RAPS Regulatory
CONVERGENCE
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Vancouver, BC

Your Regulatory Meeting Place

What's the Real Deal with Real World Evidence in Regulatory Affairs?

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RAPS REGULATORY AFFAIRS PROFESSIONALS SOCIETY
Driving Regulatory Excellence™

An FDA Timeline for RWE/RWD
in Advanced Therapies & Medical Devices

1747 — First RCT (James Lind, Scurvy)

Pre-1940s — Regulatory decisions regularly rely on anecdotal clinical evidence

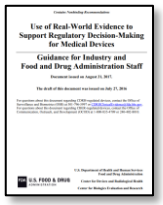
1960-62 — Drug Legislation, including Amendments of 1962

1970-76 — Medical Device Legislation, including Amendments of 1976

1996, 2001, & 2010 — CONSORT Guidelines

2016 — 21st Century Cures

2017 — *Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices* (CDRH & CBER Guidance)



EMA & FDA Big Data Initiatives

Source(s): Corrigan-Curay *et al*. Real-World Evidence and Real-World Data for Evaluating Drug Safety and Effectiveness. September 4, 2018. *JAMA Network*. https://jamanetwork.com/journals/jama/article-abstract/2697359

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What is RWE/RWD?

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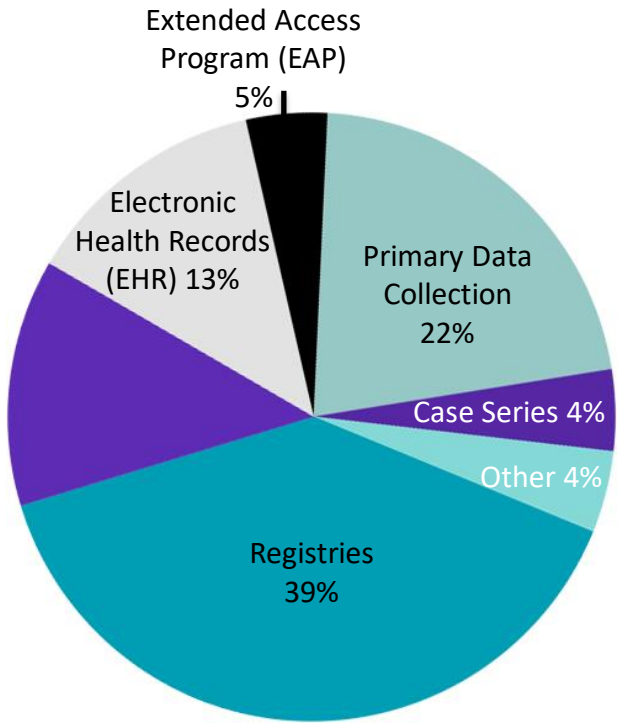
What is RWE/RWD?

Real-World Data (RWD) → Real-World Evidence (RWE) → Insights → Decisions

Real-World Data (RWD) are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.

Examples of RWD include data derived from electronic health records (EHRs), claims and billing data, data from product and disease registries, patient-generated data including in home-use settings, and data gathered from other sources that can inform on health status, such as mobile devices. RWD sources (e.g., registries, collections of EHRs, and administrative and healthcare claims databases) can be used as data collection and analysis infrastructure to support many types of trial designs, including, but not limited to, randomized trials, such as large simple trials, pragmatic clinical trials, and observational studies (prospective and/or retrospective).

Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices – FDA CDRH & CBER Guidance



Source(s): EMA Data. 2017.
https://www.ema.europa.eu/documents/presentation/presentation-session-1-use-real-world-data-pre-authorisation-what-can-it-answer-peter-mol_en.pdf

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What is RWE/RWD?

Real-World Data (RWD) → **Real-World Evidence (RWE)** → Insights → Decisions

Real-World Evidence (RWE) is the clinical evidence regarding the usage, and potential benefits or risks, of a medical product derived from analysis of RWD.

Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices – FDA CDRH & CBER Guidance

The **National Evaluation System of health Technology (NEST)**'s vision is to create a system to generate better evidence more efficiently for medical device evaluation by leveraging RWE throughout the total product lifecycle.

NEST
National Evaluation System for health Technology
Coordinating Center

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What is RWE/RWD?

Real-World Data (RWD) → Real-World Evidence (RWE) → **Insights** → Decisions

- for generating hypotheses to be tested in a prospective clinical study;
- as a historical control, a prior in a Bayesian trial[14], or as one source of data in a hierarchical model or a hybrid data synthesis;
- as a concurrent control group or as a mechanism for collecting data related to a clinical study to support device approval or clearance in a setting where a registry or some other systematic data collection mechanism exists;
- as evidence to identify, demonstrate, or support the clinical validity of a biomarker;
- as evidence to support approval or granting of an Humanitarian Device Exemption, Premarket Approval Application (PMA), or De Novo request;
- as support for a petition for reclassification of a medical device under section 513(e) or (f)(3) of the FD&C Act;
- as evidence for expanding the labeling of a device to include additional indications for use or to update the labeling to include new information on safety and effectiveness[15,16]
- for public health surveillance efforts. Through ongoing surveillance, signals are at times identified that suggest there may be a safety issue with a medical device. RWE may be used to refine these signals for purposes of informing appropriate corrective actions and communication;[17,18]
- to conduct post-approval studies that are imposed as a condition of device approval or to potentially preclude the need for postmarket surveillance studies ordered under section 522 of the FD&C Act;

Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices – FDA CDRH & CBER Guidance

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What is RWE/RWD?

Real-World Data (RWD) → Real-World Evidence (RWE) → Insights → **Decisions**

Under the right conditions, data derived from real world sources can be used to support regulatory decisions. RWD and associated RWE may constitute valid scientific evidence depending on the characteristics of the data. This guidance should not be construed to alter, or change in any way, the existing evidentiary standards applicable to FDA's regulatory decision-making; rather, it describes the circumstances under which RWD may be used to support a variety of FDA decisions based on the existing evidentiary standards. While FDA encourages the use of relevant and reliable RWD, this guidance neither mandates its use nor restricts other means of providing evidence to support regulatory decision-making. This guidance highlights some of the potential uses of RWD, and describes the factors that FDA considers when evaluating whether specific RWD is of sufficient quality to inform or support a regulatory decision. It also clarifies when an Investigational Device Exemption (IDE) may be needed to prospectively collect and use RWD for purposes of determining the safety and effectiveness of a device.

Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices – FDA CDRH & CBER Guidance

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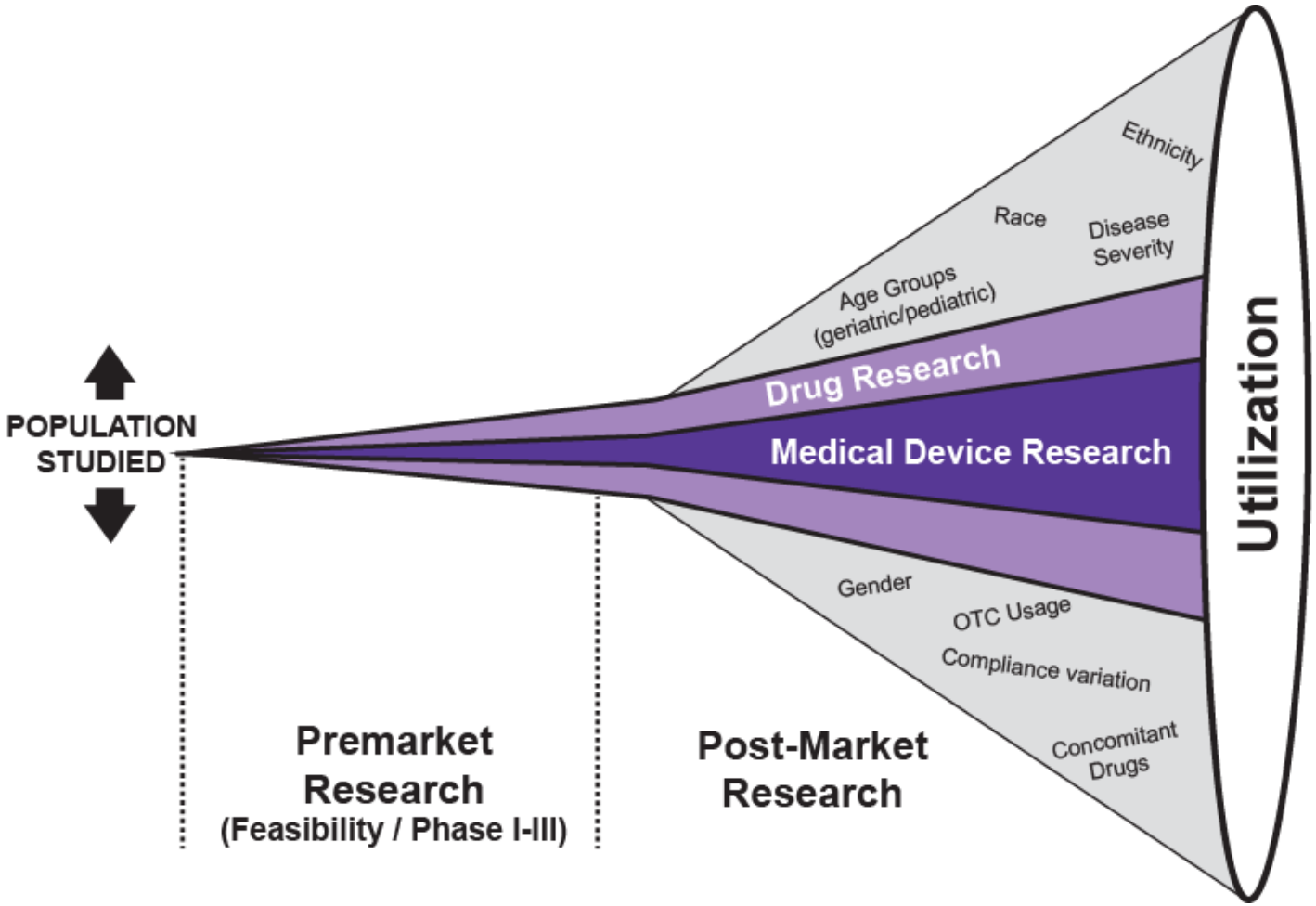
A Changing Cone of Utilization

