DigiCore

Advanced oncology real world evidence programs in America – lessons for Europe

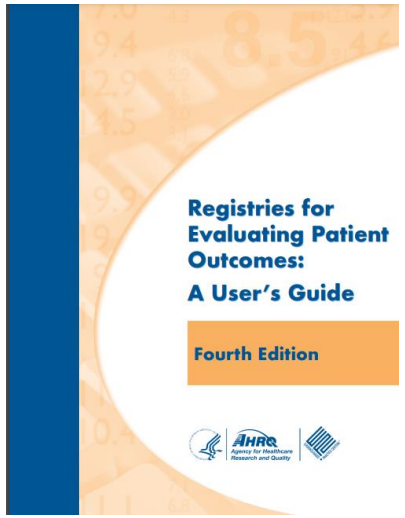
Nancy A Dreyer
Chief Scientific Officer and Sr. Vice President
IQVIA Real World Solutions

Paris, France
November 4, 2021

Commonality of viewpoints and need to scale

- An update on regulatory interest in real-world evidence (RWE)
- Lessons learned
  - High quality, relevant data is hard to find
  - Even with big data, RW endpoints may not be comparable to trials and I/E unlikely to fully match (case study)
- Magnitude of collaboration needed to achieve sample
- Network building

US government's interest in RWE has been growing steadily



Gliklich RE, Dreyer NA, Leavy M, eds.

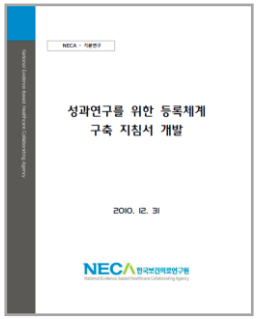
Registries for Evaluating Patient Outcomes: A User's Guide

US Agency for Healthcare Research and Quality Publication No. 13(14)-EHC111. Rockville, MD.
1st edition 2007, 2nd edition 2010, 3rd edition 2014, 4th edition 2020

- >100 contributors from industry, academia, health plans, physician societies, government, and patient advocacy groups
- 76 invited peer reviewers and public comment, including OCR, OHRP, IOM, FDA
- 64 case examples illustrate challenges and solutions

English version of book may be downloaded at
https://effectivehealthcare.ahrq.gov/products/registries-guide-4th-edition

Cited as good practice by European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ENCePP Methods Guide Rev. 9 EMA/95098/2010 Rev.9



2nd edition available in Chinese and Korean

FDA is committed to using RWE for regulatory decisions

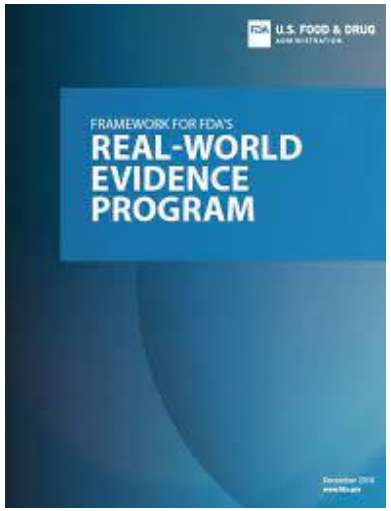
The 21st Century Cures Act (2016)

Intended to enable more rapid modernization

The Act required the FDA to craft a framework and guidance that outlines the use and considerations for RWE decision making

FDA RWE Framework (2018)

Intended to provide high level framework for using RWE for regulatory decision-making



FDA guidance due in December 2021

Sources: FDA Science and Research Special Topics

Life Science Innovators Driving RWE Impact and Value. Real World Evidence. Real Results

IQVIA's thought leadership acknowledged in new FDA draft guidance

Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products

Guidance for Industry

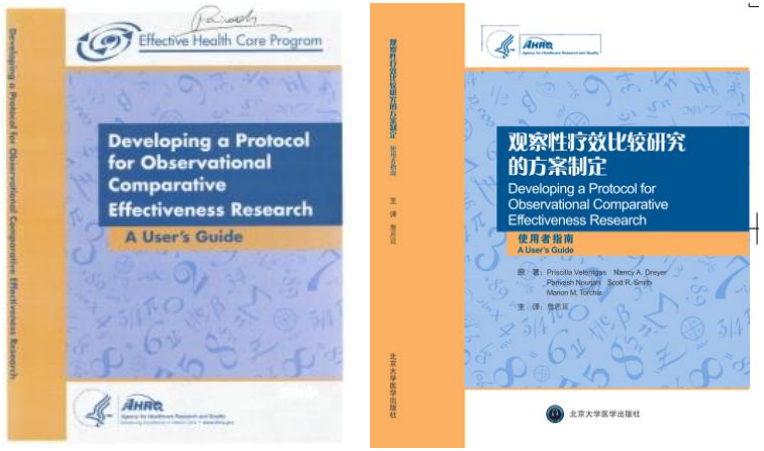
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

September 2021

Includes

- Data Relevance
- Data Capture
- Study Design
- Data Quality,
- Validation, etc.

