

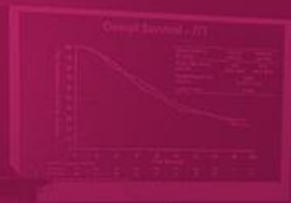
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Instituto Projeto



GERENCIAMENTO
E PRODUÇÃO



Mudança da prática clínica baseado em dados do mundo real: onde estamos?

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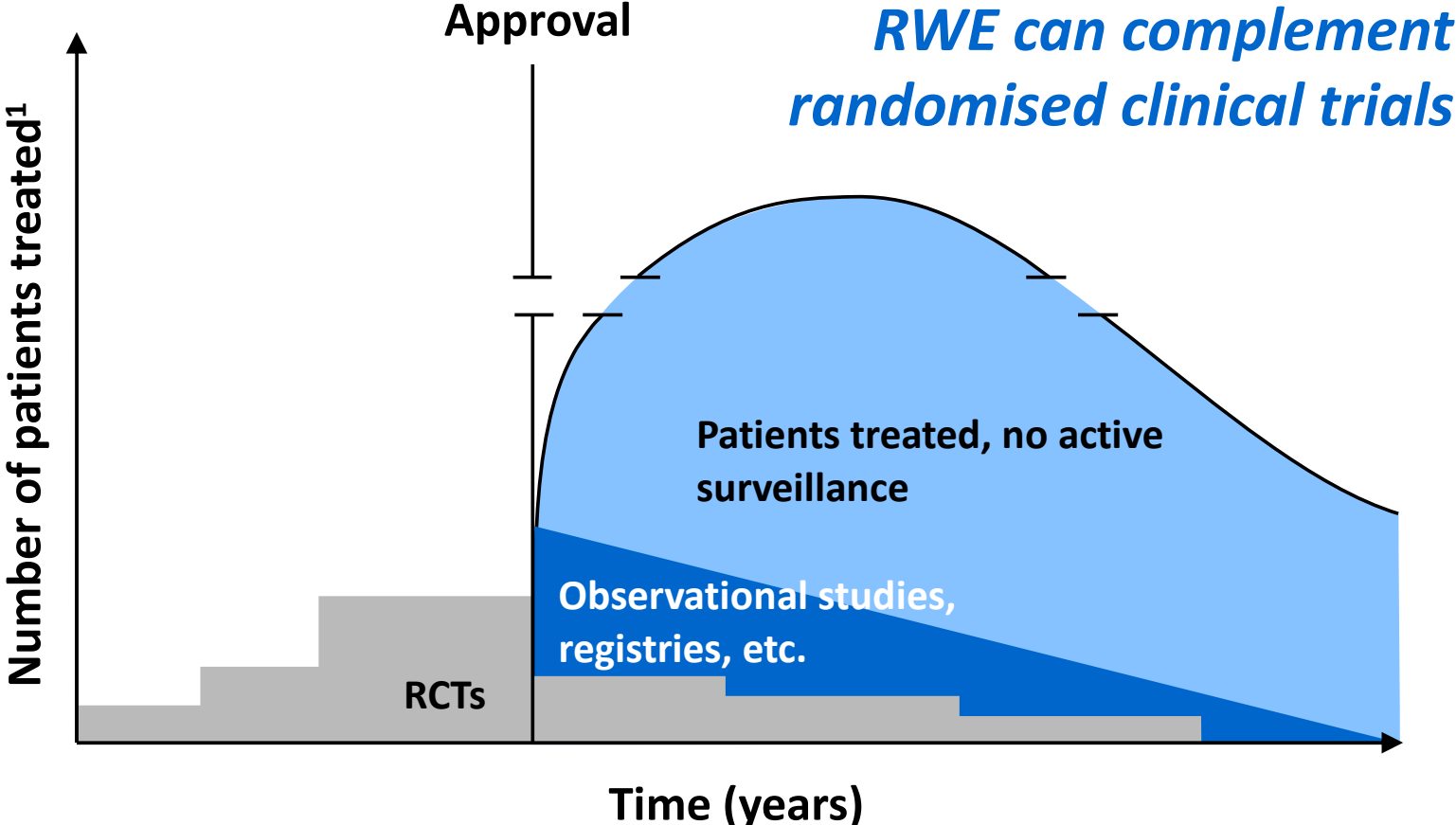
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Conflicts of interest

RD declares advisory role for Roche, Foundation Medicine, received a speaker's fee from Roche, Ipsen, Amgen, Servier, Sanofi, Libbs, Merck Sharp & Dohme, Lilly, AstraZeneca, Janssen, Takeda, Bristol Myers Squibb, GlaxoSmithKline, Gilead, research grants from Merck, Novartis, Daiichi-Sankyo, GlaxoSmithKline and AstraZeneca, and is investor in Trialing Health, S.L.