Research increasingly does not represent real populations



Source(s): Figure adapted from Breen *et al*. Real world evidence – what have we learned recently at EMA? 2018. https://www.ema.europa.eu/documents/presentation/presentation-real-world-evidence-rwe-what-have-we-learned-recently-ema-emas-pcwp-hcpwp-joint-meeting_en.pdf

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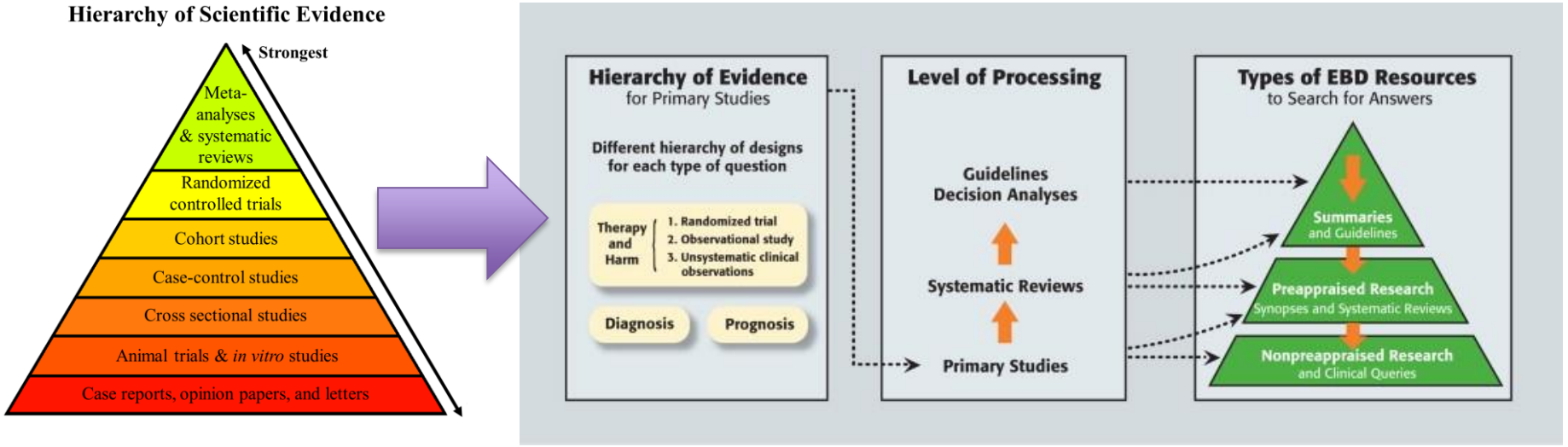
Hierarchies of Evidence

Moving Beyond the Pyramid as a Research Philosophy

MHRA
Regulating Medicines and Medical Devices

Hierarchies of evidence – It was widely agreed that traditional concepts of hierarchies of evidence should be replaced by **instead selecting evidence based on the research question** and what is most relevant and useful for answering this. This will require a robust understanding of the strengths and limitations of different types of evidence and **more research is needed to explore the impact of different evidence generation methods and methodologies for using RWE in decision-making.**



Source(s): MHRA & Academy of Medical Sciences. Next steps for using real world evidence Summary report of a FORUM follow-up roundtable held on 24 January 2018. https://acmedsci.ac.uk/file-download/7021031
Stegenga J (October 2014). "Down with the hierarchies". Topoi. 33 (2): 313–22.
Brignardello-Petersen, R., Carrasco-Labra, A., Glick, M., Guyatt, G. H., & Azarpazhooh, A. (2014). A practical approach to evidence-based dentistry: understanding and applying the principles of EBD. Journal of the American Dental Association, 145(11), 1105-1107. doi: 10.14219/jada.2014.102.
https://guides.library.utoronto.ca/c.php?g=251062&p=4144042

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PCT vs. RCT

(Or Can it be Both?)

Pragmatic clinical trials (PCTs) offer the hope that the advantages of randomization can be combined with the added relevance of results obtained in more real-world clinical settings, but these trials often remain more expensive and more complex to design than traditional RCTs.

"[PCTs offer] actionable clinical evidence at a fraction of the typical cost and time needed to conduct a traditional trial".

- NIH Health Care Systems Research Collaboratory,
Rethinking Clinical Trials:
A Living Textbook of Pragmatic Clinical Trials

Source(s): https://www.precis-2.org; http://www.rethinkingclinicaltrials.org; https://www.pcori.org/research-results/research-we-support; ICER/OHE Real World Evidence for Coverage Decisions: Opportunities and Challenges A Report from the 2017 ICER Membership Policy Summit March 2018 https://icer-review.org/wp-content/uploads/2018/03/ICER-Real-World-Evidence-White-Paper-03282018.pdf

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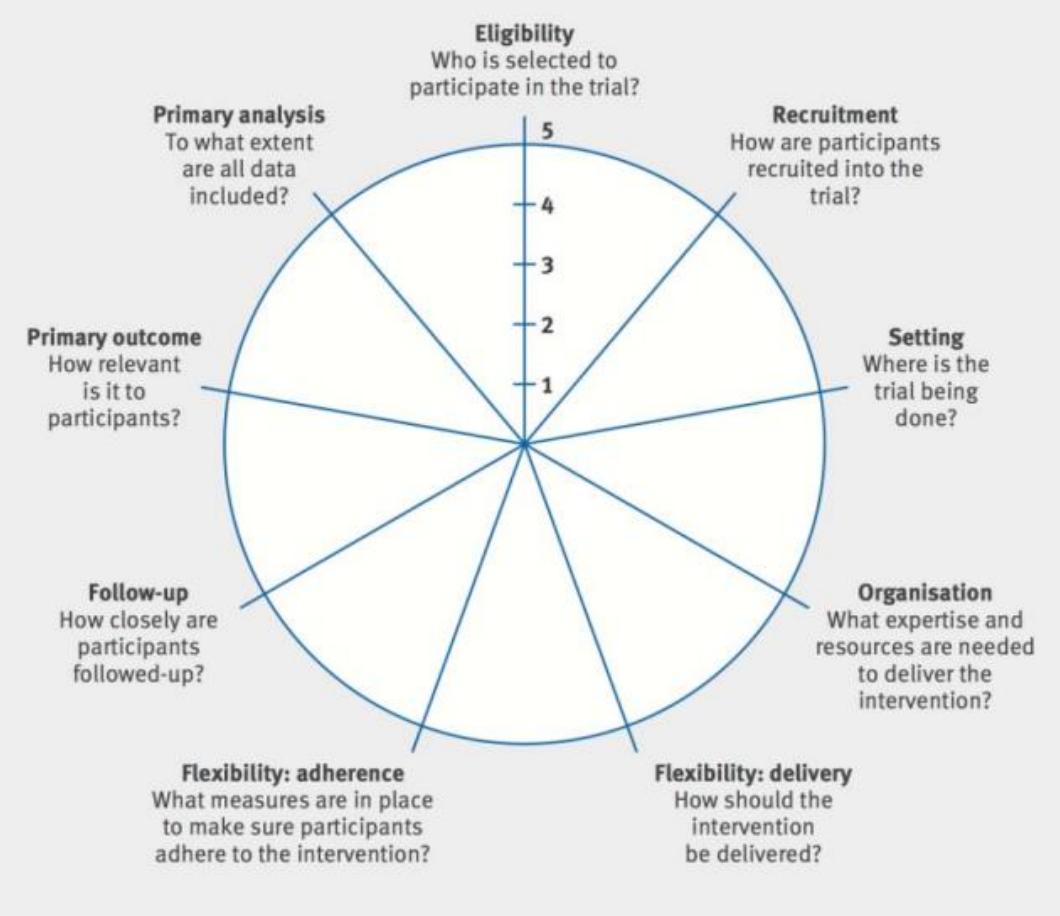
PCT vs. RCT