Cites



Velentgas P, Dreyer NA, et al, Editors
Translation led by Professor Siyan Zhan Peking University


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]

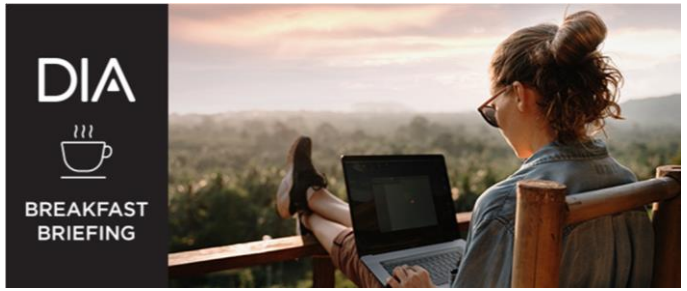
Source: www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs

Also cited by European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ENCePP Methods Guide Rev. 9 EMA/95098/2010 Rev.9

Real-world data (RWD) and real-world evidence (RWE) have been actively discussed worldwide in terms of utilization for regulatory decision-making on the benefit-risk assessment of drugs. In Japan, the Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have worked to promote the utilization of RWD and RWE throughout a medical product's lifecycle, from pre-approval through development to the post-marketing phase.

October 9, 2021

PMDA Chief Executive
Yasuhiro Fujiwara



https://globalforum.diaglobal.org/issue/october-2021/regulatory-utilization-of-real-world-data-and-real-world-evidence-in-japan/?utm_source=email&utm_medium=marketo&utm_campaign=PUB_GF_October_2021-10-09&mkt_tok=MzQ5LVNWSi0wNjgAAAGAAK2_oze7SqXnDJZZ8dTnbHO5MGfGVK4ZE5arObhD4JwsuPPHv1tgDOlb4cVVs3pd49VecbKw7kcqOK2aHZ_eaT03HHKXwIeQykazmrasKO8

China: 1st to publish Guiding Principles for using RWE

November 4 2019

附件 1

真实世界证据支持药物研发与审评的
指导原则（试行）

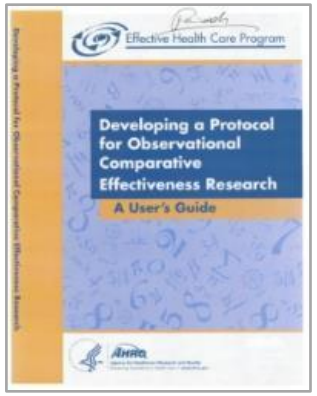
Guiding Principles for using RWE to support drug development cites many examples

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

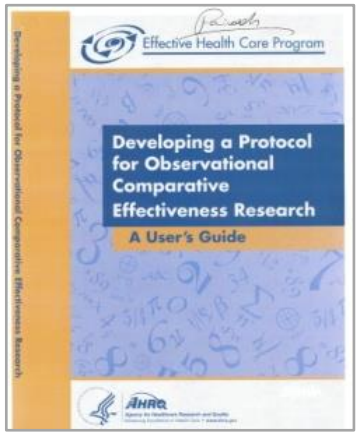
Therapeutic Innovation & Regulatory Science
1-7

DOI: 10.1177/2168479018763591
tirs.sagepub.com

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



Strong methods foundations drives good science



Written by academics, regulators and industry representatives. Describes minimal standards and best practice for study design, analysis, and causal inference

Used at US National Cancer Institute

Velentgas, Dreyer et al, Editors

Translation led by Professor Siyan Zhan Peking University Health Science Center

Professors Nancy Dreyer and Siyan Zhan

English language version available at www.effectivehealthcare.ahrq.gov/products/observational-cer-protocol

EMA is committed to realising the benefits of RWE

- Real world evidence compliments evidence from clinical trials

- Converting data to evidence to decisions requires
  - Knowing the data quality and characteristics
  - Applying robust methods
  - Understanding the evidentiary value

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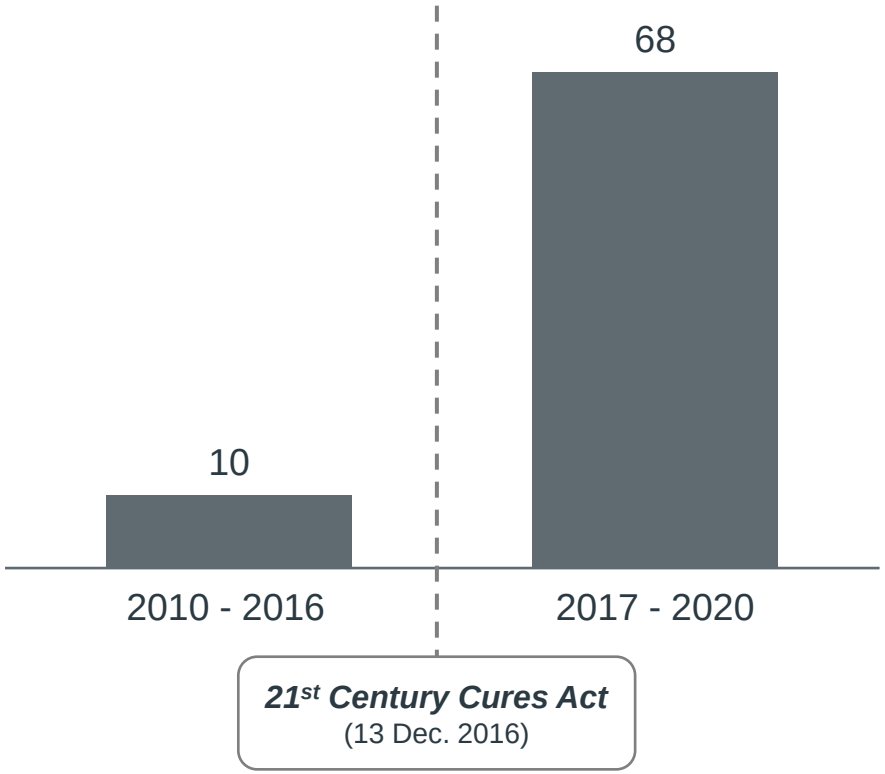
Lesson #1

