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Real World Data and Evidence in Clinical Trial Design

Natasha Pillai, MBChB MSc
Real World Insights, Basel Switzerland

Novel Clinical Trial Methodologies Workshop
Cape Town, South Africa
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+ Real world data (RWD) can enhance design and execution of **traditional clinical trials** by increasing efficiency and reducing costs

+ RWD can be applied to create efficiencies in clinical trial design, thus enabling **innovative study designs** given the right research questions (e.g. pragmatic trials, external comparator trials)

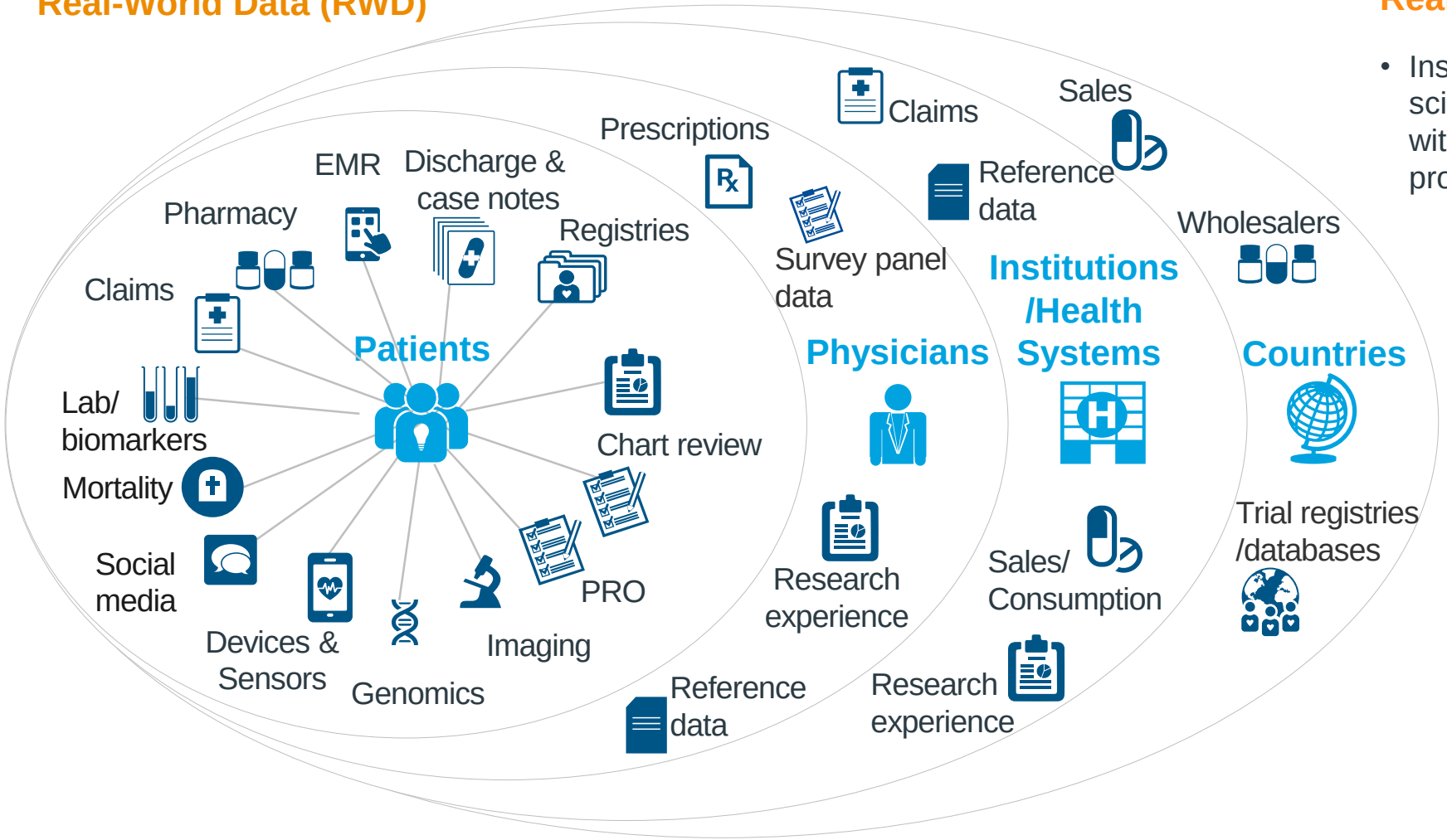
+ **RWD, evidence platforms and networks** enable routine and ad hoc evidence generation for trial design and execution

+ Discussion: the **current data landscape in (South) Africa** in the context of clinical trial design and execution

Real World Data (RWD), longitudinal, patient-level data obtained outside of traditional trials - is available in ever more quantity

Key definitions

Real-World Data (RWD)



Real-World Evidence (RWE)