PRagmatic-Explanatory Continuum Indicator Summary 2 (PRECIS-2)



Source(s): https://www.precis-2.org; http://www.rethinkingclinicaltrials.org; https://www.pcori.org/research-results/research-we-support; ICER/OHE Real World Evidence for Coverage Decisions: Opportunities and Challenges A Report from the 2017 ICER Membership Policy Summit March 2018 https://icer-review.org/wp-content/uploads/2018/03/ICER-Real-World-Evidence-White-Paper-03282018.pdf

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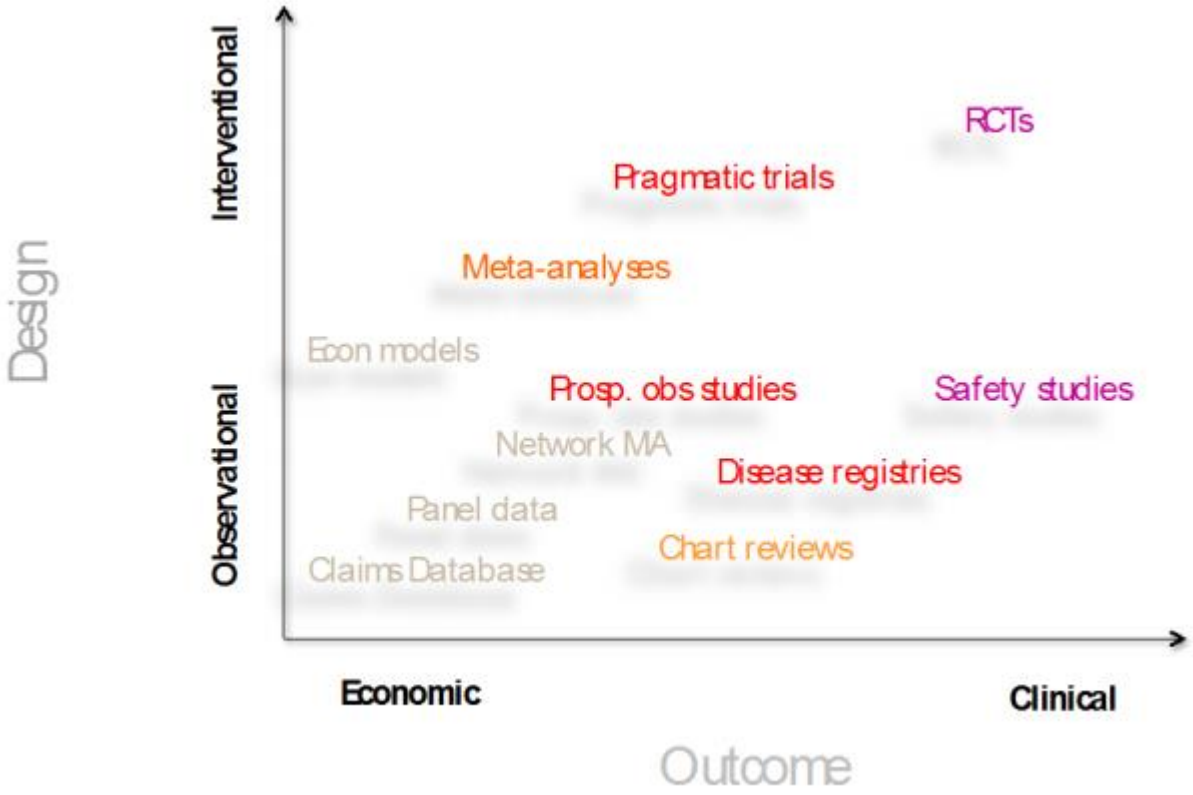
Where do RWE and PCT fit?



Source(s): Institute of Health Economics, Alberta, CAN. Real World Evidence – What role can it play in real world decision-making? 2018

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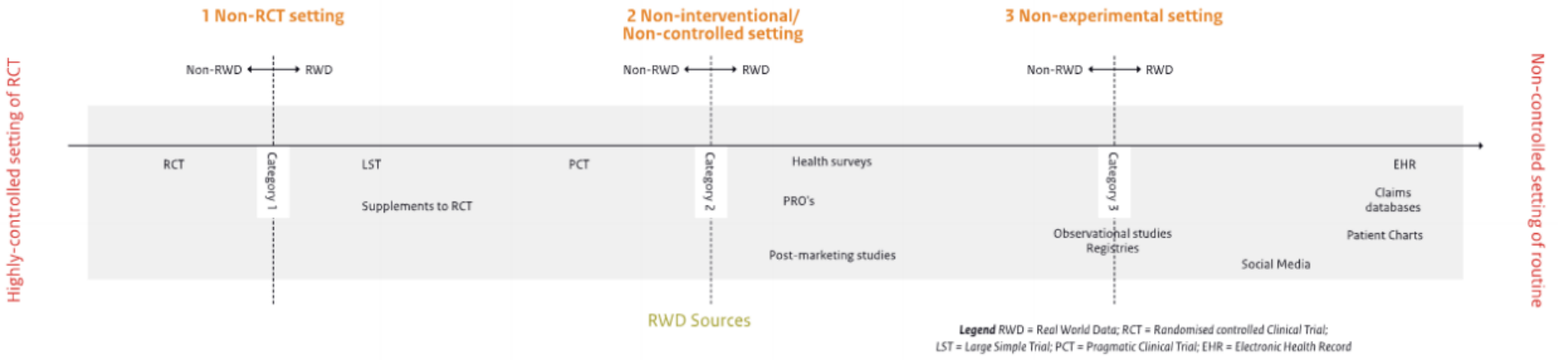
Where do RWE and PCT fit?



Source(s): Institute of Health Economics, Alberta, CAN. Real World Evidence – What role can it play in real world decision-making? 2018

