ISPOR 2023

Data Quality 2.0: The Future of Real-World Evidence in Oncology

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Agenda

Welcome & The Role of Data Empathy in Fit-For-Purpose RWE
Speaker: Javier Jimenez, Chief Medical Officer, Flatiron Health

Taking Data Quality to the Next Dimension: Approaches to Oncology RWD
Speaker: Emily Castellanos, Senior Medical Director, Flatiron Health

Outcomes for Patients with *MSI-H mCRC Treated with Standard of Care Compared with Patients Treated with Nivolumab + Ipilimumab in CheckMate-142*
Speaker: Matthew Dixon, Director, Worldwide Health Economics & Outcomes Research, Bristol Myers Squibb

RWD Quality for Health Technology Assessment Appraisal: Case Study
Speaker: Mark Lin, Senior Director, Global Evidence & Outcomes Research, Takeda

Brief Synopsis: Tying it All Together
Speaker: Javier Jimenez, Chief Medical Officer, Flatiron Health

Audience Q&A
Moderated by Javier Jimenez, Chief Medical Officer, Flatiron Health

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Why does real-world evidence (RWE) matter? Because outcomes matter.

PATIENT BIOLOGY

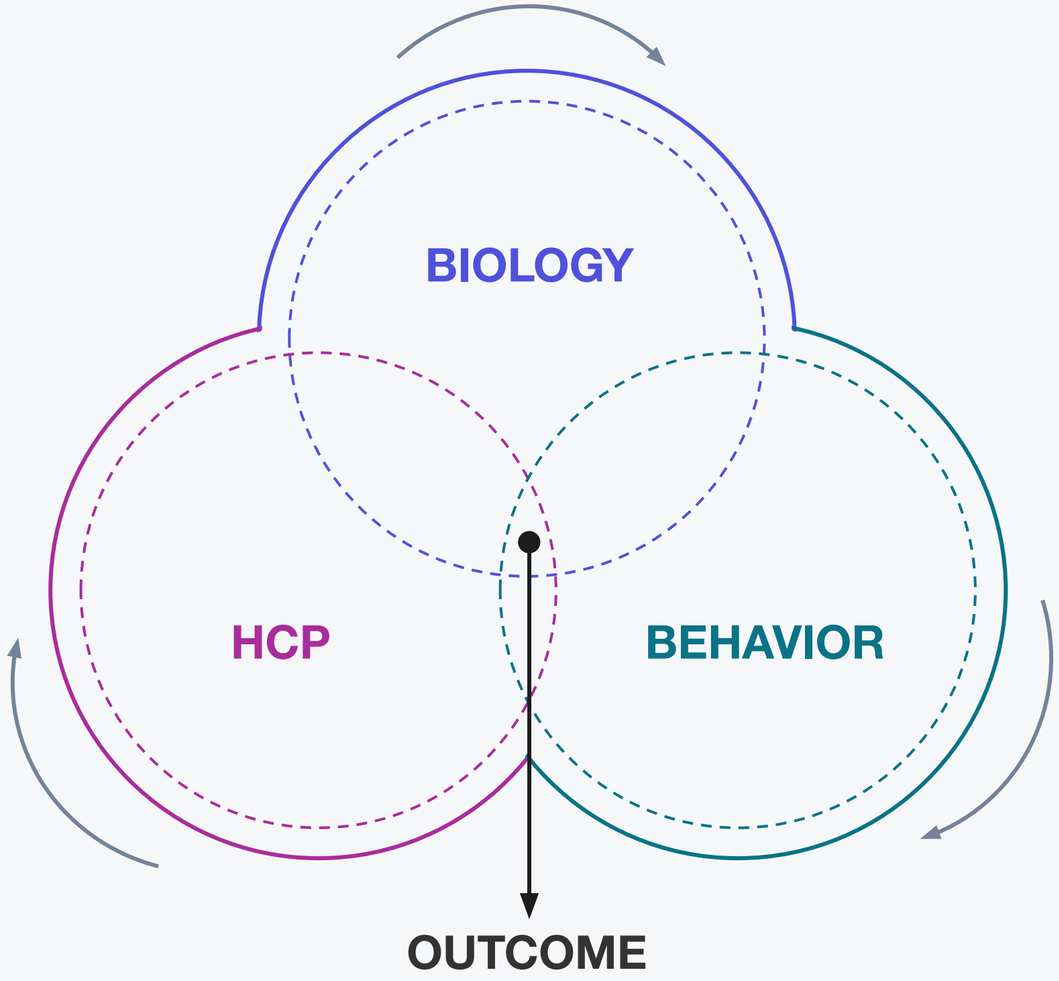
- Majority of focus in Randomized Clinical Trials (RCTs)
- Traditional biomarkers
- Focus on most endpoints

HEALTHCARE PRACTICES

- Controlled RCTs
- Real world impact
- Treatment algorithms need data
- Digital diagnostics and treatment algorithms

PATIENT BEHAVIOR

- Controlled in RCTs
- Real world impact
- Digital biomarkers
- Patient contextual information



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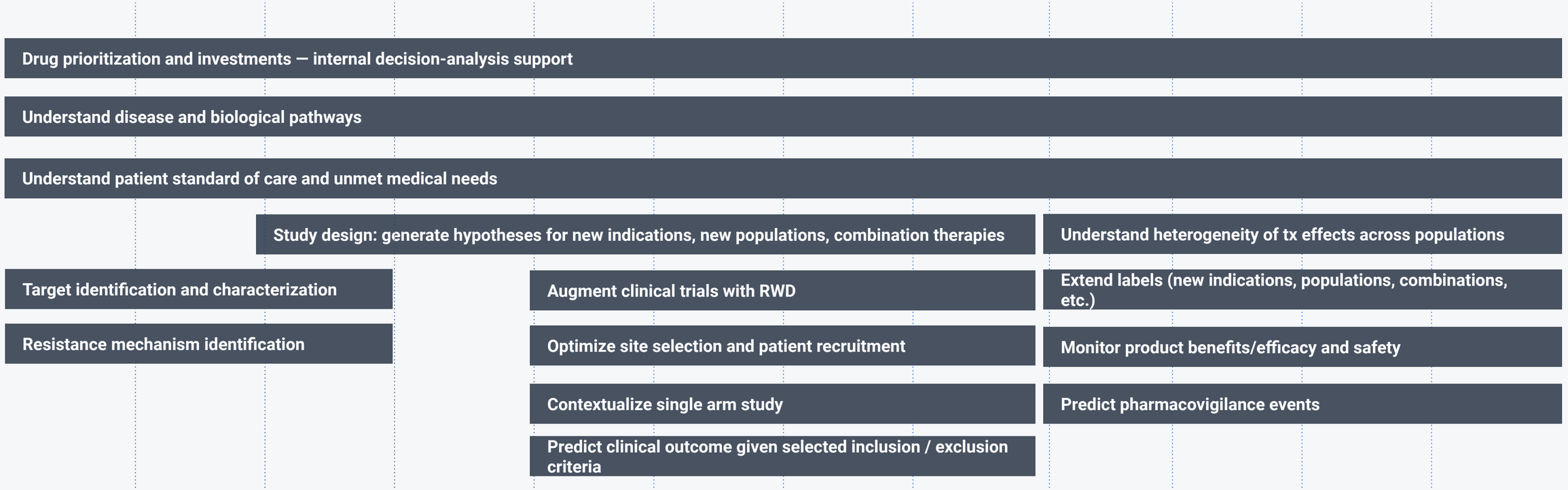
Seyfert-Margolis, V. The evidence gap. Nat Biotechnol 36, 228–232 (2018)

RWE is essential across the product life cycle.

Research
Translational and Early Development.

Development
Late Development and Regulatory.

In Market
Market Access and Commercialization.



