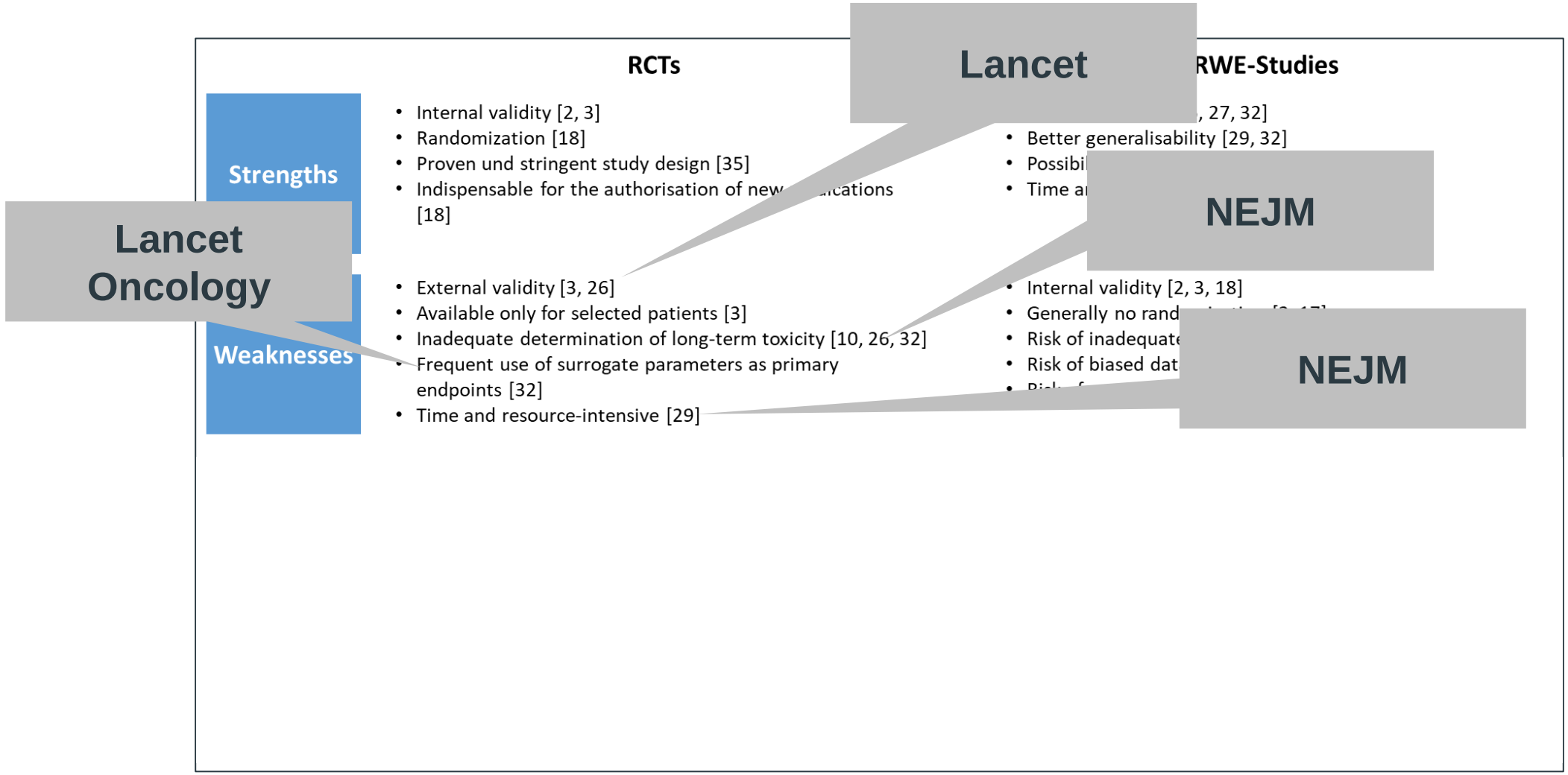
RWE using patient level data for precision oncology and regulatory filing

Benedikt Maissenhaelter, IQVIA

Table of Contents

+ Introduction
+ RWE for Precision Oncology
+ RWE for Regulatory Filings
+ Conclusion

RCTs and Real-world Evidence Studies are complementary



RCTs and Real-world Evidence Studies are complementary

	RCTs	RWE-Studies
Strengths	• Internal validity [2, 3] • Randomization [18] • Proven und stringent study design [35] • Indispensable for the authorisation of new medications [18]	• External validity [26, 27, 32] • Better generalisability [29, 32] • Possibility of long-term surveillance [35] • Time and resource-efficient [10, 29]
Weaknesses	• External validity [3, 26] • Available only for selected patients [3] • Inadequate determination of long-term toxicity [10, 26, 32] • Frequent use of surrogate parameters as primary endpoints [32] • Time and resource-intensive [29]	• Internal validity [2, 3, 18] • Generally no randomization [2, 17] • Risk of inadequate study design [2] • Risk of biased data [19, 35] • Risk of non-scientific goals [14]

Table of Contents

+ Introduction
+ RWE for Precision Oncology
+ RWE for Regulatory Filings
+ Conclusion

Examples in NSCLC

Treatment patterns and outcomes in HER2 Mut NSCLC

Scientific objectives

Primary objectives

- To describe the **demographic** and **clinical** characteristics of advanced HER2m non-squamous NSCLC patients
- To estimate **overall survival (OS)** for patients who receive standard of care (SOC), overall and stratified by geography

Secondary objective

- To describe **treatment patterns** and **treatment sequencing** for patients by geographical region

Exploratory objectives

- To estimate **Progression Free Survival (PFS)** in patients who receive SOC, overall and stratified by geography
- To estimate **OS** among the subgroup of patients who have known **driver-gene mutations**

Approach

- Retrospective population-based **natural history study design**
- Case definition: advanced non-squamous NSCLC, including:
  - **Metastatic (stage IV) non-squamous NSCLC**: patients with stage IV non-squamous NSCLC at initial diagnosis
  - **Unresectable non-squamous NSCLC**: patients with stage III disease who have no record of surgery.

Testing patterns and outcomes in HER2 Mut NSCLC

Context

- Amongst the various indications under development, Non-Small Cell Lung Cancer (NSCLC) with HER2 Alterations (Overexpression, overamplification and mutation), is of particular interest, and a comprehensive evidence generation program is currently underway to demonstrate the value to patients and HCPs
- There is a need to generate evidence and real-world data (RWD) for HER2-altered NSCLC, with evidence gaps of greatest priority being those focussed on medical and payer needs, such as testing patterns, treatment patterns and outcomes

Current objectives

- This project aims to investigate **HER2 testing patterns of NSCLC patients** by analysing real world data derived
- In addition, **biomarker overlap of HER2 mutations** with other key actionable mutations will be explored as a secondary objectives

Association of Inflammation Markers and Patient Outcomes

Study objectives

Understand outcomes (response to treatment, disease progression, overall survival) stratified by biomarkers (including genetic biomarkers and markers indicative of PTI) in NSCLC patients in a market where CRP testing is routine practice

Primary Objectives

1. Understand treatment outcomes for NSCLC patients associated with CRP levels and other PTI markers (NLR, Glasgow Prognostic Score) stratified by biomarkers (EGFR, KRAS, MET where possible)

Secondary Objectives

1. Understand prevalence of EGFR, KRAS and MET mutations
2. Understand NSCLC patient characteristics

Research questions

Treatment patterns: Which treatments are NSCLC patients receiving, stratified by stage? Which treatments are NSCLC patients stratified by EGFR, KRAS, MET mutation status?