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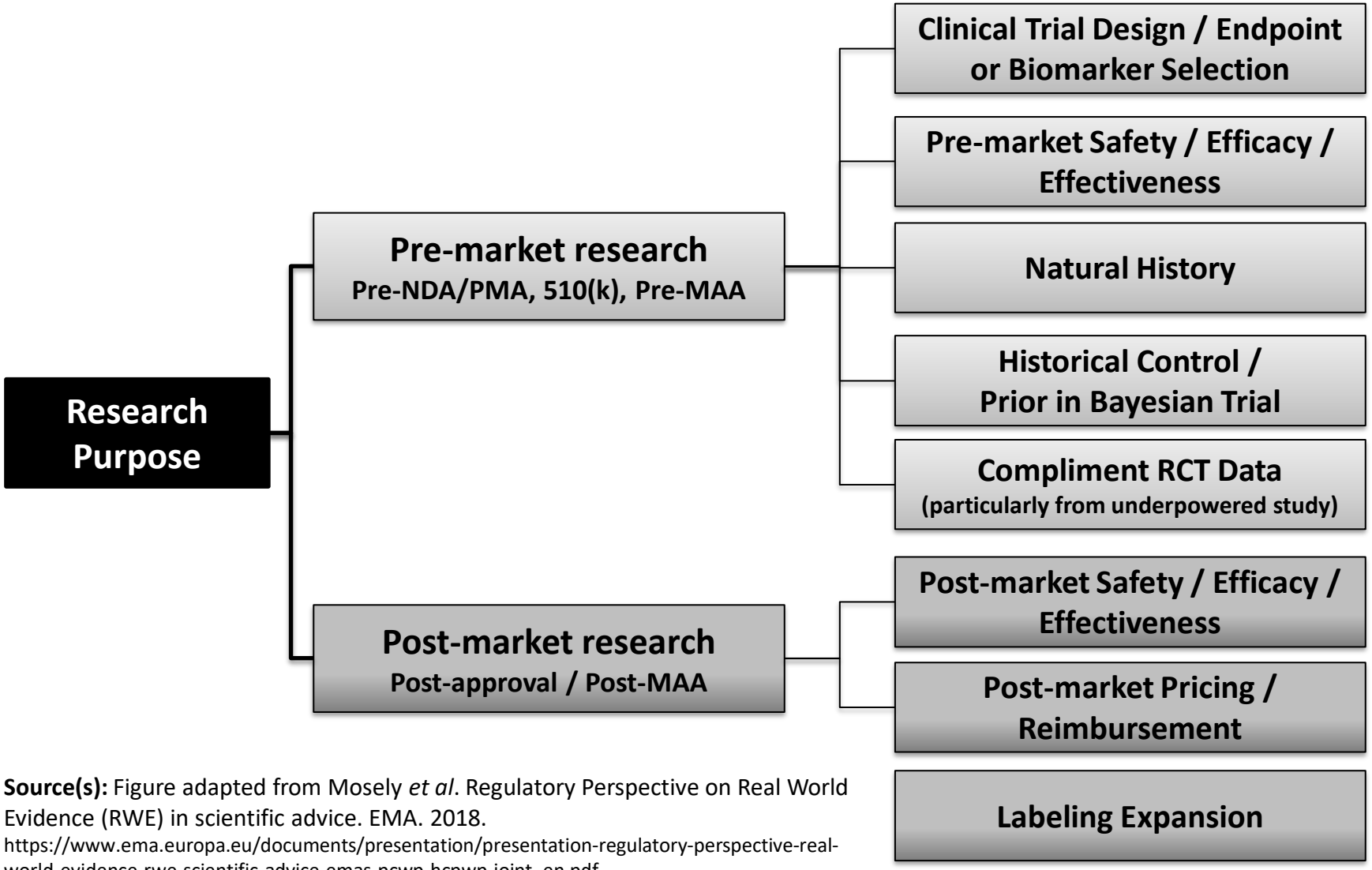
Contributions of RWE

Where does RWE fit in Regulatory Strategy?



Source(s): Figure adapted from Mosely *et al*. Regulatory Perspective on Real World Evidence (RWE) in scientific advice. EMA. 2018.
https://www.ema.europa.eu/documents/presentation/presentation-regulatory-perspective-real-world-evidence-rwe-scientific-advice-emas-pcwp-hcpwp-joint_en.pdf

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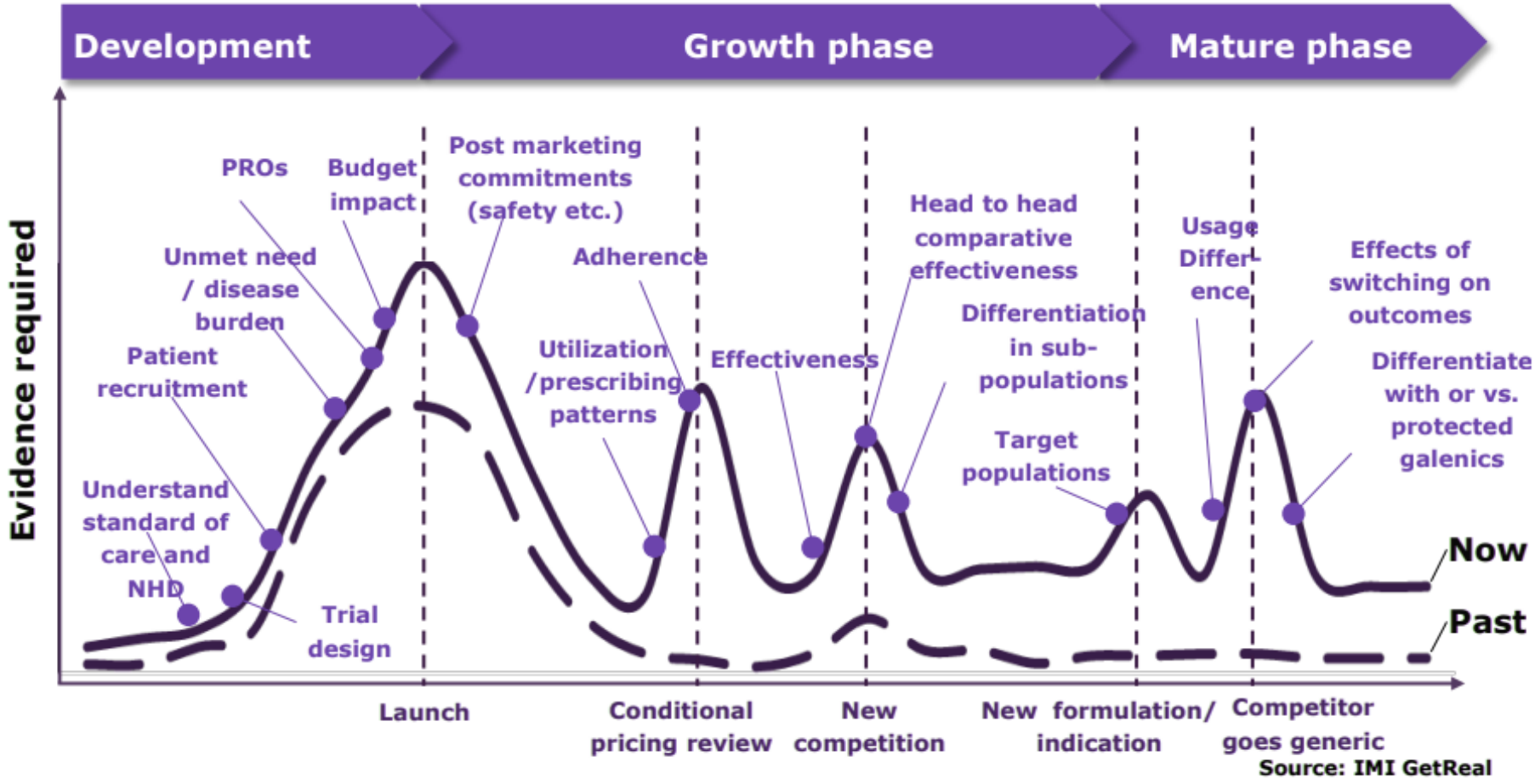
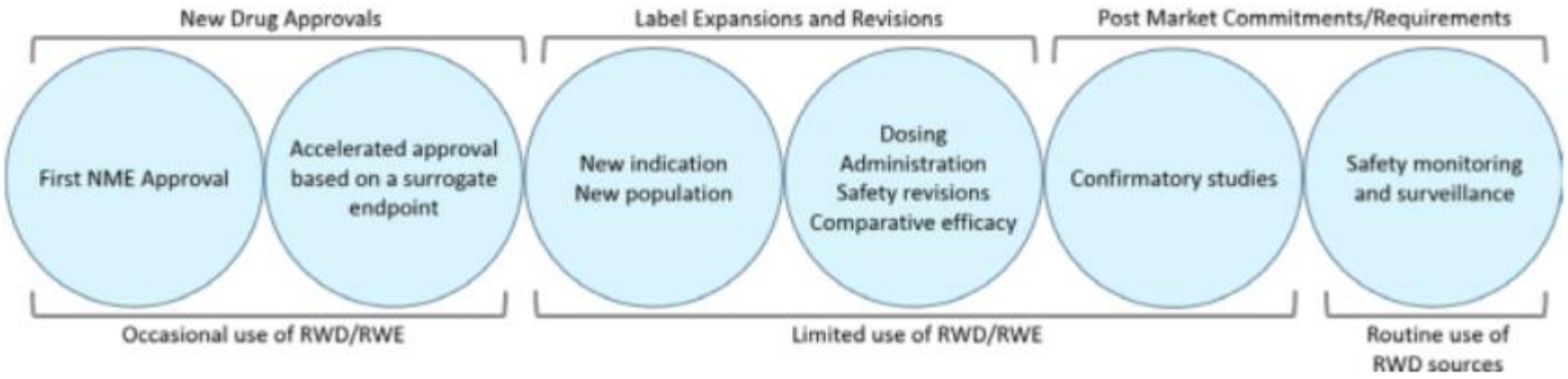
Contributions of RWE

