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RWE Best Practices: Lessons from the US

Canadian Assoc. for Population Therapeutics

Nancy A. Dreyer
Chief Scientific Officer

December 13, 2018

MEET THE SPEAKER

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Chief Scientific Officer
IQVIA

Nancy Dreyer is Chief Scientific Officer and Senior Vice President at IQVIA. She focuses on generating real-world evidence for regulators, clinicians, patients and payers through pragmatic trials and non-interventional approaches and has more than 100 publications reporting her research. She is a Fellow of both Drug Information Association, Inc. (DIA) and the International Society of Pharmacoepidemiology, is a member of the PCORI Clinical Trials Methods Advisory Panel and has been a Standing Consultant to the National Football League Health & Safety Executive Committee since 2013. She holds an appointment as Adjunct Professor of Epidemiology at the Gillings School of Global Public Health at the University of North Carolina and is a two-time recipient of PharmaVOICE magazine's annual list of 100 most influential and inspiring individuals in life sciences.

Pharma is proactively seeking to utilize real-world evidence to support regulatory decisions

Industry transformation

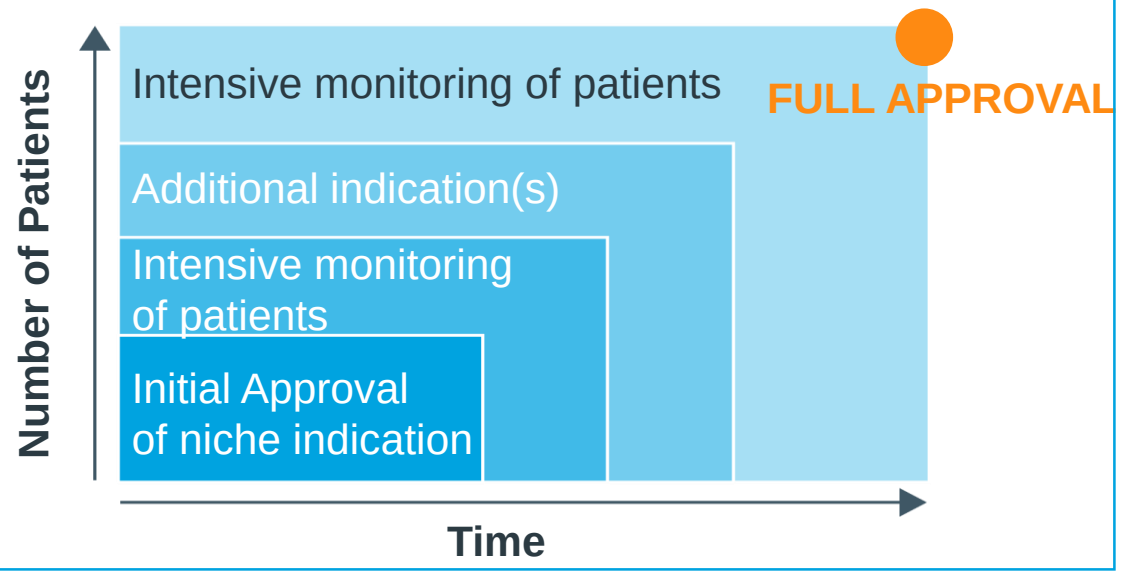
FDA

Scott Gottlieb, MD,
FDA Commissioner

"The more widespread use of RWE can make our ***medical product development process more efficient….*** *This will ultimately help us achieve* ***better outcomes, and safer and more efficient use of expensive technology****."*

EMA

EMA needs RWE to support adaptive approval pathways



FDA is mandated to develop framework and guidance for use of real-world evidence for regulatory decision-making by end of 2018

Regulatory Affairs Professionals Society 2017 Regulatory Conference, September 11, 2017 (https://www.fda.gov/NewsEvents/Speeches/ucm575400.htm)
National Academy of Sciences, September 19, 2017 (https://www.fda.gov/NewsEvents/Speeches/ucm576519.htm)

Table of Contents

Real-world data

No placebos

Claims data	From **payers' reimbursement for care** (pharmacy, outpatient, and inpatient); used to show **resource utilization and patient journey**
Electronic Medical / Health Records (EMR / EHR)	Medical history and may include risk factors, laboratory and imaging results, though data is not always accessible; shows **patient journey**; are used for **comparative effectiveness and safety**
Registries	Structured approaches to track **clinically rich data, treatment use and experienc**e along with other factors; used for product safety, comparative effectiveness & randomized registry trials
Lab & genomics data	Gathered in routine clinical practice, captures **key data** to identify appropriate patients for specific lines of therapy or to explore new theories
Social media, wearables, consumer data, etc.	Increasingly being used to gain insight **into patient behavior, their treatment experience, and risk factors**
eCRF, ePRO	May be collected for study purposes

Novel approaches in study design

APPROACHES TO GENERATE REAL-WORLD EVIDENCE

Pragmatic Randomized Studies

agent + comparator

Primary data collection

May be LINKED

Secondary data

agent + comparator

Extension Studies after RCT

agent + comparator

RCT data collection ends

LINK

Direct to patient

and/or

Secondary data

Combining existing & primary data collection

agent + comparator

Primary data collection

+

Secondary data

agent + comparator

Adding external comparators

agent

Primary data collection

+

Secondary data

comparator

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Pragmatic randomized trials

Pragmatic trials blend RCTs and observational studies by offering randomization with naturalistic follow-up

Attribute	Classic RCT	Pragmatic RCT
General use	NME, label expansion	~Label expansion, RWE for clinicians, payers & patients
Randomized	✓	✓
Study pop'n	Homogeneous	Heterogeneous
Comparator	Placebo	**Single marketed drug or "Standard of Care"**
End-points	May include intermediate endpoints	**Endpoints typically encountered in clinical care**
Follow-up	Mandated testing & visit schedule	Testing and care provided in naturalistic settings
Data Monitoring	Heavy	Lighter

Endpoints for pragmatic trials

- Outcomes should be measurable by data elements routinely collected in usual care by research-naïve, usual care sites - without extensive training or new equipment.
- No undue interference with patient care.
- May be feasible to collect supplemental data in usual care setting or use “hybrid” approaches which combine existing data with primary data collection.
- May be feasible to collect *all* data through EHR, claims or registries after randomization.

National Academy of Sciences, Engineering & Medicine

Blinding in pragmatic trials - meeting on July 17, 2018

How much could patients' and physicians' expectations of benefits and risk explain the observed effects?

- Consider this in the context of the effect size and how objective the outcomes are.

What are the limitations of where blinding can practically be used?

- Simple, individual treatments vs. complex treatment regimens, sequences, combinations, treatments that need to be changed based on personal monitoring, etc.

What information do we lose when blinding is employed?

- Diversity of patients and medical practices that will be represented.
- Likelihood of patient drop-out if/when they figure out what treatment they received.
- Impact of information yield per trial and due to budget impact.

