Real-World Evidence Generation:

Studies, databases, methods, and analytics

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THE NEXT 40 MINUTES…

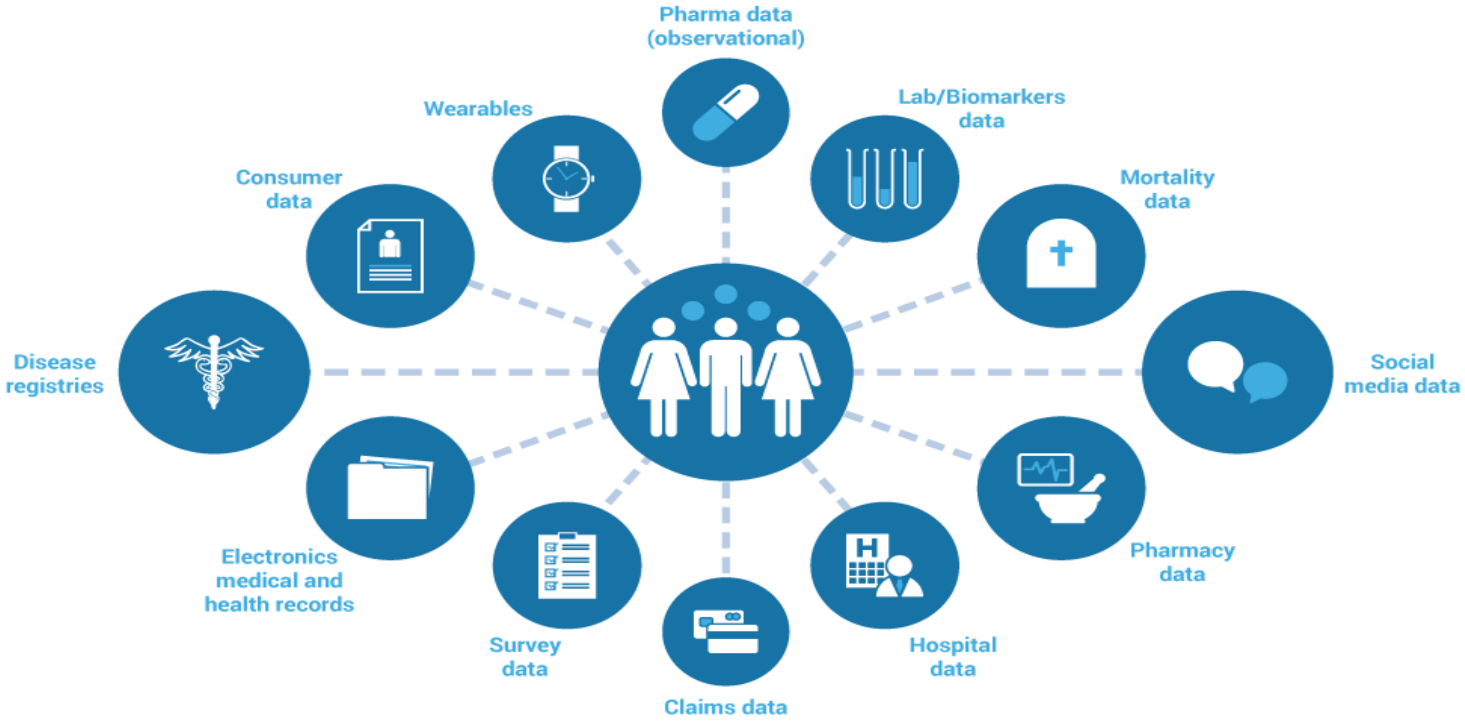
- Setting the scene: RWE definitions
- Finding appropriate RWE options
- RWD adding value to the drug development lifecycle
- Evidence synthesis and network meta-analysis
- Regulations and international standards for RWD/Observational research

WHAT IS REAL-WORLD DATA?

- Data used for decision-making that are not collected in conventional RCTs…
- i.e., collected in an observational, non-controlled, non-experimental setting

Garrison,L.P.,et al,(2007).Using RWD for coverage and payment decisions: the ISPOR RWD task force report. ISPOR Value in Health,Vol10,No5.

WHERE IS REAL-WORLD DATA?