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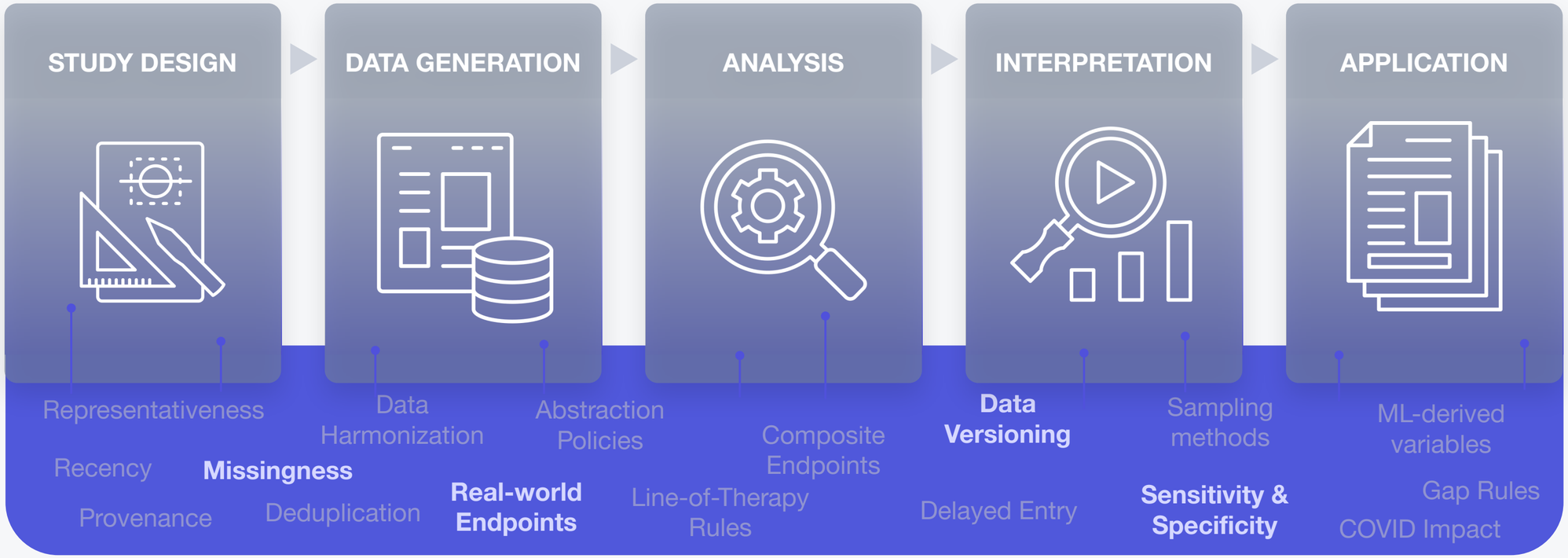
Understanding the data journey is critical to define fit-for-purpose data requirements to generate RWE



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Taking Data Quality to the Next Dimension: Approaches to Oncology RWD

Emily Castellanos, MD, MPH

Senior Medical Director,
Flatiron Health

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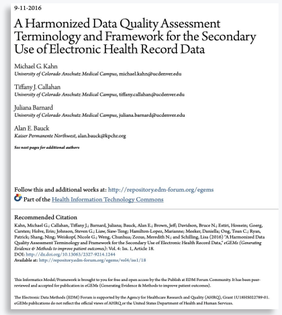
May 8, 2023

Disclosures

Dr. Emily Castellanos is an employee of Flatiron Health, which is an independent subsidiary of the Roche Group.

- Equity in Flatiron Health
- Stock ownership in Roche

How do you know if RWD quality is fit-for-purpose?


9-11-2016

A Harmonized Data Quality Assessment Terminology and Framework for the Secondary Use of Electronic Health Record Data

Michael G. Kahn
University of Colorado Anschutz Medical Campus, michael.kahn@ucdenver.edu

Tiffany J. Callahan
University of Colorado Anschutz Medical Campus, tiffany.callahan@ucdenver.edu

Juliana Barnard
University of Colorado Anschutz Medical Campus, juliana.barnard@ucdenver.edu

Alan E. Bauck
Kaiser Permanente Northwest, alan.bauck@kpchr.org

See next pages for additional authors

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The Informatics Model Framework is brought to you for free and open access by the the Publish at EDM Forum Community. It has been peer-reviewed and accepted for publication in eGEMs (Generating Evidence & Methods to improve patient outcomes).

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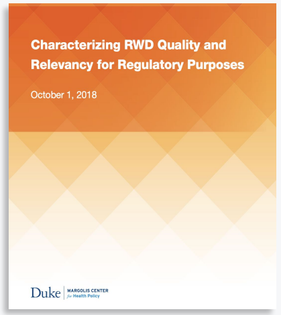
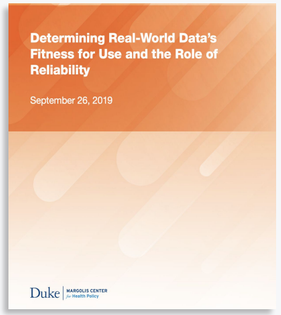
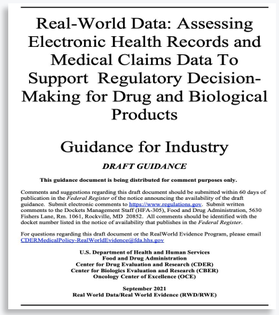
PCORI Sep'16



Duke Sep'18



FDA Sep'21


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

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

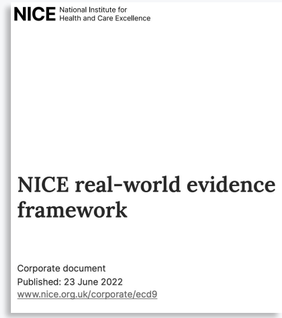
Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the Federal Register of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management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

For questions regarding this draft document or the RealWorld Evidence Program, please email CDERMedicalPolicy-RealWorldEvidence@fda.hhs.gov.

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
Real World Data/Real World Evidence (RWD/RWE)

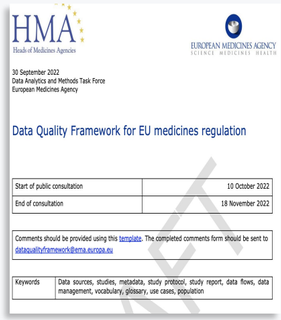
Duke Oct'19


NICE National Institute for Health and Care Excellence

NICE real-world evidence framework

Corporate document
Published: 23 June 2022
www.nice.org.uk/corporate/ecd9

NICE Jun'22


HMA
Heads of Medicines Agencies

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

30 September 2022
Data Analytics and Methods Task Force
European Medicines Agency

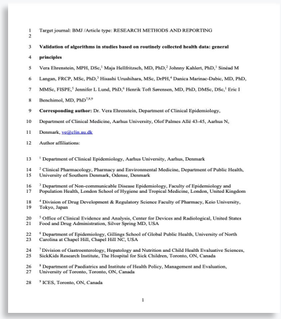
Data Quality Framework for EU medicines regulation

Start of public consultation	10 October 2022
End of consultation	18 November 2022

Comments should be provided using this template. The completed comments form should be sent to dataqualityframework@ema.europa.eu

Keywords	Data sources, studies, metadata, study protocol, study report, data flows, data management, vocabulary, glossary, use cases, population

EMA Sep'22


Target journal: BMJ /Article type: RESEARCH METHODS AND REPORTING

Validation of algorithms in studies based on routinely collected health data: general principles

Vera Ehrenstein, MPH, DSc,[1] Maja Hellfritzsch, MD, PhD,[2] Johnny Kahlert, PhD,[3] Sinéad M Langan, FRCP, MSc, PhD,[4] Hisashi Urushihara, MSc, DrPH,[5] Danica Marinac-Dabic, MD, PhD, MMSc, FISPE,[6] Jennifer L Lund, PhD,[7] Henrik Toft Sørensen, MD, PhD, DMSc, DSc,[1] Eric I Benchimol, MD, PhD[8,9]

Corresponding author: Dr. Vera Ehrenstein, Department of Clinical Epidemiology, Department of Clinical Medicine, Aarhus University, Olof Palmes Allé 43-45, Aarhus N, Denmark, ve@clin.au.dk

Author affiliations:

[1] Department of Clinical Epidemiology, Aarhus University, Aarhus, Denmark
[2] Clinical Pharmacology, Pharmacy and Environmental Medicine, Department of Public Health, University of Southern Denmark, Odense, Denmark
[3] Department of Non-communicable Disease Epidemiology, Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, United Kingdom
[4] Division of Drug Development & Regulatory Science Faculty of Pharmacy, Keio University, Tokyo, Japan
[5] Office of Clinical Evidence and Analysis, Center for Devices and Radiological, United States Food and Drug Administration, Silver Spring MD, USA
[6] Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill NC, USA
[7] Division of Gastroenterology, Hepatology and Nutrition and Child Health Evaluative Sciences, SickKids Research Institute, The Hospital for Sick Children, Toronto, ON, Canada
[8] Department of Paediatrics and Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, ON, Canada
[9] ICES, Toronto, ON, Canada

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ISPE *preprint

Quality Dimensions	Flatiron RWD	Data Quality Frameworks and Guidance				
		FDA	EMA	NICE	Duke	PCORI
Relevance • Availability • Sufficiency • Representativeness	✓	✓	✓	✓	✓	
Reliability	✓	✓	✓	✓	✓	✓
• Accuracy ○ Validation	✓	✓	✓	✓	✓	✓
○ Verification	✓	✓	✓	✓	✓	✓
• Completeness	✓	✓	✓	✓	✓	✓
• Provenance	✓	✓	✓	✓	✓	
• Timeliness	✓	✓	✓	✓		

