RWE Collaborative Advisory Group Meeting

October 1, 2018

WIFI name: DukeinDCGuest
Password: Duke1201

The Duke-Margolis RWE Collaborative

- A multi-stakeholder collaboration designed to further support and broaden RWD and RWE-related research and policy development
- The Collaborative will pursue core research and convening activities, as well as pilot opportunities, with the express aim of generating actionable information and evidence-based recommendations

Duke Clinical Research Institute
Duke-Margolis Center for Health Policy
Eli Lilly and Company
Flatiron Health
Genentech Inc
GlaxoSmithKline plc
Harvard Medical School
HealthCore
ISPOR
IQVIA
Johnson & Johnson
Multi-Regional Clinical Trials Center
National Health Council
Novartis
OptumLabs
PatientsLikeMe
Teva Pharmaceutical Industries

Observing Organizations:

FDA
NASEM

Second Annual Duke-Margolis Conference on Real-World Data and Evidence

National Press Club

October 1, 2018

Overview of Progress-To-Date

Morgan Romine, MPA

Research Director, Biomedical Innovation and Regulatory Policy,

Duke-Robert J. Margolis, MD, Center for Health Policy

October 1, 2018

In the beginning . . .

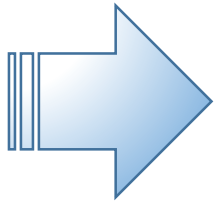
21st Century Cures Act

- While the overarching discussion is not new, it came into focus with the Cures process in Spring 2014
- Twinned with ongoing PDUFA VI discussions
- Established the general roadmap from 2016 passage to 2021:
  - Legislation -> Convening -> Framework -> Pilots -> Guidance

Priorities since 2016: Terminology

- Early Cures discussion focused on “evidence from clinical experience”
- While RWD/RWE was eventually used, legislative text left some challenges with definitions

- **Real world data (RWD)** are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources
- Common types:
  - Electronic health records
  - Payer claims data
  - Registries
  - Mobile apps and digital technologies



- **Real-world evidence (RWE)** is evidence derived from RWD through the application of research methods.
- For regulatory applications, RWE can further be defined as clinical evidence regarding the use and potential benefits or risks of a medical product derived from analysis of RWD.
- **Note: RWE can include randomized and non-randomized designs**

Priorities since 2016: Convening

- Getting the science and policy right is a multi-stakeholder endeavor
- FDA has directly funded a number of convening activities with Duke-Margolis and the National Academy of Sciences, Medicine, and Engineering
- In 2018 alone:
  - Public conferences by NASEM, Duke-Margolis, FOCR,
  - Expert workshops by UK Academy of Medical Sciences, Duke-Margolis, Bipartisan Policy Center, CTTI
  - More to come: New York Academy of Sciences, DIA RWE Conference

Priorities since 2016: Publications

FDA Publications

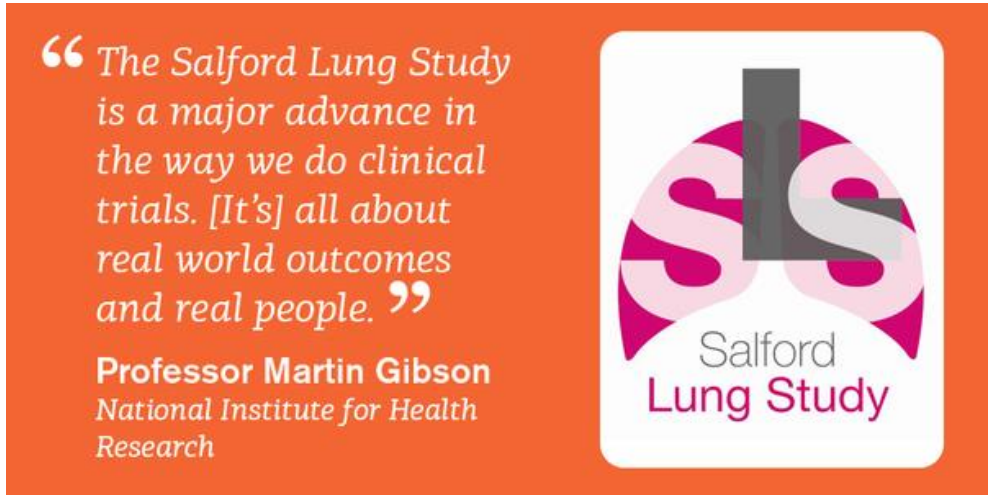
Frameworks and Proceedings

Publications

- Since January 1, 2016: 2,714 published articles with "real-world" in the title on PubMed

Priorities since 2016: Studies

- We are starting to learn from multiple pilots, registries, demonstration projects, and full-scale studies:
  - Salford Lung Study
  - ADAPTABLE
  - TVT Registry
- More proof-of-concept studies and pilot projects are needed



Where are we in 2018?

- Are we making tangible progress?
- Are conversations productively moving forward?
- Do we have the right constellation of projects, and are we avoiding duplicative efforts?
- How can we work together to support pilots and guidance development? Methods improvements and data curation sciences?

Goal for today: Can we establish achievable goals for the next year?

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U.S. FOOD & DRUG ADMINISTRATION

Real-World Evidence

FDA Update

Jacqueline Corrigan-Curay

Office of Medical Policy, CDER

October 1, 2018

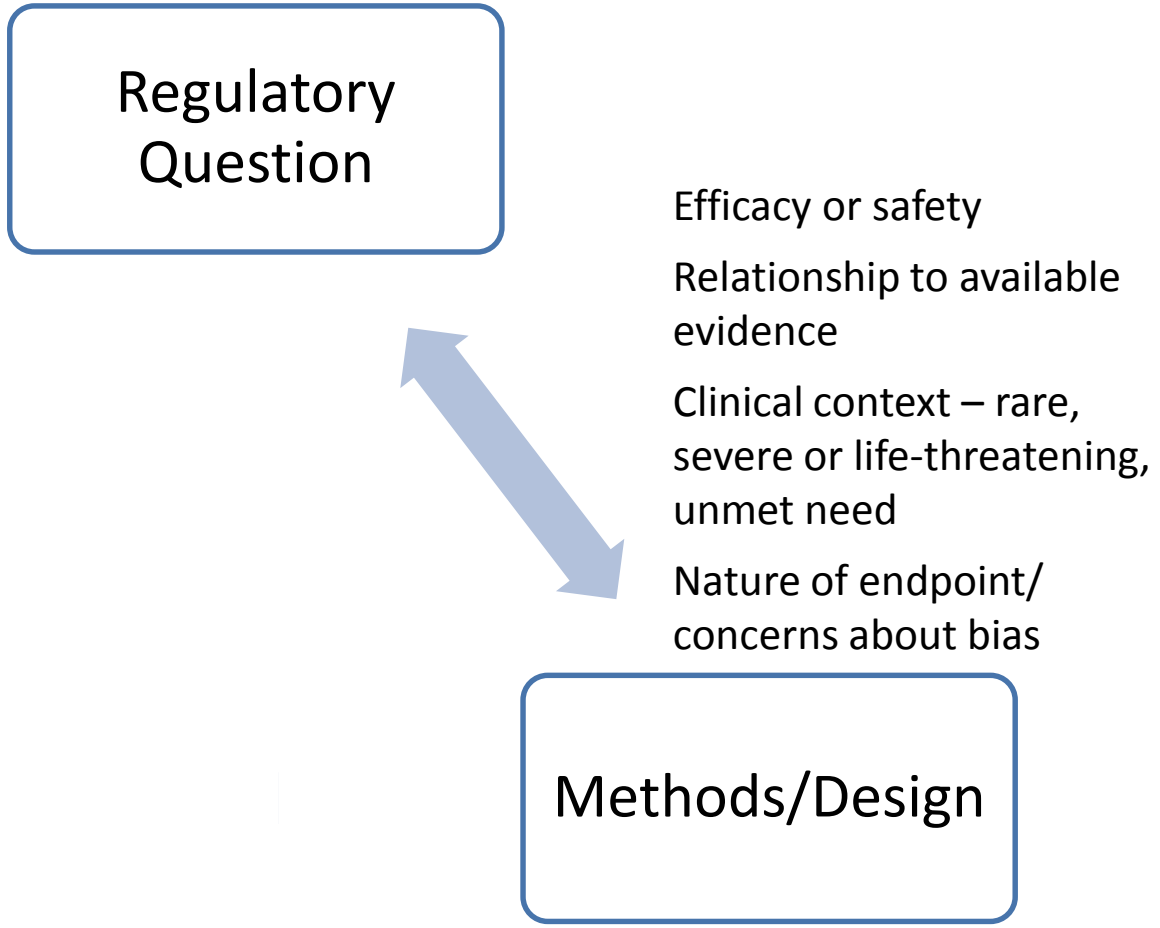
21st Century Cures Deliverables

- FDA shall establish a program to evaluate the potential use of real world evidence (RWE) to support:
  - Approval of new indication for a drug approved under section 505(c)
  - Satisfy post-approval study requirements
- Program will be based on a framework to be issued by December 2018
- Consultation with Stakeholders
- Demonstration Projects
- Guidance development - 2021

- **Real-World Data (RWD) are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.**
- **Real-World Evidence (RWE) is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD.**

Incorporating RWE Into Evidence Generation

Many factors must be considered at the same time



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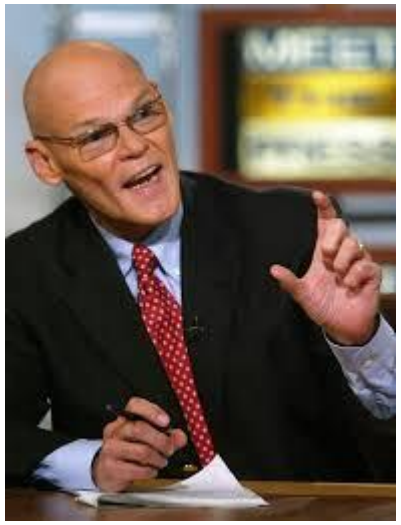
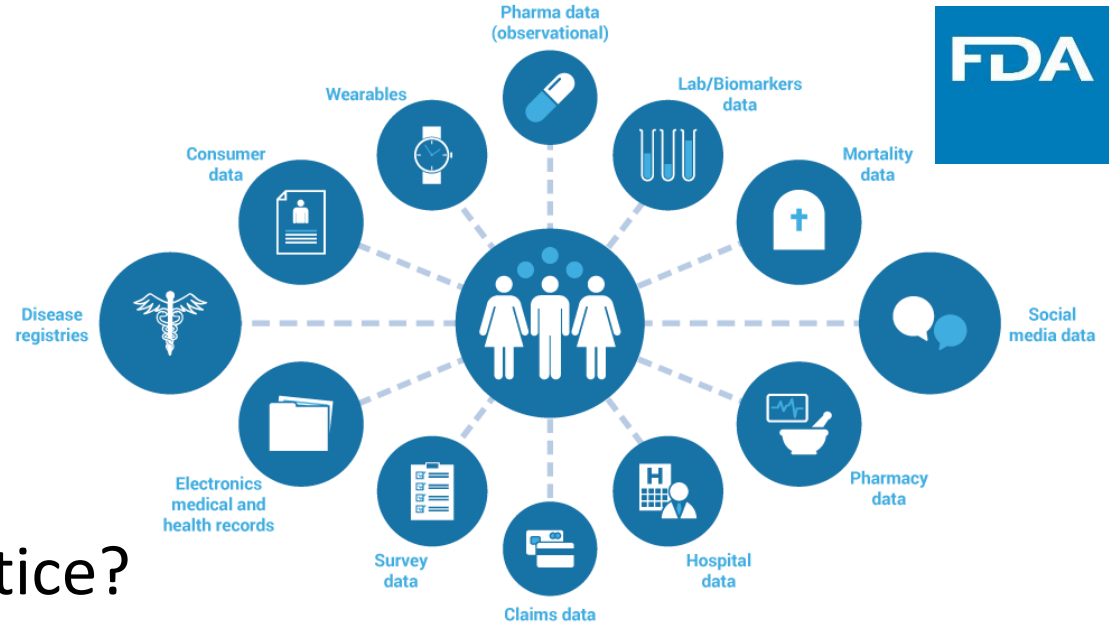


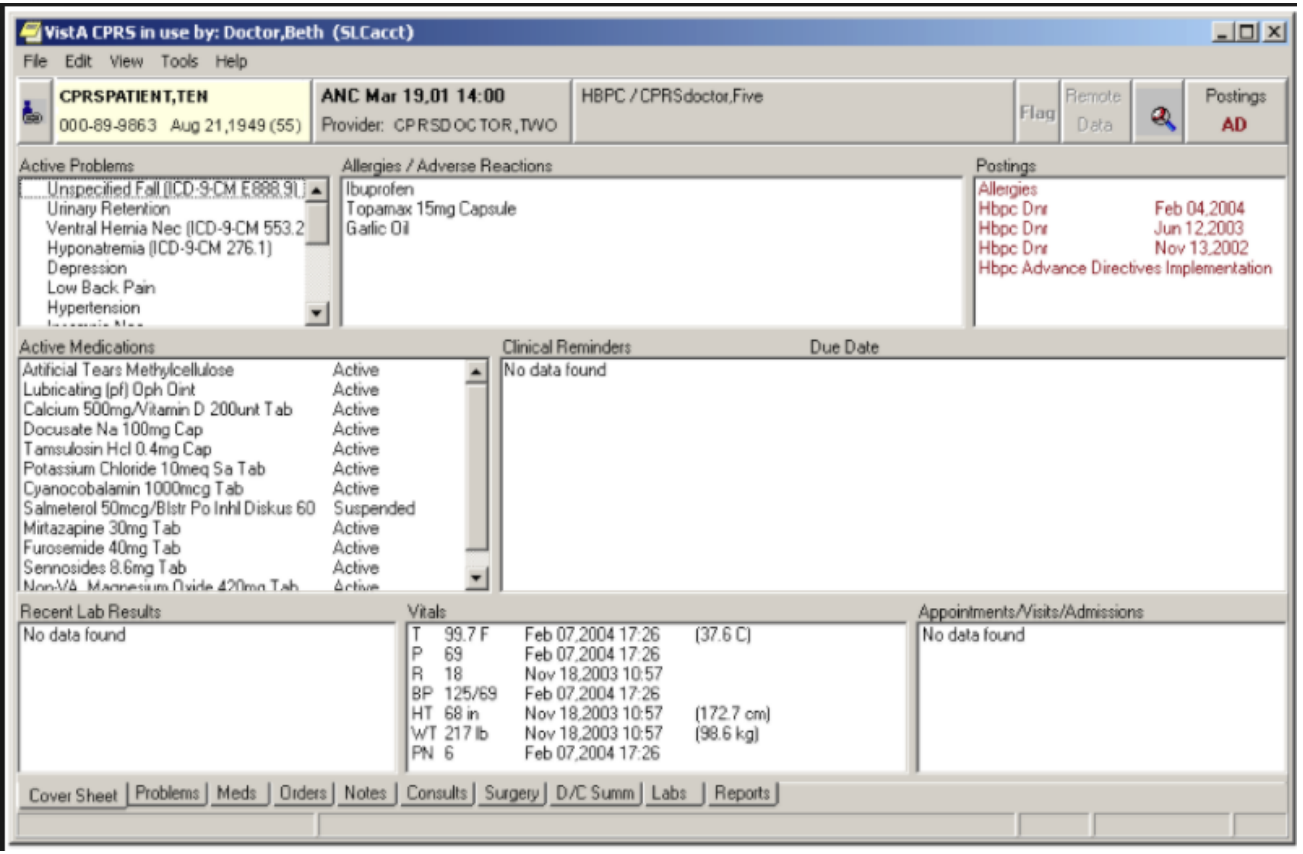
It's the data . . .



