Navigating the RWE Landscape – Success, Struggles and the Path Forward

ISPOR RWE Summit 2023

May 7, 2023

Nancy A. Dreyer, Moderator
Chief Scientific Officer Emerita
IQVIA Real-World Solutions, and adapted as needed

Dreyer Strategies LLC

Today's Speakers

- Ryan Jung, Center for Drug Evaluation and Research, US Food and Drug Administration,
- Stephen Sheffield, The National Institute for Health Care and Excellence, UK
- Wim Goettsch, National Health Care Institute (Zorgininstitut Netherlands) & Professor HTA of Pharmaceuticals, Utrecht University
- Ashley Jaska, Aetion
- Nancy Dreyer, University of North Carolina

Navigating the RWE Landscape from Regulatory Perspectives

ISPOR RWE Summit 2023

May 7, 2023 | Boston, MA

Tae Hyun (Ryan) Jung, Ph.D.

Senior Statistical Reviewer

Center For Drug Evaluation and Research

U.S. Food and Drug Administration

Agenda

Successes from the RWE Journey

Struggles in Regulatory Review

Path Forward for Future Submissions

Disclaimer

This presentation reflects the views of the presenter and should not be construed to represent the US Food and Drug Administration views or policies

Approved Drugs using RWD/E as Supportive Evidence

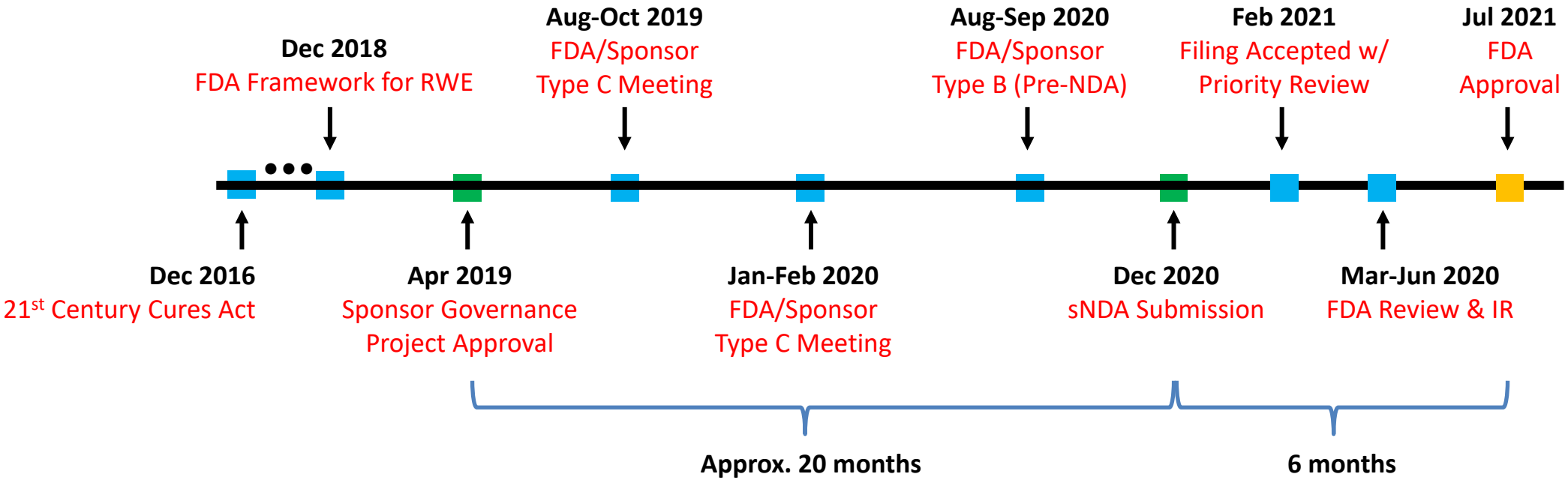
DRUG	INDICATION	APPROVAL	DATA
Carbaglu (carglumicacid)	NAGS deficiency	2010	Retrospective, non-random, unblinded case series of 23 patients compared to **historical control group**
Blincyto (Blinatumomab)	Acute Lymphoblastic Leukemia	2014	Single-arm trial, Reference group weighted analysis of patient level data **on chart review** of 694 patients at EU and US study sites
Omegaven (fish oil triglycerides)	Parenteral nutrition-associated cholestasis	2018	Two single-arm trials, matched to **historical control arm from hospital record**
Ibrance (palbociclib)	Male breast cancer	2019	**Data from electronic health records and postmarketing reports** of the real-world use of IBRANCE in male patients
Voxzogo (vosoritide)	Achondroplasia in patients 2+ years	2021	**Observational, retrospective AchNH registry** served as external control to two small supportive Phase II studies
Orencia (abatacept)	Prophylaxis of acute graft versus host disease	2021	**Registry-based clinical study** using real world data from the Center for International Blood and Bone Marrow Transplant Research

Before and After 2018 FDA RWE Framework

New Indication for Tacrolimus (Prograf®)

CDER's **first acceptance** of an "**observational study**" as an **adequate and well-controlled study** providing the **primary support** for a finding of **substantial evidence of effectiveness**

Source: Concato, John, and Jacqueline Corrigan-Curay. "Real-World Evidence-Where Are We Now?." *The New England journal of medicine* 386.18 (2022): 1680-1682.



Overview of Prograf® sNDA

Prograf® (tacrolimus): Indicated for the prevention of organ rejection in adult and pediatric patients receiving allogeneic lung transplant in combination with other immunosuppressants

FDA Approval: July 16, 2021

Key Regulatory History: Initially approved for prevention of organ rejection in patients receiving liver transplants in 1994 (later for kidney (1997) & heart (2006)), based on RCT evidence. RCTs for lung not submitted to FDA, but drug has been used widely in clinical care; Applicant submitted supplemental New Drug Application (sNDA) to FDA

Sponsor's Clinical Study

Study Design: Non-interventional (observational) treatment arm, compared to historical controls

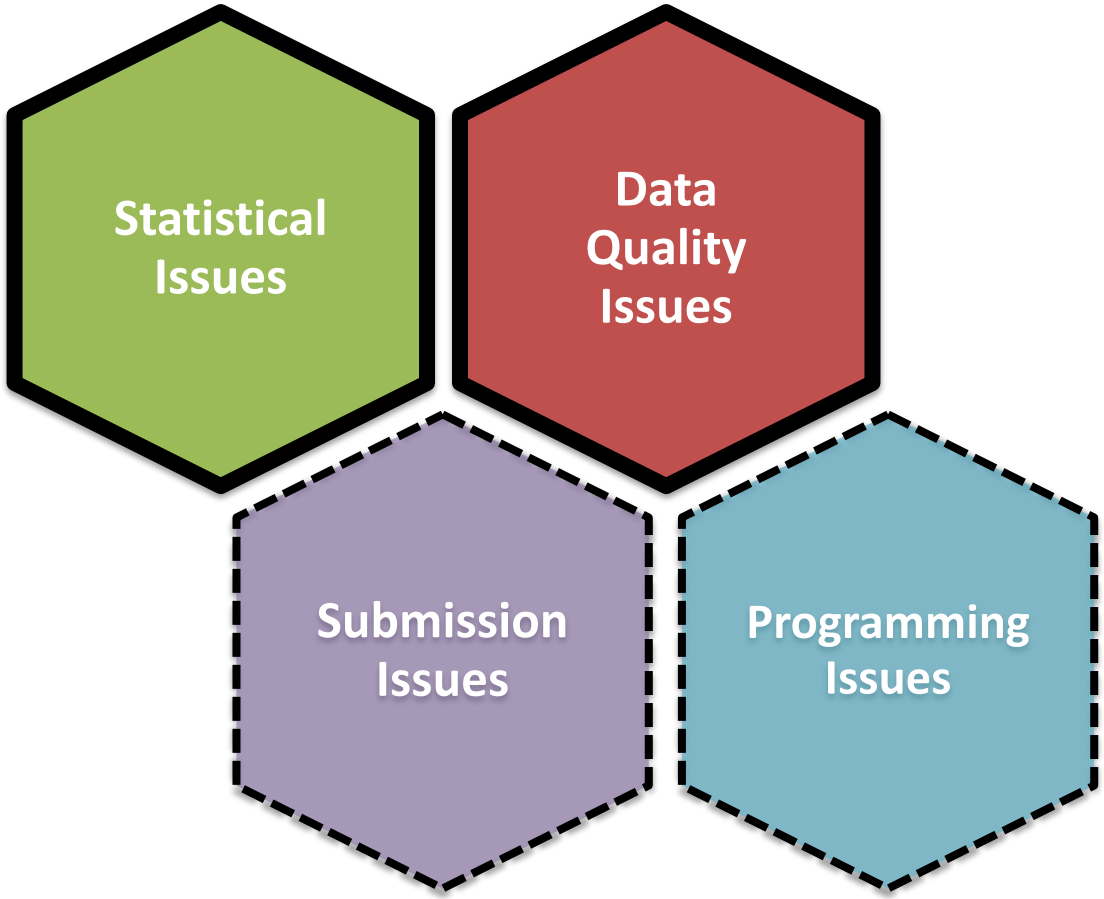
Primary Endpoint: A composite endpoint of graft failure (GF) or death (due to any cause) within one year (365 days) after transplant

Data Source: Scientific Registry of Transplant Recipients (SRTR) data on all lung transplants in US between 1999–2017

Study Population: Adult and pediatric patients in tacrolimus immediate release (TAC IR) in combination with mycophenolate mofetil (MMF) or azathioprine (AZA)

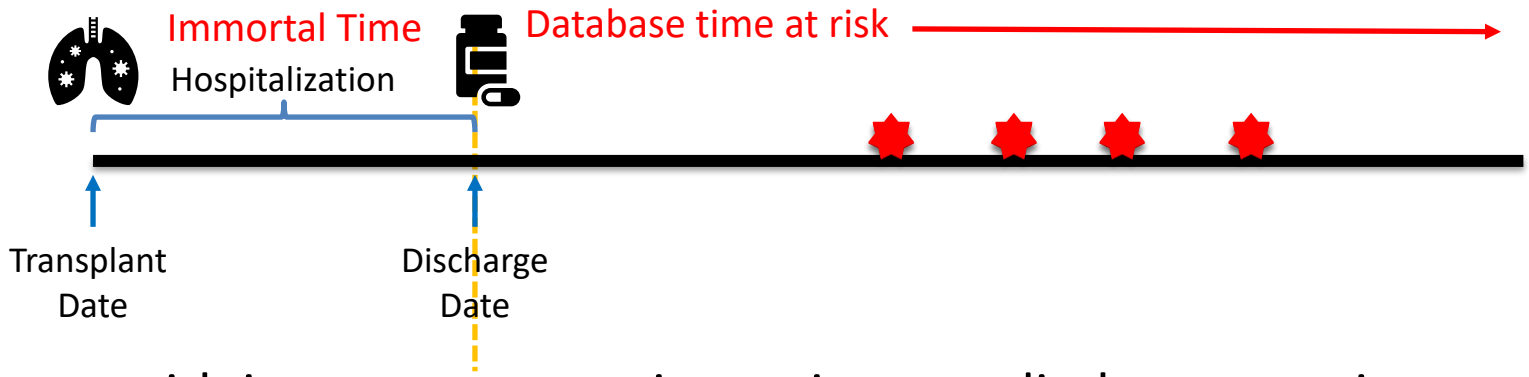
Erdman, Jay, et al. *"Lung Transplant Outcomes in Adults in the United States: Retrospective Cohort Study Using Real-world Evidence from the SRTR."* Transplantation 106.6 (2022): 1233-1242.