- **Biomarker prevalence:** What is the prevalence of EGFR, KRAS, MET mutations in NSCLC patients?
- **Clinical outcomes:** What is the current OS, PFS, response duration, response rate, TTNT of NSCLC patients overall and stratified by stage and EGFR, KRAS, MET?
- **Predictive value of CRP and other PTIs:** What is the association between CRP (and other PTI markers) and clinical outcomes overall and stratified by stage and EGFR, KRAS, MET?
- **Patient characteristics:** Are there specific patient characteristics associated with CRP and other PTI markers?

Time period

- 2014 - 2021

Patient cohort

- **Index date:** Diagnosis of NSCLC
- **Inclusion criteria:** Age ≥ 18 years at diagnosis; Male & female gender; Histologically confirmed diagnosis of NSCLC (all stages)
- **Exclusion criteria:** Patients on active treatment for malignancies other than NSCLC at time of enrolment

Study design

- Retrospective non-interventional non- comparative non-randomised cohort study

HER3-directed antibody-drug conjugate

Context

- Sponsor is evaluating the antitumor activity of a HER3-directed antibody-drug conjugate (ADC, in a phase 2 clinical trial among patients with metastatic or locally advanced NSCLC with an activating EGFR mutation (exon 19 deletion or L858R) who have received and progressed on or after at least 1 EGFR TKI and 1 platinum-based chemotherapy-containing regimen.
- Looking to recruit patients for an external comparator arm for their phase 2 clinical trial and obtain high-quality clinical RWD to bolster the medical and economic **evidence package for submission to US/EU payer and regulatory bodies**

Geographies	Audience	Timelines	Desired sample
	Payers Regulatory	• **US Regulatory**: May 2023 • **US Payer**: Jan 2024 • **EU Payer**: Jul 2024 / Jul 2025	US – 210 patients EU – 210 patients

Examples in other Solid Cancers

Metastatic triple-negative breast cancer, 2nd Line

Context

- Study objectives
  1. Describe treatment patterns for 2L vs. 3L
  2. Develop OS and PFS curves for 2L vs. 3L
- Results will be used in HTA submission

Inclusion criteria

- Age 18+
- Histologically or cytologically confirmed TNBC, defined as <1% expression for ER and PR and negative for HER2 by in-situ hybridization
- Relapsed or refractory to at least 2 prior standard therapeutic regiments for advanced / metastatic TNBC
- At least 1 treatment should have occurred during metastatic stage

Geographies

Key endpoints

OS, PFS

CDK 4/6 inhibitors in HR+/HER2- advanced/metastatic breast cancer patients

Primary objective

- To estimate real world progression free survival (rw-PFS) in HR+/HER2- advanced/metastatic breast cancer patients, who were not amenable to surgery and who were treated with a CDK 4/6 inhibitor

Study design

- The study is a multinational and multicenter, single-arm cohort study of patients with advanced or metastatic HR+/HER2- breast cancer treated with a CDK 4/6 inhibitor. This study will be conducted retrospectively with secondary use of data collected in a standardized manner. Only anonymized data will be analyzed.
- The current study does not aim to collect any data that have been generated specifically for the purposes of the research, through prospective collection from diagnostic or monitoring procedures.
- **Index date (Baseline)**: defined as the date of first treatment with a CDK 4/6 inhibitor
- **Index period**: The patients fulfilling the inclusion criteria will be identified during the period *01-Jan-2018* and onwards
- **Follow-up period:** No minimum follow-up period
- **Study period:** The period between *01-Jul-2017* and *30-Jun-2021* to allow 6 months pre-index period.

Inclusion/Exclusion criteria

- ✓ Age ≥ 18 years at ribociclib / alpelisib treatment initiation.
- ✓ Male & female gender.
- ✓ Confirmed diagnosis of locally advanced/metastatic not amenable to surgery HR+/HER2- BC (progressed following prior therapy or *de novo*) for whom the treating physician took the decision to initiate treatment with ribociclib / alpelisib.
- ✓ Patients with at least one prescription for a CDK 4/6 inhibitor during the period *01-Jan-2018* to *30-Jun-2021*

- ✗ Patients participating in any interventional clinical trial that includes investigational or marketed products at the time of enrollment. (Patients participating in other investigator-initiated research or NIS can be included as long as their standard of care is not altered by the study)
- ✗ Patients on active treatment for malignancies other than advanced breast cancer (aBC) at the time of enrollment.

HER2+ met. / loc. adv. GC / GEJ

Context

- Evidence need for **RWD on HER2+ met. / loc. adv. GC / GEJ** patients to compare the efficacy / safety of novel drug and current SOC
- Sponsor would like to conduct a **natural history study** to describe the demographic and clinical characteristics, treatment paradigm, and outcomes of HER2-overexpressing locally advanced or metastatic gastric or GEJ adenocarcinoma patients receiving SoC in Europe, which will be used together with data from the two phase 2 trials *to support payers decision making, and potentially regulatory and / or HTA submission*

Objectives

The primary objectives of this study are:

- To describe the demographic and clinical characteristics of patients with HER2 overexpressing locally advanced or metastatic gastric or GEJ adenocarcinoma and receiving SoC in Europe (Full cohort, 2L+ cohort, 3L+ subcohort where patient counts allow).
- To describe the treatment paradigm and overall survival (OS) of patients with HER2-overexpressing locally advanced or metastatic gastric or GEJ adenocarcinoma receiving SoC in Europe (Full cohort, 2L+ cohort, 3L+ subcohort where patient counts allow).
- To describe the time to discontinuation (TTD) and time to next treatment (TTNT) of patients with HER2-overexpressing locally advanced or metastatic gastric or GEJ adenocarcinoma receiving SoC in Europe (Full cohort 2L+ cohort, 3L+ subcohort where patient counts allow).

The exploratory objectives of this study are:

- To describe the real-world progression free survival (rwPFS) for each cohort (full cohort, 2L+ cohort, 3L+ subcohort).

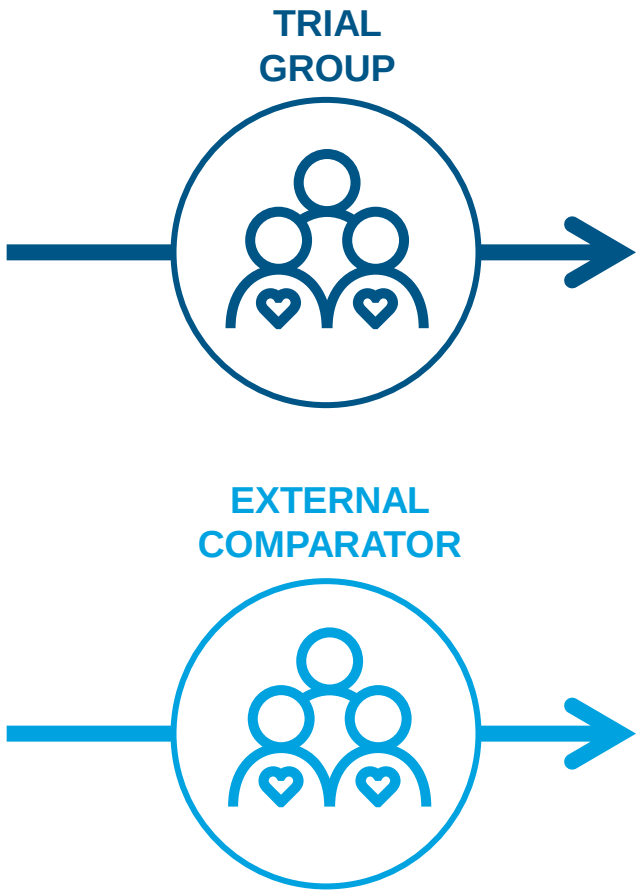
Table of Contents

+ Introduction
+ RWE for Precision Oncology
+ RWE for Regulatory Filings
+ Conclusion