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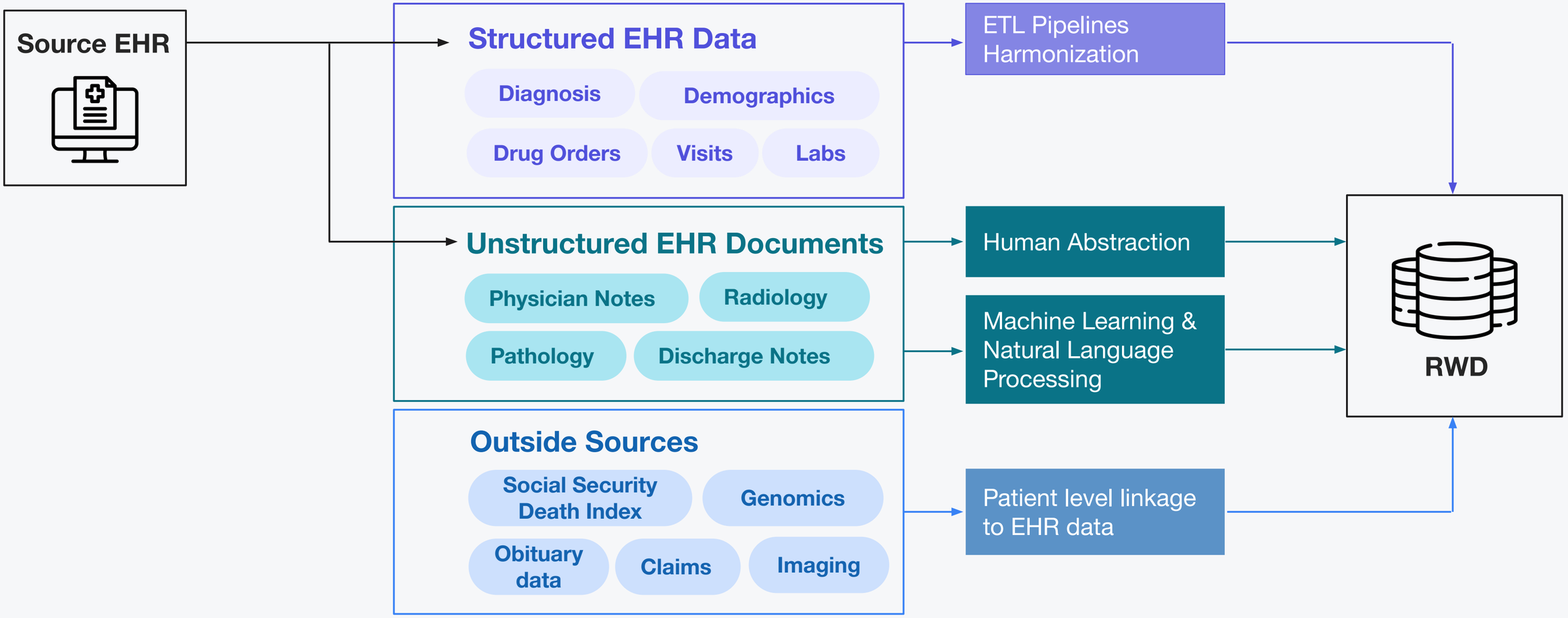
Flatiron Health RWD combines structured and unstructured data from the EHR with integrations from non-EHR data to capture the experience of patients with cancer



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Assessing Flatiron Health RWD

RELEVANCY

Relevancy is defined as the availability of critical variables and sufficient number of representative patients within the appropriate time period to address a given use case.

AVAILABILITY

REPRESENTATIVENESS

SUFFICIENCY

- Direct access to oncology-based EHRs **enhances availability of clinically rich oncology data**
- **3.4 million** cancer patients from **>280** academic and community cancer clinics
- **Patient records since Jan 2011 enables** 10+ years of longitudinal clinical history

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Assessing Flatiron Health RWD

RELIABILITY

Reliability is defined as the degree to which data represent the clinical concept intended, as assessed by

ACCURACY

COMPLETENESS

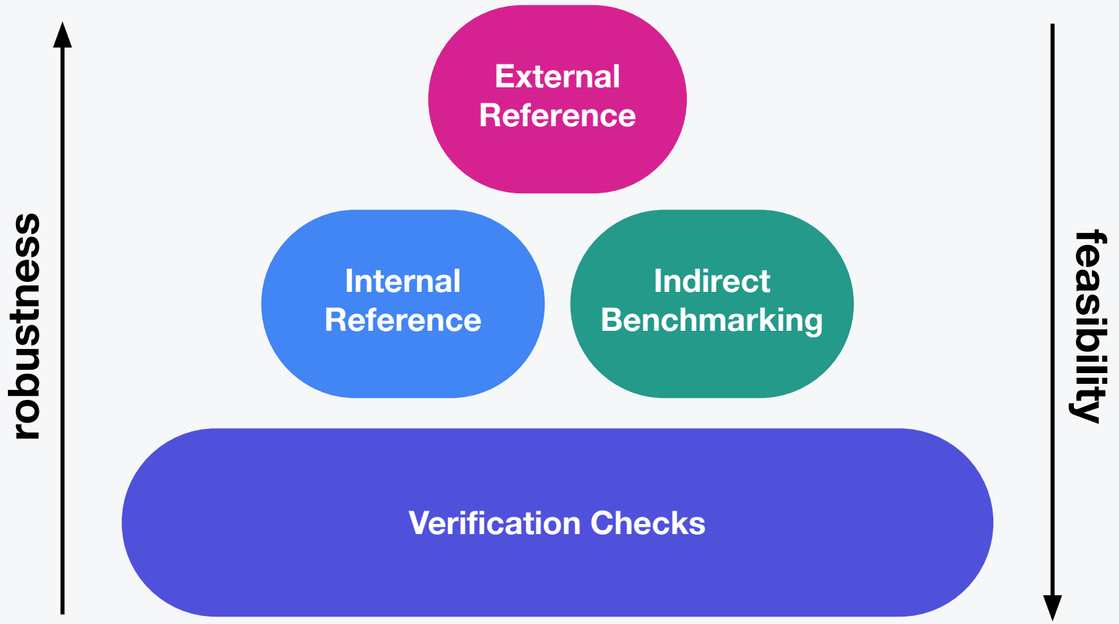
PROVENANCE

TIMELINESS

- Clear conceptual and operational definitions **for variable curation**
- **Infrastructure to support** standardized, measurable, and/or repeatable processes
- Clinical and scientific expertise **informs the approach to quality assessment**

Accuracy: Overview of Validation Approaches

Range of validation approaches:



Points of validation:

- Field Level
- Patient Level
- Site Level
- Sub-Cohort of Cohort Level

Types of validation output:

- Sensitivity, Specificity
- Positive and Negative Predictive Values
- Descriptive Statistics
- Agreement Metrics
- Completeness Rates
- Error Rates

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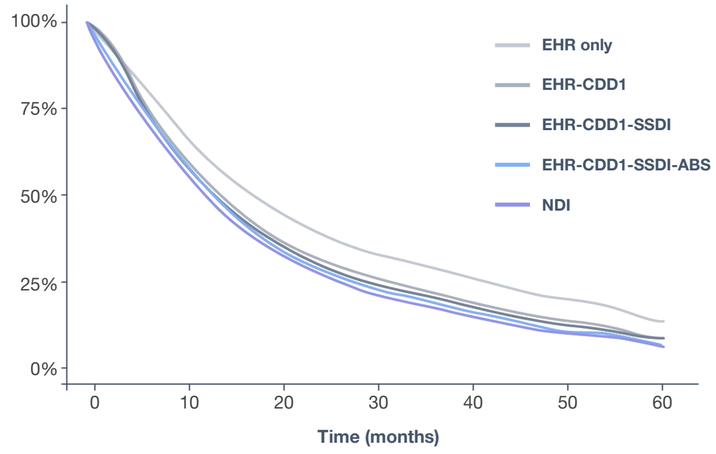
Examples of validations using a range of approaches: balancing feasibility, robustness, and scalability

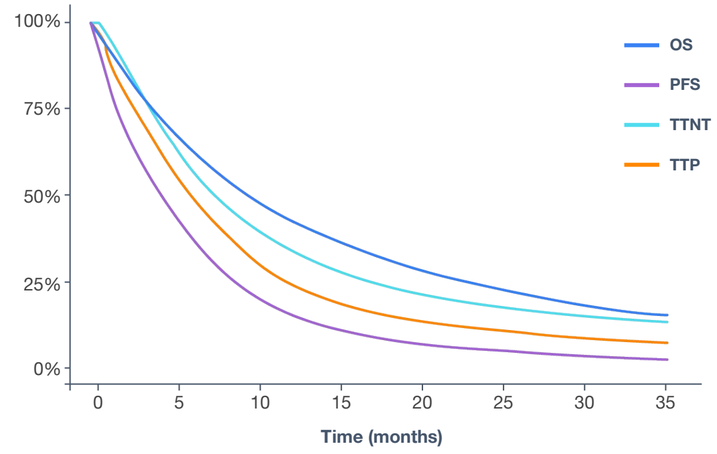
External Validation



Ref: Curtis et al.