Four Key Issues from the Prograf RWE Review



Statistical Issue

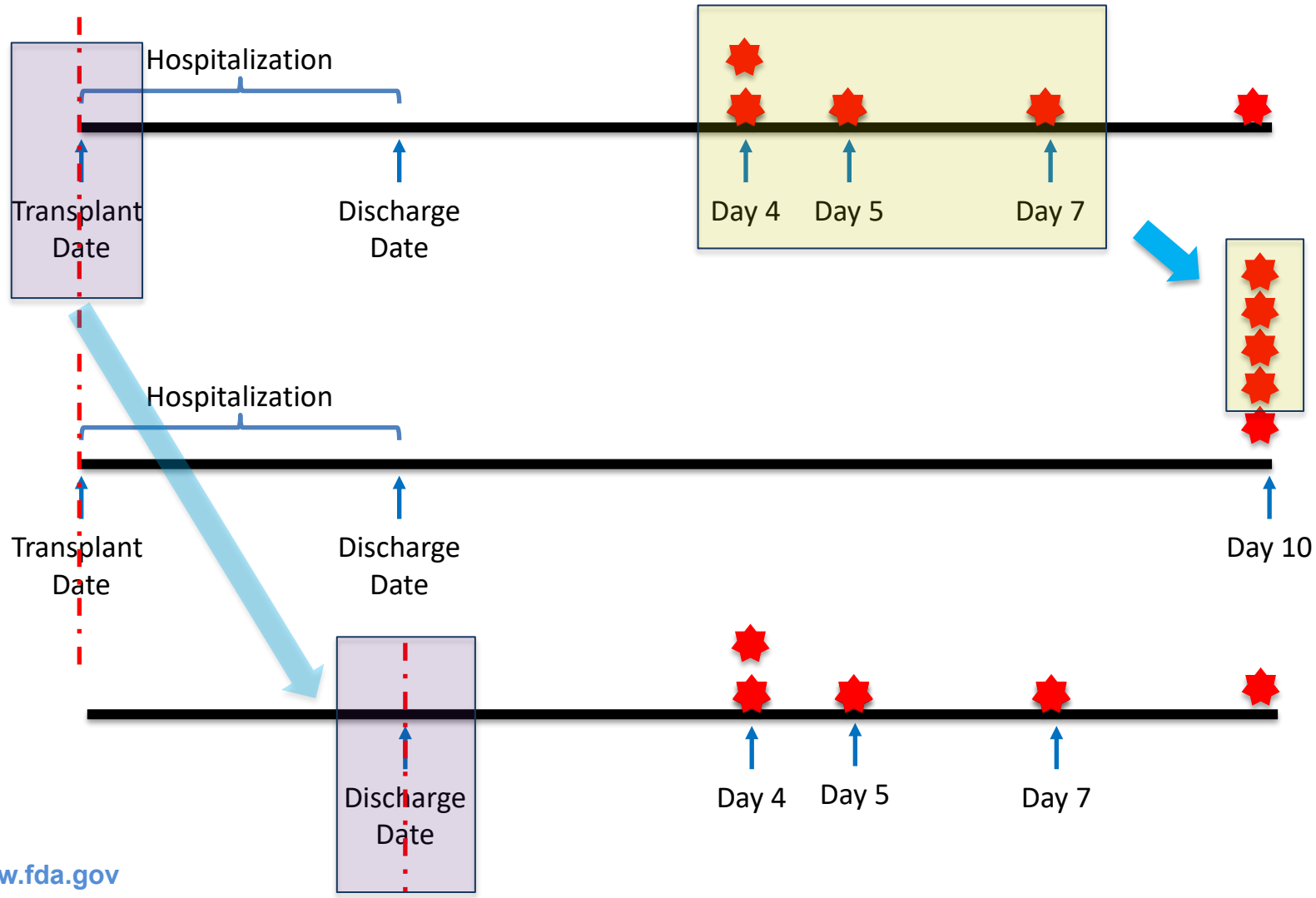
- Sponsor **changed primary analysis after looking the results**: 4 events from 15K subjects led to non-robust estimate with 86% survival in TAC IR + MMF arm of the adult population
- Sponsor **proposed post-hoc analysis** and manually shifted data to improve survival (91%)
  - Not specified in the Statistical Analysis Plan
  - Conducted only in TAC IR + MMF arm of the adult population



- Treatment with immunosuppressive regimen at discharge requires a patient to survive after transplant through discharge
- Analysis requires or conditional on graft survival until discharge and time at risk effectively begins at the date of discharge

Statistical Issue

TAC IR + MMF in adult population



Primary analysis

86% survival

Post-hoc analysis

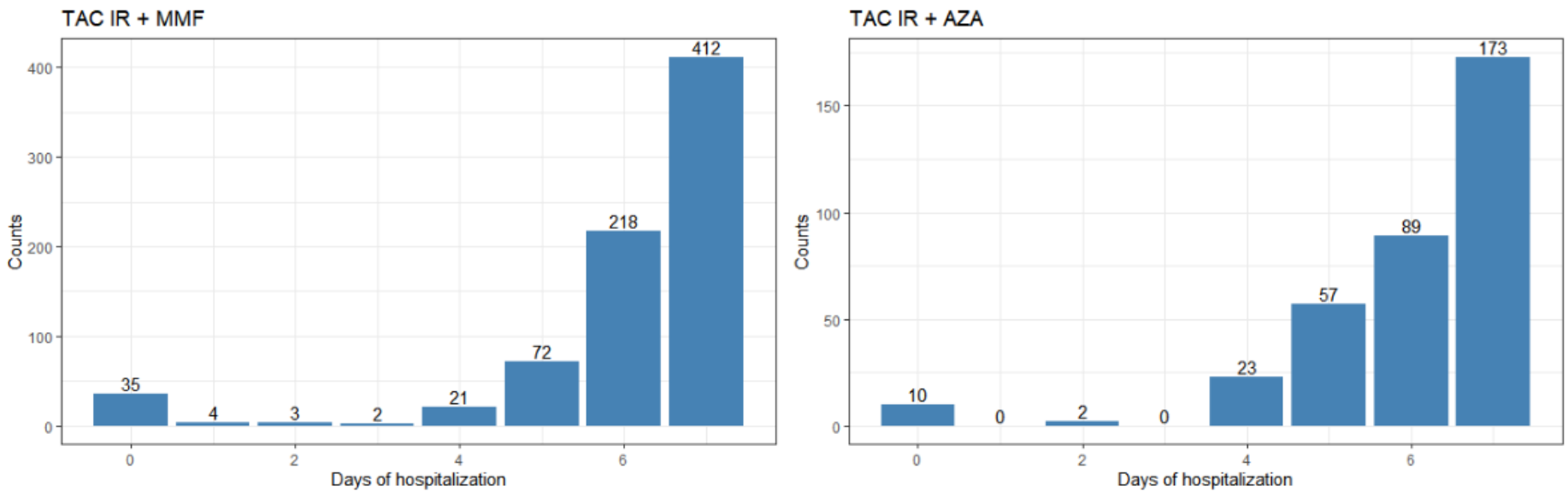
91% survival

Sensitivity analysis

91% survival

Data Quality Issue

Length of Hospitalization in TAC IR + MMF and TAC IR + AZA



- **Possible Reasons for Unusual Distribution of Length of Hospitalization**
  - Data entry errors, where transplant center staff provided the same date for transplant and discharge
  - Patient was discharged from inpatient service to another unit and transplant center staff entered that date

Seizing Opportunities and Learning from Failures

- **RWD/RWE bring opportunities**
  - to increase the diversity of populations and reflect actual clinical settings/practices
  - to improve study efficiency by making use of existing data while maintaining evidentiary standards
  - Lessons from Prograf
    - It is important to ensure data reliability and relevance
    - Prespecification in the protocol/SAP is still important in RWE application
    - Robust scientific rationale should be provided to explain the issue
    - Multifaceted aspects of accuracy should be carefully assessed, and any data quality issues should be addressed and documented
- **RWD/RWE is neither a short cut nor a magical box**

Drug Name	Purpose	Study Design	Major Review Issues
Drug A	Unclear what the purpose of this submission is, as previous RCT failed.	Single arm trial using external control	**Questionable comparability** between RWD and trial data due to changes in standard of care and differences in inclusion/exclusion criteria.
Drug B	Label change to add RWE on effectiveness	Pragmatic	• Source of EHR data is **unclear** • **Reliability and relevance** of the EHR data **not addressed**

Machine Learning/Artificial Intelligence

STATISTICS IN BIOPHARMACEUTICAL RESEARCH
2022, VOL. 00, NO. 0, 1–5
https://doi.org/10.1080/19466315.2022.2108135

The Use of Machine Learning in Regulatory Drug Safety Evaluation

Di Zhang, Jaejoon Song, Sai Dharmarajan, Tae Hyun Jung, Hana Lee, Yong Ma, Rongmei Zhang, and Mark Levenson

Division of Biometrics VII, Office of Biostatistics, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD

ABSTRACT

There has been growing interest of using machine learning (ML) methods with real-world data (RWD) to generate real-world evidence (RWE) to support regulatory decisions. In the U.S. Food and Drug Administration (FDA), ML has been applied in both prediction and causal inference problems for drug safety evaluation. The ML applications include health outcome identification, missing data imputation, risk factor identification, drug utilization discovery and causal inference study. We demonstrate the present utility and future potential of ML for regulatory science. We then discuss the challenges and considerations when using ML methods with RWD to generate RWE. Specifically, we focus on the transparency and reproducibility issue of using ML, the potential of ML and natural language processing (NLP) for missing data in RWD , training data issue for rare events, and interpretability of studies using ML.

ARTICLE HISTORY
Received December 2021
Accepted July 2022

KEYWORDS
Causal inference; Prediction; Post-marketing; Natural language processing; Real-world data; Real-world evidence

- Rarely used in efficacy NDA/BLA reviews
- Increasing usage in PMR reviews (random forest, natural language processing etc.)
- Internal/External collaborations

Thank you

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Navigating the RWE Landscape - Successes, Struggles, and the Path Forward – at NICE

Dr. Stephen Duffield
Associate Director
Data and Analytics team

ISPOR RWE Summit: 7th May 2023

NICE National Institute for Health and Care Excellence

Disclaimer : *opinion and interpretation of SJ Duffield, not NICE!*

NICE Vision for RWE

1. RWD access
2. Use of RWE
3. Capability building
4. Signposting
5. Partnership and research

NICE's RWE Framework

Published June 2022

Aims to:

- Increase use of RWE to fill evidence gaps and improve recommendations
- Improve quality and transparency of RWE studies that inform guidance
- Inform critical appraisal of RWE studies
- Increase trust in high-quality RWE studies

Describes

- Where and how RWE can be used to improve recommendations
- Best-practices for planning, conducting, and reporting RWE studies

TA855: Mobocertinib for EGFR Exon 20 insertion-positive NSCLC after platinum chemotherapy

Evidence submission

- Single arm phase 1 and 2 trial
- Adjusted indirect comparison
- No prior clinical trials or RWE studies
- US and German RWD combined from Flatiron data and cohort data from a German Chart Review

Committee concerns

- not provided enough information on data provenance, accuracy and suitability
- not explored the effect of missing data
- Unclear if appropriate to pool sources of RWD
- Was case-mix of comparator treatments relevant to UK practice?

