RWE to support changes to labeling about drug product effectiveness, including

- adding or modifying an indication, such as a change in dose, dose regimen, or route of administration
- adding a new population, or
- adding comparative effectiveness or safety information

Many methods are discussed, including pragmatic trials and external comparators, but no guidance provided yet

"As the breadth and reliability of RWE increases, so do the opportunities for FDA to make use of this information"
Scott Gottlieb, Former FDA Commissioner, *National Academy of Science, Engineering & Medicine,* Examining the Impact of RWE on Medical Product Development, Sep. 19, 2017

Sources: FDA Framework for FDA's Real-World Evidence Program_December 2018

Japan echoes growing interest in regulatory use of RWD

Pharmaceutics and Medical Devices Agency guidance on RWD submissions scheduled for release in 2020

PMDA Chief Executive Yasuhiro Fijiwara
Society for Regulatory Science of Medical Products
September 6, 2019, Tokyo

- The envisaged use in regulatory submissions would be first seen in limited areas such as rare diseases …or to establish safety measures.
- PMDA has already launched pilot-based regulatory consultation services for the use of registry data in new drug applications.
- Guidelines planned for March 2020 will be shaped by learnings from the pilot consultation services. They will include the agency’s basic position on RWD use in submissions and “points to note” to ensure integrity.
- Draft guidelines will be put up for public comments, with the final version expected to be announced in the next fiscal year.

Big Data Report from EMA

February 13, 2019

- Summarizes taskforce reports on regulatory acceptability of big data
- Big data offers evidence which may be derived from unstructured, heterogeneous and unvalidated data of unknown provenance and unknowns around potential bias with additional uncertainties of accuracy and precision
  - Data are generated under different scenarios and for different purposes which rarely includes medicines regulation
  - Data ownership resides with multiple stakeholders many of which have no need to engage with the regulatory system

Sources: http://www.hma.eu/506.html

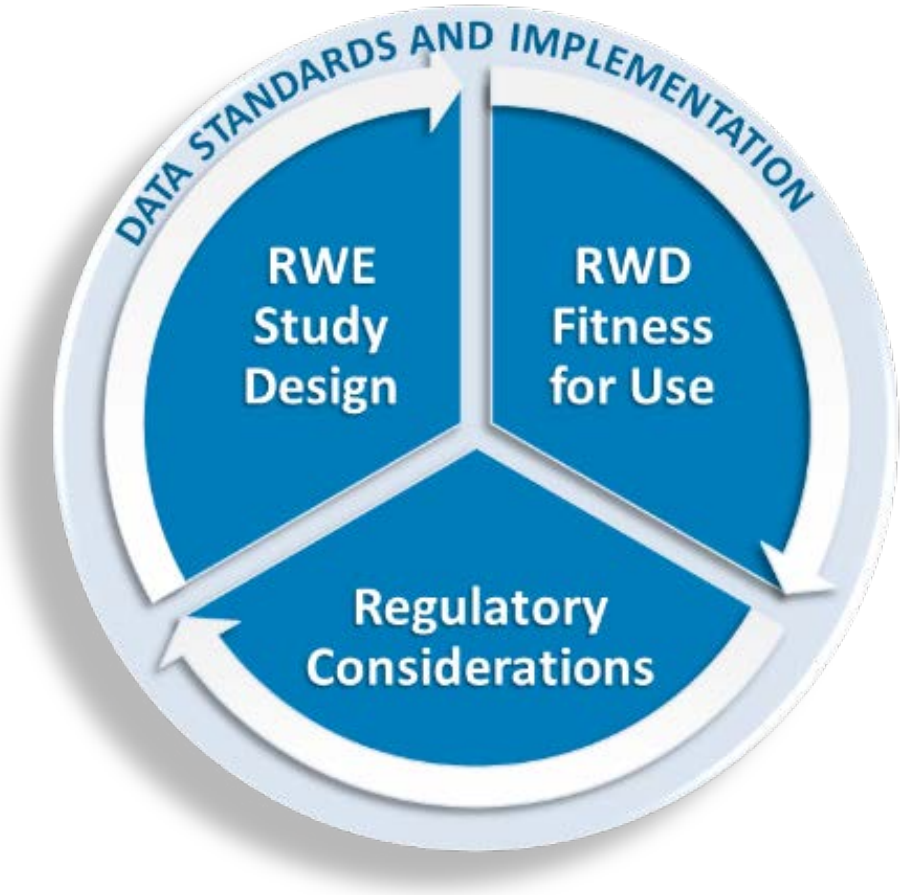
Same interests and challenges everywhere

Synopsis of the results from the industry survey in the EMA Big Data Report

	Companies (> 250 employees)	SMEs (< 250 employees)
Greatest impact of big data:	• Target identification • Patient stratification and personalised medicines • Post-authorisation safety	• Outcome identification • Informing on patients reported outcomes • Diseases prevalence
Highest concerns on the validity of big datasets:	• RWE data sets • Social media	• "-omics" • Imaging datasets
Key challenges in the use of big datasets:	• Data access • Data privacy • Data harmonisation	• Data security • Data validation • Data reproducibility
Greatest international challenges:	• Harmonisation on many aspects within and between countries including on access rules, data protection/privacy, data standards, collection, validation. • Data quality • Data access	
Regulatory measures to address these challenges:	• Need for clear regulatory guidance (including on usability of big data in regulatory decision) for better harmonisation (see above row) • Facilitation of access to the data, fostering data sharing	

Sources: http://www.hma.eu/506.html, table 1

Framework for Evaluating RWD/RWE for Use in Regulatory Decisions



- Are the RWD are fit for study purpose?
- Is the trial or study design likely to provide adequate scientific evidence to answer or help answer the regulatory question?
- Does the study conduct meets FDA regulatory requirements?

RWE: Guidance for Evaluating the Quality of Observational Studies of Comparative Effectiveness

grace PRINCIPLES

A Validated Checklist
for Evaluating the Quality of Observational Cohort Studies for Decision-Making Support

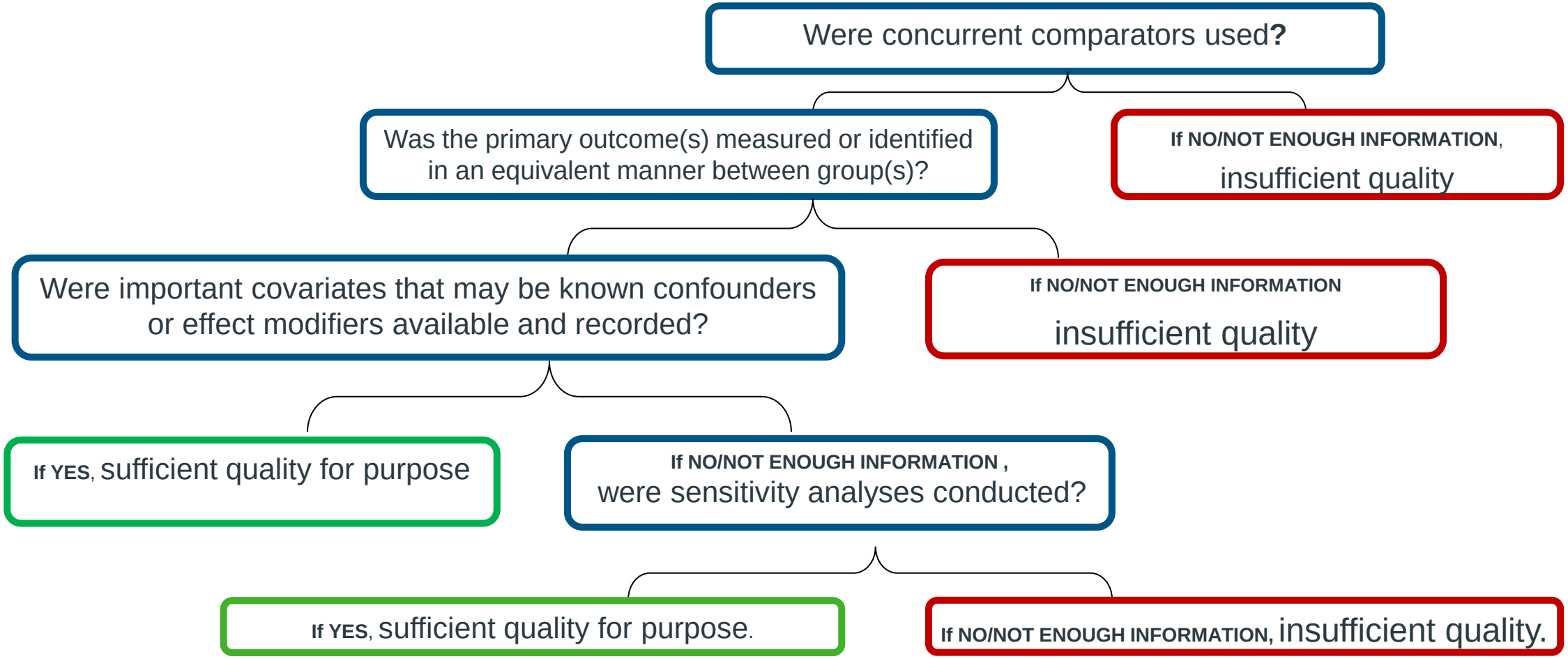
Citation
Dreyer NA, Bryant A, **Velentgas** P. The GRACE Checklist: A Validated Assessment Tool for High Quality Observational Studies of Comparative Effectiveness. *Journal of Managed Care & Specialty Pharmacy* 2016; 22(10) 1107-1113