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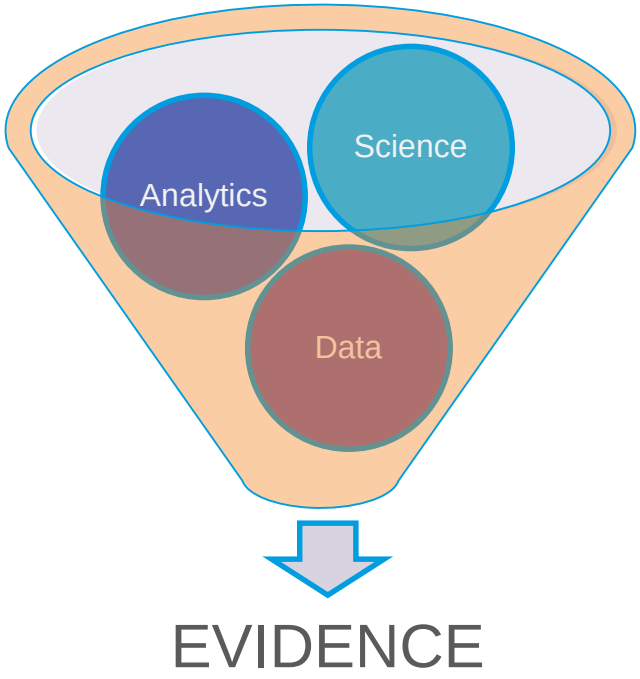
In scarcely an instance have I been able to obtain hospital records fit for any purpose of comparison… if wisely used [hospital records] could tell us more of the relative value of particular operations and modes of treatment

Florence Nightingale

REAL-WORLD EVIDENCE



The new currency in healthcare

- Setting the scene: RWE definitions
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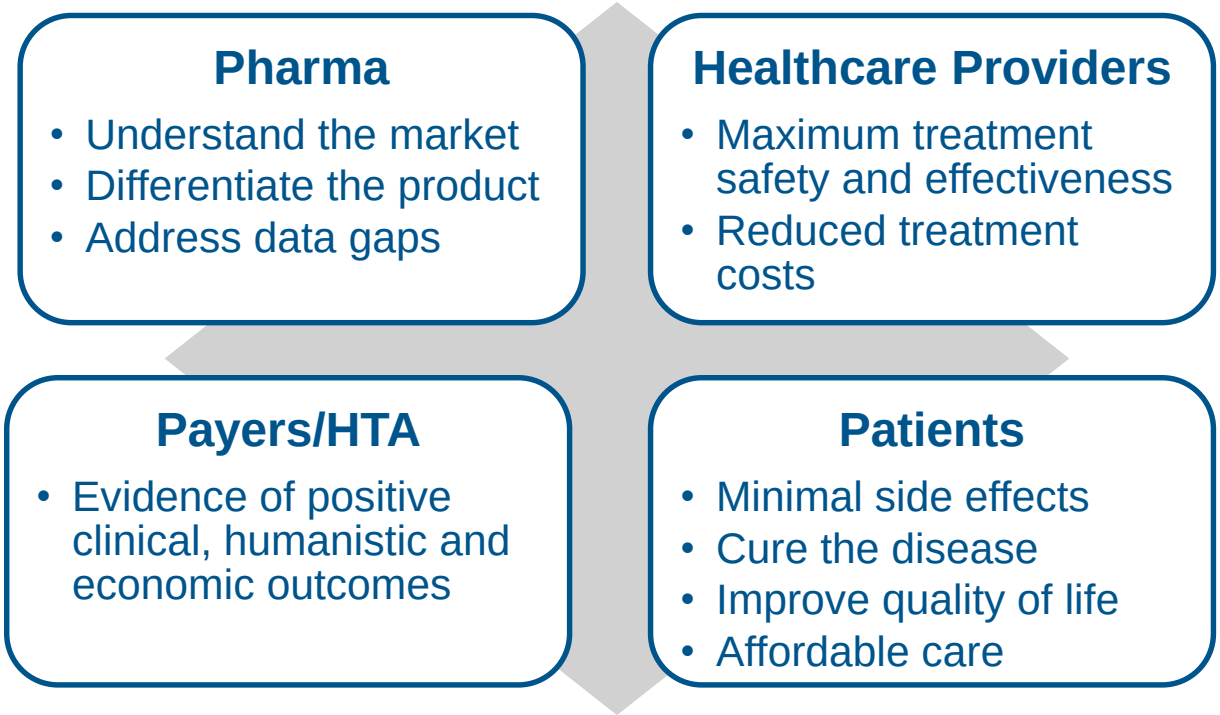
HEALTHCARE IS CHANGING