Pragmatic randomized trials – opportunities & challenges

Pragmatic

Opportunities

- Pragmatic outcomes are of interest to patients, clinicians, and payers
- Randomization is trusted.
- Randomization assures enough treated patients for study and product use as needed for study, regardless of label
- Comparators used in typical practice are of interest to patients, clinicians and payers.
- More diverse care providers and sites make results more generalizable
- Much lower cost than comparable RCT
- May leverage existing data through linkage

Challenges

- Harder to show superiority using active comparators
- Real-world settings and diverse patients add variability,
- Multiple comparators pose analytic challenges
- Larger study sizes may be needed to assure enough comparators of interest are included
- Treatment rarely blinded, so formal analyses used to quantify the potential impact of bias on effect estimates
- Sponsor generally needs to balance or cover treatment co-payments. In Europe, must pick up entire study drug cost

pRCT accepted by FDA for label expansion

Pragmatic

INVEGA SUSTENNA is the first and only antipsychotic to have the FDA approve the inclusion of real-world data in product labeling (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

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

- High-risk schizophrenic patients enrolled from non-traditional sources like homeless shelters
- 444 patients were randomized to a flexible-dosed monthly injection vs orals, and followed for 15 months.
- 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.

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Extension studies

Extend follow-up after a RCT through direct to patient contact

Extension

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

Value Points:

- Can measure long-term benefits/risk
- Much lower cost than extending follow-up through RCT framework:
  → < $5k vs >$15K per patient
- Bulk of budget is directed to following up potential CVD events (not all patient information)
- Reduces number of sites needed, simplifying operations

Our Approach:

- Direct to patient follow-up for effectiveness (up to 10 yrs)
- Follow-up both treated and placebo patients
  - 10,000 patients from 100 sites selected by us, multicountry
  - Patients are consented before trial ends by RCT sites
  - Single investigative site per country
- Selected clinical validation for events of special interest

Extension study:

Direct-to-Patient Extension Study in Oncology

Extension

Combining interventional and observational phases for a light-touch long-term extension solution

Client Challenge

- Continue access to treatment for patients with solid tumors and follow those patients that had completed treatment to **understand long-term clinical benefit.**
- Conduct this study in a **cost-effective and light-touch** manner.

The IQVIA Solution

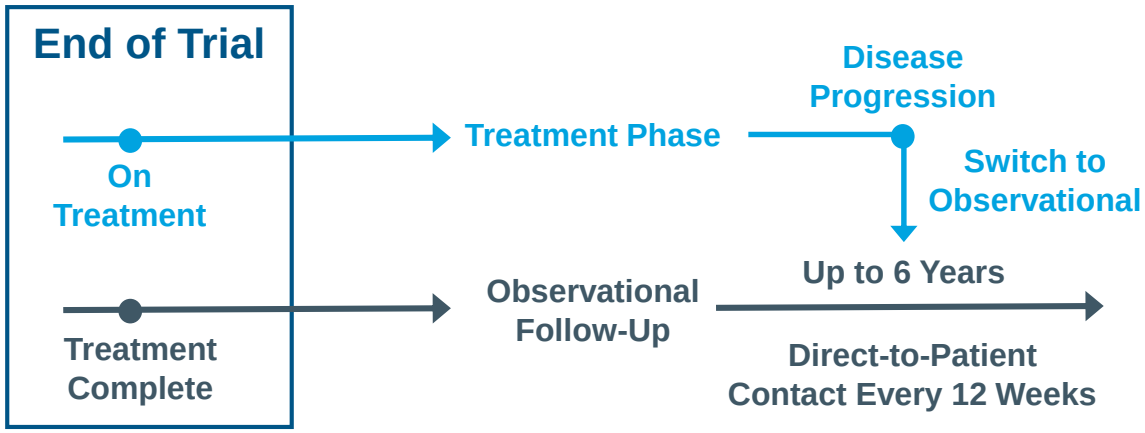
- A **hybrid design** to enable continued site-based treatment for patients until disease progression, and long-term survival follow-up direct-to-patient.
- IQVIA's **global direct-to-patient infrastructure** enabled a light-touch long-term follow-up strategy through its experienced call center.

Outcomes: Treatment until disease progression or unacceptable toxicity ; survival

Total Number of Indications: 4 (not just oncology)

Total Number of Patients: ~300

Total Number of Countries: 25



Extension Study – “Follow the molecule”

Key Principle: Extension studies across all TAs fall under a common study design framework

- One umbrella/common protocol which all parent trials roll into
- Often **both patient cohorts** – on investigation product and off investigational product - are followed
- Each umbrella/common protocol has a single database
- Individual patient follow-up data can be linked to the parent trial
- Drug is supplied as long as patient responds and until the product is approved and commercially available

- Data collection is minimal with ONLY outcomes and **serious** safety events
- Emphasis on direct to patient follow up, clinical validation of events of special interest, and investigator management
- May be feasible to link EMR and Health Insurance Claims to patient data, where accessible

- The extension study *may be* completed upon drug approval

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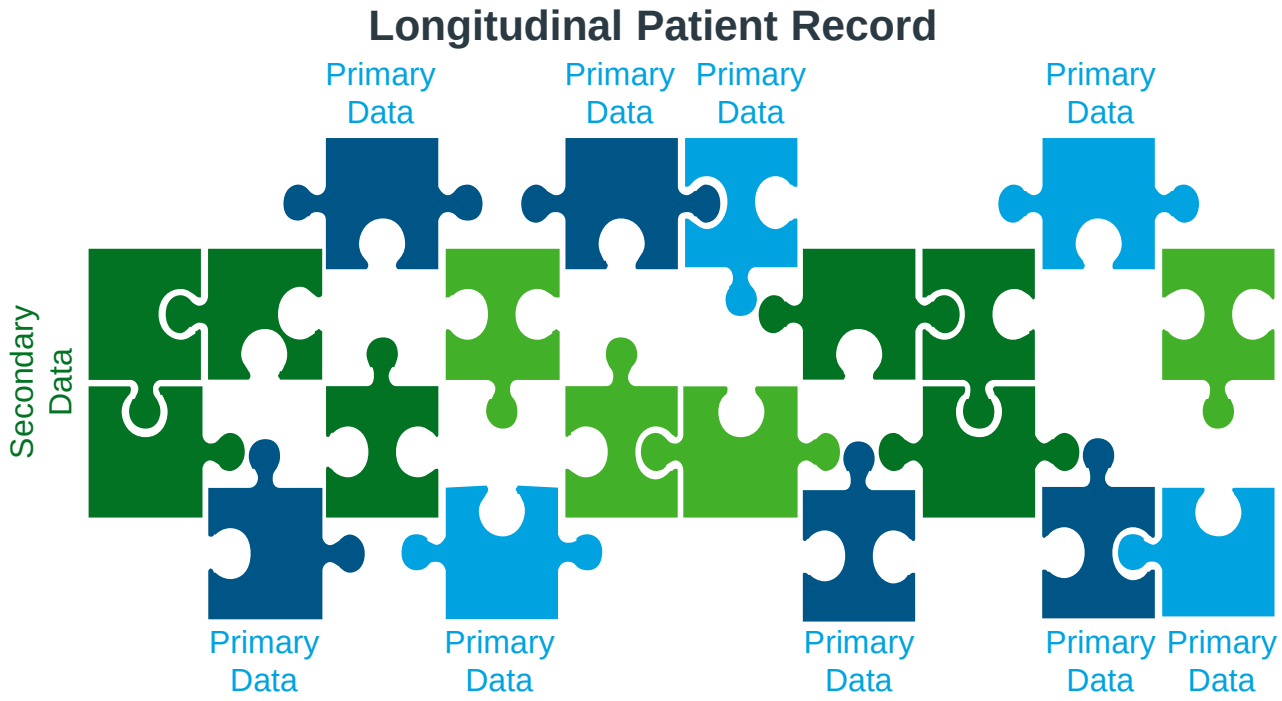
Enriched studies combine primary and secondary data collection