- Is it captured routinely in clinical practice?
  - Consistent measurement across systems/providers

    How do we measure this?
  - Is the frequency of assessment sufficient for evidence generation?
  - Are the data collected from a unique subset of patients, or it representative?
  - What is the quality of the data?
  - Is it possible to capture in multiple data bases, e.g. claims/EHRs for cross verification?
  - How much of the data is missing and is it random?
  - If there are gaps, how do we fill them?

Understanding Data Curation



Structured Data

≠

Clean Data

Mark Nagy, VP, Global Patient Outcomes and Real World Evidence at Eli Lilly & Co. pointed out the difficulty in obtaining specific information in datasets. His team found that in one dataset there were 1,000 different ways HBA1C was being reported.

Making Real World Evidence Less 'Messy' To Help With Drug Pricing

17 Sep 2018 Pink Sheet Pharma intelligence

Understanding the Relationships

JAMA Cardiology | Original Investigation

Accuracy of Medical Claims for Identifying Cardiovascular and Bleeding Events After Myocardial Infarction
A Secondary Analysis of the TRANSLATE-ACS Study

Patricia O. Guimarães, MD; Arun Krishnamoorthy, MD; Lisa A. Kaltenbach, MS; Kevin J. Anstrom, PhD; Mark B. Effron, MD; Daniel B. Mark, MD, MPH; Patrick L. McCollam, PharmD; Linda Davidson-Ray, MA; Eric D. Peterson, MD, MPH; Tracy Y. Wang, MD, MHS, MSc

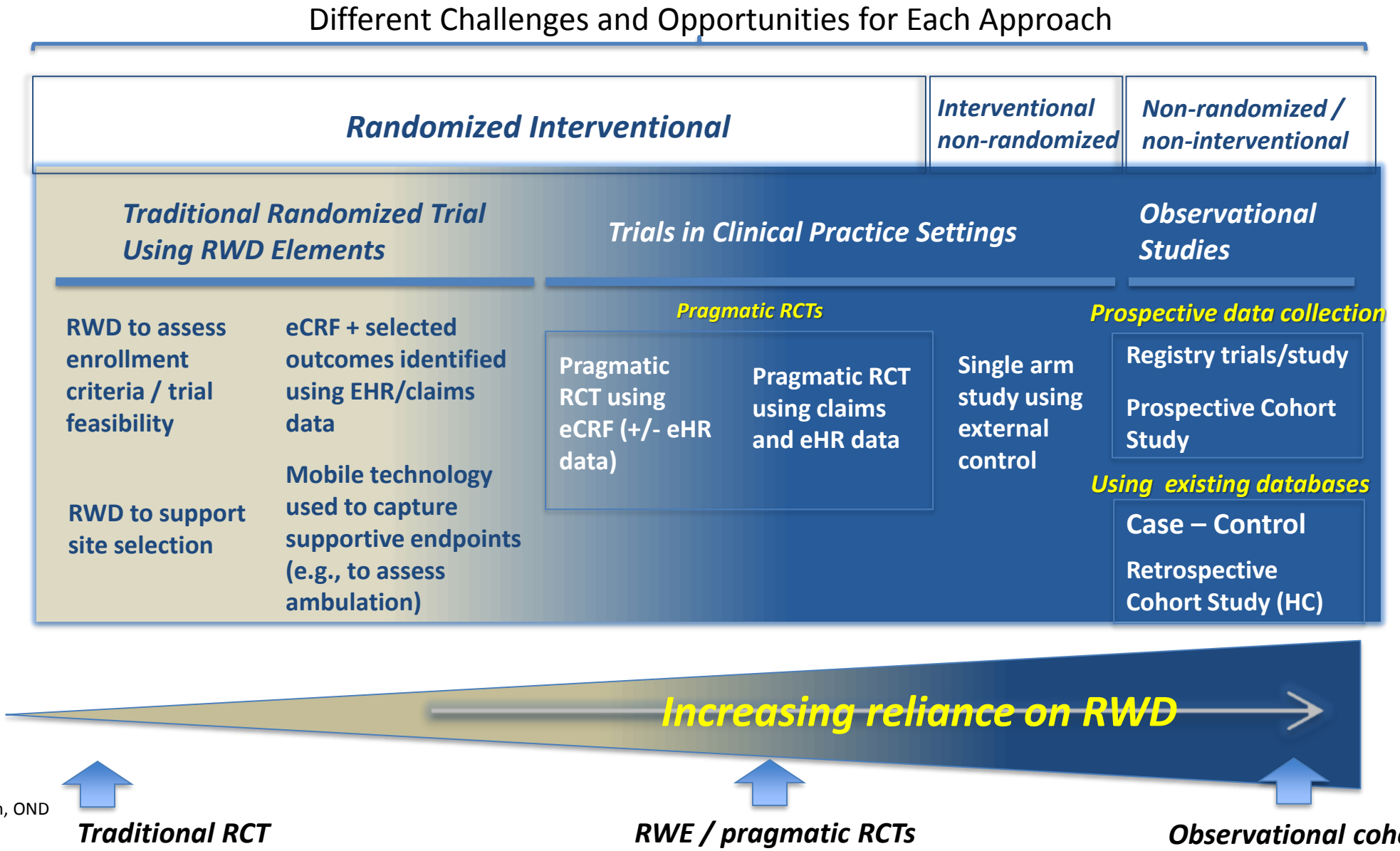
Agreement between medical claims–identified and physician- adjudicated events was modest, with a κ of 0.76 (95%CI, 0.73 to 0.79) for MI and 0.55 (95%CI, 0.41 to 0.68) for stroke events. In contrast, agreement between medical claims–identified and physician - adjudicated bleeding events was poor, with a κ of 0.24 (95% CI, 0.19 to 0.30) for any hospitalized bleeding event and 0.15 (95%CI, 0.11 to 0.20) for moderate or severe bleeding on the GUSTO scale

Establishing a Framework to Evaluate Real-World Endpoints

July 2018

- There is **notable correlation between several real-world endpoints and overall survival (OS),** indicating that real-world endpoints have the potential for evaluating treatment benefit.
- The range of OS observed in clinical trials used to approve checkpoint inhibitors is **highly similar** to the range observed in real-world populations, demonstrating that in this case the results from the clinical trial are generalizable to the broader population.

Wide spectrum of potential uses of RWD / RWE in clinical studies



Courtesy of Peter Stein, OND

Randomization and RWE

Pink Sheet
Pharma intelligence

CEO Clive Meanwell, The Medicines Company emphasized the ongoing need for randomization in real world data studies.
"**We are assuming that all randomized trials are done before approval and then afterwards you forget about randomization, he said. "When you look at real world data and you are trying to interpret what they mean we cannot throw out randomization. I think that would be a disaster**."
"I don't see enough commitment to randomization in real world research. I think it's very easy to pick up a database" and have programmers unpack it "and come to some very spurious conclusions for good or for ill," he stated.

SOUNDING BOARD

Real-World Evidence — What Is It and What Can It Tell Us?

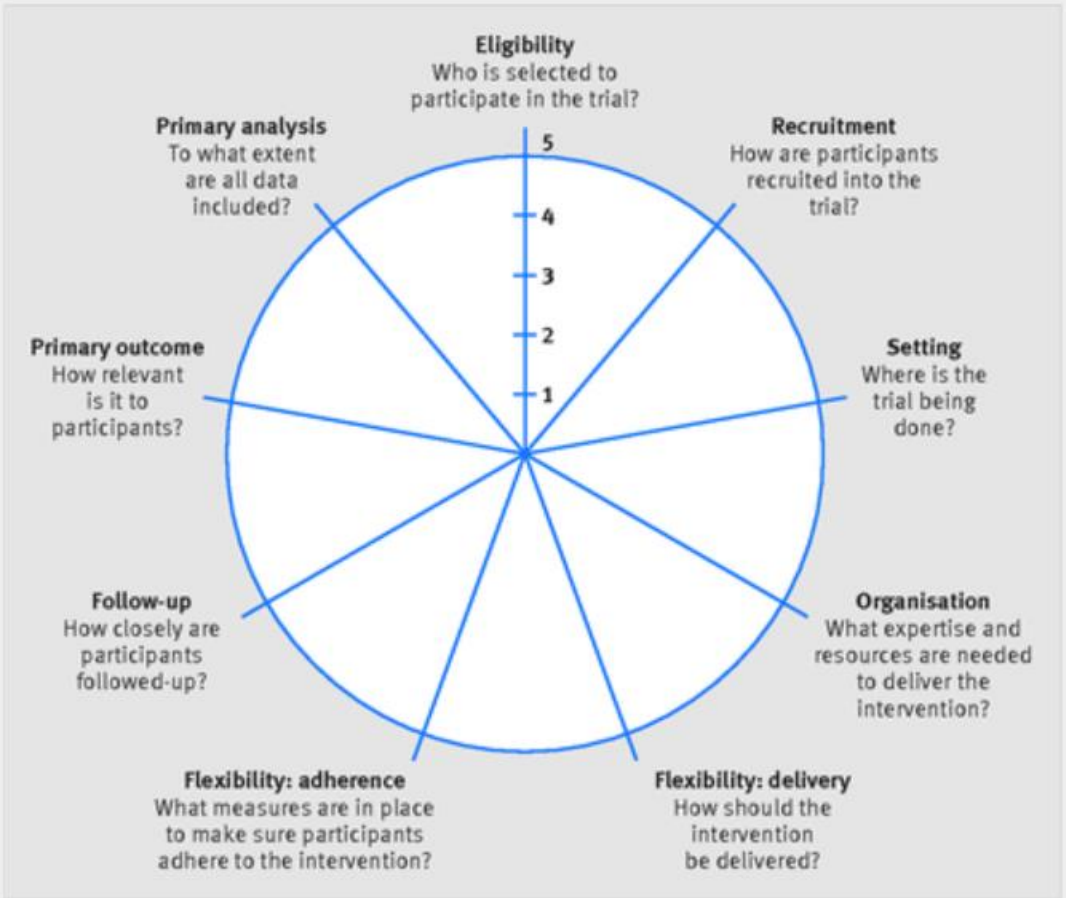
Rachel E. Sherman, M.D., M.P.H., Steven A. Anderson, Ph.D., M.P.P., Gerald J. Dal Pan, M.D., M.H.S., Gerry W. Gray, Ph.D., Thomas Gross, M.D., M.P.H., Nina L. Hunter, Ph.D., Lisa LaVange, Ph.D., Danica Marinac-Dabic, M.D., Ph.D., Peter W. Marks, M.D., Ph.D., Melissa A. Robb, B.S.N., M.S., Jeffrey Shuren, M.D., J.D., Robert Temple, M.D., Janet Woodcock, M.D., Lilly Q. Yue, Ph.D., and Robert M. Califf, M.D.

- As we adapt the tools and methods of traditional trials to real-world settings, we must consider the components of such trials that are critical to obtaining valid results and minimizing bias

- Incorrect to contrast the term “real-world evidence” with the use of randomization in a manner that implies that they are disparate or even incompatible concepts.

Opportunity – Trials with Pragmatic Features

- Identification of relevant questions for practitioners and patients
- Selection of an intervention that can be appropriately delivered in a clinical practice setting
- For studies of approved drugs, streamline data collection, e.g. AEs
- Integration of clinical data across health care systems to maximize data capture
- If needed utilize mobile technologies to fill in the gaps, including the capture of patient reported outcomes



Many trials can have 'pragmatic elements' while maintaining rigorous standards for data collection and assessment

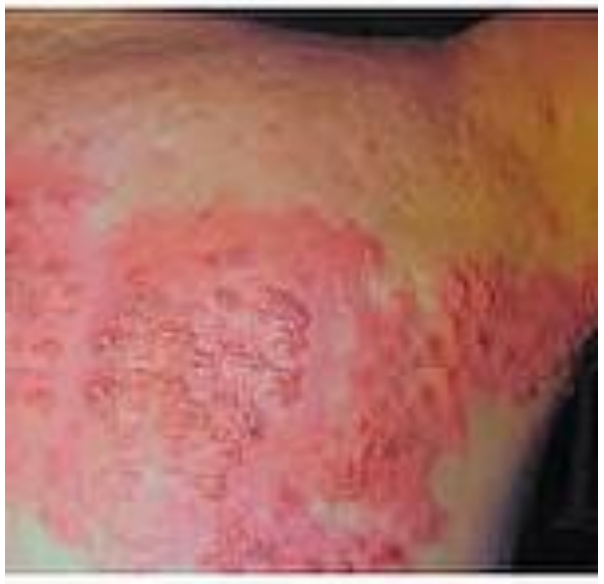
Non-Randomized Studies – Where Are They Being Used?

- **Currently in oncology and rare diseases where small populations or other considerations, e.g., ethical considerations may make RCTs difficult to do.**
  - **Use of RWD may add robustness to the external control**
  - **Contribute to post market commitments**
    - **2017 - Indication for Kalydeco (ivacaftor) expanded from 10 mutations to 33 mutations based in part on in-vitro data**
      - **PMC** Conduct a 3-year, single arm, observational study to further understand the clinical response to ivacaftor in various subgroups of CF patients with CFTR mutations deemed responsive to ivacaftor based on in vitro evidence.

MERCK Zostavax for Herpes Zoster (HZ)

Pre-approval efficacy trials

- **Shingle Prevention Study (SPS) -**
  - Double-blind, placebo-controlled (DBPC) RCT 38,546 individuals > 60
  - Median follow-up 3.1 years - reduction in risk of developing HZ 51% across all ages



- **ZOSTAVAX Efficacy and Safety Trial (ZEST)**
  - DBPC RCT of 22,439 individuals 50-59 years of age
  - Median follow-up 1.3 years - reduction in risk of developing HZ incidence 69.8%

- **Post Marketing Commitment to study long-term efficacy in ages 50-59**
  - Prospective observational study run by Kaiser Permanente Northern California
  - Data on > 1.3 million members 50 years and older, with over 390,000 individuals who received Zostavax and 100,000 individuals with more than 5 years follow up post vaccination
  - **Section 14 – Clinical Studies-Updated**: Vaccine effectiveness (VE) against HZ for 50-59 over first 3 years following vaccination and for individuals > 60 over five years

Additional Opportunities?