- Cost and capacity challenges
- Increase in R&D costs and drug prices
- Informed patients, aging population, and personalized treatments
- Growing use of evidence syntheses and outcomes research
- Technology advances enabling data analysis

RWE: INCREASED DEMAND

DECISION-MAKING PERSPECTIVES



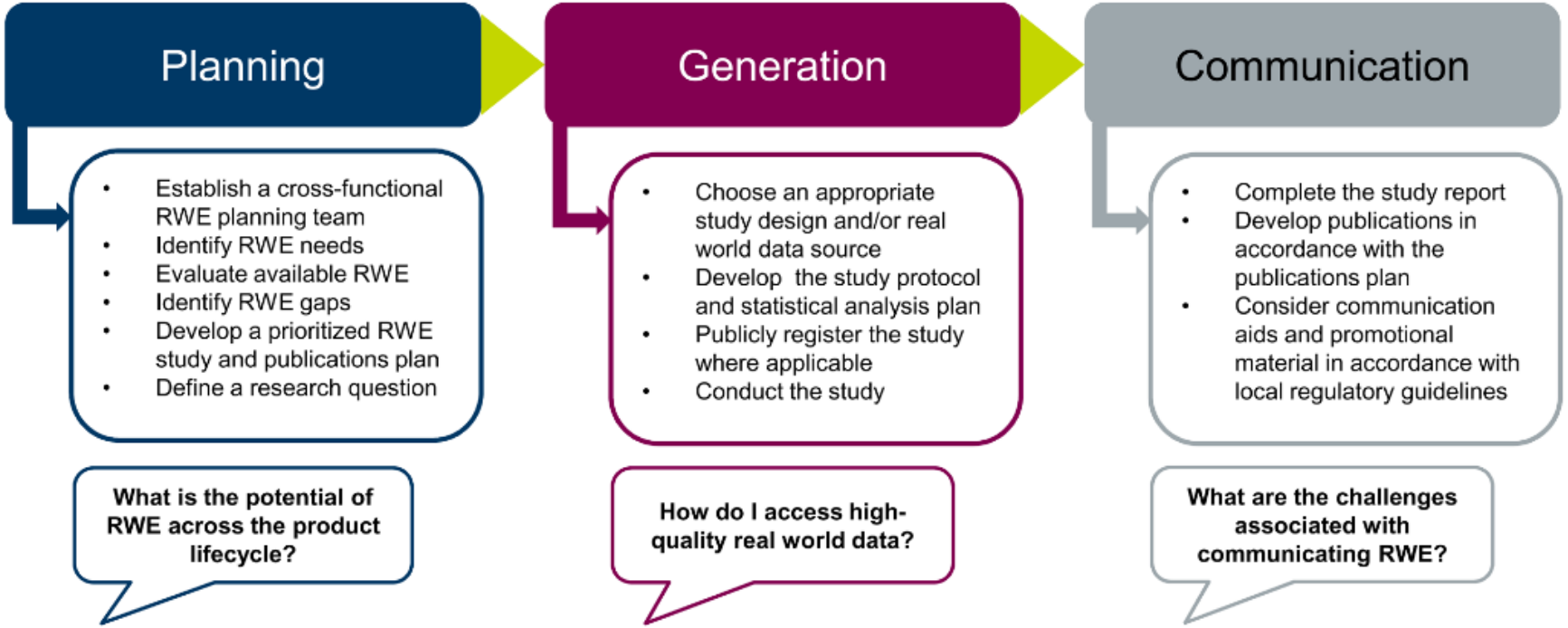
(SOME OF) RWE OBJECTIVES

- Scientific (hypothesis generation)
- Clinical (improving standards of care),
- Commercial (market access, value demonstration)
- Regulatory (long-term safety and effectiveness)
- Patient-centered (humanistic, economic outcomes)