Company response

- Completed DataSAT and RECORD-PE reporting templates for both RWD sources.

Scenario analyses:

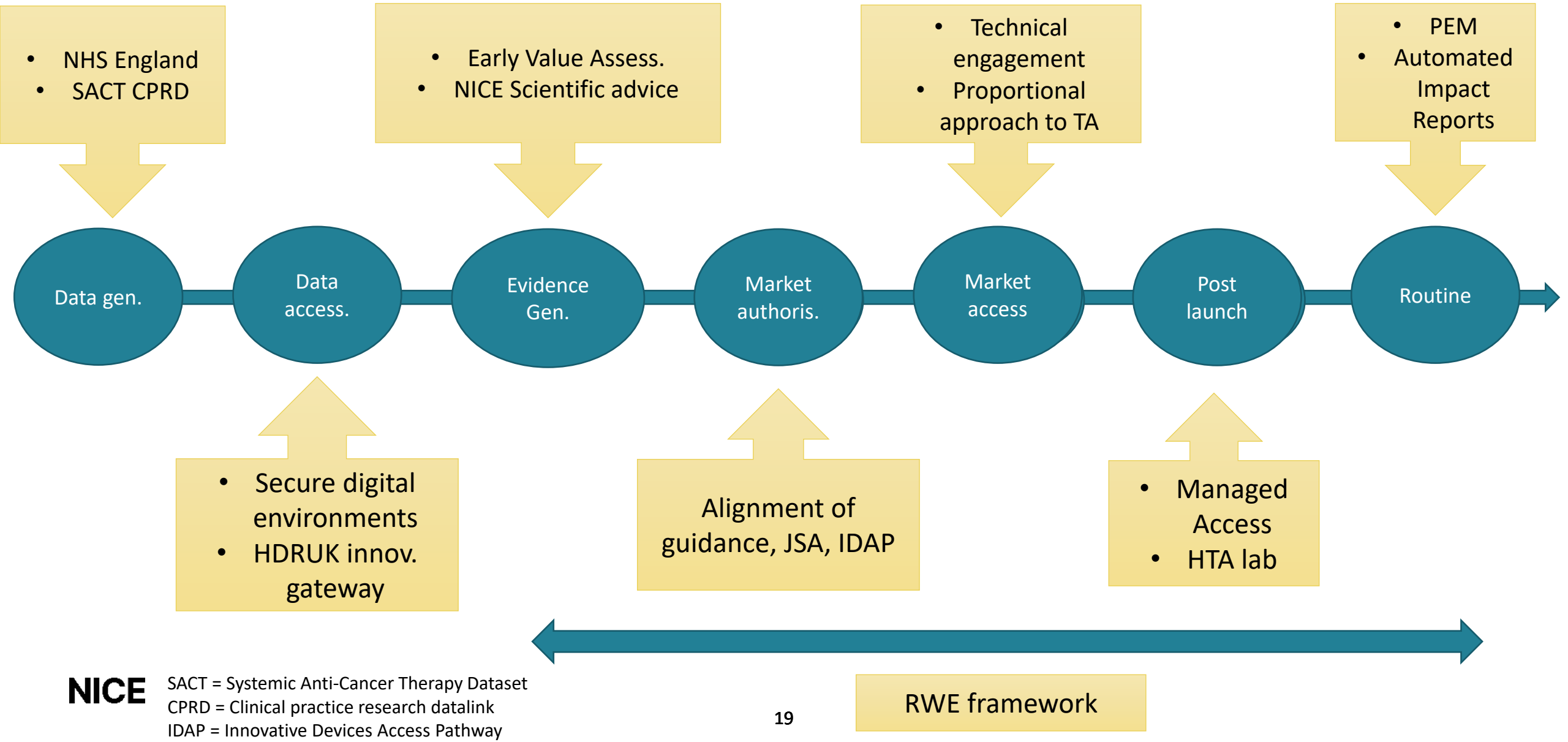
- excluding EGFR TKIs from the real-world data
- MI for missing ECOG
- Reporting results for sources of real-world evidence separately (rather than pooled).

Positive recommendation!

BUT "the level of uncertainty could have been reduced if the company had shown that a systematic approach had been taken to selecting real-world evidence sources"

NICE

NICE stewards RWE across evidence lifecycle



SACT = Systemic Anti-Cancer Therapy Dataset
CPRD = Clinical practice research datalink
IDAP = Innovative Devices Access Pathway
JSA = Joint Scientific Advice, PEM = Post-evaluation monitoring

Challenges in HTA

- Need for organisational upskilling to build confidence appraising RWE and appreciation of its role in answering questions complimentary to RCT data
- Framework gaps - data discoverability and selection
- Timeliness of data access
- Low hanging fruit not yet seized – transparency
- High hanging fruit not yet familiar – QBA
- Unclear influence of RWE in managed access
- Development of national/subnational data collections
- Medtech

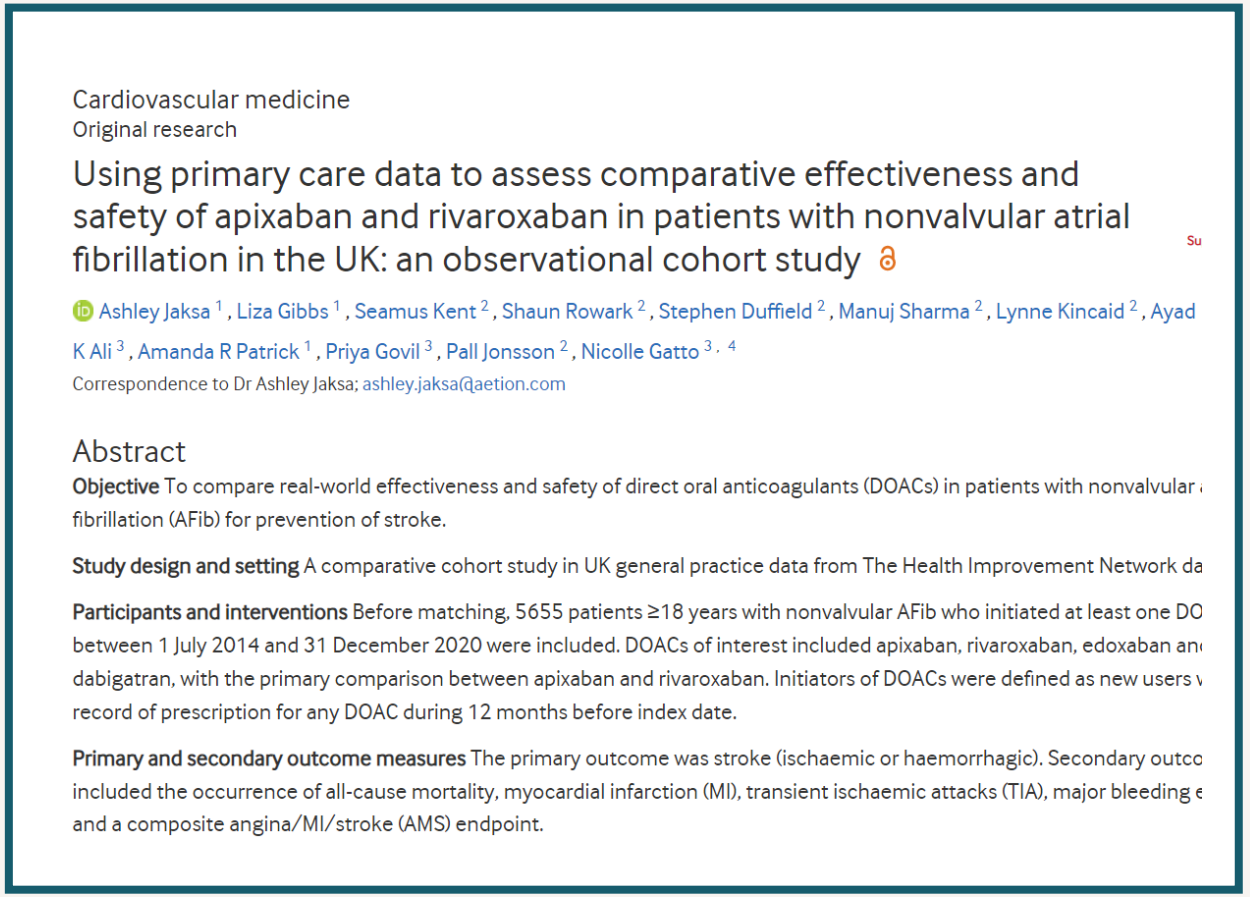
NICE

Casirivimab plus imdevimab, nirmatrelvir plus ritonavir, sotrovimab and tocilizumab for treating COVID-19 (TA878 - under appeal)

*"The committee noted the results of **Hill and Mirchandani (2022)** that compared the outcomes of a randomised controlled trial with non-randomised studies on COVID-19 treatments. **The authors questioned the validity of non-randomised studies** when their outcomes contradict the outcomes from a randomised controlled trial. The authors cautioned against using non-randomised evidence independent of randomised evidence for regulatory decisions. **The committee was willing to accept the OpenSAFELY data on relative treatment effectiveness as supplementary evidence to the trial evidence** and for modelling estimates for hospitalisation rates. **The committee cautioned against solely relying on non-randomised evidence** when making conclusions on treatment effect."*

Challenges in Clinical Practice Guidelines

- Need for organisational upskilling to build confidence appraising RWE and appreciation of its role in answering questions complimentary to RCT data
- Required paradigm shift is larger
  - Traditional reliance on published evidence
  - Greater reliance on RCT for comparative effects
- Need for in-house analysis (resource)
- Timely access to/analysis of RWD not currently supported by inflexible processes



Cardiovascular medicine
Original research

Using primary care data to assess comparative effectiveness and safety of apixaban and rivaroxaban in patients with nonvalvular atrial fibrillation in the UK: an observational cohort study

Ashley Jaksa [1], Liza Gibbs [1], Seamus Kent [2], Shaun Rowark [2], Stephen Duffield [2], Manuj Sharma [2], Lynne Kincaid [2], Ayad K Ali [3], Amanda R Patrick [1], Priya Govil [3], Pall Jonsson [2], Nicolle Gatto [3, 4]
Correspondence to Dr Ashley Jaksa; ashley.jaksa@aetion.com

Abstract

Objective To compare real-world effectiveness and safety of direct oral anticoagulants (DOACs) in patients with nonvalvular fibrillation (AFib) for prevention of stroke.

Study design and setting A comparative cohort study in UK general practice data from The Health Improvement Network da

Participants and interventions Before matching, 5655 patients ≥18 years with nonvalvular AFib who initiated at least one DO between 1 July 2014 and 31 December 2020 were included. DOACs of interest included apixaban, rivaroxaban, edoxaban an dabigatran, with the primary comparison between apixaban and rivaroxaban. Initiators of DOACs were defined as new users v record of prescription for any DOAC during 12 months before index date.

Primary and secondary outcome measures The primary outcome was stroke (ischaemic or haemorrhagic). Secondary outco included the occurrence of all-cause mortality, myocardial infarction (MI), transient ischaemic attacks (TIA), major bleeding e and a composite angina/MI/stroke (AMS) endpoint.