High quality, relevant data is hard to find

RW endpoints in FDA oncology submissions

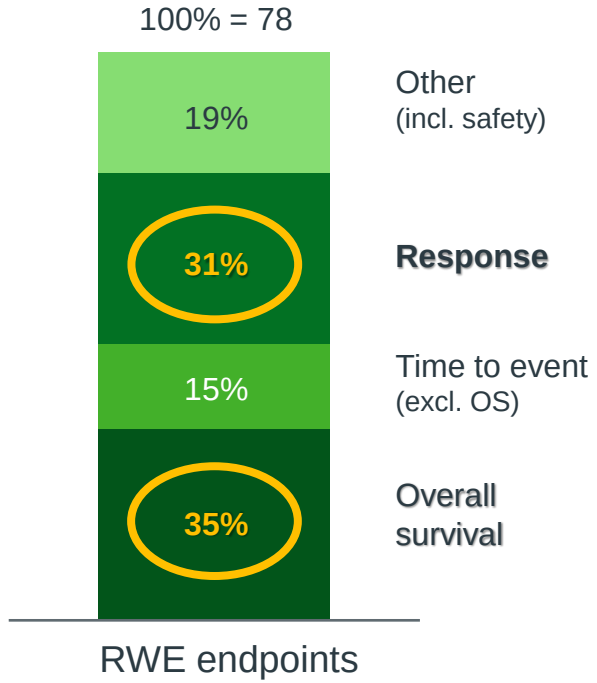
FDA oncology submissions that included RWE



Submissions by type of cancer

- 68% solid tumour
- 22% haematology
- 10% pediatric

RWE endpoints used



Source: D. Rivera et al, Journal of Clinical Oncology 39, no.15_suppl., May 2021

External comparator provides context for single arm trial

BAVENCIO®

- **Conditionally approved** in 2017 by the EMA for metastatic Merkel cell carcinoma based on tumor response
- The JAVELIN Merkel 200 trial was an **open label**, **single arm**, multi-center study
- **Real-world benchmark** established in the Europe as supportive data through a **de-novo registry collaboration**

Benchmark for EMA

	JAVELIN Clinical Trial N = 88	Real-World Benchmark EU Registry N = 29
Overall Response Rate	33%	10%
# of Responding Patients	29	3
Median Duration of Response (Months)	86% > 6 45% > 12	1.9

Becker JC, Lorenz E, Ugruel S, et al: Evaluation of real-world treatment outcomes in patients with distant metastatic Merkel cell carcinoma following second-line chemotherapy in Europe. Oncotarget, July 13, 2017

External comparator provides context for single arm trial

BAVENCIO®

- **Conditionally approved** in 2017 by the FDA for metastatic Merkel cell carcinoma based on tumor response.
- The JAVELIN Merkel 200 trial was an **open label, single arm,** multi-center study
- **Real-world benchmark** established using data from an oncology EMR network

Benchmark for FDA

	JAVELIN Clinical Trial N = 88	Real-World Benchmark Oncology EMR N = 14
Overall Response Rate	33%	29%
# of Responding Patients	29	4
Median Duration of Response (Months)	86% > 6 45% > 12	1.7

Cowey CL, Mahnke L, Espirito J, et al.: Real-world treatment outcomes in patients with metastatic Merkel cell carcinoma following treated with chemotherapy in USA, Future Oncology, June 13, 2017