Enriched studies

Enriched

≥2 methods of data collection are integrated to increase researchable data



Benefits:

- ✓ Optimise study design
- ✓ Generate high quality, longitudinal patient data
- ✓ Address broader/multiple research questions
- ✓ Establish approach for longer-term follow up
- ✓ Drive efficiency – Speed to insights

Situations where Enriched may be preferred to traditional RCT:

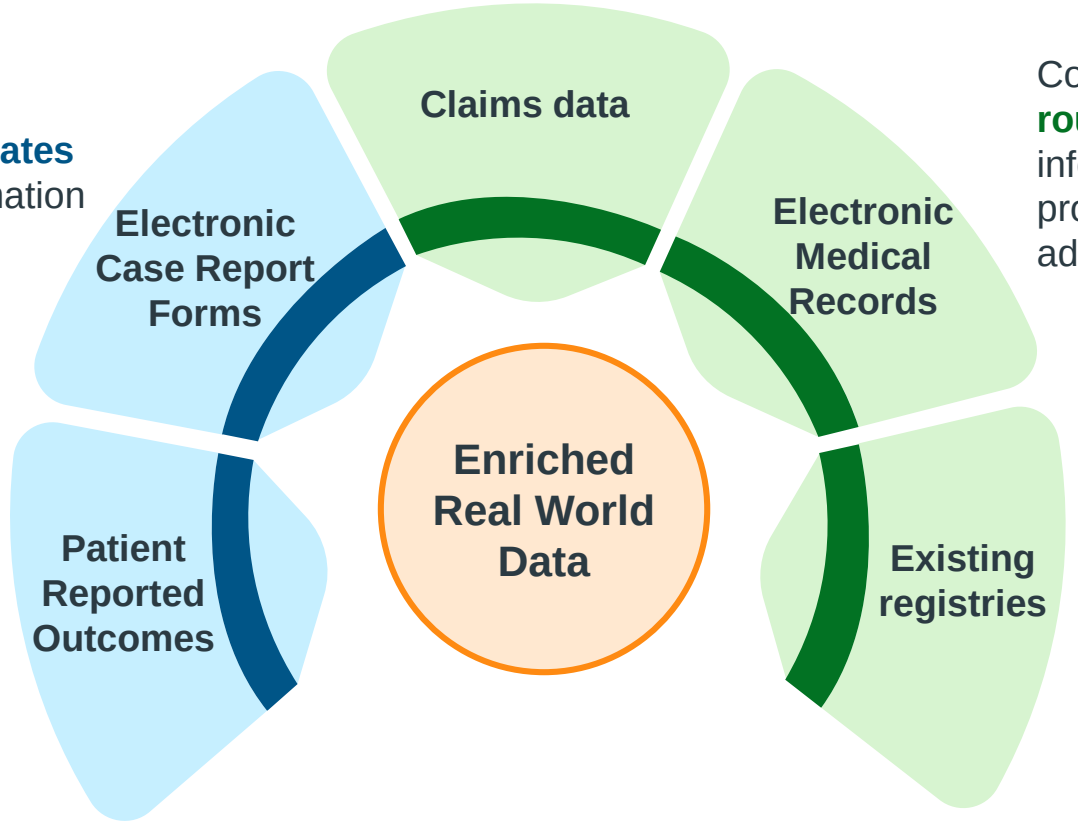
- Having access to **strong foundational data** (e.g. EMR, claims) where enrichment is only required to collect key study variables
- **TAs** where the patient perspective through capture of PROs is critical; enable linkage of PROs to clinical data
- **Chronic diseases** where long-term follow-up is required to evaluate outcomes in a more efficient manner
- **Data from disparate sources** required, such as deep clinical information combined with full healthcare resource utilization costs

Various types of data can be used to enrich a study

Enriched

Completed by **physicians** during **routine practice**; containing information about healthcare utilisation

Completed by **physicians/delegates** during studies; Containing information collected **as per protocol**



Completed by **physicians** during **routine practice;** Containing information required by the healthcare provider for the management and administration of care

Completed by **patients** enrolled in the study; Containing information about the patients' health such as quality of life, functional status, adherence, treatment satisfaction, etc. collected as per **protocol/routine practice**

Previously collected uniform data; Containing data for a **specified research need and population**

Data extracted from each source is linked at the Patient Level using unique identifiers and combined into one comprehensive data set

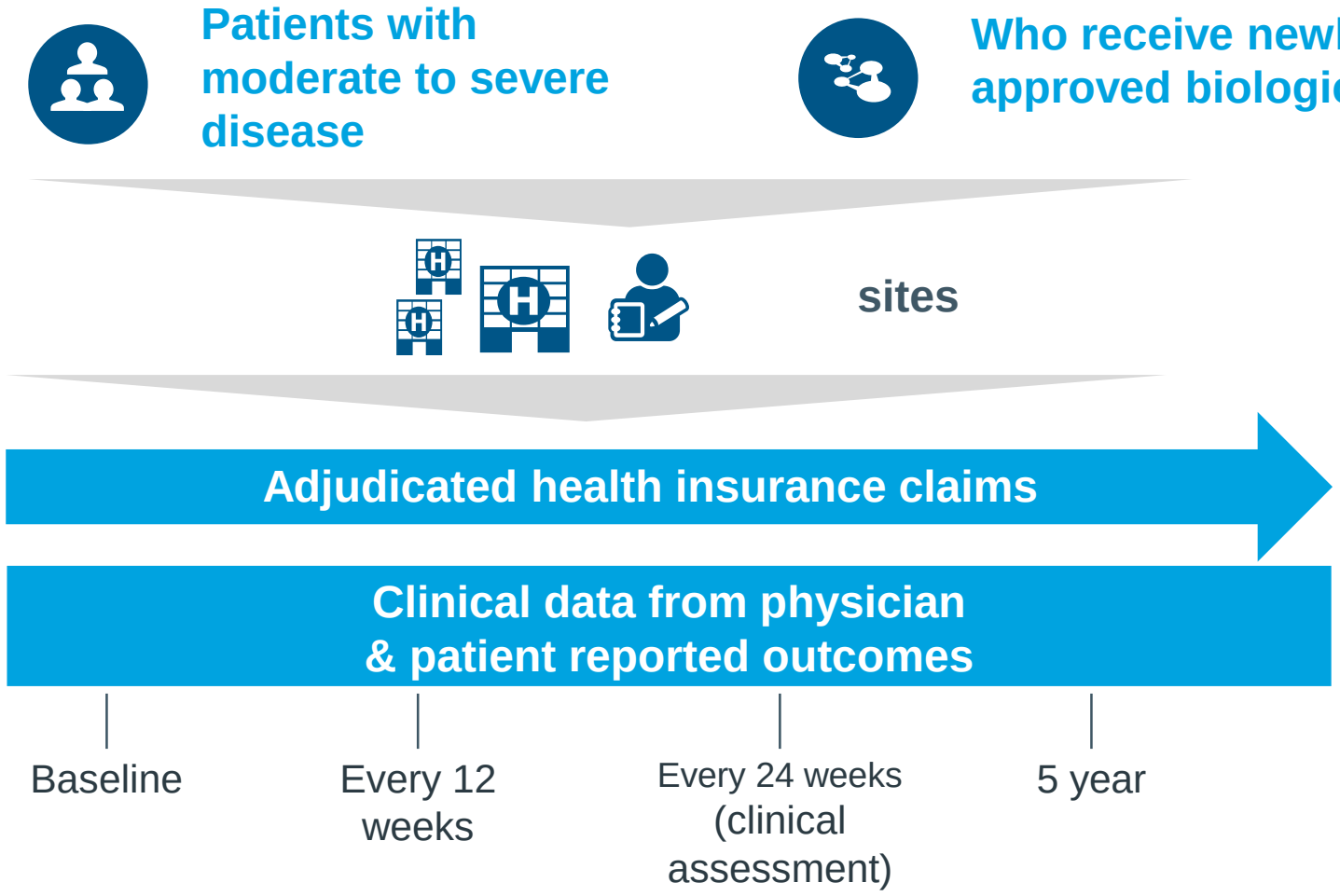
Type of primary data collection Type of secondary data collection