NICE

Summary

- NICE's RWE Framework describes best-practices for planning, conducting, and reporting real-world evidence studies
- This framework is being used to aid communication between developers and NICE committees regarding expectations around quality and reporting, as well as for in-house analysis
- Challenges remain:
  - Upskilling and culture change
  - Improving data knowledge and discoverability, timely access, suitability of national and subnational data collections for NICE decision making
  - Piloting new models of evaluation and more flexible guideline update structures
  - Sustainable models for bespoke analysis of RWD

NICE

NICE National Institute for Health and Care Excellence

Thank you

National Health Care Institute

Management of Disease-Specific Patient Registries for Monitoring Expensive Pharmaceuticals

Initial experiences from 4 case studies

Wim Goettsch, MSc, PhD
Special Advisor HTA ZIN &
Professor HTA of Pharmaceuticals, Utrecht University

ISPOR RWE Summit 2023
7 May 2023
Boston, MA, USA

Zorginstituut Nederland starts new project: Managing patient registries for expensive drugs

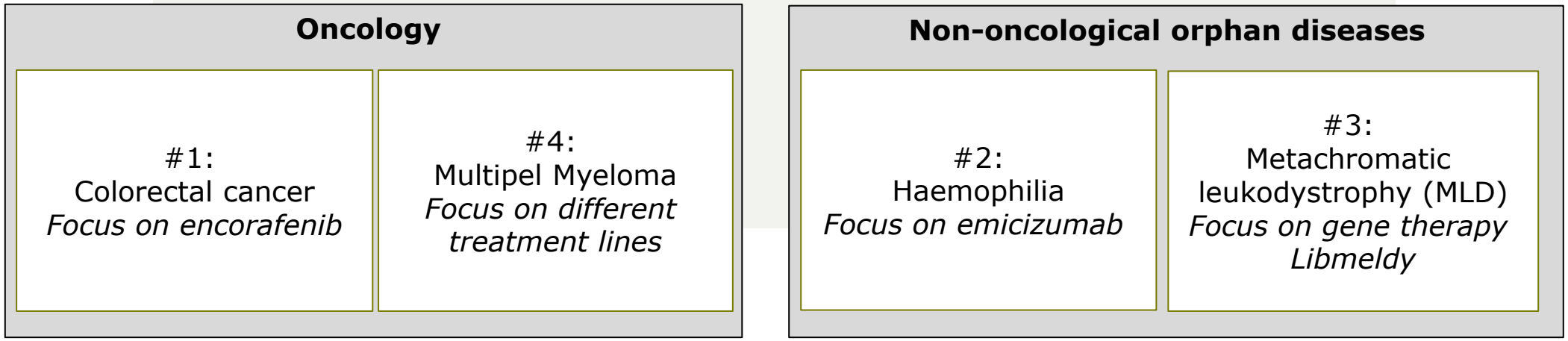
News item | 02-04-2019 | 13:00

Expensive drugs for specialist medical care are increasingly gaining market entry, while uncertainty still exists about their (cost-)effectiveness, their proper positioning in treatment and/or their right indication setting. Moreover, these drugs are often automatically accepted into the standard health care benefit package, under a full price, while these products may still not be fully developed. For those reasons, the *Zorginstituut* is starting a new project entitled 'Managing registries for expensive drugs'. The objective is to better measure outcomes of treatment with new drugs in practice. It also involves managing how information from clinical practice is structurally recorded in these registers.

Activities from ZIN on registries & RWD within the project

- Provide national guidance on disease-specific patient registries for the monitoring of expensive pharmaceuticals (ZIN)
- Focus on oncology and non-oncological orphan diseases
- Four case-studies with existing or new patient registries with the goal to use them for HTA on newly marketed expensive drugs
- Focus on both the initial assessment as well on a life-cycle approach (MEAs and reassessment)
- Strong involvement of stakeholders such as clinicians, patients, health insurers, regulators and pharma companies
- International collaboration is important especially for orphan medicinal products & ATMPs

Case-studies within the ZIN project (2021-2023)



Goals of the case-studies

- Facilitate development of disease-specific patient registries for HTA of expensive pharmaceuticals
- Set the standard for other patient registries

Specifically;

- High quality data on real-world effectiveness, cost-effectiveness, QoL and safety of expensive drugs
- Perform a study on (cost-)effectiveness of a new expensive pharmaceutical in real-world
- Develop methodological toolbox to transform the real-world data in real-world evidence
- Input for framework on governance, legal and privacy issues
- Proving ground for setting up an IT-infrastructure

Some preliminary results

- We established minimal data sets with involvement of all stakeholders (patients, clinicians, regulators, payers and industry)
- For one case-study, MLDi, an international patient registry was established including an internationally agreed common data set
- We used the REQUEST tool to assess the data quality including the transparency of the patient registries
- For two case-studies we also used the HARPER template to define the research question
- Currently, we are assessing the detailed final reports from the four case- studies

Schoenmakers et al.
Orphanet Journal of Rare Diseases (2022) 17:48
https://doi.org/10.1186/s13023-022-02189-w

Orphanet Journal of Rare Diseases

RESEARCH Open Access

Modified Delphi procedure-based expert consensus on endpoints for an international disease registry for Metachromatic Leukodystrophy: The European Metachromatic Leukodystrophy initiative (MLDi)

Daphne H. Schoenmakers[1,2,3], Shanice Beerepoot[1,4,5], Sibren van den Berg[2,3], Laura Adang[6], Annette Bley[7], Jaap-Jan Boelens[8], Francesca Fumagalli[9], Wim G. Goettsch[10,11], Sabine Grønborg[12], Samuel Groeschel[13], Peter M. van Hasselt[14], Carla E. M. Hollak[2,3], Caroline Lindemans[5,15], Fanny Mochel[16,17], Peter G. M. Mol[18,19], Caroline Sevin[20,21], Ayelet Zerem[22,23], Ludger Schöls[24,25] and Nicole I. Wolf[1*]

Finance

involved

Context REQueST Tool

https://www.eunethta.eu/request-tool-and-its-vision-paper/

eunethta

EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

Joint Action 3

MILESTONE

Milestone 5.15 Final validated Standards Tool for Registries in HTA prepared

Date of submission	30-09-2019
Work package	5
Activity Centre	Post-Launch Evidence Generation (PLEG) and Registries – Strand B2
Author(s)	National Institute for Health and Care Excellence, NICE (UK) Croatian Institute of Public Health, HZJZ (Croatia) Agency for Health Quality and Assessment of Catalonia, AQuAS (Spain) French National Authority for Health (Haute Autorité de Santé), HAS (France) - *work package lead*
Dissemination level	Public

Co-funded by the Health Programme of the European Union

Revision History

Revision no.	Date	Author
1	06-09-2017	Maja Valentić (MV) (HZJZ)
2	22-12-2017	MV, Hannah Patrick (HP) (NICE)
5	12-07-2018	MV, HP, Helen Powell (HeP) (NICE), Irena Guzina (IG) (HAS)
7	17-04-2019	HP, HeP
8	25-05-2019	MV, HP, HeP, Emmanuel Gimenez (EG) (AQuAS)
9,1	03-05-2019	MV, HP, HeP, IG, Jae Long (JL) (NICE)
9,7	30-09-2019	Maja Valentić (HZJZ), Hannah Patrick (NICE), Helen Powell (NICE), Irena

Proceed to introduction

Acknowledgements

The REQueST tool has been developed by the following EUnetHTA partners:

Role	Organisation
Authors	National Institute for Health and Care Excellence, NICE (UK) Croatian Institute of Public Health, HZJZ (Croatia) Agency for Health Quality and Assessment of Catalonia, AQuAS (Spain) French National Authority for Health (Haute Autorité de Santé), HAS (France) - *work package lead*
Co-authors	Italian Medicines Agency, AIFA (Italy) Galician Agency for Health Technology Assessment, avalia-t (Spain) National Authority of Medicines and Health Products, INFARMED (Portugal)
Reviewers	Agencia Española de Medicamentos y Productos Sanitarios, AEMPS (Spain) Agenzia Nazionale per i Servizi Sanitari Regionali, Agenas (Italy) Agency for Health Technology Assessment and Tariff System, AOTMiT (Poland) Azienda Zero, AZIENDA (Italy) Ministero della Salute, DGFDM IT (Italy) National Evaluation Center of Quality and Technology, EKAPTY (Greece) Finnish Medicines Agency, FIMEA (Finland) Federal Office of Public Health, FOPH (Switzerland) Institute for Quality and Efficiency in Health Care, IQWIG (Germany) National Institute of Health, ISS (Italy) Public Agency of the Republic of Slovenia for Medicinal Products and Medical Devices, JAZMP (Slovenia) National Institute of Public Health, NIJZ (Slovenia) National Institute of Pharmacy and Nutrition, NIPN (Hungary) Norwegian Medicines Agency, NoMA (Norway) National School of Public Health Management and Professional Development, NSPHMPDB (Romania) Swiss Network for Health Technology Assessment, SNHTA (Switzerland) Dental and Pharmaceutical Benefits Agency, TLV (Sweden) University Hospital A. Gemelli, UCSC GEMELLI (Italy) National Health Care Institute, ZIN (The Netherlands)

The following external organisations provided comments on the REQueST tool:

Role	Organisation
Stakeholder and/or public consultees	Alliance for Regenerative Medicine, ARM Analysis Group (USA) European Association of Hospital Pharmacists, EAHP European Coordination Committee of the Radiological, Electromedical and Healthcare IT Industry, COCIR European Federation of Pharmaceutical Industries and Associations, EFPIA European Federation of Statisticians in the Pharmaceutical Industry, EFSPI European Forum for Primary Care, EFPC European Free Trade Association, EFTA European Medicines Agency, EMA European Organisation for Rare Diseases, EURORDIS European Organisation for Research and Treatment of Cancer, EORTC European Patients' Forum, EPF European Public Health Association, EUPHA European Society of Cardiology, ESC European Union of General Practitioners, UEMO ICON Commercialisation & Outcomes (Ireland) Office for Life Sciences, OLS (UK) Red Argentina Pública de Evaluación de Tecnología Sanitaria (Argentina) Synergus RWE (Sweden) University of Manchester (UK) University of Zurich (Switzerland)

- REQueST will support consistent evaluation of the suitability and reliability of registries for HTA
- REQueST will be useful to registry owners to develop the quality of their registry

Area	Item	Colour rating
Methodological Information	1. Type of registry	
	2. Use for registry-based studies and previous publications	
	3. Geographical and organisational setting	
	4. Duration	
	5. Size	
	6. Inclusion and exclusion criteria	
	7. Follow-up	
	8. Confounders	
Essential Standards	9. Registry aims and methodology	
	10. Governance	
	11. Informed consent	
	12. Data dictionary	
	13. Minimum data set	
	14. Standard definitions, terminology and specifications	
	15. Data collection	
	16. Quality assurance	
	17. Data cleaning	
	18. Missing data	
	19. Financing	
	20. Protection, security and safeguards	
Additional Requirements	21. Interoperability and readiness for data linkage	
	22. Data sources	
	23. Ethics	

No Knock-out criteria; will the Registry be potentially suitable to answer HTABs' questions? This is about scope > does it suit my registry-based study question?

Knock-out criteria; all need to be green. This is about the quality of the Registry itself.

4 steps with the case studies

- Registry owner and independent reviewer complete REQueST Tool for case study registry
- Independent reviewer compares provided answers
- Provided answers are discussed among registry owner and independent reviewer
- Compile lessons learned into Memo report to improve the REQueST Tool and further its implementation (ongoing)

Some results

- There are significant differences between the information provided by registry owners and what is publicly available
  - ➢ *Information gaps should be fed back to the registry owners so they can make necessary alterations. OR Tool should be completed by registry owners only and HTA body only assesses their answers and provided documentation.*

- Discussing the provided answers among the registry owner and reviewer is helpful and creates mutual understanding.
  - ➢ *A comparison exercise may not always be possible or wanted. But scheduling a meeting to discuss the registry owner's answers should be considered to lift any unclarities.*

- Assessment criteria items 9-20 are multi-interpretable, try to make them uniformly operable.
- The assessment criteria are not fully operational. When something should be classified as green is not clearly described.
- In the current situation none of the case studies will likely meet all knock-out criteria.
- Position of REQueST Tool and its subsequent implications are not always clear.