FDA has used a combination of RWD to guide decisions

Male Breast Cancer Label Extension for Ibrance

Opportunity

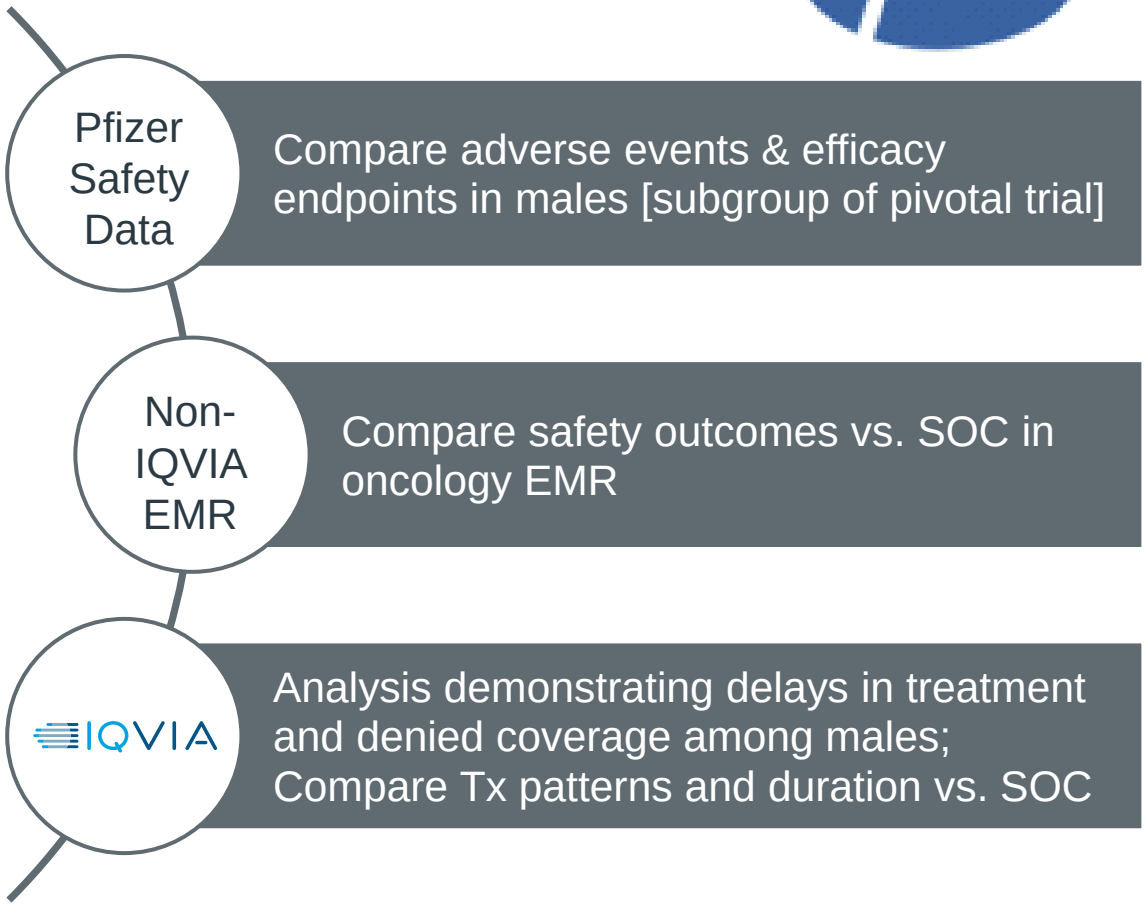
A rare condition not suited to a traditional RCT

Real-World Data Approach

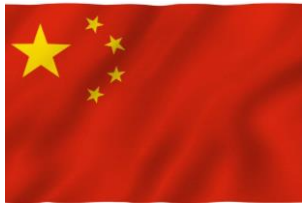
Three RWD studies plus reanalysis of pivotal trial data were used to demonstrate efficacy and safety among male population

Value

- ✓ Regulatory-grade data
- ✓ FDA label extension for research drug



China's National Medical Products Administration granted label expansion based on RWE extracted from medical records



Bevacizumab was approved in 2015 in combination with chemotherapy (carboplatin and paclitaxel) for 1st line treatment of late stage unresectable advanced, metastatic or recurrent squamous non-small cell lung cancer.

Label modified In October 2018 to include combination with platinum-based chemotherapy based on medical record reviews. *"**Finding were consistent with global population data…confirming the efficacy and safety of Bevacizumab combination therapy from multiple perspectives**" Commentary noted benefits of these RWD.

Real world study of regimen containing bevacizumab as first-line therapy in Chinese patients with advanced non-small cell lung cancer

Puyuan Xing*, Yuxin Mu*, Yan Wang, Xuezhi Hao, Yixiang Zhu, Xingsheng Hu, Hongyu Wang, Peng Liu, Lin Lin, Zhijie Wang & Junling Li

National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Thorac Cancer 2018;9:805-13

Comparison of bevacizumab plus chemotherapy with chemotherapy alone in advanced non-small-lung cancer patients

Ning Tang
Zhehai Wang

Department of Oncology, Shandong Cancer Hospital and Institute, Jinan, Shandong, People's Republic of China

Onco Targets Ther 2016;9:4671-9

Comparative Effectiveness of Pemetrexed-platinum Doublet Chemotherapy With or Without Bevacizumab as First-line Therapy for Treatment-naive Patients With Advanced Nonsquamous Non–small-cell Lung Cancer in China

Xiaoyou Li, MD[1,#]; Muhammad Abbas, MD[1,2,#]; Yun Li, MD[1,2]; Yue Teng, MD[1]; Ying Fang, MD[1]; Shaorong Yu, MD[1]; Yi Wen, PhD[3]; Li Wang, MD, PhD[1]; and Meiqi Shi, MD[1]

Clin Ther 2019;41:518-29

Lessons #2

Even with big data, RW endpoints may not be comparable to trials and I/E unlikely to fully match

Using a Public-Private Collaboration to validate RW endpoints

Case Study

Friends of Cancer Research: Laura Lassiter, Mark Stewart, Jeff Allen, and Ellen Sigel

Federal Collaborators

FDA

NCI

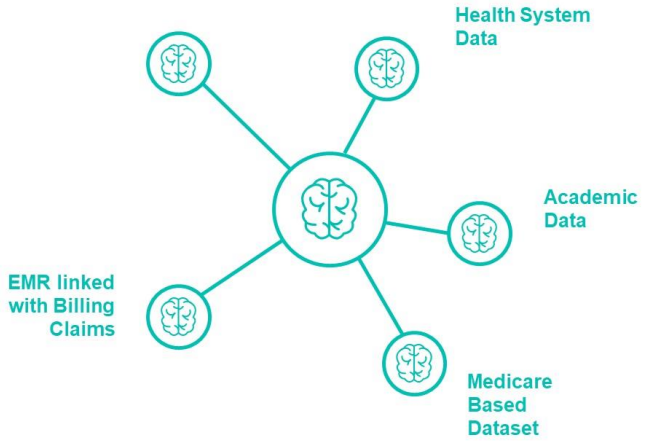
HEALTHCARE RESEARCH ORGANIZATIONS

- Aetion
- ASCO CancerLinQ/Concerto HealthAI
- Cancer Research Network
- COTA
- Flatiron Health
- IQVIA™
- Mayo Clinic
- McKesson
- NCI SEER-Medicare Linked Database
- OptumLabs®
- Syapse
- Tempus