Recommendations

- **International Society of Pharmacoepidemiology (ISPE)**
  Citation: Guidelines for Good Pharmacoepidemiology Practice. *Pharmacoepidemiology & Drug Safety* 2016 25:2-10
- ***Journal of Managed Care and Specialty Pharmacy (JMCP)***
  Citation: Happe LE: Announcing New Article Categories. *J Manag Care Spec Pharm*, 2015 Dec;21(12):1102-1103
- **National Institute for Health and Clinical Excellence**
  Citation: NICE DUS Technical Support Document 17: The use of observational data to inform estimates of treatment effectiveness in technology appraisal. Methods for comparative individual data. Report by the Decision Support Unit, May, 2015
- **National Pharmaceutical Council (NPC)**
- **European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP)**
  Citation: Guide on Methodological Standards in Pharmacoepidemiology (Revision 5). EMA/95098/2010

GRACE Checklist for RWE: 11 questions on data & methods

Classification & Regression Tree (CART) of expert raters: example



Dreyer NA et al. The GRACE Checklist: A Validated Assessment Tool for High Quality Observational Studies of Comparative Effectiveness . *J Managed Care & Specialty Pharmacy* 2016; 22(10) 1107-1113

GRACE Checklist for RWE: 11 questions on data & methods

Classification & Regression Tree (CART) analysis

Were concurrent comparators used?

Single best quality predictor (71% sensitivity; 81% specificity) for composite endpoint of

- ***expert assessments,***
- ***impact factor of journal where published and***
- ***number of article citations***

If YES, the article is considered sufficient quality for purpose

Were sensitivity analyses conducted?

If YES, sufficient quality for purpose.

If NO/NOT ENOUGH INFORMATION insufficient quality.

Dreyer NA et al. The GRACE Checklist: A Validated Assessment Tool for High Quality Observational Studies of Comparative Effectiveness . *J Managed Care & Specialty Pharmacy* 2016; 22(10) 1107-1113

When RWD are good for regulatory use

This must be a contextual exercise as no simple formula will work

Considerations for determining suitability of RWD

- Data elements must meet major study objectives
- Data do not need to be 100% complete or accurate, since sensitivity analyses and modeling can be used to address missing data and quantify likely impact of bias.
- Data needs to be reasonably curated and the process should be documented

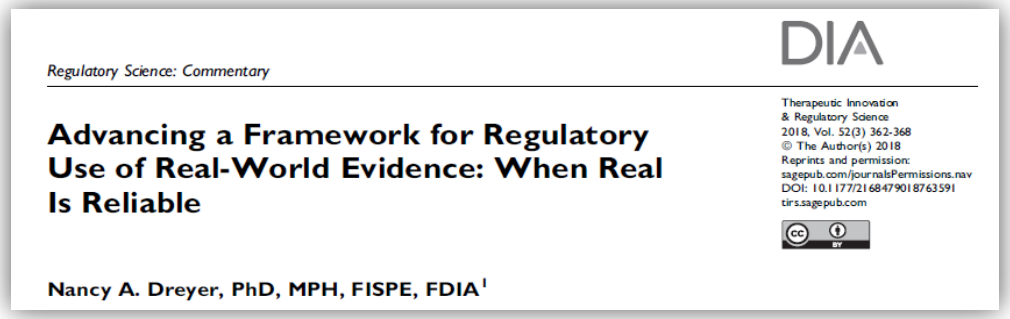
Received: 4 October 2018 | Revised: 12 October 2018 | Accepted: 16 October 2018
DOI: 10.1002/pds.4697

COMMENTARY

WILEY

Considerations in characterizing real-world data relevance and quality for regulatory purposes: A commentary

Cynthia J. Girman[1] | Mary E. Ritchey[2] | Wei Zhou[3] | Nancy A. Dreyer[4]



DIA

Regulatory Science: Commentary

Advancing a Framework for Regulatory Use of Real-World Evidence: When Real Is Reliable

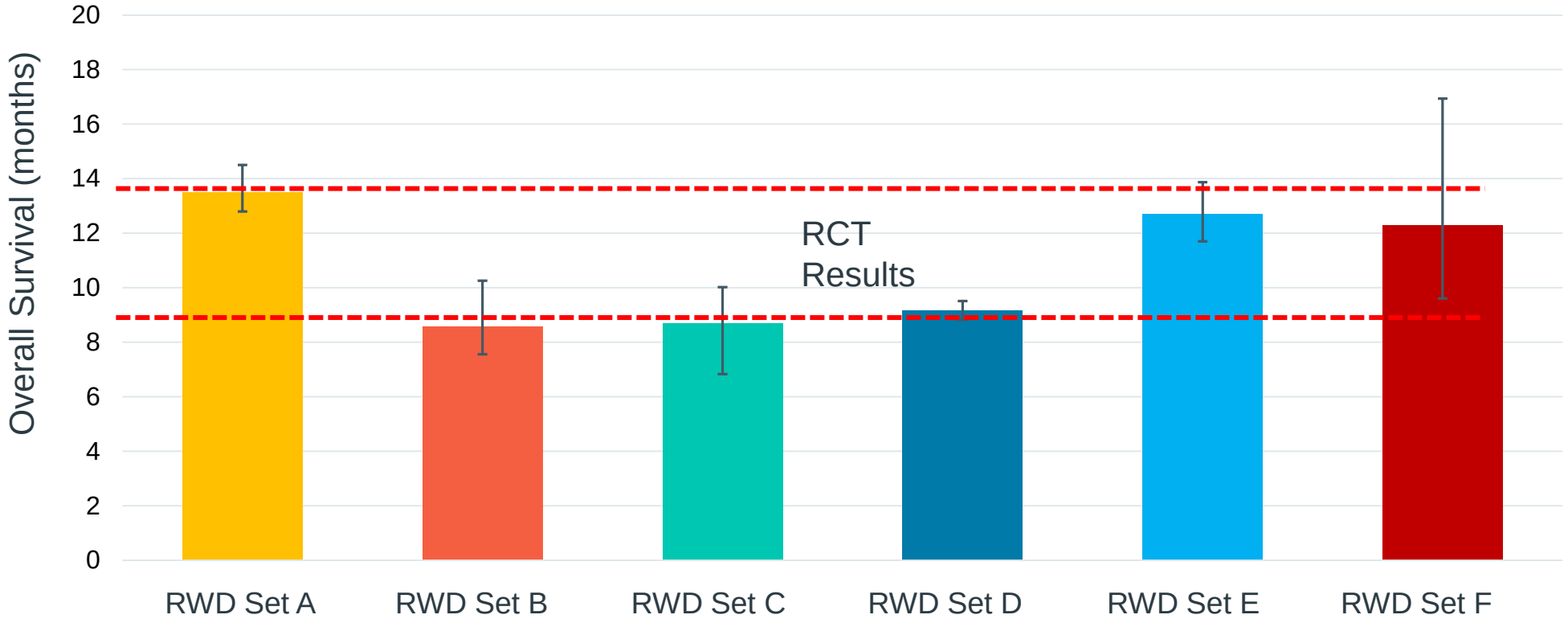
Therapeutic Innovation & Regulatory Science
2018, Vol. 52(3) 362-368

DOI: 10.1177/2168479018763591
tirs.sagepub.com

Nancy A. Dreyer, PhD, MPH, FISPE, FDIA[1]

Establishing real-world endpoints: Overall Survival

Comparing RWD to RCT in advanced NSCLC patients treated with immune checkpoint inhibitors