HARPER Template

ScienceDirect

Contents lists available at sciencedirect.com
Journal homepage: www.elsevier.com/locate/jval

ISPOR Report

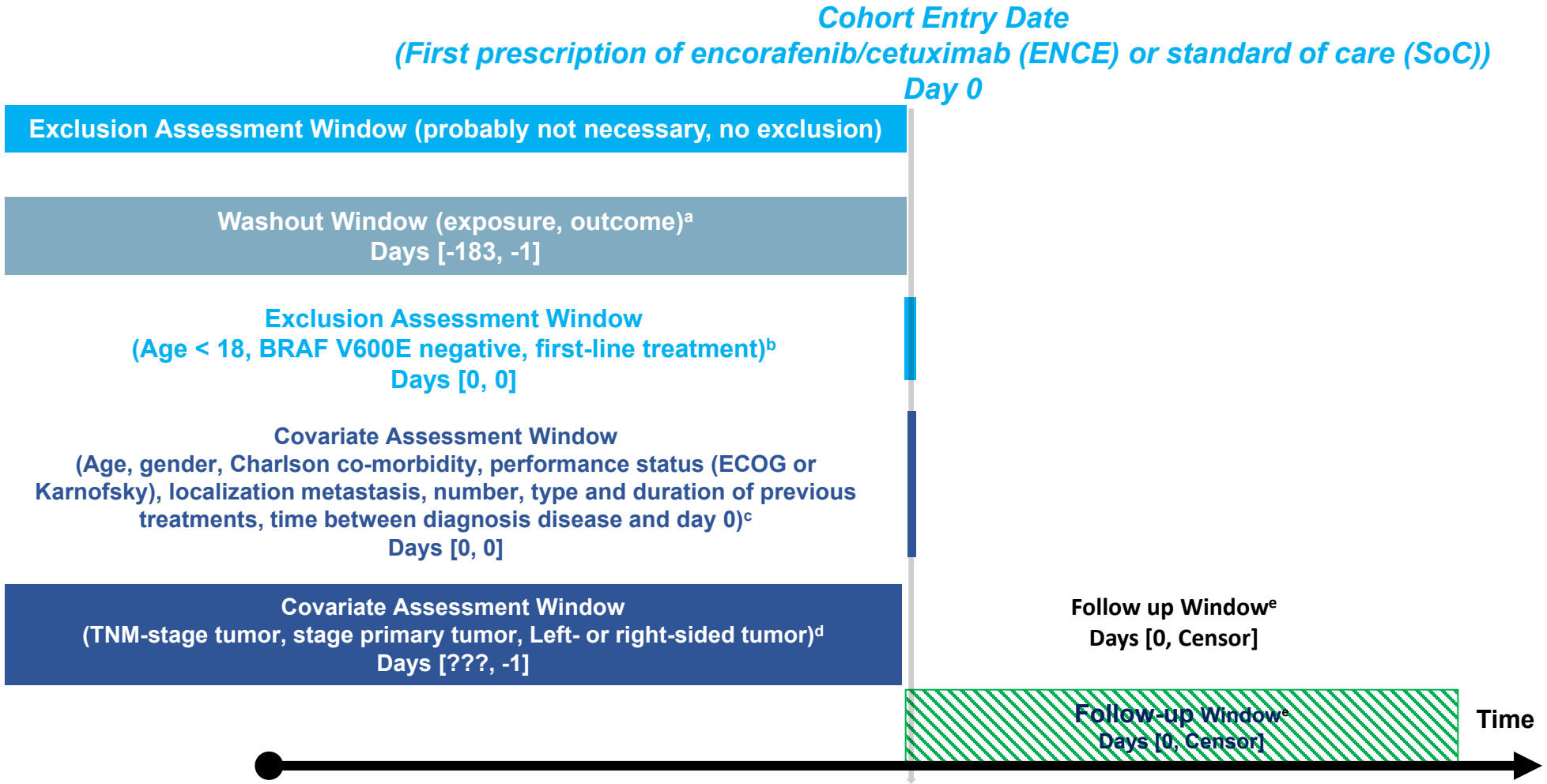
HARmonized Protocol Template to Enhance Reproducibility of Hypothesis Evaluating Real-World Evidence Studies on Treatment Effects: A Good Practices Report of a Joint ISPE/ISPOR Task Force

Shirley V. Wang, Anton Pottegård, William Crown, Peter Arlett, Darren M. Ashcroft, Eric I. Benchimol, Marc L. Berger, Gracy Crane, Wim Goettsch, Wei Hua, Shaum Kabadi, David M. Kern, Xavier Kurz, Sinead Langan, Takahiro Nonaka, Lucinda Orsini, Susana Perez-Gutthann, Simone Pinheiro, Nicole Pratt, Sebastian Schneeweiss, Massoud Toussi, Rebecca J. Williams

Primary objective and research question case study 1 (CRC)

Objective:	To compare overall survival (OS) in patients > 18 years with metastatic colorectal carcinoma with a BRAF V600E mutation who have shown progression after first line treatment and have indicated informed consent for longitudinal observational data collection as part of the PLCRC and are treated with a combination of encorafenib and cetuximab compared to controls who are treated with SoC for a period of a maximum of 2 years (or 4 years). Patients who receive SoC will be included retrospectively as well prospectively.
Hypothesis:	Overall survival will be improved with encorafenib and cetuximab compared to standard of care.
Population (mention key inclusion-exclusion criteria):	Patients with BRAF V600E-mutant metastatic colorectal cancer who progressed after at least of one line of treatment
Exposure:	Initiation of encorafenib in combination with cetuximab
Comparator:	Standard of care. In the Netherlands, SoC in second line is treatment with irinotecan or FOLFIRI and in third line a combination of trifluridine and tipiracil or palliative care. There will be 2 comparator arms. One will be initiation of SoC using concurrent years of data with the exposure arm. The other comparator group will be initiators of SoC using historical controls from years of data prior to availability of encorafenib/cetuximab.
Outcome:	Overall Survival (OS)
Time:	Follow up from day after initiation of therapy until the first of outcome, discontinuation, add/switch therapy, disenrollment, end of study period, nursing home admission, death, progression of therapy, others to be discussed.
Setting:	Inpatient care
Main measure of effect:	Hazard Ratio .

Graphical presentation of exposure-based cohort entry where the cohort entry date is selected prior to application of exclusion criteria (this is specific for the encorafenib/cetuximab study, not for the whole PLCRC)



a. The question is whether any washout window is necessary. It can be assumed that patients will be included after recurrence of the tumor and first line treatment has failed/stopped
b. Patients younger than 18 years, BRAF V600 E negative or are still on first-line treatment will be excluded
c. Assessment of these covariates will take place once at day 0
d. These are covariates that will be assessed retrospectively over a longer period. (and can change over this period) The exact duration of this period is still under discussion
e. Earliest of: outcome of interest, death, cancer progression, stop of therapy (treatment failure etc, switch of therapy etc (angioedema), disenrollment, 365 or 730 days of follow-up, end of the study period)

Conclusions

- Case studies are providing more insight in how data from registries can help HTA
- Definition of standard data sets which are agreed on with all stakeholders is crucial
  - Collecting data on quality of life/PROMS and resource use in the routine setting is difficult
- For assessing data quality of the registry and increase the transparency of the subsequent research question, tools such as REQueST and HARPER are essential.
- Many registries can still not make use of the data that are captured in EHR.
- Structural funding and governance should be consistently organised
- Better coordination on the collection of the healthcare information on a national and international level will be crucial
  - Further international collaboration is pivotal, for instance through EHDS and DARWIN-EU

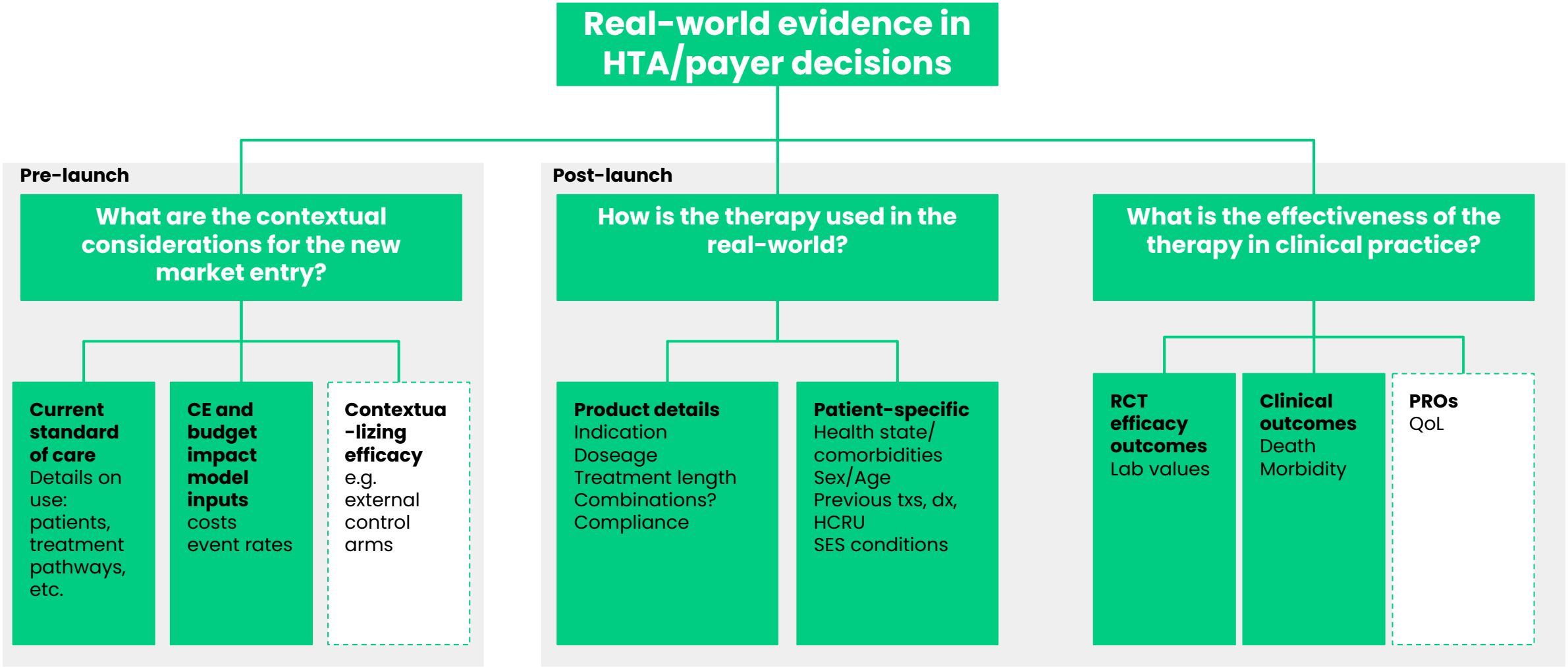
Navigating the RWE Landscape: successes, struggles and the path forward