External Comparators

Concept

External Comparator: *A cohort of patient data used to add comparative context to a research trial*



External Comparator Characteristics:

- Patient cohort derived from ***real-world data (RWD)***
- Patients ***mirror the inclusion / exclusion criteria*** for the trial
- ***Trial outcomes are examined*** in the RWD external comparator cohort
  - → ***Context to trial results***
  - → ***Direct comparison to index cohort***

An External Comparator can add value when an internal control is not feasible or sufficient to help demonstrate treatment benefit

Internal Control

Not feasible because:

- Unethical to randomize
- Rare outcomes so impractical to randomize
- Patients unwilling to participate due to risk of not receiving drug

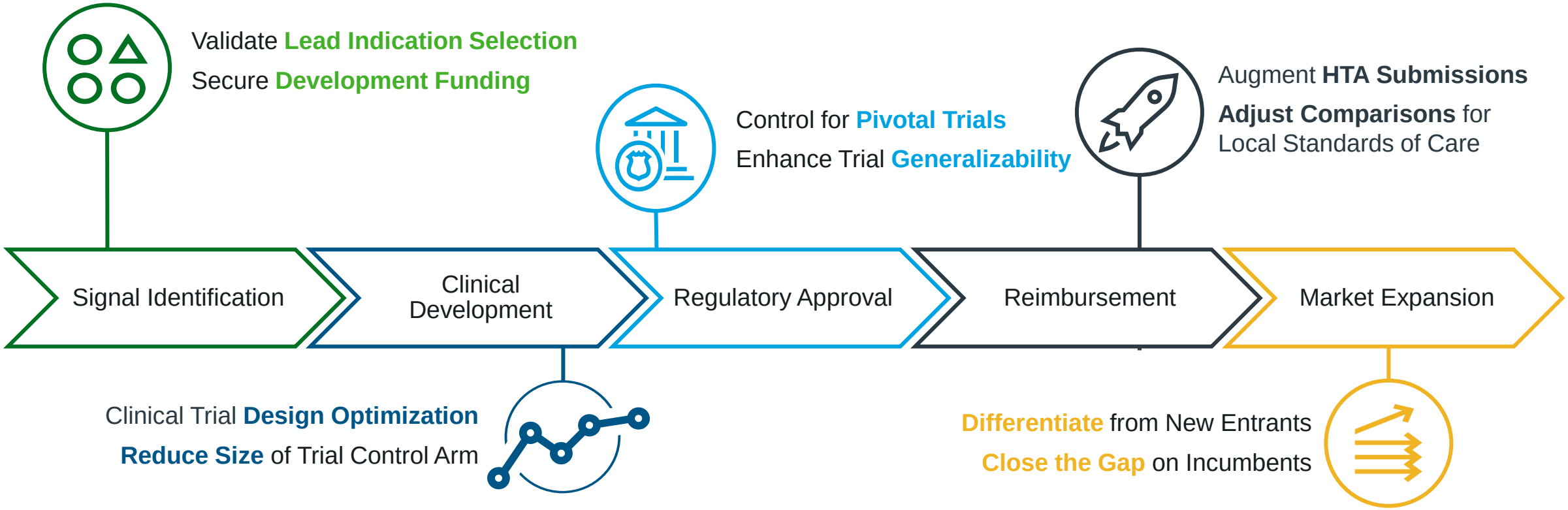
Treatment Group

External Comparator

- Patient cohort derived from real-world data (RWD)
- Patients match the inclusion / exclusion criteria for the trial
- Benchmark the efficacy data from the treatment group in a cohort of similar patients

External Comparators can provide value across the full treatment development lifecycle

Use Cases for External Comparators



External Comparators for Market Authorization

A growing number of regulatory decisions are informed by RWE across several therapeutic areas for effectiveness determination

				FDA		EMA		NMPA
				Approval	Label Expansion	Conditional Approval	Approval	Label Expansion
External Controls	Pfizer	BAVENCIO	Metastatic Merkel cell carcinoma	2017 Accelerated*		2017		
	BIOMARIN	Brineura (cerliponase alfa)	Infantile batten disease	2017			2017	
	GILEAD	YESCARTA	Diffuse large B-cell lymphoma	2017			2018	
	Kite	KYMRIAH	Diffuse large B-cell lymphoma				2018	
	FRESENIUS KABI	Omegaven®	Parenteral nutrition-associated cholestasis	2018				
	AMGEN	BLINCYTO (blinatumomab)	B-cell precursor acute lymphoblastic leukemia in 1st/2nd complete remission with MRD ≥ 0.1%		2018		2019	
	TB Alliance, MYLAN	Pretomanid	Lung Tuberculosis (TB)	2019			2020	
	Daiichi-Sankyo	ENHERTU	HER2+ Breast Cancer	2019			2019	
	avexis	zolgensma (onasemnogene abeparvovec-xioi)	Spinal muscular atrophy	2019			2019	
	janssen	Balversa (erdafitinib)	Metastatic bladder cancer with FGFR3 or FGFR2 mutations	2019			2019	
	Roche	ROZLYTREK entrectinib	ROS1-positive metastatic NSCLC/NTKR-fusion positive solid tumors	2019			2020	
	astellas, SeattleGenetics	PADCEV	Metastatic urothelial cancer	2019				
	CLINUVEL	SCENESSE	Erythropoietic protoporphyria (EPP)	2019			2014	Pending
Pragmatic	janssen	INVEGA SUSTENNA paliperidone palmitate	Schizophrenia		2018			
Other RWE	amneal PHARMACEUTICALS	TEPADINA	Pediatric class 3 beta-thalassemia		2017			
	NOVARTIS	LUTATHERA	SSTR-positive (GEP-NETs)	2018			2017	
	Genentech IN BUSINESS FOR LIFE	AVASTIN bevacizumab	Metastatic or recurrent squamous NSCLC in combination with platinum-based chemotherapy					2018
	Pfizer	IBRANCE	HR+, HER2- advanced/metastatic breast cancer in males		2019			
	Genentech IN BUSINESS FOR LIFE	POLIVY polatuzumab vedotin-piiq	Relapsed or refractory diffuse large B-cell lymphoma	2019			2020	
	Seqirus A CSL COMPANY	FLUAD TETRA	Influenza	2020			2020	

MRD = minimal residual disease; SSTR = Somatostatin receptor; GEP-NETs = gastroenteropancreatic neuroendocrine; tumors; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor Sources: IQVIA internal expertise

*Cells highlighted in green represent that the usage of RWE/RWD is mentioned in the assessment report upon approval of the drug

RWD can support supplementary approvals of products seeking indication expansion

CASE STUDY
Label Expansion

Situation

- Pfizer wanted to gain approval for a breast cancer indication expansion to include **male breast cancer**
- Low prevalence limited the feasibility of conducting randomised trails