Definitions



RCTs: randomised clinical trials

Real World Data

Clinical trial



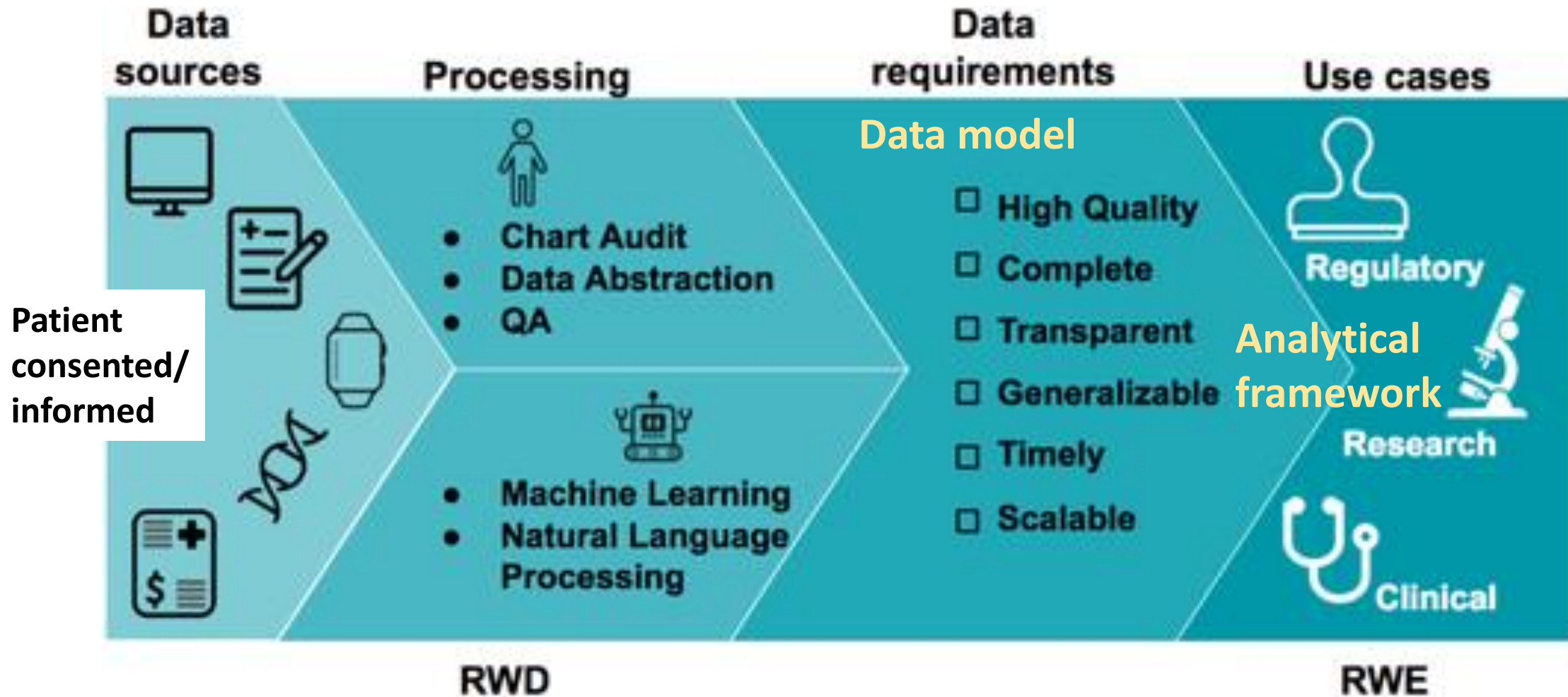
Perfect data → Imperfect patient

Real world data

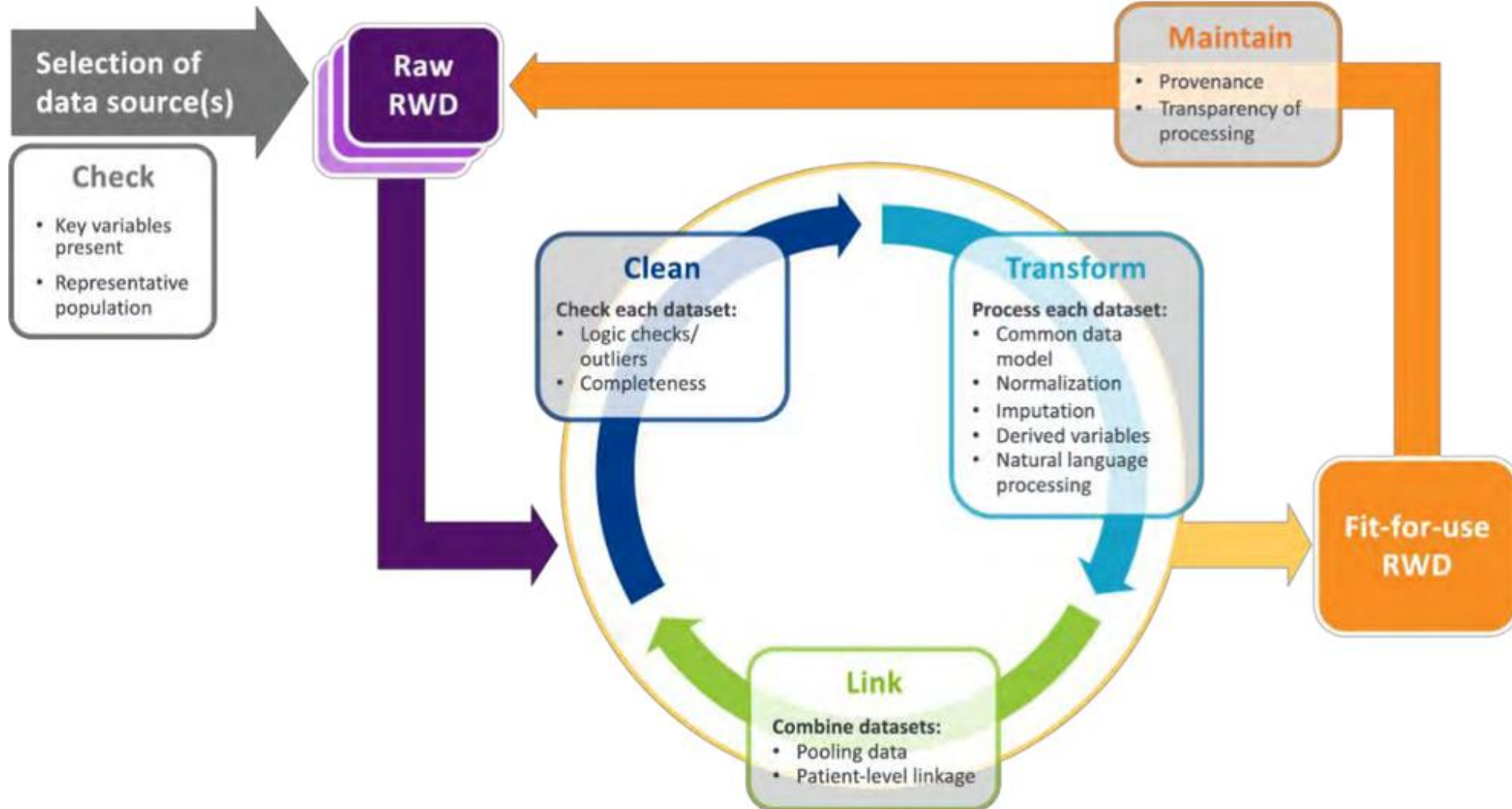
Gaps between evidence and practice

Imperfect data → Perfect patient

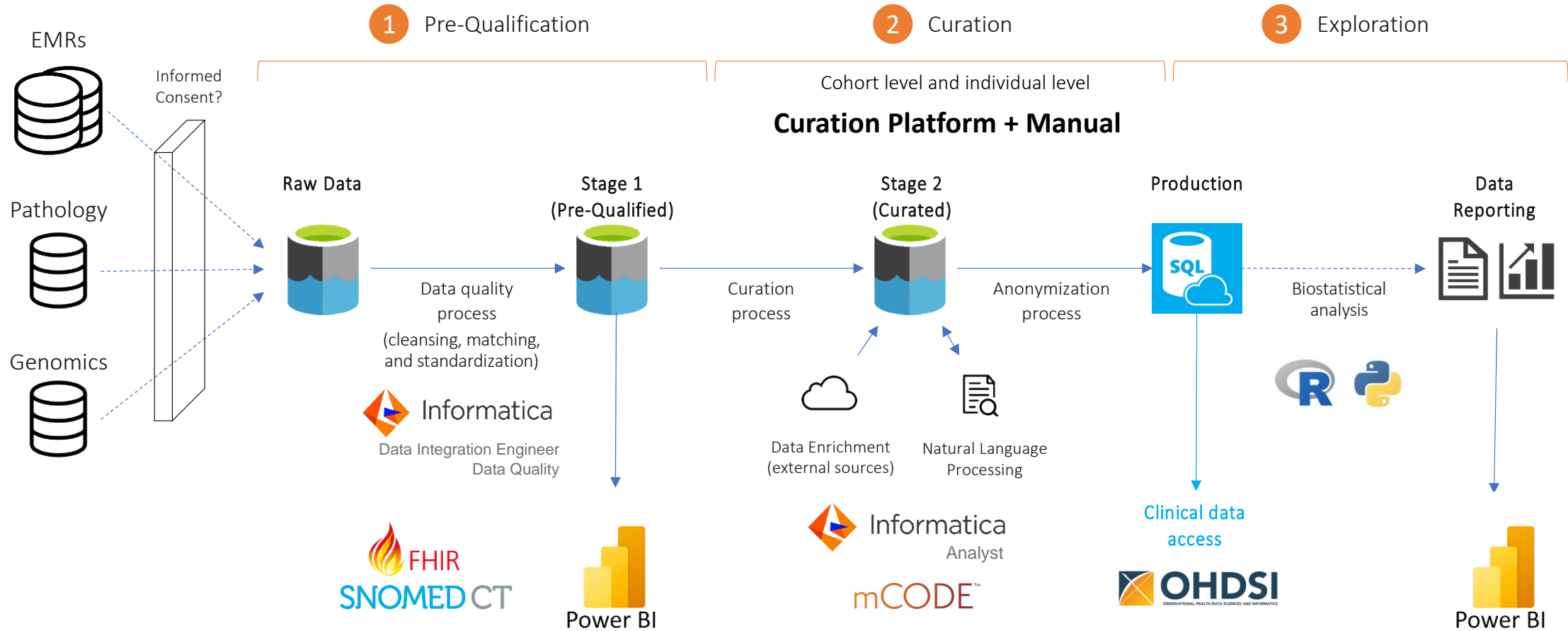
Scale-up the journey from RWD to RWE



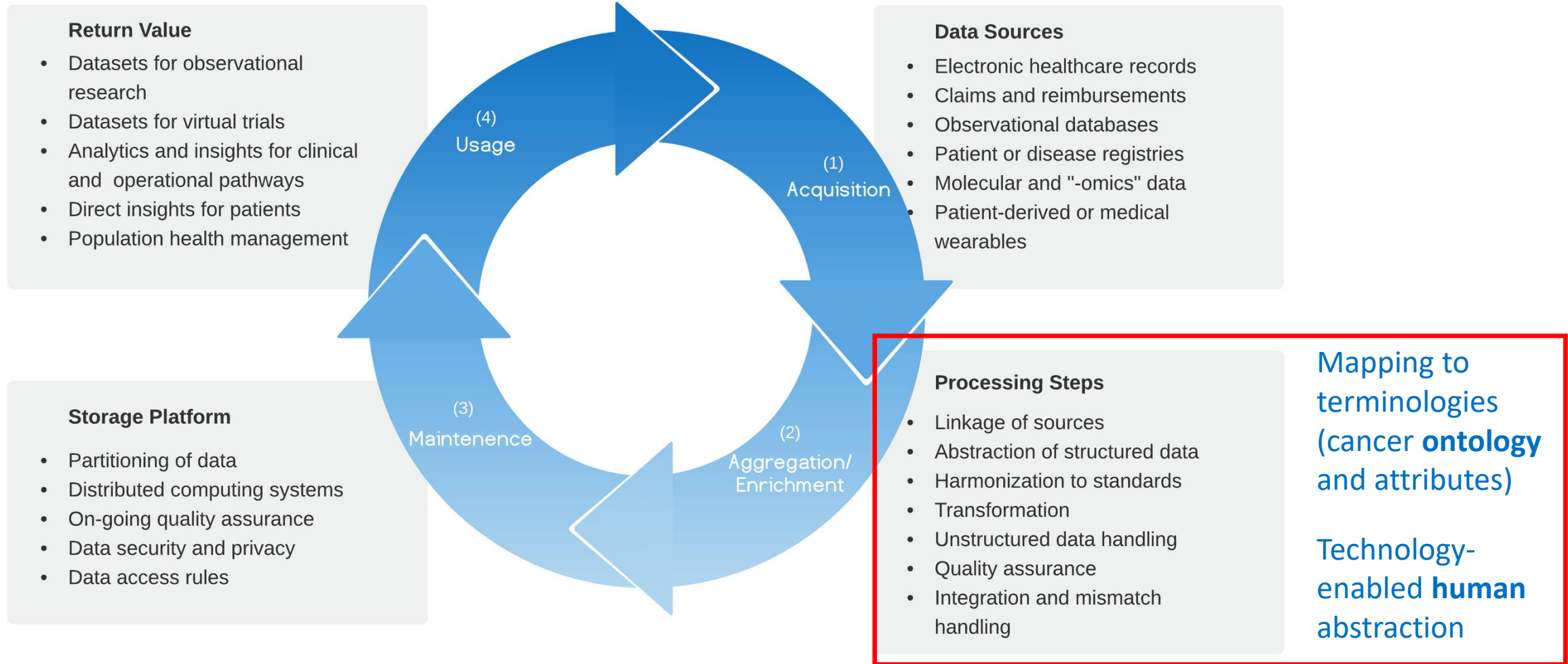
Fit-for-purpose RWD generation scheme



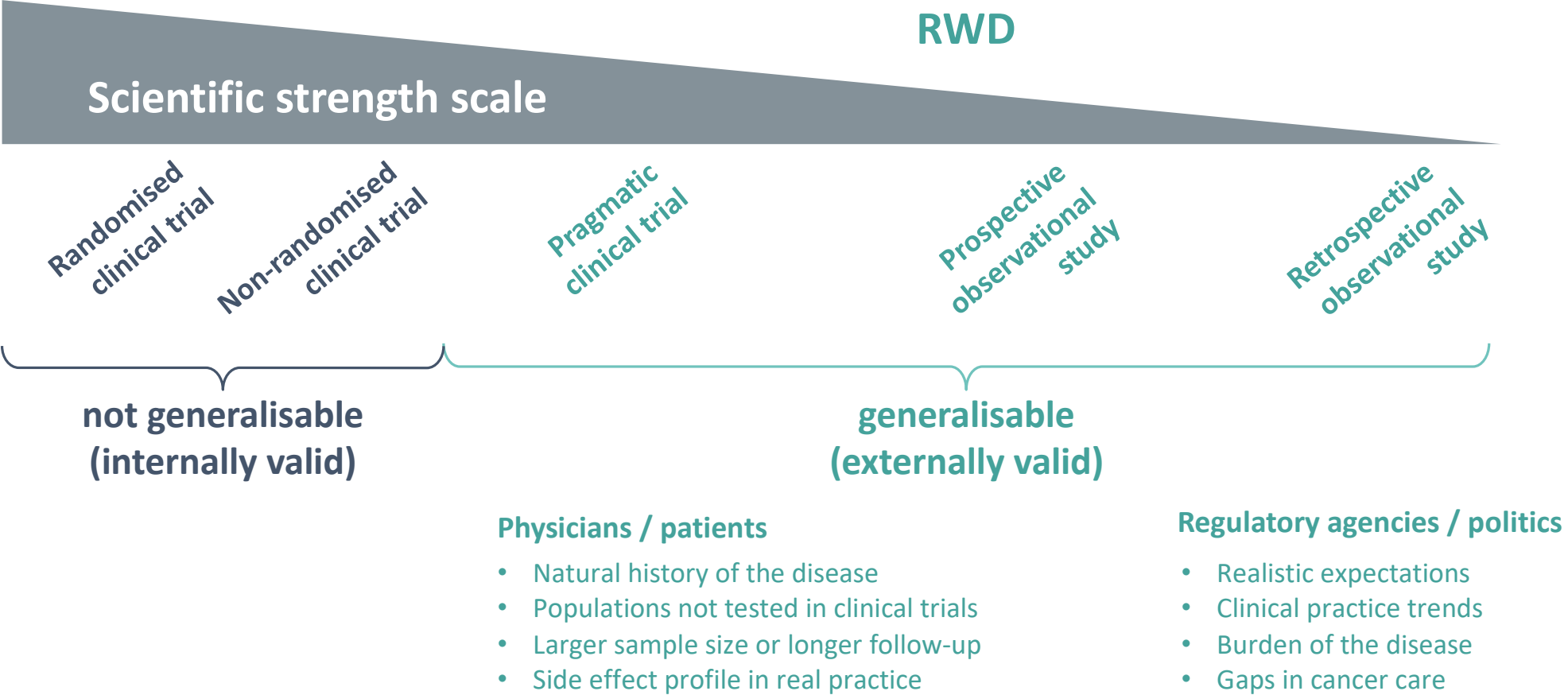
RWD generation scheme at Oncoclínicas



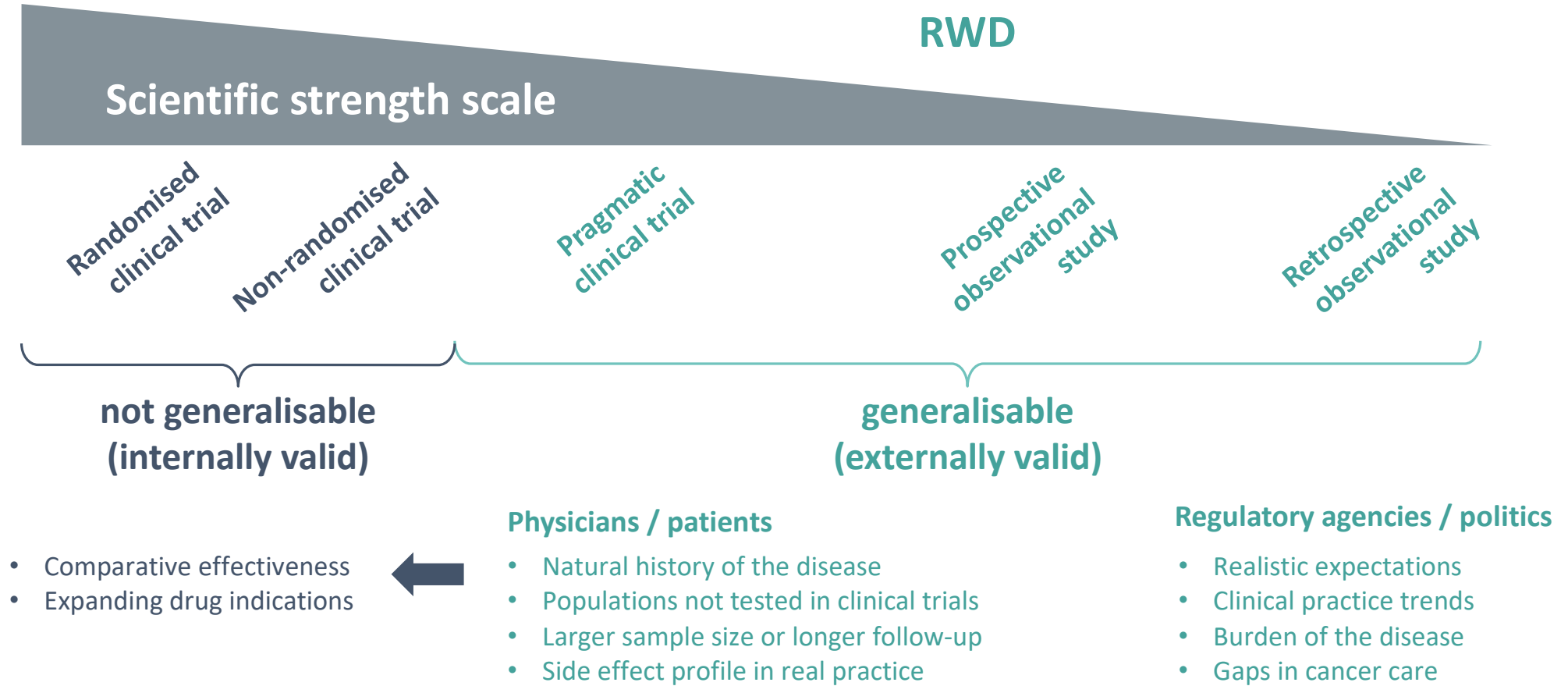
RWD/RWE generation process



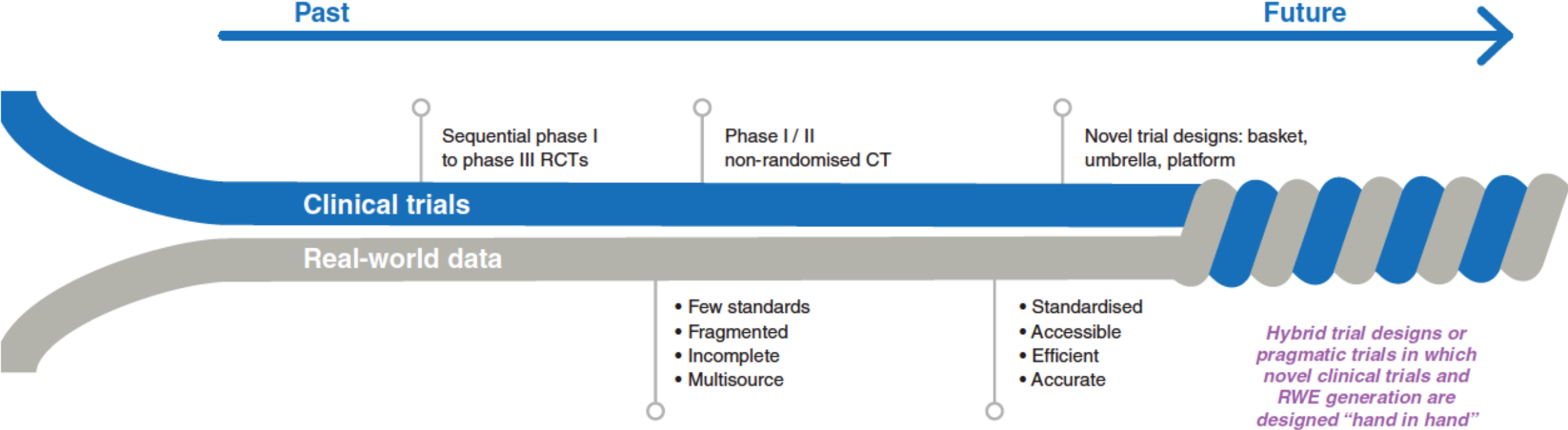
RWD versus Clinical Trials to generate evidence



