從A到Z線上藥學論壇

真實世界證據如何支持新藥可近性

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What are real-world data (RWD) & real-world evidence (RWE)?

Real-world data (RWD)

Data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources

Real-world evidence (RWE)

Clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD

Claims databases (e.g., NHIRD)

Electronic health records (EHR)

Product / disease registries

Patient-reported data or survey

Collected from other sources

Labs/Genomics

- **Fit-for-purpose data**
- **Appropriate study methods**
- **Appropriate study conduct & reporting**

RWD is a necessary, but not sufficient, condition to produce RWE.

Definitions by US FDA

Some clarifications of RWD & RWE

Common misconceptions or inaccurate statements

- RWD simply means observational data
- RWE is everything but a randomized trial

✓**RWE can sometimes involve randomization, and not all non-RWE is randomized.**

✓**RWE can be generated by different study designs or analyses, including but not limited to randomized trials (e.g., pragmatic trials) and observational studies (prospective and/or retrospective)**

	Interventional	Non-interventional
Not real world	Conventional RCTs	X
Real world (RWD)	Pragmatic trials	Observational studies

RWE

What is pragmatic trial?

Explanatory trials: aim to evaluate the efficacy of an intervention in a well-defined and controlled setting

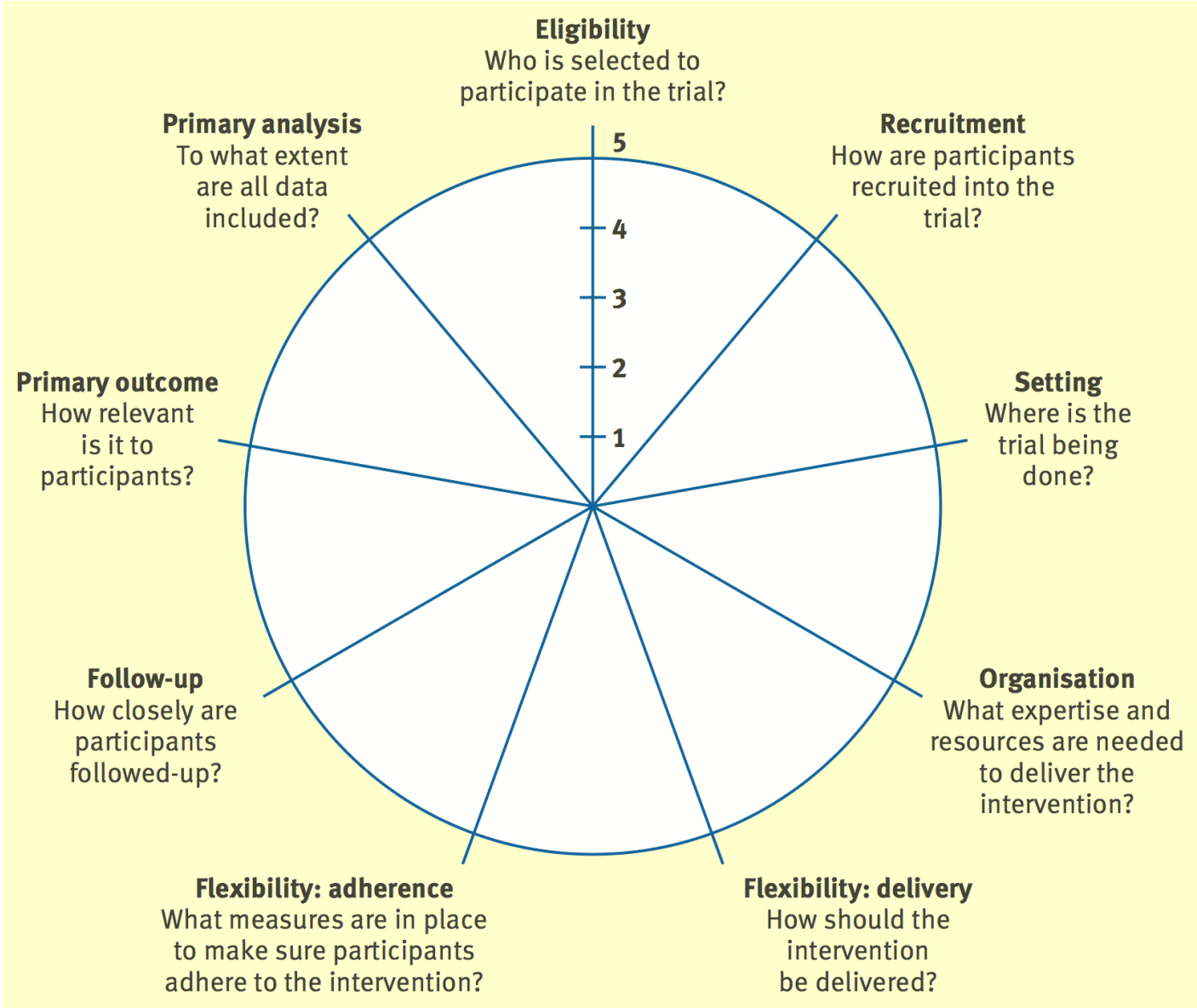
Pragmatic trials: designed to test the effectiveness of the intervention in a broad routine clinical practice

(Schwartz and Lellouch, 1967)

Pragmatic trials:

- Heterogeneous patient population
- Flexible adherence to study protocol
- Patients assessed during routine clinical practice
- Provides real-world data

PRECIS-2 tool for **pragmatic trials**



BMJ 2015;350:h2147.

US FDA

US FDA and Taiwan's actions related to RWD and RWE

2016

21st Century Cures Act (21 U.S. Code § 355 g), Title III, Subtitle C Sec. 3022 Real World Evidence

2017

1 (Final) Guidance for Industry
- Use of RWE to Support Regulatory Decision-Making for Medical Devices (2017/07)

2018

◆ **Framework for FDA's Real-World Evidence Program (Dec, 2018)**

1 (Final) Guidance for Industry
- Use of EHR Data in Clinical Investigations (2018/07)

2019

1 **Draft** Guidance for Industry
- Submitting Documents Using RWD and RWE to FDA for Drugs and Biologics (2019/05)