Composite Mortality Variable validated using the National Death Index

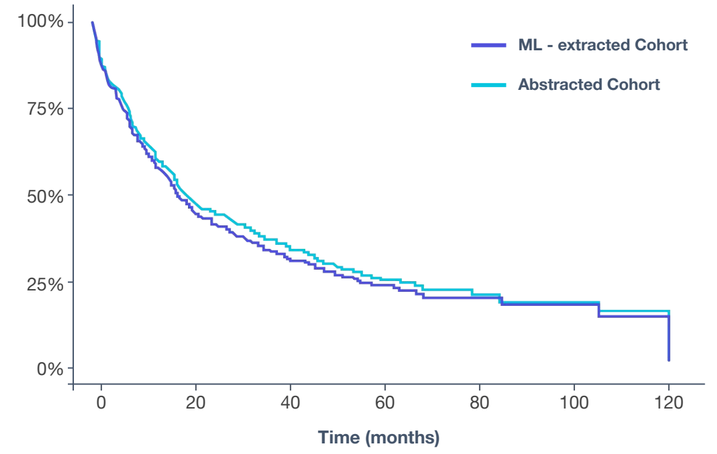
Indirect Benchmarking



Ref: Griffith et al.

Validation of novel real world progression variable by correlation to literature and related endpoints

Internal Reference Standard



Ref: Benedum et al.

Validation of ML-extraction vs human abstraction using a replication analysis

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Accuracy: Verification

Verification checks serve as a proxy for accuracy

Conformance the compliance of data values with internal relational, formatting, or computational definitions or standards

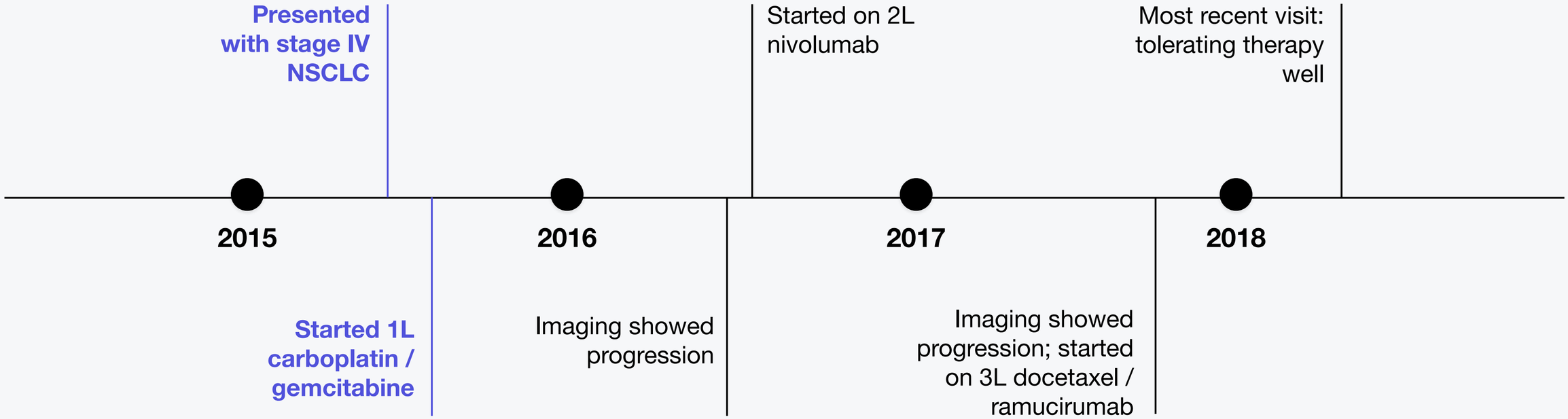
Plausibility the believability or truthfulness of data values

Consistency the stability of a data value within a dataset, across linked datasets, or over time

Plausibility: data are logically believable

TEMPORAL PLAUSIBILITY

Treatment start dates in close proximity to advanced diagnosis



Completeness is also critical to reliability

Evaluating completeness of EHR-based RWD requires **data empathy:** understanding of source documentation, and how data flows from the clinic to the final dataset

- Controls and process are put in place to monitor completeness
- Integration of sources within or beyond the EHR can improve completeness

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Summary

Quality is not measured in a single number — multiple dimensions are needed to determine fitness-for-purpose!

Addressing quality in EHR-based RWD requires cross-disciplinary expertise implemented across the data lifecycle: clinical medicine, medical informatics, engineering, data management operations, and quantitative science.

To generate real world **evidence**, the analytic approach matters as well.

Questions? Comments? Email: **ecastellanos@flatiron.com**

WW HEOR/Oncology

Outcomes for Patients with MSI-H mCRC Treated with Standard of Care Compared with Patients Treated with Nivolumab + Ipilimumab in CheckMate-142

May 8, 2023

Matt Dixon, PharmD, PhD
Director, Worldwide HEOR, Oncology
Bristol Myers Squibb

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Disclosure

- Matthew Dixon is a paid employee of Bristol Myers Squibb and owns shares in Bristol Myers Squibb.

Background

Unmet Need for More Effective Therapies in Microsatellite Instability-high (MSI-H)/Deficient Mismatch Repair (dMMR) mCRC

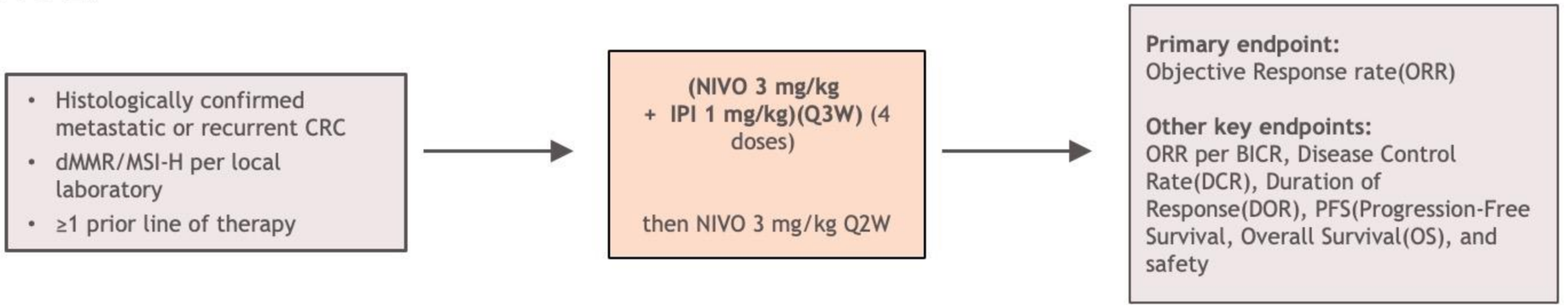
- Modest efficacy with systemic therapy in 2L+ mCRC, despite newer options[1-5]

- Prognostic and predictive value of MSI-H/dMMR is gaining recognition in mCRC[6,7]:
  - Worse OS
  - Conventional chemotherapy & biologics show less efficacy

- Modest efficacy and toxicity beyond first-line (1L) treatment highlight unmet need for more effective therapies

CheckMate-142 Overview

- CheckMate142 (NCT02060188) is an ongoing phase 2 study evaluating nivolumab monotherapy or combination therapy in adults with unresectable dMMR/MSI-H mCRC
- Cohort 2:



- Nivolumab + low-dose ipilimumab approved in US, EU, and Japan for dMMR/MSI-H mCRC patients who progressed after chemotherapy
- Recent 5-year follow-up showed long-term benefit of nivolumab + low-dose ipilimumab in previously treated dMMR/MSI-H mCRC[8]

Research Objective

Compare real-world outcomes in later-line treatment of MSI-H/dMMR mCRC patients with standard of care (SOC) versus nivolumab + ipilimumab (CheckMate-142).