- **For approved drugs, what questions do we need to think about when considering non-randomized designs for supplemental indications?**
  - **Would the study build on existing evidence of effectiveness?**
  - **Are there potential advantages to a non-randomized design?**
    - **Assessing an outcome that is rare or requires long term follow-up making an RCT difficult**
  - **Do we need "empirical equipoise*" in clinical practice in choice of therapy?**
  - **Could the endpoint be influenced by patient or physicians assessment of the therapy?**
  - **Are relevant covariates captured in the data and can they be controlled for?**
  - **Are the results consistent across databases and with existing effectiveness evidence**
    - **Are there ways to assess the impact that unmeasured bias might have on the results?**
  - **Others?**

***Walker, A, Patrick, A. ….. Schneeweiss, S., Comparative Effectiveness Research 2013 3:11–20**

Transparency is Key

Future Medicine

JOURNALS BOOKS ABOUT US CONTACT US

JOURNAL OF COMPARATIVE EFFECTIVENESS RESEARCH, VOL. 6, NO. 1 | EDITORIAL

Building trust in real-world evidence and comparative effectiveness research: the need for transparency

thebmjopinion Latest Authors Topics

Improving transparency and replicability of healthcare databases to increase credibility of "real world" evidence

December 15, 2017

PharmaSUG 2018 - Paper RW-06

Improved Transparency in Key Operational Decisions in Real World Evidence

Rebecca Levin, Irene Cosmatos, Jamie Reifsnyder
United BioSource Corp.

Good Practices for Real-World Data Studies of Treatment and/or Comparative Effectiveness: Recommendations from the Joint ISPOR-ISPE Special Task Force on Real-World Evidence in Health Care Decision Making

PDS Pharmacoepidemiology & Drug Safety

Marc L. Berger[1,*], Harold Sox[2], Richard J. Willke[3], Diana L. Brixner[4], Hans-Georg Eichler[5], Wim Goettsch[6], David Madigan[7], Amr Makady[6], Sebastian Schneeweiss[8], Rosanna Tarricone[9], Shirley V. Wang[8], John Watkins[10], C. Daniel Mullins[11]

1. *A priori*, determine and declare that a study is a Hypothesis Evaluation Treatment Effectiveness (HETE) study or an Exploratory study based on conditions outlined below
2. Post a HETE study protocol and analysis plan on a public study registration site prior to conducting the study analysis.
3. Publish HETE study results with attestation to conformance and/or deviation from the study protocol and original analysis plan. Possible publication sites include a medical journal, or a publicly available web-site.
4. Enable opportunities to replicate HETE studies (i.e., for other researchers to be able to reproduce the same findings using the same data set and analytic approach). The ISPE companion paper lists information that should be reported in order to make the operational and design decisions behind a RWD study transparent enough for other researchers to reproduce the conduct of the study.
5. Perform HETE studies on a different data source and population than the one used to generate the hypotheses to be tested unless it is not feasible (e.g., another data set is not available)
6. Authors of the original study should work to publicly address methodological criticisms of their study once it is published.
7. Include key stakeholders (patients, caregivers, clinicians, clinical administrators, HTA/payers, regulators, manufacturers) in designing, conducting, and disseminating HETE studies.

We All Share a Common Goal – Meeting the Patient's Needs

- **Transparency**
- **Privacy**
- **Ensuring our conclusions about a drug's effectiveness is based on appropriate evidence**

- *"[W]e have a natural tension between bringing new innovation and creativity and breakthroughs in the areas of pharmaceutical drugs and medical devices to the market, and on the other hand, protecting the public by approving only safe and efficacious products."*

Senator Ted Kennedy 1997

Cited in Jennifer Kulynych, Will FDA Relinquish the Gold Standard for New Drug Approval - Redefining Substantial Evidence in the FDA Modernization Act of 1997, 54 Food & Drug L.J. 127 (1999)

Acknowledgements

- Robert Ball
- Khair ElZarrad
- Peter Stein
- David Martin
- Dianne Paraoan

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Meeting Regulatory Standards with Fit-For-Purpose RWE

Gregory Daniel, PhD, MPH

Deputy Director & Clinical Professor,

Duke-Robert J. Margolis, MD, Center for Health Policy

October 1, 2018

Thank you to the working group

Marc Berger
ISPOR

William Crown
OptumLabs

Benjamin Gutierrez
GlaxoSmithKline plc

Morgan Hanger
PatientsLikeMe

Stacy Holdsworth
Eli Lilly and Company

Gracie Lieberman
Genentech, Inc.

Panagiotis Mavros
Janssen

Sally Okun
PatientsLikeMe

Soulabha Ramachandran
GlaxoSmithKline plc

Amy Rudolph
Novartis Pharmaceuticals Corporation

Khaled Sarsour
Genentech, Inc.

Kristin Sheffield
Eli Lilly and Company

Eileen Thorley
PatientsLikeMe

Richard Willke
ISPOR

Recent legislation directs FDA to explore further uses of RWE within the regulatory framework

Prescription Drug User Fee Act VI

- Requires FDA to enhance use of RWE for use in regulatory decision-making
- FDA must:
  - Hold a public workshop with key stakeholders (e.g., patients, industry, academia) by the end of 2018
  - Initiate (or fund) activities (e.g., pilot studies or methodology development projects) aimed at addressing key concerns and considerations in the use of RWE by the end of 2019
  - Issue draft guidance by the end of 2021

21st Century Cures Act

- Requires FDA to establish a program to evaluate the 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 issue:
  - A draft framework for this program by the end of 2018
  - Draft guidance by the end of 2021

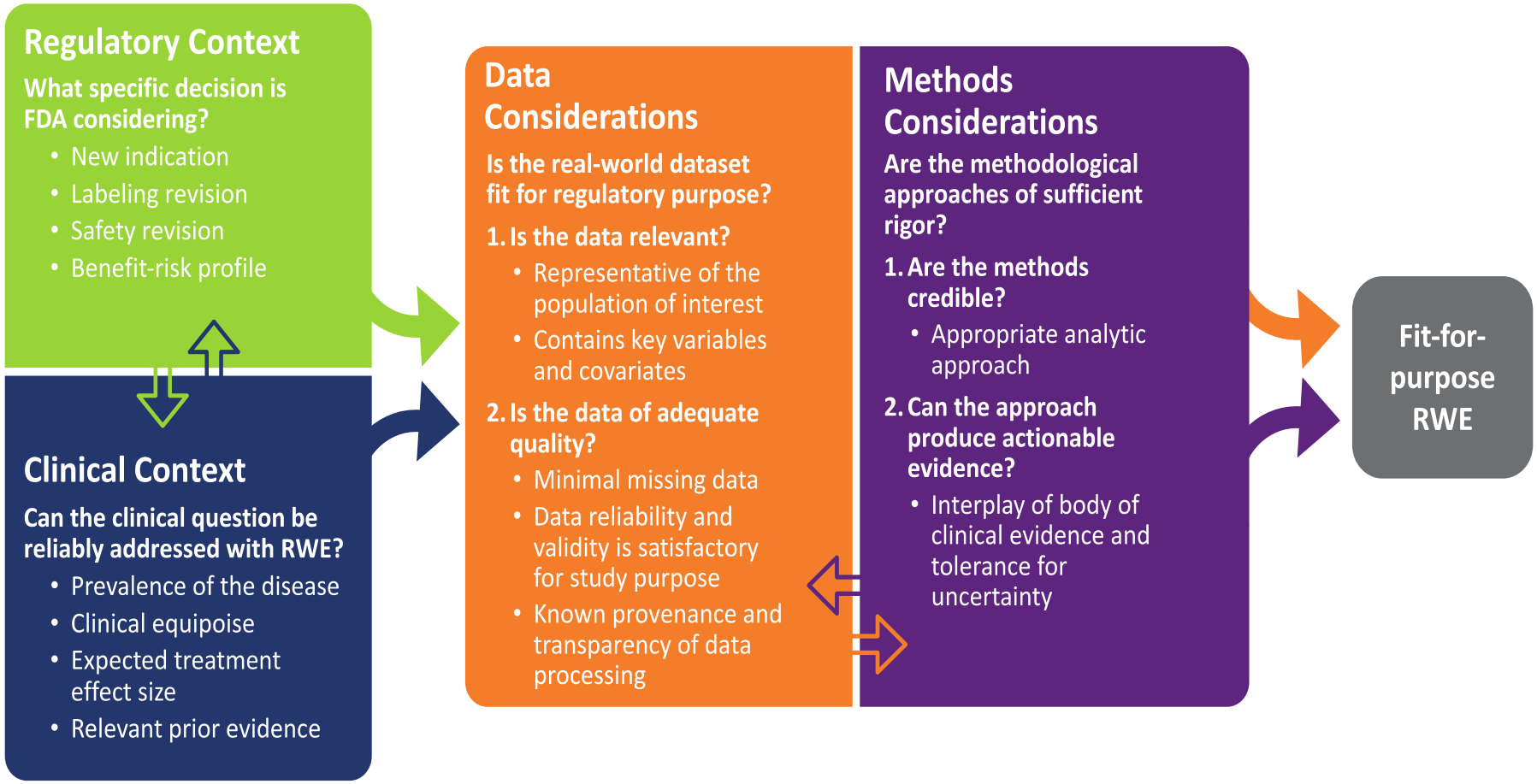
Value of using RWE for estimating treatment effects?

- Traditional RCTs will continue to be the gold standard for drug development
- RWE offers the opportunities (versus RCTs) to develop evidence that:
  - Includes broader populations/uses more typical of routine practice
  - Includes effects on longer-term endpoints and endpoints more relevant to patients, providers, payers
- While concerns around validity and reliability can and will exist, observational RWE studies can:
  - Provide an opportunity to develop robust evidence using high quality data and sophisticated methods for producing causal-effect estimates when randomization is infeasible
  - Enable longer follow-up to better understand long term outcomes
  - Be conducted in more cost-effective and efficient ways for certain types of clinical questions

Value of using RWE to support regulatory decisions?

- Leveraging RWE to support new indications and label revisions
  - Can help accelerate high quality RWE earlier in the product lifecycle, providing more relevant evidence to support higher quality and higher value care for patients
  - Incorporating RWE into product labeling can lead to better-informed patient and provider decisions w/more relevant information
- Ultimate regulatory acceptability, however, will depend upon how robust these studies can be – that is, how well they minimize the potential for bias and confounding

Considerations for pursuing RWE has many components



Companies will need to weigh multiple factors

- Strength of the relevant prior evidence (Clinical Context)
- Remaining uncertainties and evidentiary gaps being addressed by the observational RWE (Clinical Context)
- Credibility of the study design (observational or randomized) and resultant RWE (Data and Methods Considerations)
- Specific regulatory decision being made (Regulatory Context)
- Degree of regulatory flexibility that may be warranted (Regulatory Context)

Overarching Question:

Can we meet regulatory standards with credible, robust RWE?

Fit-for-*regulatory*-purpose RWE will need to map to regulatory standards

*"Reports of **adequate and well-controlled** investigations provide the primary basis for determining whether there is '**substantial evidence**' to support the claims of effectiveness for new drugs.*

Therefore, the study report should provide sufficient details of study design, conduct, and analysis to allow critical evaluation and a determination of whether the characteristics of an adequate and well-controlled study are present"

21 CFR 314

Fit-for-*regulatory*-purpose RWE will need to map to regulatory standards

- AWC studies, per 21 CFR 314.126, have the following characteristics:
  - A protocol and results report containing a clear objective statement and summary of proposed methods and analysis
  - Use of a valid comparison with a control (placebo, dose, active, historical, etc.)
  - A method of selecting patients that adequately assures they have the disease
  - A treatment assignment method that minimizes bias and ensures comparability, between arms, ordinarily randomization
  - Measures to minimize subject, observer, and analyst bias, such as blinding
  - Well-defined and reliable methods for assessing patient response
  - Adequate analytical plan for assessing the effects of the drug

More work needs to be done

- For randomized RWE (e.g., PCTs) → While methods and data collection questions remain, meeting the substantial evidence standard using is somewhat straightforward
- For observational RWE → What factors into the decision to pursue?

Adequate and well-controlled

- How do we know if observational study(ies) can be considered AWC?
- What should they look like?
  - Appropriate comparisons
  - Balanced groups
  - Adequate control for observed biases

Substantial evidence

- If an evidence package includes AWC observational study(ies), what factors into substantial evidence?
  - Treatment effect size?
  - Multiple studies with consistency?
  - Strength of relevant prior evidence?
  - Regulatory flexibility due to the disease or high unmet need?
  - Specific regulatory question?