RWD versus Clinical Trials to generate evidence

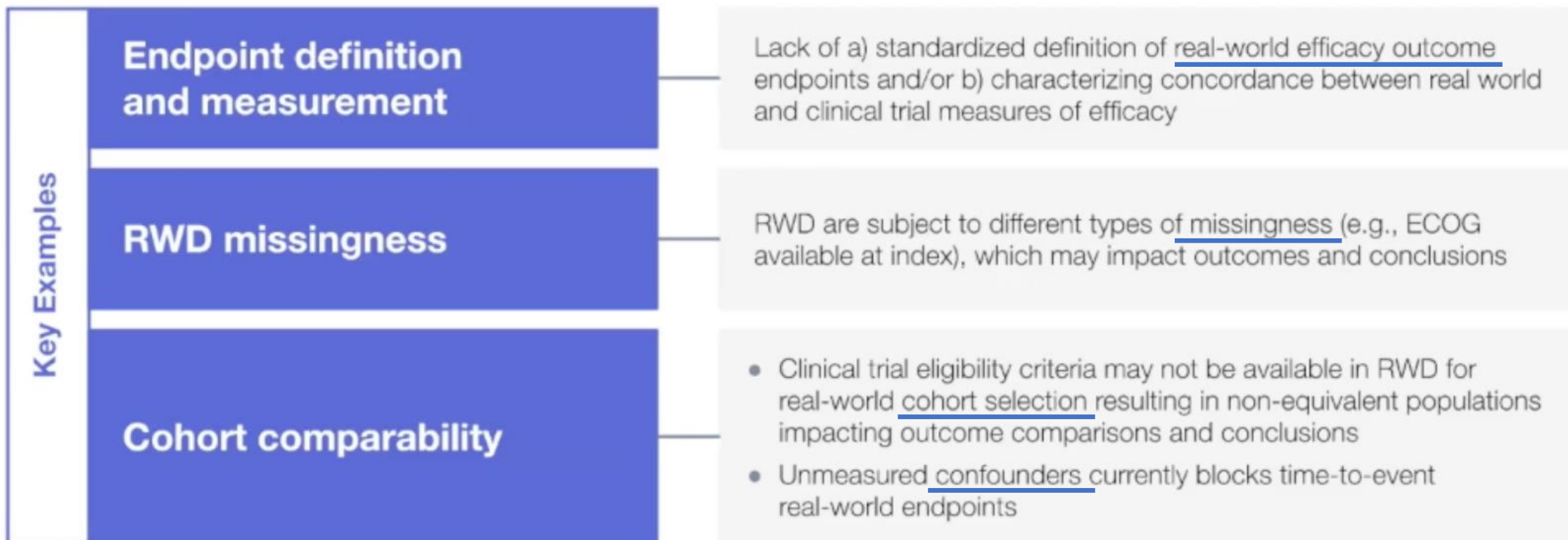


Hybrid model of RWD and Clinical Trials



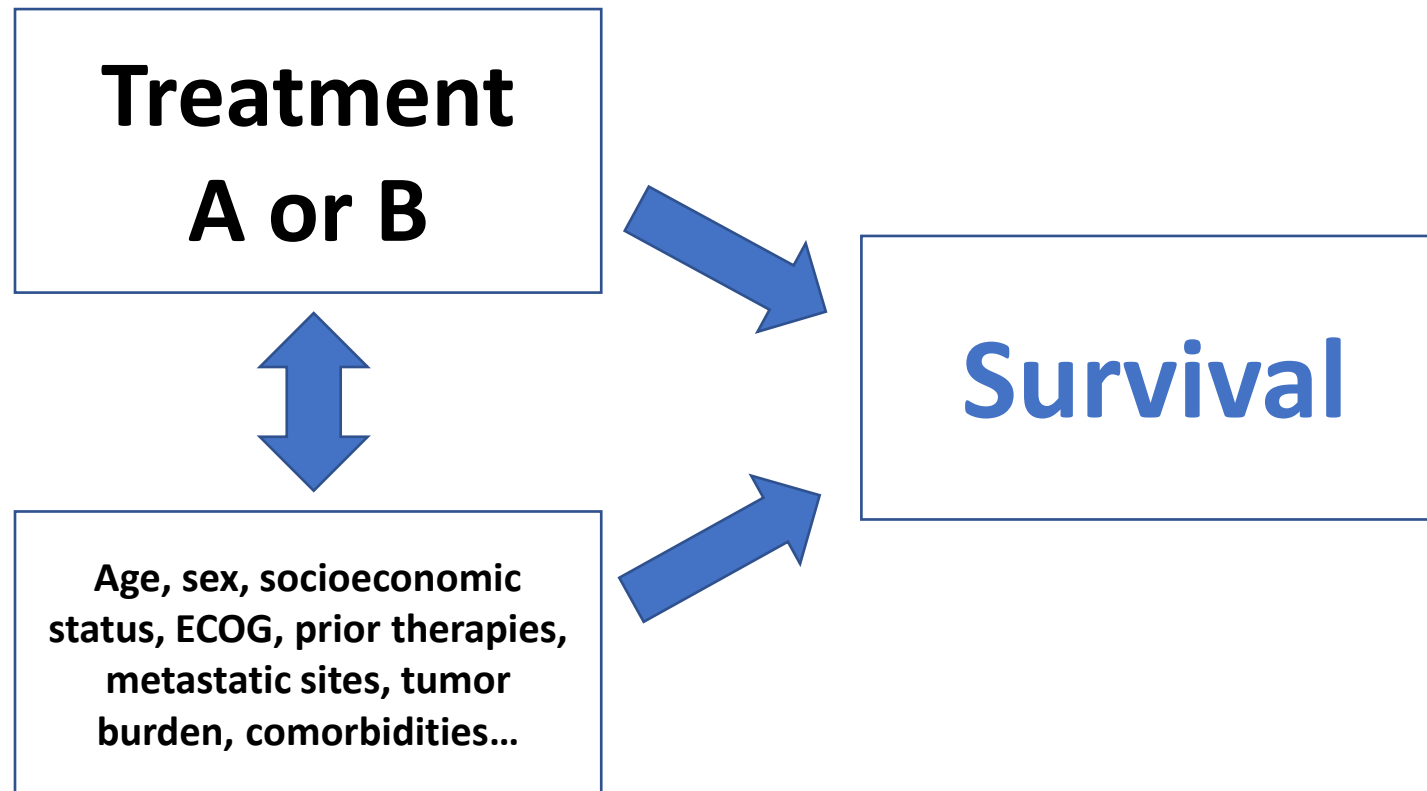
Common limitations of RWD/RWE

Shortage of best practices when extracting, harmonizing and analyzing data

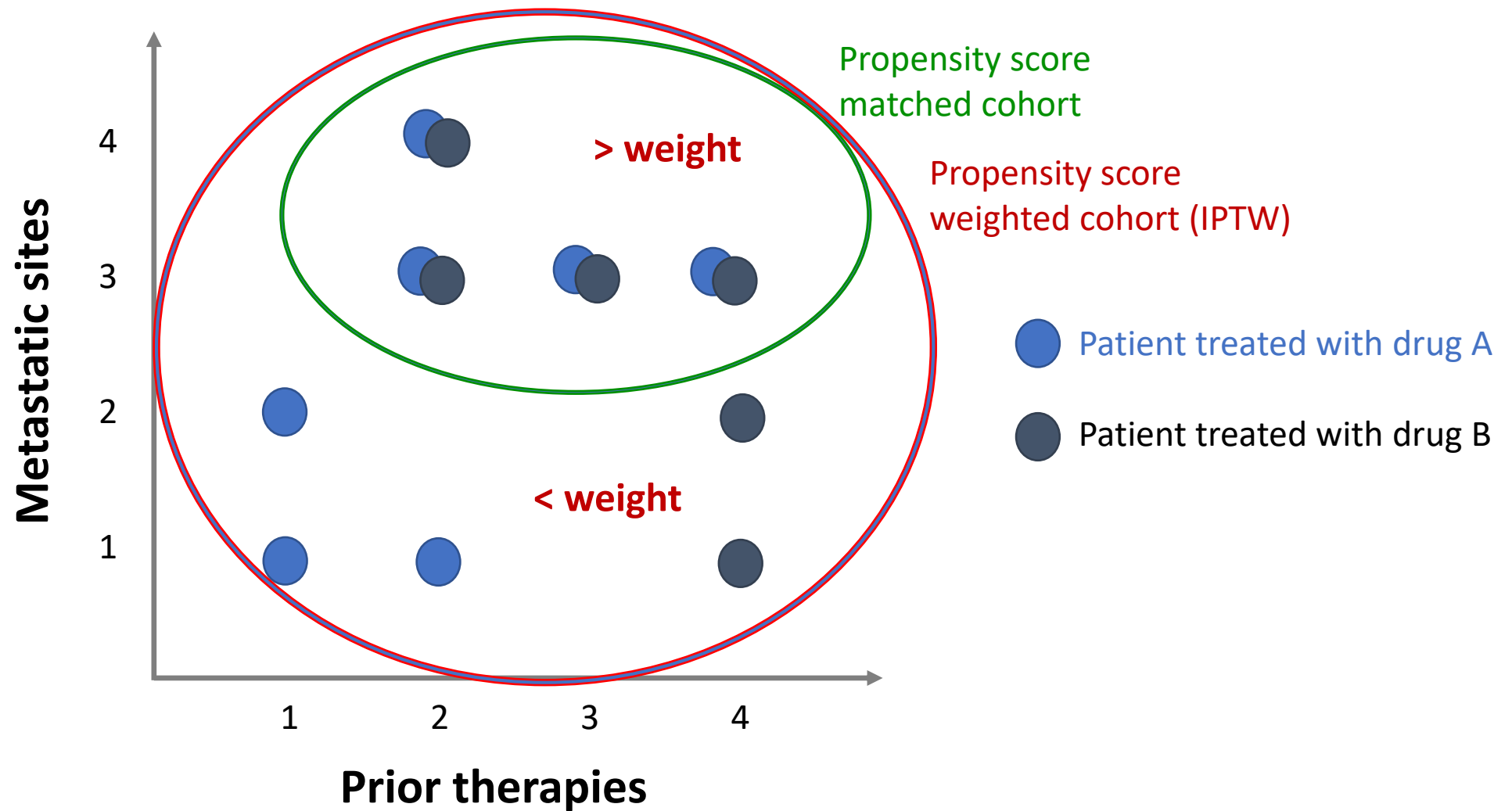


Confounding by indication

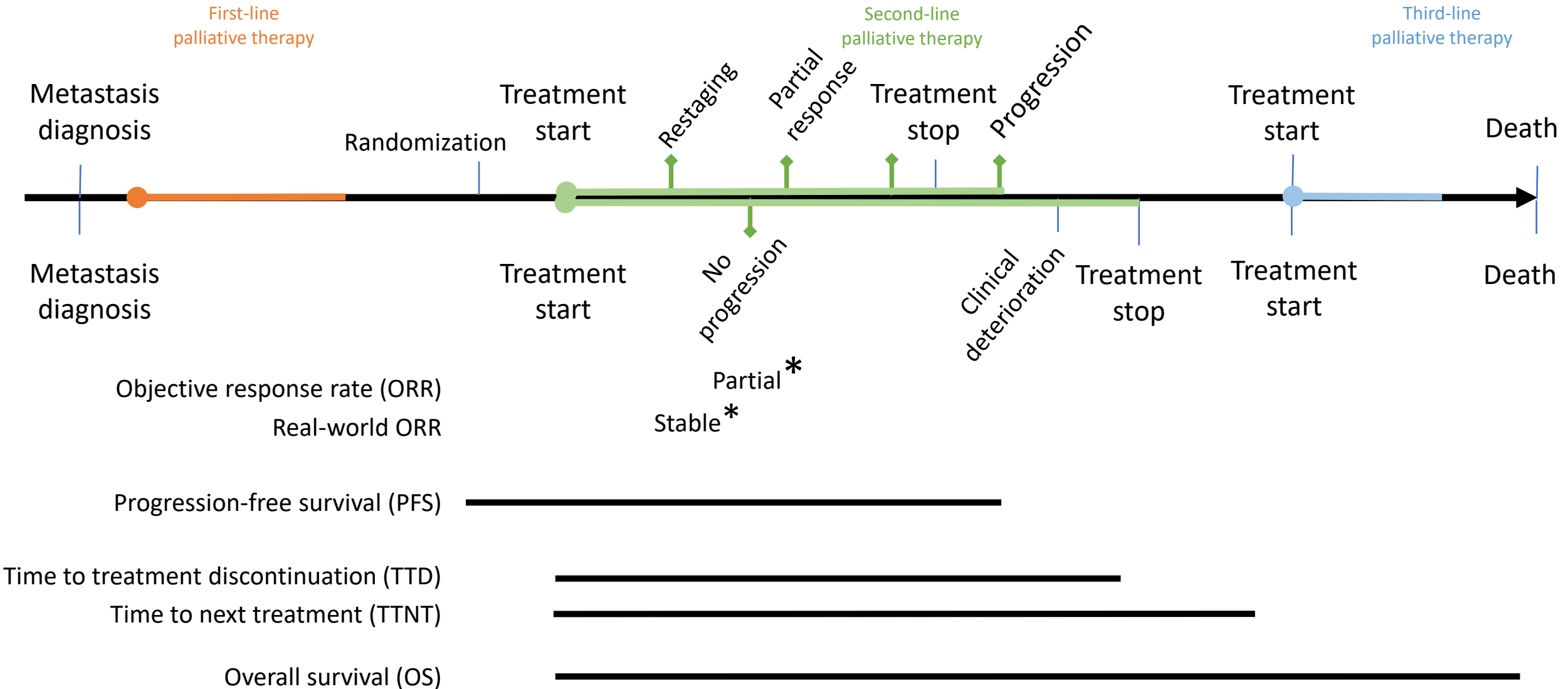
Outcome depends not only on intervention but also on reasons for the indication (physician choice).



Propensity score (PS)