EMR & claims from six de-identified sources

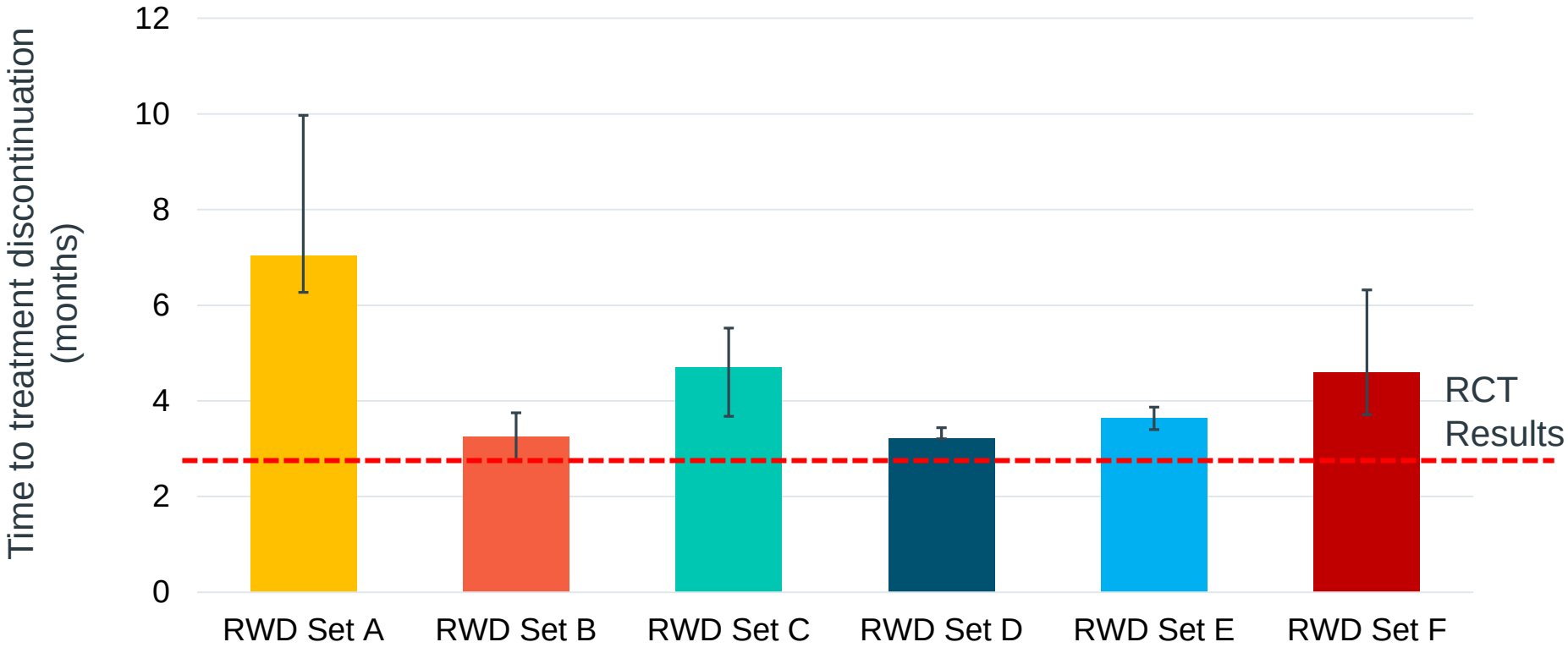
IQVIA
flatiron
pcornet
OPTUM Labs
COTA
KAISER PERMANENTE

Presented July 10, 2018,

Sources: Stewart M, Norden AD, Dreyer N et al. JCO Clin Care Informatics. Epub July 23, 2019. https://ascopubs.org/doi/full/10.1200/CCI.18.00155

Treatment patterns are often different in RW settings

Time to treatment discontinuation:
comparing RWD to RCT in advanced NSCLC treated with immune checkpoint inhibitors



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Sources: Stewart M, Norden AD, Dreyer N et al. JCO Clin Care Informatics. Epub July 23, 2019. https://ascopubs.org/doi/full/10.1200/CCI.18.00155

Establishing the validity of patient-reported medication use

Case study funded by the European Commission under the Innovative Medicines Initiative PROTECT

Objective: Assess medication use and other potential risk factors throughout pregnancy as reported by pregnant women, and the suitability of such data for research purposes

Methods: Self-reported medication use compared with data from electronic health records, national prescription data, and regional prescribing practices

Results

- 83% took ≥ 1 non-pregnancy-related med during pregnancy or prior month; 24% only used non-prescription medications; 7% reported **not** using prescribed meds
- Added information on potential risk factors, including recreational drug use, alcohol, smoking, education.
- Compared DK National Prescription register ,83% agreement for prescription meds for chronic conditions; 54% for meds indicated for short-term use

Key Lessons

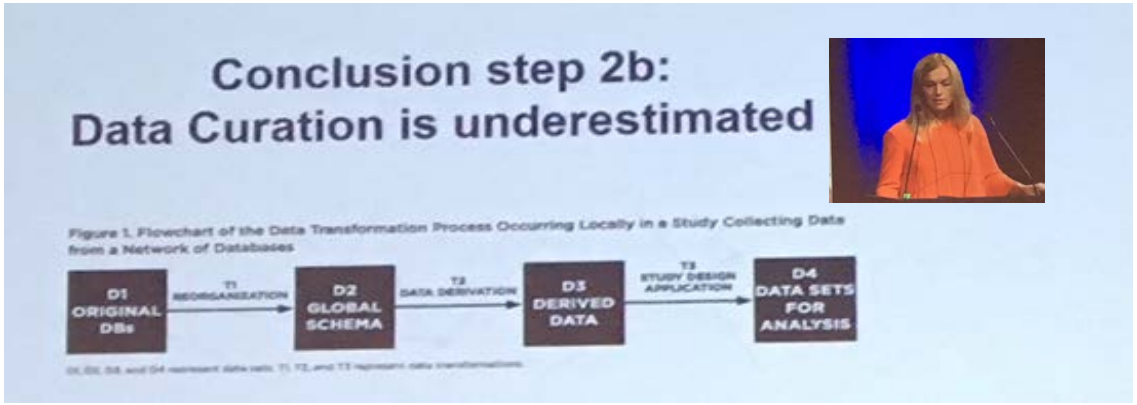
- **Direct to consumer studies can provide important data not found in EHR or prescription databases**
- **Validation of clinical outcomes of special interest may be warranted**

Dreyer et al. Direct-to-patient research: piloting a new approach to understanding drug safety during pregnancy **JMIR Public Health & Surveillance** 2015; 1(2); e22. doi:10.2196
Richardson et al. An int'l study of…advertisement methods to facilitate study participant self-enrolment …. **JMIR Public Health and Surveillance 2016;** 2(1) e13: 1-10.

Recognizing RWD that is Fit for Purpose

Data quality should be examined in the following terms

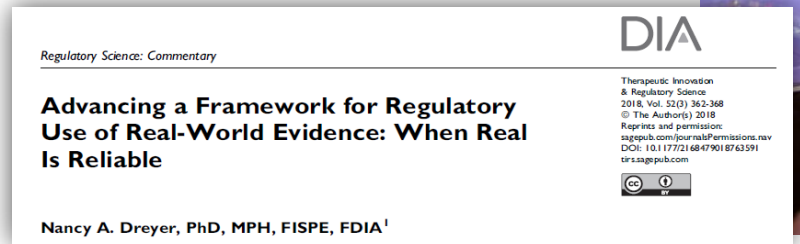
- Provenance
- Structure
- Integration
- Rate of accumulation
- Curation



Professor Miriam Sturkenboom, 2018 International Conference of Pharmacoepidemiology and Therapeutic Risk Management

*"Data quality is considered the **biggest challenge** for the use of big data for regulatory decision-making …across Europe and the ultimate validation of the derived evidence."*

HMA-EMA Joint Big Data Task Force Report, 13 Feb 2019


Regulatory Science: Commentary

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Advancing a Framework for Regulatory Use of Real-World Evidence: When Real Is Reliable

Therapeutic Innovation & Regulatory Science 2018, Vol. 52(3) 362-368

Nancy A. Dreyer, PhD, MPH, FISPE, FDIA[1]

Nancy Dreyer accepted DIA Inspire Award for Best Author, 2019 for publication on "Advancing a framework for regulatory use of RWE: When real is reliable

When is RWD good enough to be reliable?

FRAMEWORK FOR FDA'S REAL-WORLD EVIDENCE PROGRAM

Recommendations on data sources and quality

Relevance: are there sufficient details on exposure, covariates, outcomes for study purpose? RWD should be representative of patients with the target condition and have sufficient size and follow-up to be able to demonstrate benefit

Reliability of RWD via data accrual, data assurance stemming from minimizing data collection errors, RWD analyses prospectively defined.