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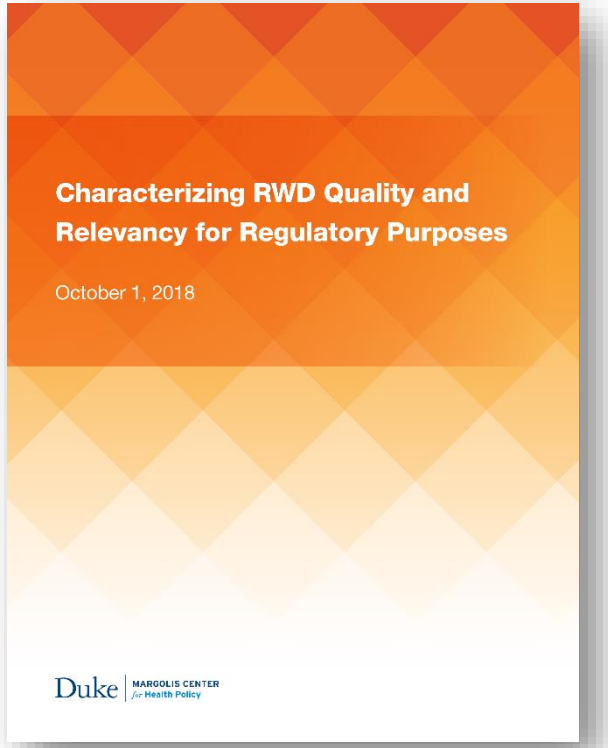
Characterizing RWD Quality and Relevancy and for Regulatory Purposes

Christina Silcox, PhD

Managing Associate

Duke-Robert J. Margolis, MD, Center for Health Policy

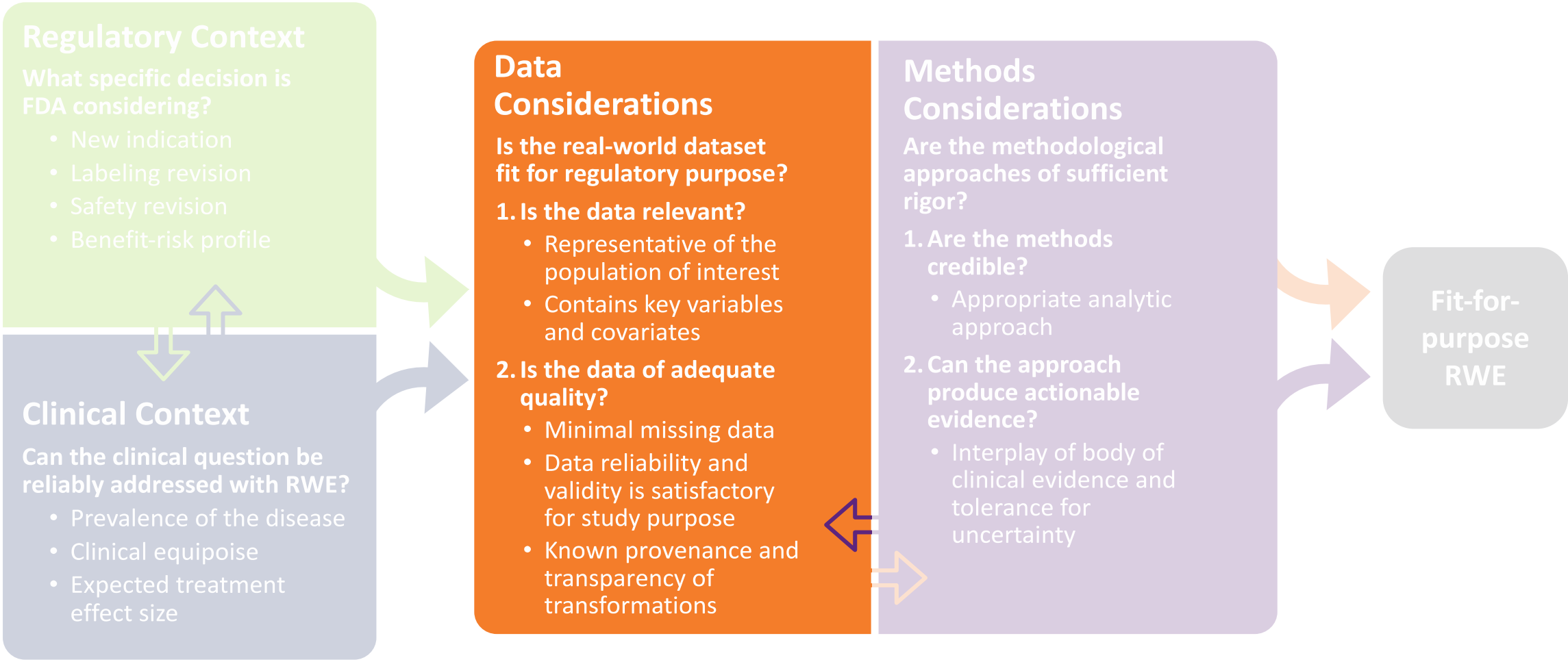
October 1, 2018



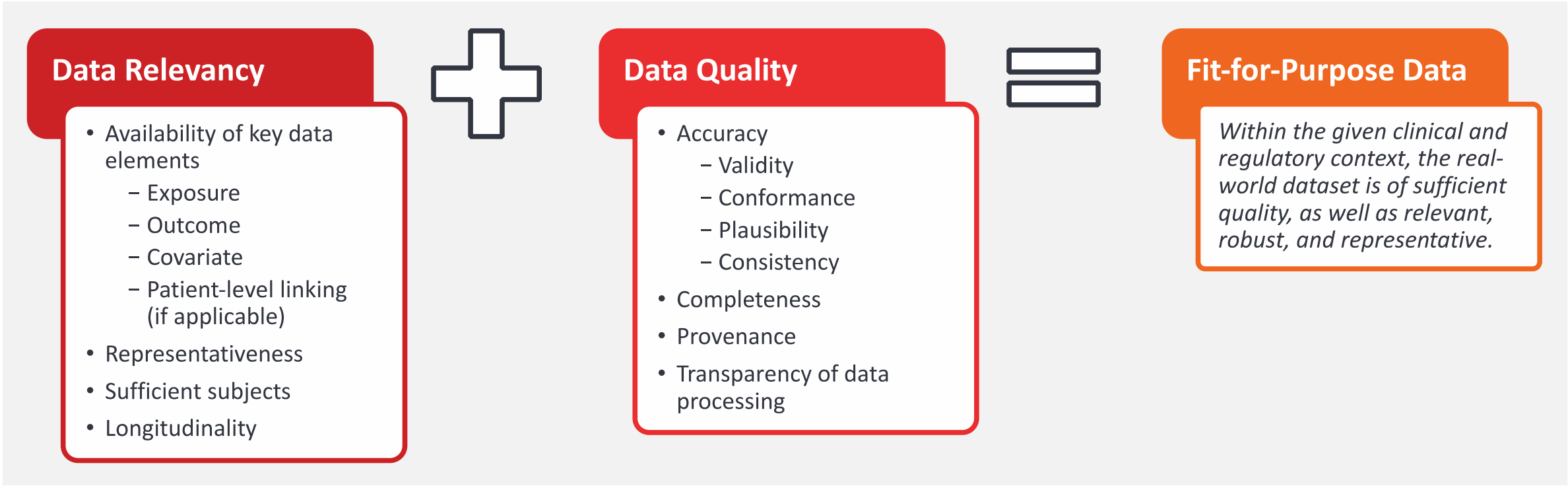
Real-World Data (RWD)

Data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources

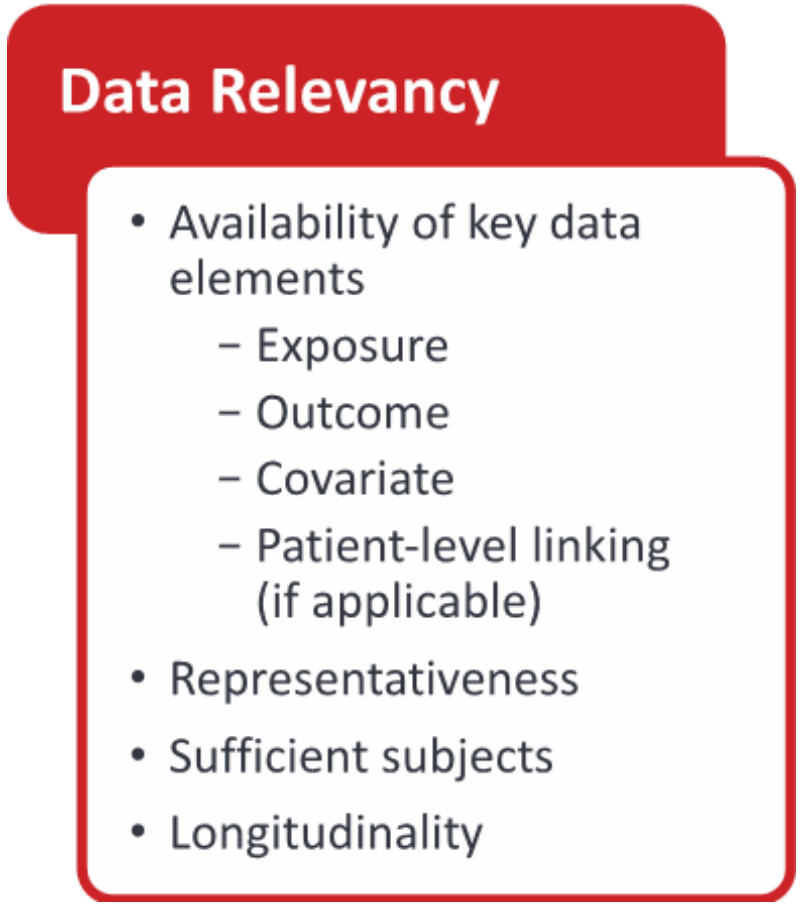
Framework


Regulatory Context
What specific decision is FDA considering?
• New indication
• Labeling revision
• Safety revision
• Benefit-risk profile
Clinical Context
Can the clinical question be reliably addressed with RWE?
• Prevalence of the disease
• Clinical equipoise
• Expected treatment effect size
Data Considerations
Is the real-world dataset fit for regulatory purpose?
1. Is the data relevant?
• Representative of the population of interest
• Contains key variables and covariates
2. Is the data of adequate quality?
• Minimal missing data
• Data reliability and validity is satisfactory for study purpose
• Known provenance and transparency of transformations
Methods Considerations
Are the methodological approaches of sufficient rigor?
1. Are the methods credible?
• Appropriate analytic approach
2. Can the approach produce actionable evidence?
• Interplay of body of clinical evidence and tolerance for uncertainty
Fit-for-purpose RWE

Evaluating relevancy and quality



Data relevancy



- Are the patients in the dataset representative of the population of interest (i.e., patients using or who will be using the medical product)?
- Are critical data fields representing exposures, covariates, and outcomes present? If not, are these variables able to be algorithmically derived using data fields that are present?
- If more than one data source is required, are data fields present that permit accurate linking at the patient-level?
- Are there sufficient persons and follow-up time in the data source to demonstrate the expected treatment effect including adequate capture of potential safety events?

Data quality

- Are the patients in the dataset representative of the population of interest (i.e., patients using or who will be using the medical product)?
- Are critical data fields representing exposures, covariates, and outcomes present? If not, are these variables able to be algorithmically derived using data fields that are present?
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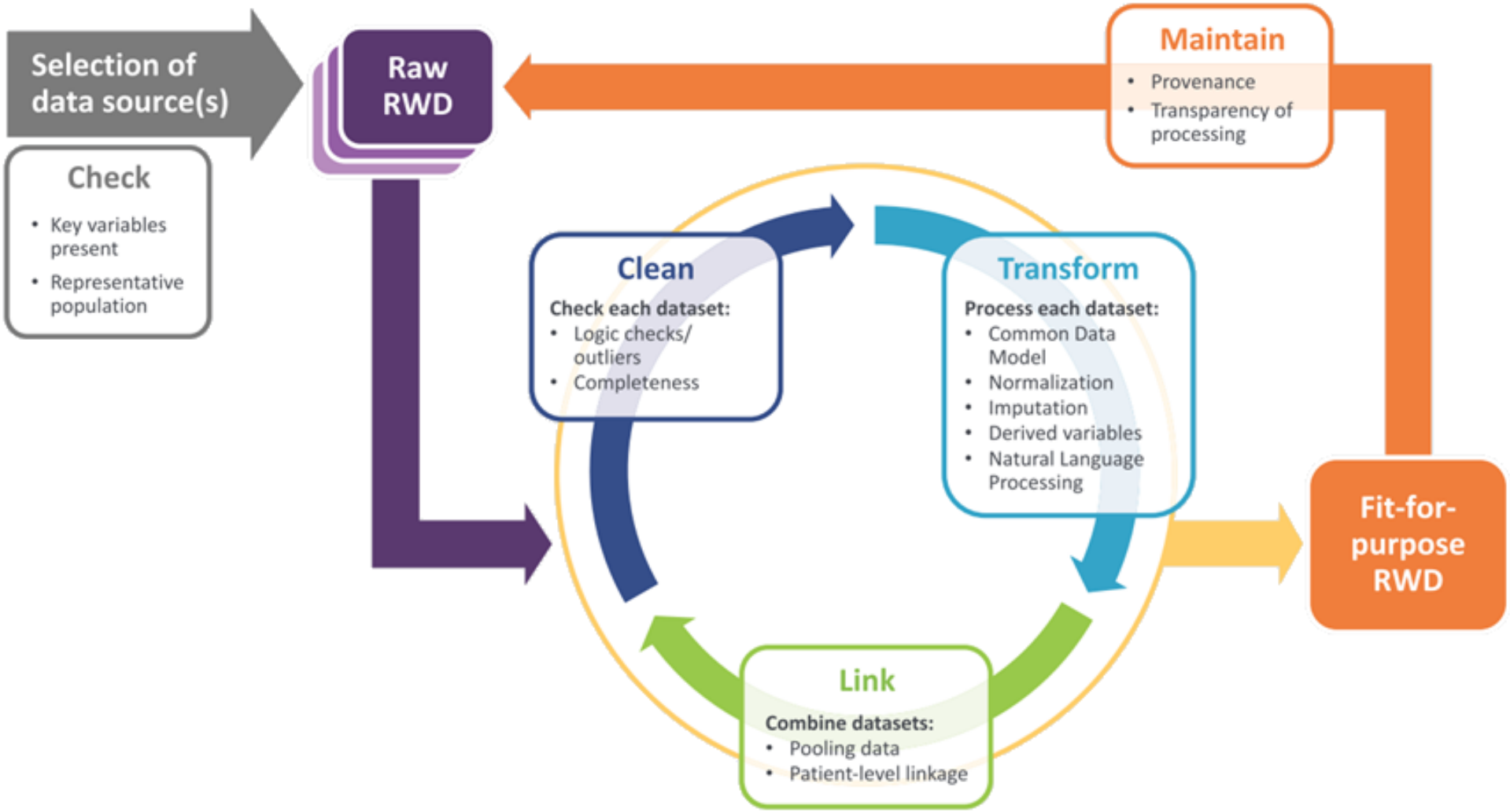
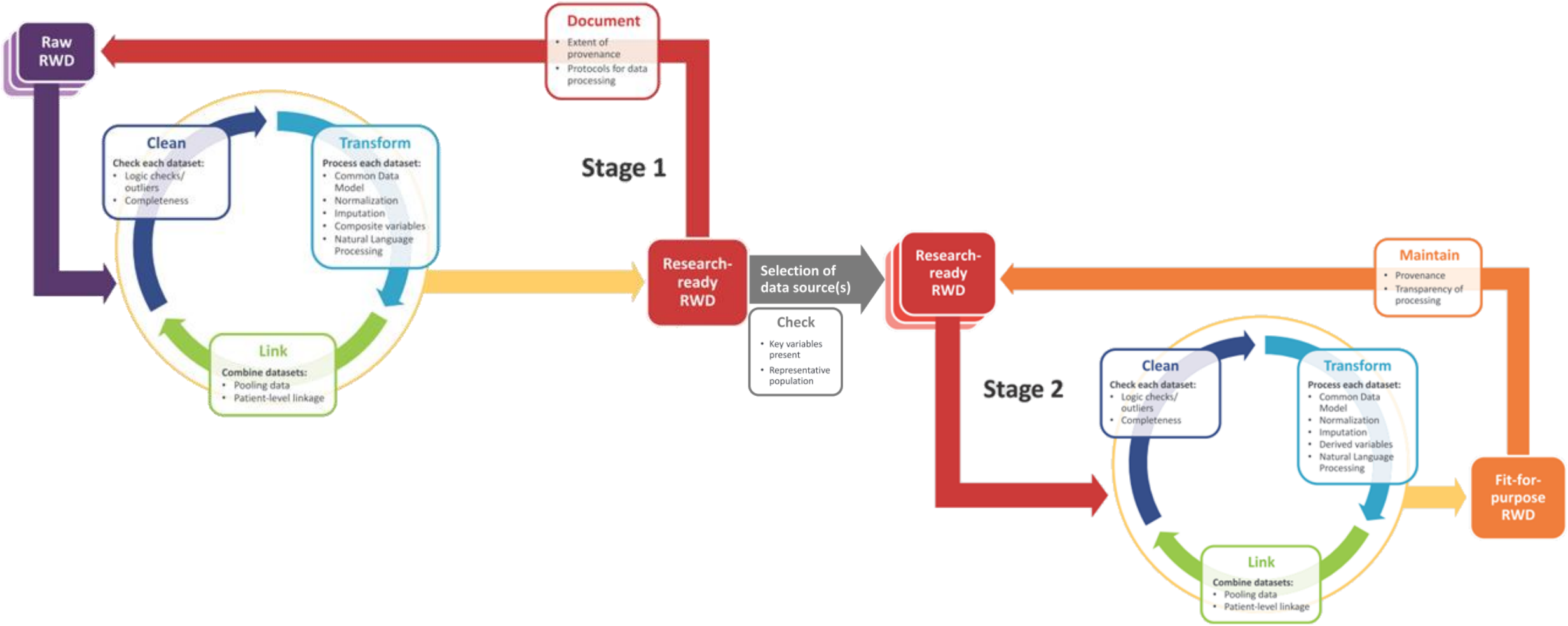
- Are there sufficient persons and follow-up time in the data source to demonstrate the expected treatment effect including adequate capture of potential safety events?