ISPOR RWE Summit
Boston, MA
May 7, 2023

Disclosures

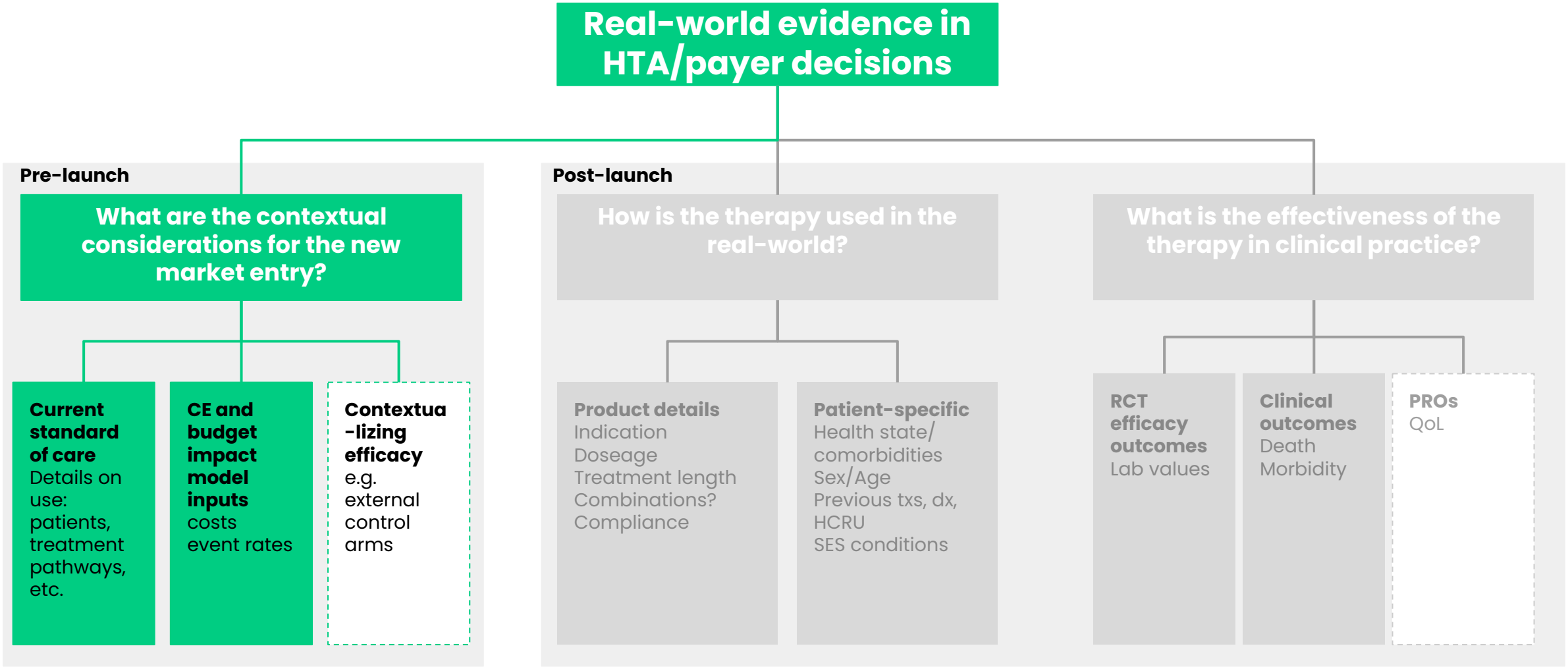
Ashley is an employee and has an ownership stake in Aetion, Inc.

Opportunity for RWE for HTAs/payers



Adapted from Facey, et al (2020)'Real-world evidence to support payer/HTA decisions about highly innovative technology in the EU- actions for stakeholders,' TLV's (2020) 'RWD report', and HTx (2020) 'Overview of the development of the use of RWD including a review of international consensus methods currently developed.'

Opportunity for RWE for HTAs/payers



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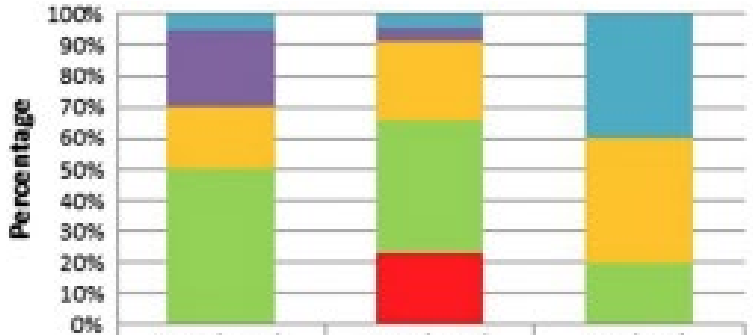
As needed/ if available

Pre-launch

Successes: RWE is often used to contextualize natural history, HCRU, costs

- RWD/RWE is not new to HTA agencies
- RWD/RWE is used to understand:
  - patient population,
  - treatment pathways,
  - natural history of disease,
  - HCRU, and
  - costs



	NICE (n=10)	SMC (n=13)	ZIN (n=2)
Quality-of-life data	5%	4%	40%
Resource Use	25%	4%	0%
Costs	20%	26%	40%
Long-term effectiveness	50%	43%	20%
Not included	0%	23%	0%

Fig. 3 Inclusion of RWD in CEAs across the 3 agencies and reasons for inclusion per agency

Using Real-World Data in Health Technology Assessment (HTA) Practice: A Comparative Study of Five HTA Agencies

Amr Makady[1,2] · Ard van Veelen[2] · Páll Jonsson[3] · Owen Moseley[4] · Anne D'Andon[5] · Anthonius de Boer[2] · Hans Hillege[6] · Olaf Klungel[2] · Wim Goettsch[1,2]

Pre-launch

Struggles: RWE for comparative effectiveness

In a review of HTA agency methods and RWE guidance documentation, current and future acceptance of RWE comparative effectiveness studies is low

	Agency Use of RWE	
	Comparative effectiveness	
	Current	Future
AEMPS & REvalMed		
AIFA		
EUnetHTA21		
G-BA & IQWiG		
HAS		
TLV		
ZIN		
NICE		
CADTH		
ICER		
Chuikyo		
PBAC		

Key	N/A	Virtually no current/future use	Low current/future use	Limited current/future use	Moderate current/future use

Pre-launch

Struggles: RWE for comparative effectiveness

- Reviewed 7 external control arm (ECA) case studies across 3 regulators (FDA, EMA, HC) and 5 HTA agencies (NICE, G-BA, HAS, CADTH, PBAC)
- Evaluated agency commentary on ECA

ECA CRITIQUE CATEGORY	EXPANDED DETAIL
GENERALIZABILITY	
SoC inconsistent over time	Treatment practices have changed over time and thus, the generalizability of the external control group is questionable
ECA non-generalizable to clinical practice	ECA patient population was derived from outside the country of interest and/or ECA and market authorization did not match
MITIGATION OF CONFOUNDING	
Unmeasured confounding	All important known confounders were not available in the data and/or were not included in the adjustment analysis
Unjustified confounders	Confounders used in adjusting were not justified - no rationale provided regarding why the variable was considered a confounder
Naive comparison	No adjustment for confounders was executed
OTHERS	
Selection bias	Individuals or groups in a study differ systematically from the population of interest leading to a systematic error in an association or outcome. Includes differences related to start of follow-up time (eg. immortal time bias)
Incorrect adjusting methods	Incorrect adjustment methods were used
Inconsistent outcomes definitions	Outcome variables were defined differently in the clinical trial vs. RWD
Data loss / Insufficiency	Due to matching the power to detect effect was reduced

Pre-launch

Blinatumomab Ph- ALL: Summary of ECA critiques

ECA CRITIQUE CATEGORY	U.S. Reg: FDA	EU Reg: EMA	UK HTA: NICE	Germany HTA: G-BA	France HTA: HAS	Canada Reg: HC	Canada HTA: pCODR	Australia HTA: PBAC
SoC inconsistent over time				✓		✓	✓	✓
ECA non-generalizable to clinical practice	•							
Unmeasured confounding	•		•		✓		✓	
Unadjusted confounders								✓
Naive comparison								
Selection bias						✓	✓	
Incorrect adjusting methods				✓				✓
Inconsistent outcomes definitions					✓	✓		
Data loss / Insufficiency								
Agency decision	Accelerated approval	Accelerated approval	Recommended with restrictions (only if discount provided)	Non-quant. additional benefit	Recommended for 2L: ASMR III, SMR Substantial	Accelerated approval	Recommended with restrictions for # of cycles	Recommended with # cycle restrictions (after resubmissions)
ECA influence	HIGH	MED-HIGH	LOW	LOW	HIGH	LOW	LOW	HIGH

Large percentages of patients in ECA had comparable efficacy endpoints

FDA noted that key differences (e.g., age, LoT) were accounted for; HAS and pCODR had criticisms

NICE mentioned that arms are balanced

✓ Critique was mentioned by the regulatory or HTA body.

Pre-launch

Struggles: RWE for comparative effectiveness

Key themes in review of 7 ECAs across 3 regulators and 5 HTA agencies

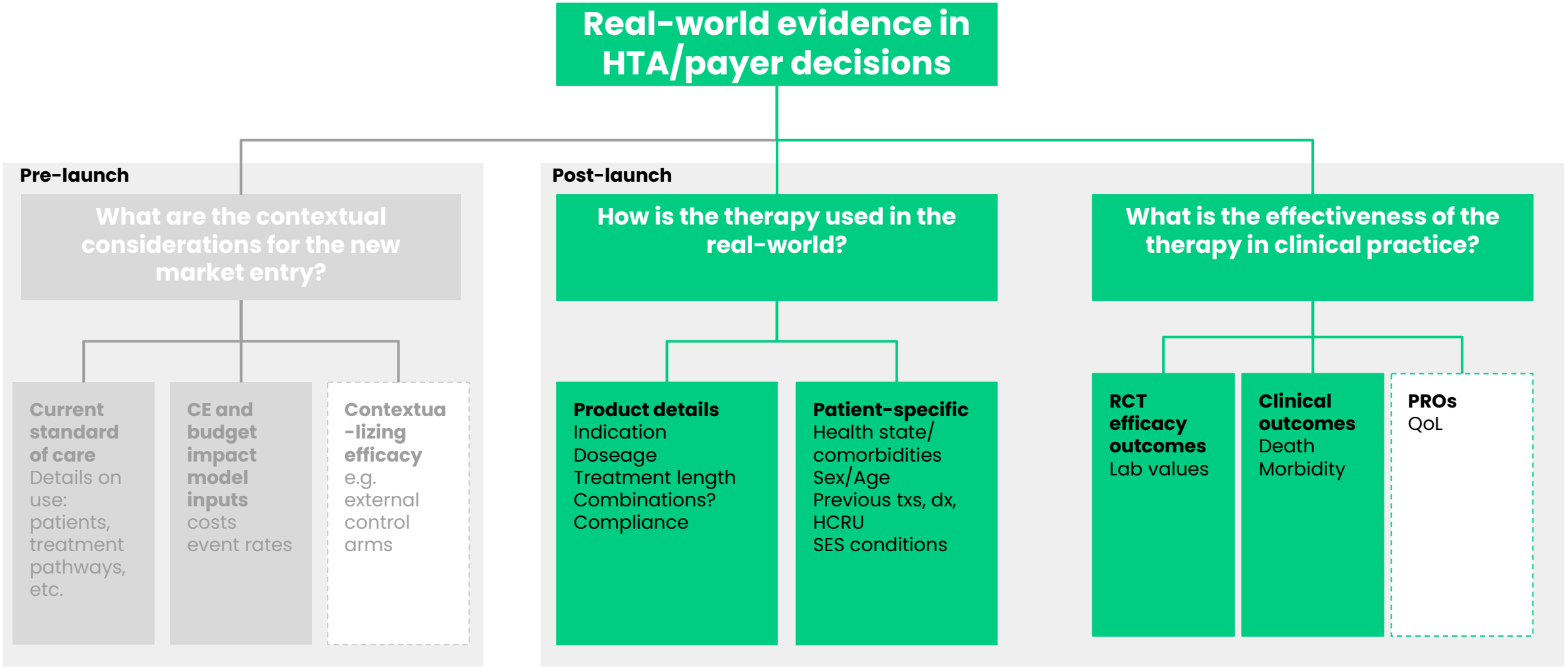
- Critiques of the ECA evidence were common
- Most prevalent critiques were methodological
  - Selection bias
  - Unmeasured confounding
- Common methodological challenges can potentially be mitigate with high-quality, fit-for-purpose data and study design