Study Design

Study Design and Data Source

Comparative effectiveness study

Flatiron Health oncology EHR data Jan 2013 - Jan 2021 N=146	CM-142 Cohort 2 trial data May 2015 - Oct 2020 database lock N=119

Key eligibility criteria

Inclusion	
• ≥18 years of age at index	• mCRC
• ECOG PS 0–1	• MSI-H/dMMR
• ≥1 prior line(s) of treatment with at least a fluoropyrimidine, and oxaliplatin or irinotecan in the metastatic setting	
Exclusion	
• Immunotherapy (IO) for mCRC at 1L/2L	• Active brain metastases or leptomeningeal metastases
• Clinical trial drugs in pre-index period	• Active, known or suspected autoimmune disease

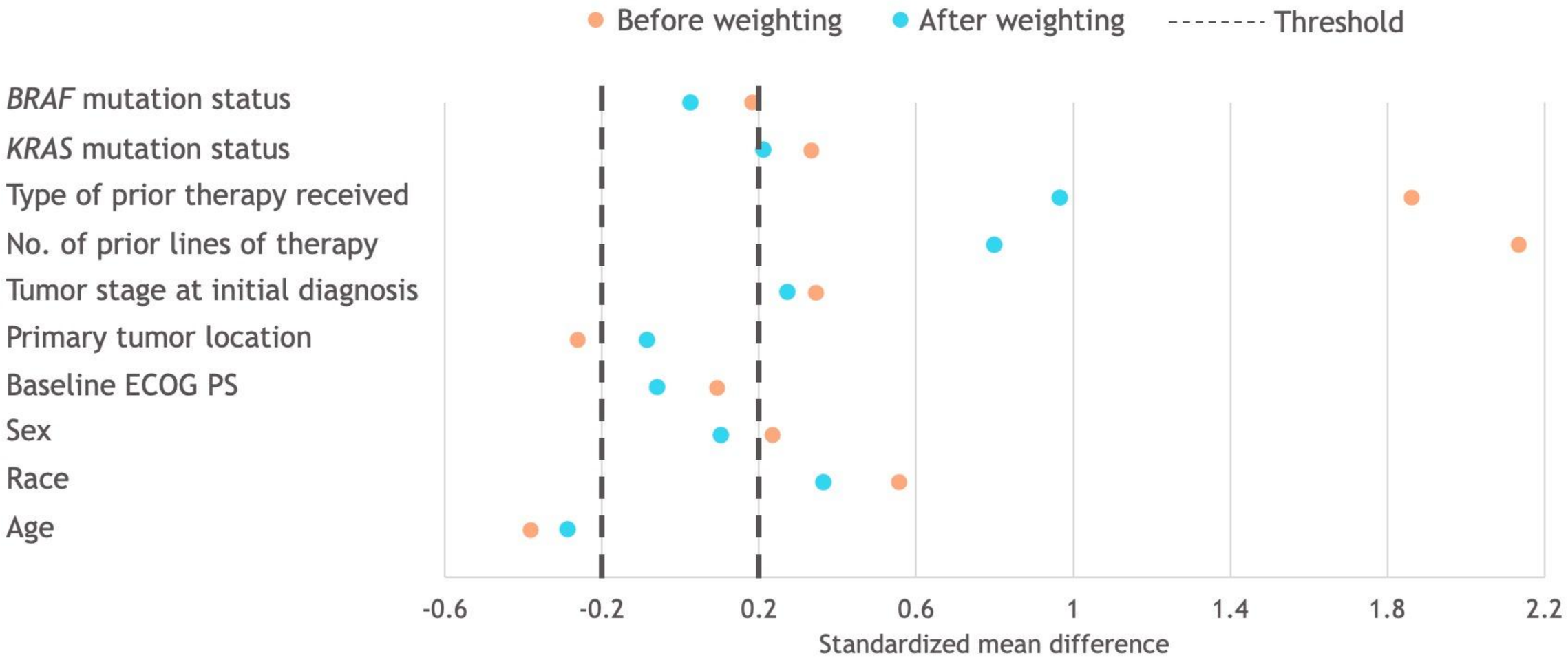
Analysis

- Primary adjusted OS analysis: IPTW with stabilized weights
- Relevant confounders selected based on clinical feedback and identification by systematic literature review
- Hazard ratios (HRs) calculated using doubly robust Cox proportional hazards model to control for residual confounding
- Sensitivity analyses:
  1. Unadjusted univariate model
  2. Multivariable adjustment
  3. Propensity score matching

ECOG PS, Eastern Cooperative Oncology Group Performance Status; EHR, electronic health record; IPTW, inverse probability of treatment weighting.

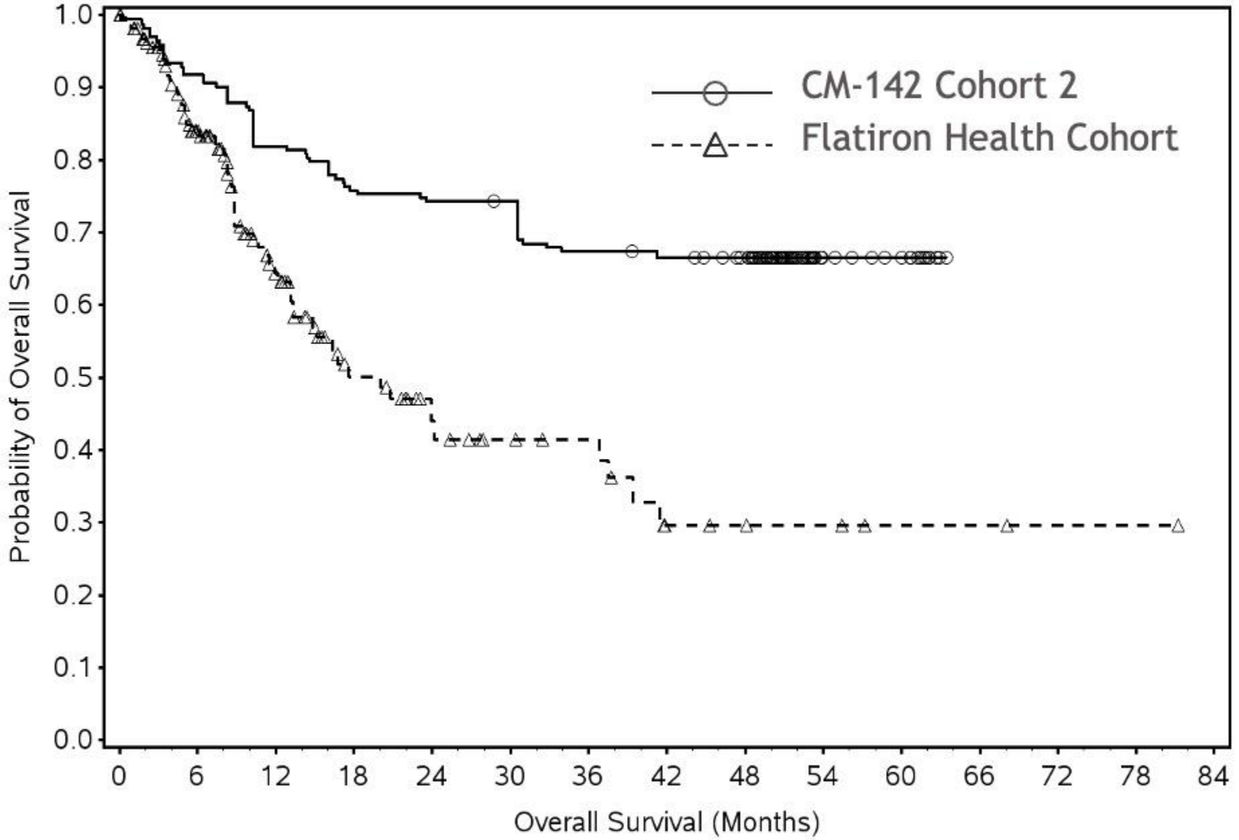
Results

Pre- & Post-IPTW Baseline Characteristics Balance Plot[9]



Standardized mean difference was obtained from CM-142 minus Flatiron using trimmed stabilized weights when combining the mean and standard deviation.
The stabilized IPTW were trimmed at the maximum of the minimum weight and the minimum of the maximum weight. A threshold of 0.2 was used to indicate potentially important imbalances.
ECOG PS, Eastern Cooperative Oncology Group Performance Status; IPTW, inverse probability of treatment weighting.

Overall Survival Adjusted Using Trimmed Stabilized IPTW[9]



	CM-142 Cohort 2 N = 119	Flatiron Health Cohort N = 146
Died, %	32.6	37.4
Censored, %	67.4	62.6
Median OS, months (95% CI)[a]	NR (NR, NR)	20.0 (7.5, 32.6)
HR (95% CI), P-value[b]	0.36 (0.17, 0.80) P = 0.01	

[a]Median of time to event was from adjusted product-limit estimates with trimmed stabilized IPTWs.
[b]HR of CM-142 Cohort 2 to Flatiron Health Cohort. HR, CI, and P-value were based on a Cox model and using trimmed stabilized IPTWs at min of max weight and at the max of min weight, as well as adjusted for unbalanced covariates.

Based on Kaplan-Meier estimates. Symbols represent censored observations.