Solution

- Real-world evidence (RWE) was collected from multiple sources, including pharmacy / medical claims from an IQVIA's insurance database, Oncology EMR, Flatiron Health's breast cancer database and Pfizer's global safety database
- RWE was used to create safety profiles for men and women, and provide information on outcomes, treatment pattern and duration

Results

- RWE endpoints were able to provide real-world tumor response and safety data
- Granted approval as supplemental NDA (sNDA) for indication expansion by the FDA in 2019
- FDA approval was granted in less than year at a fraction of the cost of attempting a randomised clinical trial all despite in-class competition
- Ibrance was the first CDK 4/6 inhibitor in the US indicated in combination with an aromatase inhibitor for the first-line treatment of men living with HR+, HER2- metastatic breast cancer

Key Takeaways

- ✓ RWE can support innovative approaches for label expansions in major markets
- ✓ Real-world data from a variety of sources can be leveraged together to improve regulatory decisions, particularly within oncology and rare disease therapeutic areas

> *We are expanding the indication for Ibrance to include male patients based upon data from post-marketing reports and electronic health records showing that the safety profile for men treated with Ibrance is consistent with the safety profile in women treated with Ibrance,"*
>
> *- Richard Pazdur, MD, director of the FDA's Oncology Center of Excellence*

Market Authorization for novel drug in DLBCL / FL

Overall objective

To establish **external comparator** cohorts of real-world (1) **R/R DLBCL in the third line or later (3L+) patients** and (2) **R/R FL grade 1-3a 3L+ patients,** to provide context to the results of a human CD20xCD3 bispecific antibody phase 2 clinical trial, as part of the sponsor's submission to regulatory bodies

Target audience

- Regulatory bodies
- Published for the scientific community

Cohorts of interest

- Relapsed/refractory DLBCL patients
  - **Diagnosed on or after Jan 1, 2010** and
  - Received a **3rd or later LOT between January 1, 2015 and April 30, 2021**
- Relapsed/refractory FL grade 1-3a patients
  - **Diagnosed on or after Jan 1, 1998** and
  - Received a **3rd or later LOT between January 1, 2015 and October 31, 2020**

Study objectives

Primary objective

- To evaluate real-world objective response rate (ORR) in cohorts of interest

Secondary objectives

- To evaluate the following real-world outcomes in cohorts of interest:
  - Overall survival (OS)
  - Progression-free survival (PFS)
  - Time to next treatment (TTNT)
  - Complete response (CR) rate
  - Duration of response (DOR)
  - Disease control rate (DCR)
  - Histological transformation (HT) (FL only)

Study timelines

Contracting: Aug 2021 – March 2022

Data collection: March – July 2022

Ethics Committee applications: Sept 2021 – March 2022

Geography

Use of External Comparators for regulatory purposes continues to follow an undefined roadmap, but with increasing precedent

1. With innovation comes uncertainty, but there is **clear value to having context to understand the impact of a product**

2. **The need must be present:** "…when using a parallel assignment control arm is unethical or not feasible, and usually when the effect size is expected to be large based on preliminary data" *

3. **Likelihood of success maximized by early engagement** with regulators and payers prior to execution
   - Provision of and feedback on protocol synopsis with proposed analytic methods strengthens study and allows scientific discussion – "Give us a chance to say no"

4. **Tailor External Comparators to the research question and stakeholder**
   - A regulator will be most interested in similarity to the trial population
   - A payer will be most interested in similarity to their population
   - This may require multiple comparator arms to address multiple objectives

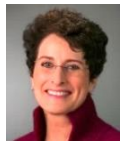
*Framework for FDA's Real World Evidence Program, December 2018

IQVIA is partnering with industry and regulators to set standards

Helping set standards for fit-for-purpose RWE

- AHRQ Patient Registries Guide
- FOCR Working Group
- AHRQ Observational CER Guide
- Duke-Margolis Working Group
- GRACE Initiative
- Observational Medical Outcomes Partnership
- ENCePP Guide
- 4,800+ publications

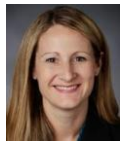
Experts and industry leaders



Nancy A. Dreyer, PhD, MPH, FISPE, FDIA
IQVIA Chief Scientific Officer and Fellow of DIA, Class of 2017

Stella Blackburn, MA, MSc, FRCP(ed), FFPM, SM.
Formerly Risk Management Development and Scientific Lead at the European Medicines Agency (EMA) for 17 years

Marni Hall, PhD, MPH, MA
Former Director of regulatory science (Surveillance and Epidemiology) at the FDA



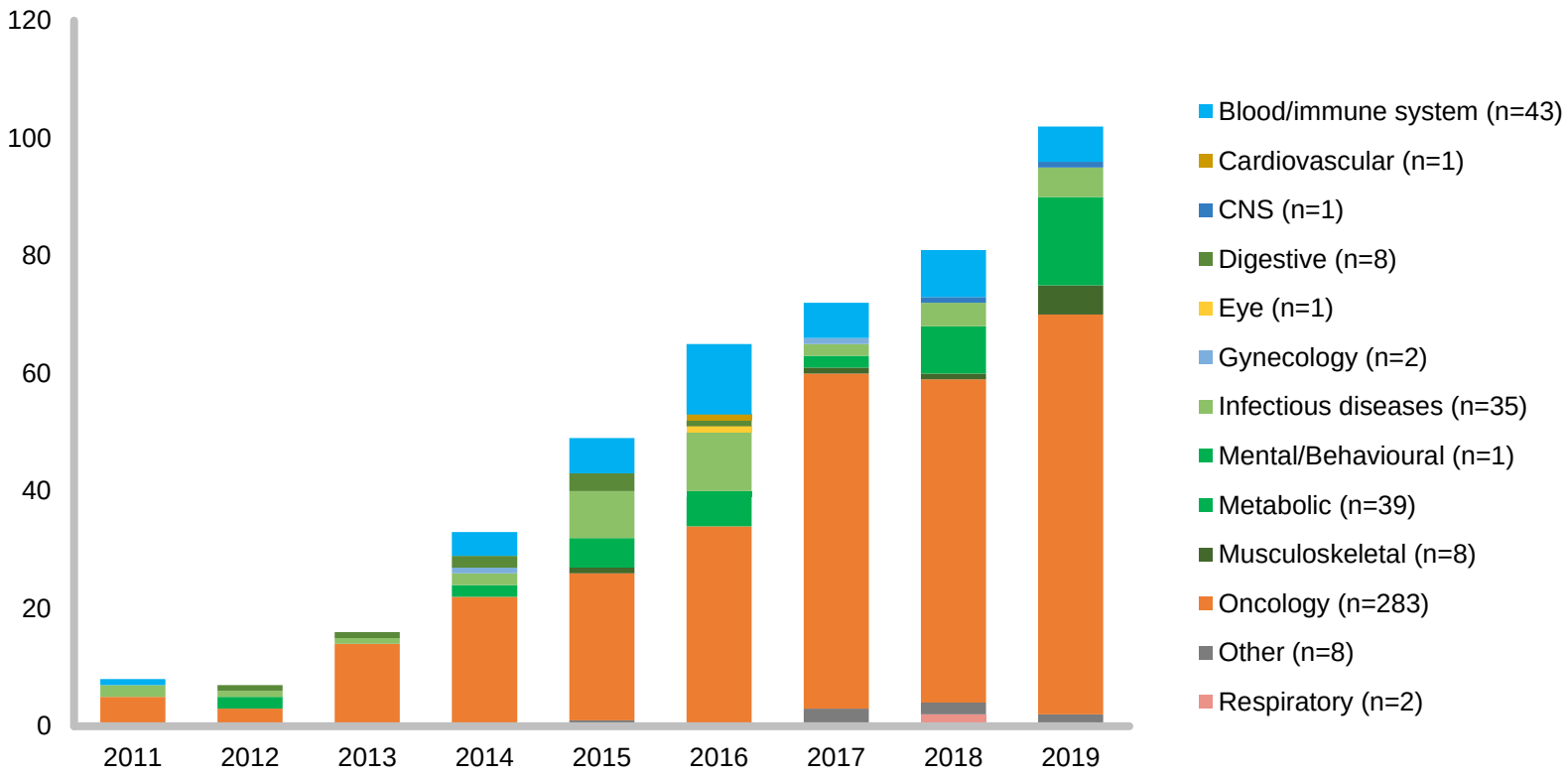
Jennifer B. Christian, PharmD, MPH, PhD, FISPE
Fellow of the Institute of Medicine, and Duke Margolis Methods Working Group Member