Pre-launch

Path forward: RWE Guidance outlining expectations

	Does the HTA body have official RWE Guidance?	
HTA Body (Country)	**Current Guidance**	**Notes**
TLV (Sweden)	Pilots	No official guidance, however, TLV has completed pilots on the use of RWD to evaluate how drugs are used in clinical practice as part of Sweden's value-based pricing approach.
ZIN (Netherlands)	No	
NICE (England)	Yes	RWE Framework (2022); Guidance is geared toward researchers designing RWE studies and it outlines best practices separately for descriptive and comparative effectiveness RWE studies.
HAS (France)	Yes	RWE for the Assessment of Medical Products and Devices (2021); Methodological guide on the conduct of RWE studies which focuses on 'why implement an RWE study' and 'how to conduct an RWE study for HAS evaluations.' Feb 2023 paper in BMJ EBM on conditions appropriate for RWE based external control arms.
AIFA (Italy)	No	
IQWiG/G-BA (Germany)	Yes	Concepts for the Generation of Routine Practice Data (2020); focuses on the relevance of registry-based studies for benefit assessment.
AEMPS (Spain)	No	
EUnetHTA21 (EU)	N/A	Methods guides are currently in development, some referencing RWE, which may signal the need for future RWE guidance before the 2025 joint clinical assessments.
CADTH (Canada)	Yes	RWE Guidance (draft 2022); focused on reporting standards for RWE studies and not RWE methods/best practices.
ICER (US)	Yes	A Framework to Guide the Optimal Development and Use of RWE for Coverage and Formulary Decisions/RWE for Coverage Decisions: Opportunities and Challenges (2018). These guidance documents provide a very high-level overview of how RWE can be used and some methodological considerations.
Chuikyo (Japan)	No	
PBAC (Australia)	No	

Opportunity for RWE for HTAs/payers



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As needed/ if available

Post-launch use of RWE

Successes

Many ongoing projects that explore the role of RWE in addressing evidence gaps and uncertainties post launch

Struggles

- Shifting to health technology management
- Prioritizing evidence gaps relevant for RWE studies
- Executing RWE studies
    - potential shift of evidence generation burden to HTA agencies/payers?

Path forward: Focus on multi-stakeholder collaborations and efficiencies

- Spinal Muscular Atrophy Learning Project
- Developing process for prioritization of evidence gaps/ uncertainties
- Multi-stakeholder collaboration to ensure post-launch evidence generation is most impactful

AETION

cadth Canada's Drug and Health Technology Agency

- Methods based work to improve data access and facilitate efficiencies


frontiers | Frontiers in Medicine

Transferability of real-world data across borders for regulatory and health technology assessment decision-making

Ashley Jaksa[1*], Patrick J. Arena[1,2], Kelvin K. W. Chan[3,4], Rami H. Ben-Joseph[5], Páll Jónsson[6] and Ulka B. Campbell[1]

[1]Scientific Research and Strategy, Aetion, Inc., New York, NY, United States, [2]Department of Epidemiology, University of California, Los Angeles, Los Angeles, CA, United States, [3]Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON, Canada, [4]Canadian Centre for Applied Research in Cancer Control, Toronto, ON, Canada, [5]Big Data Real World Evidence, Jazz Pharmaceuticals, Palo Alto, CA, United States, [6]National Institute for Health and Care Excellence, Manchester, United Kingdom

Thank you.

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Navigating the RWE Landscape - Successes, Struggles, and the Path Forward

ISPOR Real-World Evidence Summit
Boston

May 7 2023

Nancy A. Dreyer
Adjunct Professor of Epidemiology, UNC
Chief Scientific Officer, IQVIA Real-World Solutions, Retired

Dreyer
Strategies LLC

Navigating the RWE Landscape:

A few perspectives on the path forward

- We have new types of digital health technologies that can be used in everyday settings to measure changes that are clinically meaningful.
- Recruitment and retention remain challenging, especially for long-term follow-up for safety, effectiveness and milestone- or outcomes-based payments.
- There are no substitutes for RWE about well-characterized study groups to quantify the benefits and risks of medical products in diverse populations.

J Neuromuscul Dis. 2022;9(2):335-346. doi: 10.3233/JND-210743.

Stride Velocity 95th Centile: Insights into Gaining Regulatory Qualification of the First Wearable-Derived Digital Endpoint for use in Duchenne Muscular Dystrophy Trials

Laurent Servais [1] [2], Karl Yen [3], Maitea Guridi [3], Jacek Lukawy [3], David Vissière [4], Paul Strijbos [3]

Affiliations + expand

PMID: 34958044 PMCID: PMC9028650 DOI: 10.3233/JND-210743

Free PMC article

The Proposed Gait Variables measured with a valid and suitable wearable device and system [1]* quantifies a patient's ambulation ability in a continuous manner across five different variables:

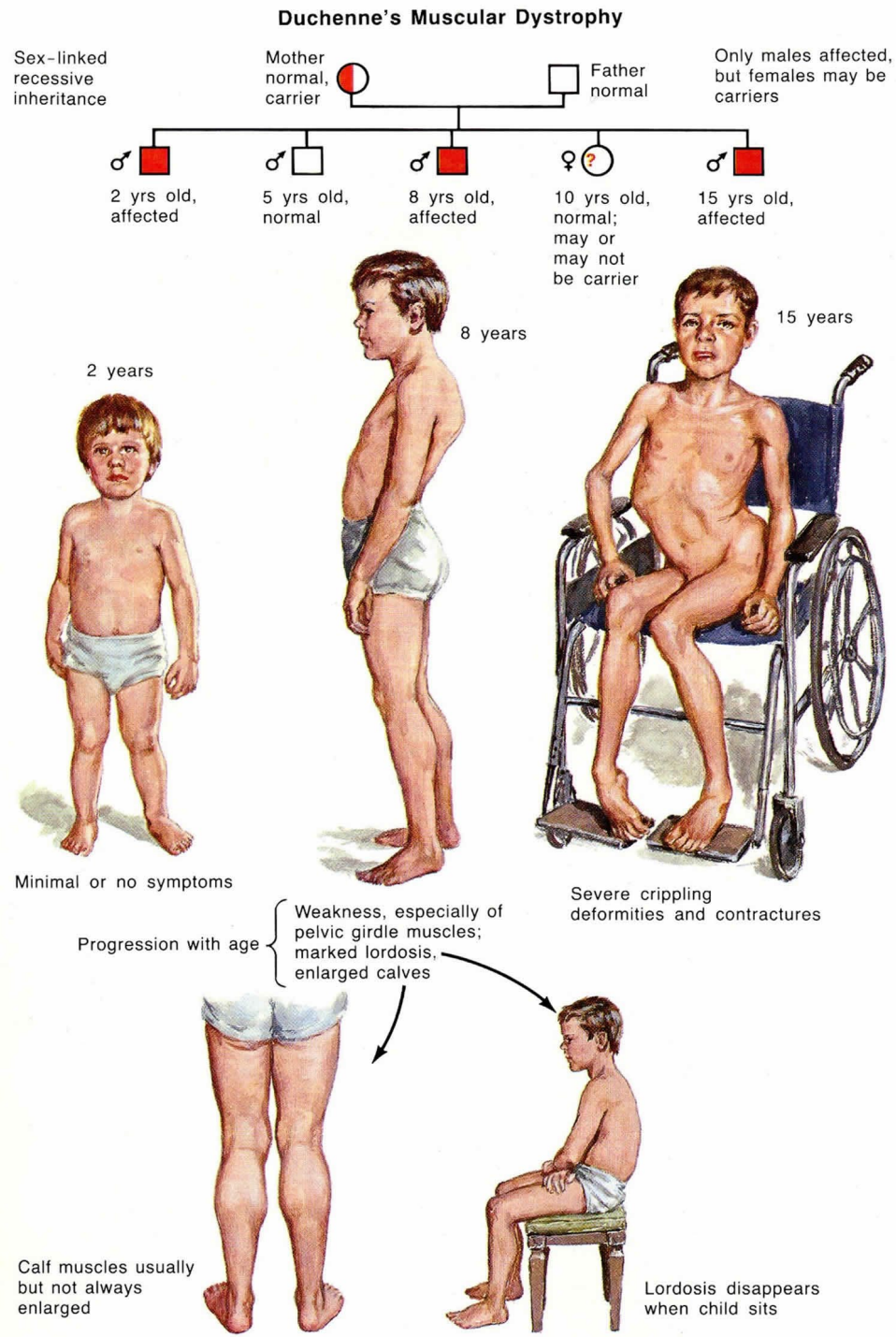
- the 95th percentile of the stride velocity measured at the ankle,
- the median stride velocity measured at the ankle,
- the 95th percentile of the stride length measured at the ankle,
- the median stride length measured at the ankle,
- and the distance walked/recorded hour.

The gait parameters are detected directly every time the wearer walks.

To validate relevant measures for ambulant DMD subjects, the following work has been done to date by the applicant:

1. A study of the validity of gait measures by demonstrating that the distance measured from reconstruction of ankle trajectory of ambulant patients as assessed by the magneto-inertial sensor corresponds to the real distance as measured manually (validity study).
2. Measurement of the variability of gait variables and studying the influence of poor compliance and missing data to generate recommended minimal use.
3. Cross validating these measures with 6MWT and NSAA.
4. Studying the sensitivity to change over a 6 month and a 1 year period in patients older than 6 years old and walking less than 450 m in 6MWT.

In the sections below, CHMP's scientific considerations are presented, as well as the applicant's initial questions, issues raised by the Agency for clarification and discussion during the procedure, and finally the applicant submissions, and responses to questions.