Friends of Cancer Research Initiatives to promote precision oncology

1 Increase Counts and Coverage

- If similar cohorts can be built across sources, data can be pooled in order to meet study needs
- The combination or sources can also alleviate biases inherent in any individual data source



2 Understand Utility of readily available endpoints

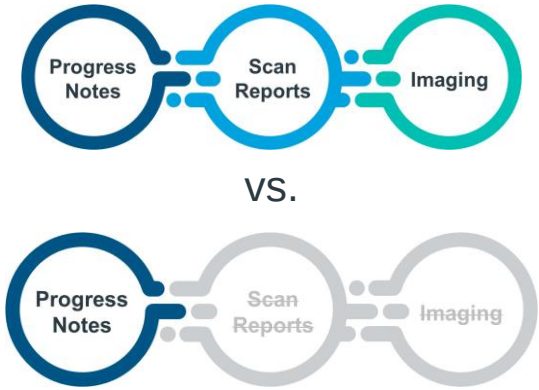
- Treatment based endpoints are readily available across claims and EMR datasets
- Understanding correlation of endpoints such as Time to Treatment Discontinuation to Overall Survival can allow for more efficient studies for some use cases

	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]

3 Validate Generation of Key Clinical Endpoints

- Endpoints such as Response and Progression cannot be derived in same method as clinical trial data
- Understand how varying levels of detail impact precision of these endpoint will inform what data sources can be used for more advanced purposes (regulatory submission)



Collaboration evaluates cancer endpoints

Real-World Derived Endpoint Definitions Developed for use Across RWD types

Overall survival (OS)

- Length of time from the index date to the date of death, or disenrollment (need to define gap in enrollment)
- For claims data, health plan disenrollment date is incorporated if deaths are not captured among those who leave health plan coverage

Time to Next Treatment (TTNT)

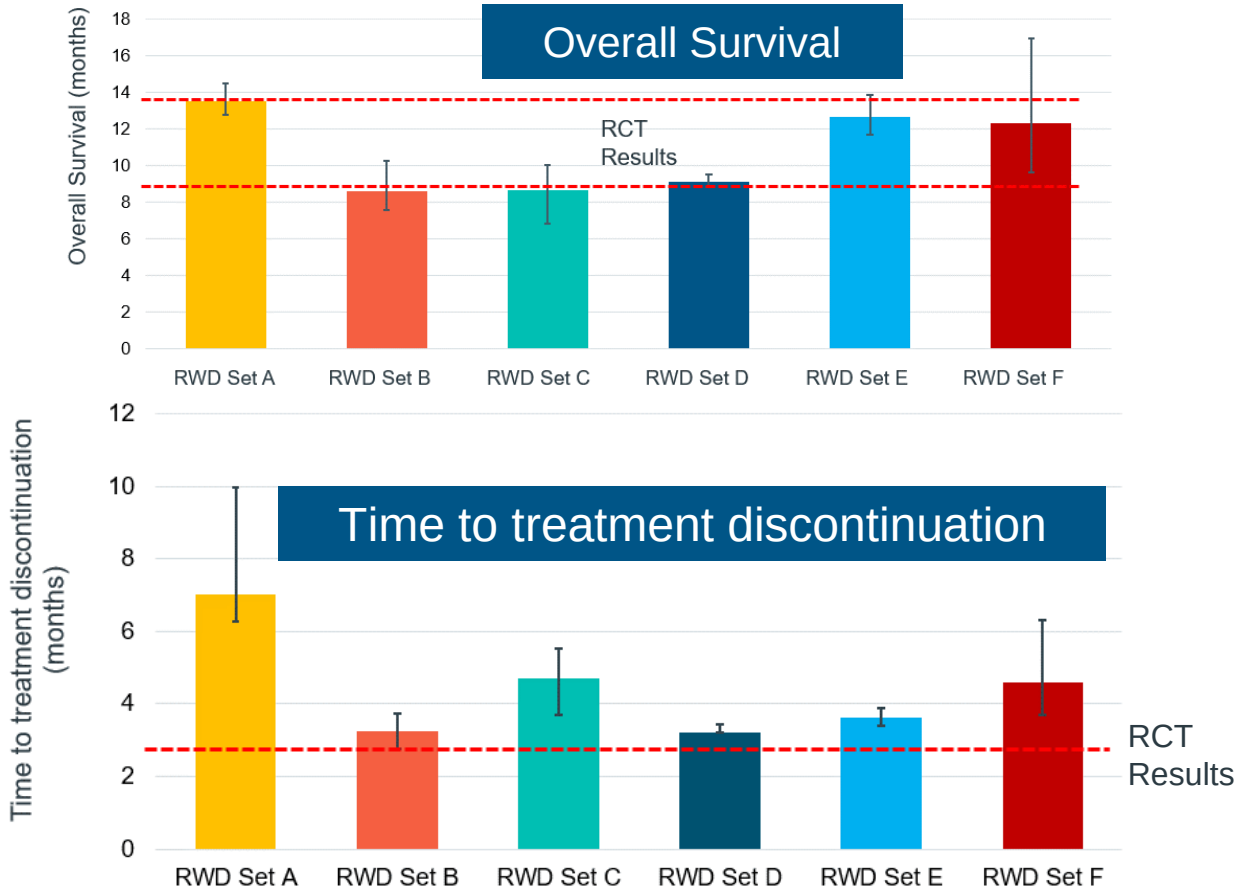
- Length of time from treatment initiation date to the date the patient received an administration of a new systemic treatment regimen or to their date of death if there is a death prior to having another systemic treatment regimen