2021

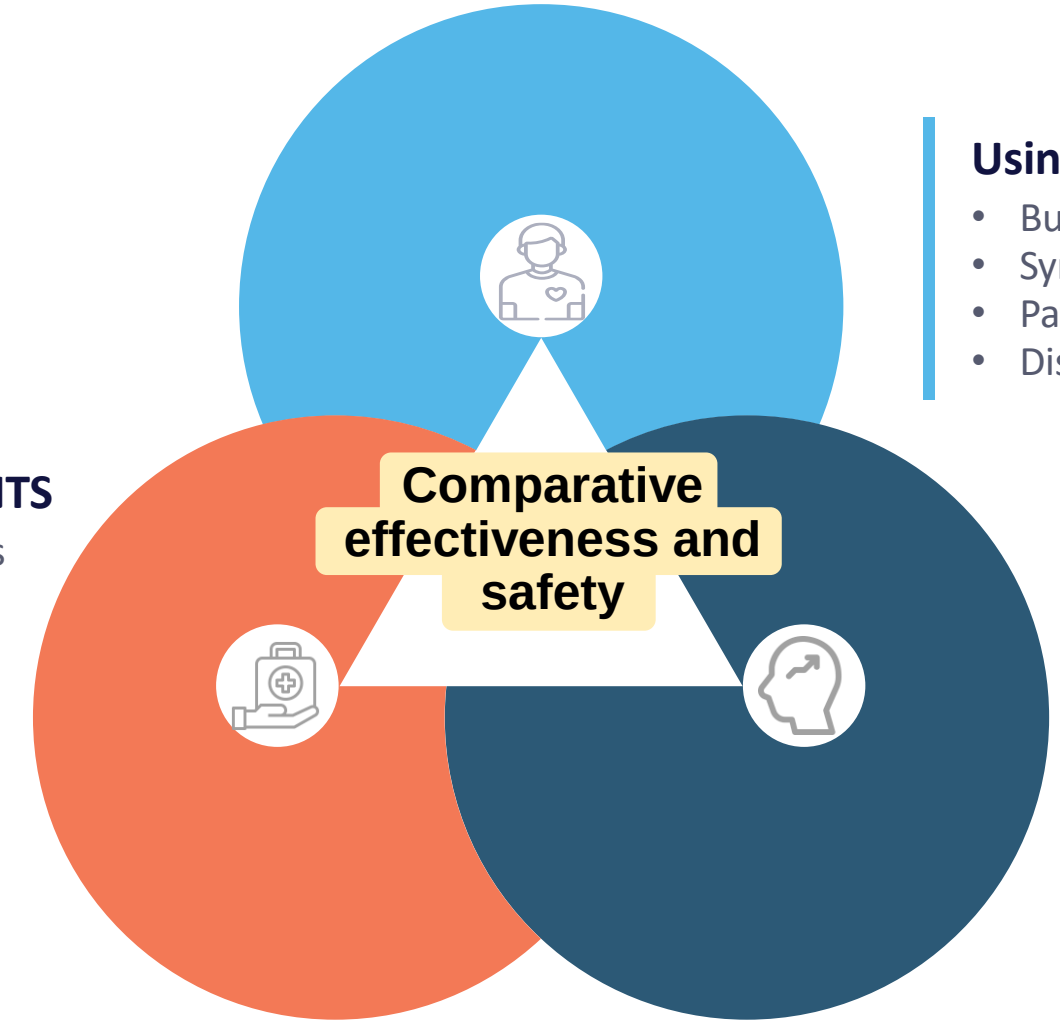
4 **Draft** Guidance for Industry (To Support Regulatory Decision-Making for Drug and Biological Products)
- RWD: Assessing EHR and Medical Claims Data (2021/09)
- Data Standards for Submissions Containing RWD (2021/10)
- RWD: Assessing Registries (2021/11)
- Considerations for the Use of RWD and RWE (2021/12)

Taiwan Food and Drug Administration
FDA 衛生福利部食品藥物管理署

財團法人醫藥品查驗中心
Center For Drug Evaluation

2020/07 真實世界證據支持藥品研發之基本考量
2020/11 採用電子病歷資料進行臨床研究指引
2021/01 真實世界證據的研究設計 - 務實性臨床試驗的考量重點
2021/03 真實世界數據 - 關聯性與可靠性之評估考量
2021/07 使用真實世界數據/真實世界證據作為申請藥品審查技術文件應注意事項
2022/03 使用電子健康照護資料執行藥品流行病學安全性研究指引 **(草案)**
2022/04 真實世界數據與證據輔助醫療器材決策管理參考文件

Use of RWD for generating RWE



Using RWD about PATIENTS/DISEASES

- Burden of disease, epidemiology
- Symptom burden
- Patients in routine practice
- Disease biology

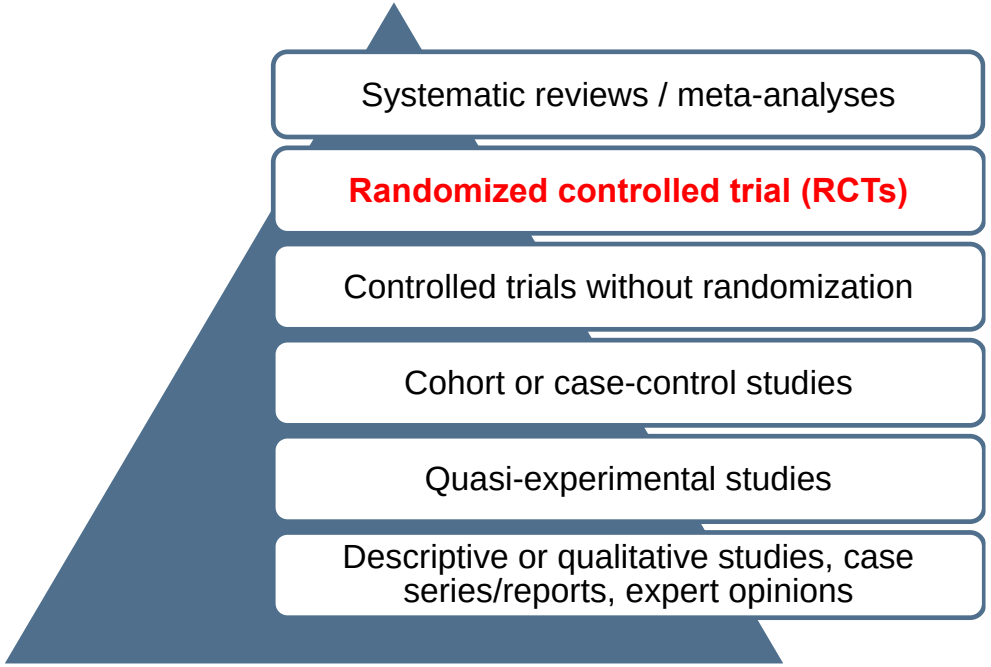
Using RWD about TREATMENTS

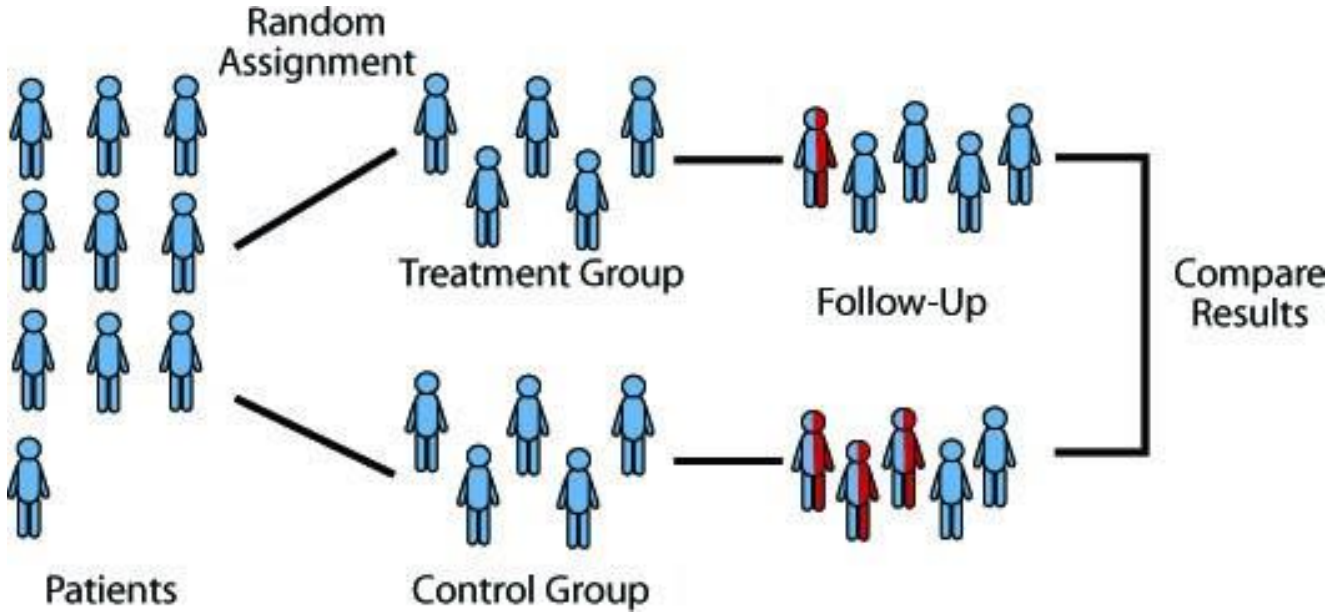
- Treatment utilization & patterns
- Access to care (e.g., disparity)
- Quality of care (e.g., guideline concordance)

Using RWD about OUTCOMES

- Race disease, patient populations, or outcomes
- Outcome reality check
- System-level perspectives
- Disease economics

Why randomized controlled trial (RCTs) present the gold standard of evidence?