Raw to fit-for-regulatory-purpose RWD



Research-ready databases



Documentation recommendations

- Selection of RWD
- Processing RWD
- Fit-for-regulatory-purpose RWD

Documentation recommendations

- Selection of RWD
  - Confirmation that the RWD contains the pre-identified critical data fields as well as a sufficient and representative population for generalization of results to the population of interest
  - The extent of traceability and provenance of the data from initial collections to when the investigators acquired it.
  - Initial assessment/discussion of potential selection and information bias associated with the selected data source
- Processing RWD
- Fit-for-regulatory-purpose RWD

Documentation recommendations

- Selection of RWD
- Processing RWD
  - Cleaning
    - Documentation of the cleaning process, including validation of data against transparent standards and removal of erroneous data
    - Summary measures of data completeness and identified errors
  - Transforming
    - Transformation procedures for RWD should be documented, including the purpose, historical uses, and any performance metrics
    - Critical transformations such as data imputation, algorithmic data summarization, and de-identification may require more information on the changes to the data post-hoc
  - Linking
    - Data linkages constitute either pooling common datasets to increase sample size or patient-level linking of disparate datasets to increase data richness
    - Performance metrics for procedures that link datasets should be reported
    - Critical differences in each distinct dataset should be reported, including varying methods of measurement for common data fields, selection bias, and changes in standards
    - Procedures for adjudicating conflicting data for unique individuals or observations should be reported
- Fit-for-regulatory-purpose RWD

Documentation recommendations

- Selection of RWD
- Processing RWD
- Fit-for-regulatory-purpose RWD
  - Assessments of selection bias from data sources;
  - Assessments of information bias from data sources;
  - Impact of assumptions and procedures from data cleaning, transformation, de-identification, and linkages;
  - Assessment of changes in key data element capture and coding over time;
  - Measurements of accuracy for critical data fields, such as consistency with source, sensitivity, and specificity of calculation and/or abstraction;
  - Historical or verified validity measures of critical data fields; and
  - Assessments of data completeness by field and over time.

Thank you to the working group

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Lisa Wruck
Duke University

Second Annual Duke-Margolis Conference on Real-World Data and Evidence

National Press Club

October 1, 2018

Pilot project data: Correlation of real-world endpoints to overall survival among immune checkpoint inhibitor-treated aNSCLC patients

Jeff Allen, PhD
Friends of Cancer Research

October 1, 2018

Establishing a Framework to Evaluate Real-World Endpoints

Project Goals: Explore potential endpoints that may be fit for regulatory purposes as well as assessing long term benefits of a product	
Project Focus	Evaluate the performance of real-world endpoints across multiple data sets by focusing on a common question: ***What outcomes can be evaluated for advanced NSCLC (aNSCLC) patients treated with immune checkpoint inhibitors?***
Research Objectives	Objective 1: Characterize the demographic and clinical characteristics of aNSCLC patients treated with immune checkpoint inhibitors Objective 2: Assess ability to generate real-world endpoints (OS, PFS, TTP, TTNT, TTD) in aNSCLC patients treated with immune checkpoint inhibitors, and segmented by clinical and demographic characteristics Objective 3: Assess performance of real-world endpoints (PFS, TTP, TTNT, TTD) as surrogate endpoints for overall survival (OS)
Study Design	This is a retrospective observational analysis of data derived from electronic health record (EHR) and claims based databases. The datasets generated for the study will include all relevant, retrospective patient-level data available for eligible individuals up to the data cutoff date, pending approval by a third-party de-identification.
Data Partners	**Cota, Flatiron Health, IQVIA, Kaiser Permanente/CRN, Mayo Clinic/OptumLabs®, and PCORnet/University of Iowa**

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Real-World Endpoint Assessment

Real-world derived endpoint definitions

Overall survival (OS)

- *Data definition / computation*: length of time from the date the patient initiates the PD-(L)1 regimen to the date of death. Patients without a date of death will be censored at their last known activity.

Time to Next Treatment (TTNT)

- *Data definition / computation*: length of time from the date the patient initiates the PD-(L)1 regimen to the date the patient initiates their next systemic treatment. When subsequent treatment is not received (e.g., continuing on current treatment), patients will be censored at their last known activity.

Time to Treatment Discontinuation (TTD)

- *Data definition / computation*: length of time from the date the patient initiates the PD-(L)1 regimen to the date the patient discontinues treatment. Patients still on treatment will be censored at their last known activity.

Definition of progression in aNSCLC as evident in the EHR

A **progression event** is a distinct episode in which the treating clinician concludes that there has been growth or worsening in the aNSCLC. The progression event (and date) is based on review of the patient chart.

Progression Free Survival (PFS)

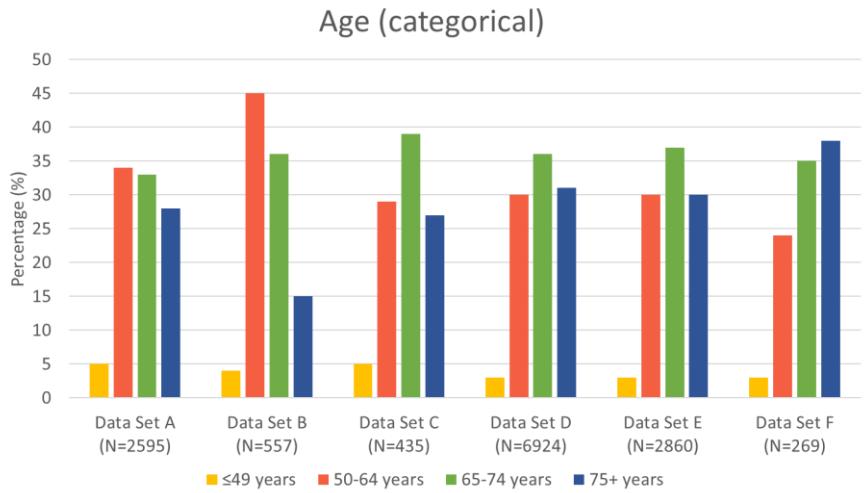
- *Data definition / computation*: length of time from the date the patient initiates the PD-(L)1 regimen to the date that a progression event as evident in the EHR is documented in the patient's chart or the patient passes away. Patients without a progression event or date of death will be censored at the end of the patient's chart.

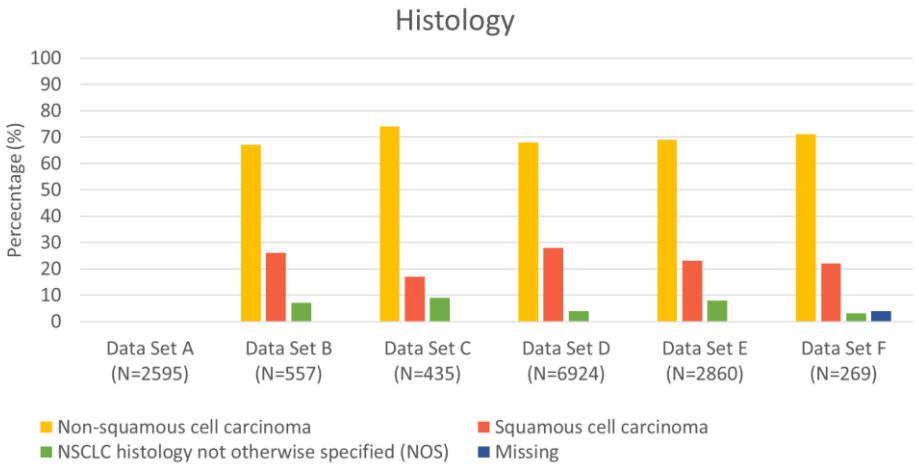
Time to Progression (TTP)

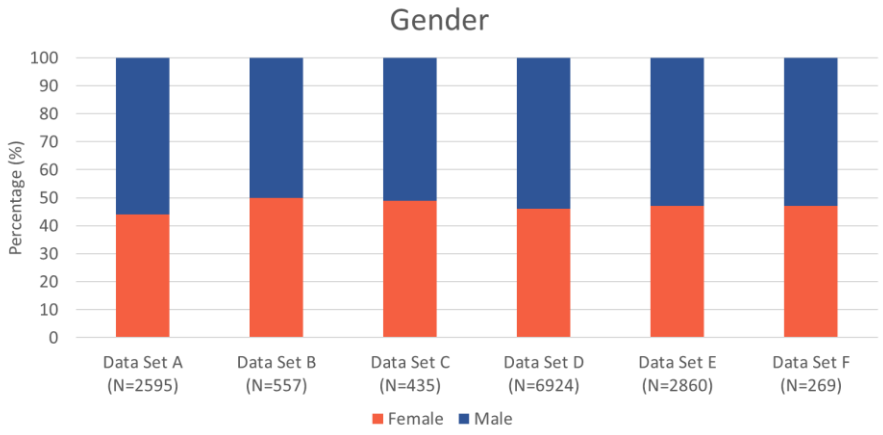
- *Data definition / computation*: length of time from the date the patient initiated the PD-(L)1 regimen to the date that a progression event as evident in the EHR is documented in the patient's chart (excludes death as an event). Patients without a progression event will be censored at the end of the patient's chart.

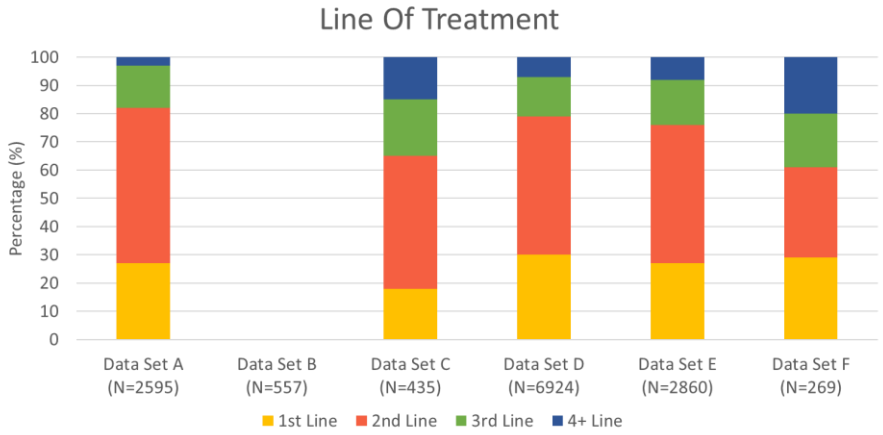
Shared demographic and clinical characteristics among data sets

Table 1









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Real-world Overall Survival (OS), Time to Discontinuation (TTD) & Time to Next Treatment (TTNT)

Table 2

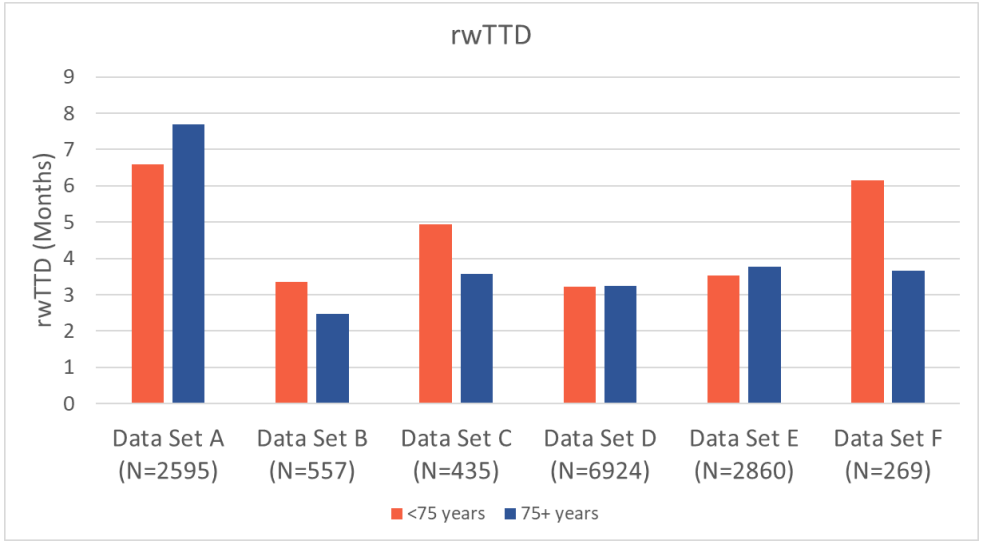
Data Set	rwOS	rwTTD	rwTTNT
Data Set A	13.50 [12.80, 14.50] #	7.03 [6.27, 9.97]	22.50 [NA]
Data Set B	15.78 [12.2, 24.59]; 8.58 [7.56, 10.26] *	3.25 [2.76, 3.75]	
Data Set C	8.67 [6.83, 10.02]	4.70 [3.68, 5.52]	11.60 [8.80, 16.10]
Data Set D	9.15 [8.82, 9.51]	3.21 [3.21, 3.44]	14.03 [12.89, 15.15]
Data Set E	12.69 [11.7, 13.87]	3.63 [3.40, 3.87]	12.07 [11.24, 13.48]
Data Set F	12.30 [9.61, 16.94]	4.60 [3.71, 6.32]	12.50 [9.29, NA]

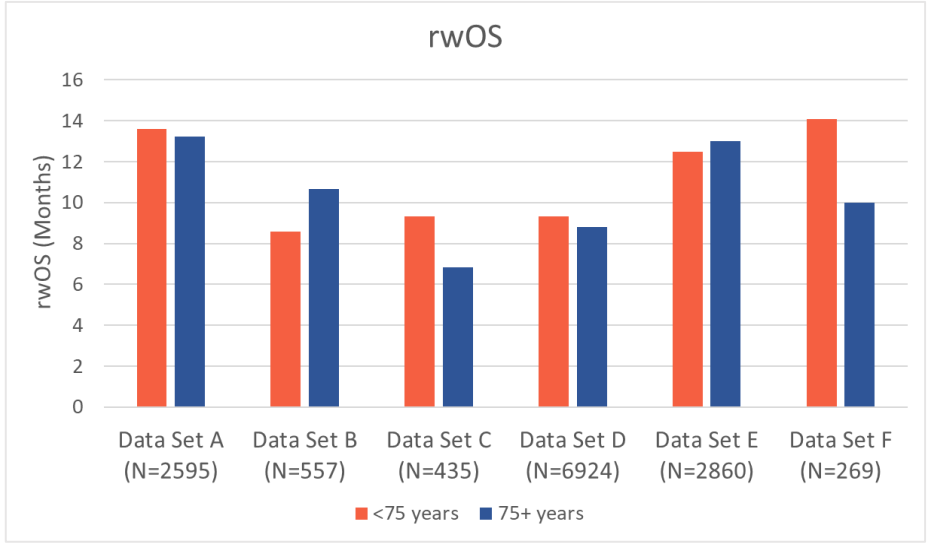
OS was calculated as days between I/O initiation and disenrollment.