Time to Treatment Discontinuation (TTD)

- Treatment initiation date to the date the patient discontinues frontline treatment
- The frontline treatment discontinuation date is defined as the last administration or non-cancelled order of all drugs contained within the same frontline
- Length of time from the regimen
- Discontinuation is defined as having a
  - Having a subsequent systemic therapy regimen after the frontline treatment
  - Having a gap of more than 120 days with no systemic therapy following the last administration; or
  - Or having a date of death while on the frontline regimen

Real-world endpoints in “research-ready” RWD networks

Example: Advanced NSCLC patients treated with immune checkpoint inhibitors



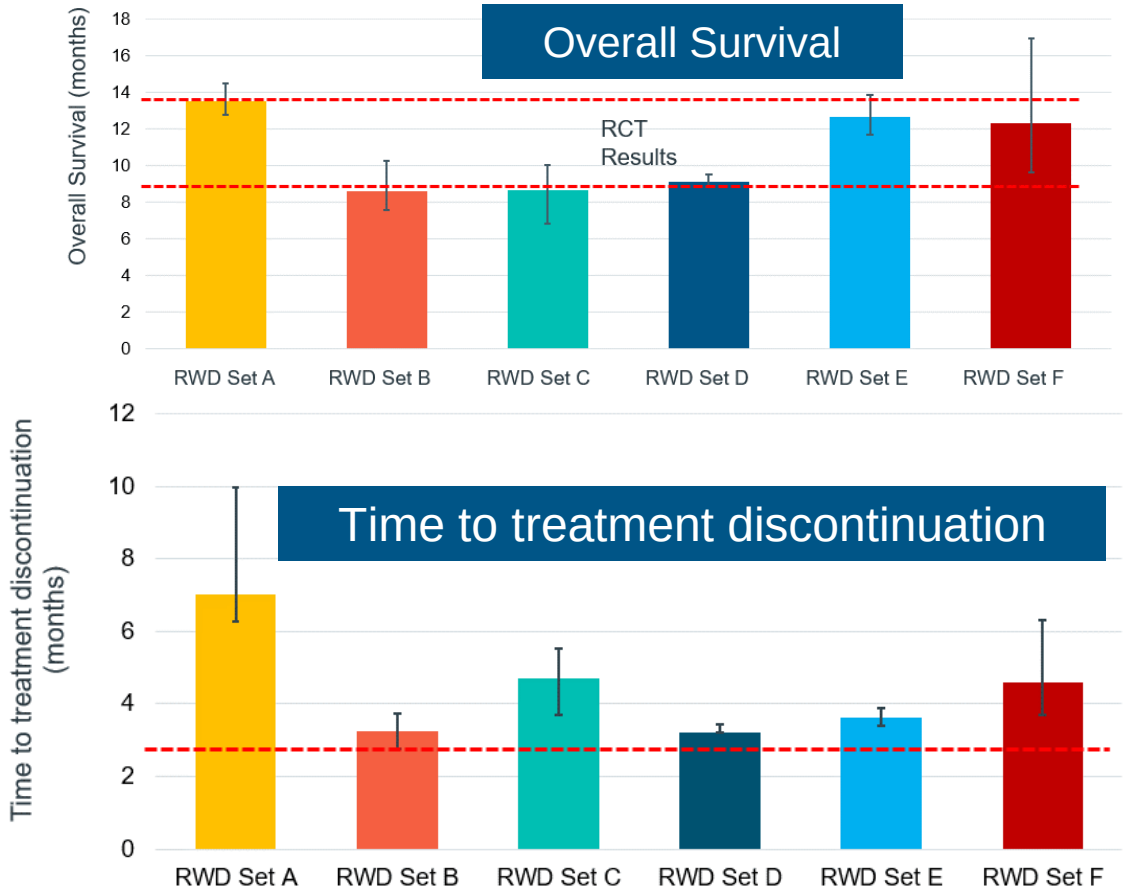
EMR & claims from six de-identified sources

IQVIA
flatiron
pcornet
OPTUM Labs
COTA
KAISER PERMANENTE
FRIENDS of CANCER RESEARCH

Dreyer NA, Hall M, Christian JB. Modernizing regulatory evidence with trials and real-world studies. TIRS 2020, https://doi.org/10.1007/s43441-020-00131-5
Stewart M, Norden AD, Dreyer N et al. JCO Clin Care Informatics. Clinical Care Informatics 2019. 3:1-15. PMID: 31335166

Assembling RWD for 6,924 roughly similar comparators required a base of ~23 million cancer patients (~0.3/1000)