Adding RW Data to Enhance ROI for new biologic

Enriched

Non-interventional study of treatment with newly approved biologic to inform insights on:

- Clinical disease activity
- Treatment patterns
- Patient-reported outcomes
- Adverse Events
- Health-related resource utilization & costs



Delivery of a global enriched, mosaic study

Diabetes registry for top 10 pharma client that enrolled over 15,000 total patients

- The IQVIA team conducted an **upfront data assessment** to determine where secondary data could be incorporated into the delivery strategy.
- To augment a primary data collection approach in many countries, five countries were identified as opportunities to utilize an enriched approach.
  - In those five countries, **data for >1,000 patients was extracted from EMR and existing registries** and was complemented with PRO and additional eCRF data.

Client Benefit:

- Use of EMR data to inform execution strategy.
- Easily address additional research questions through querying EMR data.

Sweden: >225 Patients

Norway: >75 Patients

Denmark: >40 Patients

France: >260 Patients

Canada: >375 Patients

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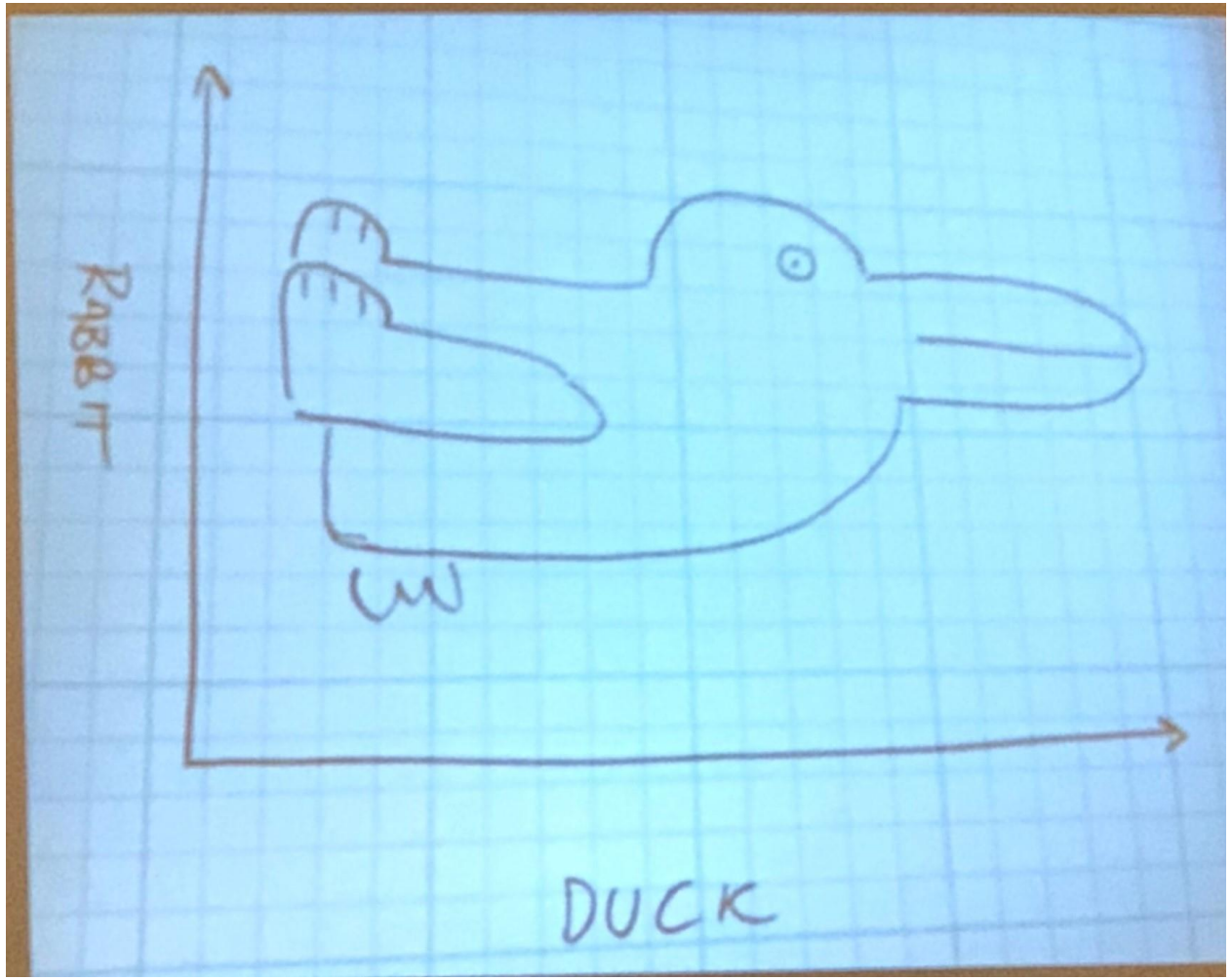
Adding external comparators

External comparators for single arm trials



Perspective is everything

- Comparative evidence is more convincing than data only on treated patients.
- Sometimes randomization to placebo or Standard of Care is not ethical or feasible.
- Historical data may not be as persuasive as contemporary data due to changes in medical practice, diagnostics, access to health care, etc.

Augmentation with external comparators allow data from outside the trial to document benefit

Single arm trial + *RW comparator*

REAL-WORLD COMPARATOR

Data from existing records (e.g. registries, EMR, chart reviews, claims) collected retrospectively or prospectively are used to provide historical or contemporaneous comparators. *Sometimes called synthetic comparators.*

REAL-WORLD BENCHMARK

Real-world data are used to provide context on outcomes. No direct comparison is made with the trial data.

COMPARATORS FROM CLINICAL TRIALS

Placebo or other treated group within RCT data are used for comparison. Success depends on having data on the patients and measures of interest.

Statistical methods may be used to account for differences in groups at baseline.

Comparator

Label expansion of a medical device using a real-world comparator

Direct-to-Patient Device Registry

- Patients identified and enrolled via prescription
- Direct-to-patient recruitment and surveys via clinically staffed call center
- Outcome assessed by diagnosis in medical billing records of treating clinician

Patients Matched Via Propensity Score

Commercial Claims Database

- Comparators identified from health insurance claims
- Claims data used to capture medical history and outcomes
- Outcome assessed by presence of diagnosis in billing records

Accelerated product approval based on a single-arm trial with a real-world benchmark

Comparator

BAVENCIO®

- Approved in 2017 under **FDA accelerated approval** for metastatic Merkel cell carcinoma based on tumor response and duration of response. Also approved by EMA and PMDA.
- The JAVELIN Merkel 200 trial was an **open label**, **single arm**, multi-center study.
- **Real-world benchmarks** established in the US and Europe as comparators.