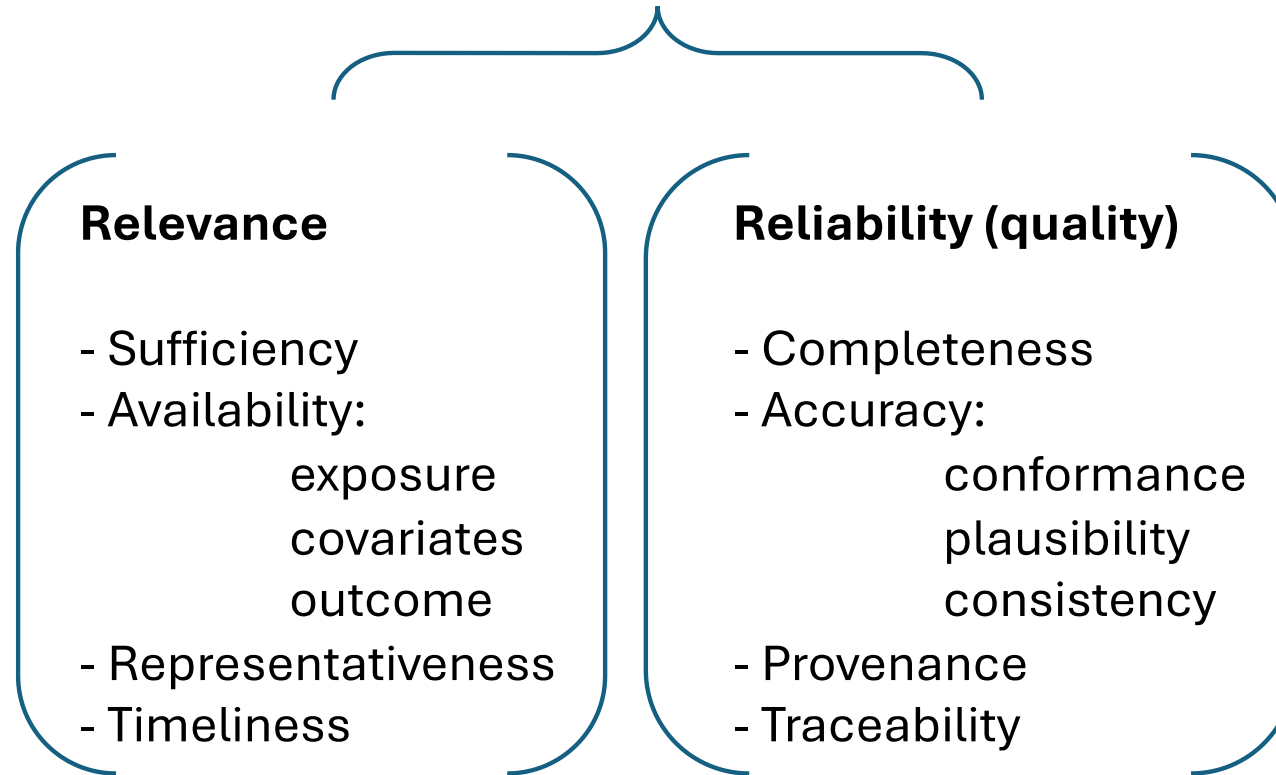


Endpoints in Clinical Trials and RWD studies



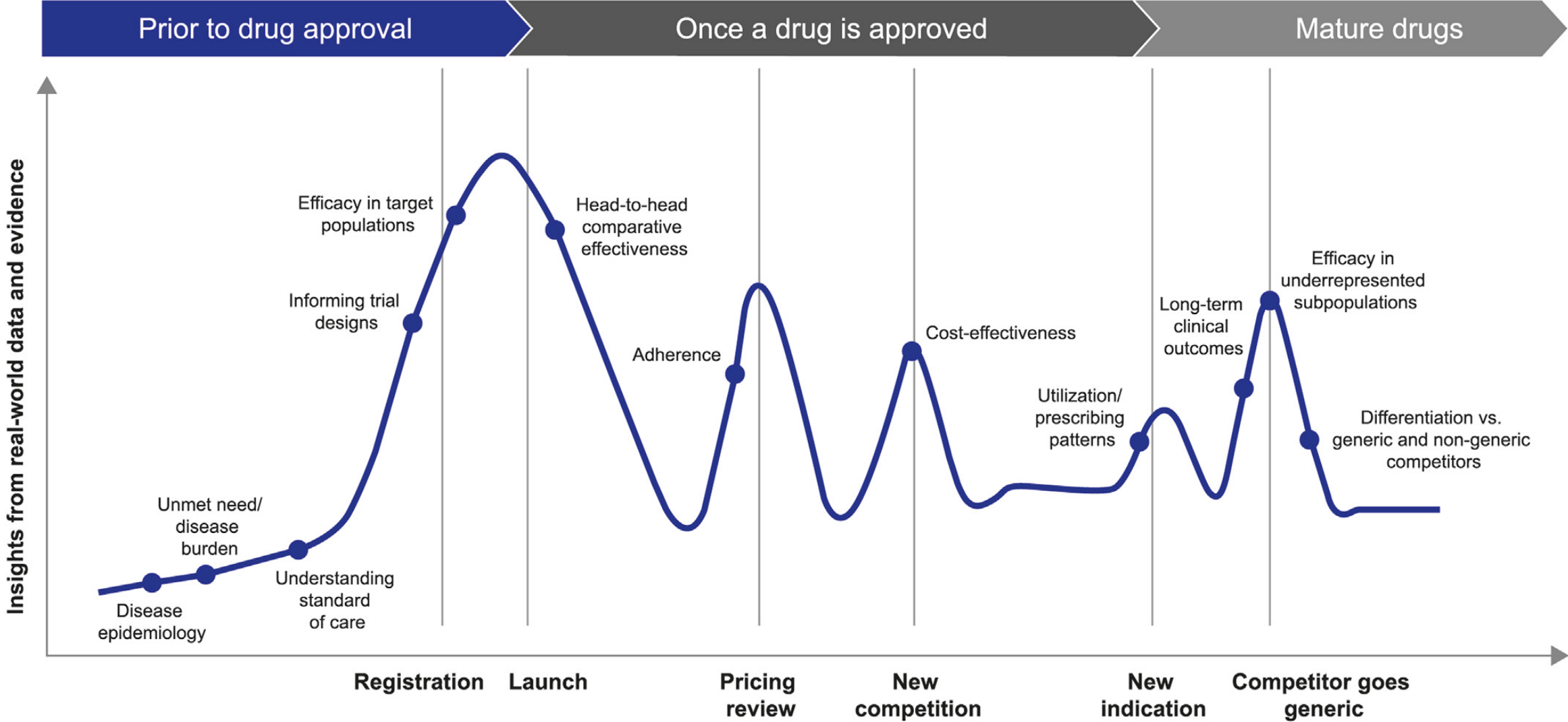
Framework for relevance and reliability of RWD

Fit-for-use RWD?



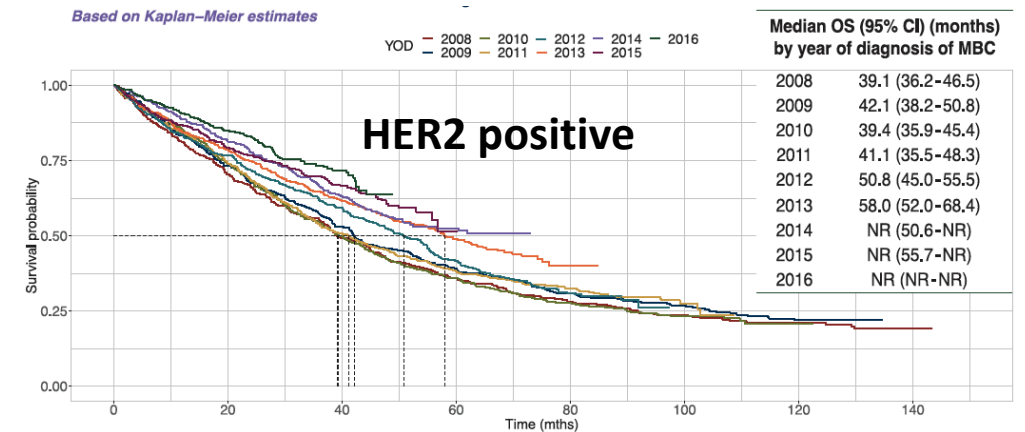
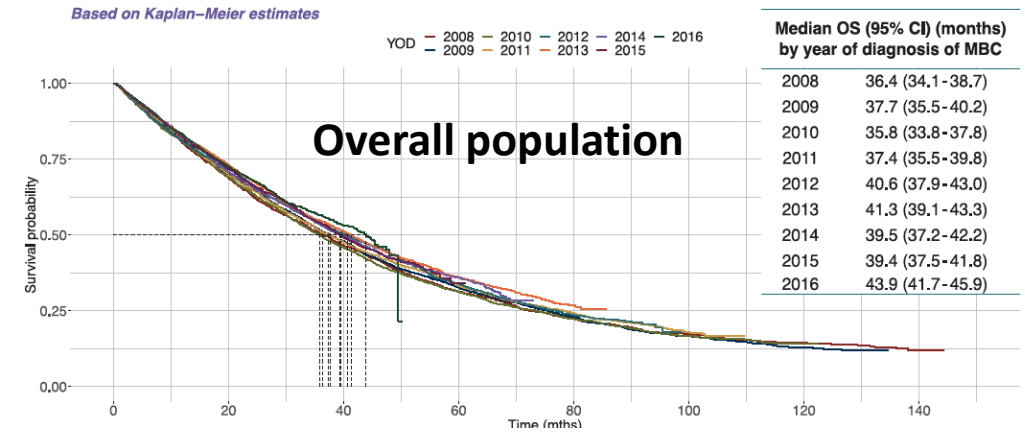
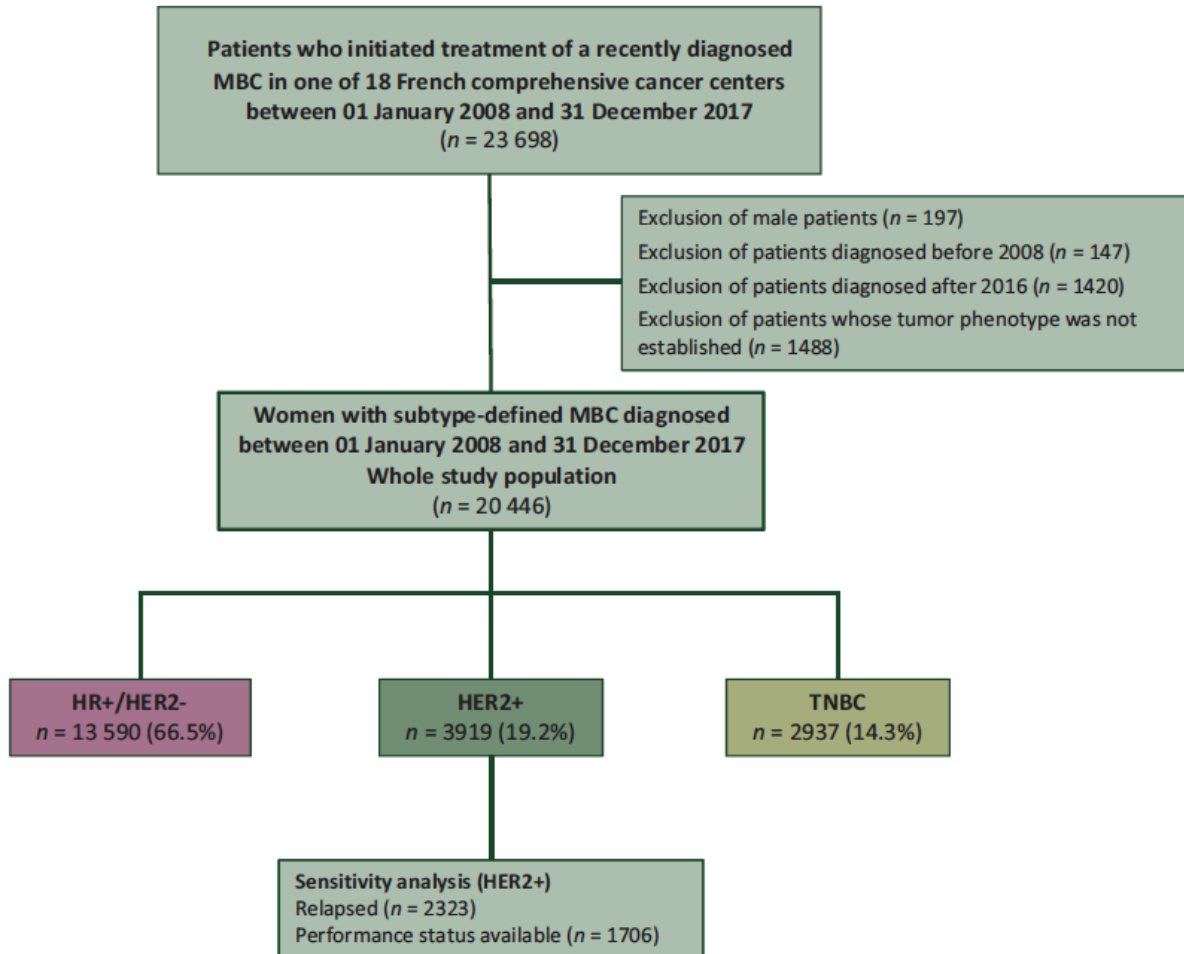
Transparency in methods (collection, curation, transformation) and limitations.

RWD use cases in the drug life cycle



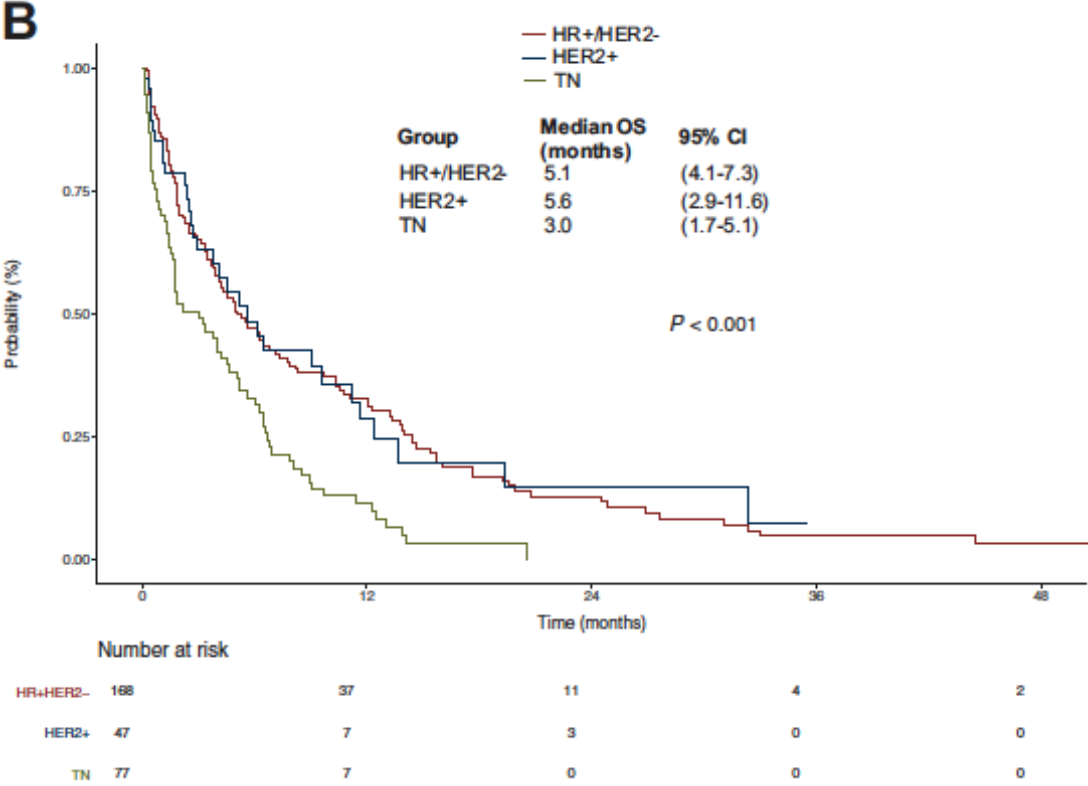
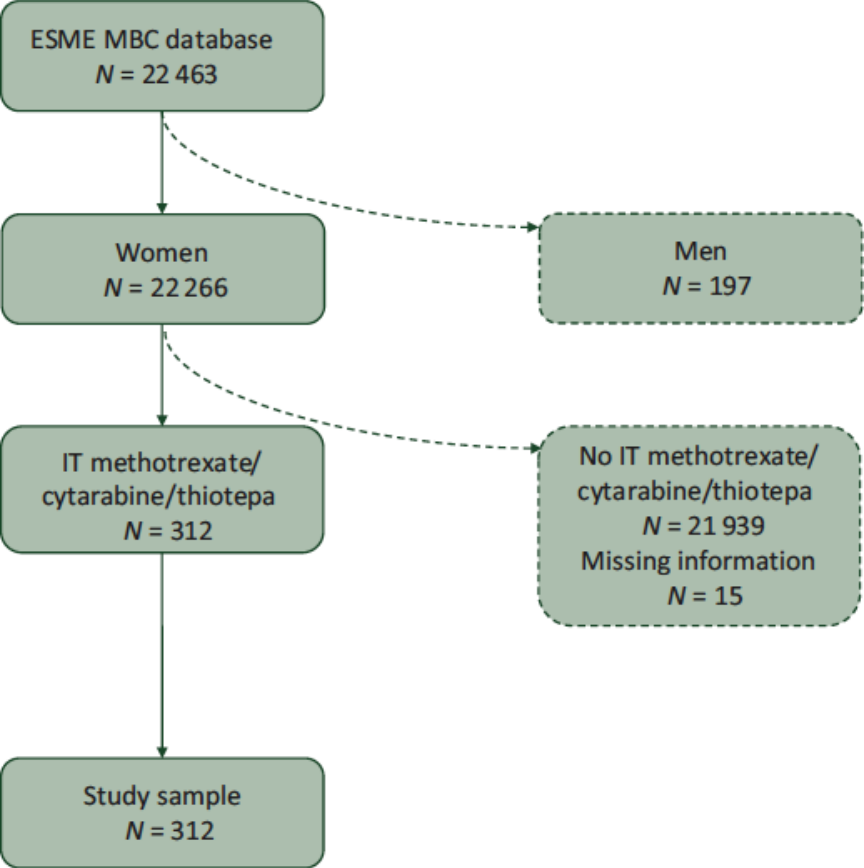
Use cases: impact of access to therapies