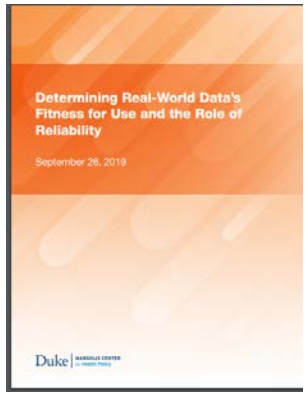
Reporting: RWD sources should follow reporting standards and document data elements and definitions, data aggregation methodology and data collection time windows

Transparent source verification and auditing procedures for completeness and consistency

Common data model with common terminologies, vocabularies, coding schemes is needed to work with RWD across multiple sources

Addressing RWD gaps requires a variety of RWD sources

2nd Annual Duke Margolis Conference on RWD and RWE



Duke-Margolis Center for Health Policy
Recommendations for Data Curation
September 23, 2019

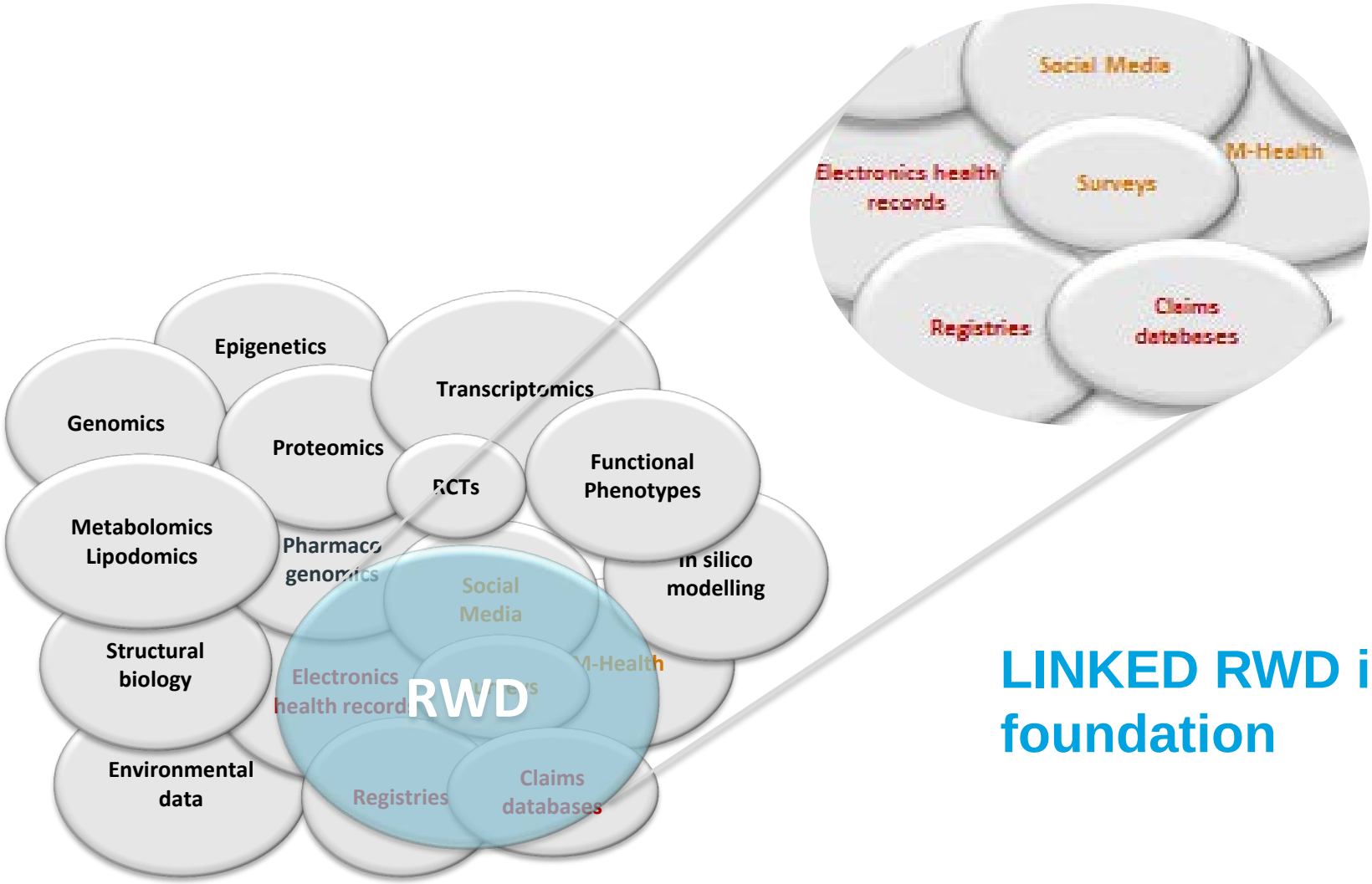
Sources: U.S. Food & Drug Administration. (2018, December). Framework for FDA's Real-World Evidence Program.
https://healthpolicy.duke.edu/events/developing-real-world-data-and-evidence-support-regulatory-decision-making

IMS Health & Quintiles are now

IQVIA™

Study designs that rely on innovative use of RWD

Linking study-specific data collection with big data



LINKED RWD is the foundation

Innovative study design that use RWE

INNOVATIVE EXTENSION

Follow patients after RCT completion
The goal is to determine long-term value

Can reduce study cost by ≤ 60% compared conventional approaches

PRAGMATIC

Pragmatic trials evaluate effectiveness of a randomized intervention in real-life conditions

Can lead to cost reductions on the order of 50%

EXTERNAL COMPARATOR

Provide information on clinical benefit when a control group may not be feasible or ethical

Can lead to cost and time savings. Increases the value of single-arm studies

ENRICHED

Combine primary and secondary data

Can lead to both cost and time savings, access to more information

Extending follow-up after a clinical trial

Understanding long-term benefits of treatment through direct-to-patient research

Approach

- Direct to patient follow-up for effectiveness (up to 10 years)
- Follow both treated and placebo patients
- Consent patients for new study before trial ends
- Single investigative site per country where possible
- Selected clinical validation for events of special interest - here, Major Adverse Coronary Events, (MACE)

Our Value

- Roughly 1/3 cost of using RCT framework for follow-up
- Bulk of budget is directed to following up potential MACE

The FDA granted Invega Sustenna a label expansion based on evidence from a pragmatic RCT

INVEGA SUSTENNA® paliperidone palmitate extended-release injectable suspension

The first and only antipsychotic for which the inclusion of real-world data led to a label expansion by FDA (January 3, 2018)

Landmark Study Shows Once-Monthly Long-Acting Therapy INVEGA® SUSTENNA® (paliperidone palmitate) Significantly Delayed Time to Relapse in Patients with Schizophrenia Compared to Daily Oral Antipsychotic

First prospective, randomized clinical trial to reflect context of "real world" issues in treating schizophrenia, including recent incarceration and substance abuse

Study design

- 15 month, 50 site-randomized, open-label, active controlled study of 444 adults with schizophrenia
- Broad enrollment criteria
  - Mean age: 38 years
  - 60% of patients had comorbid substance abuse
  - Mean time since release from last incarceration: 42 days
- Primary endpoint: time to first treatment failure including psych hospitalization, arrest/incarceration, treatment discontinuation, increased psych services to prevent psych hospitalization, suicide, etc.

Sources: Alphs L, Benson C, Cheshire-Kinney K et al. J Clin Psychiatry 2015:76(5):554-561