Nocturnal itch may not sound bad, unless you have it

How to Adopt Nocturnal Scratch as a Digital Endpoint for Atopic Dermatitis

September 8, 2022
Lucy Cesnakova

Atopic dermatitis (AD) affects up to 2.4% of the world's population, with itching and scratching being the predominant and most burdensome symptoms for patients. Scratching, both during the day and night, drastically diminishes the quality of life for people with AD as they experience daily pain, discomfort, poor sleep, lack of energy, and even discrimination for inflamed and itchy skin. Using digital technologies to study AD patients' conditions in their home environment, we can now better understand their symptoms and collect data to help clinical

Novel types of data that continuous recordi
by biosensors can provide

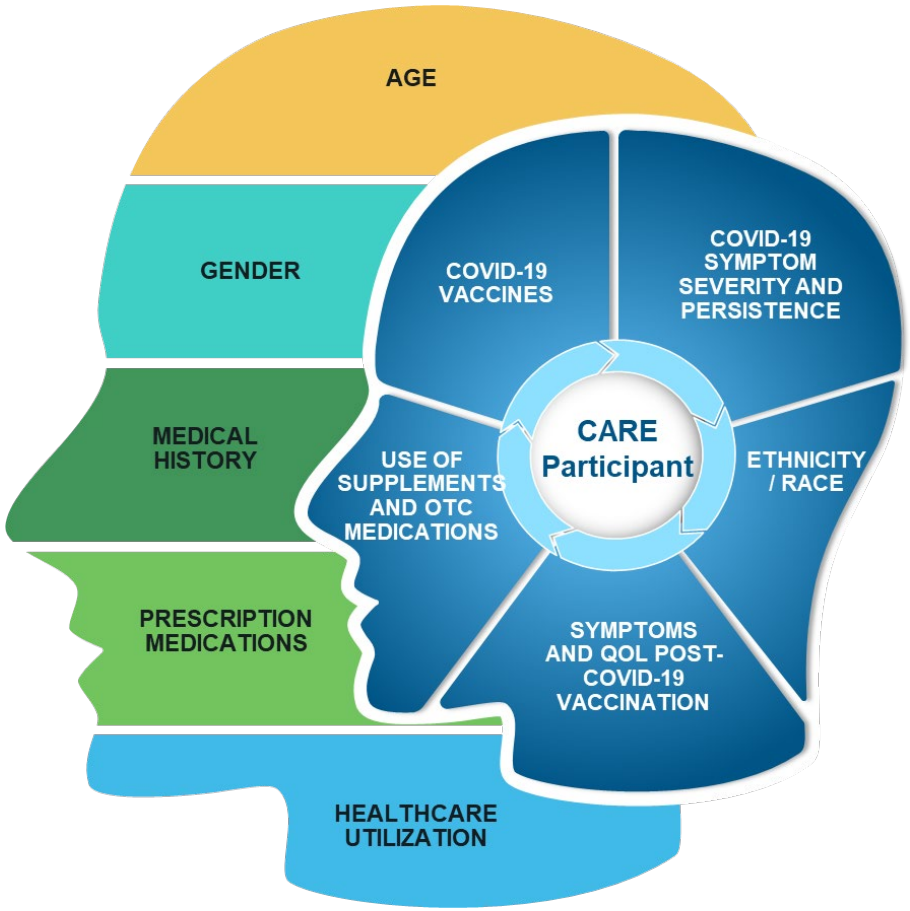
Opportunities	Examples
Richer data instead of snapshots	- average steps per day v.s. 6MWD, - continuous glucose monitoring v.s. HBA1C
Ability to detect rare events	- arrhythmias, seizures, apneic spells
Data from patients who cannot report	- scratching in infants with atopic dermatitis, sleep in patients with dementia
Dose response information	- on/off effects in Parkinson's
New types of measurement	- Accelerometer measurements of gait stability that may predict falls - Measurements of coughing, sneezing, tremor - Behavior patterns in dementia or depression

Understanding Priorities for the Use of Digital Health Technologies Day 1

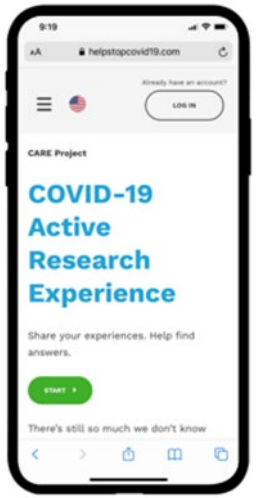
Duke Margolis
1.45K subscribers
Subscribe

Person-reported health data tokenized for record linkage

IQVIA Covid-19 Active Research Experience (CARE) project



www.helpstopCOVID19.com



- ✓ A community source for studying symptom presence and severity and other information not always available in electronic health records or other real-world data (RWD) (N ~28,000)
- ✓ Targeted recruitment supports enrollment of subgroups of special interest, e.g., pregnancy
- ✓ Linked with other RWD in US
- ✓ Supported in part by the FDA

- Dreyer NA et al. Self-reported symptoms from exposure to Covid-19 provide support to clinical diagnosis, triage and prognosis. **Travel Med Infectious Dis** 2020: 38:101909
- Dreyer NA et al. Identification of a Vulnerable Group for Post-Acute Sequelae of SARS-CoV-2 (PASC): People with autoimmune disease. **Intl J Gen Med** 2021: 14:3941
- Dreyer NA et al. How frequent are acute reactions to COVID-19 vaccination and who is at risk? **Vaccine** 2022; 40 (12): 1904-1912
- Brinkley E et al. COVID-19 vaccinations in pregnancy **Am J Perinatology, 2022** May 6.
- Reynolds MW et al. COVID-19 vaccination breakthrough infections in a real-world setting. **Infection and Drug Resistance** 2022:15 5167–5182
- Reynolds MW et al. Evaluating Real-World COVID-19 Vaccine Effectiveness Using a Test-Negative Case-Control Design. **J Comp Effectiveness**, 2022 Nov;11(16):1161-1172.

Consent for record linkage was required for study participation

"The information you provide may be put through a deidentification process. This nonidentified data may be linked with other nonidentified data."

CARE linkage elements are first and last name, date of birth, gender and zip code

Diverse participants will join on-line studies

COVID-19 Active Registry Experience (CARE) Project, *N=28,360*

Race (N)	27,932
Black or African American	2,099 (7.51)
White	21,972 (78.66)
Asian	941 (3.37)
American Indian or Alaska Native	606 (2.17)
Native Hawaiian/Pacific Islander	119 (0.43)
Other	2,195 (7.86)
Multi-race (selection of >1 race)*	1,007 (3.61)

Ethnicity (N)	27,410
Hispanic or Latino	3,212 (11.72)

Gender (N)	28,360
Female	20,964 (73.92)
Male	6,917 (24.39)
Transgender	117 (0.41)
Other	328 (1.16)
Not disclosed	34 (0.12)

https://doi.org/10.1016/j.vaccine.2021.12.072

Source: Data cut: April 2, 2020-February 23, 2023

Cell and gene therapies require 5-15 years of follow-up

Follow-up challenges differ for therapies administered in infancy vs those used to extend life

DRUG DISCOVERY WORLD
DDW
turning science into business

The challenges and trends of cell & gene therapies

There's no doubt that cell and gene therapies present some of the most exciting opportunities for emerging drugs. This area of medicine, which turns our own bodies into agents of combat to fight disease, has quickly become one of the most promising fields in treating deadly diseases such as cancer central nervous system disorders and even musculoskeletal conditions.

Last year saw the sector surge, with levels of investment hitting an all-time high at $22.7 billion, compare to $19.9 billion in 2020, according to the Alliance for Regenerative Medicine's (ARM's) Regenerative Medicine: Disrupting the Status Quo report. And whilst clinical trials activity decreased by around 15% compared to 2020, last year still saw a number of regenerative medicines reach the bedside. Among thes include Zolgensma, Novartis' gene therapy drug for spinal muscular atrophy (SMA), which made headline in the UK for its £1.79 million price point per dose. This year too is off to a strong start, with two multiple myeloma CAR-T therapies approved from both Legend Biotech/Janssen and Bristol Myers Squibb/bluebird bio.

Frequent criticisms of RWE and refutations

Frequent Criticisms

- Bad data (inconsistent, reconstructed from sometimes scanty notes, missing data of interest)
- Sample was biased in its selection and not representative

Refutations

- Scientific findings ideally serve to describe nature in a way that is not limited to one time and one place
- Causal mechanisms should be repeatable in different populations

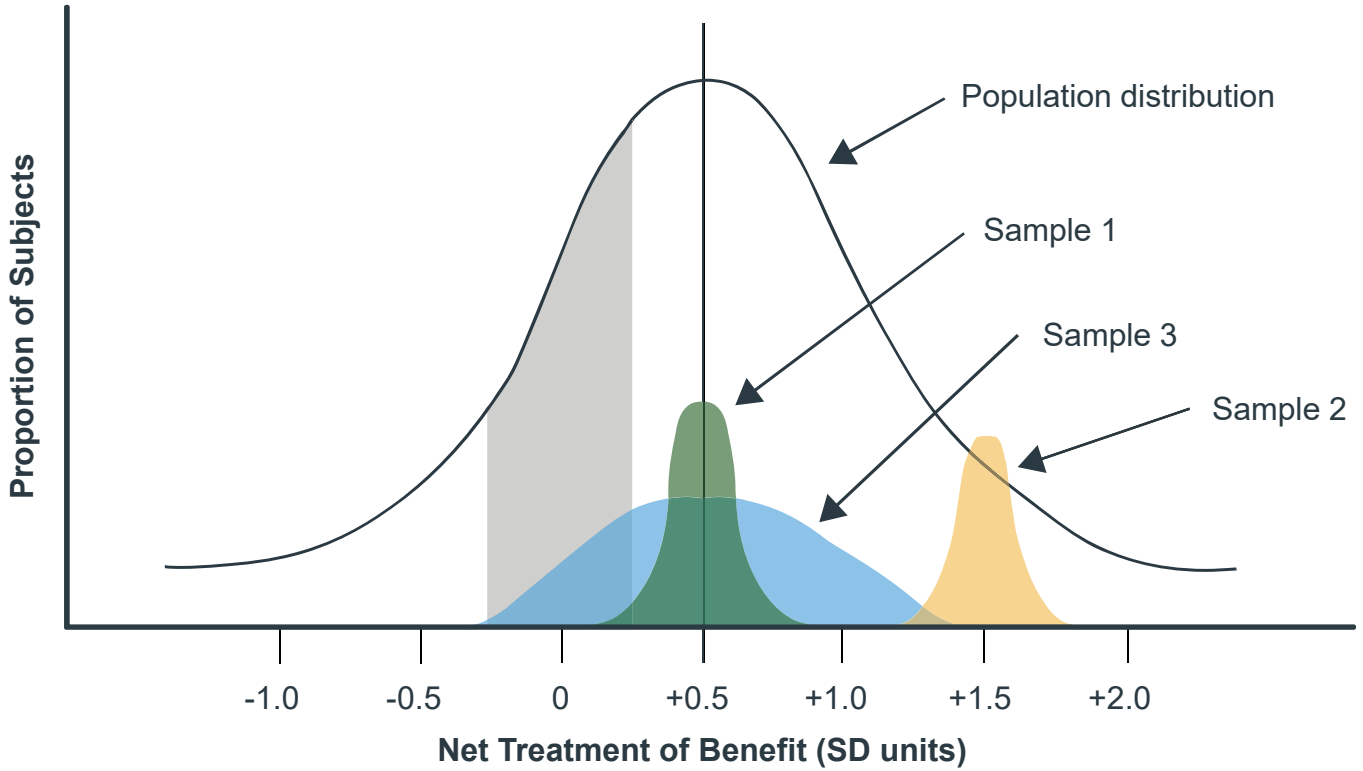
> Paradoxical as it may seem, statistical representativeness leads to particular statements about the world, not general statements about nature

Kenneth Rothman et al.

Why representativeness should be avoided.

Int' l J Epi 2013: 42:1012-14

We should not expect every study to be representative of all demographics, geographies or health-care sectors



Sampling illustration from Kravitz et al. Milbank Q. 2004;82:661-687

Thank You

Nancy A. Dreyer

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ISPOR

Improving healthcare decisions

Closing Remarks

Richard Willke, PhD, ISPOR

ISPOR Real-World Evidence Summit 2023

May 7, 2023