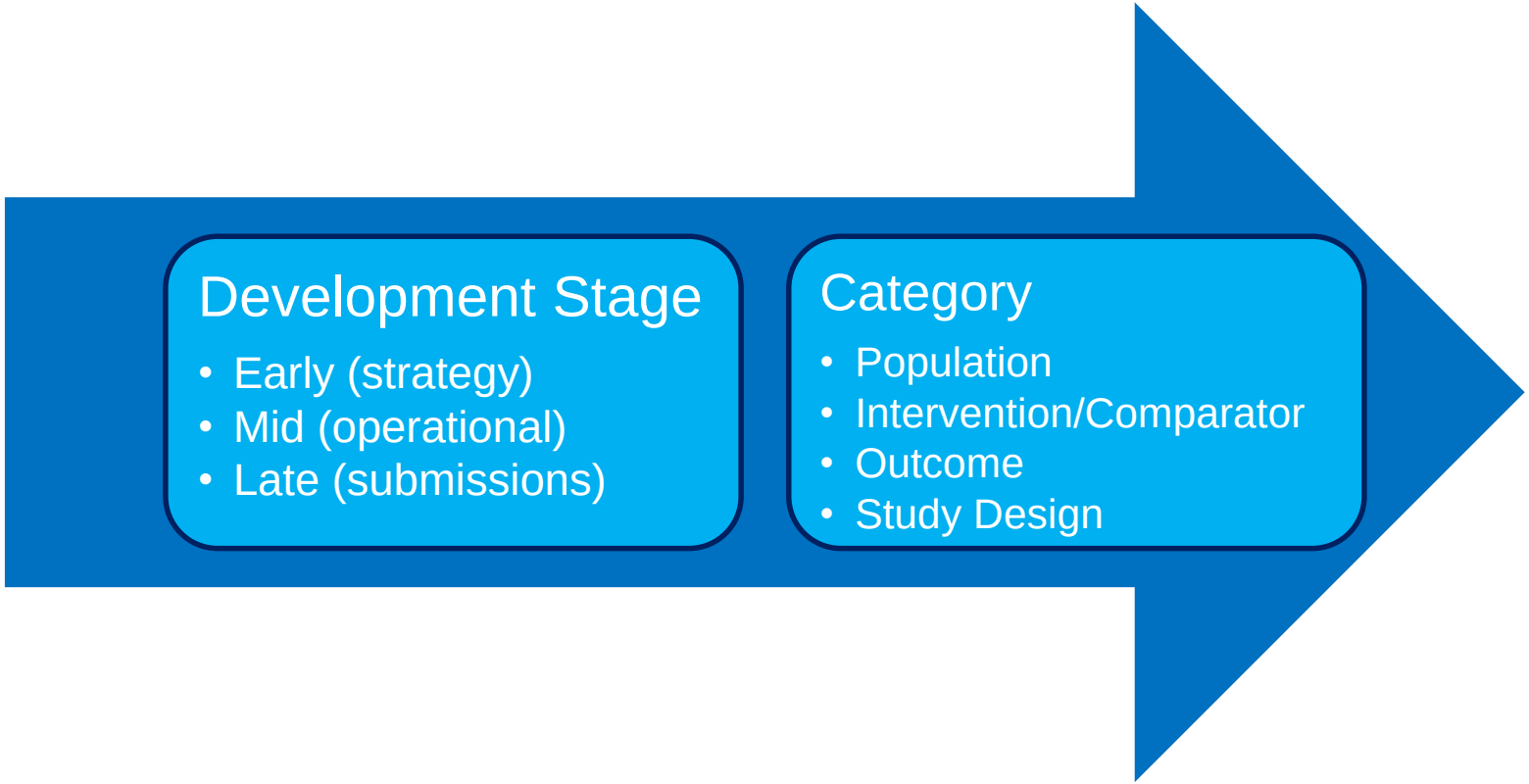
Specific examples:

- Long term safety and effectiveness
- Evaluate the disease prevalence and progression
- Analyze current standard of care, and healthcare utilization
- Provide patients with access to yet unapproved drug
- Evaluate and develop Patient-Reported Outcomes
    - Therapy Satisfaction, Quality of Life, Burden of illness, Adherence etc.