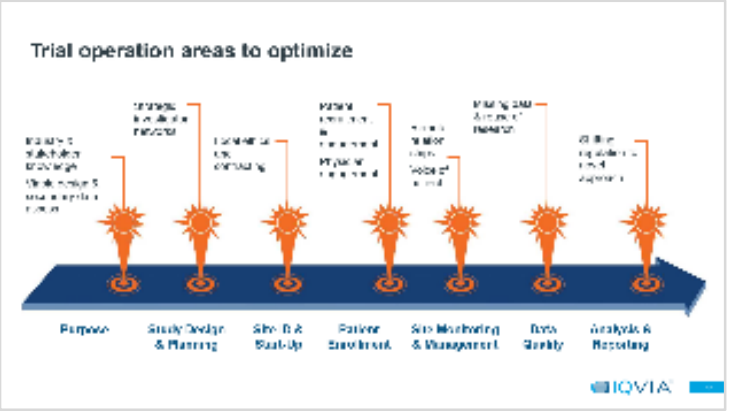
- Insights generated from RWD using appropriate scientific and/or generated commercial analytics with the intention to support a claim or belief to produce evidence for multiple stakeholders

Value of data sources can be substantially increased through linkage

We can leverage RWD for innovative trial design and execution

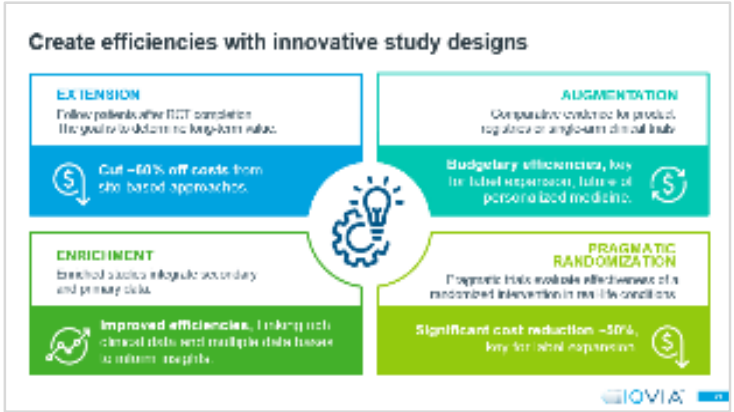
BETTER TRADITIONAL STUDIES

Improved **execution** of traditional studies, more **precise selection** of sites, reduced timelines and errors



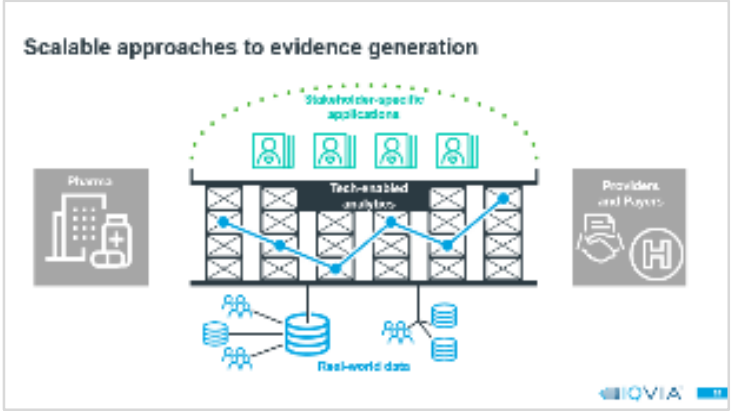
INNOVATIVE STUDY DESIGN

Novel study designs and technology-enabled protocol design allowing for fast and cost effective data collection



SMARTER EVIDENCE GENERATION

Reusable, scalable approaches to evidence generation driven by advance analytics and machine learning