A new twist: randomized registry trials

NEJM 2013;369:1587-97. TASTE Trial

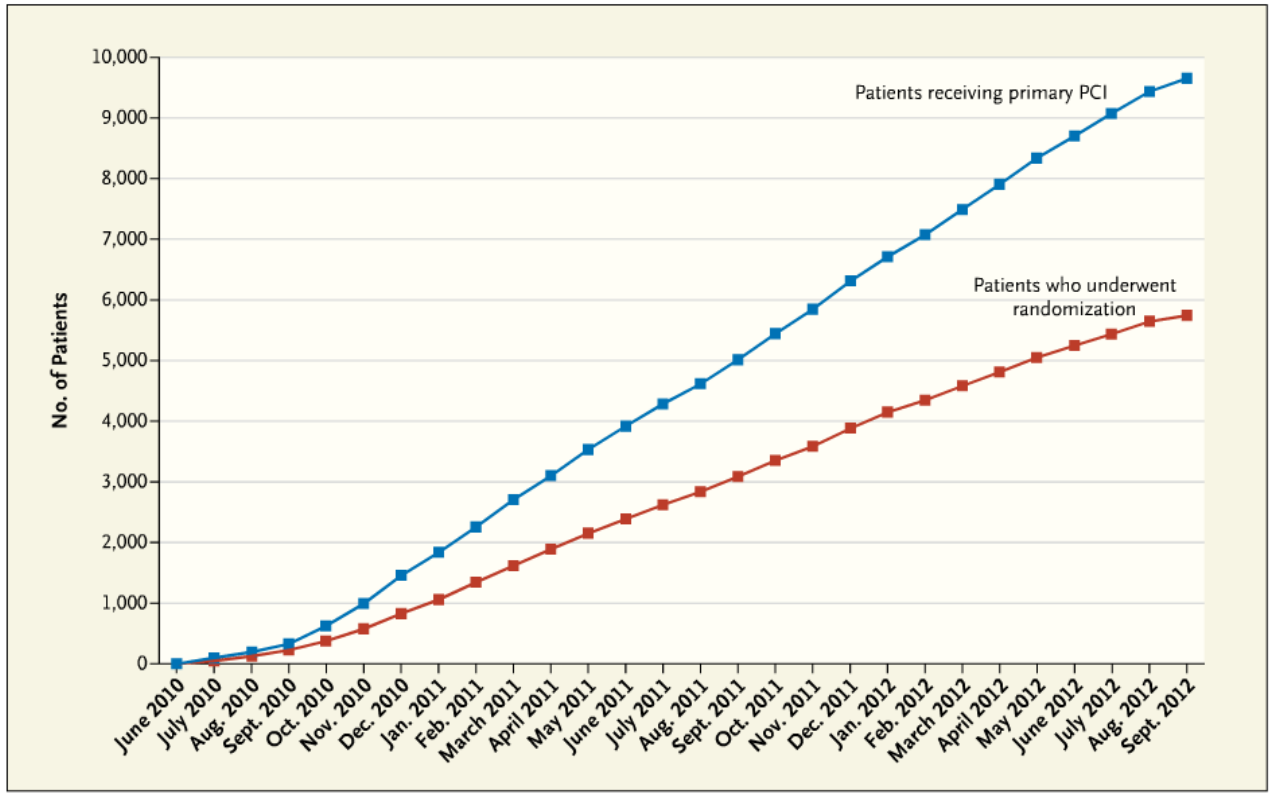
Patients enrolled from a registry, randomized and followed through standard registry data collection

- 7012 patients randomized from 11,709 eligible
- Also followed cohort that did not undergo randomization
- Primary end-point: all cause mortality at 30 days
- Followed entirely through existing record systems in a Swedish registry

Research question:

Does thrombus aspiration before PCI improve 30-day mortality?

Answer: No



Rapid Randomization in the TASTE Trial, with Enrollment of Most Patients Receiving Primary Percutaneous Coronary Intervention (PCI).

Adapted from the Institute of Medicine (www.iom.edu/~/media/Files/Activity%20Files/Quality/VSRT/LST%20Workshop/Presentations/Granger.pdf). The incremental cost of the Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia (TASTE) trial was $300,000, or $50 for each participant who underwent randomization.

RWE in regulatory decisions about comparative effectiveness

2017 - Q1 2019*

				FDA		EMA	
				Approval	Label Expansion	Conditional Approval	Approval
Pragmatic RCT	Janssen	INVEGA SUSTENNA	Schizophrenia		✓(2018)		
Contemporary RW Comparators	Pfizer	BAVENCIO avelumab	Metastatic Merkel cell carcinoma	✓(2017) Accelerated*		✓(2017)	
	BIOMARIN	Brineura (cerliponase alfa)	Infantile batten disease	✓(2017) Full			✓(2017)
	GILEAD Kite	YESCARTA (axicabtagene ciloleucel)	Diffuse large B-cell lymphoma	✓(2017) Full			✓(2018)
	NOVARTIS	KYMRIAH (tisagenlecleucel)	Diffuse large B-cell lymphoma				✓(2018)
	FRESENIUS KABI	Omegaven	Parenteral nutrition-associated cholestasis	✓(2018) Full			
	AMGEN	BLINCYTO (blinatumomab)	B-cell precursor acute lymphoblastic leukemia in 1st / 2nd complete remission with MRD ≥ 0.1%		✓(2018) Accelerated		✓(2019)
Historical RW Comparators	amneal	TEPADINA	Pediatric class 3 beta-thalassemia		✓(2017) Full		
	NOVARTIS	LUTATHERA	SSTR-positive (GEP-NETs)	✓(2018) Full			✓ (2017)

*Pfizer's 2019 Ibrance approval for male breast cancer was based on reviews of EMR for safety

Legend: GEP-NETS: gastroenteropancreatic neuroendocrine tumor HER2: human epidermal growth factor receptor 2 HR: hormone receptor MRD: minimal residual disease SSTR: somatostatin receptor

RWE included in the label

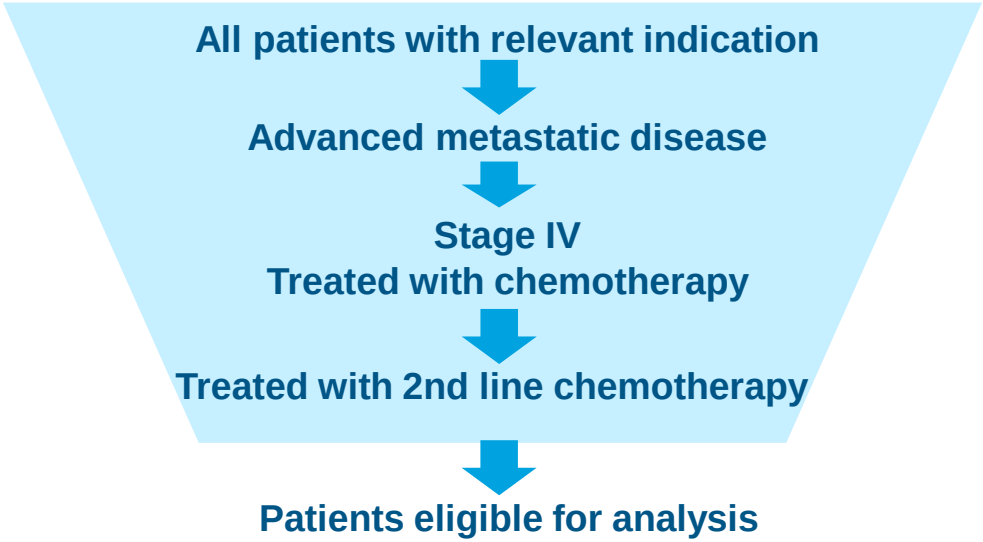
Real world data comparators for single arm clinical trial – approval of NME for rare cancer indication

Objective

Primary objective: Assess overall response rate based on best objective response to standard chemotherapy
Cohort: Niche carcinoma patients being drug treated in 2nd line - from existing registry in Western Europe and EMR in USA

Aim: Use real world data as comparator for single arm clinical trial for novel mAb

Approach



Results

- Response to chemotherapy was very limited
- The primary outcome of standard chemotherapy was even worse than expected
- **Novel mAb confirmed as new treatment option by FDA and EMA in 2017**

Response	N = 34
Complete response, n (%)	0
Partial response, n (%)	3 (8.8)
Stable disease, n (%)	3 (8.8)
Progressive disease, n (%)	28 (82.4)
Objective response rate (95% CI), %	8.8 (1.9-23.7)

Data from European study

Real-world comparison data facilitates rapid drug approval

BLINCYTO® (blinatumomab) for injection
35 mcg single-dose vial

Real-world comparators provided context for regulatory filing of single arm Phase 2 trials

ORIGINAL ARTICLE

Blinatumomab vs historical standard therapy of adult relapsed/ refractory acute lymphoblastic leukemia

N Gökbuget[1], M Kelsh[2], V Chia[2], A Advani[3], R Bassan[4], H Dombret[5], M Doubek[6], AK Fielding[7], S Giebel[8], V Haddad[9], D Hoelzer[1], C Holland[10], N Ifrah[11], A Katz[2], T Maniar[12], G Martinelli[13], M Morgades[14], S O'Brien[15], J-M Ribera[14], JM Rowe[16], A Stein[17], M Topp[18], M Wadleigh[19] and H Kantarjian[15]

We compared outcomes from a single-arm study of blinatumomab in adult patients with B-precursor Ph-negative relapsed/ refractory acute lymphoblastic leukemia (R/R ALL) with a historical data set from Europe and the United States. Estimates of complete remission (CR) and overall survival (OS) were weighted by the frequency distribution of prognostic factors in the blinatumomab trial. Outcomes were also compared between the trial and historical data using propensity score methods. The historical cohort included 694 patients with CR data and 1112 patients with OS data compared with 189 patients with CR and survival data in the blinatumomab trial. The weighted analysis revealed a CR rate of 24% (95% CI: 20–27%) and a median OS of 3.3 months (95% CI: 2.8–3.6) in the historical cohort compared with a CR/CRh rate of 43% (95% CI: 36–50%) and a median OS of 6.1 months (95% CI: 4.2–7.5) in the blinatumomab trial. Propensity score analysis estimated increased odds of CR/CRh (OR = 2.68, 95% CI: 1.67–4.31) and improved OS (HR = 0.536, 95% CI: 0.394–0.730) with blinatumomab. The analysis demonstrates the application of different study designs and statistical methods to compare novel therapies for R/R ALL with historical data.