Christina Mack, PhD, MSPH
Co-Chair of the MDEpiNet Scientific Oversight Committee and Chair of the ISPE Medical Devices Special Interest Group

External Comparators for HTA Submissions

There are an increasing number of submissions of single-arm clinical data packages to HTA bodies

Single Arm trial submissions to HTA bodies, Globally, Up to Dec 2019



Key Findings

- **433 single arm trial submissions** covering >100 drug/indication combinations
- Submissions covered **21 different countries** with top 5 being UK, France, Canada, Germany and Australia
- **65% of submissions were in oncology or heam-onc.** indications

HTA submissions incorporating RWD External Comparators were most likely to receive a positive recommendation

External Comparator use and HTA recommendation for Single Arm trial submissions

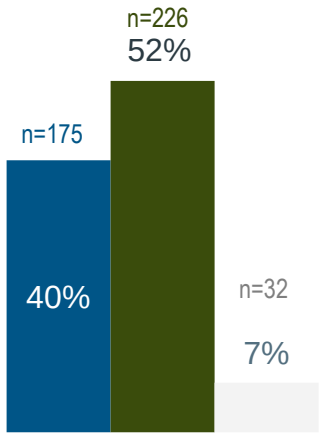
	Type of External Comparator	Recommendation				Total
		Multiple	Negative	No Record	Positive	
External Comparator Used	Real World Data (RWD)*		26	10	51	87
	Prior Clinical Trials (CTs)		30	23	51	104
	Prior CTs and RWD		12	7	16	35
	Unclear**	1	13	3	15	32
	None	3	73	24	75	175
	Grand Total	**4**	**154**	**67**	**208**	**433**

Key Findings

- **52% of cases used some kind of external comparator** in their submission
- Submissions with an RWD External Comparator have highest success (**59%**)
- In comparison, submissions based on the single-arm trial only were successful in **43%** of submissions

*Including registries, database or chart review studies
**Including Expanded Access and Expert Opinion
Source: Use of External Comparators for Health Technology Assessment Submissions Based on Single-Arm Trials; Patel, Dony et al. Value in Health, Volume 24, Issue 8, 1118 - 1125

Most single-arm trial HTA submissions were accompanied by an external comparator



Patel et al. (2011-2019)

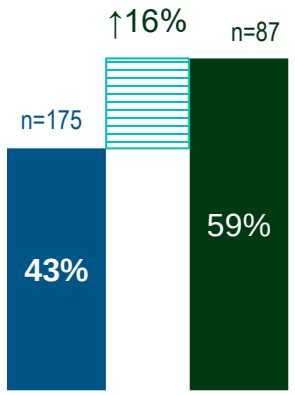
Change in proportion of single-arm trial HTA submissions with an external comparator of any type as Patel et al. dataset is filtered to recent oncology submissions in select markets

n = total n of SAT only submissions; n= total n of SAT + EC of any type; n= total n of submissions with supplementary evidence that was unclear, originating from expanded access programs or expert opinions

**Select markets: US, UK, Germany, France, Italy, Spain, Poland*
Acronyms – SAT: Single-Arm Trial, EC: External Comparator, HTA: Health Technology Assessment
Source: IQVIA HTA accelerator. Please note small sample will affect overall interpretation of results. There may also be reasons other than ECs that may impact positive results e.g. orphan drug status, as HTA decisions are multi-factorial

Analysis of recent oncology HTA submissions show an increasing importance of RW Comparators on positive outcomes

The acceptance rate gap between SAT alone vs. SAT + RWD EC widens from the original Patel et al. publication, when limited to recent (oncology) submissions i.e., increasing temporal trend of acceptance of SAT + RWD EC (opposite is true of SAT alone)



Patel et al. (2011-2019)

SAT Only SAT + RWD EC

Change in acceptance rate of single-arm trial vs. single-arm trial + real-world data external comparator with most recent oncology submissions in select markets

n = total n of SAT only submissions (irrespective of outcomes) ; n= total n of SAT + RWD EC submissions (irrespective of outcomes)

**Select markets: US, UK, Germany, France, Italy, Spain, Poland*
Acronyms – SAT: Single-Arm Trial, EC: External Comparator, HTA: Health Technology Assessment
Source: IQVIA HTA accelerator. Please note small sample will affect overall interpretation of results. There may also be reasons other than ECs that may impact positive results e.g. orphan drug status, as HTA decisions are multi-factorial

Leveraging IQVIA's Haem-Onc research network to run a multi-site RW External Comparator Arm Study

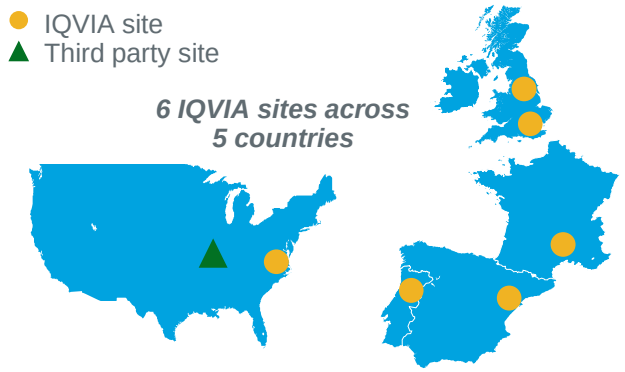
CASE STUDY
Rare NHL External Comparator Study

Situation

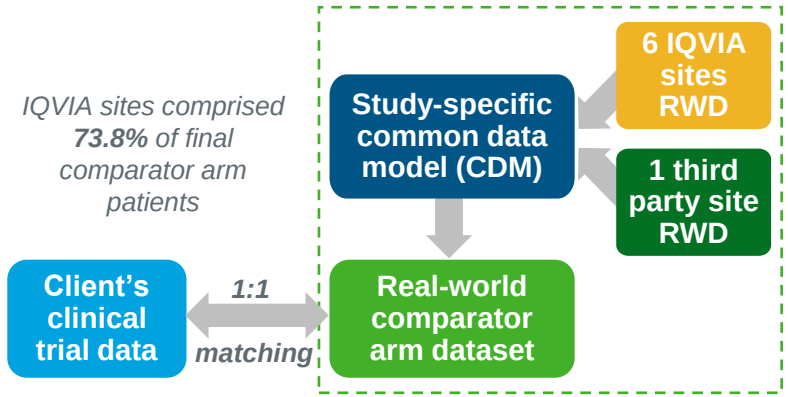
Client sought to develop contextual evidence for their single arm trial to compare **efficacy** of a 3L+ indicated pipeline asset in patients with a rare type of Non-Hodgkin's Lymphoma (r/r iNHL)