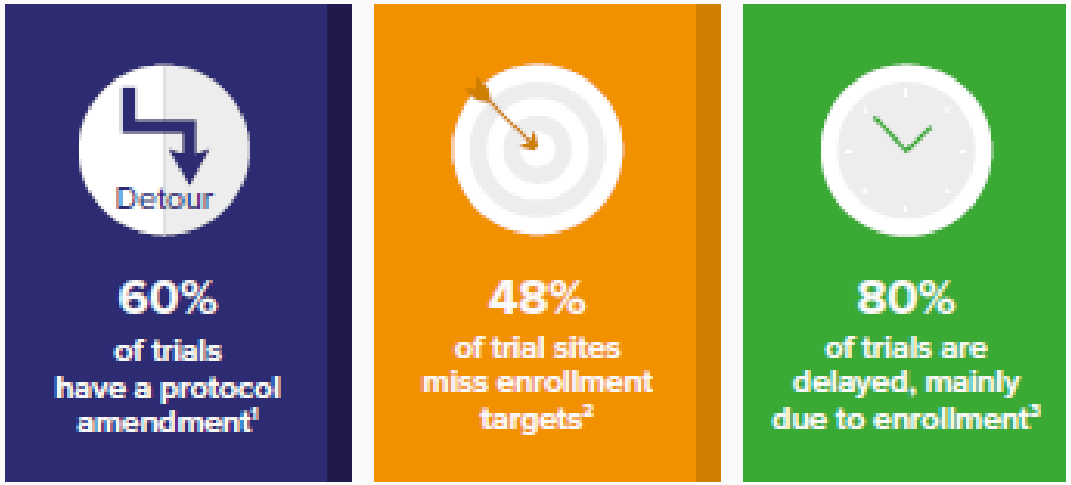


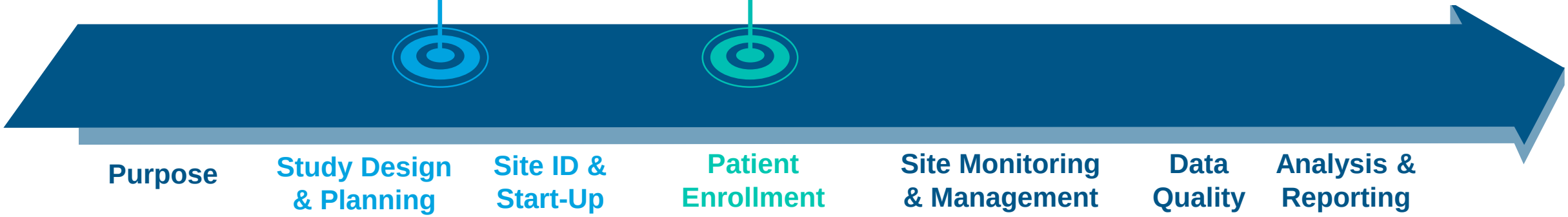
RWD for scalable, technology enabled efficient execution of traditional studies throughout the study lifecycle

Databases allow **evidence driven study design** and **efficient identification of sites** with larger patient pools

De-identified data assets to guide **sample representativeness**

Clinical development challenges



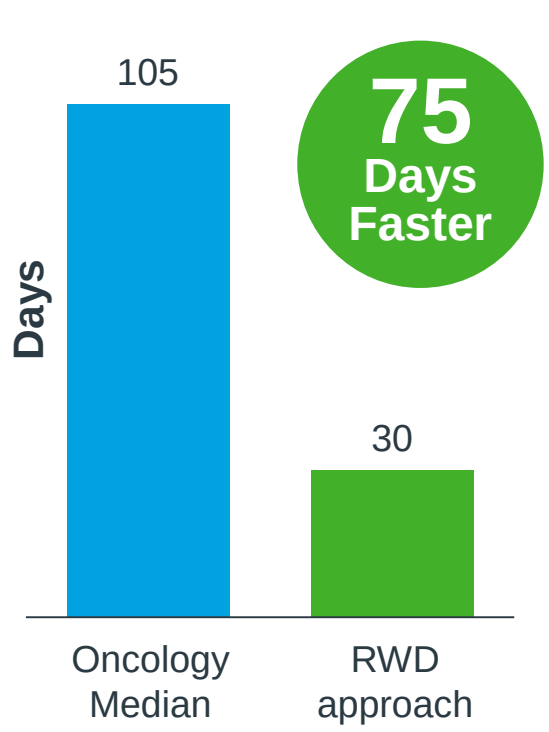


Using fit-for-purpose **technology** and **quality processes** ensuring approaches are **acceptable to regulatory agencies**

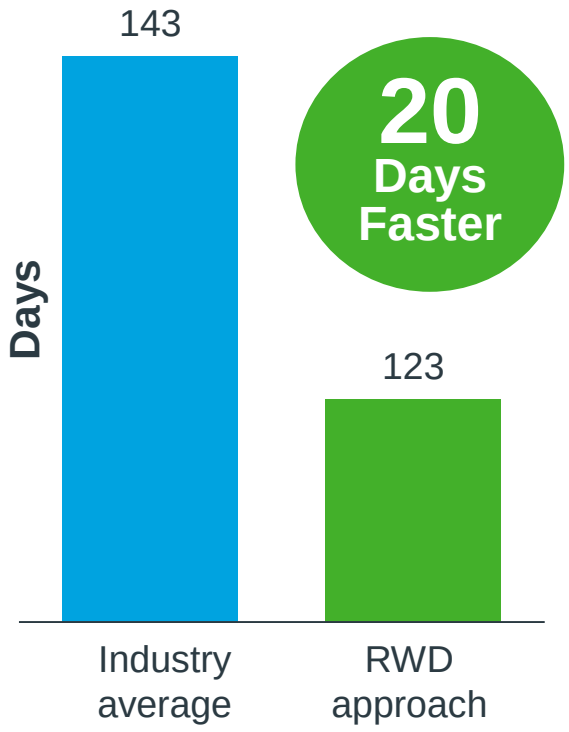
RWD has already been demonstrated to speed up clinical trial execution by enabling predictions of the right patient

CASE STUDY

Oncology RWD in PhIII trial



SITE IDENTIFICATION



FIRST PATIENT ENROLLED

ENROLLMENT MONTHS

IQVIA®

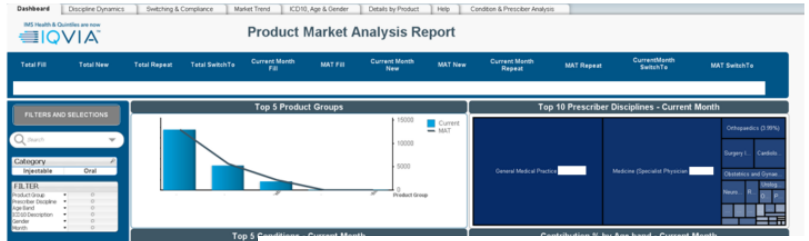
In Africa, RWD includes claims and prescription data that can be used to inform clinical trial design and execution