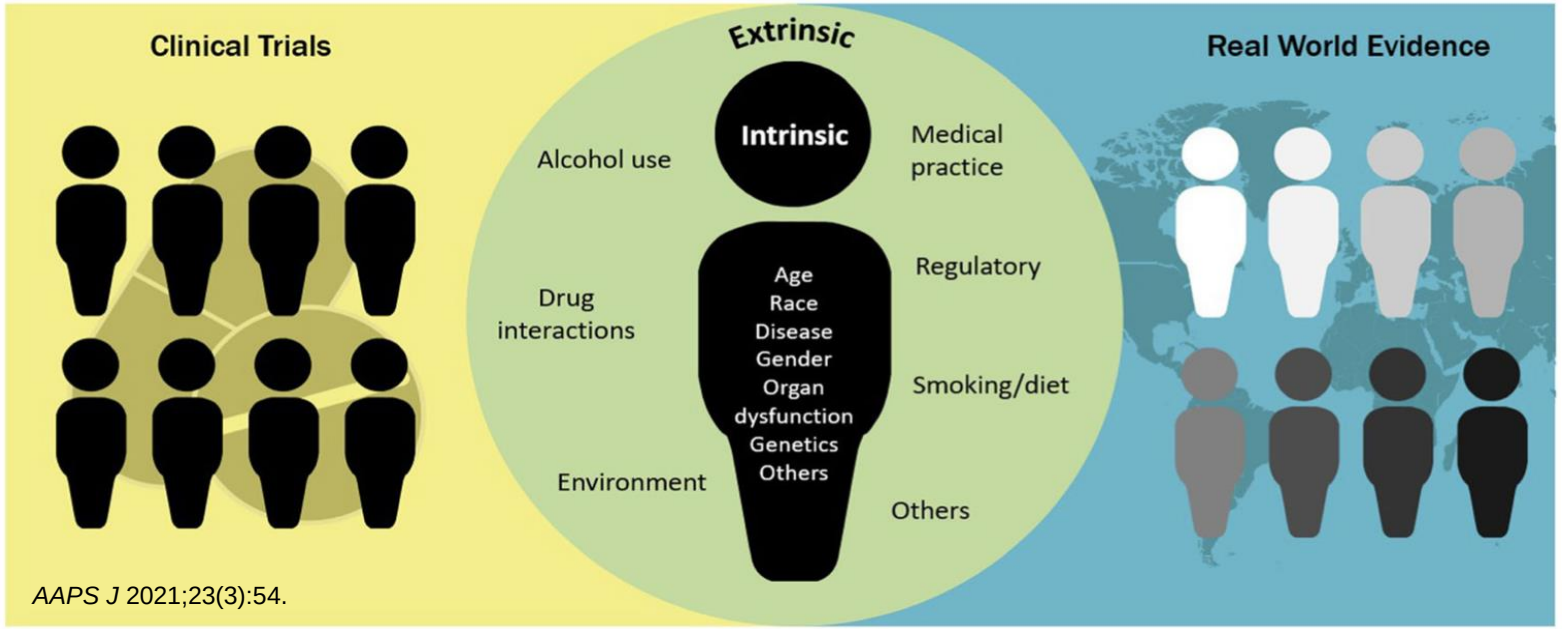




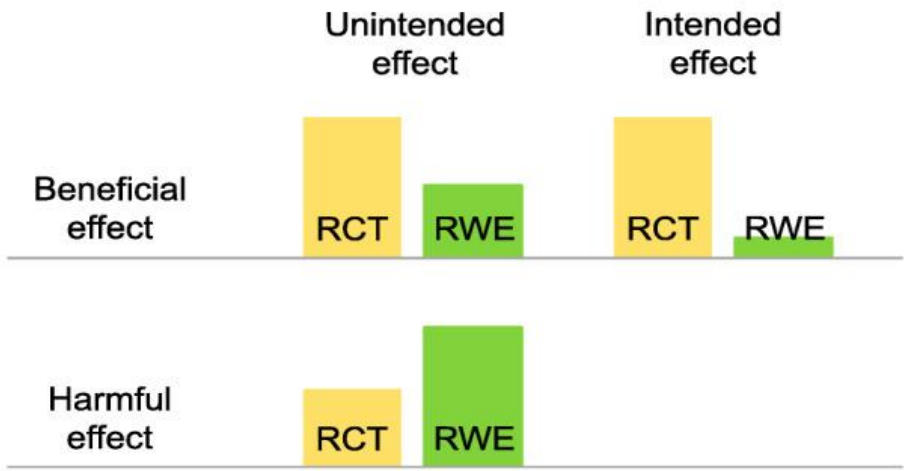
**Randomization process ensures that both measured and unmeasured confounding factors are balanced across treatment and control groups.*

http://www.tfljournal.org/staticpages/index.php?page=Common-Experimental-Designs

Why can real-world studies **augment** RCTs to address clinical issues?



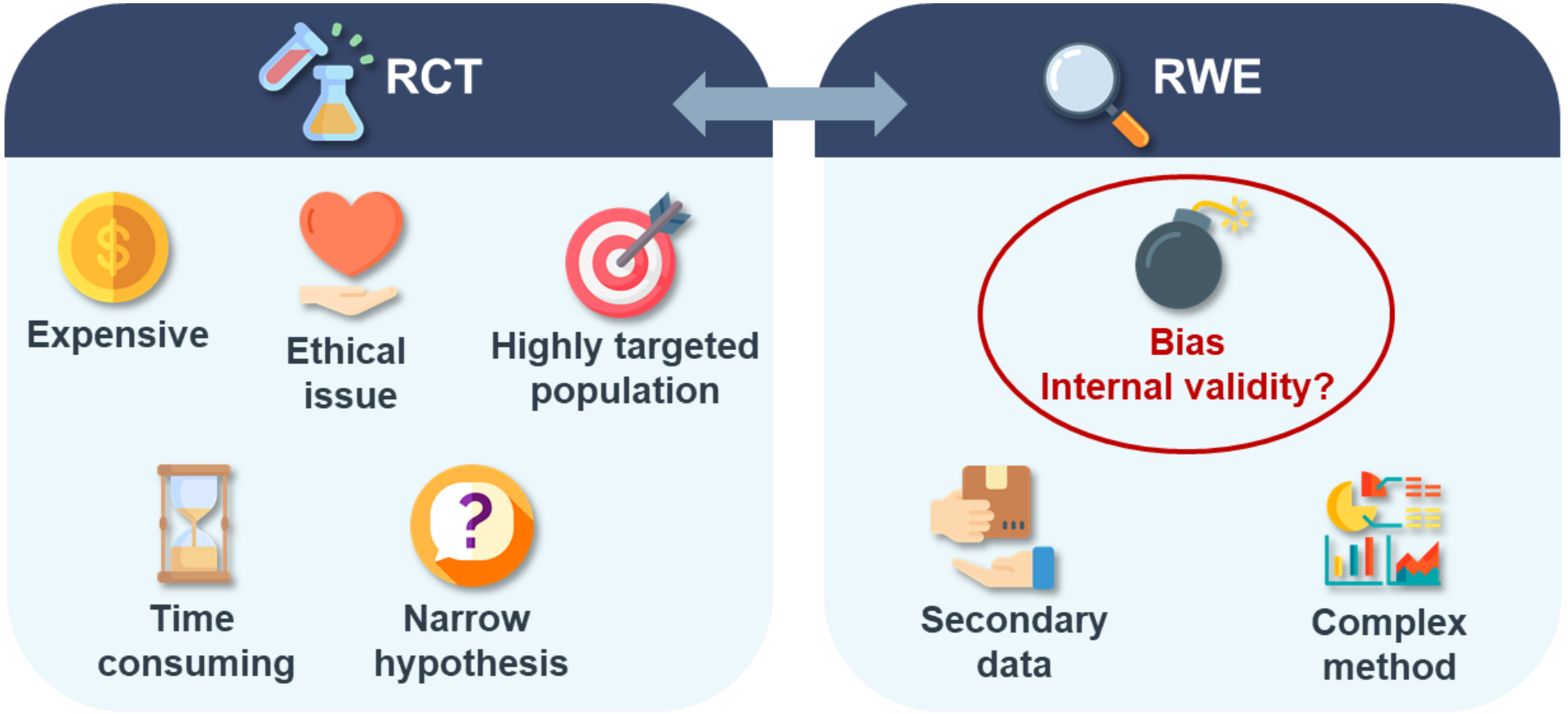
AAPS J 2021;23(3):54.