Blood Cancer Journal (2016) **6,** e473; doi:10.1038/bcj.2016.84; published online 23 September 2016

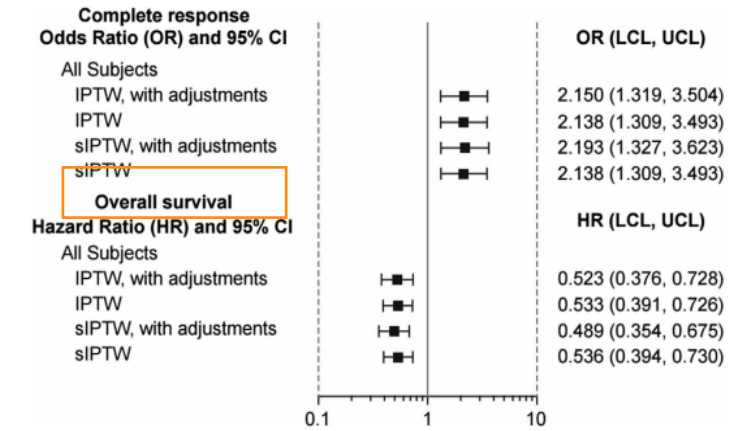


Figure 2. Comparison of complete response and overall survival between blinatumomab clinical trial patients and historical patients. Outcomes were analyzed using both the IPTW and sIPTW approaches: Odds ratio (OR) for achieving a CR/CRh (blinatumomab patients) or CR (historical patients) and hazard ratio (HR) for overall survival.

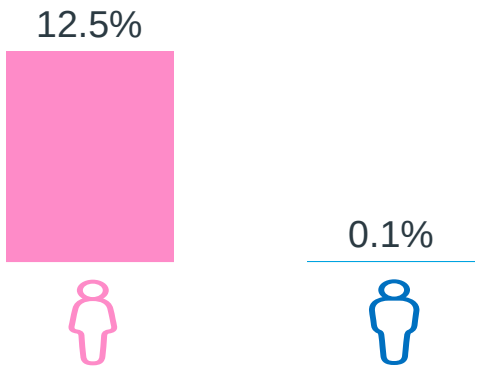
Strong benefit evident in the trial (treated) population compared to the 'control' population

CASE STUDY

Real World Data for FDA decisions on Label Expansion

Rarity of BC in men limits the feasibility of randomized trials

Lifetime risk of developing invasive breast cancer



Women treatment guidelines recommended to men with BC

RWD was used to describe IBRANCE® (palbociclib) benefits for men with BC

IQVIA™ — *Pharmacy/medical claims* → *Tx pattern and duration*

flatiron — *EMR* → *Real World clinical response*

Confirmed clinical benefit from the addition of Ibrance to endocrine therapy

Evidence generated was accepted by the FDA

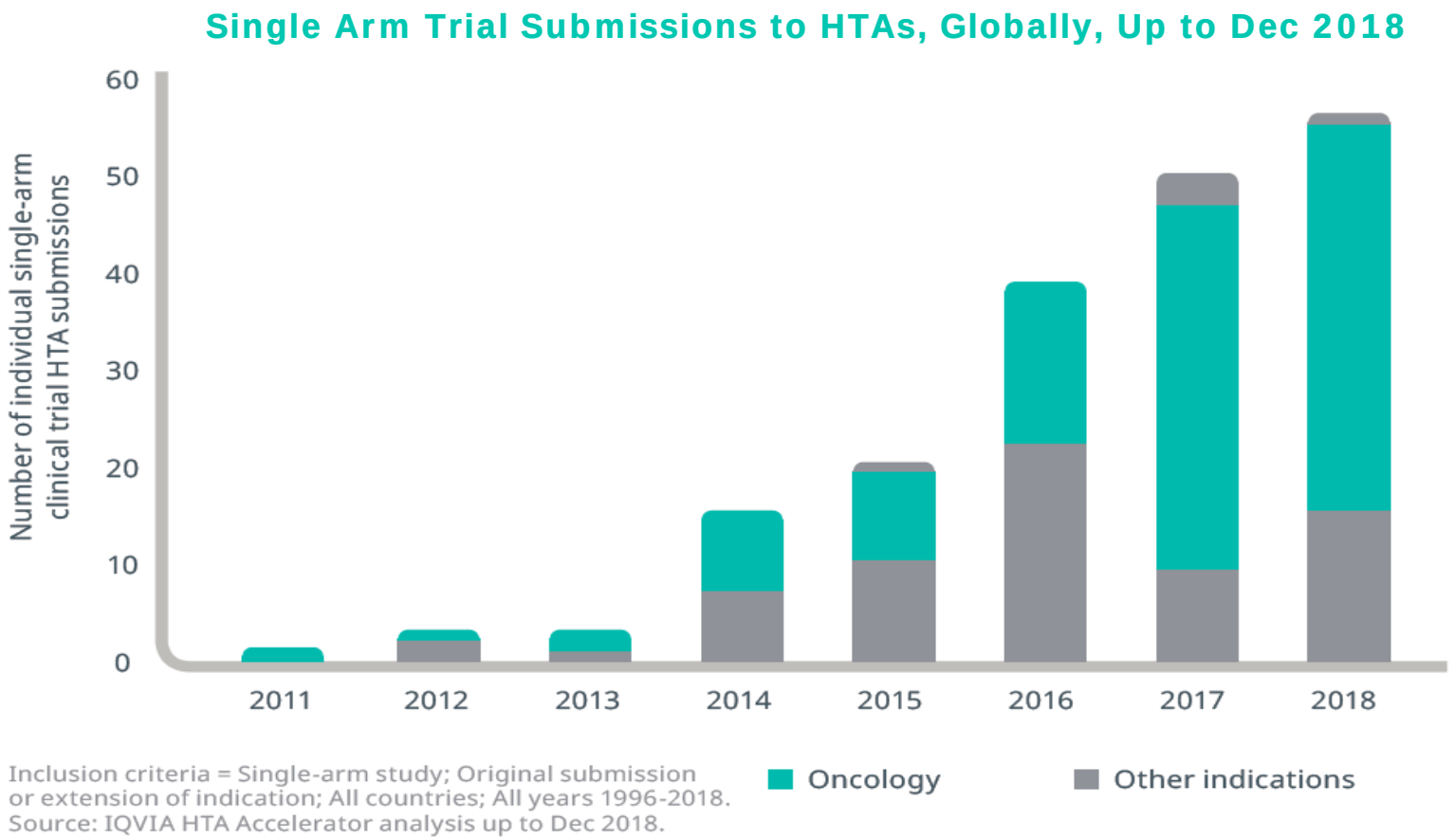
*"We are **expanding the indication** for Ibrance to include male patients **based upon data from postmarketing reports and electronic health records** showing that the **safety** profile for men treated with Ibrance is consistent with the safety profile in women treated with Ibrance,"*

- Richard Pazdur, MD, director of the FDA's Oncology Center of Excellence

"The smart use of this innovative approach helped Pfizer expand its addressable market"

Sources: FDA, breastcancer.org, ASCO

Use of External Comparators For HTA Submissions



Key Findings

- 179 single arm submissions covering 102 drug/indication combinations
- Increase in submissions of single-arm clinical data packages to HTA bodies
- External comparators were used in 52% of submissions
- **Positive HTA outcome was received for 61% of submissions with external comparators vs 50% without**

Source: Patel D et al. Use of External Comparators for HTA Submissions – An Analysis of HTA Accelerator, Poster at 35th ISPE, August 2019, Philadelphia

Link of EHR and sports data are used for orthopedic injury research in professional sports

Sports Health
A Multidisciplinary Approach

Lessons on Data Collection and Curation From the NFL Injury Surveillance Program

Nancy A. Dreyer, PhD,*† Christina D. Mack, PhD,‡ Robert B. Anderson, MD,§‖ Edward M. Wojtys, MD,¶ Elliott B. Hershman, MD,# and Allen Sills, MD**

Background: "Research-ready" evidence platforms that link sports data with anonymized electronic health records (EHRs) or other data are important tools for evaluating injury occurrence in response to changes in games, training, rules, and other factors. While there is agreement that high-quality data are essential, there is little evidence to guide data curation.

Hypothesis/Purpose: We hypothesized that an EHR used in the course of clinical care and curated for research readiness can provide a robust evidence platform. Our purpose is to describe the data curation used for active injury surveillance by the National Football league (NFL).