Sell out Data: Dispense to patients (RSA / Kenya / Nigeria; 90% coverage)
- **Patient demographics**
- Key prescribers
- Key products used
- Regional dispensing

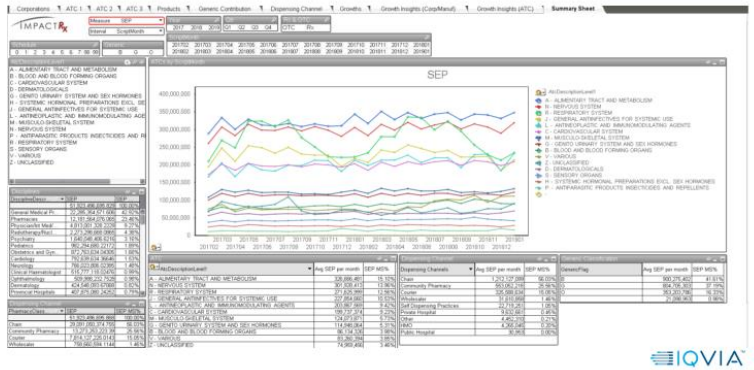
Clinic data / Vaccines (RSA):
- **Link to patient outcome to determine clinical trial endpoints**
- **Patient demographics**
- Patients traveling behavior / willingness to travel
- Key prescribers
- Split between private and public sector patients
- Patient compliance

Claims data (RSA; 25% coverage):
- **Insight into patient journey**
- **Patient demographics**
- Prescribers;
- Regional distribution
- Point of care
- **Trial endpoints** (reimbursement focus is on relapse, disability and adverse events)

Market profile



Sell Out Data



Market profile report (RSA; 25% of Schemes, 50% insured lives):
- **Patient demographics**
- Key prescribers
- Patient compliance
- Patient numbers

But innovative evidence generation is not only “how to do things right” – but first about “how to do the right things”

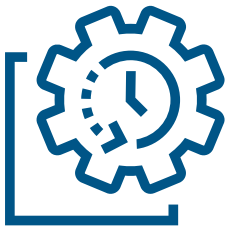
I

Consider new approaches to generate RWE

- Pragmatic trials
- Extension studies
- Direct to patient FU
- Registry studies
- Enriched studies

“Right design for the question“

II



Optimise study design and execution

- Model in-/ exclusion criteria
- Quantify patient pools
- Prioritze countries
- Identify top sites
- … Next Gen/AI

“Right tools for study execution“

+ RWD can enhance design and execution of **traditional clinical trials** by increasing efficiency and reducing costs

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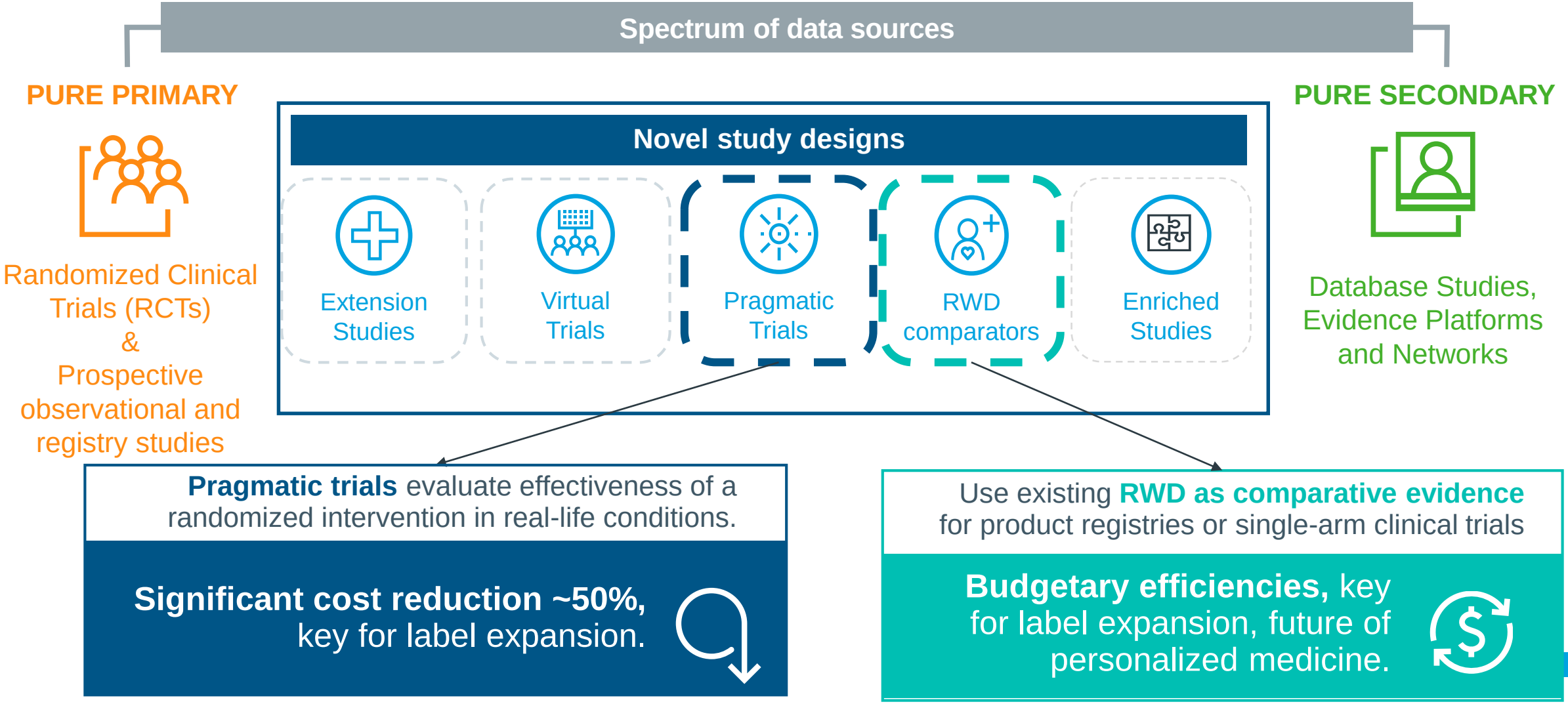
+ **RWD, evidence platforms and networks** enable routine and ad hoc evidence generation for trial design and execution