- Enrolls patients under-represented in (or excluded from) RCTs
- Study patients with different characteristics
- Allows direct treatment comparison
- Longer follow-up period (also useful for long-term toxicities)
- Potentially larger number of patients (esp. useful for capturing less frequent outcomes)
- Pharmacoeconomic data within a specific country or health system

AAPS J 2021;23(3):54.
Clin Pharmacol Ther 2017;102(6):924-33.
Oncologist 2020;25(5):e746-52.

Limitations for RCT vs. RWE



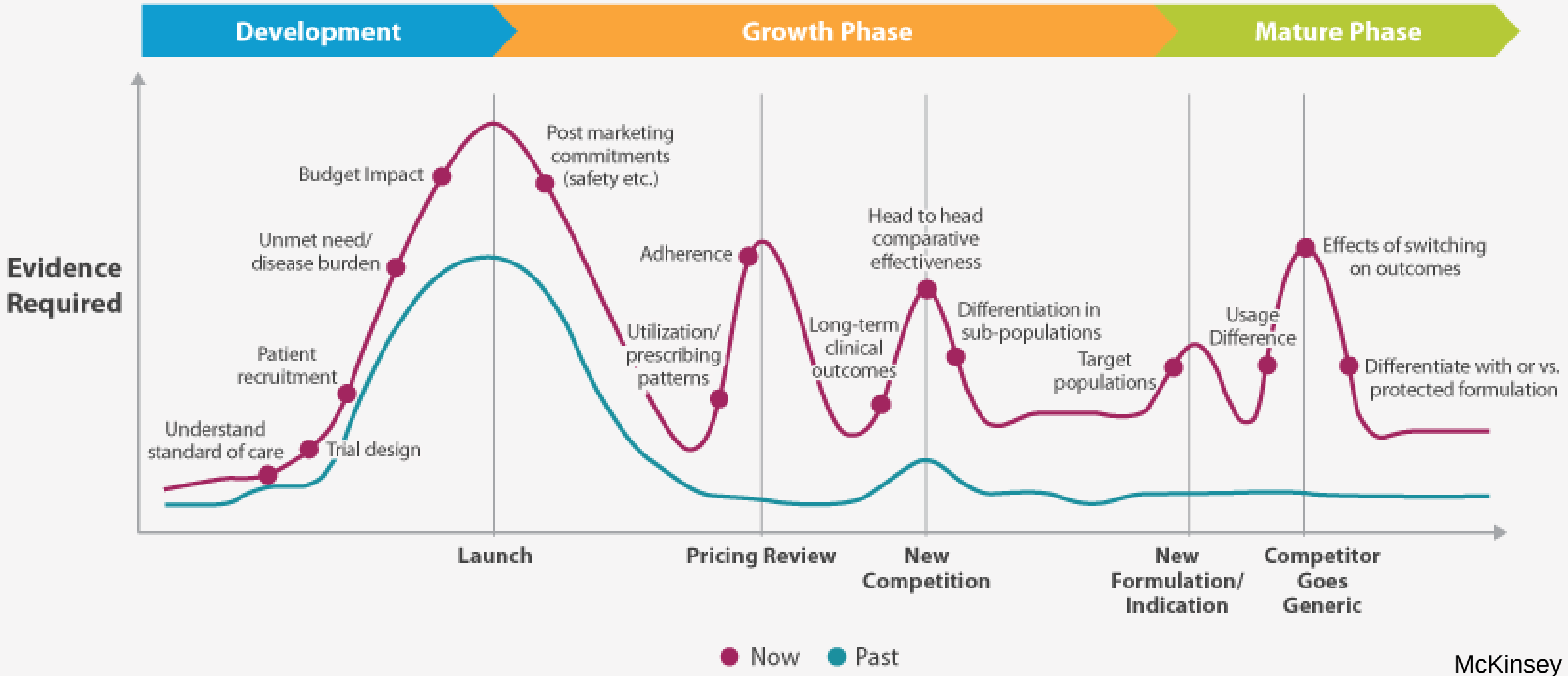
“RWE and RCTs should be seen as complementary, each having strengths and weaknesses, with their relative importance depending on the regulatory question”

A vision for use of RWE in EU medicines regulation
News published by **EMA**, 24/11/2021

How does RWE support the development and access of new drugs?

RWE Intensifying Across Product Lifecycle

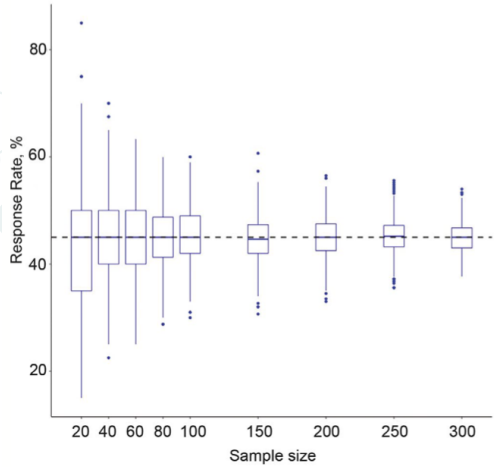
- 精進及輔助臨床試驗設計
- 藥品上市前的療效證據輔助
- 藥品上市後的監視及安全性評估
- 上市後仿單資訊的變更



McKinsey

真實世界證據如何支持新藥可近性

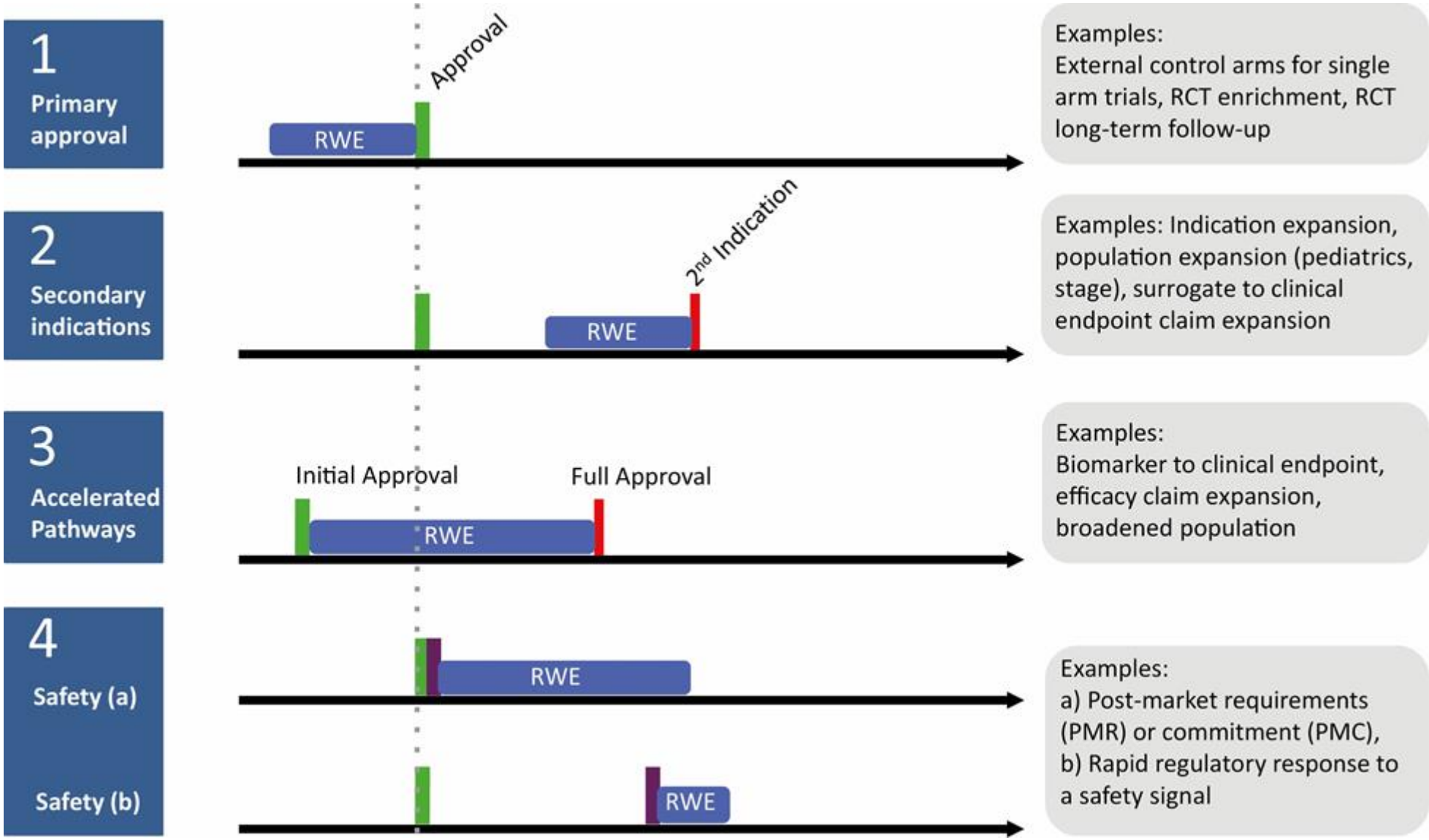
Main barriers for conducting RCT
for rare conditions or precision medicine