	JAVELIN Study N = 88	Real-World Benchmarks	
		US EMR N = 14	EU Registry N = 29
Overall Response Rate	33%	29%	10%
# of Responding Patients	29	4	3
Median Duration of Response (Months)	86% > 6 45% > 12	1.7	1.9

Real-world comparator data facilitates rapid drug approval

Citation: Blood Cancer Journal (2016) **6**, e473; doi:10.1038/bcj.2016.84

www.nature.com/bcj

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

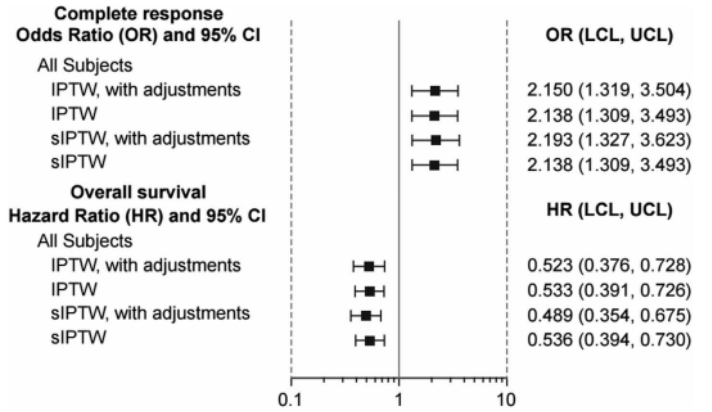


Figure 2. Comparison of complete response and overall survival between blinatumomab clinical trial patients and historical patients. Outcomes were analyzed using both the IPTW and sIPTW approaches: Odds ratio (OR) for achieving a CR/CRh (blinatumomab patients) or CR (historical patients) and hazard ratio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

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

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

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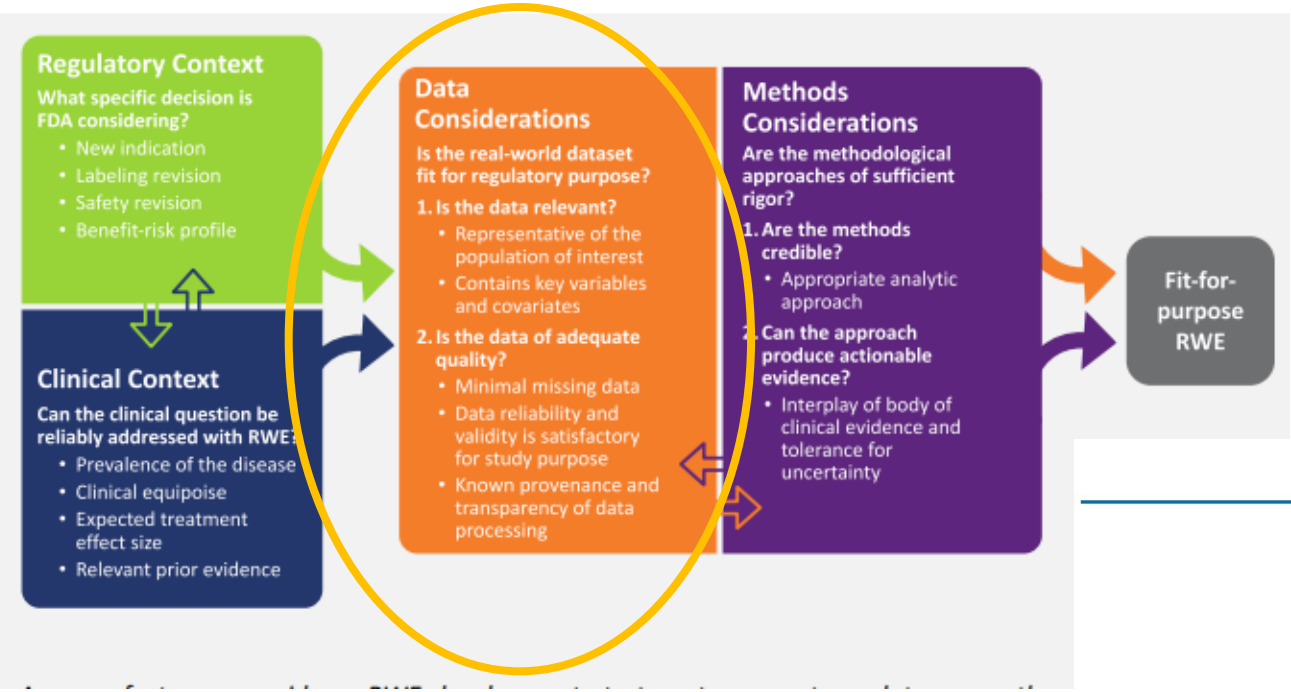
Data must be fit for purpose

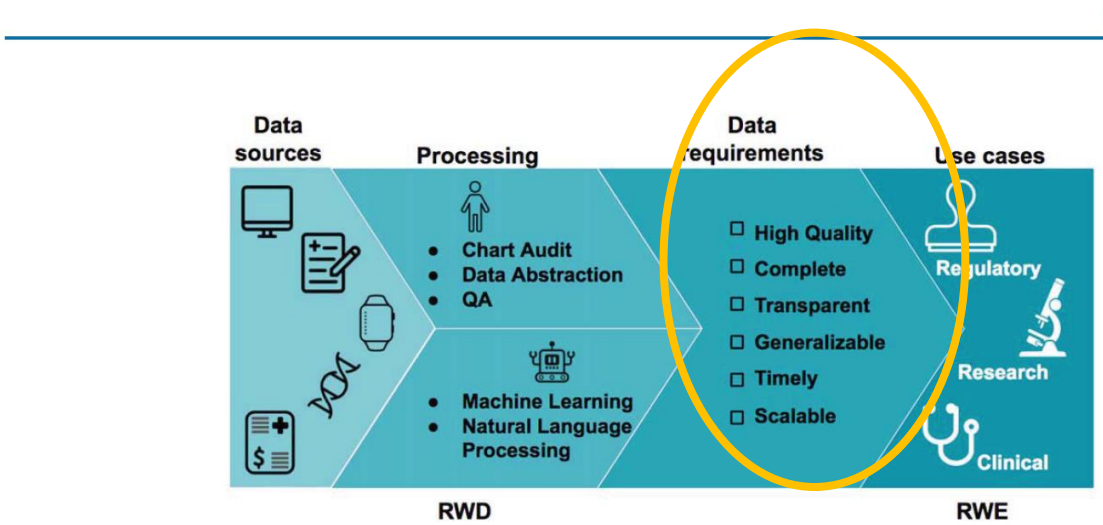
— Curation
— End-point validation

“Regulatory-grade” RWE?