Journal of Athletic Training 2019;54(5):000–000
doi: 10.4085/1062-6050-18-19

www.natajournals.org

JAT
JOURNAL OF ATHLETIC TRAINING

The Establishment and Refinement of the National Basketball Association Player Injury and Illness Database

Christina D. Mack, PhD, MSPH*; Peter Meisel, MSPH†; Mackenzie M. Herzog, PhD, MPH*; Lisa Callahan, MD‡; Eva E. Oakkar, PhD, MS*; Taylor Walden, MS†; Joseph Sharpe, ATC§; Nancy A. Dreyer, PhD, MPH*; John DiFiori, MD‡‡

*IQVIA Real-World & Analytic Solutions, Research Triangle Park, University of North Carolina, Chapel Hill; †National Basketball Association, New York, NY; ‡Hospital for Special Surgery, New York, NY; §National Basketball Athletic Trainers Association, Charlotte, NC

Sources: http://espn.go.com/nba/story/_/id/16009403/cutting-edge-injury-prediction-prevention

IMS Health & Quintiles are now

Future state

Right Source for the Right Data

Patient Health Records

- Demographics, medical history, structured patient information
- Medication information
- Clinical measures
- Labs

*chart review or EHR

Direct from Patient

- Additional demographics, medical information
- Treatment satisfaction, compliance
- Lost work productivity, activity impairment
- Patient diaries
- PROs

Devices and Wearables

- Movement, sleep, heart rate
- Compliance with treatment, device use

Insurance Claims Data / Billing Records

- 360° view of patient medical journey regardless of treatment center
- Objective evidence of health care system encounters/ resource utilization
- Outpatient prescription fills

KEYS TO SUCCESS

Investigate best place to find the patients

Full feasibility for key data elements

Don't restrict to one data source

Right data from the right place

A continual process of evidence generation & product differentiation through use of linked data

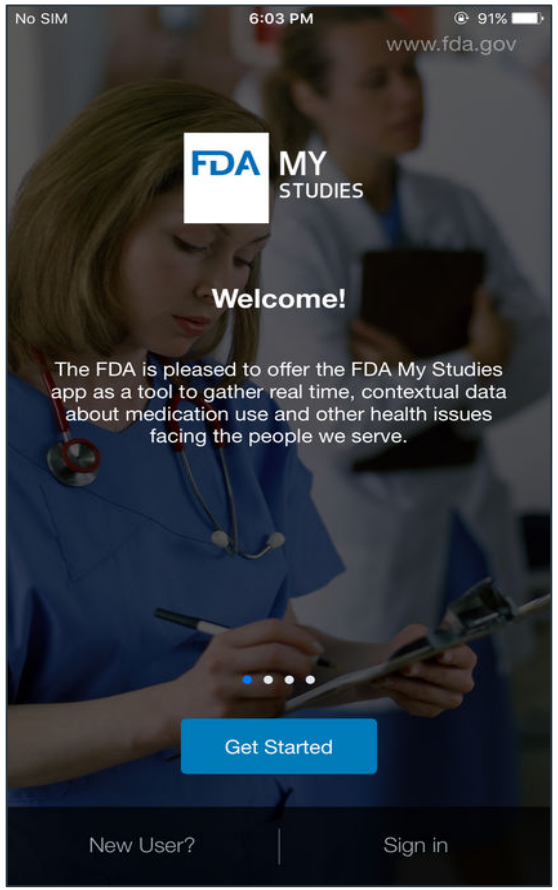
More opportunities for insight into the patient experience

More is possible

More is acceptable

Enrich & augment	Add “voices” from patients and providers
Curate	Increase quality and usability in a systematic, effective manner
Link	Expand the value of data by linkage, while recognizing the challenge of quality, unbiased linkages

Combining new and existing RWD
FDA's new App captures and integrates patient-generated data



FDA MyStudies screenshot

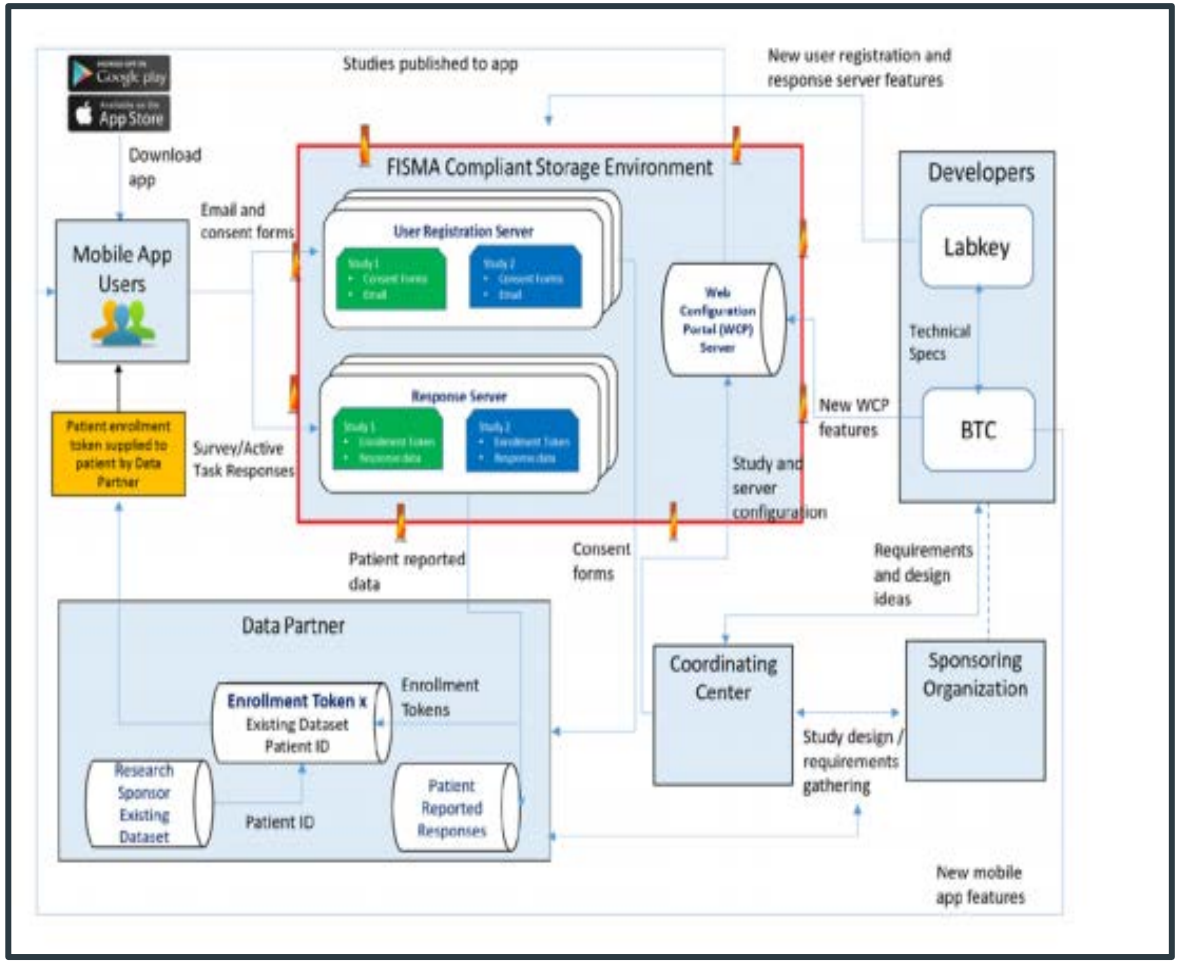
MyStudies App Key features

- Open source customizable digital tool (for iOS and Android) that can be rebranded by researchers and developers
- Gateway capability: works for multi-site trials across multiple therapeutic areas and health outcome measures
- Ability for study sponsors to reconfigure app and patient data storage systems
- Backend architecture is secure and auditable, and compliant with necessary regulations such as 21 CFR Part 11 and FISMA

Sources: https://www.fda.gov/drugs/science-research-drugs/fdas-mystudies-application-app
FDA CDER – Small Business and Industry Assistance Webinar. Introduction to MyStudies App (09 May 2019) (https://sbiaevents.com/mystudies/)

During the pilot study, data elements were stored in multiple environments consistent with the storage architecture model

Data storage and access environment



Data storage and access rights

Survey response data

- LabKey stored the data
- LabKey, Kaiser Permanente could access the data

Linked medical records data

- Kaiser Permanente stored the data
- Only Kaiser Permanente could access the data. It was not released to LabKey, Harvard Pilgrim or FDA

Sources: https://www.fda.gov/drugs/science-research-drugs/fdas-mystudies-application-app
FDA CDER – Small Business and Industry Assistance Webinar. Introduction to MyStudies App (09 May 2019) (https://sbiaevents.com/mystudies/)