+ Discussion: the **current data landscape in (South) Africa** in the context of clinical trial design and execution

Innovative RWE Study Designs

Right approach to the right question to generate relevant evidence



What are Randomized Pragmatic Trials?

The key is randomization, generalizability, effectiveness and safety

Clinical trials that measure effectiveness (or the degree of beneficial effect of a drug or intervention in real clinical practice) by testing a full range of patients who might be treated with the drug or intervention, including those with variable adherence, co-morbidities and polypharmacy

Roland & Torgerson. BMJ 1998; 316:285

Pragmatic trials are trials that take place where routine care occurs, such as community clinics, hospitals, and health systems and they involve diverse, representative populations and multiple, heterogeneous settings

Bipartisan Policy Center. Using real-world evidence to accelerate safe and effective cures. June 2016

Pragmatic trials aim to generate real-world evidence on the (relative) effects of treatments, generalizable to routine practice.

IMI Get Real
JCE 2017

https://www.bmj.com/content/350/bmj.h2147

Pragmatic trials blend RCTs and non-interventional/observational studies by offering randomization in a real-world setting

Attribute	Classical RCTs	Pragmatic RCTs	Non-Interventional and Observational Studies
Purpose	New molecular entity (NME), label expansion	Label expansion? RWE for clinicians, payers and patients	
Randomized	Yes	Yes	No
Study Population	Homogeneous	Heterogeneous	
Comparator	Placebo	Single marketed drug or 'standard of care'	
Endpoints	May include intermediate endpoints	Endpoints typically encountered in clinical care	
Follow-up	Mandated testing and visit schedule	Testing and care provided in natural settings	
Data Monitoring	Heavy	Light	

Pragmatic Trial Won Label Expansion

INVEGA SUSTENNA is an antipsychotic that was approved by the FDA with real-world data included in product labeling (Jan 3 2018)

Randomised controlled trial

- ✓ Prospective
- ✓ Randomised
- ✓ Open-label with blinded event monitoring
- ✓ 15-month, head to head trial vs commonly prescribed oral antipsychotics

Pragmatic Trial design

- ✓ Flexible Rx interventions
  - Allowed dosing flexibility and concomitant medication
  - Oral antipsychotics could be deselected prior to randomisation
- ✓ Included patients typically excluded from clinical trials
  - Comorbid substance misuse
  - Hx of incarceration
  - Unstable living conditions
- ✓ Rx adherence was monitored by not required to complete the trial

Landmark Study Shows Once-Monthly Long-Acting Therapy INVEGA® SUSTENNA® (paliperidone palmitate) Significantly Delayed Time to Relapse in Patients with Schizophrenia Compared to Daily Oral Antipsychotic

First prospective, randomized clinical trial to reflect context of "real world" issues in treating schizophrenia, including recent incarceration and substance abuse

- 15 month, 50 site randomized, open-label, active controlled study
- Key patient characteristics (n=444)
  - Mean age 38 years
  - 60% of patients had comorbid substance abuse
  - Mean time since release from last incarceration=42 days
- Primary endpoint: time to first treatment failure including psych hospitalization, arrest/incarceration, treatment discontinuation, increased psych services to prevent psych hospitalization, suicide, etc.