ESME French Metastatic Breast Cancer cohort



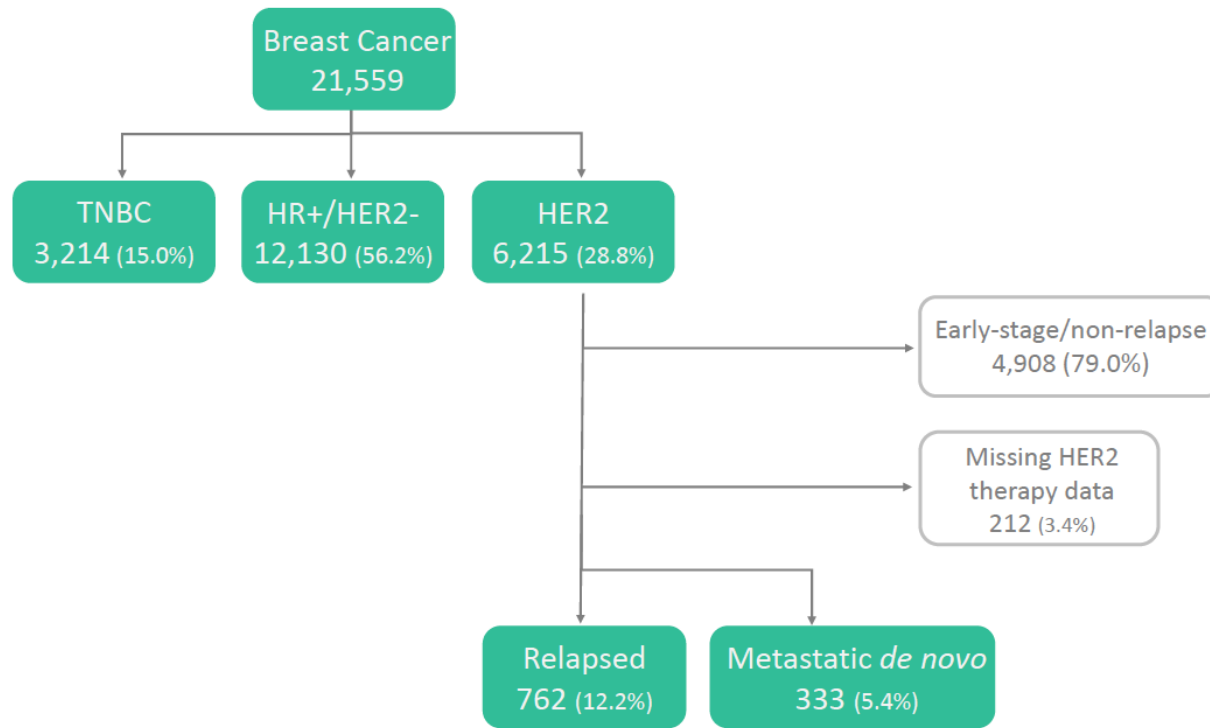
Use cases: natural history rare population/ unmet need

Intrathecal therapy for leptomeningeal metastasis



Use cases: treatment patterns/ sequence of therapies

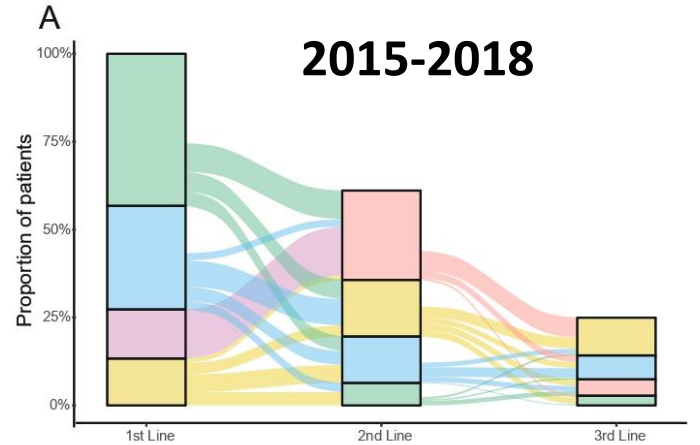
anti-HER2 therapies in HER2+ metastatic breast cancer



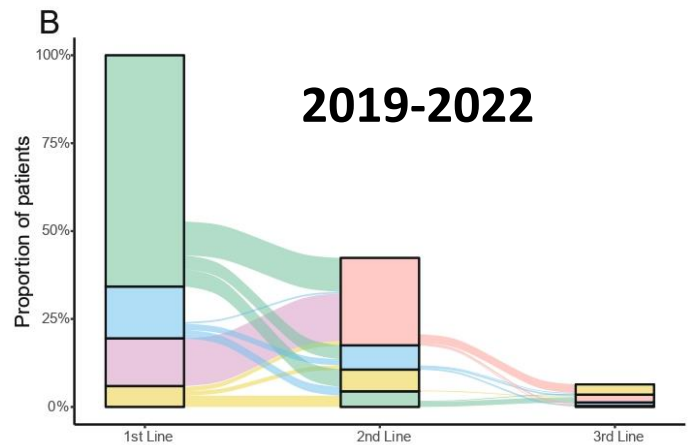
Patients Characteristics	N (%)
Gender	
Female	1,085 (99.1)
Male	10 (0.9)
Age (years)	
Median	58
Range	27-99
Elderly (≥ 65)	326 (29.7)
Brazilian region	
Southeast	729 (66.6)
Northeast	287 (26.2)
Other	79 (7.2)
Exposure to metastatic treatment lines	
1 st Line	1,095 (100)
2 nd Line	593 (54.2)
3 rd Line	198 (18.1)
Prior (neo)adjuvant therapies	
Trastuzumab	664 (87.1)
Pertuzumab + Trastuzumab	98 (12.9)
Therapies in metastatic setting	
Pertuzumab + Trastuzumab	647 (59.1)
Trastuzumab + Chemotherapy	374 (34.2)
T-DM1	318 (29.0)
Other	284 (25.9)

Use cases: treatment patterns/ sequence of therapies

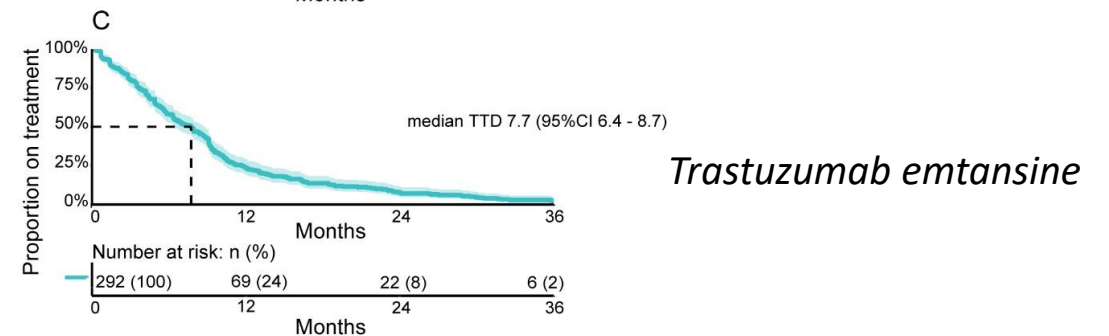
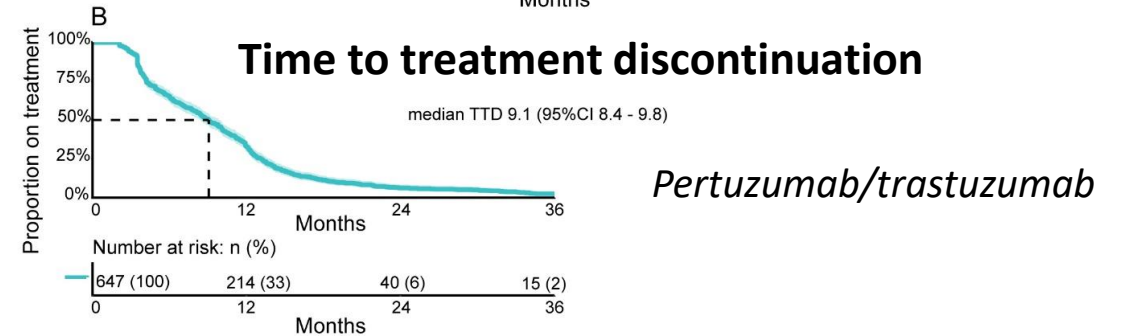
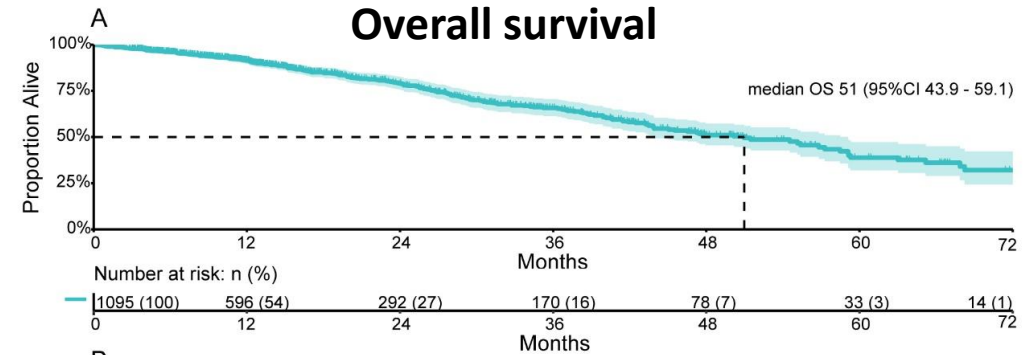
anti-HER2 therapies in HER2+ metastatic breast cancer



Protocol ■ Pertuzumab & Trastuzumab ■ Trastuzumab & Chemo ■ T-DM1 ■ Others ■ Missing



Protocol ■ Pertuzumab & Trastuzumab ■ Trastuzumab & Chemo ■ T-DM1 ■ Others ■ Missing

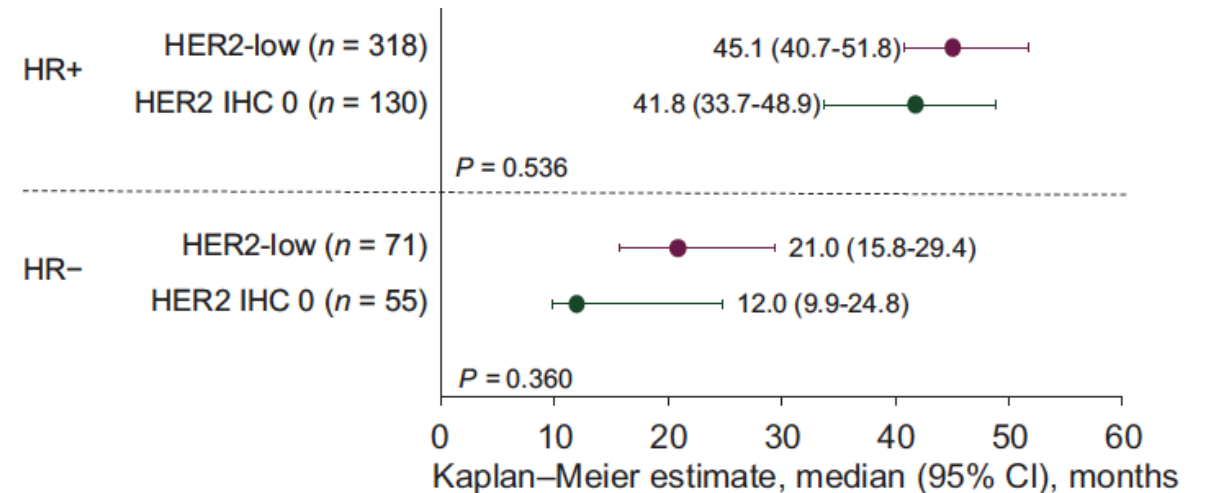


Use cases: biomarker validation and prognosis

HER2 low status (comparison of 4B5 and non-4B5 antibodies and real-world outcomes)

	Agreement on HER2-low (positive percent agreement ^a), <i>n/N</i> (%)
All	446/510 (87.5)
Assay	
Ventana 4B5	318/352 (90.3)
Non-Ventana 4B5 ^c	121/150 (80.7)

Overall survival metastatic setting

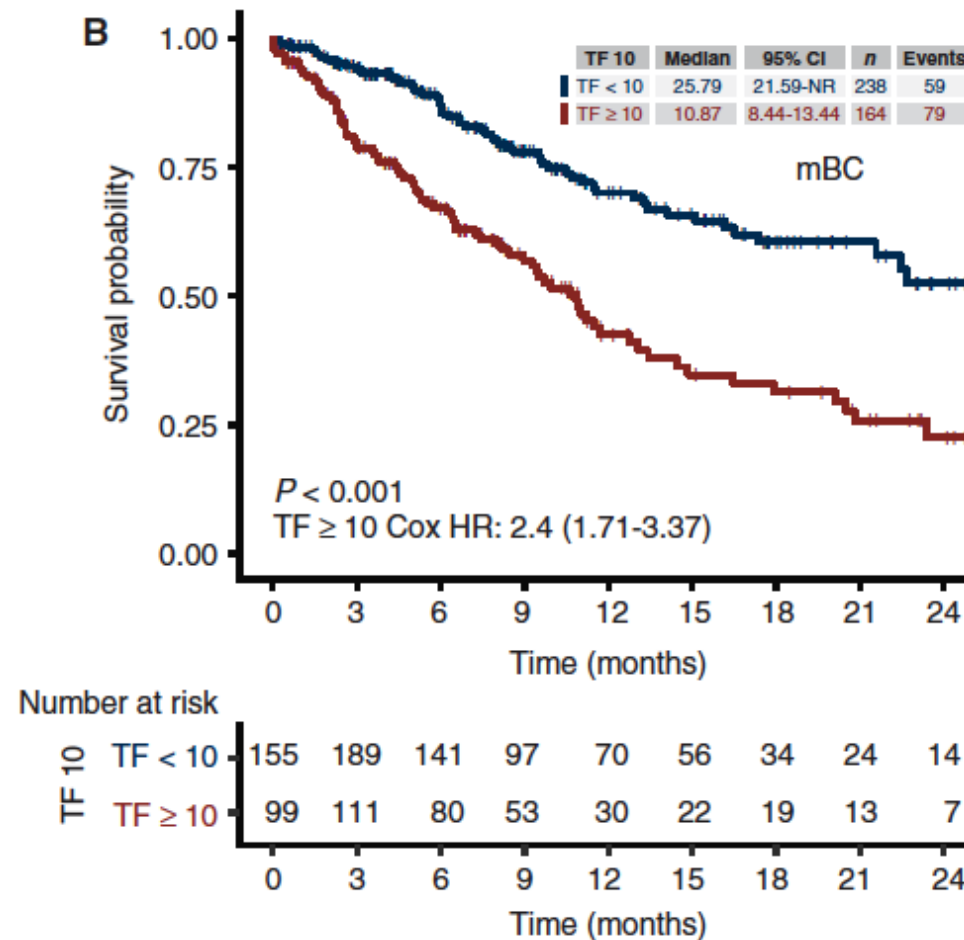


30% of cases HER2 0 (non-4B5) shifted to HER2-low (4B5)