Solution

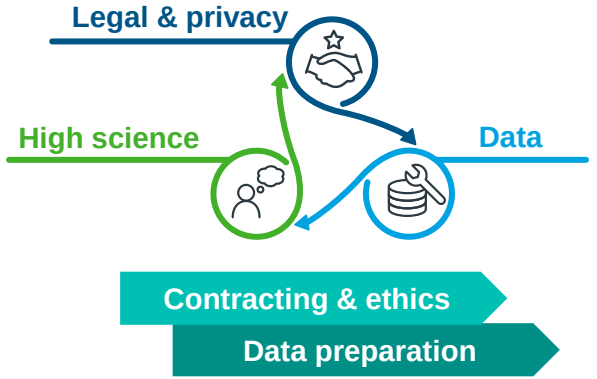
1 Established network of leading research centers in NHL covering key geographies



2 Fit-for-purpose payer-relevant dataset, harmonised across sites & countries



3 Integrated delivery approach for parallel contracting, ethics, and data preparation



Enablers

- ✓ Existing relationships with centers across Europe and in the US
- ✓ RWD expertise & bespoke CDM to enable site data to be harmonized and pooled for analysis
- ✓ Propriety algorithms to align LoT definitions
- ✓ Advanced scientific methodology to reuse patients across cohorts
- ✓ Collaborative & agile multi-disciplinary team of experts
- ✓ Good relationships and key familiarity with sites to accelerate contracting & ethics processes

Impact

Abstract & **presentation** of study results at **European Haematology Association (EHA) Congress**[1]

Client submitted **study outputs** to support both **HTA** and context for **regulatory submissions**

Sufficient patients to carry out **1:1 matching** to clinical trial, despite **rarity** of indication

Accelerated data acquisition in **9 months** (compared to **typical timeline of 12-18 months**)

RW(D/E): real-world (data/evidence) | Haem-Onc: Haematology-Oncology | r/r: relapsing/remitting | NHL: Non-Hodgkin's Lymphoma | HTA: health technology assessment | CDM: common data model | LoT: line of therapy

1. Ghione P et al. A comparison of clinical outcomes from zuma-5 (axicabtagene ciloleucel) and the international scholar-5 external control cohort in relapsed/refractory follicular lymphoma (r/r FL). *European Hematology Association Congress* 2021

Case study: external comparator in a rare sarcoma indication with potential requirement for tissue

CASE STUDY
External comparator

Situation

- Sponsor partnered with IQVIA to generate an external comparator arm to benchmark effectiveness of their **cell therapy** vs. current standard of care (scope: US, Canada, Europe) to **support regulatory & payer submissions**
- Primary objective of the external comparator is to measure **overall survival** (OS)
- Challenges include: rare tumour type, potential requirement to **test biological samples for biomarkers** which were **not captured in routine clinical practice**

Progress to date

- **Identified >180 potential data sources, including biobanks, individual treatment centers and trial sites** for assessment of ability to support generation of the external comparator
- **>40 data sources assessed and 20 selected** via feasibility questionnaires and interviews
- **Study designed** from both epidemiological and operational perspectives – retrospective data collection of 10 years
- **Discussions with three regulatory or HTA agencies.** Helpful and positive guidance received (written and verbal)

Project learnings to date

- **Early engagement with clinical team** is critical – trial endpoints are often not reliably captured in the real world (e.g., ORR, PFS)
- **Start planning early** – identification, assessment and contracting of data sources takes time
- **Seek early regulatory advice** – new channels in place (e.g. FDA RWE mailbox) for engagement before formal submission
- **Nest external comparator within a natural history study** – this allows publications of routine care treatment patterns which improves understanding of the management of rare diseases, and allows for different ‘baskets’ of treatments to be used in the external comparator for different audiences
- **Chart review is the optimal approach** – many databases have good patient volumes, but don’t have the depth of clinical information or ability to validate data points to withstand regulatory scrutiny. This will vary between therapy areas

External Comparators can provide value across the full treatment development lifecycle

Use Cases for External Comparators

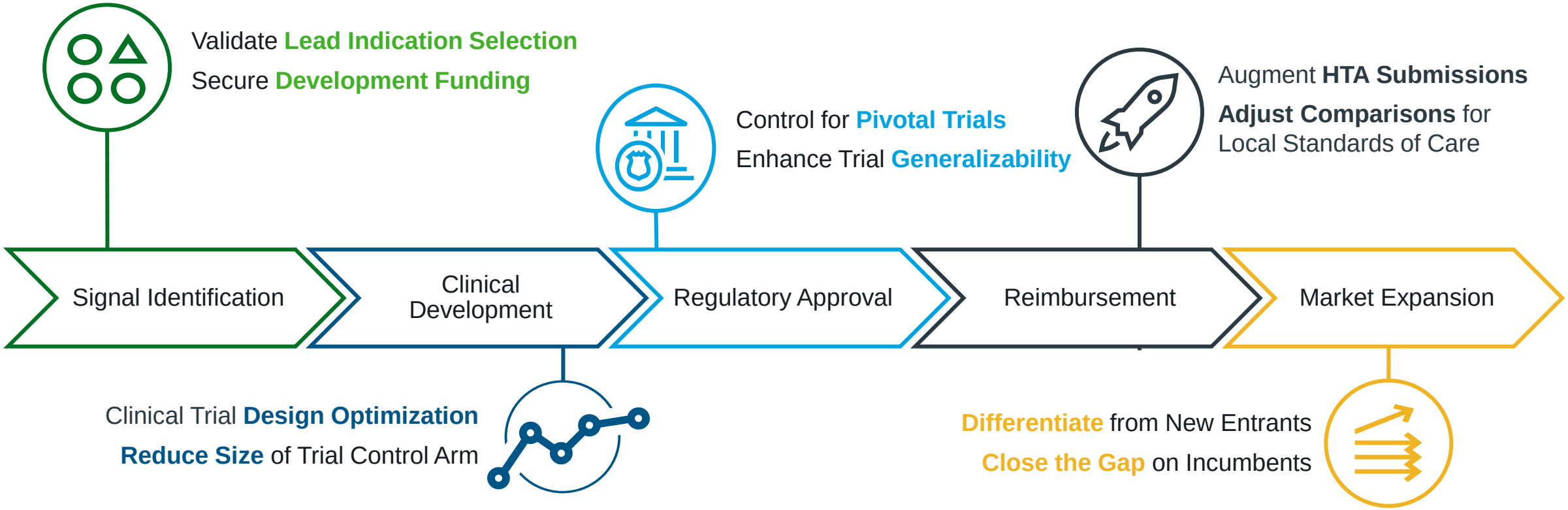


Table of Contents

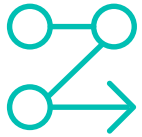
+ Introduction
+ RWE for Precision Oncology
+ RWE for Regulatory Filings
+ Conclusion

Re-usable cancer network architecture enables efficient study start-up and execution

Trusted healthcare partnerships

Collaborations with top cancer treatment centres, with engagement of clinicians.