Alphs L, Benson C, Cheshire-Kinney K et al. J Clin Psychiatry 2015:76(5):554-561

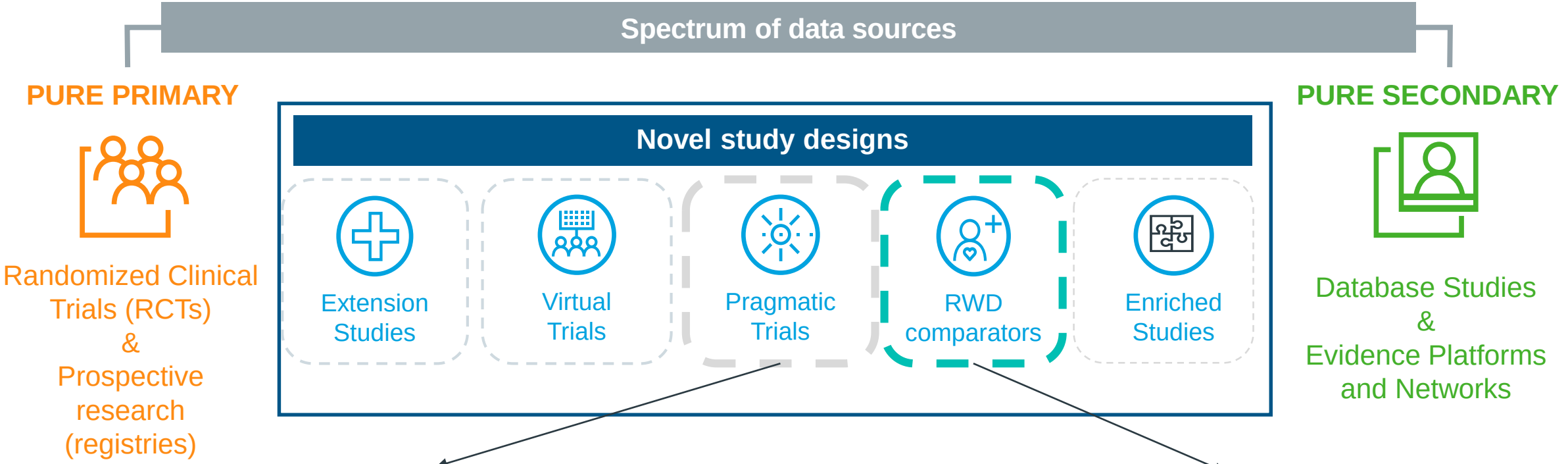
Case Study- Tradeoffs Phase IIIB vs Phase IV randomized pragmatic trial

Crohn's Study- 13 countries, 250 patients, 150 sites

	Phase IIIB	Phase IV RPT	Opportunities & Challenges
Comparator	• (Double-blinded)	• Blinding Analysis/Assessors only	• Blinding assessments/analysis rather than treatments
CRF	• Extensive • Many endpoints	• Focused	• Endpoints used in clinical practice like Harvey Bradshaw Index
Adverse Events	• All	• Serious adverse events and serious adverse events of special interest	• Investigators burn out entering AEs so best to use SAEs unless all AEs required
Monitoring	• 100% source data verification	• 2 onsite & remote visits/year • Monthly calls	• More concern about data quality & missing data
Follow-up	• Visits	• Electronic • Phone • Visits	• Limit observation timeframe to 52 weeks; • Use traditional post-marketing safety channels for follow-up
Cost without drug Cost/patient	**~ $26 M** **$104K/pt**	**~ $14 M** **$58K/pt**	

Innovative RWE Study Designs

Right approach to the right question to generate relevant evidence



Pragmatic trials evaluate effectiveness of a randomized intervention in real-life conditions.

Significant cost reduction ~50%, key for label expansion.

Use existing **RWD as comparative evidence** for product registries or single-arm clinical trials

Budgetary efficiencies, key for label expansion, future of personalized medicine.

CASE STUDY

Real-World Benchmark

Accelerated product approval based on a single-arm trial with a real-world benchmark in a rare disease

BAVENCIO® (avelumab)

- Approved in 2017 under **FDA accelerated approval** for metastatic Merkel cell carcinoma based on tumor response.
- The JAVELIN Merkel 200 trial was an **open label**, **single arm**, multi-center study
- **Real-world benchmarks** established in the US and Europe as comparators

	JAVELIN Study N = 88	Real-World Benchmarks	
		US EMR	EU Registry
Overall Response Rate	33%	29%	10%
Median Duration of Response (Months)	86% > 6 45% > 12	1.7	1.9

External comparators provide context to single-arm data and improve the probability of success with stakeholders