Advanced NSCLC patients treated with immune checkpoint inhibitors



RCT Results

EMR & claims from six de-identified sources

IQVIA
flatiron
pcornet
OPTUM Labs
CTA
KAISER PERMANENTE
FRIENDS of CANCER RESEARCH

Dreyer NA, Hall M, Christian JB. Modernizing regulatory evidence with trials and real-world studies. TIRS 2020, https://doi.org/10.1007/s43441-020-00131-5
Stewart M, Norden AD, Dreyer N et al. JCO Clin Care Informatics. Clinical Care Informatics 2019. 3:1-15. PMID: 31335166

Observations from Jeff Allen, Friends of Cancer Research

- It is **possible to coordinate the efforts across numerous real-world oncology data organizations** to reach high-level alignment on important data elements and definitions for real-world endpoints in the context of a focused research question
- The depth of data varied across data providers and distinct characteristics were identified among the cohorts provided by each organization, likely attributable to the characteristics of the data source and the underlying population being capturing
- It is **possible to identify a similar directionality in treatment effect** of IO as compared to chemotherapy in RWE **consistent with findings in recent clinical trials**
- We demonstrate correlation between real-world OS and other real-world endpoints, including in datasets with near complete mortality data, indicating the potential use of rwTTD/TTNT as **a proxy endpoint for treatment effectiveness in real-world studies**

Slides courtesy of Jeff Allen, President & CEO, Friends of Cancer Research, 2021

Huge research networks are needed

The US is well on the way to large scale linked data (only top 6 networks shown)

	TEMPUS	Syapse	flatiron	Guardian Research Network	FOUNDATION MEDICINE	ORIEN
Description	*Oncology genomics data platform leveraging AI to generate insights for care delivery*	*The US Real-World Evidence Alliance supporting regulatory affairs for Pharma*	*Database platform aggregates leveraging clinical and financial data from EMR billing systems to support cancer care*	*A non-profit a consortium of community health systems capturing clinical & genomic data to support cancer outcomes & trial matching*	*Cancer genomics profiling & decision insights company*	*Academic-Industry alliance with informatics backbone supporting trial matching*
# centres	*?*	*400-450*	*~290*	*85*	*?*	*19*
# industry partners	*8*	*4*	*15*	*~10*	*65*	*1*
# oncology lives	*3.5m patient records*	*~2.2m lives (estimated)*	*1.6m patient records*	*>2m lives*	*500K lives*	*286K lives*

DIGICORE is one of many global partnerships in oncology RWE that IQVIA is supporting (US & EU)

PROMETHEUS

International cancer registries for activist patient groups

Advancing a Framework for Regulatory Use of Real-World Evidence

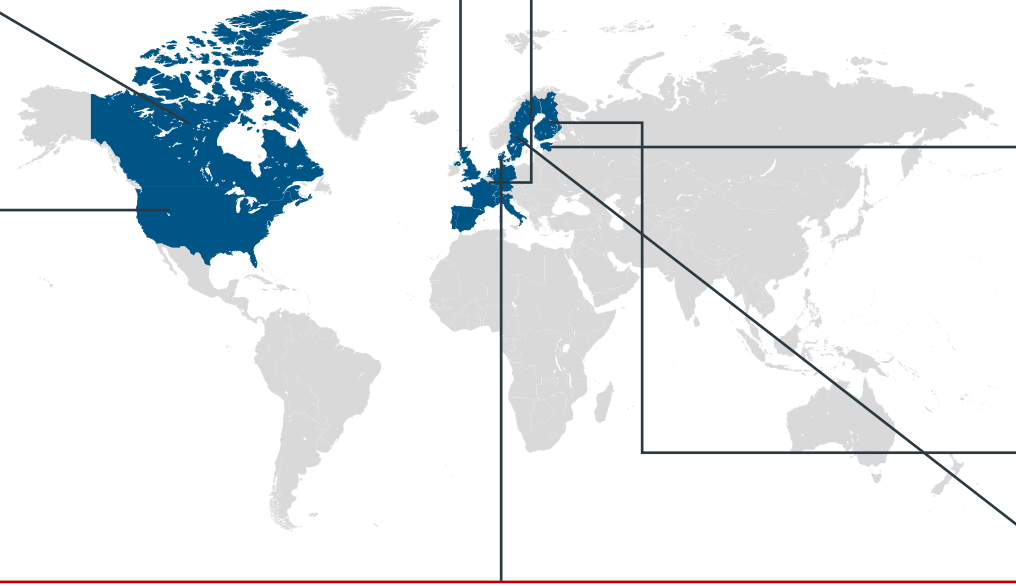
MULTIPLE MYELOMA Research Foundation

FRIENDS of CANCER RESEARCH

Guardian Research Network

Genomics england

National genome sequencing program to support rare disease & cancer pt's



DANISH NATIONAL GENOME CENTER

National genome sequencing program to support personalised treatment

deCODE genetics

Subsidiary of Amgen, exploring genetic risk factors for Cancer

DigiCore

An EU Digital Institute for Cancer Outcomes Research, and a practical answer to RWD studies

estonian genome center university of tartu

Population based biobank at the University of Tartu exploring genomic biomarkers

FINNGEN

Large public-private partnership with a nationwide network of Finnish biobanks

gms

Genomics Medicine Sweden sequencing pt samples to improve diagnostics & care provision

DIGICORE is one of many global partnerships in oncology RWE that IQVIA is supporting (Middle East, Africa and Asia)