- **Difficult to recruit patients** due to rarity
- **Incomplete understanding of natural history** to inform trial design
- Need for **trial designs adapted to the small population size and clinical heterogeneity**
- Control arm randomization to ineffective standard therapy **raises ethical concerns**
- Molecular analyses requirements may **delay treatment** (precision medicine)
- Need for **more sensitive outcome** measures to quantify disease
- **Organizational challenges** as a consequence from the need for multinational RCTs
- Need for **involvement of all the stakeholders** in the study design and conduct

Trials 2017;18(1):556.

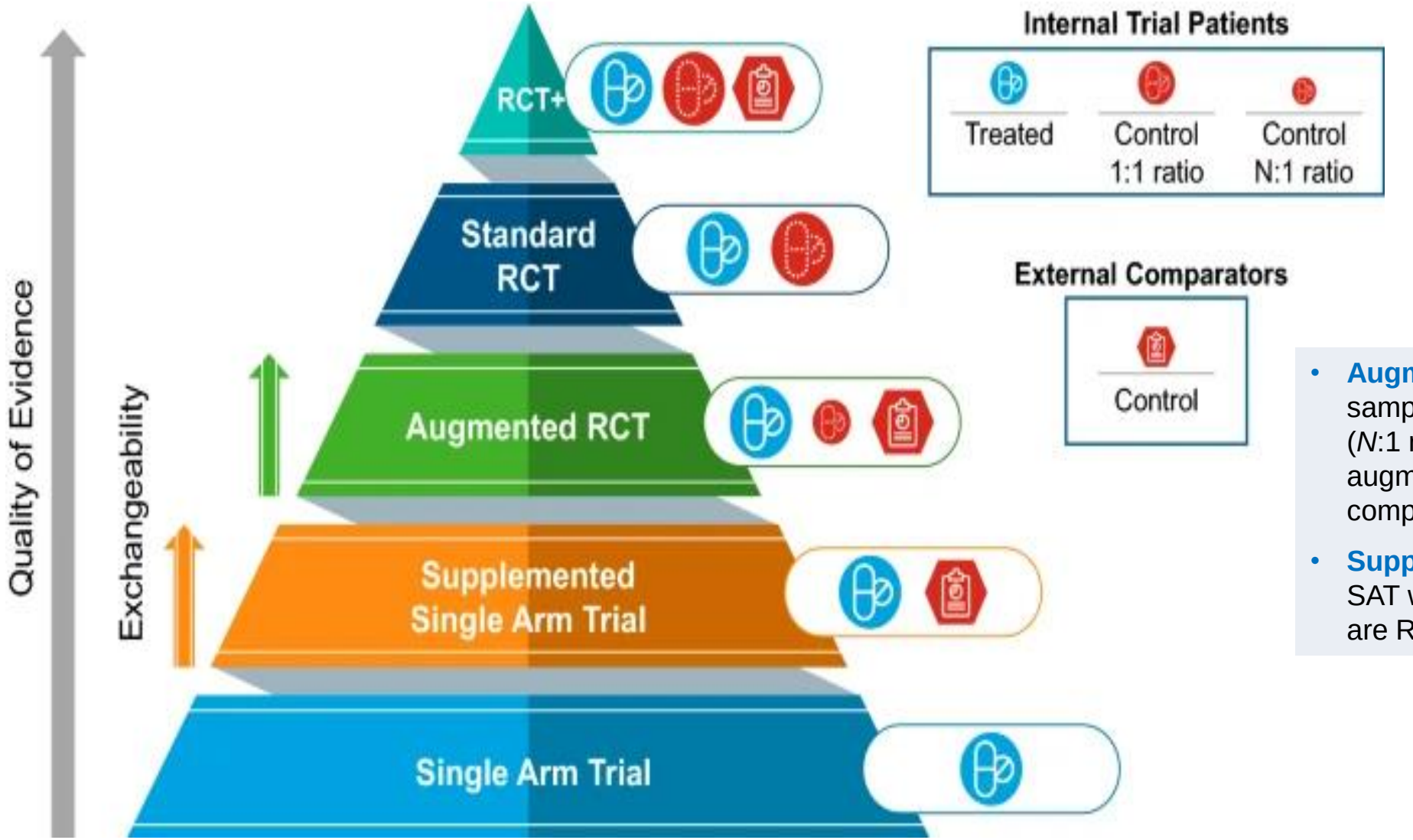
Contributions of RWE for regulatory and coverage decision-making



Endocr Rev 2021:42(5):658-90.