Conclusion

Conclusion

- Supportive evidence contextualizing OS among patients with MSI-H/dMMR mCRC treated with nivolumab + ipilimumab versus historical SOC

- Historical SOC demonstrated a median OS of 20.0 months (95% CI 7.5, 32.6), while median OS for nivolumab + ipilimumab was not reached with median follow-up of 49.7 months
  - HR = 0.36 (95% CI 0.17, 0.80) for CM-142 Cohort 2 versus Flatiron Health Cohort

- Results support current treatment recommendations for 2L+ MSI-H mCRC & combination immunotherapy

- HTA feedback focused on covariate identification and unmeasured confounding

Final Thoughts on Data Quality

- Identify fit-for-purpose data
  - Landscaping review, Clinical & Medical feedback, literature review for covariate identification

- Flatiron advantage for this study:
  - Relevance (covariates, outcomes, sample)
  - Documentation of validation processes & reputation
  - Relatively complete data for key covariates
  - Historical SOC arm passed ‘sense’ check compared to publication clinical outcomes

References

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RWD Quality for Health Technology Assessment Appraisal: Case Study

H. Mark Lin, PhD
Sr Director, Global Evidence and Outcomes Research
Takeda Pharmaceuticals

Takeda

Better Health, Brighter Future

Disclosure

- Dr. H. Mark Lin is an employee of Takeda Pharmaceutical Company Limited and owns Takeda stock (or “may own stock”)
  or Employment with Takeda and Takeda stock ownership
- We thank the patients, their families, and their caregivers. We thank the mobocertinib EXCLAIM investigators and their team members at each study site; and colleagues from Takeda

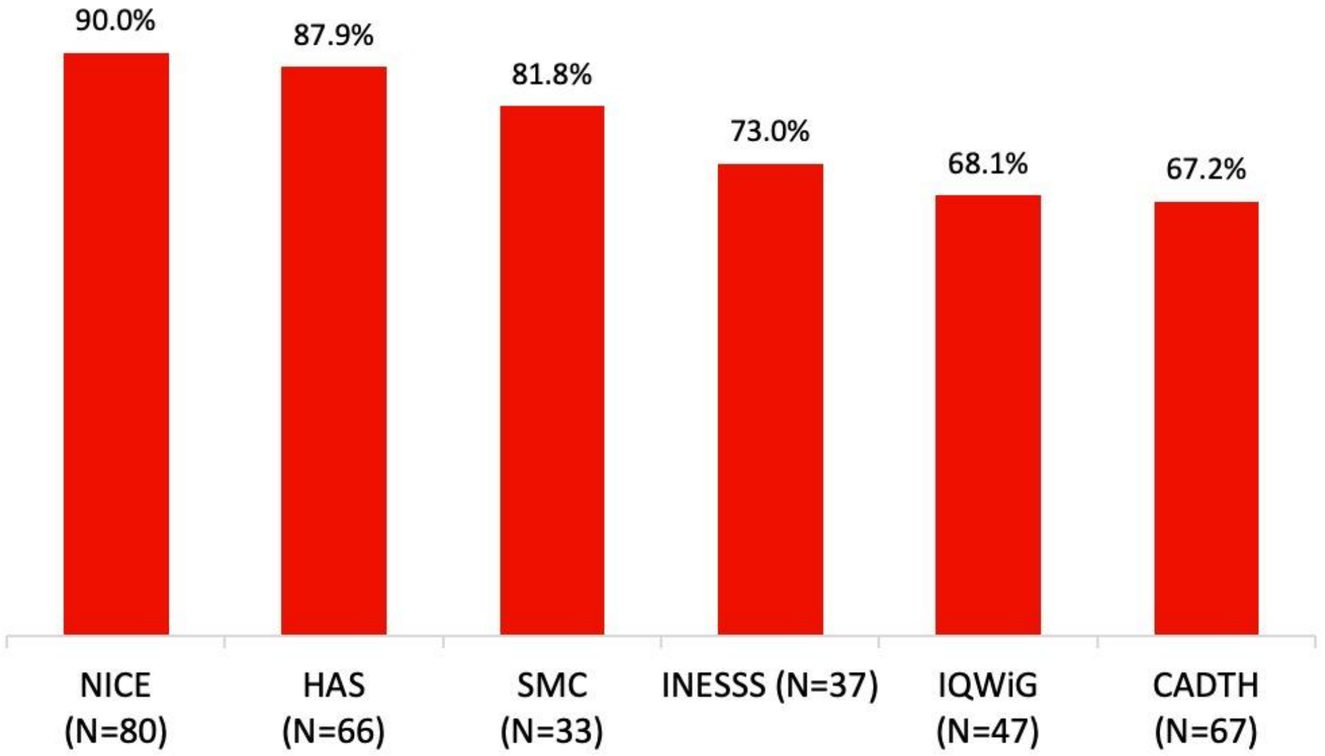
Outline

- General trend of RWE in HTA
- Mobocertinib case
- Real-world data selection and NICE requirement
- Lessons learned

Reception to Oncology RWE by HTA Agency

RWE studies were generally well-received by Health Technology Assessment (HTA) agencies

Acceptance rate of RWE studies by HTA agency



RCTs are considered as gold standard, but RWE has been used as supplemental evidence for HTA submission.

The highest acceptance rate of RWE was with **NICE (90%)**, followed closely by **HAS (87.9%)**, and **SMC (81.8%)**

RWE can be used for a range of purposes for HTA submissions, such as population identification, comparative effectiveness, economic model parameters,
or post-reimbursement RWE commitment etc.

CADTH: Canadian Agency for Drugs and Technology in Health; HAS: Haute Autorit ´e de sant´ e; INESSS: Institut national d'excellence en sante´ et en services sociaux; IQWiG: Institut fu¨ r Qualita¨ t und Wirtschaftlichkeit im Gesundheitswesen; NICE: National Institute for Care and Excellence; SMC: Scottish Medicines Consortium; STA: Single technology assessment

Source: Harricharan et al, EVALUATION OF THE EXTENT OF REAL-WORLD EVIDENCE (RWE) USED WITHIN HEALTH TECHNOLOGY APPRAISALS (HTA) IN ONCOLOGY: A COMPARATIVE STUDY OF SIX HTA AGENCIES, ISPOR 2021

Case Study: Mobocertinib for NSCLC With EGFR Exon 20 Insertions

Indication

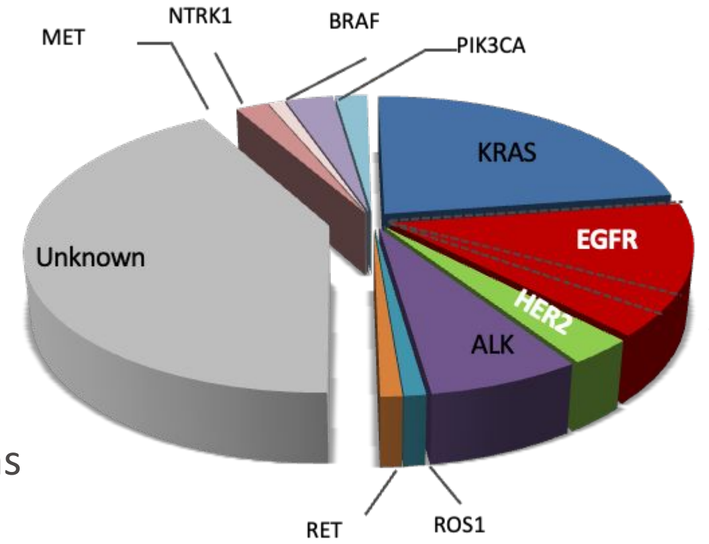
- Mobocertinib is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy

Key timeline

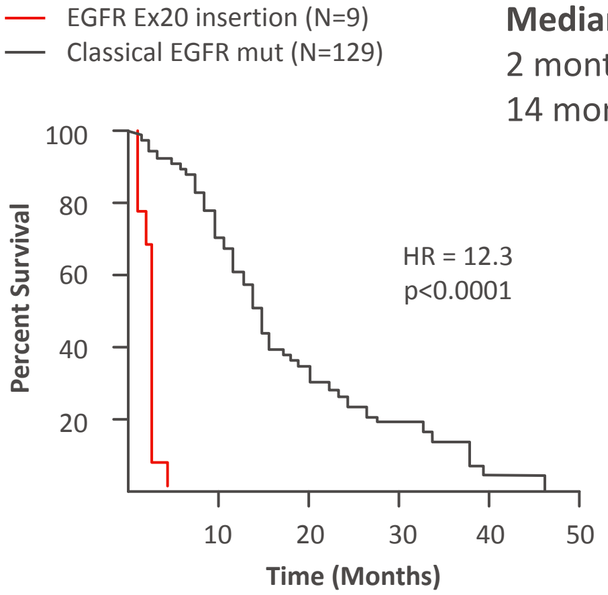
Source: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-mobocertinib-metastatic-non-small-cell-lung-cancer-egfr-exon-20; https://www.nice.org.uk/guidance/ta855

Patients with EGFR Exon 20 insertion+ NSCLC have poor outcomes relative to the historically available therapies

- Non-small cell lung cancer (NSCLC) represents up to 85% of all lung cancers
- NSCLC is highly heterogeneous with different driver mutations



Progression-free survival of 1st / 2nd generation EGFR TKIs



Median PFS
2 months
14 months

PFS of patients with EGFR ex20 insertion is significantly worse than PFS for patients with classical EGFR mutations

- No approved targeted therapies existed specifically for NSCLC with EGFR exon 20 insertion mutations at the time of development
- Classical EGFR TKIs are associated with poor treatment outcomes for patients with EGFR exon 20 insertion mutations