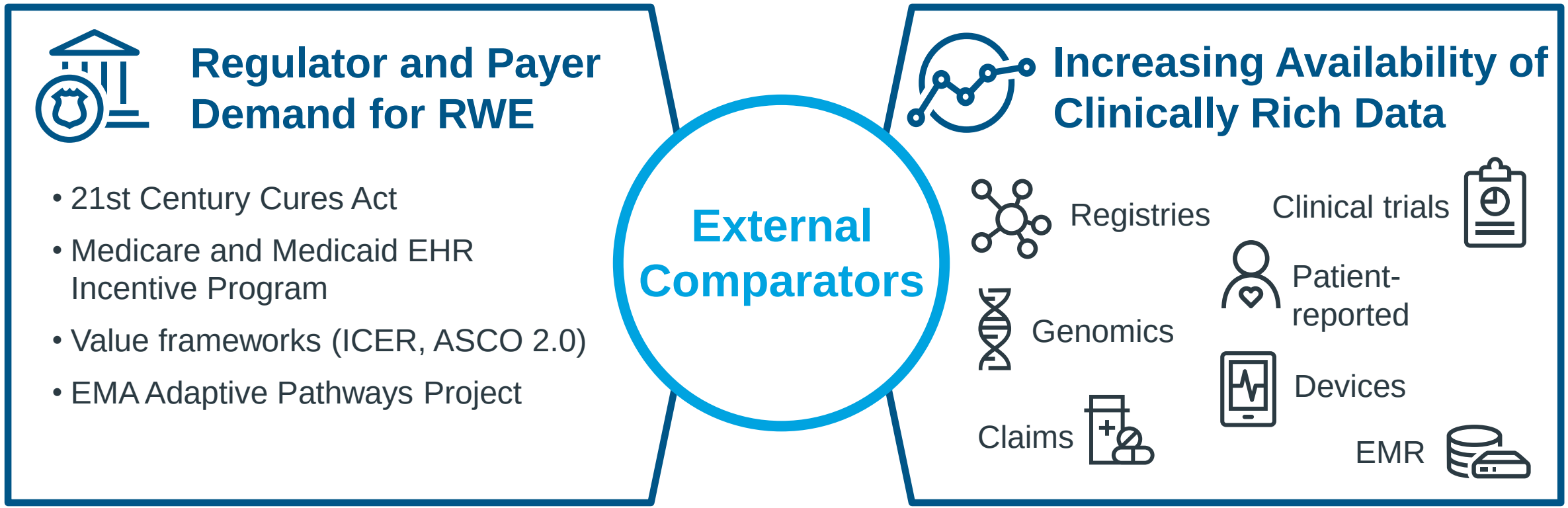
Add context to single-arm data

- Rare patient population
- Impractical or unethical to have placebo arm
- Post-marketing requirement

Add value to development

- Increase probability of success with regulators and payers
- Potentially expedite label expansion, market access and product launch
- Provide a comparator where it cannot otherwise be obtained

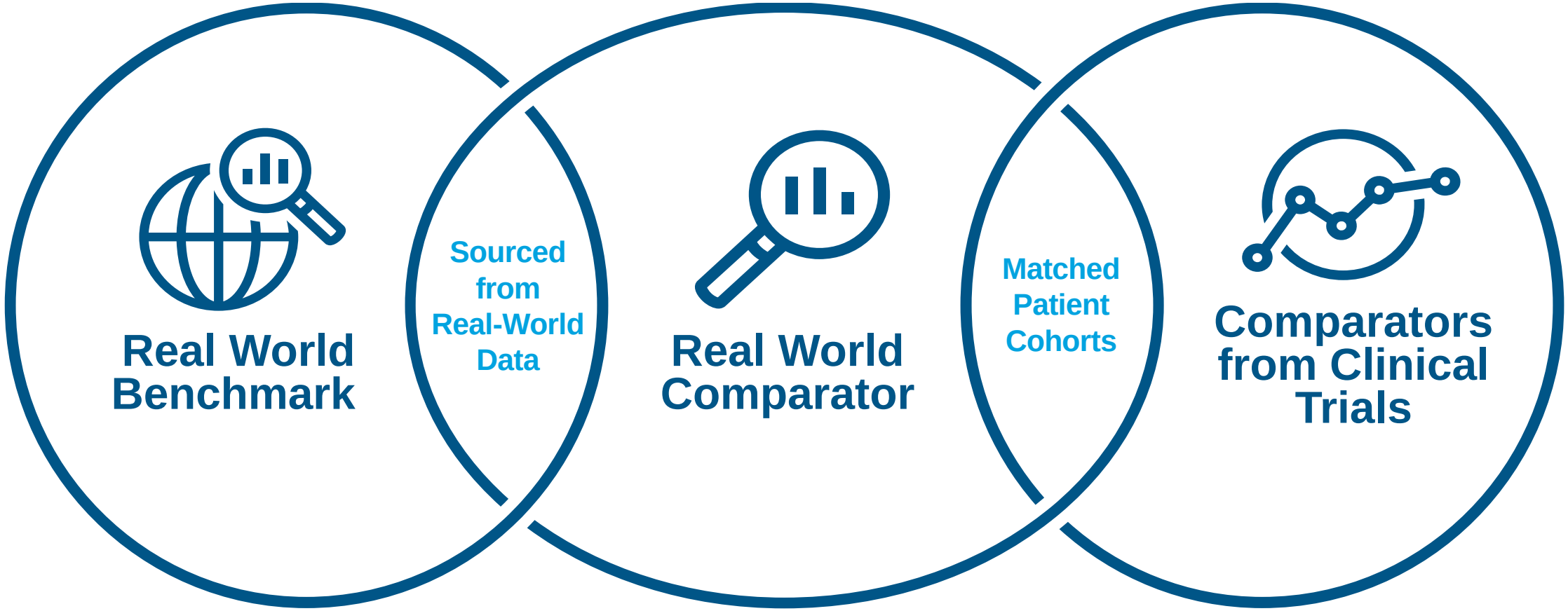
Favorable conditions for expanded use of external comparators



There is a need to "enhance our perspective and ***bring data to supplement/guide clinical judgement****"*

- Sean Khozin, MD, MPH, FDA Project Data Sphere 2018 on External Comparator Approach

External comparators are built from existing or prospectively collected data outside of the primary research project



The type of external comparator used for each study will depend on the specific research question and data availability

Challenges to delivering studies with external comparators

Defining and executing on the optimal strategy to **address regulator and payer questions within the right timeframe**

Navigating an evolving regulatory environment with **no established guidance** for developing external comparators

Access to **clinically rich data on a global scale** and the expertise and experience to correctly analyze and interpret that data