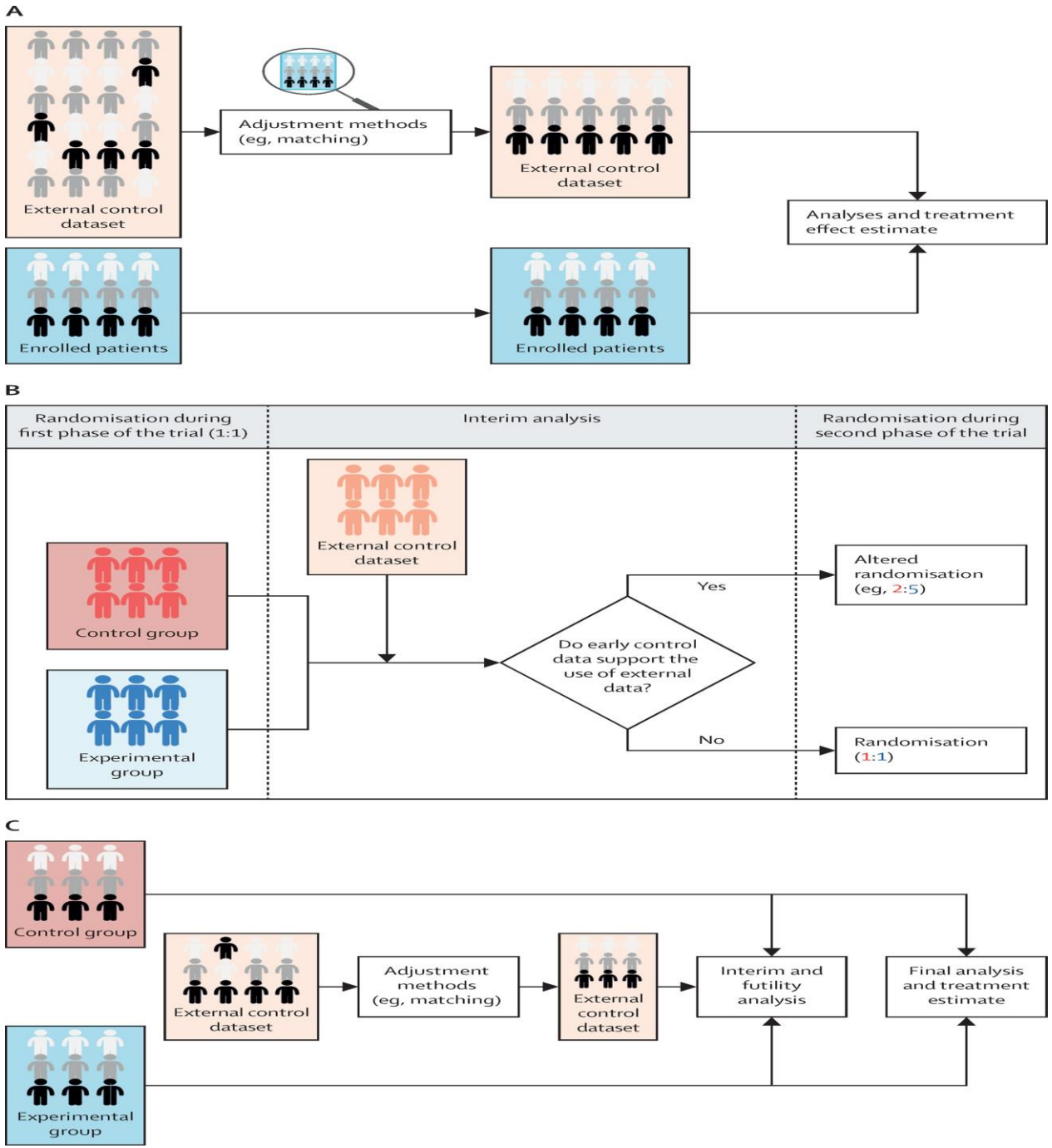
Single arm trial (單臂臨床試驗) – with/without external control (外部對照組)

Hierarchical framework (for quality of evidence offered by RWD external comparator designs)

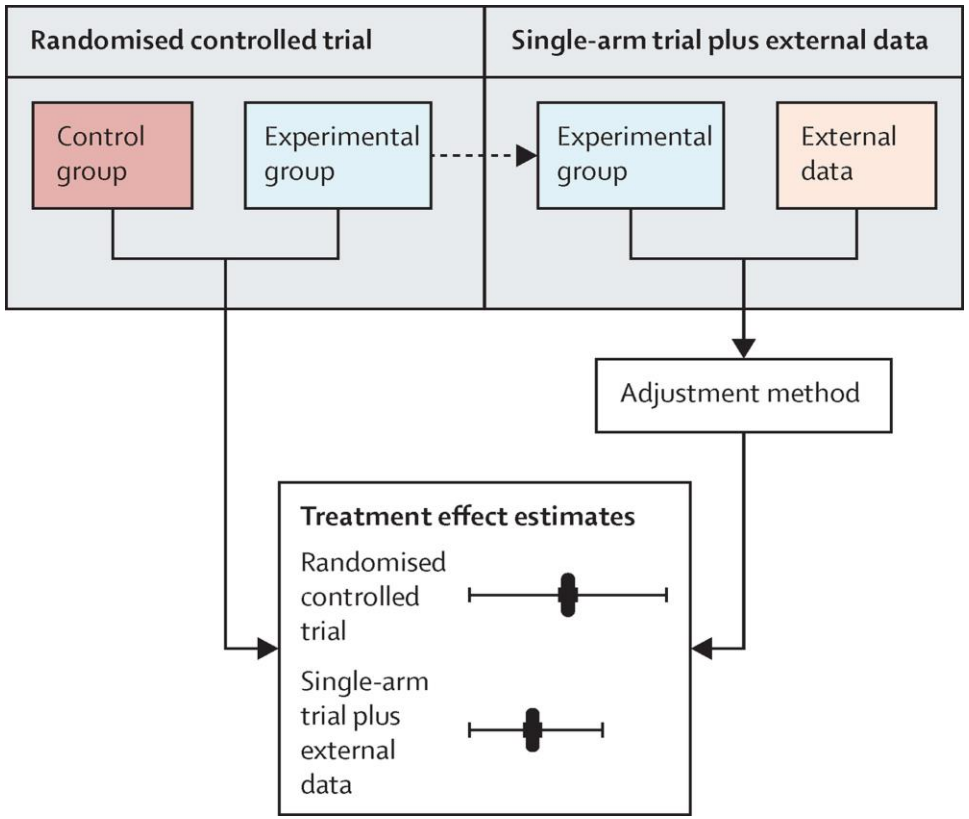


- **Augmented RCT:** RCT with reduced sample size in the internal control arm (*N*:1 randomization ratio), which is then augmented with RWD external comparators.
- **Supplemented SAT (single-arm trial):** SAT wherein the sole source of controls are RWD external comparators.

Lancet Oncol 2021;22(10):e456-e465.



"**exchangeability**": how well the unexposed (comparator) group provides an approximation for the disease experience of the exposed group, had they not been exposed



Drug Saf 2020;43(7):623-633.

What to consider when interpreting the studies with external control?

- Features of data
  - Randomized or not
  - Concurrency
  - Systematically collected or not (e.g., tumor assessments)
  - Robustness of endpoints
  - Relevant data available (e.g., to identify the population of interest at baseline, to determine if cohorts were comparable)
  - Individual-patient data vs. summary statistics only
- Other possible bias
  - Selection bias
  - Between study variability

Examples of RWE submitted in support of regulatory approval

	Clinical trial	RWE	Approval
BAVENCIO (avelumab) Metastatic Merkel cell carcinoma and urothelial carcinoma	Prospective, **single-arm**, open label, phase 2	Retrospective EHR data collection (as historical control)	Accelerated approval FDA and EMA, 2017 (Approved by TFDA and covered by NHI)
IBRANCE (palbociclib) Men with HR-positive, HER2-negative advanced or metastatic breast cancer	**N/A**	Retrospective EHR, claims data and post-marketing safety report collection	Label expansion FDA, 2019 (Label expended by TFDA)

Full (vs. accelerated) approvals mostly shared the following characteristics:

- High magnitude of efficacy in the pivotal trial
- Designations of orphan disease
- Breakthrough therapy
- Priority review
- No advisory committee meeting held (i.e., no uncertainty in efficacy or safety for the FDA to call for an advisory committee meeting)

Clin Cancer Res 2022;28(1):27-35.

RWE in support of FDA oncology product registration (2015-2020)

(New drug application [NDA] and biologics license application [BLA] approvals)

Oncology new therapy approvals with RWE

Step 1: Oncology NDAs and BLAs from 2015 to 2020
N = 133 (100.0%)

↓

Step 2: NDAs and BLAs that included RWE for efficacy
N = 11 (8.3%)
[avelumab, axicabtagene ciloleucel, entrectinib, erdafitinib, polatuzumab vedotin-piiq, selinexor, avapritinib, capmatinib, tafasitamab, tazemetostat (NDA 211723), tazemetostat (NDA 213400)]

- *None predated 2017!*
- *The most common data source was chart review, and the most common primary endpoint was overall response rate, as in the pivotal trial.*

Oncology supplemental application approvals with RWE

Step 1: All oncology NDA and BLA supplements from 2015 to 2020
N = 573 (100.0%)

↓

Step 2: Supplements for new oncology indications
N = 249 (43.5%)