Source: 1. Leduc C et al., Ann Oncol 2017;28:2715–2724. 2. Jorge S et al. Braz J Med Biol Res 2014;47:929–39. 3. Kobayashi Y & Mitsudomi T. Cancer Sci 2016;107:1179–86. 4. Arcila M et al. Mol Cancer Ther 2013;12:220–29. 5. Oxnard G et al. J Thorac Oncol 2013;8:179–84.3. Robichaux et al WCLC 2016 and Yasuda H, et al. Sci Transl Med. 2013;5:216ra177

Mobocertinib: Phase 1/2 Single-Arm Study Design[1,2]

Prior Platinum:
n=6

Phase 1 Dose Escalation: 3+3 Design (Advanced non–small cell lung cancer; ECOG PS <2)

Phase 2 Expansion: **Mobocertinib 160 mg QD** | Phase 2: Primary endpoint - ORR by RECIST v1.1 | Secondary endpoints - PFS, OS

Prior Platinum:
n=22

Cohort 1
Refractory EGFR exon 20 insertion; no active, measurable CNS metastases*

Cohort 2
Refractory HER2 exon 20 insertion or point mutation; no active, measurable CNS metastases

Cohort 4
Treatment-naive or refractory other EGFR mutations: ±T790M, uncommon EGFR

Cohort 6
Treatment-naive EGFR exon 20 insertions

Cohort 3
Refractory EGFR or HER2 exon 20 insertions or point mutations with measurable, active CNS metastases*

Cohort 5
Refractory EGFR exon 20 insertion with prior response to EGFR TKI

Cohort 7
Refractory other tumor types (non-NSCLC) with EGFR/HER2 mutations

Prior Platinum:
n=86

EXCLAIM Extension Cohort (N=96)
Previously treated patients with EGFR exon 20 insertions

Locations: United States only for phases 1 and 2; United States, European Union, and Asia for phase 2 extension cohort.
Active CNS metastases: untreated or treated and progressing; measurable CNS metastases: ≥10 mm in longest diameter by contrast-enhanced MRI.
*Active or measurable (but not both) CNS metastases permitted. 1. Ramalingam S, et al. ASCO. 2021 (Abstr 9014). 2. Zhou C et al. JAMA Oncol. 2021;7:e214761.

Mobocertinib Platinum-Pretreated Population (PPP Cohort: Demographics, Baseline Characteristics, and Efficacy)

Characteristic	PPP Cohort (N=114)[a]
Median age, years (range)	60 (27–84)
Female, %	66
Race, %	
Asian	60
White	37
Black	3
ECOG PS, %	
0	25
1	75
History of smoking, %	
Never	71
Current	2
Former	27
Prior systemic anticancer regimens[b], %	
1	41
2	32
≥3	27
Prior platinum therapy, %	100
Prior EGFR TKI therapy, %	25
Prior immunotherapy, %	43
Baseline brain metastases, %	35

IRC Assessments*	PPP Cohort (N=114)
Confirmed ORR, % (95% CI)	28 (20-37)
Median DOR, months (95% CI)[c]	15.8 (7.4-19.4)
Confirmed DCR, % (95% CI)[d]	78 (69-85)
Median PFS, months (95% CI)	7.3 (5.5-9.2)
Median OS, months (95% CI)	20.2 (14.9-25.3)
Investigator Assessments	
Confirmed ORR, % (95% CI)*	35 (26-45)
Median DOR, months (95% CI)[c,*]	13.9 (5.6-19.4)
Confirmed DCR, % (95% CI)[d,*]	78 (69-85)
Median PFS, months (95% CI)*	7.3 (5.6-8.8)

*Data cutoff: November 1, 2021.
[a]Percentages may not add up to 100% because of rounding. [b]Patients could have been counted in more than 1 category. [c]DOR per Kaplan-Meier estimates. [d]DCR defined as complete response or partial response, or best response of stable disease for at least 6 weeks after initiation of study drug.
Source: Zhou C et al. JAMA Oncol. 2021;7:e214761; Ramalingam SS et al. ESMO 2022 (Abstract 988P).

Use of Multiple RWD as an External Comparator for Single Arm Trials

- In the absence of direct comparison evidence from a head-to-head randomized controlled trial, indirect comparison with external controls can be used to bridge the gap of comparative evidence
- RWE from Japan, China are also being generated

- Data sources for external controls
  - Real-world data, e.g., electronic health records (EHR), claims, medical chart review study, registries
  - Other clinical trials

Multiple real-world data sources used to support mobocertinib single arm trial in NICE submission

Germany Medical Chart Review

Patients with Stage IV NSCLC EGFR exon 20 insertions treated in 12 German academic centers

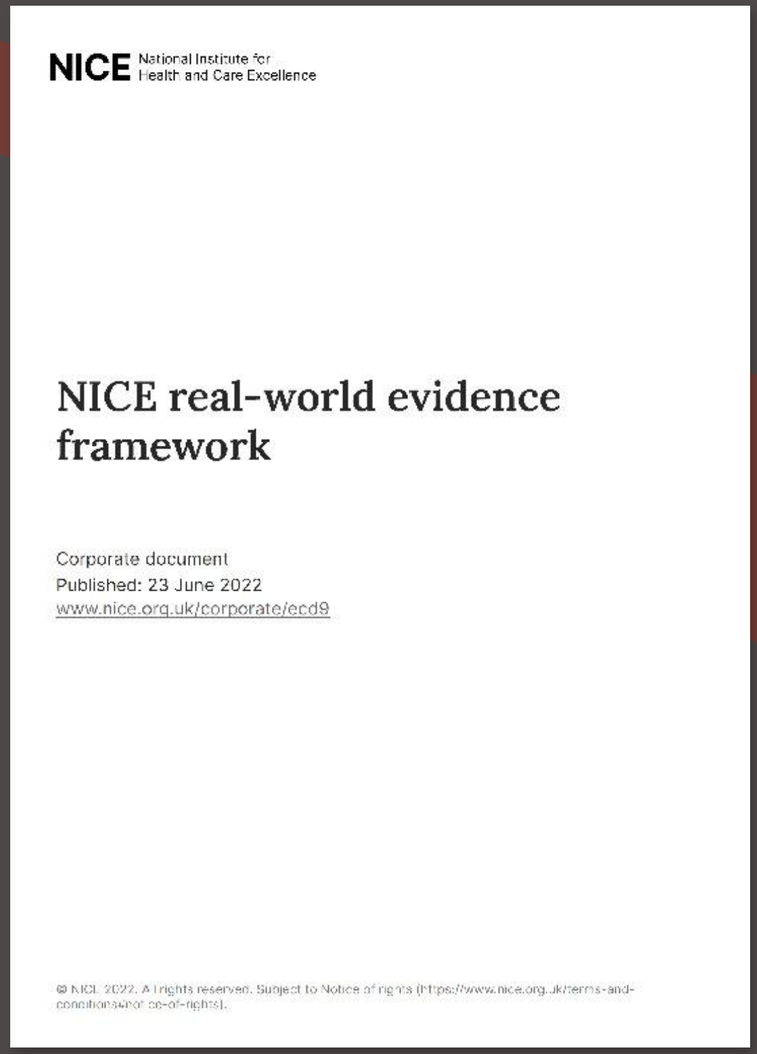
- High quality data curated by investigator
- Provide data source outside of US
- Detailed clinical endpoint (ORR, PFS, OS etc)
- Sample size: Patients with EGFR exon 20 insertion+ NSCLC 1st line in the database (N=104)

US Flatiron EHR-derived Database

Longitudinal, demographically and geographically diverse derived from de-identified electronic health record data

- Agency is familiar with this database from prior submissions
- Detailed clinical endpoint (ORR, PFS, OS etc)
- Sample size: Patients with EGFR exon 20 insertion+ NSCLC 1st line in the database (N=237)

RWD Framework With NICE Submission



NICE National Institute for Health and Care Excellence

NICE real-world evidence framework

Corporate document
Published: 23 June 2022
www.nice.org.uk/corporate/ecd9

Additional NICE Guidelines on Data Source and Study Reporting Tool

Goal	Tool and Guideline

Assessing Data Suitability	• Sufficient information should be provided to understand the data source, its provenance, quality and relevance in relation to the research questions.
	• The **Data Suitability Assessment Tool (DataSAT)** may be used to provide consistent and structured information on data suitability
	  ○ **Data provenance**: the characteristics of the data, data collection, coverage, and governance
	  ○ **Data quality**: completeness and accuracy of key study variables
	  ○ **Data relevance**: the data content, differences in patients, interventions and care settings between the data and the target population in the NHS, and characteristics of the data such as sample size and length of follow up.

Study Reporting	Reporting of studies should be sufficient to enable an independent researcher with access to the data to reproduce the study, interpret the results, and fully understand its strengths and limitations. Several reporting checklists identify key reporting items for: • Observational studies (EQUATOR network and STROBE guidelines) • Observational studies of routinely collected data (RECORD guidelines) • Studies of comparative effects (the RECORD statement for pharmacoepidemiology [RECORD-PE]) Also, the START-RWE tool has been developed to help the presentation of study data, methods and results across use cases.