Privacy protecting IT infrastructure



Infrastructure supports transfer and storage of anonymised patient level data, with sites required to meet the same standards.

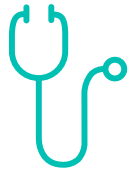
Information governance framework

GDPR compliance and gold standard Information Governance written into architecture and contracting. No transfer of patient-identifiable data.

Previously-agreed contracting templates

Pre-agreed master collaboration agreement (MCA) dramatically reduces burden of contracting for individual studies.

Fit-for-purpose data access models



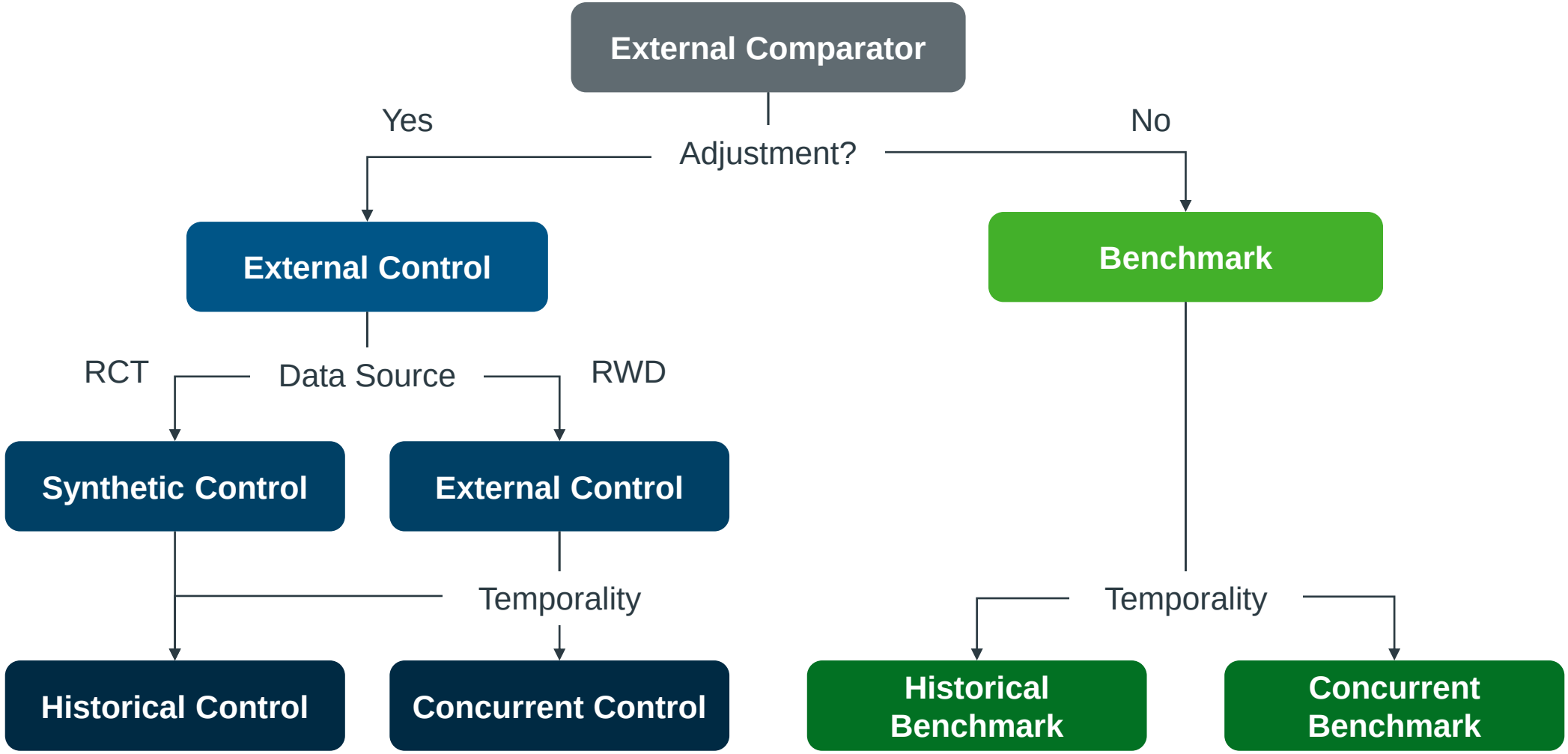
Different models of data access offered to sites to maximise flexibility whilst maintaining robust processes.

Proprietary Common Data Model

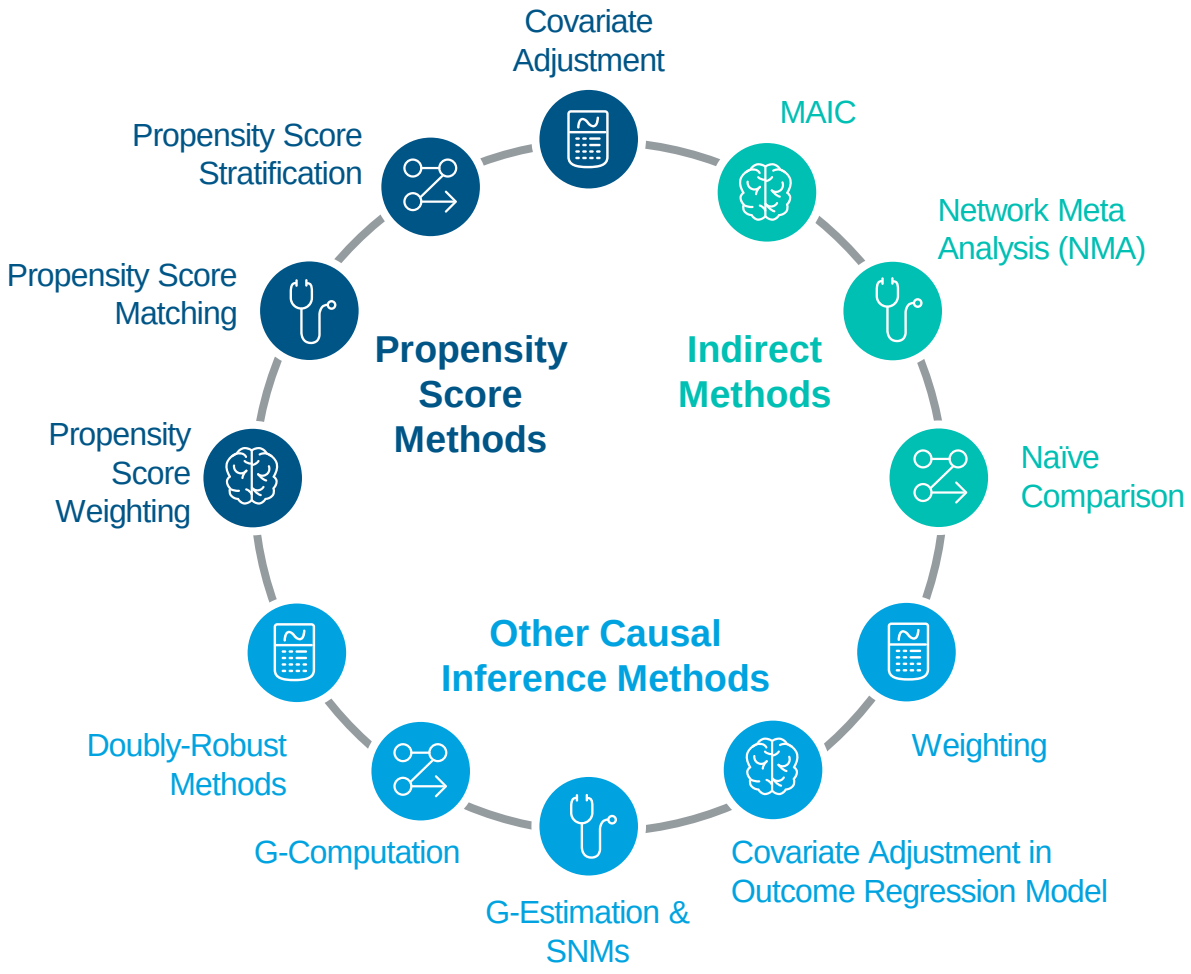
Drive harmonisation of data elements extracted across multiple sites to maximise the analytical potential of multi-site studies.