Figure 1. Considerations for generating RWE fit for regulatory purposes

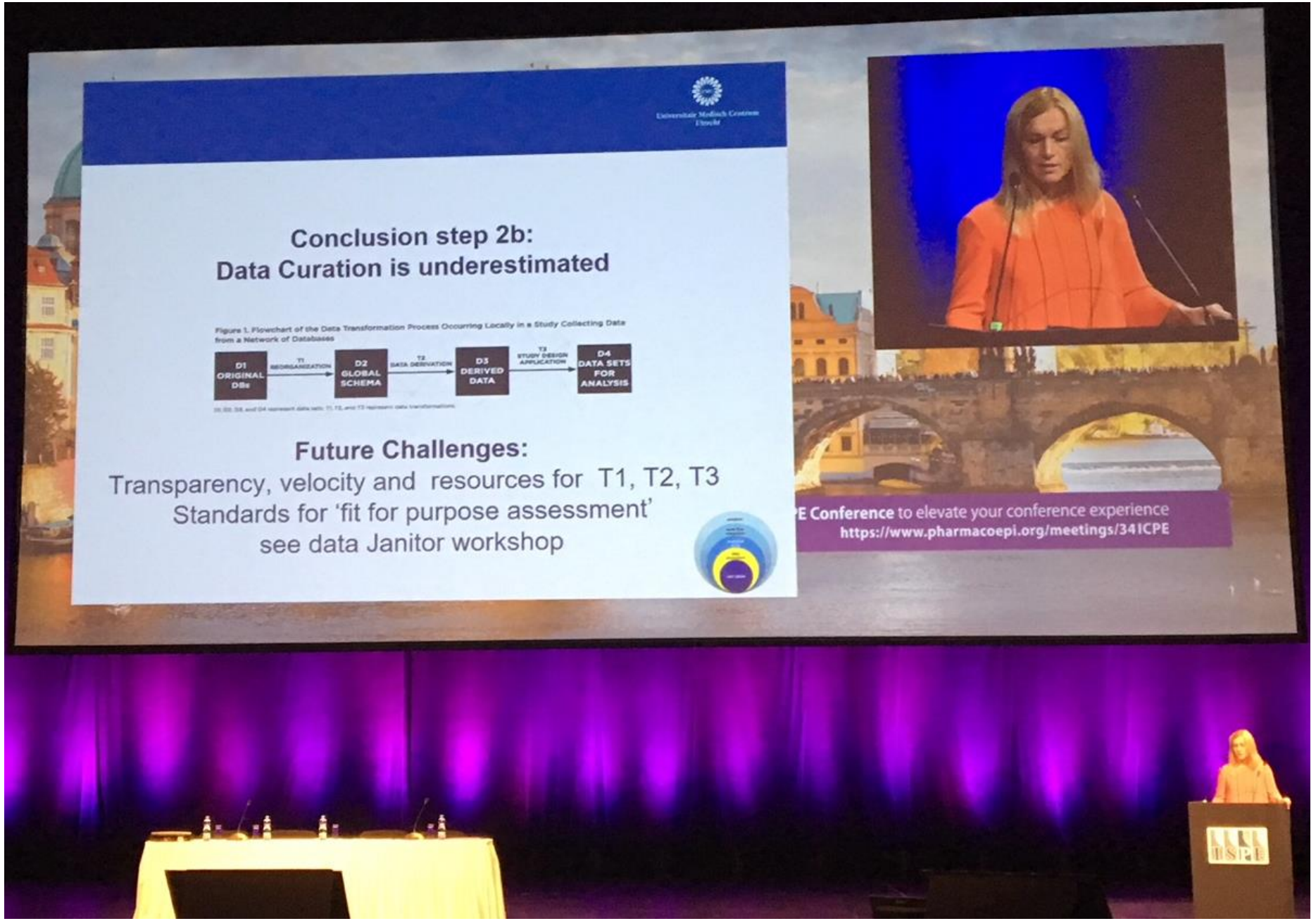


White paper on “Characterizing RWD Quality and Relevancy for Regulatory Purposes.’ October 1, 2018. Duke Margolis Center for Health Policy released at 2nd Annual Duke Margolis Conference on RW data and evidence



Miksad RA, Abernathy AP. Harnessing the power of RWE: a checklist to ensure regulatory-grade data quality. Clin Pharmacol & Ther 2018; 103 (2) 202-205.

Figure 1 The journey from data to evidence. Real-world data (RWD) are data that are routinely collected in the form of electronic health records (EHRs), patient disease registries, wearables, genomic datasets, medical claims registries, and others. These data can be aggregated, linked, and processed to produce key conclusions in the form of real-world evidence (RWE). The proposed checklist can be used to assess if the quality of the RWD is regulatory-grade.



- Curation is more than just checking data for completeness and consistency.
- It also includes checking derived data and combined data.

Endpoints matter:

Establishing a framework to validate RWD for regulatory decision-making

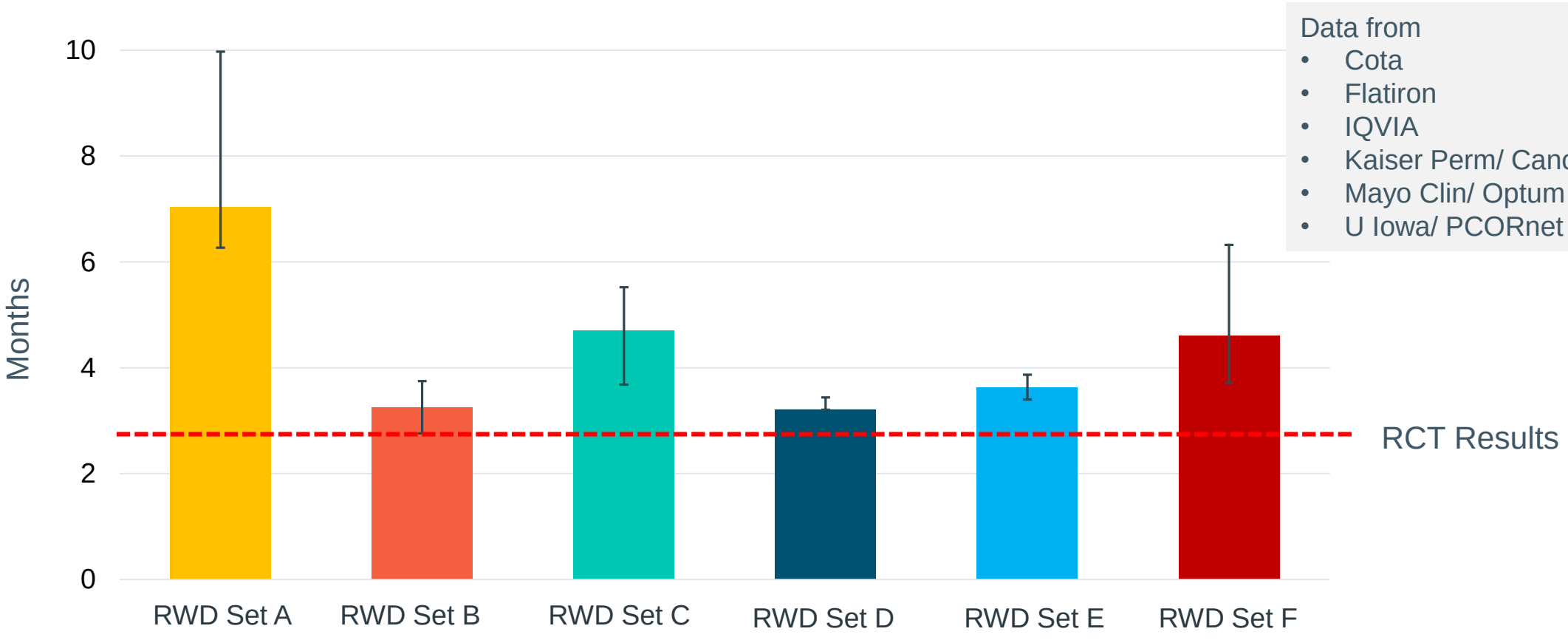
Pilot Supports Real-World Endpoints as Surrogates for Overall Survival