External Comparator Check List

1. How well do the data characterize "must-have" exposures & outcomes of interest?

- *Should the selection of patients vary by region? Assess standard of care by region and over time as a first step.*

2. How reliable are the outcomes that are readily recorded & accessible?

- *Compare missingness and definitions of outcomes to single-arm study*

3. Have patients been followed for the desired length of time?

- *Need to compare to single-arm study for same length of time*

4. What is the potential for bias & how much is it likely to impact the expected effect?

- *Use methods to control/adjust for differences in populations at baseline if possible*

Dreyer NA. Advancing a framework for regulatory use of real-world evidence: When real is reliable.
Therapeutic Interventions and Regulatory Affairs 2018; 52(3) 362-36

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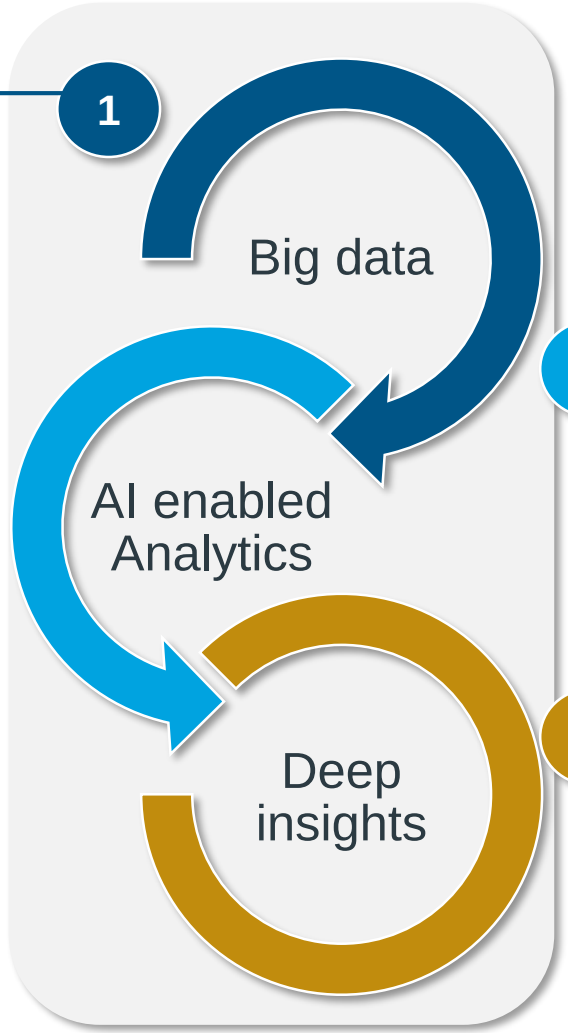
Big data and AI-enabled analytics offer unparalleled insights for multiple stakeholders

Big data: capture diverse sets of real world data

Patient profile data	EMR data	Out-comes data	Claim data
(genotype and / or phenotype profiling)	(historic patient data on disease, co-morbidit-ies and treatment)	(clinical and patient reported outcomes)	(payer relevant claims' data)

Data integration platforms

Data aggregation models



AI enabled analytics

2

Smart algorithms* to understand relationship between treatment design and sequencing and medical/ QoL/economic/social outcomes (pattern recognition)

Value generated or demonstrated for multiple stakeholders

3

Patient: *Receives right treatment at the right time*

Physician/Nurse: *Treatment decision support*

Payers: *Better budget management decisions, RWE enabled innovative contracting*

Pharma: *R&D and commercial optimisation*

*Machine learning, predictive analytics, natural language processing, other emerging AI approaches

An Oncology network across multiple geographies enables routine and ad hoc evidence generation

CASE STUDY
Oncology Network

- Registry/EMR 'off-the-shelf'
- Registry/EMR + 'enhancement'
- Claims
- Panel
- Non-interventional studies

5 countries covered by the data network

3,000 patients

9 datasets

3 indications

Will deliver >10 scientific papers annually, aligned with key conferences

- IQVIA utilized a pan-European data assessment and custom data sourcing to build an RWD oncology network for organization-wide use
- Enabling routine and ad hoc evidence generation, the network is supporting
  - Engagement with investigators, academics and regulators
  - Selection of trial comparators
  - Optimized late-phase research
  - Local reimbursement plans

There are multiple initiatives being undertaken globally and regionally in Africa to improve Oncology databases and networks

External initiatives

Pfizer · Cipla · NCCN National Comprehensive Cancer Network® · CLINTON HEALTH ACCESS INITIATIVE · IBM

AFRICAN CANCER COALITION

NOVARTIS

American Cancer Society® · ASCP American Society for Clinical Pathology

REPUBLIC OF KENYA
MINISTRY OF HEALTH

REPUBLIC OF KENYA
MINISTRY OF HEALTH

Roche

IQVIA initiatives

Cancer care roadmap in association with PReMA Pharmaceutical Research & Manufacturers Association

European Oncology Evidence Network

code collaboration for oncology data in europe

IMPACT Improving Management for Patients and Access to Cancer Therapies

Middle East Cancer Repository

Universal healthcare coverage is a global aspirational goal.

We need data to identify gaps and generate insights that can support this goal and drive optimal patient care

IMS Health & Quintiles are now

Thank you