Use cases: biomarker discovery (clinico-genomics)

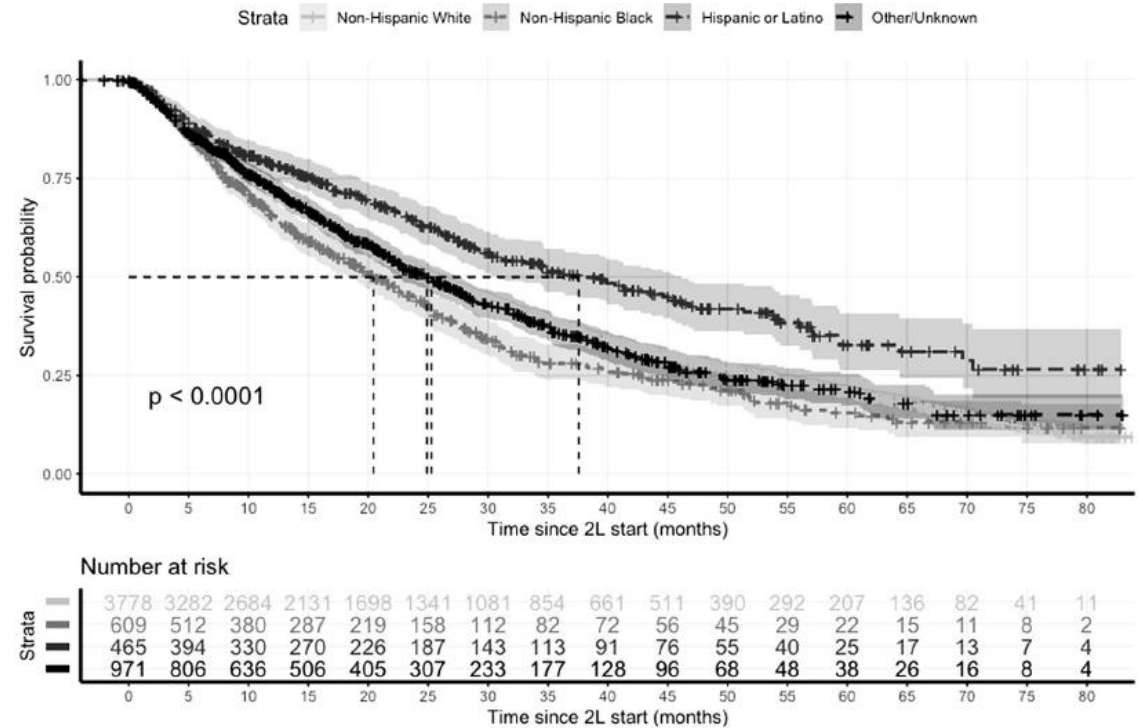
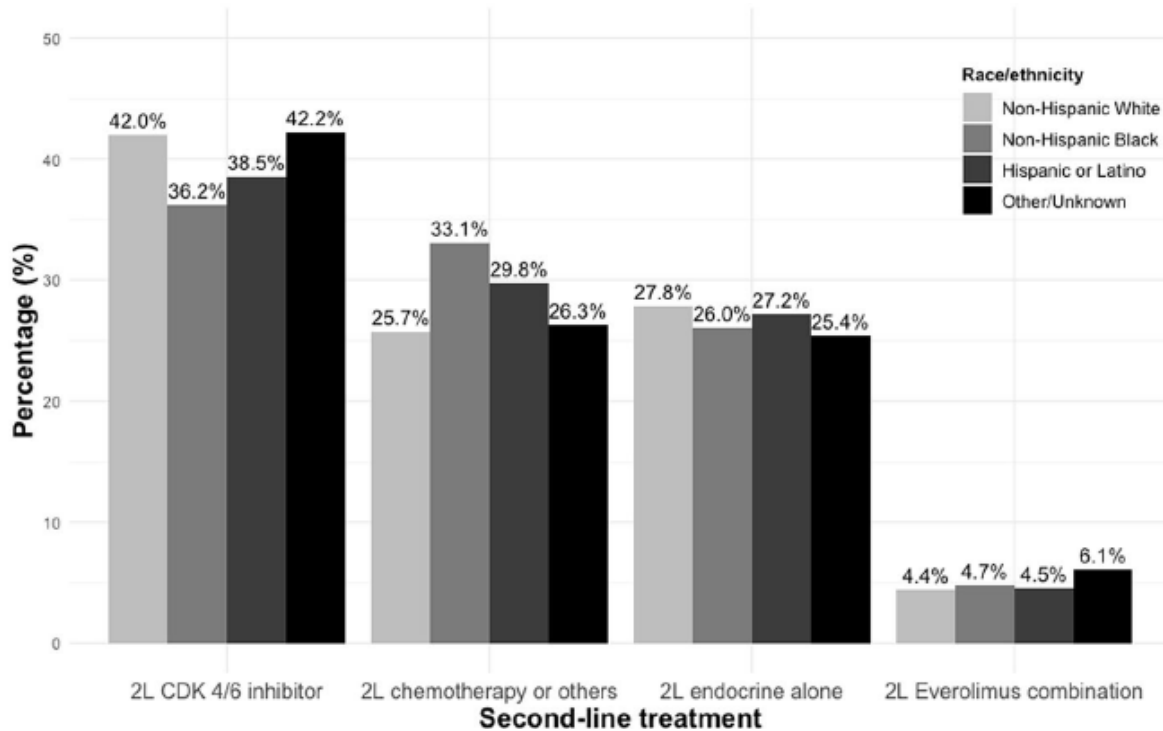
Liquid biopsy ctDNA burden (Tumor Fraction) in Flatiron-Foundation Medicine database

Tumor Fraction (TF):
surrogate of disease burden/
independent prognostic factor



Use cases: inequities in cancer care

Treatment patterns and outcomes in 2L HR+/HER2- metastatic breast cancer according to race/ethnicity



Use cases: comparative effectiveness (RWD vs. RWD)

Breast cancer outcomes with Palbociclib combined with AI versus AI (P-Reality-X)

Table 1. Patient demographic characteristics.

Characteristic	Unadjusted cohort			Cohort after stabilized inverse probability treatment weighting		
	Palbociclib + aromatase inhibitor (n = 1324)	Aromatase alone (n = 1564)	Standardized difference	Palbociclib + aromatase (n = 1572)	Aromatase alone (n = 1137)	Standardized difference
Age, y						
Mean (SD)	67.1 (9.6)	70.9 (9.7)	-0.3949	69.4 (10.8)	69.5 (8.2)	-0.0161
Median (inter-quartile range)	67 (61-74)	72 (64-80)		70 (63-78)	70 (63-79)	
Insurance, n (%)						
Commercial health plan plus any other	388 (29.3)	507 (32.4)	-0.0674	474 (30.2)	353 (31.0)	-0.0182
Commercial health plan	332 (25.1)	325 (20.8)	0.1023	372 (23.7)	251 (22.1)	0.0375

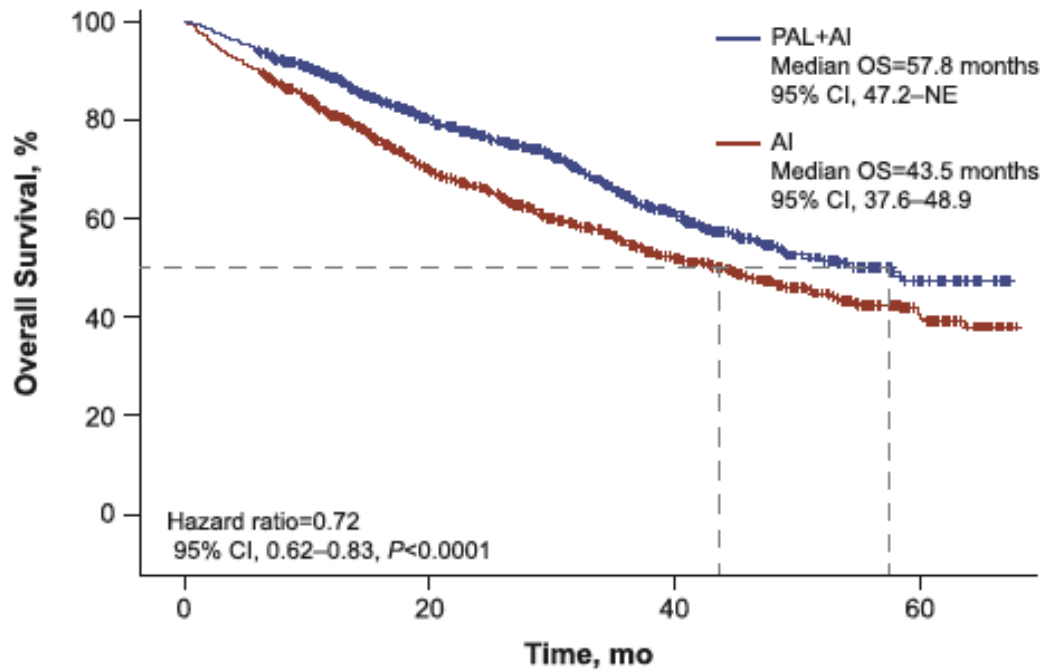
Use cases: comparative effectiveness (RWD vs. RWD)

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Eastern Cooperative Oncology Group performance status, n (%)						
0	499 (37.7)	397 (25.4)	0.2672	472 (30.1)	348 (30.6)	-0.0126
1	318 (24.0)	334 (21.4)	0.0636	362 (23.0)	259 (22.8)	0.0066
2, 3, or 4	153 (11.6)	271 (17.3)	-0.1647	251 (15.9)	169 (14.9)	0.0290
Not documented	354 (26.7)	562 (35.9)	-0.1992	487 (31.0)	361 (31.7)	-0.0160
Visceral disease, n (%)						
Visceral disease, n (%)	444 (33.5)	404 (25.8)	-0.1692	460 (29.3)	337 (29.7)	0.0085
Bone-only disease, n (%)						
Bone-only disease, n (%)	519 (39.2)	599 (38.3)	-0.0185	589 (37.5)	440 (38.7)	0.0253
Brain metastases, n (%)						
Brain metastases, n (%)	26 (2.0)	50 (3.2)	0.0778	26 (1.7)	43 (3.8)	0.1310
Interval from initial breast cancer diagnosis to metastatic breast cancer diagnosis, n (%), y						
De novo	541 (40.9)	464 (29.7)	0.2359	530 (33.7)	390 (34.3)	-0.0110
≤1	40 (3.0)	66 (4.2)	-0.0642	74 (4.7)	43 (3.8)	0.0442

Use cases: comparative effectiveness (RWD vs. RWD)

Breast cancer outcomes with Palbociclib combined with AI versus AI (P-Reality-X)

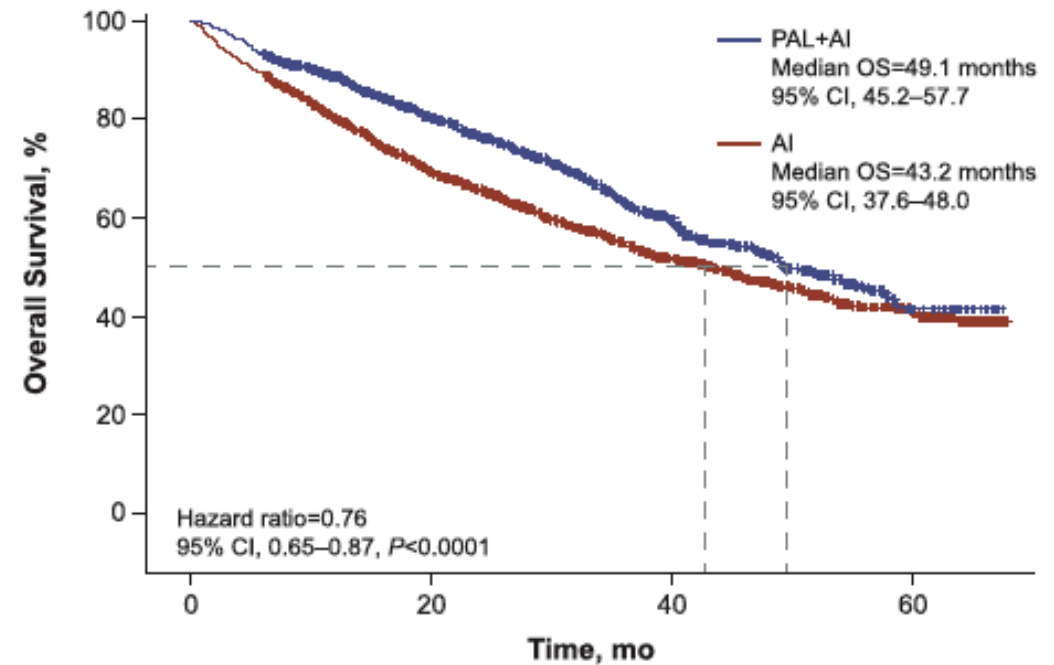
Propensity score matching



Patients at risk, n:

PAL+AI	939	884	731	579	450	349	261	184	122	76	40	11
AI	939	846	711	585	485	394	326	262	186	117	62	18

Inverse probability treatment weighting

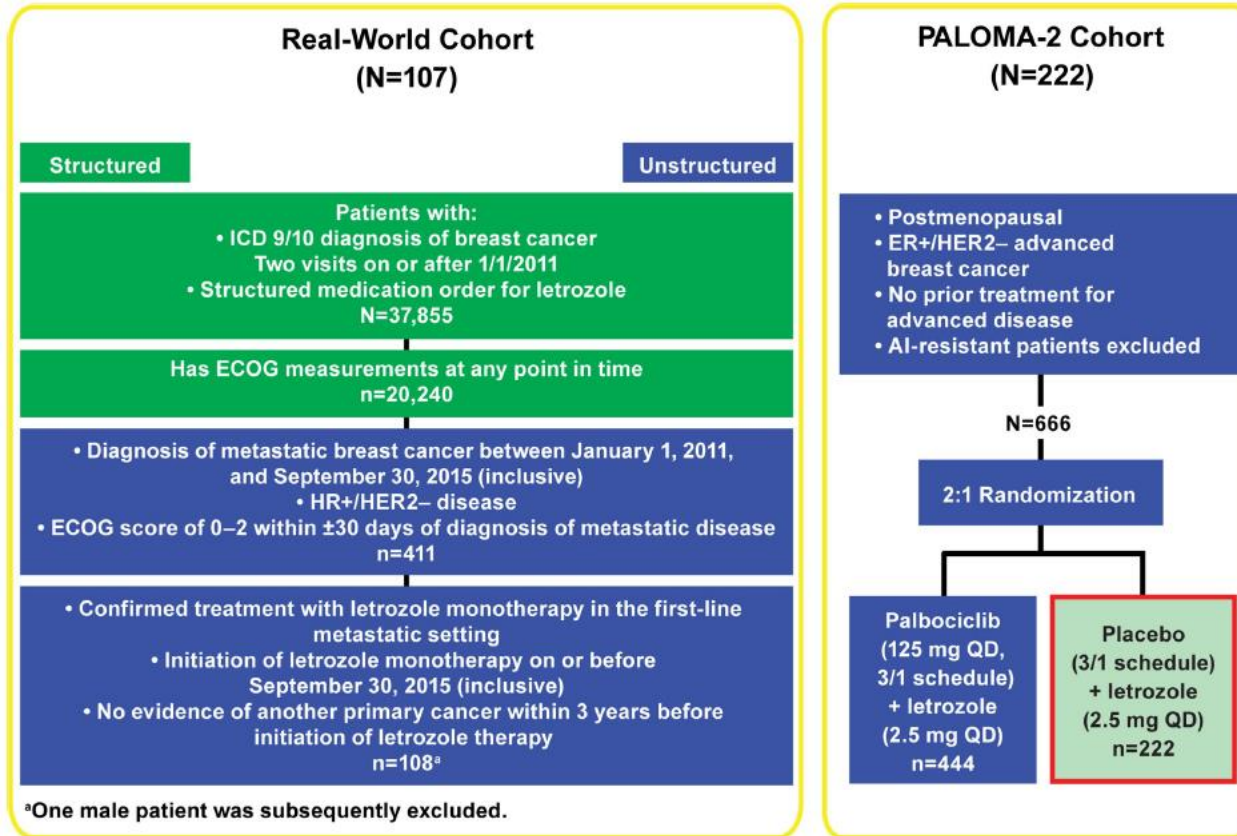


Patients at risk, n:

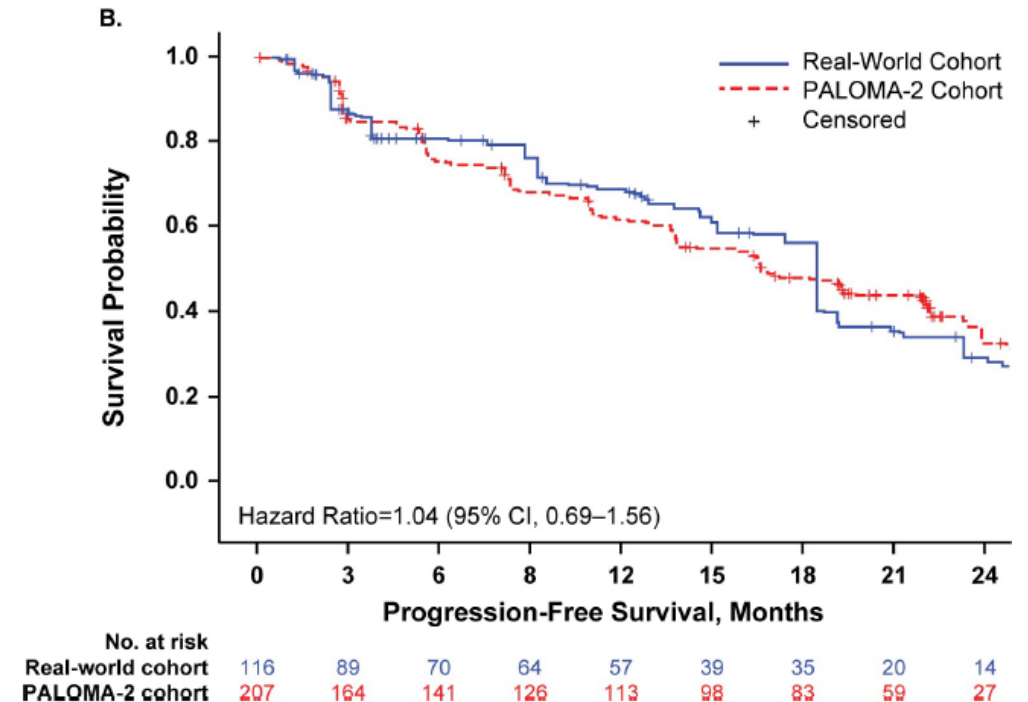
PAL+AI	1572	1465	1214	988	775	588	435	296	192	112	53	14
AI	1137	1014	852	697	577	463	380	299	210	135	73	21

Use cases: comparative effectiveness (RWD vs. RCT)

Breast cancer outcomes with Palbociclib combined with Letrozole comparable RWD and RCT



Propensity weighting



Use cases: potential for external control arms

Colorectal cancer outcomes with regorafenib compared with contemporary RCT

TABLE 1. Cohort Attrition for the FH and CGDB EC Arms

Eligibility Criterion	FH Patients, No. (%)
Patients with mCRC in the FH database (September 2019 data cut) who were present in the two previous monthly data cuts	21,826 (100)
Patients with mCRC in the CGDB (Q1 2020 data cut)	
Age \geq 18 years at mCRC diagnosis	21,824 (100)
Record of any systemic treatment for mCRC	17,304 (79.3)
Regorafenib treatment in 3L+	993 (4.5)
No activity gaps > 90 days before 3L+ regorafenib treatment start	782 (3.6)
\geq 2 lines of chemotherapy before 3L+ regorafenib treatment start	768 (3.5)
Received fluoropyrimidine, irinotecan, and oxaliplatin before 3L+ regorafenib treatment start	599 (2.7)
No prior treatment with regorafenib, an MEK inhibitor, immunotherapy, or a clinical study drug	569 (2.6)
Adequate hematologic and end-organ function	401 (1.8)
No disqualifying conditions based on the IMblaze370 protocol	388 (1.8)
ECOG PS 0 or 1	203 (0.9)
Initiation of first-line therapy between 14 days before and 90 days after mCRC diagnosis	184 (0.8)

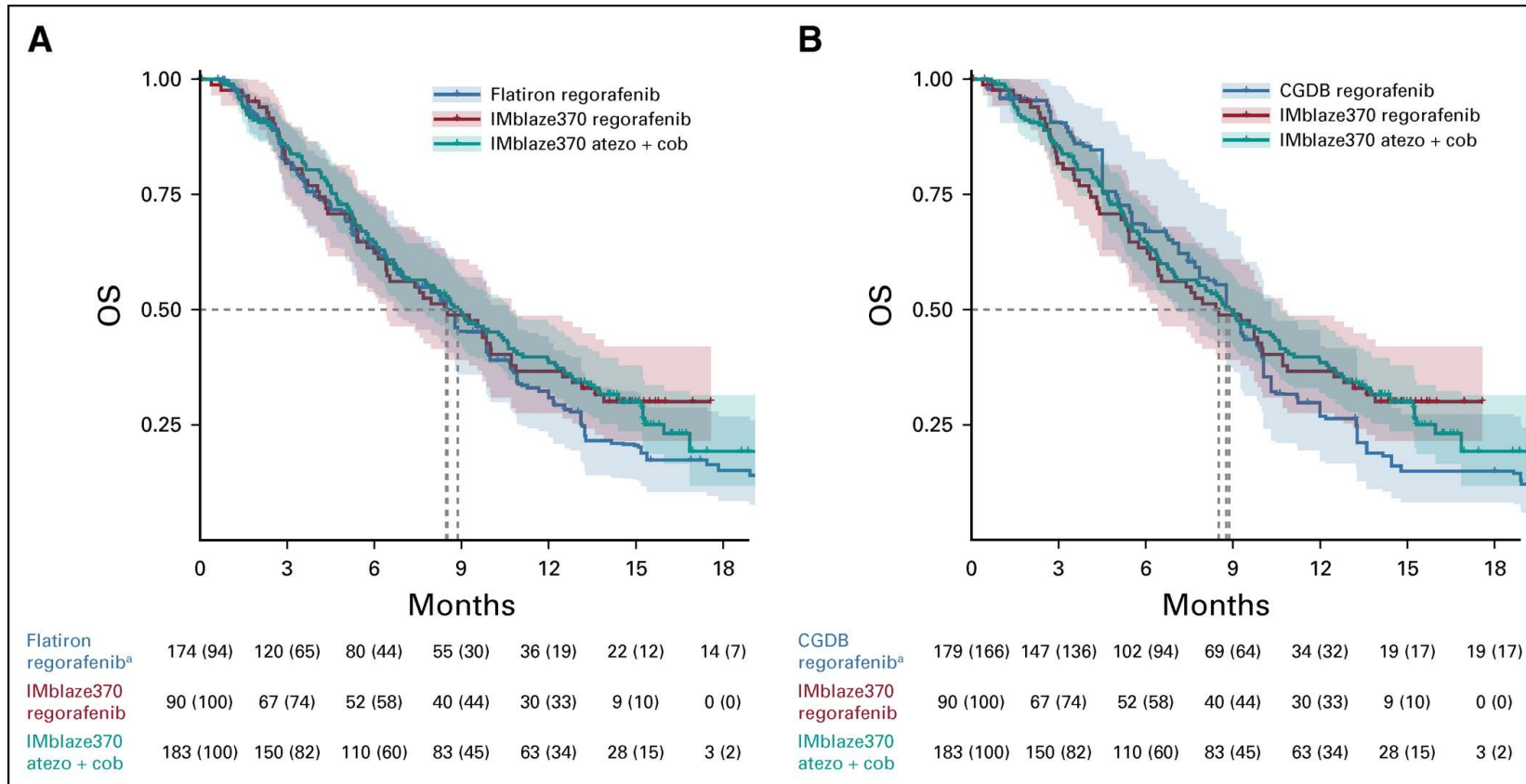
RWD



Eligible for external
control arm

Use cases: potential for external control arms

Colorectal cancer outcomes with regorafenib compared with contemporary RCT



Use cases: synthetic controls

NSCLC RET fusion comparison of TTD/OS of non-RCT and RWD immunotherapy

Design



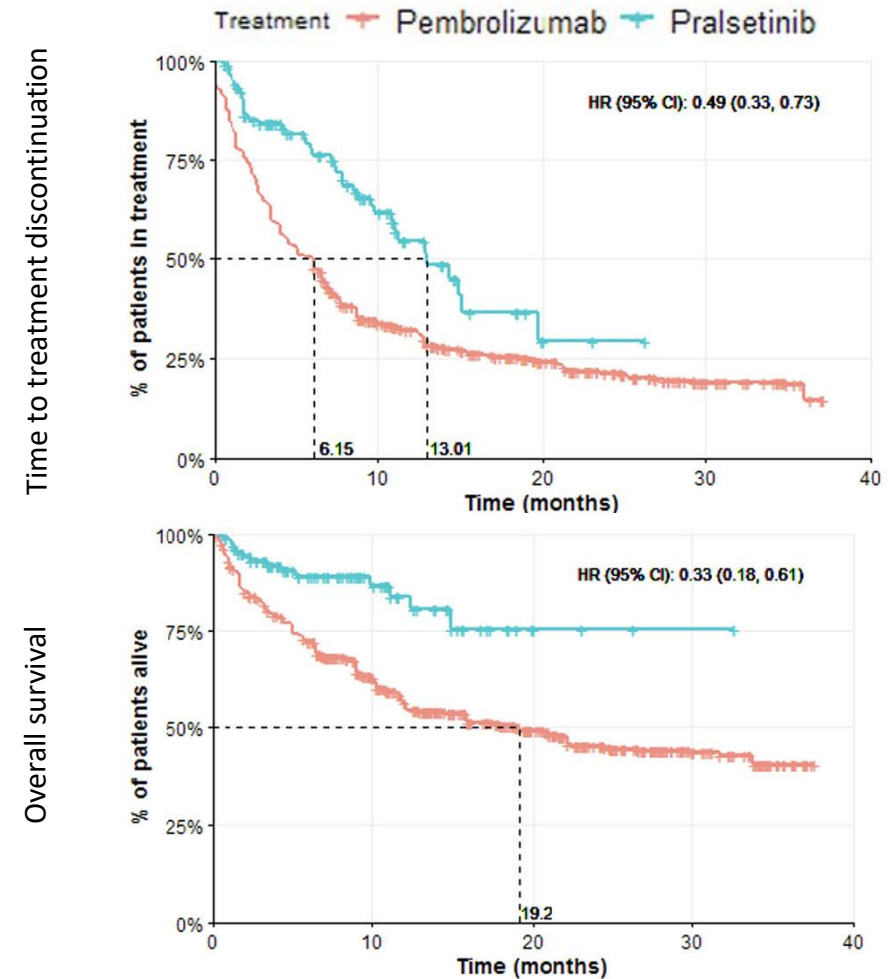
Retrospective RWE
from FMI-Flatiron
database