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 demographic & 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 Objective 3: Assess performance of real-world endpoints (PFS, TTP, TTNT, TTD) as surrogate endpoints for overall survival (OS)
Study Design	Retrospective analysis of data derived from electronic health records and claims databases. The datasets generated for the study include all relevant, retrospective patient-level data available for eligible individuals up to the data cutoff date.

https://www.focr.org/news/biocentury-pilot-supports-real-world-endpoints-surrogates-os

Presented July 10, 2018

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



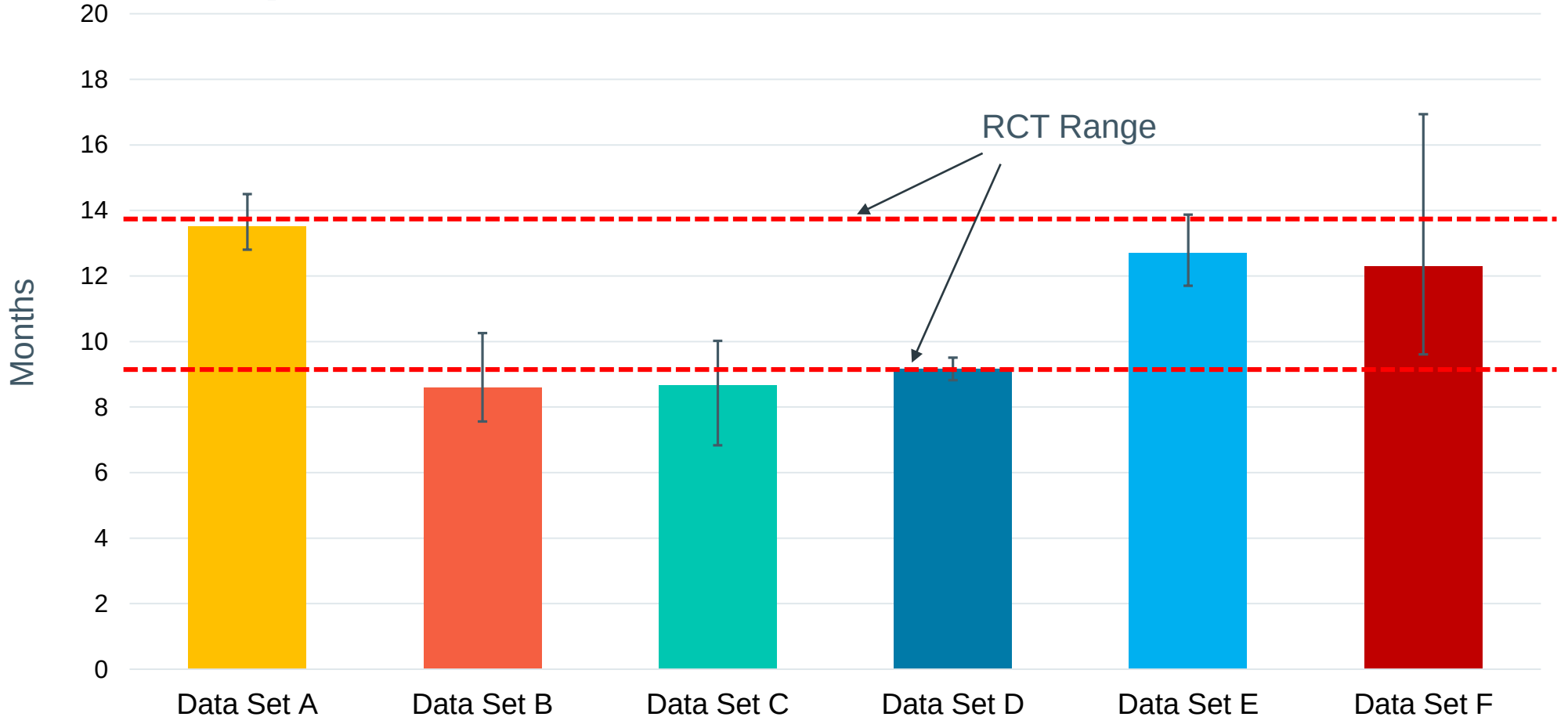
Data from
- Cota
- Flatiron
- IQVIA
- Kaiser Perm/ Cancer Res Network
- Mayo Clin/ Optum labs
- U Iowa/ PCORnet

Presented July 10, 2018
For more information, see www.focr.org

FRIENDS of CANCER RESEARCH

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

Overall survival: RW to RCT in advanced NSCLC patients treated with immune checkpoint inhibitors



Presented July 10, 2018
For more information, see www.focr.org

FRIENDS of CANCER RESEARCH

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

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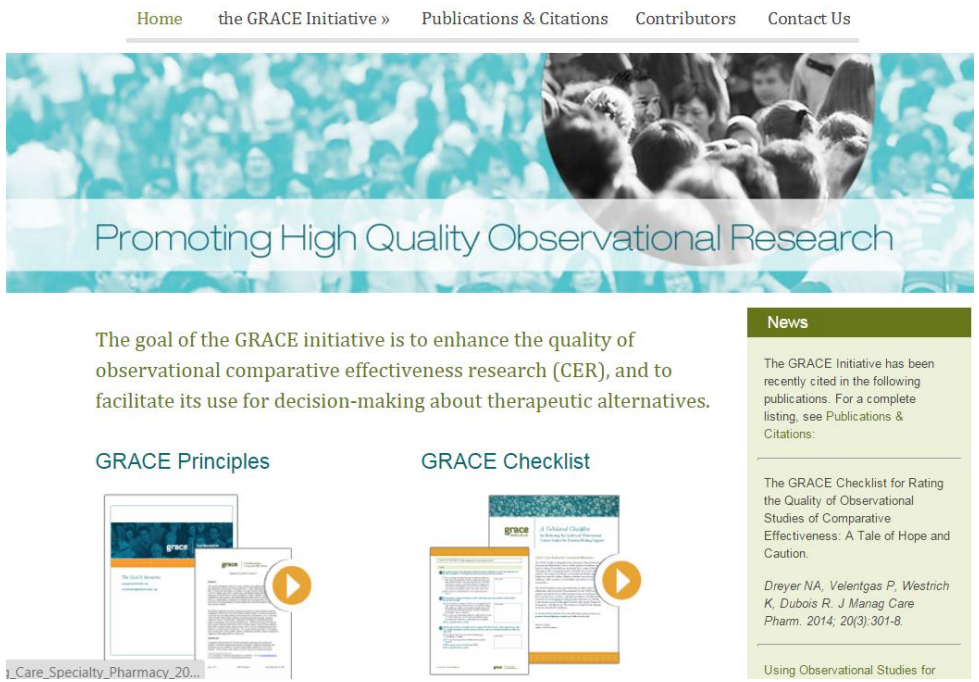
How to recognize when real-world evidence is reliable enough for a given study purpose?

GRACE: Good Observational Research for Comparative Effectiveness



www.graceprinciples.org

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Guide on Methodological Standards in Pharmacoepidemiology (Revision 7)

ENEPP
uropean Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ISPE
INTERNATIONAL SOCIETY FOR PHARMACOEPIDEMIOLOGY

NHS
National Institute for Health and Clinical Excellence

- Dreyer NA, Schneeweiss S, McNeil B, Berger ML, Walker A, Ollendorf D, Gliklich RE: GRACE Principles: Recognizing high-quality observational studies of comparative effectiveness. Am J Managed Care 2010;16(6):467-471
- Dreyer NA. Using observational studies for comparative effectiveness: Finding quality with GRACE. J Comparative Effectiveness Research 2013; 2(5):413-418.
- Dreyer NA, Velentgas P, Westrich K, Dubois R. The GRACE Checklist for Rating the Quality of Observational Studies of Comparative Effectiveness: A Tale of Hope and Caution. J Managed Care & Specialty Pharmacy 2014;20(3):301-08.
- 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.