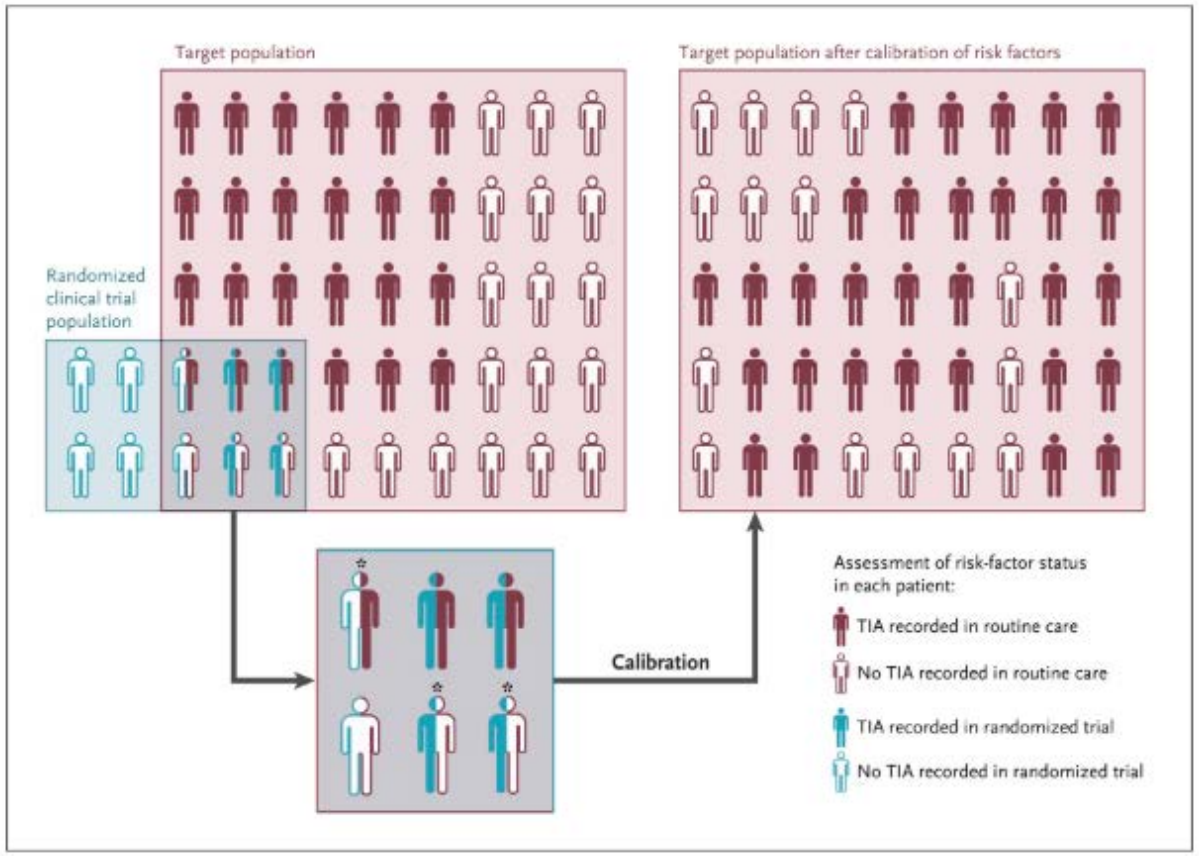
Audit trails for the MyStudies app

A look towards evidentiary requirements?

- Mobile technology should record the date and time that the data are captured and this information should be transmitted or recorded in the durable database
- The first durable database should capture
  - Date and time that the data enter the durable database
  - Data originator for each data element
    - Patient
    - Mobile Technology (e.g., biosensor)
    - EHR
- An audit trail should track modifications to the data and include data element identifiers that reflect the date, time, and data originator and the reason for the change
  - Modified or corrected data should not obscure previous entries

Sources: Slide courtesy of David Martin, FDA

More linkage of RWD with clinical trial data



- Calibrate risk-factor Measurement between clinical trial participants and target patient population
- Use overlap between two groups for calibration

Make a stronger story for clinicians and payers through linkage of RCT and RW data

See Najafzadeh M, Schneeweiss S. N Engl J Med 2017; 376:1203-1205DOI: 10.1056/NEJMp1614720:

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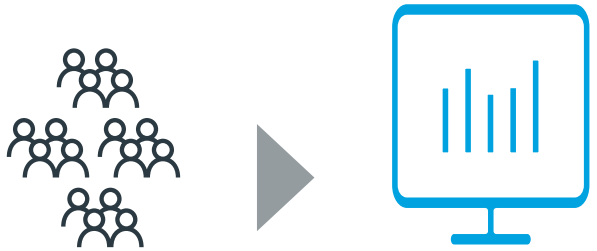
Changing data approaches to meet regulatory demands



Study-driven primary data collection

Leveraging existing networks + registries

- 80% less data needed for primary collection
- Significantly reduced HCP/site burden

up to 40% productivity improvement

Opportunity

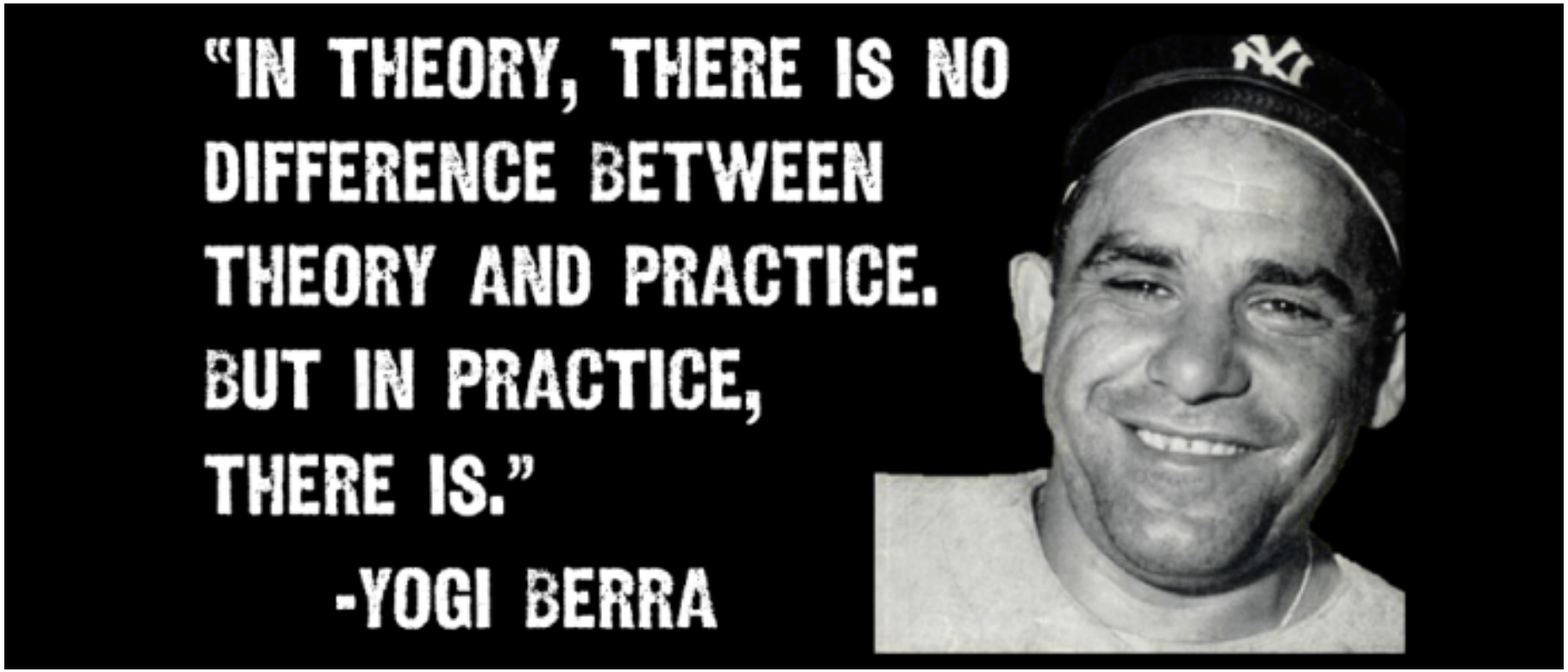
- Combine and curate data from patients, physicians, etc. with transactional and other health data to assess effectiveness and safety of newly launched products compared to other available treatments over time.
- Data may come from pharmacies, wholesalers, providers, payers, claims processors, etc.

Challenge

- Reconciling de-identification goals and standards in research v. privacy

1. Linking to de-identified data can compromise de-identification risk thresholds
2. Patient consent does not trump data supply agreements

Case study is for illustrative purposes only. Results may vary.


"IN THEORY, THERE IS NO
DIFFERENCE BETWEEN
THEORY AND PRACTICE.
BUT IN PRACTICE,
THERE IS."
-YOGI BERRA

Contact information

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