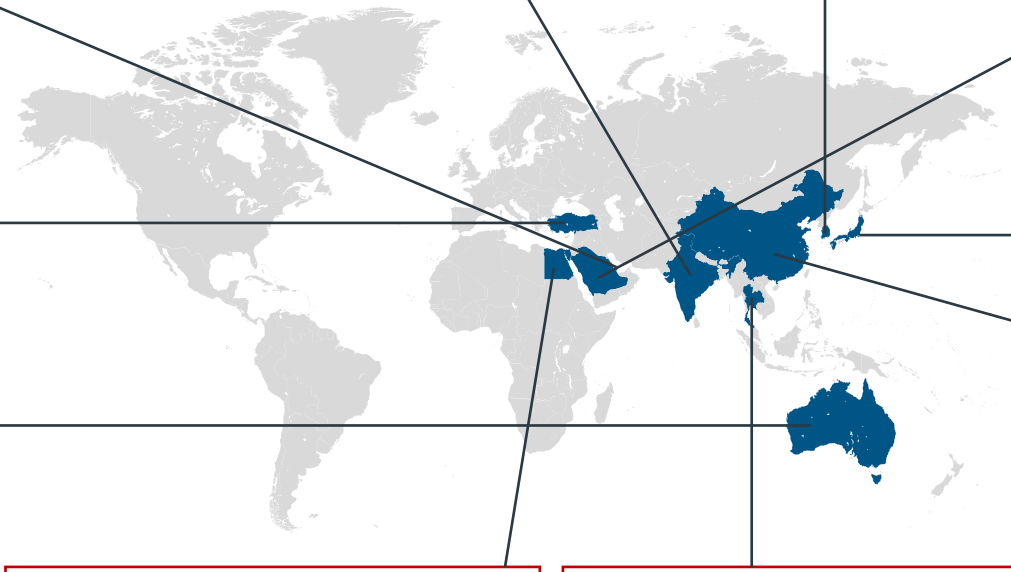
Building Qatar Biobank for precision medicine research

Genome India Project, national genome sequencing program to improve care provision

EXPLORE – Lung Cancer (Samsung Medical Centres, 3 of 5 main national Tx centres)

Build the 1st non-white Reference Genome

Turkish Genome Project, national genome sequencing program to build biobank & improve care in cancer & RD



Gene discovery and gene annotation solutions for cancer

Minderoo Paediatric Oncology Network over 8 centres

National precision oncology programme running in 26 centres

Digital trial platform enabled with the Australian alliance

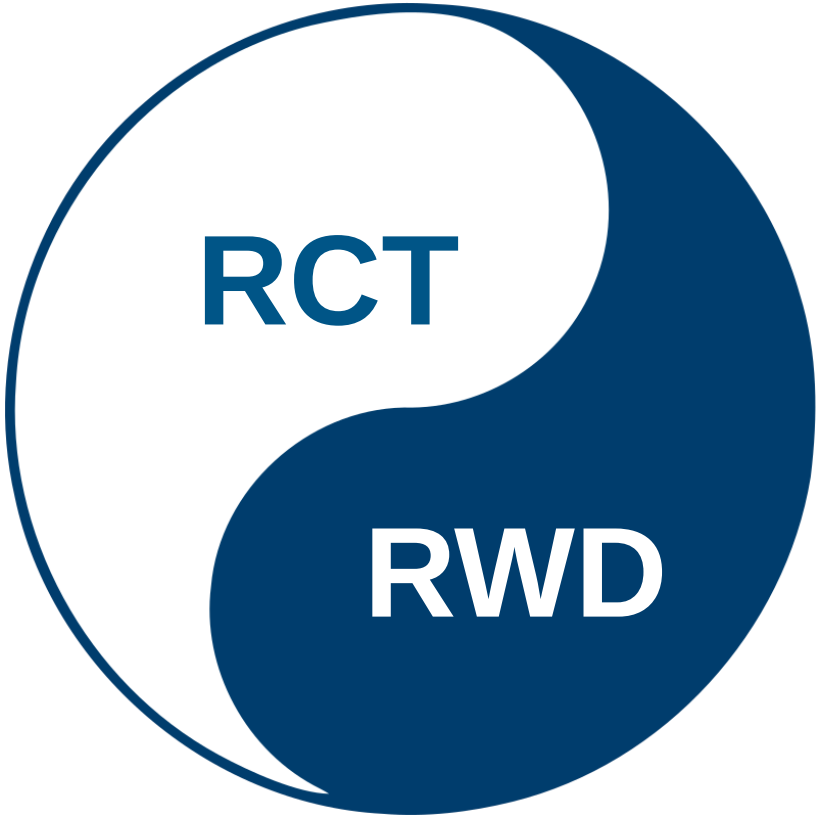
Strategic partnerships with various oncology data partners (GSC, LinkDoc) providing access to multi-center onco-EMR data for sponsored research

Egyptian Human Genome Sequencing Project building reference genome to support care provision

Genomics Thailand, national genome sequencing program to improve care provision

“Far better an approximate answer to the right question, which is often vague, than an exact answer to the wrong question, which can always be made precise.”

John W. Tukey (1962) Annals of Mathematical Statistics 1962;33:1-67



Thank you

Nancy A. Dreyer

Chief Scientific Officer & SVP
Head, Center for Advanced Evidence Generation
IQVIA Real World Solutions

Nancy.Dreyer@IQVIA.com