Integrating RWE across the product lifecycle



Contributions of RWE

Integrating RWE across the product lifecycle



Source(s): Berger et al. 2017

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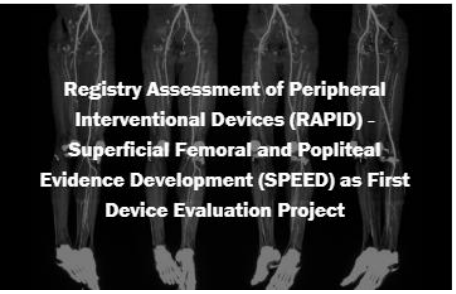
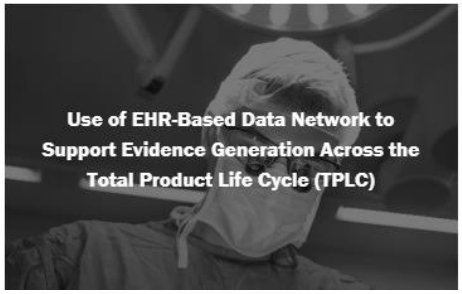
Demonstration Projects Across RWE

NESTcc has identified and selected 11 key demonstration projects to provide proof of concept for scalable approaches to evidence generation across device types and across the total product life cycle. These early NESTcc Demonstration Projects are studies that contribute to the field of Real-World Evidence (RWE) within the medical device ecosystem.





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Coordinating Center

Source(s): NEST Demonstration Projects. 2018
https://nestcc.org/demonstration-projects/

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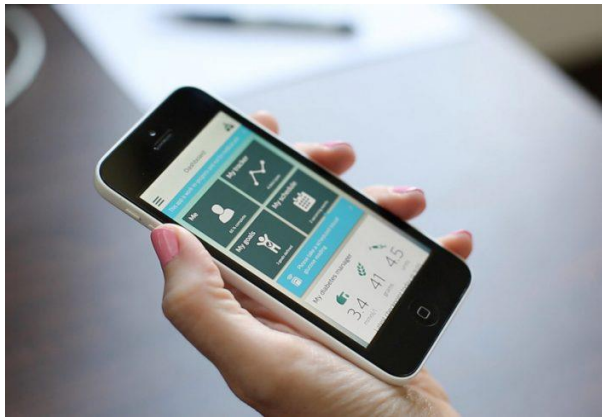
Developing and Implementing Sustainable Real-World Evidence (RWE) Infrastructure for In Vitro Diagnostics (IVDs) Through Systemic Harmonization and Interoperability for Enhancement of Laboratory Data (SHIELD)

Overview: A harmonization and mapping of in vitro diagnostic (IVD) related codes to create infrastructure to support IVDs for future pre- and post-market needs, this project includes pilots planned in antimicrobial susceptibility/resistance, opioid screening and confirmatory testing, testing for acute kidney injury, and diagnosis of sepsis.
Impact for NESTcc: This project could assist in the mapping of relevant codes to improve interoperability of information related to IVDs.
Organization(s): The U.S. Food and Drug Administration (FDA)
Collaborators Include: 5 government offices, 7 IVD manufacturers, 5 healthcare systems, and 10 professional organizations and standards developers

Post-Market Medical Device Surveillance With a Novel mHealth Platform

Overview: The project will test the feasibility of using a mHealth app for post-market surveillance in patients (1) after sleeve gastrectomy and (2) after catheter-based atrial fibrillation ablation. Outcomes collected will include enrollment times, patient participation, dropout, completion of patient-reported outcome measure queries, and user satisfaction and burden.
Impact for NESTcc: The systematic process used to test and validate the mHealth app and assess its feasibility of use will provide insight and produce a framework for future use of mHealth apps in the post-market setting. Learnings will be extendable to pre-market evidence generation use-cases in the future.
Organization(s): Johnson & Johnson, U.S. Food and Drug Administration (FDA), Me2Health, Yale-Mayo Clinic Center for Excellence in Regulatory Science and Innovation (CERSI)



Overview: Registry Assessment of Peripheral Interventional Devices (RAPID) is a program that developed a global case report form that will allow for total product life cycle (TPLC) regulatory decisions. Under the RAPID program we aim to run a series of projects and studies (i.e. SPEED). The SPEED project is the first project under the RAPID program and it was designed to develop objective performance criteria (OPC) for devices used for the treatment of peripheral arterial disease (PAD) with the aim to support and likely accelerate label expansions of Peripheral Vascular Intervention (PVI) devices.
Impact for NESTcc: Use of Real-World Data (RWD) to develop Objective Performance Criteria (OPCs) to ultimately accelerate regulatory decisions for PVI Devices.
Organization(s): MDEpiNet Executive Operations Committee;
Over 36 organizations including 3 registries/societies, 7 federal agencies, 12 device manufacturers, and 16 others

Registry Assessment of Peripheral Interventional Devices (RAPID) - Superficial Femoral and Popliteal Evidence Development (SPEED) as First Device Evaluation Project

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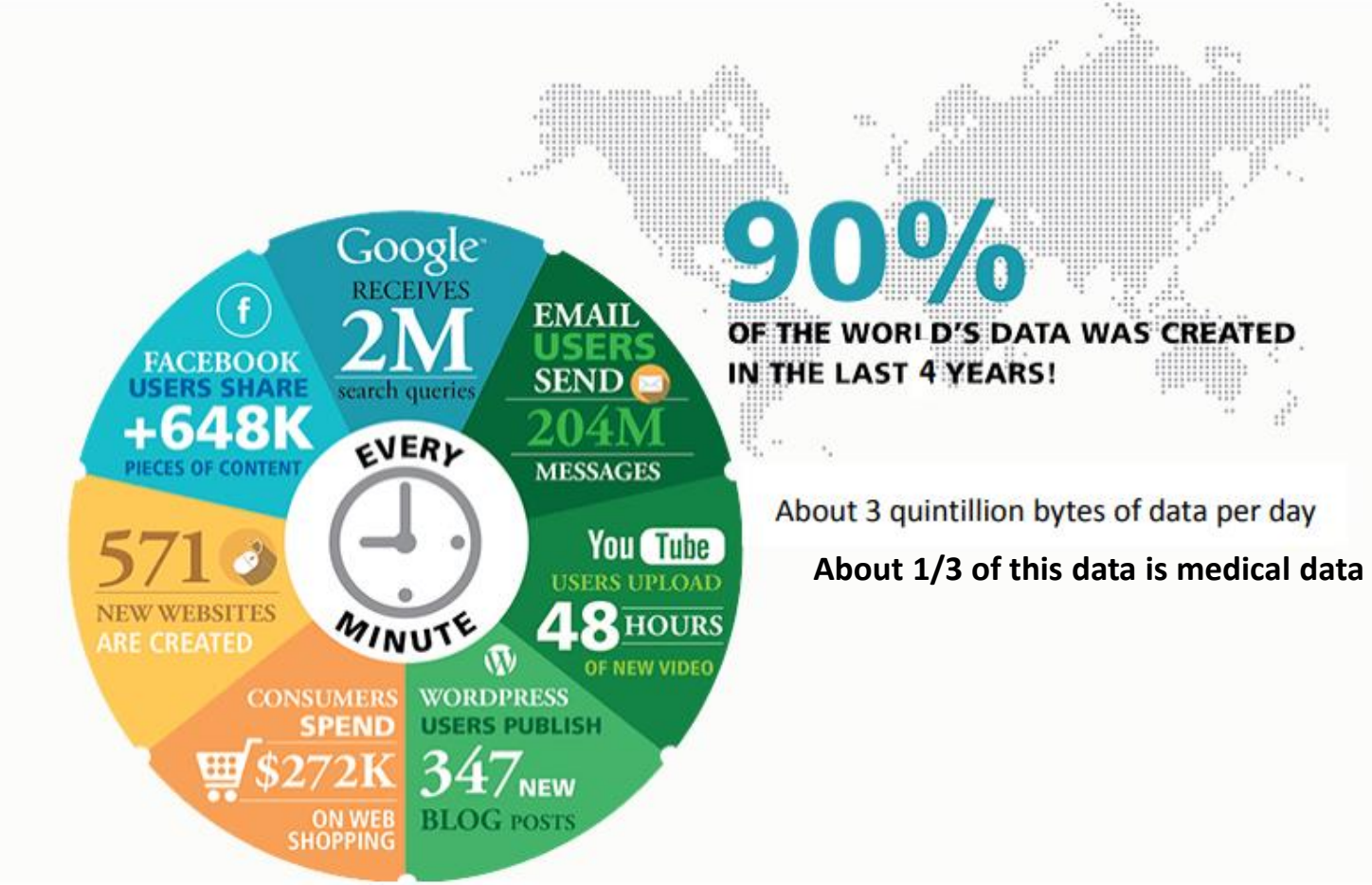
What's 'Big Data' Got to Do With it?