* Sites with social security or state death data, censored at estimated earliest date such data should be available if no death was observed

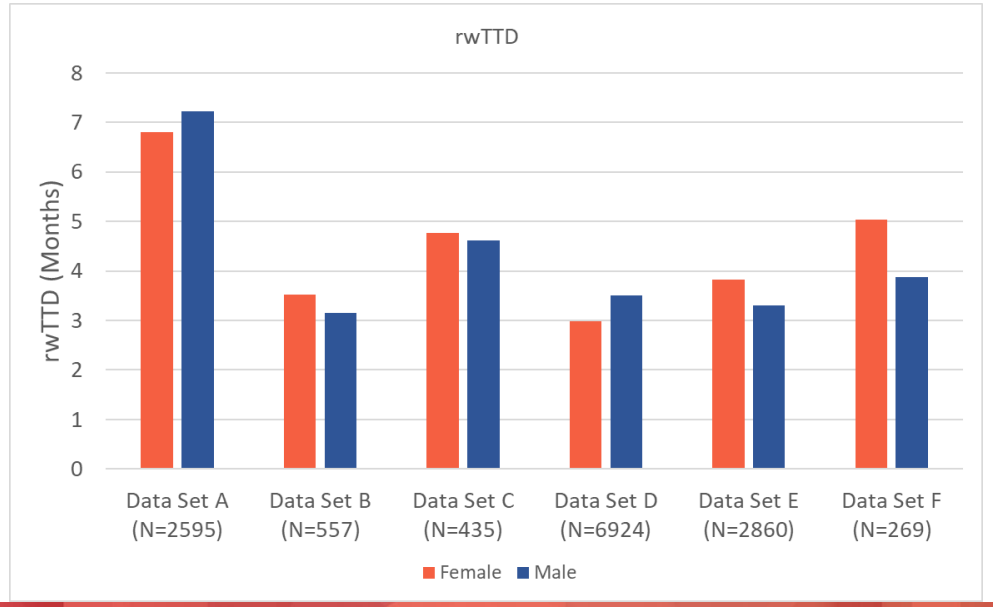
Table 2

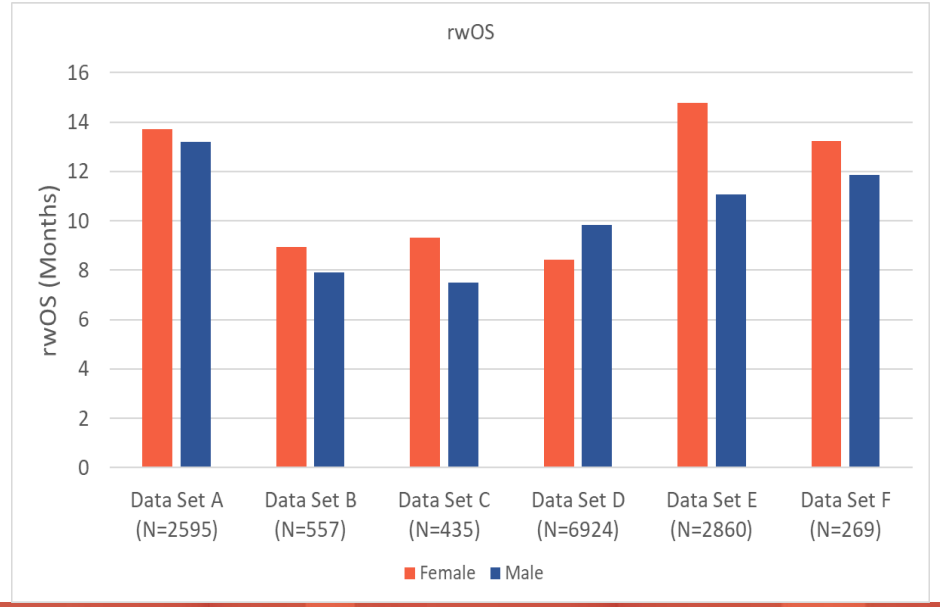
Age (Binary)





Gender





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Correlation between real-world overall survival and real-world extracted endpoints

	rwOS vs rwTTNT		rwOS vs rwTTD	
Data Set	**N**	**Correlation [95% CI]**	**N**	**Correlation [95% CI]**
Data Set A	83	0.36	254	0.63
Data Set B			225	0.62 [0.54, 0.69]
Data Set C	96	0.70 [0.58, 0.79]	295	0.89 [0.86, 0.91]
Data Set D	1203	0.61 [0.57, 0.64]	4337	0.80 [0.79, 0.81]
Data Set E	358	0.62 [0.54, 0.68]	1456	0.77 [0.75, 0.79]
Data Set F	39	0.46 [0.33, 0.81]	142	0.80 [0.66, 0.85]

	rwOS vs rwPFS		rwOS vs rwTTP	
Data Set	**N**	**Correlation [95% CI]**	**N**	**Correlation [95% CI]**
Data Set D	4337	0.75 [0.74, 0.76]	2286	0.60 [0.57, 0.63]
Data Set F	142	0.84 [0.62, 0.86]	55	0.56 [0.21, 0.71]

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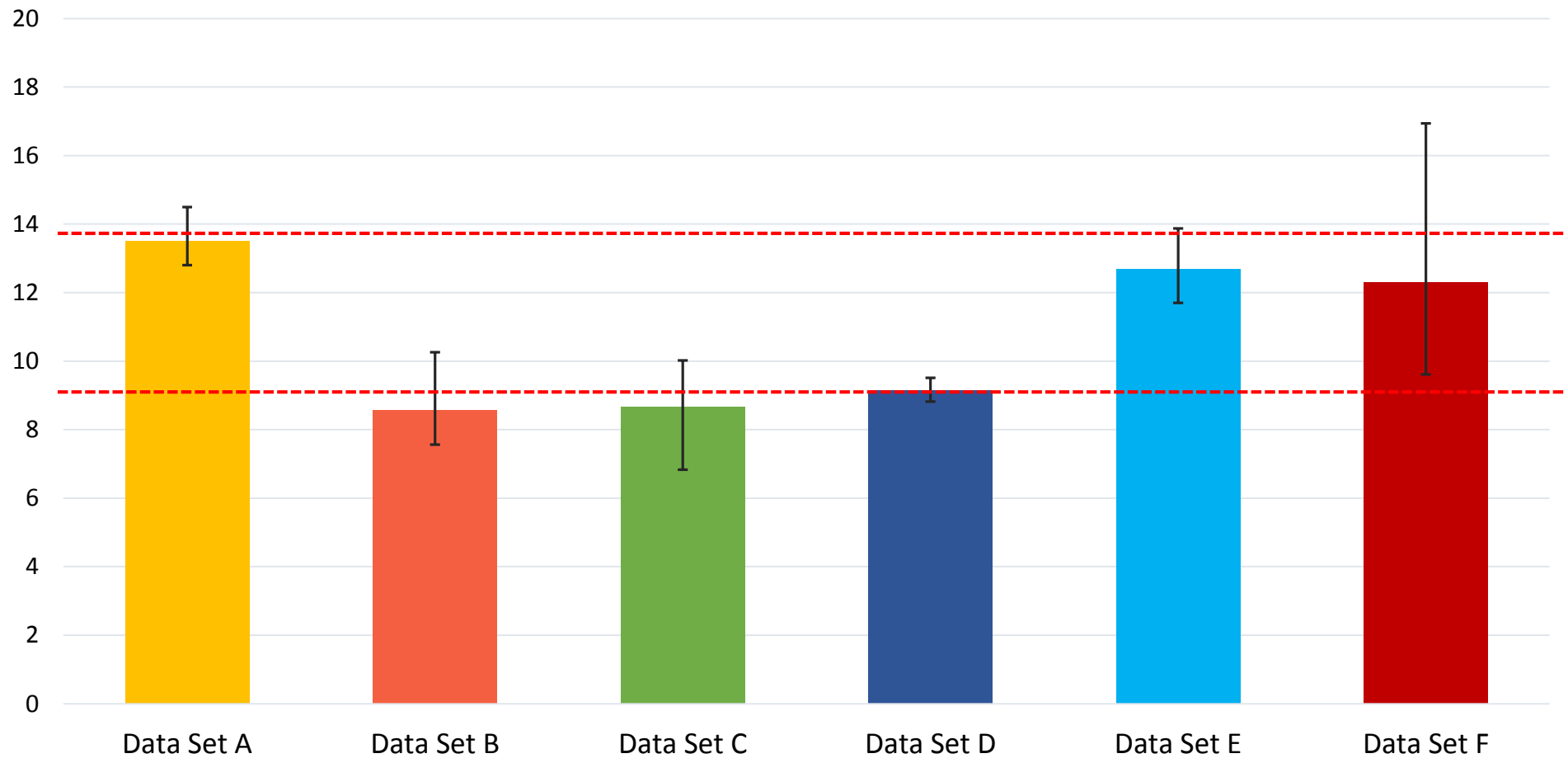
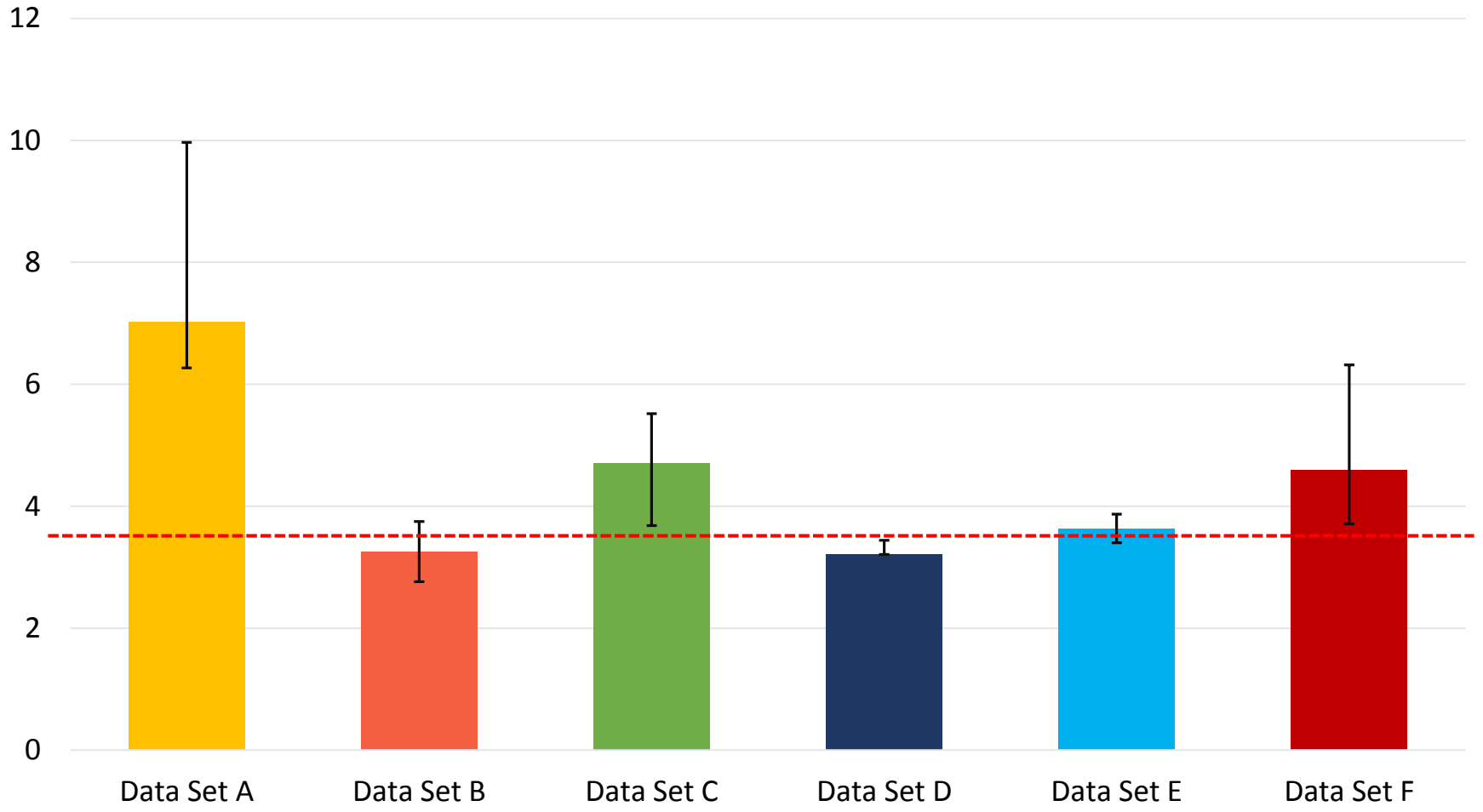
Real-world Overall Survival



FRIENDS of CANCER RESEARCH

G Huang, et al. Oncotarget. (2018) 9(3) 4239-4248.

Real-world Time to Treatment Discontinuation



FRIENDS of CANCER RESEARCH

Y Gong, et al. JCO. (2018) 36 suppl; abstract 9064.

Conclusions

1. There is a high level of shared characteristics among the varying data sets despite varying sample sizes, data capture processes, and data sources demonstrating the feasibility of identifying aNSCLC patients treated with immune checkpoint inhibitors from diverse RWD sources.