DataSAT – Provenance (e.g. Flatiron)

The characteristics of the data, data collection, coverage, and governance

Data Source
- Flatiron EHR

Type of Data Source
- Structured and unstructured EHR

Data Collection
- Demographics, diagnostic, disease info, clinical characteristics, lab value, treatment and outcome

Geographical
- 280 community oncology practices and several academic cancer centres

Time Period
- Jan 2011-Feb 2020

Data Governance
- De-identified under HIPAA

Data Management and Quality Assurance
- Quality management systems (QMS), QA, QC

Linkage
- Mortality data, SSDI

Purpose of Data Collection
- De-identified EHR for routine practice

Care Setting
- Community and academic oncology clinics

Population
- 2.4 million US patients

Data Preparation
- Structured data, Unstructured data and Derived (e.g. line of therapy)

Data Specification
- Data dictionary

Other Document
- Publication

DataSAT – Data Quality

Details of data quality includes the variable definition, quality (accuracy or completeness), how quality was assessed, and assessment results

Study Variable	Target Concept	Operational Definition	Quality Dimension	How Assessed	Assessment Result
What type of variable (e.g., population eligibility, outcome)	Define the target concept (e.g., myocardial infarction [MI])	Define operational definition. (e.g., MI defined by an ICD-10 code of I21 in the primary diagnosis position)	Choose: accuracy or completeness	Describe how quality was assessed. Provide reference to previous validation studies if applicable.	Provide quantitative assessment of quality if available. (e.g., 'positive predictive value 85% (75% to 95%)')

Population Definition

- Advanced NSCLC with EGFR exon 20 insertion
- Method of confirmation by PCR or NGS

Outcome

- OS is confirmed by social security death index, 97% accuracy
- Real-world response rate, and PFS were extracted from clinical notes and revealed a strong association with trial-based ORR or PFS

Other Variables

- Comorbidity, ECOG etc
- Confirmation and completeness assessed by abstraction

DataSAT - Relevance

The available data content, differences in patients, interventions and care settings between the data and the target population in the NHS, and key characteristics of the data such as sample size and length of follow up

Population

- Align with trial

Care Setting / Treatment Pathway

- Related to UK treatment

Availability of Key Study Elements

- Outcome endpoints
- Variables to be matched

Study Period

- Recent data

Timing of Measurement

- Real world practice
- Longitudinal

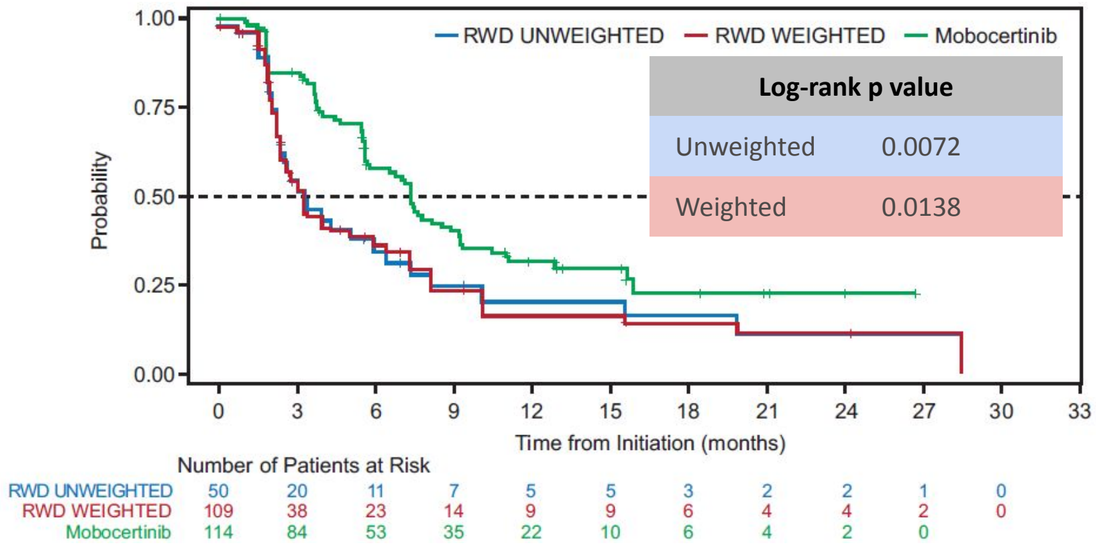
Follow-up

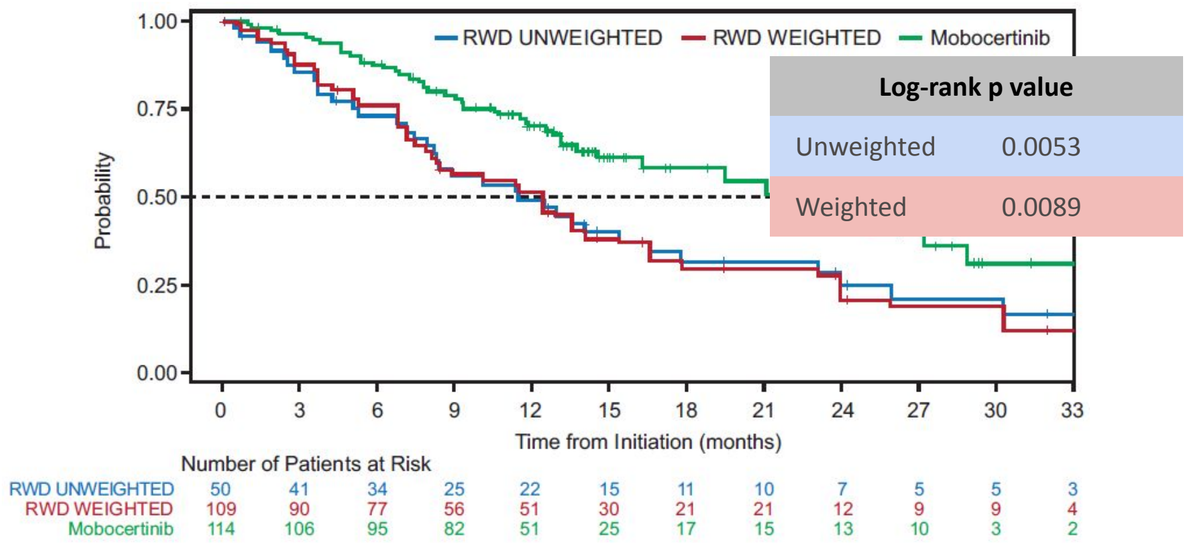
- Sufficient for assessing the outcomes

Sample Size

- 1st line, 2nd line
- Reasonable sample size

Example of ITC Analysis (Before and After Propensity Score Weighting)





- Data analysis for illustration only
- Variables presented included in the models are age, gender, smoking history, baseline BM, time from initial dx.
- Final analysis was conducted after adaptation/localization based on the feedback from KOLs regarding prognostic factors and effect modifiers.

Source: Ou et al, Comparative effectiveness of mobocertinib and standard of care in patients with NSCLC with EGFR exon 20 insertion mutations: An indirect comparison, Lung Cancer, 2023

NICE Comments

The Final Appraisal Document (FAD) outlined the positive recommendation for mobocertinib:

> *"The committee acknowledged the known limitations with real-world evidence. But it considered that it can be valuable for resolving gaps in knowledge when best-practice methods are applied, such as those described in the NICE real-world evidence framework.*
>
> *It also acknowledged the rarity of exon 20 insertion mutation-positive NSCLC and the lack of direct comparative efficacy data. This meant that the* ***real-world evidence may have been the best available source of evidence for the comparator arm****."*

> *"Overall, the committee concluded that some areas of uncertainty remained and some of this uncertainty was currently unresolvable. It noted that 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."*

Lessons Learned for Future

- Start real-world analyses early, think about both **global regulatory** approval as well as **local access requirements** when designing study. Manufacturers need to balance all the different requirements from those agencies and recommendations from organizations when selecting the right data to support submissions globally.
- In the case of NICE submission, apply **NICE RWE Framework** to ensure robust real-world data identification and analysis.
    - Use pre-defined systematic searches to identify RWE sources, inform the choice of dataset
    - Apply RWE checklists (e.g. RECORD-PE and Data-SAT) to validate strengths and robustness of data
- Early **cross-functional collaboration** and engagement

Tying it all together

D A T A Q U A L I T Y

D A T A E M P A T H Y

flatiron

Audience Q&A

Matthew Dixon, Director,
Worldwide Health Economics &
Outcomes Research, BMS

Mark Lin, Senior Director,
Global Evidence &
Outcomes Research, Takeda

Emily Castellanos,
Senior Medical Director,
Flatiron Health

Javier Jimenez,
Chief Medical Officer,
Flatiron Health

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