Appendix

External Comparator design considerations:
Current view of terminology



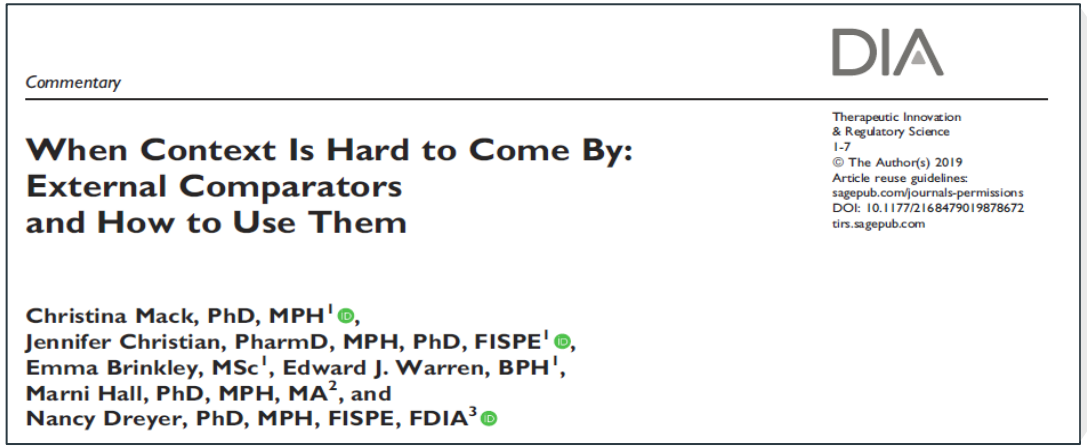
Defining the right analysis for an External Comparator is critical



Recommendations

- The most commonly used methods are Propensity Score Matching and IPTW
- Propensity Score Matching typically requires a larger sample size to fully achieve matching objective
- Direct comparisons are becoming more routinely used in regulator-directed ECs, while indirect comparisons remain common in payer-directed ECs
- Sensitivity analyses are particularly important in this setting

IQVIA, through its knowledge and experience, is at the forefront of shaping External Comparator industry standards



Commentary

DIA

Therapeutic Innovation & Regulatory Science
1-7
© The Author(s) 2019
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/2168479019878672
tirs.sagepub.com

When Context Is Hard to Come By: External Comparators and How to Use Them

Christina Mack, PhD, MPH[1], Jennifer Christian, PharmD, MPH, PhD, FISPE[1], Emma Brinkley, MSc[1], Edward J. Warren, BPH[1], Marni Hall, PhD, MPH, MA[2], and Nancy Dreyer, PhD, MPH, FISPE, FDIA[3]

Presented on External Comparators at methodology workshop at the 2019 MDEpiNet Meeting

Contributing to Industry-Shaping Collaborations:

Medical Device Epidemiology Network

Project Data Sphere

Duke MARGOLIS CENTER for Health Policy

FRIENDS of CANCER RESEARCH

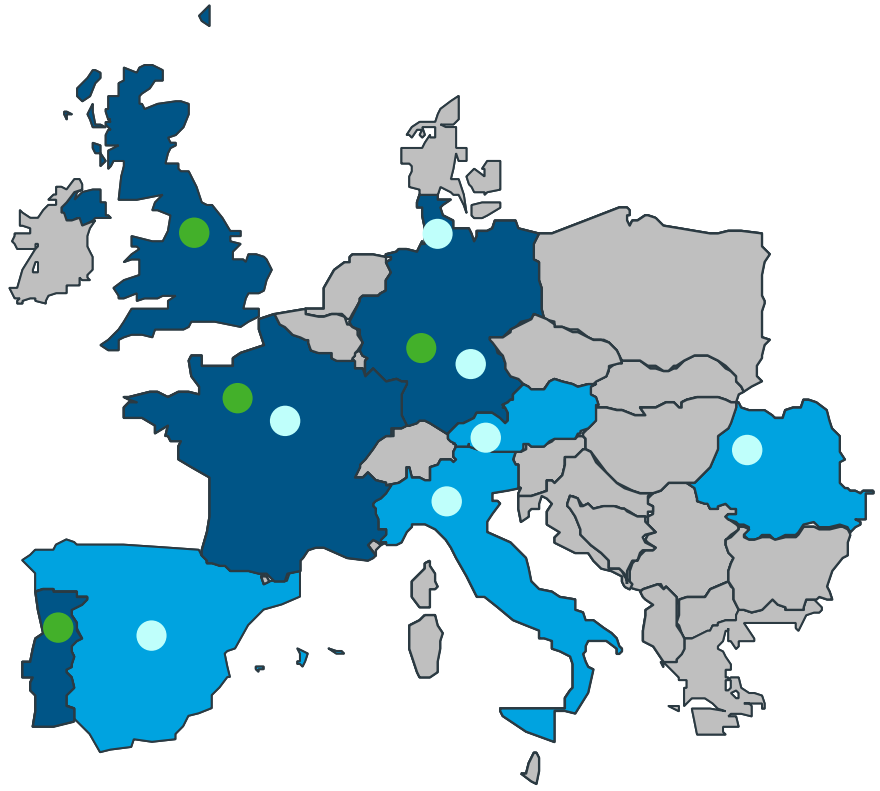
Publications:

"*Advancing a Framework for Regulatory Use of Real-World Evidence: When Real is Reliable*" – Therapeutic Innovation & Regulatory Science

"*When Context is Hard to Come By: External Comparators and How to Use Them*" – Therapeutic Innovation & Regulatory Science

"*An Exploratory Analysis of Real-World End Points for Assessing Outcomes Among Immunotherapy-Treated Patients With Advanced Non-Small-Cell Lung Cancer*" – JCO Clinical Cancer Informatics

IQVIA's Oncology Evidence Network (OEN) is a group of hospitals ready to run real world studies and efficiently evaluate feasibility



- **Core network of four hospital sites** covering ~25,000 treated oncology patients/year
- Each site fully operational with:
  - Master service agreement for quick study initiation
  - Comprehensive research data repositories
  - Staffed on-site teams consisting of oncologists, data scientists, coders
  - Mapped information governance processes
- **+ >10 further specialist pre-contracted sites and registries** adding >20,000 treated patients per year

Benefits for External Comparators:

- ACCESS: 5x + higher protocol acceptance rate
- FASTER: database only designs can deliver in ~6-9 months vs ~12-18 eCRF
- BIGGER: ~4 to 8 times more patients per site per study
- FLEXIBLE: can deliver database to eCRF, or direct database transfer
- SAMPLE READY: can access biobanks/ path stores for drugs with biomarkers