2. The pilot project demonstrated that several extractable endpoints from EHR and claims data correlate with OS. Further validation is required to determine whether these endpoints are reliable surrogates for OS outside of a traditional clinical trial and whether they can support regulatory and payer decision-making.

3. Assessment of extracted endpoints from EHR and claims data demonstrate that efficacy of immune checkpoint inhibitors is relatively consistent across a variety of patient characteristics, such as age and sex.

4. Survival among patients as assessed through EHR and claims data fall within the range of median OS values observed in several immune checkpoint inhibitor trials.

Potential Next Steps

Purpose	Potential projects	Policy implications
RWE Methodology	• Standardize extraction algorithms • Define real-world endpoints • Methods for data linkage	• Inform FDA guidance • Promote consistency and robustness of RWD
Inform clinical trial designs	• Characterizing patient populations receiving therapies in real world • Historical/synthetic controls • Methods for internal randomization of datasets	• Opportunities for expanding eligibility criteria • Improve understanding of efficacy in single arm studies
Indication and label expansion or refinement	• Assess efficacy in rare cancer types • Assess optimal dosing and duration of treatment • Exploration IO combinations	• Establish uses of RWE in regulatory decision-making • Inform FDA guidance development • Establish guidelines for cross-labeling and legal feasibility
Access and reimbursement	• Comparative effectiveness studies • Measure efficacy among different patient populations	• Inform pricing decisions • Inform value-based pricing models
Demonstrating value	• Assess safety and/or occurrence of late stage toxicities • Measure healthcare utilization and hospitalization rates • Confirmation of clinical benefit • Measure patient experience outcomes	• Inform patient focused drug development guidance

Acknowledgements

Participating Data Partners

- Cota
- Flatiron Health
- IQVIA
- Kaiser Permanente/Cancer Research Network
- Mayo Clinic/OptumLabs®
- University of Iowa/ PCORnet

Project Team

- Mark Stewart, PhD
- Laura Lasiter, PhD
- Diana Merino, PhD
- James Wu, MSc, MPH

- FDA
- NCI
- PCORI

FRIENDS of CANCER RESEARCH

Second Annual Duke-Margolis Conference on Real-World Data and Evidence

National Press Club

October 1, 2018

RWE Demonstration Projects

David Martin, MD, MPH
Associate Director for Real World Evidence Analytics
Office of Medical Policy
FDA Center for Drug Evaluation and Research

Duke-Margolis Conference on Real World Data and Evidence

October 1, 2018

Disclosure and Disclaimer

- David Martin received funding from the Patient Centered Outcomes Research Trust Fund to develop the FDA My Studies Mobile App
- No conflicts of interest to disclose
- The views expressed are those of the author and should not be construed as FDA's views or policies
- The mention of commercial products, their sources, or their use in connection with material reported herein is not to be construed as either an actual or implied endorsement of such products by the Department of Health and Human Services

Current Benchmark

- Substantial evidence standard unchanged
  - Goal is to distinguish the effect of the drug from other influences such as spontaneous change in disease course, placebo effect, or bias
  - Routine practices
    - Probabilistic control of confounding through randomization
    - Blinding
    - Controlled/Standardized outcome assessment
    - Adjudication criteria
    - Audits

Three big opportunities

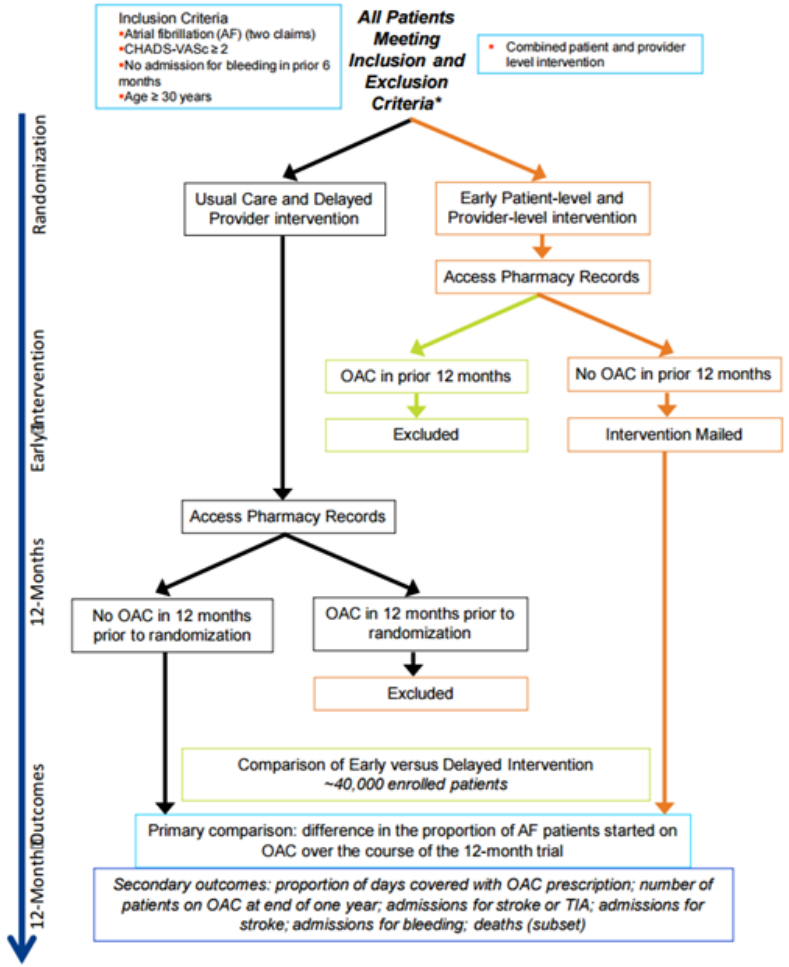
- **Expand the quantity, quality, and diversity of RWD**
  - Broaden the range of RCT endpoints that can be captured
  - Increase statistical power
  - Reduce the number of unmeasured confounders
  - Engage with patients through mobile technology
- **Gain practical experience with "Real World" randomized designs and registries**
  - Inform regulatory considerations
- **Assess the performance of non-interventional designs**
  - "Pressure test" widely accepted designs
  - Consider new paradigms

Endpoints in FDA Registrational trials 2007-2015

Type of Endpoint	% of NDA	Examples of Endpoints Measured
Chemistry data	11	HBA1c, pregnancy test, GFR
Hematology	6	Severe neutropenia Apheresis yield > 5 million CD34+ cells/kg
Pathology	2	Increase/decrease of parabasal cells; biopsy proven acute rejection, clearing of anterior chamber cells
Microbiology	6	Sustained virological response, plasma viral load, conversion to negative sputum
Imaging +/- (survival, clinical signs)	17	Bone mineral density; vertebral fractures, spleen volume, progression free survival
Physiological/ functional measurement	9	6 minute walk, normal sinus rhythm, FEV1, sleep studies
Clinical event /clinical sign	19	Death, hospitalization, MACE, MS relapse, Lice free head
CRO/PRO	30	Toronto western spasmodic torticollis rating scale, Hamilton depression rating scale, Rheumatology scale ankylosing spondylitis scale, psoriasis severity index, seizures, sleep, prostate symptom score

Impact Afib

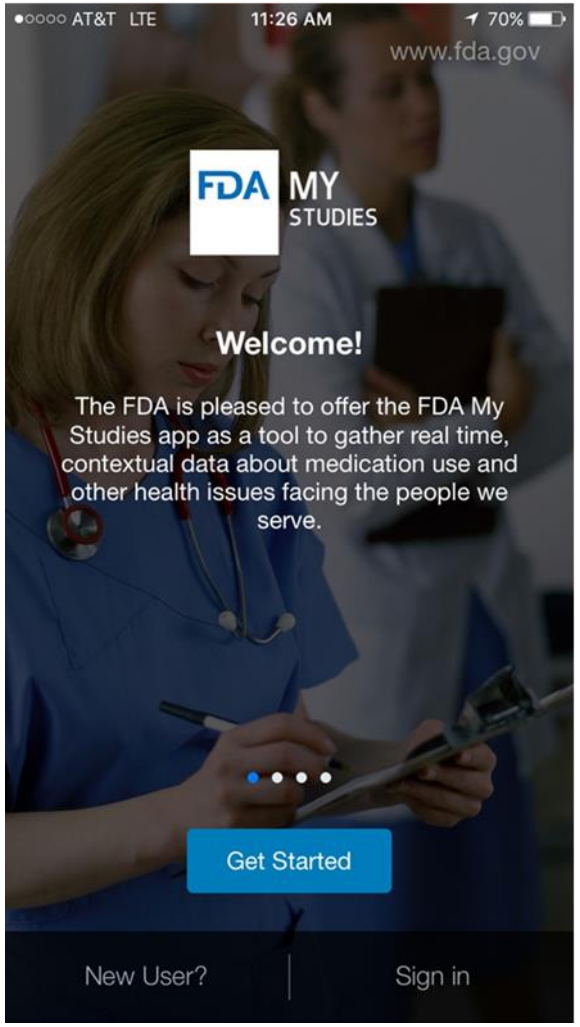
A schematic diagram below shows the design of the first 12 months of the study:



*Baseline characteristics of delayed and early intervention cohorts will be taken from the same time point at randomization from a dataset that is archived at randomization, while exclusion criteria for evidence of OAC medication fill or P2Y12 antagonist use was determined at randomization for the early intervention cohort and 12 months post-randomization for the delayed intervention cohort.

- Implementation of an individually randomized controlled trial within the FDA-Catalyst distributed database environment
- Intervention materials include letter from health plan to describe project, patient brochure (additional information on AF and OACs), and patients pocket card (tool to facilitate conversation between patients and providers)
- Wave 1 and 2 outreach to (~40K) patients and providers in early intervention arm mailed
- Current Activities:
  - Preparing to send delayed intervention arm
  - Finalizing Statistical Analysis Plan for FDA review
- Expected Timeline:
  - Report that summarizes descriptive information on trial cohort by Spring 2019
  - Report that summarizes the findings of the trial for primary and secondary endpoints by Winter 2019 and then 1 year later Winter 2020

FDA My Studies



- **Mobile App**
  - Standard frameworks - ResearchKit (iOS), ResearchStack (Android)
  - Gateway capability
- **Web-based configuration portal**
- **Secure Storage Environment**
  - FISMA and 21 CFR Part 11 complaint
  - Partitioned for distributed research
  - Responses can be downloaded in broadly compatible formats (e.g., SAS, R, Excel, etc.)

RELIANCE

- **RofLumilast or Azithromycin to prevent COPD Exacerbations**
  - Randomized “real world” trial
  - **Azithromycin** - macrolide with anti-inflammatory properties
  - **Roflumilast** - noncorticosteroid anti-inflammatory; phosphodiesterase type 4 inhibitor
  - Both guideline recommended but Roflumilast is FDA approved for this indication
- **FDA-Catalyst will align with the trial by providing linkage to CMS claims data**
  - Linkage for outcomes and exposures
  - Participants will consent to linkage in addition to the existing trial data collection mechanisms (e.g., electronic health records and periodic telephone contact with participants)

Limit JIA

- **Randomized "real world" trial in patients with Limited Juvenile Idiopathic Arthritis** (<=4 joints affected and no uveitis)
  - **Six month course of subcutaneous Abatacept** (T cell co-stimulation inhibitor) **plus usual care** with NSAIDs and intra-articular glucocorticoids **vs. usual care alone**
  - **Outcome:** extension to more than 4 joints, new uveitis, and/or need for treatment with systemic medication at 18 months

- **FDA-Catalyst is planning to align with the trial by providing support from the My Studies App**
  - Collection of primary outcome (uveitis) from ophthalmology appointments (also reminders for appointments)
  - Potential support for the Childhood Arthritis & Rheumatology Research Alliance (CARRA) Registry

SPARC IBD

- **SPARC Inflammatory Bowel Disease cohort within the IBD Plexus research exchange platform**
  - Provider based recruitment of individuals >18 years of age with a confirmed IBD diagnosis

- SPARC participants will be included in the **PCORI Comparative Effectiveness of Biologic or Small Molecule Therapies in Inflammatory Bowel Disease study** (prospective cohort for patient reported outcomes)
- **FDA-Catalyst will align with the registry by providing support from the My Studies App**

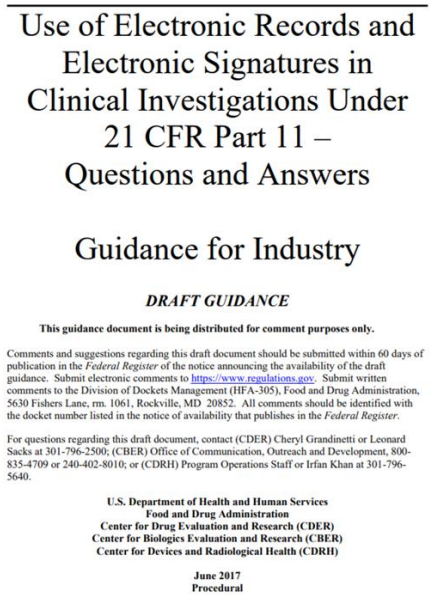
CARE

- **COPD, Asthma, and Respiratory disease Effectiveness (CARE) for 21st Century Cures**

- **Collaboration launched by CDER Office of New Drugs, Division of Pulmonary and Rheumatology Products and the Office of Medical Policy**
  - Feasibility assessments to support comparative effectiveness studies in claims
  - “Prereplication” of the RELIANCE trial using a non-interventional study design
  - Two additional observational comparative effectiveness studies

Data Quality Considerations

- **Provenance**
  - Goals: Ensure authenticity, integrity, (and confidentiality)



Use of Electronic Records and Electronic Signatures in Clinical Investigations Under 21 CFR Part 11 – Questions and Answers

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Cheryl Grandinetti or Leonard Sacks at 301-796-2500; (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010; or (CDRH) Program Operations Staff or Irfan Khan at 301-796-5640.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

June 2017
Procedural

- **Relevance**
  - Cohort/Subject selection
    - Adequate assurance they have the medical condition to be treated
  - Endpoints
    - Reliable methods of assessment
    - Criteria to assess response
  - Confounding/Bias
    - Groups are comparable with respect to pertinent variables that might independently affect outcome

Assessment of Non-Interventional Designs

- High throughput replication over three years to provide empirical evidence base to inform the potential level of confidence in high quality non-interventional designs
- FDA reviewers and researchers from the BWH/HMS Division of Pharmacoepidemiology jointly
  - Selected 40 trials in which claims data are sufficiently fit for purpose in a research environment
    - Oral hypoglycemic, novel oral anticoagulant, antiplatelet, antihypertensive, anti-osteoporosis, asthma, COPD, heart failure, anti-arrhythmic, and lipid lowering medications
  - Concurred with pre-specified measures of agreement
  - Reviewed an implementation process
- Goal
  - 30 completed by March 2020

Implementation Process

1. Prospective engagement with FDA during protocol development and initial feasibility and power calculations
2. FDA review of final definitions of cohort identification, exposure, outcome, and covariates
3. While blind to differential outcome, final power analyses and covariate balance checks are completed – joint go/no go decision
4. Study protocol registered on ClinicalTrials.gov
5. Analyze outcome data and calculate effect measures
6. Document findings
7. Apply prespecified measures of agreement
8. Audit trail visible to FDA throughout the process – FDA sub-team may at its option engage in additional post-hoc sensitivity analyses for training purposes


FDA
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ADMINISTRATION

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National Press Club

October 1, 2018

MULTI-REGIONAL CLINICAL TRIALS
THE MRCT CENTER of BRIGHAM AND WOMEN'S HOSPITAL and HARVARD

OPTUM Labs®

Observational Patient Evidence for Regulatory Approval and uNderstanding Disease (OPERAND)

Barbara E. Bierer, MD, MRCT Center
Paul Bleicher, MD, PhD, OptumLabs
William Crown, PhD, OptumLabs

Regulatory Imperatives are Driving the Interest in Real World Evidence

- Under the *Prescription Drug User Fee Act* (PDUFA) VI FDA has mandated that:
  1. by the end of FY 2018, FDA must conduct a public workshop focused on RWE;
  2. by the end of FY 2019, FDA must fund pilot and methodology specifically targeted toward RWE and regulatory decision-making; and
  3. by end of FY 2021, FDA must publish draft guidance for RWE applications.