GRACE Principles are part of the Guidelines for Good Pharmacoepidemiologic Practice (GPP)
PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2016; **25**: 2–10

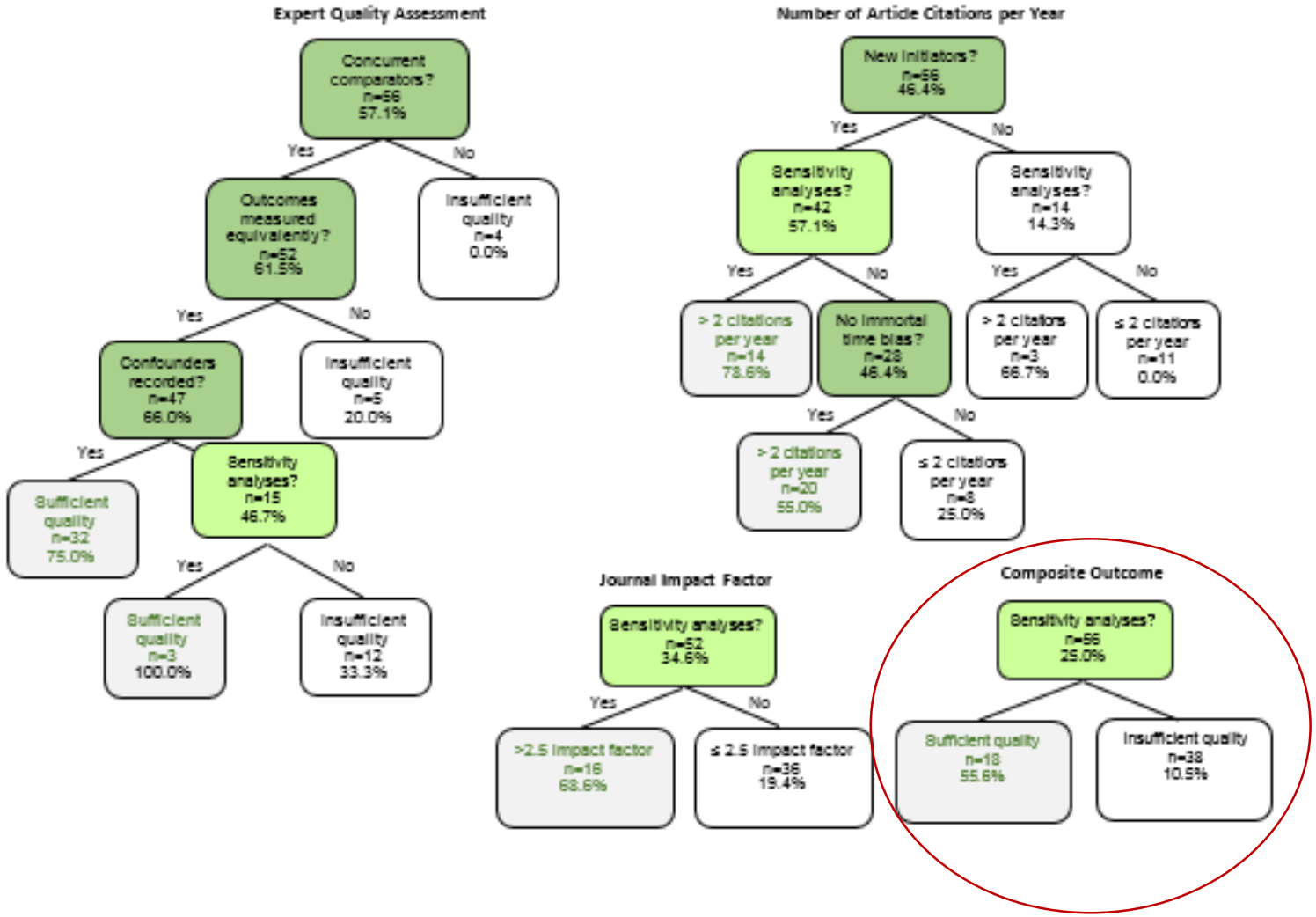
Journal of Managed Care & Specialty Pharmacy

December 2015 Vol. 21, No. 12 www.amcp.org

Research articles should follow reporting standards based on the design of the study:

- CONSORT for clinical trials
- STROBE for observational studies
- CHEERS for health economic evaluations
- ✓ GRACE for observational studies of comparative effectiveness

Classification and Regression Tree Analysis was used to compare 56 article assessments against 3 external quality indicators



Sensitivity 71%
Specificity 81%

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

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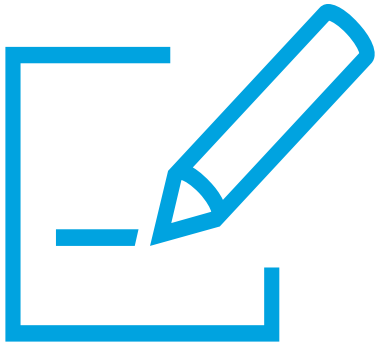
In summary

Our guiding principles for RWE

RWE should embrace diversity of datasets and patient populations, shifting focus to the merit of individual studies and RWD used.

Better to have some good evidence than none. RWD that falls short of optimal length of follow-up or study size may still reveal clear evidence to support regulatory decisions, particularly as they relate to subgroups.

Until data becomes more standardized, develop standardized approaches to evaluating data and analytic methods.



Dreyer NA. Advancing a framework for regulatory use of real-world evidence: **Therapeutic Interventions and Regulatory Affairs**, 2018
http://journals.sagepub.com/doi/full/10.1177/21684790187635 91

Designing studies that are fit for purpose

Start here

1) Who is audience? What type of evidence are they expecting and are they open to innovation?

2) Is product on the market and accepted by payers?

3) Are comparators needed? Consider single comparator vs “standard of care,” possibility of having contemporary comparators, and need for randomization and/or blinding.

4) How much follow-up is needed?

   - What is expected induction time for risks and benefits?
   - What are stakeholders expectations for follow-up period?

5) Are existing data accessible & sufficient? If not, use primary data collection and consider data linkage for added value.

Then consider

1) How well do the data characterize “must-have” exposures and outcomes of interest?

2) How reliable are the outcomes that are readily recorded & accessible?

3) Are sufficient numbers of patients of interest likely to be available?

4) What is the likelihood that patients have been followed for the desired length of time?

5) What is the potential for bias and how much is it likely to impact the expected effect?

Real-World Evidence: Relevance and Quality

- Determining when RWD is fit for regulatory use is a contextual exercise – no simple formula will work.
- Data elements must meet major study objectives, but do not need to be 100% complete or accurate to the same detail as RCT. We use sensitivity analyses & have methods to address missing data.
- Data, without a reasonable curation and documentation, should be suspect.

See Girman CJ, Ritchey ME, Zhou W, Dreyer NA. Considerations in characterizing RWD relevancy and quality for regulatory purposes: A commentary. Pharmacoepidemiology & Drug Safety 2018; DOI: 10.1002/pds.4697.

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