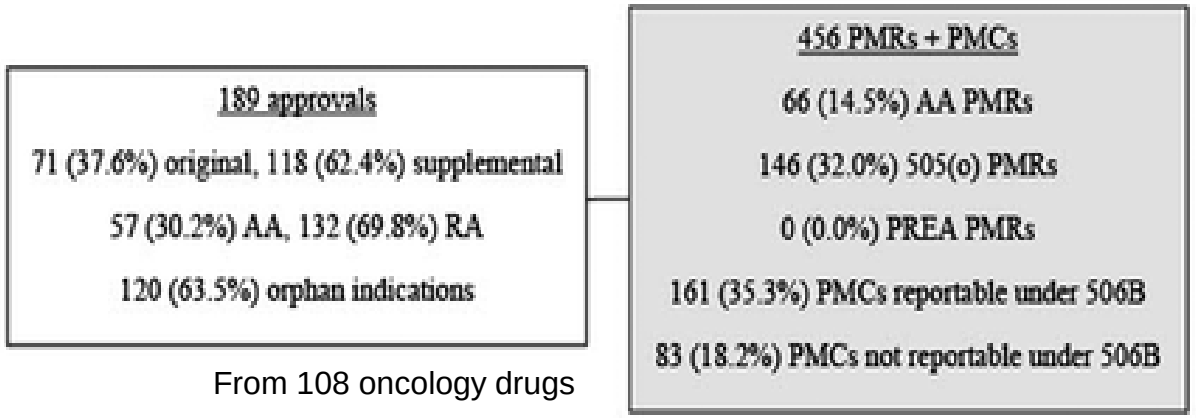
↓

Step 3: NDA and BLA supplements that included RWE for efficacy
N = 2 (0.8%)
(blinatumomab and palbociclib)

Clin Cancer Res 2022;28(1):27-35.

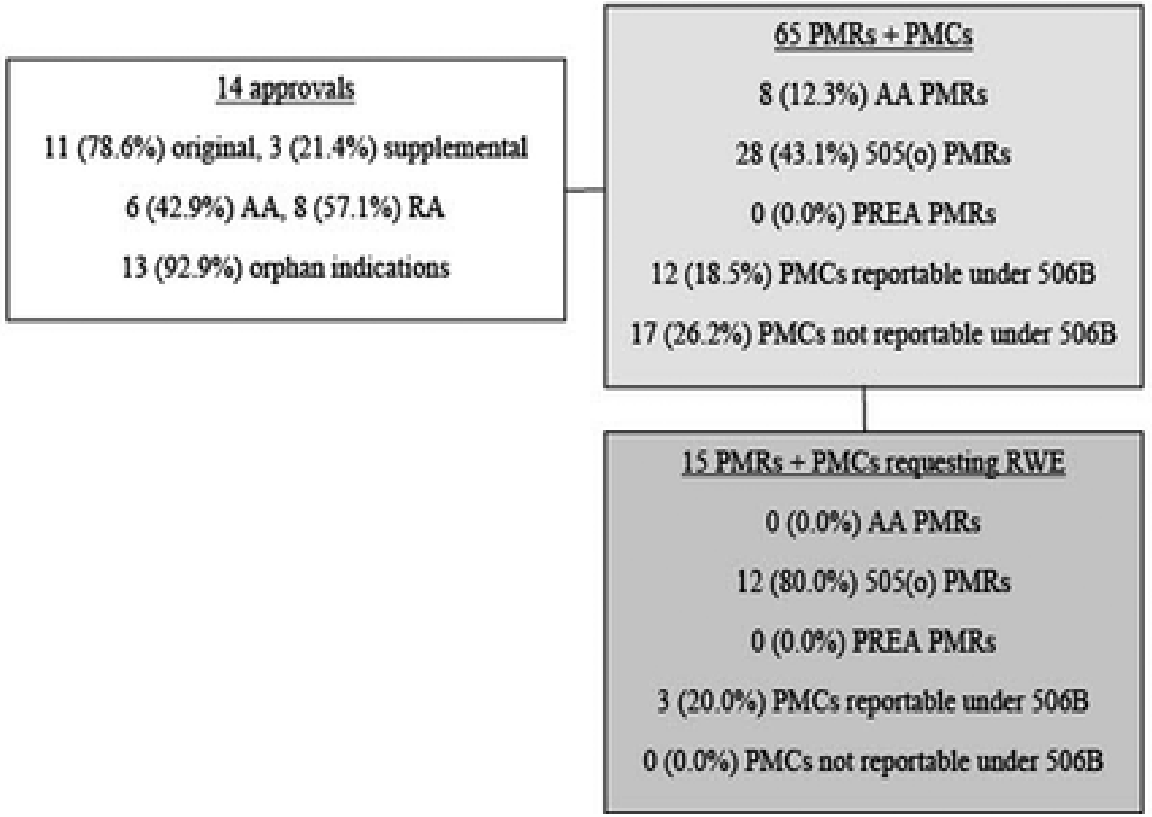
RWE in support of FDA post-approval study requirements for oncology drugs (2017-2020)

All oncology drug approvals & associated PMRs/PMCs



From 108 oncology drugs

Oncology drug approvals with PMRs or PMCs that included requests for RWE



AA = accelerated approval
RA = regular approval

PMC = post-marketing commitment
PMR = Post-marketing requirement
PREA = Pediatric Research Equity Act

Expert Rev Anticancer Ther 2022;22(6):657-66.

Examples of RWE *rejected* by U.S. FDA

Drug	FDA approval date	Type of RWE	Regulatory action supported	Limitations of RWE identified by FDA reviewers	FDA decision
Erdafitinib	April 12, 2019	EHR data and next-generation sequencing data as historical control for clinical efficacy	Original marketing application approval for locally advanced or metastatic urothelial carcinoma and susceptible FGFR3 or FGFR2 genetic alterations	Small sample size Selection bias Misclassifications Missing data	Rejected
Selinexor	July 3, 2019	EHR data as historical control for efficacy	Original marketing application approval for RRMM	Small sample size Immortal time bias Selection bias Misclassifications Confounding Missing data	Rejected
Entrectinib	August 15, 2019	EHR data as historical control for efficacy	Original marketing application approval for metastatic non-small cell lung cancer with *ROS1*-positive tumors	Small sample size Selection bias Missing data Analysis considered post-hoc as protocol was not submitted in advance	Rejected

Common identified critiques by FDA:

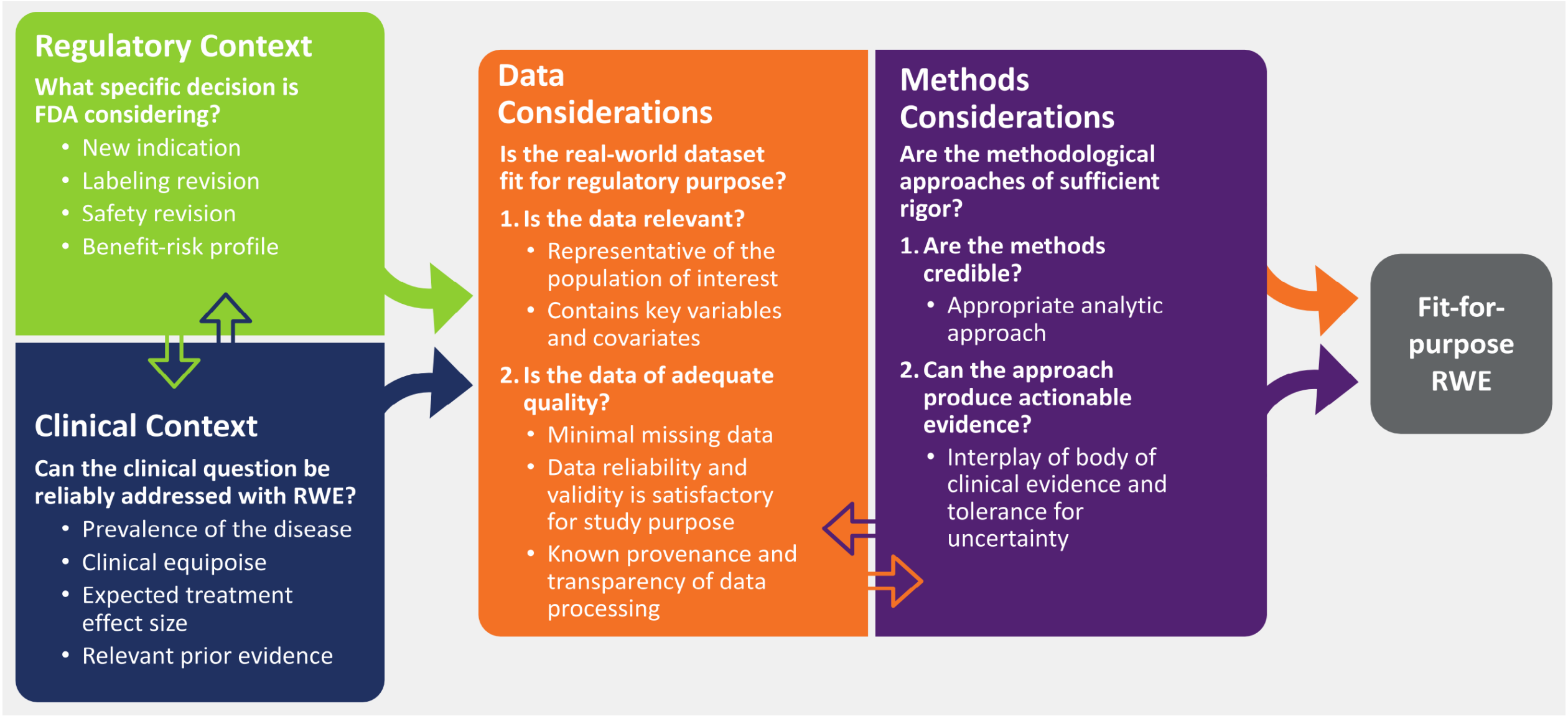
Lack of

- Prespecified study protocol
- Inclusion/exclusion criteria matching to the trial
- Comparability of endpoint definitions
- Methods to minimize confounding and address unmeasured confounding
- Plans to handle missing data

Value Health 2020;23(10):1358-65.
Clin Cancer Res 2022;28(1):27-35.

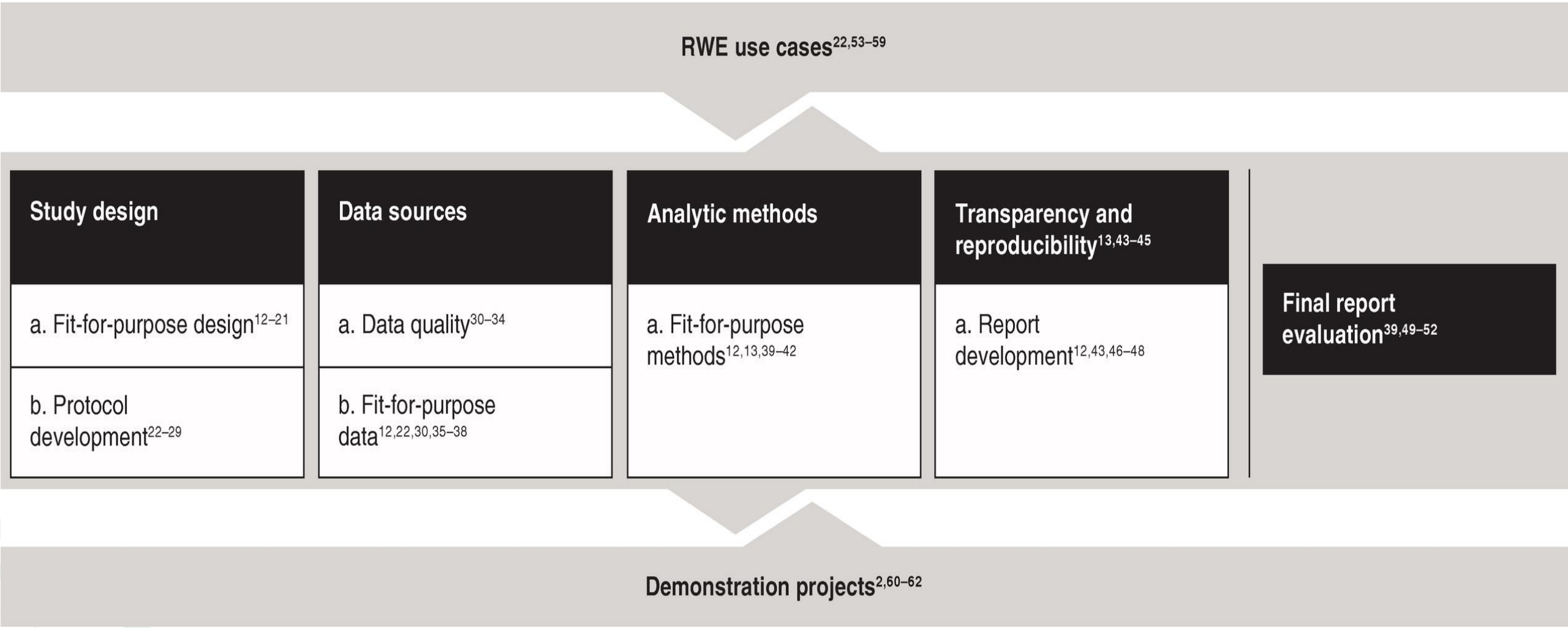
How do we generate RWE with high quality?

Considerations for Generating RWE Fit for Regulatory Purposes



Duke Margolis Center for Health Policy, 2018
Characterizing RWD Quality and Relevancy for Regulatory Purposes

Building blocks of RWE



J Comp Eff Res 2021;10(9):711-31.

Growing use of RWE

- **Replicating, extending, supplementing data from traditional prospective clinical trials**
  - To **characterize outcomes for excluded or underrepresented populations in trials** (e.g., elderly, minority groups, poor performance status)
  - To **understand comparative effectiveness and cost-effectiven**ess
  - To **capture long-term outcomes**
  - To **identity less common or late-term adverse effects**
- **Supporting clinical trial design and operational planning for studies** (e.g., site selection, patient recruitment), **especially for rare cancer type or understudied populations**
- Developing **external control arms**
- Developing **pragmatic clinical trials**
- **Support regulatory approval and funding decisions**
  - To **define conditional reimbursement schemes or managed-entry agreements** (e.g., risk sharing, value-based contracting)

Increasing use of RWE for healthcare and health policy decisions (in Taiwan)

Authorities	Major uses	Relative importance of RWE for decision making
Healthcare providers 	Clinical practice guideline; Clinical decision supporting system (CDSS)	• Disease burden assessment +++ • Clinical assessment if classical trials not available ++++ • Safety assessment of treatment ++++ • Disease and prognosis prediction +++++
Taiwan Food and Drug Administration (TFDA)	Pre-approval decisions	• Supporting evidence for investigational drug development (e.g., disease burden, practice pattern) +++
	Post-approval decisions	• Post-approval drug assessment & safety surveillance +++++ • Label changes and new indication assessment +
National Health Insurance Administration (NHIA)	Health technology assessment (HTA); Pricing & coverage decision	• Clinical outcomes for emerging technologies +++ • Epidemiological data ++++ • Cost of illness and disease burden ++++ • Health-related quality of life, utility & patient preference ++ • Parameters for cost-effectiveness modelling +++ • Parameters for budget impact analysis (incl. drug utilization & treatment patterns) ++++ • Conditional reimbursement schemes or managed-entry agreements +++

Modified from: Sun et al. *BMJ* 2018;360:j5262.

Take Home Messages

- Although RCTs remain the gold standard for establishing the efficacy of new treatments, many clinical and policy questions can be addressed with the help of RWE.
- For drug development, efficacy data from single-arm trials can be complemented by external control real-world studies. In addition, a greater proportion of safety and efficacy data generation for oncology drugs shifts to the post-marketing setting (e.g., PMR/PMC).
- However, a high level of insight should be applied to the quality of the data and methodology used in RWD studies, especially when generating RWE to meet high evidentiary standards. It is essential to understand and properly assess potential biases when using RWE for decision making.