- The 21st Century Cures Act mandates (section 3022) that FDA propose a framework and enact a program to evaluate RWE to support approval of new indications and to satisfy post-approval requirements.

OPTUM Labs™

OPERAND Technical Expert Panel (TEP) Participants

OPERAND Co-Leads

MRCT:

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- Hayat Ahmed

OptumLabs

- Paul Bleicher
- Bill Crown
- Scott Wallace
- Anjlee Joshi

Sponsors* & TEP Participants

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***Pfizer:**	Margaret MacDonald
***Sanofi:**	Javier Jimenez
***Optum Life Sciences**	David Dore
***UCB:**	David Miller
***Amgen:**	Cathy Critchlow
GlaxoSmithKline:	John Graham
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PhRMA:	Maria Apostolaros and Kristin Dolinski
Duke-Margolis Center for Health Policy:	Greg Daniel

MULTI-REGIONAL CLINICAL TRIALS
THE MRCT CENTER of BRIGHAM AND WOMEN'S HOSPITAL and HARVARD

OPTUM Labs®

OPERAND Program Aims

- To determine whether observational studies using RWE replicate RCTs submitted for regulatory decision-making
- To develop empirical data to understand data quality—and the limitations of RWD—from various data sources (e.g. Claims, EHR) and the assumptions necessary to use such data for replication.
- To determine whether and how the addition of EHR to Claims data improves sensitivity and utility of data, and thus RWE utility.
- To determine the sensitivities and variability of various statistical approaches given a common dataset and a common goal
- Following replication, to determine how RWE informs understanding of effectiveness for on-label indications in approved populations.

Pilot Study Design (2x2) – Target Trial Replication

Focus: On-label effectiveness in defined subgroups

Number of Teams & Trials	Two academic institutions will replicate two identical target trials
Data	• (1) Claims data alone and (2) Claims + EHR– sensitivity analysis • Data will be restricted to inclusion and exclusion criteria of pivotal RCT and on-label indication for Phase IIA
Methodology	Bootstrapping methods along with bias analysis will be used to understand variability in treatment effect estimates
Documentation	Research team must lay out assumptions and choices made when emulating trials
Approach	To ensure comparability, the teams will: • Be given a common clinical question and the study RCT protocol • Be given defined set of anticipated methods • Have flexibility to use their own methods in certain areas • Initially, be restricted to inclusion/exclusion criteria When analysis complete, TEP will reconvene to discuss next steps

Methods

- Quasi-experimental Design
- Each study uses a core set of methods but is allowed to use additional methods as well.
  - Selected methodologies may depend on trial chosen
- Possible core methods
  - Multiple regression (OLS, logistic, negative binomial, etc.)
  - Propensity score matching
  - Inverse probability treatment weights
- Possible additional methods
  - G estimation
  - Differences in differences
  - Instrumental variables
  - Regression discontinuity analysis
  - Targeted Maximum Likelihood Estimation
- Sensitivity analyses—claims alone versus claims plus clinical. Bootstrapping to illustrate bias and variance in different estimation approaches and use of different data types.
  - Including progressive widening of included populations to inform sensitivities

Evaluation of RCTs

- Time since approval
- Nature of comparator
- “Hard” inclusion/exclusion/endpoints in claims
  - At least one trial of two
- Inclusion in OptumLabs data
- Within data:
  - Number of individuals on target drug
  - Number of initiators
- Global versus US trials

Collaborations

- Harvard RCT Replicate Initiative (sharing common trial ATE methodology)
- Duke Margolis Center
- FDA

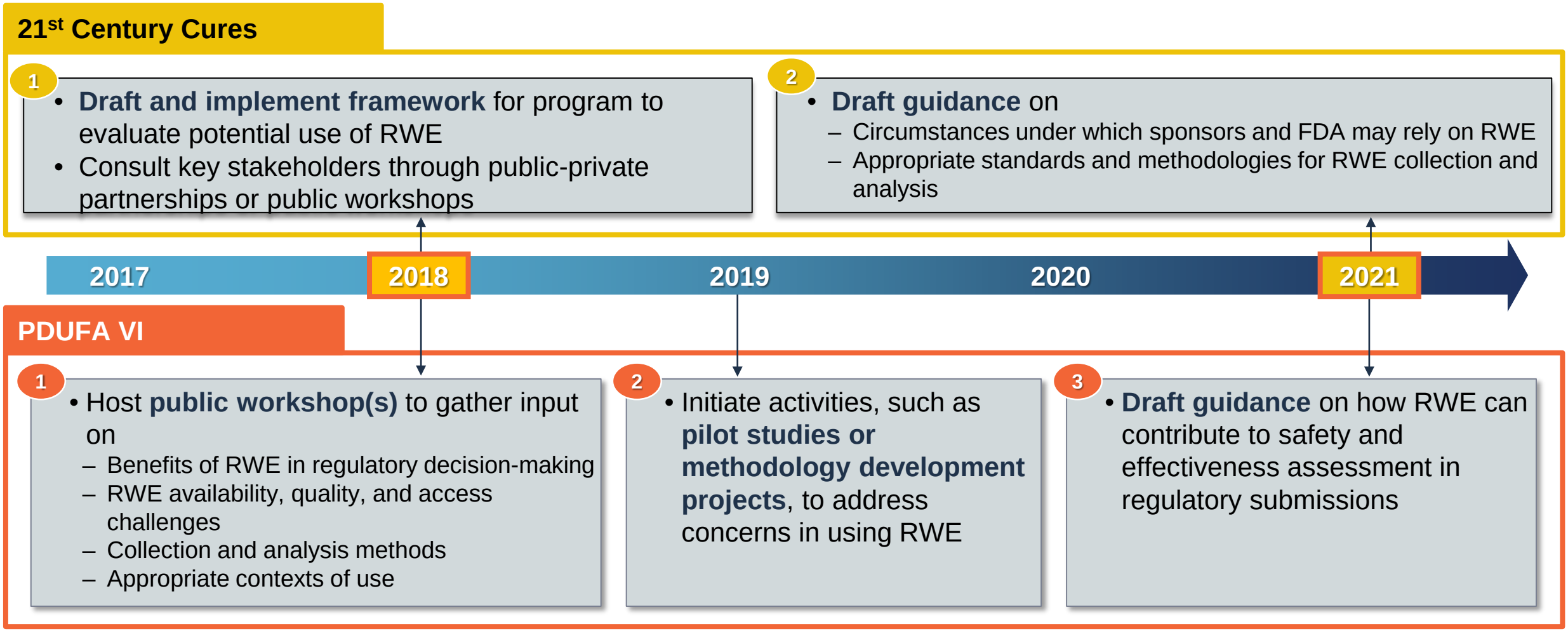
Session V: Setting Goals for 2019

Richard Moscicki, MD
Chief Medical Officer and Executive Vice President,
Science and Regulatory Advocacy

PhRMA
RESEARCH • PROGRESS • HOPE

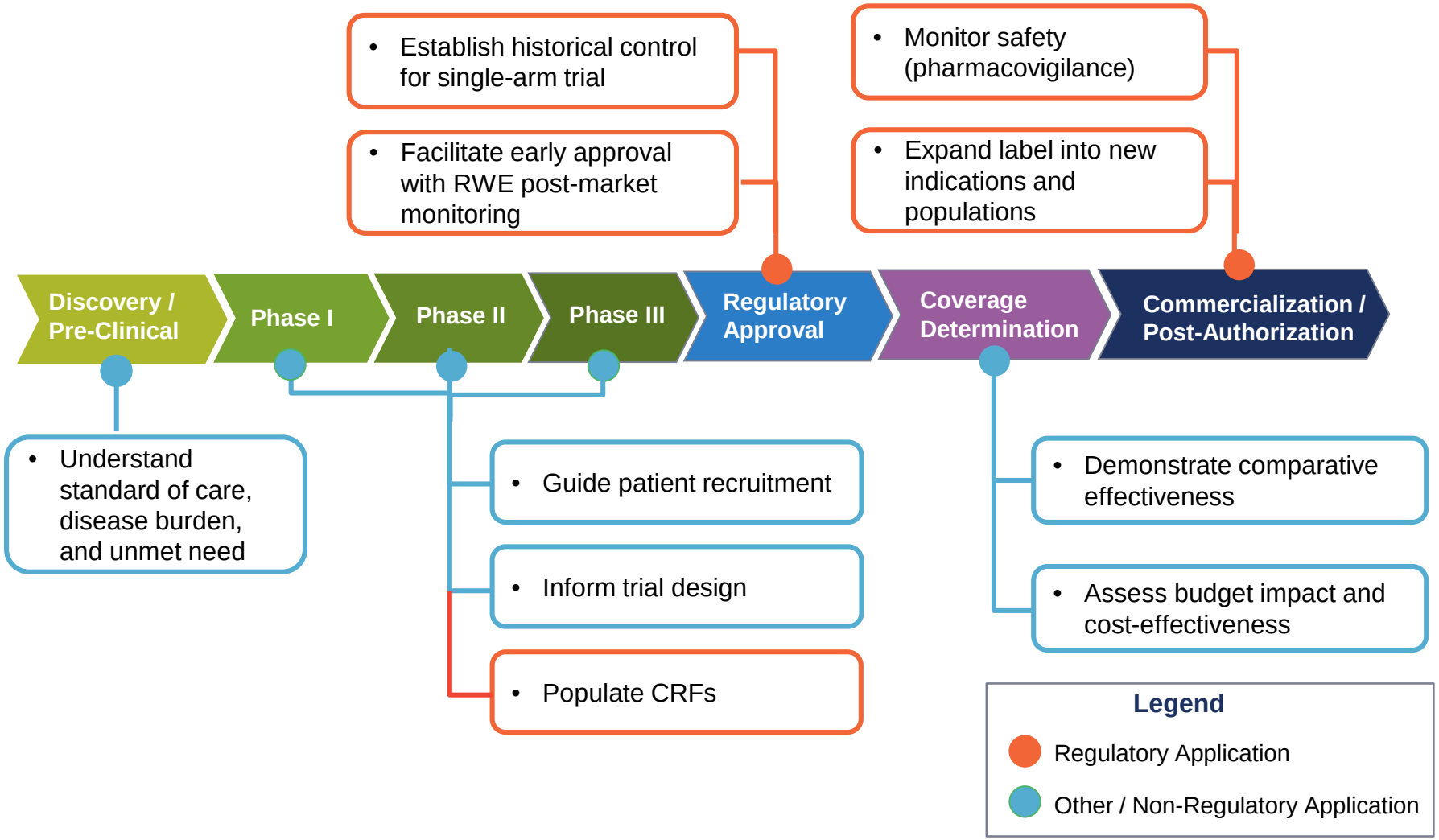
Second Annual Duke-Margolis Conference on Real-World Data and Evidence

RWE Guidance Timelines Under 21st Century Cures and PDUFA VI



Uses of RWE Throughout the Drug Lifecycle

There are many potential applications of RWE throughout the product lifecycle, only some of which are regulatory in nature.



Regulatory Framework

Key Areas for Successful Use of RWE in Regulatory Decision-Making

- **Clarity** from regulators on the parameters of utilizing RWE in drug applications
- **Experience** and predictability for sponsors and regulators in the submission and review of RWE in drug applications
- **Interoperability** of electronic data to enhance flow of information and data capture
- **Acceptance** by regulators of new and innovative uses of RWE in regulatory decision-making
- **Integration** of RWE with other drug development tools

Clarity in Regulatory Expectations

- Clarifying the regulatory framework relating to the use of RWE is a critical step to help broaden its adoption. Future FDA RWE draft guidance should:
  - Leverage existing guidelines
  - Address timing of expected meetings between FDA and sponsors
  - Not be prescriptive
  - Contain flexibility based on study and disease context (Fit-For-Purpose)

- Drug or disease characteristics which may impact the appropriateness of RWE could include:
  - Availability of other therapeutic options
  - Urgency of the disease being addressed
  - Size of the patient population
  - Drug effect size

- Deliverables of 21st Century Cures and PDUFA VI will provide regulatory predictability and tangible guidance to both industry and the FDA

Experience Using RWE in Regulatory Decision-Making

- Continuous learning pilots provide the necessary experience for sponsors and FDA to understand how best to integrate RWD/RWE into regulatory decision-making

- Characteristics of pilots could include:
  - Anchoring on Use Cases
  - Mirroring Successful Pilot Programs
  - Open Enrollment
  - Agreement on public sharing of information

- Ongoing research projects from multiple stakeholders using observational data to replicate clinical trial findings

Interoperability of Data and Systems

- Data and systems standards should be actively pursued and refined, appropriately balancing the long-term nature of such activities with the short-term need to improve data access and integration

- The incorporation of evidence into health management should meet basic standards of terminology/data labels, timeliness, transparency, evidence base, and clinical appropriateness

- All healthcare stakeholders should share the responsibility of creating and enforcing efficient guidelines, processes, standards, and robust safeguards for improved transparency, data collection and access, and methodological rigor with protection of proprietary information

Acceptance of RWE and Novel Methodologies

- Acknowledge the value of RWE in regulatory decision-making
- Acknowledge that RWE has unique advantages
- Near term opportunities to enhance uses of RWE for regulatory decision-making
  - Approval of supplemental indications
  - Fulfillment of post-marketing requirements and commitments

Integration of RWE into Drug Development