Source(s): Khozan. FDA. 2018. https://www.hl7.org/documentcenter/public_temp_45359812-1C23-BA17-0C78A074D09A2AB0/calendarofevents/other/PartnersInteroperability/Sean%20Khozin.pdf

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What's 'Big Data' Got to Do With it?

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

HMA
Heads of Medicines Agencies

"Analysis of data of medicines in the 'real world', i.e. in normal conditions of use, has the potential to support regulatory decision-making throughout the product life cycle. In 2017, EMA and the NCAs established **a new task force to explore how big data can be used to support research**, innovation and robust medicines development for the benefit of human and animal health."

Source(s): EMA Annual Report 2017.
https://www.ema.europa.eu/documents/annual-report/2017-annual-report-european-medicines-agency_en.pdf

FDA

IDEA LAB

Information Exchange and Data Transformation (INFORMED) is an initiative in big data that includes investigations into the use of real world data for clinical evidence generation and prospective pragmatic clinical trials, testing the utility of biosensors and the internet of things to quantify intrinsic and extrinsic (e.g., environmental) factors influencing the patient's experience, identifying opportunities for machine learning and artificial intelligence to improve existing practices, and exploring the utility of open-access platforms and emerging technologies such as blockchain to enable secure exchange of health data at scale.

Source(s): FDA. Information Exchange and Data Transformation (INFORMED). 2018.
https://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/oce/ucm543768.htm

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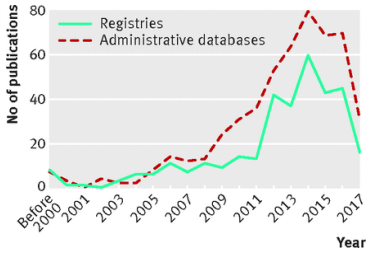

Global RWD Sources

		Database	Patients (M)	Access
Japan	MHLW	National claims database	126	Primarily academic, significant data cleaning
US	CMS	Medicaid/Medicare claims databases	120	Primarily academic, has limitations
France	SNIIRAM	National claims database	60	Limited to academics and policy experts
UK	PMSI	National hospital claims database	60	Limited to academics, future uncertain due to privacy concerns
	CPRD	Electronic medical record (EMR) data from 10% general practitioners	53	80% of drug companies purchase access
	HES	English hospital EMR database	15	None, data concerns
Germany	AOK, WIdO		24	
	Barmer GEK	Regional public sickness funds claims data	9	Primarily academic, has limitations
	TK, Wineg		7	
Denmark	sundhed.dk	National cross-linked healthcare databases	6	Primarily academic, has limitations

Source(s): Adapted from McKinsey data 2018

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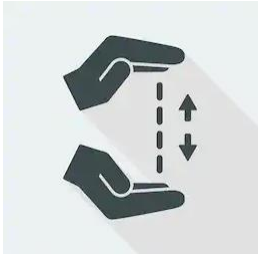
The Benefits of 'Big Data'

BREADTH

large numbers of individuals get us closer to the underlying source population – potential reduction in selection bias?



DEPTH

increasing amount of data on each individual increases the chance that we will have measures of likely confounders – potential reduction in information bias

DIVERSITY

different types of data offer the potential to "cross check" findings for any particular data source – potential to enhance control for residual bias and/or improve generalizability?

Source(s): Martin, D. FDA. FDA Approaches to Analytical Challenges Posed by Big Data. 2018. https://www.ema.europa.eu/documents/presentation/presentation-fda-approaches-analytical-challenges-posed-big-data-david-martin_en.pdf

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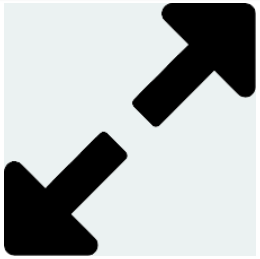
The Challenges of 'Big Data'



VOLUME

Large volumes of data can be difficult to analyze due to non-linearity, class imbalance, variance and bias, and modularity issues.

VARIETY/VERACITY

Heterogeneity, noise, dirty data, and uncertainty of data can complicate analysis

Velocity

Changes in data real-time, accessibility issues, concept drift, and distribution of random variables can pose issues.

Source(s): Martin, D. FDA. FDA Approaches to Analytical Challenges Posed by Big Data. 2018. https://www.ema.europa.eu/documents/presentation/presentation-fda-approaches-analytical-challenges-posed-big-data-david-martin_en.pdf

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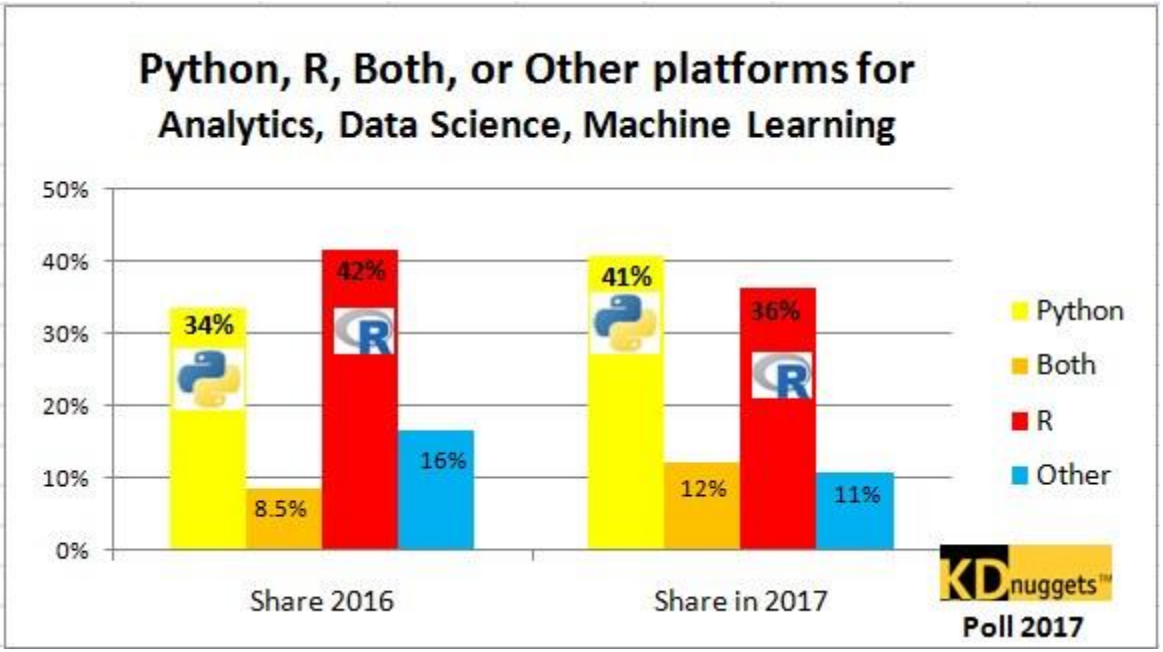
RWE, Analytics, and Big Data

Increasingly ‘big data’ requires thoughtful and intentional analytics. While often not designed with RWE use in mind, new fields in data science are emerging that enable better analytics and integration with systems like EHR to gain population insights.

While SAS is conventional in clinical trials settings, where data is controlled and homogeneous, tools like **Python and R are gaining popularity** in RWE data science.