N = 686, patients
unknown for *RET*
fusions

Used propensity
score weighting
approaches

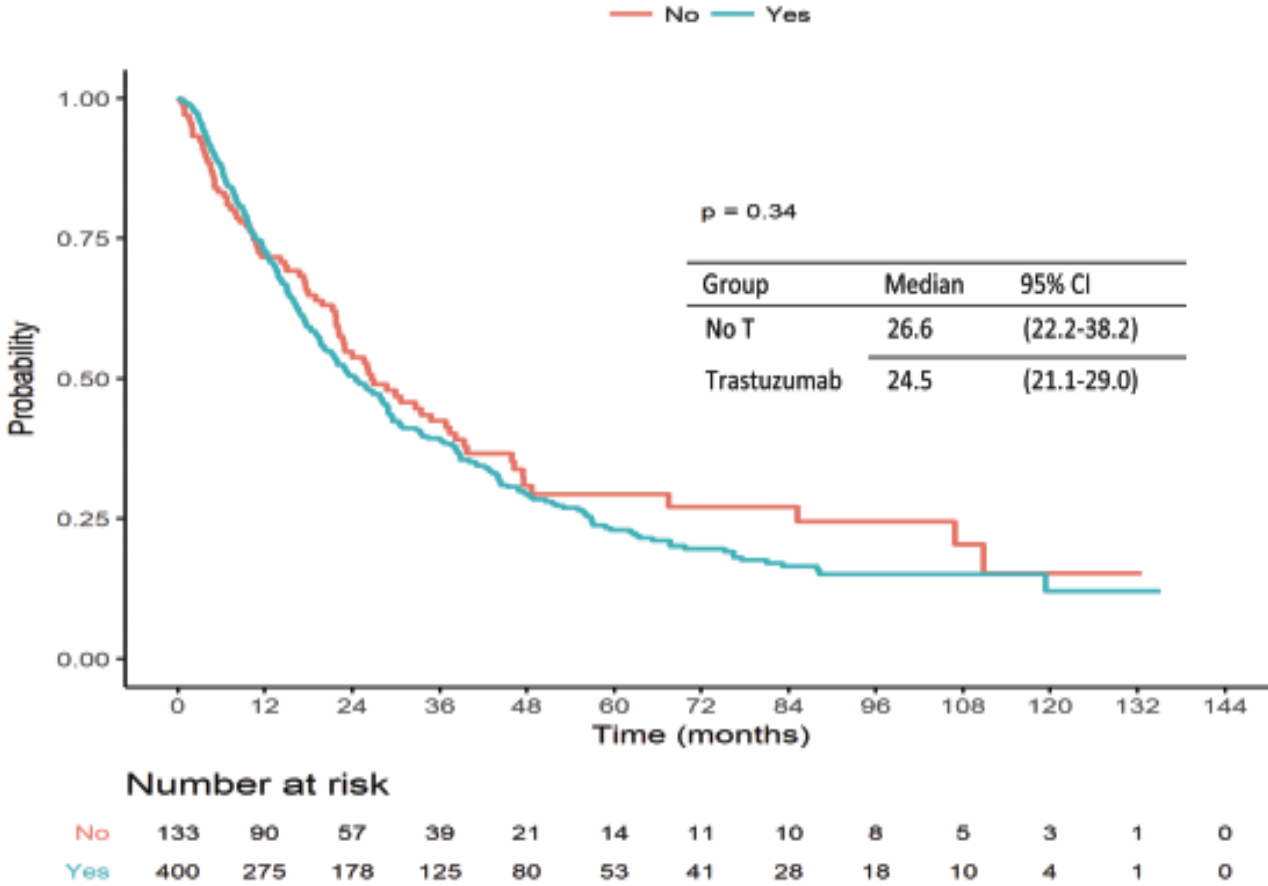
Pembrolizumab in
first-line setting

Study endpoints:
TTD and OS



Use cases: inform clinical trial design (strata)

Impact of (neo)adjuvant trastuzumab on outcomes of metastatic HER2+ BC with early relapse (6-24 months)



Use cases: post-marketing commitment

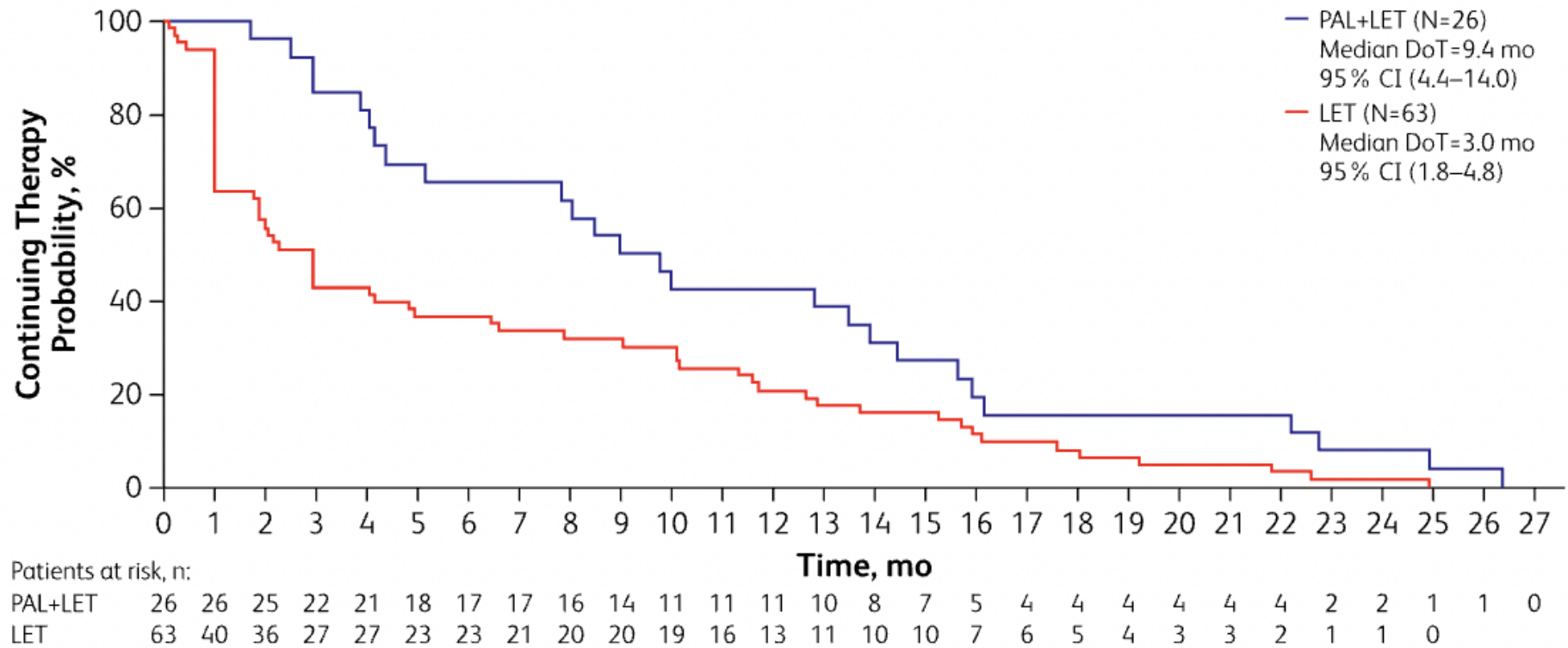
Pembrolizumab in tumor-agnostic MSI-high indication

		All [N=148]	CRC [N=43]	Endometrial [N=43]	Gastric/GEJ [N=19]	Other [N=43]*
Age at pembro Initiation, Median[IQR]		69.0 [58.0;75.2]	70.0 [57.0;78.0]	67.0 [58.0;72.0]	71.0 [64.0;80.0]	68.0 [57.5;74.0]
Female gender, n (%)		96 (64.9%)	24 (55.8%)	43 (100%)	7 (36.8%)	22 (51.2%)
Last ECOG around pembro start, n (%)	0-1	57 (78.3%)	29 (87.9%)	18 (58.1%)	15 (93.8%)	28 (80.0%)
	2+	25 (21.7%)	4 (12.1%)	13 (41.9%)	1 (6.25%)	7 (20.0%)
	Missing	33 (22.3%)	10 (23.3%)	12 (27.9%)	3 (15.8%)	8 (18.6%)
Has any MMR gene Alteration, n (%)		62 (41.9%)	20 (46.5%)	13 (30.2%)	6 (31.6%)	23 (53.5%)
TMB Score, Median [IQR]		32.2 [21.3;46.9]	42.6 [31.0;55.5]	19.1 [16.0;29.4]	40.0 [32.6;48.1]	31.5 [24.2;41.3]
Follow-up from pembro start, Median [IQR]		8.28 [2.30;14.1]	7.95 [2.37;13.0]	9.36 [3.04;18.6]	7.82 [1.91;9.74]	7.16 [1.94;14.4]

	Total N	N at risk at 12-mos	12-mos OS, % [95% CI]
All Patients	148	49	62.0 [53.4-71.9]
Colorectal	43	13	69.9 [54.5-89.6]
Endometrial	43	16	61.9 [47.1-81.4]
Gastric/GEJ	19	4	46.4 [24.2-89.0]
Other*	43	16	59.7 [45.6-78.1]

Use cases: label expansion

Palbociclib + letrozole in male HR+ breast cancer



FDA/EMA perspective

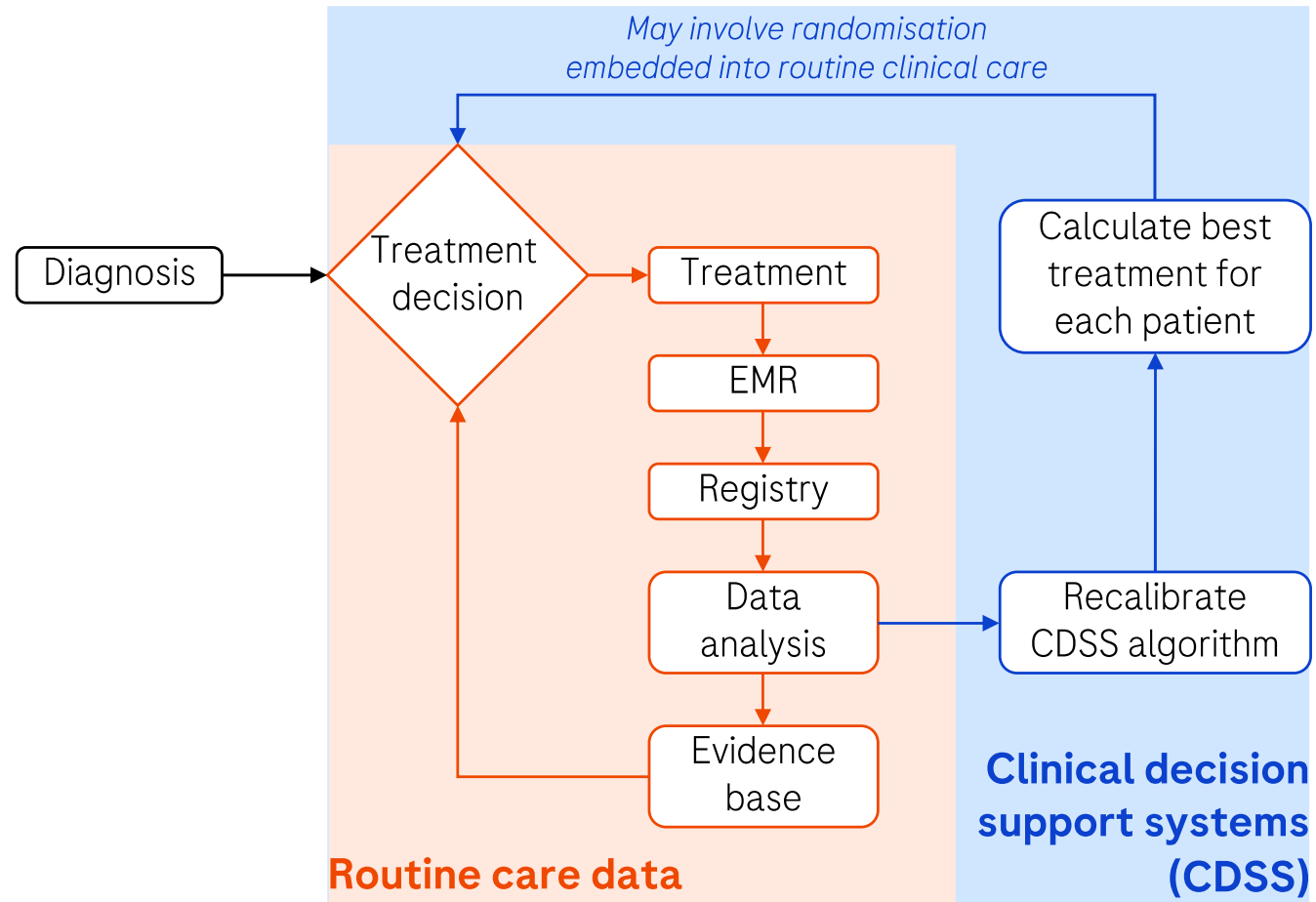
- Acceptance to include RWD on a case-by-case basis
- Endorse no one type of RWD over another
- Requirement for high-quality fit-for-use RWD
- Requirement for robust and consistent statistical methodologies
- Encourage early (and continued) multi-stakeholder dialogue
- Need transparency of RWD studies

Situation in the US/EU

	US	EU
<i>Source</i>	Healthcare data aggregators Claims databases Retrospective Private setting	University hospitals National cancer registries Prospective Public setting
<i>Leaders</i>	Industry	Academia
<i>Priority</i>	Commercial (industry)	Methodology (standards)
<i>Regulation</i>	Favorable	Unfavorable (GDPR)

Clinical-Decision Support Systems (CDSS)

Overview of a learning healthcare system



Take-home messages

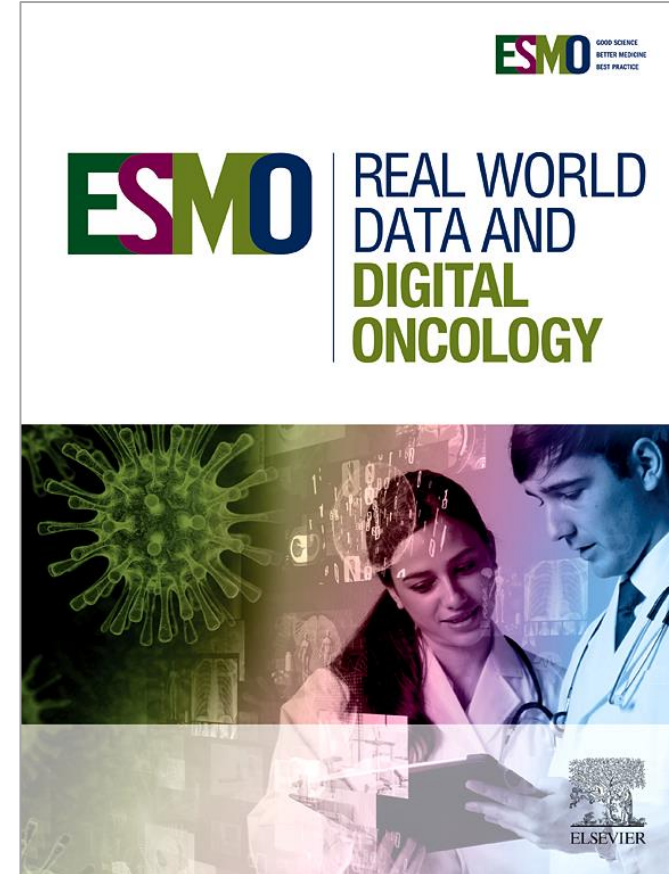
- RWD can complement clinical trial evidence.
- High-quality fit-for-use data is critical (human curation).
- Analytical framework well-defined and statistical tools are improving.
- Regulatory framework is advancing.
- Physicians and patients will be rewarded with CDSS based on RWD.



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Health services management

RWD—adoption and impact of new drugs and technologies, treatment optimization, health economics modelling, new payment models

Digital oncology—clinical informatics solutions, feasibility and impact of medical devices in routine care



Regulatory issues

RWD—external and synthetic controls, post-marketing requirement and commitment, safety and tolerability, patient-reported outcomes and experiences, populations not represented in clinical trials

Digital oncology—software monitoring and impact assessment, risk management

Research opportunities

RWD—guidelines and methodology standards, disease characterization, practice patterns, gaps in access or care delivery, characterization of unmet needs, comparative effectiveness, trial emulation, trial design and execution, pragmatic trials, clinical-genomics cohorts

Digital oncology—model or software validation, clinical implementation and usability, human-machine interaction

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