RWE, Analytics, and Big Data

Challenges of data analysis for RWE with R and Python include:

- Working differences between trial statisticians/data managers and data scientists
- Scope creep and impact of exploratory reports
- Interactions with agency when using non-SAS format for analysis
- Ability of regulatory professionals to bridge the communication gap between programmers and others, and articulate need for various analytical methods
- Inconsistent harmonization of data reporting standards for RWE

By Frits Ahlefeldt

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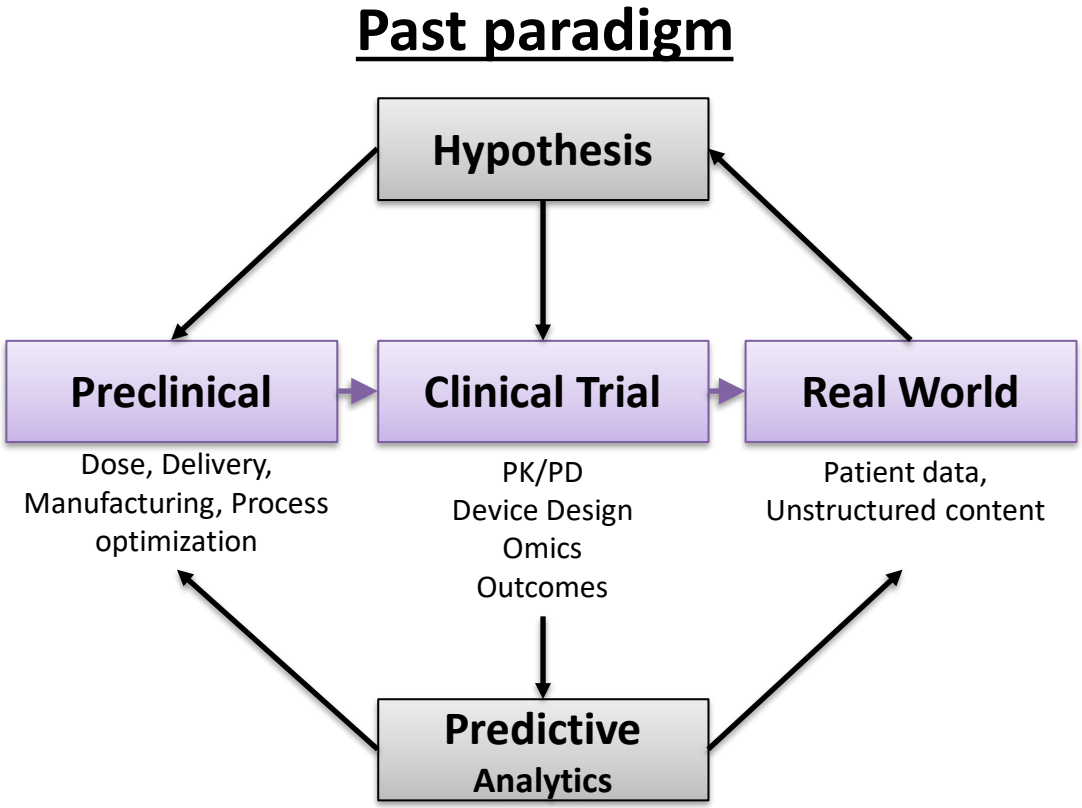
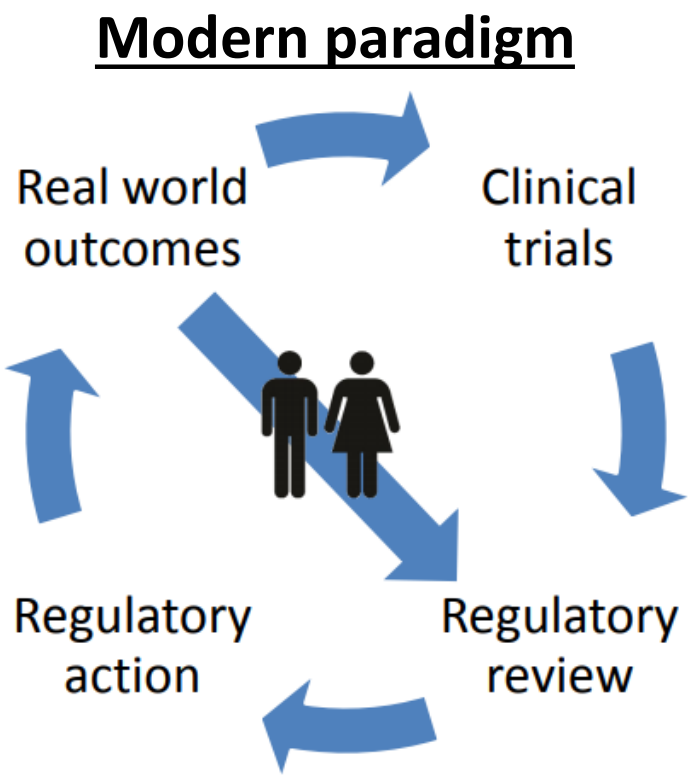
Learning Healthcare Systems

Big Data makes possible 'Learning Healthcare Systems'





Source(s): Khozan. FDA. 2018. https://www.hl7.org/documentcenter/public_temp_45359812-1C23-BA17-0C78A074D09A2AB0/calendarofevents/other/PartnersInteroperability/Sean%20Khozin.pdf

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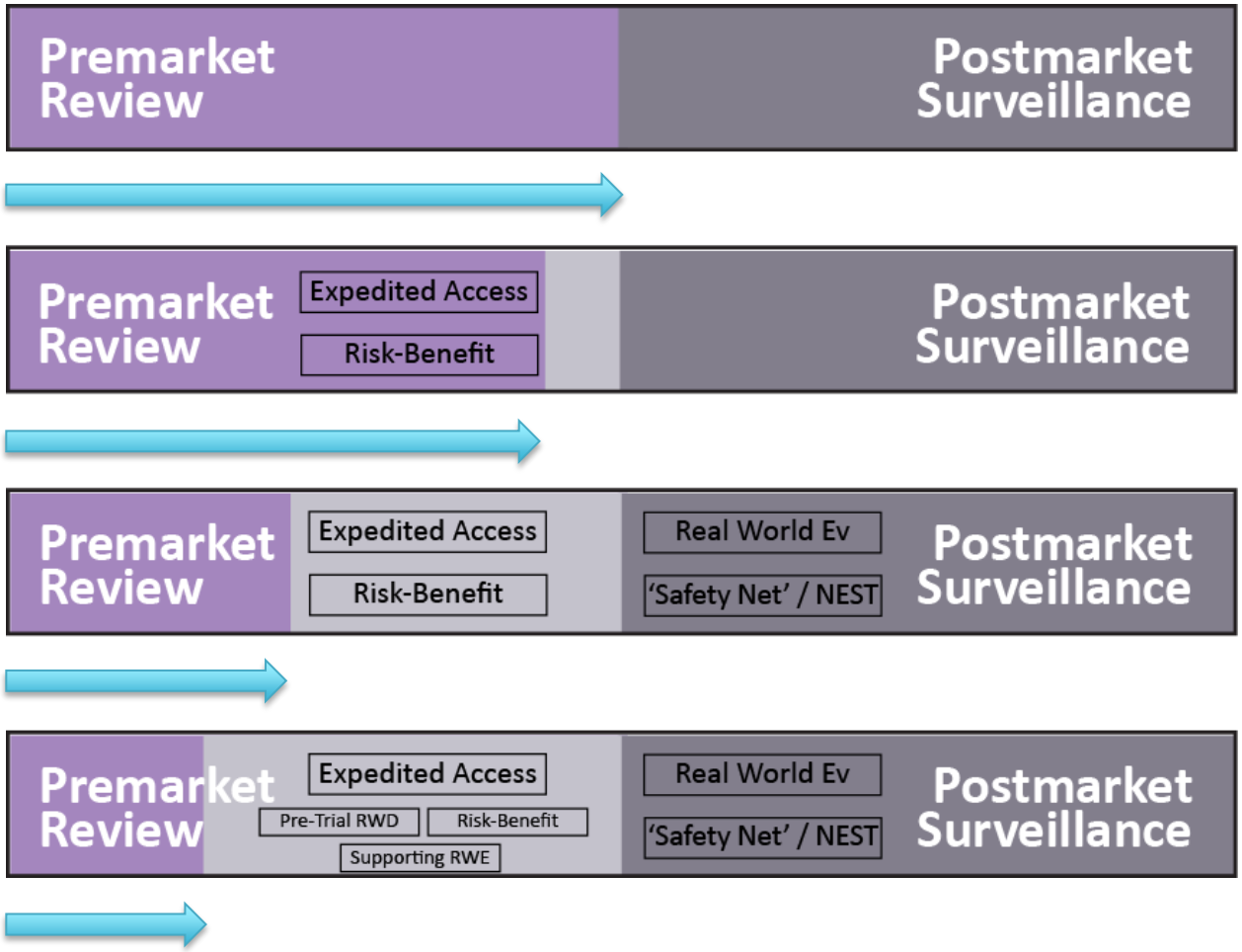
RWE to Reduce Time-to-Market

Time-to-market can be reduced by integrating RWE into multiple areas of the product lifecycle.



RWE for Advanced Therapies

Outcomes-based contracting/reimbursement: payment is linked via rebate levels or other mechanism to demonstrated real-world outcomes of patients, such as:

- Novartis agreement with CMS where CMS will cover Kymriah® (CAR-T therapy) only if patients respond within the first month after treatment
- Merck agreed to provide rebate payments to Cigna and Prime Therapeutics for its MS drug Rebif if hospital visits were required due to relapses (QuintilesIMS, 2013).

Source(s): Khozan. FDA. 2018. https://www.hl7.org/documentcenter/public_temp_45359812-1C23-BA17-0C78A074D09A2AB0/calendarofevents/other/PartnersInteroperability/Sean%20Khozin.pdf

	Key Pitfalls/ Challenges Observed	Opportunities to Address Challenges using RWE	Illustrative Case Examples
Building the Baseline	• Defining who the target patient is and how they get there, especially in indications with "softer" diagnostic criteria • Defining BOI, especially in rarer indications and those with uncertain diagnostic criteria	• Demonstrate regenerative medicine comparative efficacy with complete characterization of pre-treated and SOC-treated patients • Generate natural history data to establish course of disease • Demonstrate lack of effective treatment options	**Successes:** Tisagenleucel (CAR-T therapy) in acute lymphoblastic leukemia (ALL) used RWE approaches to define natural history and BOI in target patients, keys to measuring value vs. alternative options[12] GSK2696273 in ADA-SCID started data collection early on in clinical development, with 7-year median follow-up demonstrating durable long-term therapeutic effect (92%) against established baseline[12-17]
Priming the Pump	• Identifying where to find sufficient target patients to reach trial recruitment goals and adequate powering	• Retrospective data analysis to identify relevant subgroups	**Challenges:** Ixmyelocel-T in critical limb ischemia faced difficulty defining target patients contributing to slow pivotal trial recruitment, insufficient powering to meet primary endpoint, and only met secondary/surrogate endpoints[18,19]
Pulling Through the Value Story	• Avoiding evidentiary uncertainty in demonstrating "transformative" product value • Adequately capturing critical measures of value to align with anticipated product pricing	• Characterize implications of surrogate endpoints to help establish SOC baseline • Run indirect treatment comparisons alongside pivotal studies • Anticipate need for retrospective analyses of trial data to identify patient subpopulations • Real-world, post-market, follow-up plan for safety and effectiveness coupled with a risk sharing strategy to help enable uptake • Natural history data to establish course of disease	**Successes:** Tisagenleucel (CAR-T therapy) single-arm pivotal study in ALL leveraged RWE approaches to demonstrate transformative benefit vs. most-relevant comparator **Challenges:** Talimogene laherparevec in unresectable metastatic melanoma did not include sufficient direct or indirect comparisons to the most-relevant comparators and patients with differing BRAF status to demonstrate added benefit in Germany, which may have been addressed alongside the pivotal study[20] Alipogene tiparvovec in lipoprotein lipase deficiency (LPLD), moderate efficacy based on surrogate endpoints (blood triglycerides/chylomicron levels), unclear value relative to price given variable patient response, and non-sustained effect beyond 6-12 months[21] Sipuleucel-T in metastatic, hormone-refractory prostate cancer showed 4 months improvement in OS but not PFS, confounding true benefit in relation to commercial strategy; early retrospective subpopulation analysis may have uncovered greater benefit in certain patient types to hone value story at launch[22,23]

Source(s): Mihos et al. 2018. Leveraging Real-World Evidence for Regenerative Medicine and Advanced Therapy Success Beyond the Regulator

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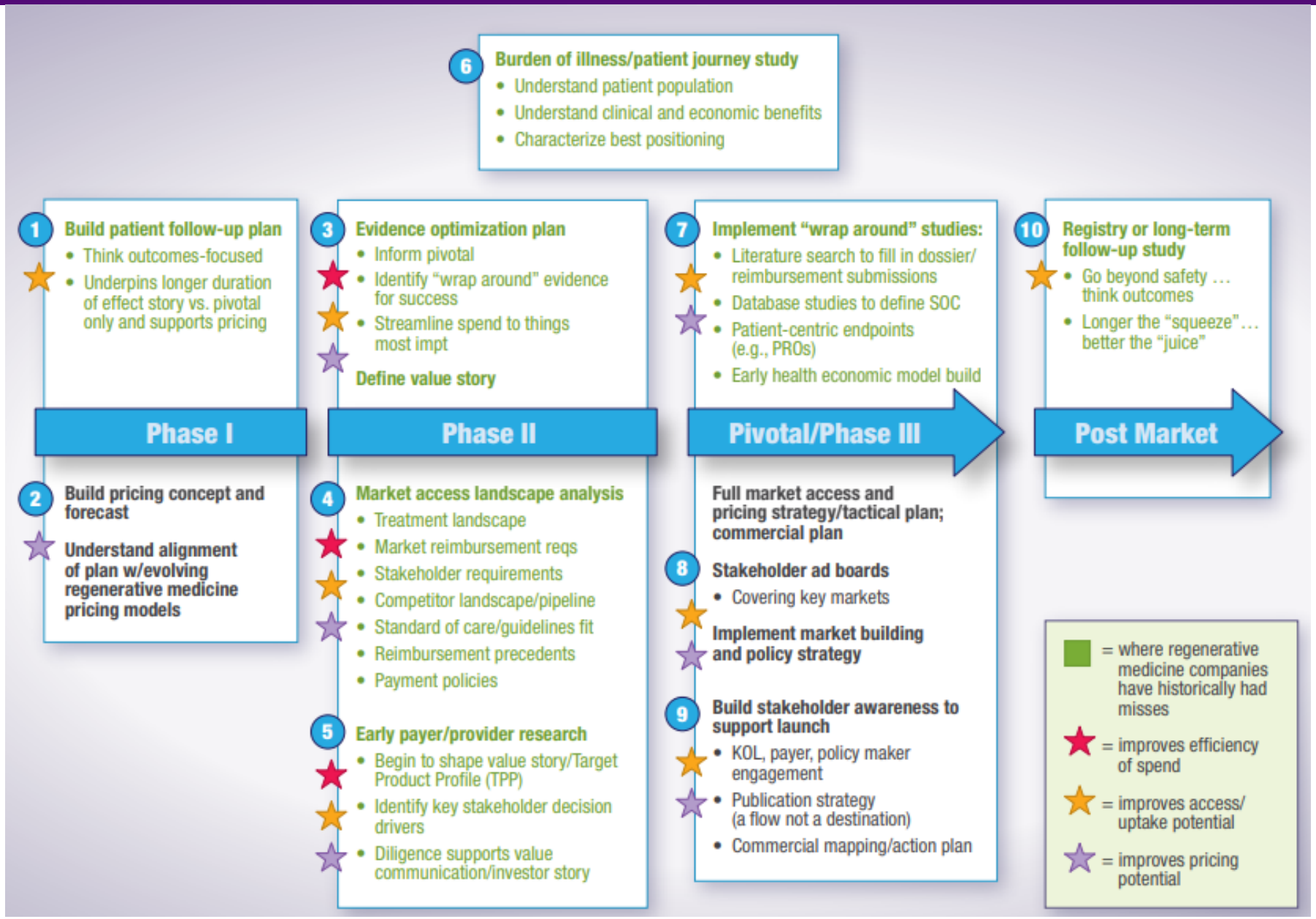

Source(s): Adapted from Mihos et al. 2018. Leveraging Real-World Evidence for Regenerative Medicine and Advanced Therapy Success Beyond the Regulator

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Innovative Use of RWE
in Medical Devices & Advanced Therapies

- **Rare diseases**, either to identify endpoints for pivotal trials OR as inclusive natural history studies
- **Diagnostic and preventive indications**, where RWE enables assessment of slowly progressive disease and confirmation of surrogate outcomes
- **Simple registry-based trials** for large populations, increasing patient population diversity

Thank you

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"As more opportunities arise to gather reliable data from the real-world use of medical devices, there's also more opportunities to use this data to generate evidence to support the more efficient development of new innovations and inform the safe and effective use of existing products in real-world settings"

- Scott Gottlieb, M.D., Commissioner of the Food and Drug Administration

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