THE RWE JOURNEY



FINDING RWE OPTIONS

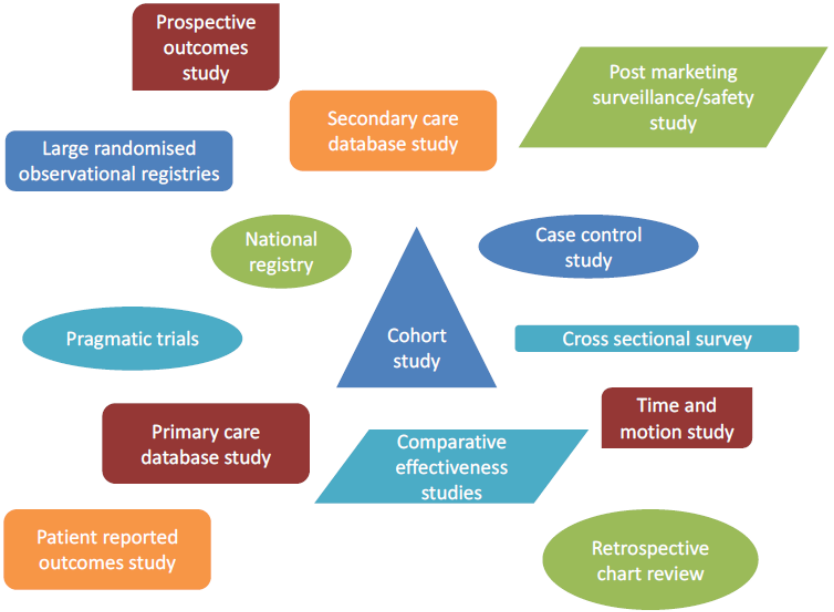


(SOME OF) POTENTIAL ISSUES

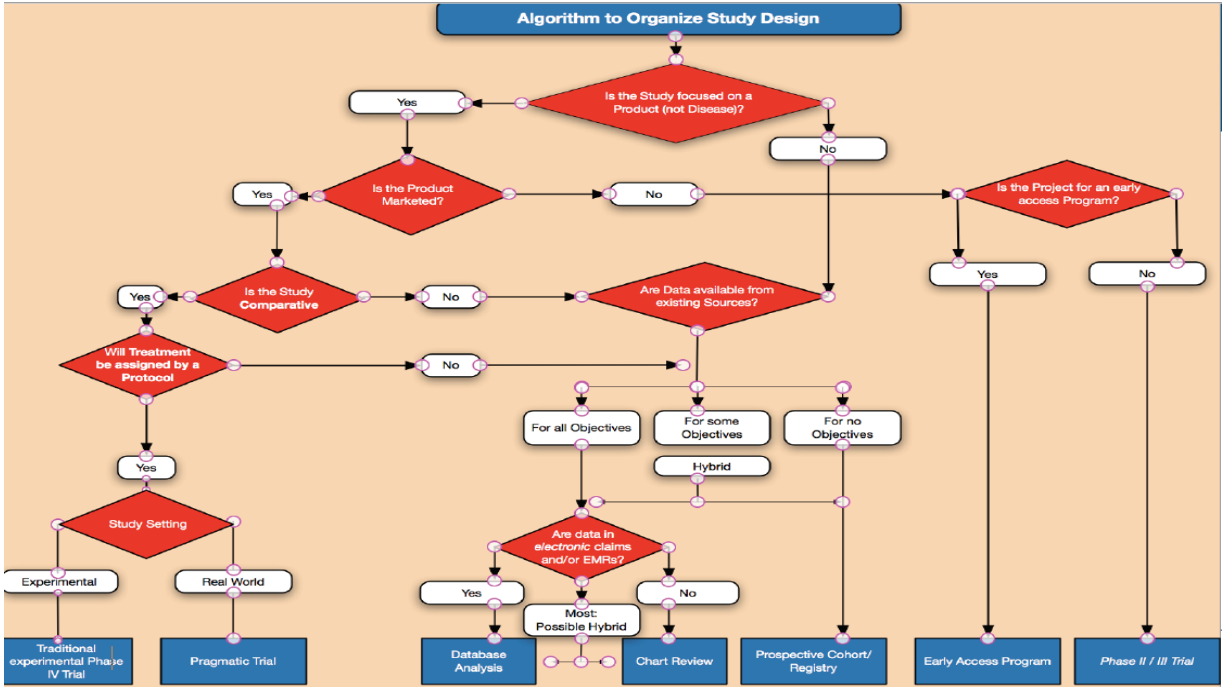
- Trial population differs from usual practice
- Disease area is not well defined
- Administration of therapy/stopping rules/adherence is inconsistent with usual practice
- Trial comparators do not include current usual care or standard of care
- Trial outcomes not considered to be measures of effectiveness
- High risk of biased comparisons from observational (non-randomised) data
- Modelling of final outcomes from trial efficacy is not robust
- Trial treatment pathway is not generalisable to usual practice
- Other study design choices limit generalisability
- Evidence available is from single arm trials only

RWE OPTIONS

- Pragmatic clinical trial
- Modified RCT
  - population enrichment
  - cohort multiple RCT
  - comprehensive cohort study
  - cluster RCT
- Epidemiology studies and modelling
- Evidence synthesis, such as NMA
- Trial design based on NMA
- Methods to adjust bias
- Modelling to predict outcomes, re-weighting trial data



DECISION ALGORITHMS

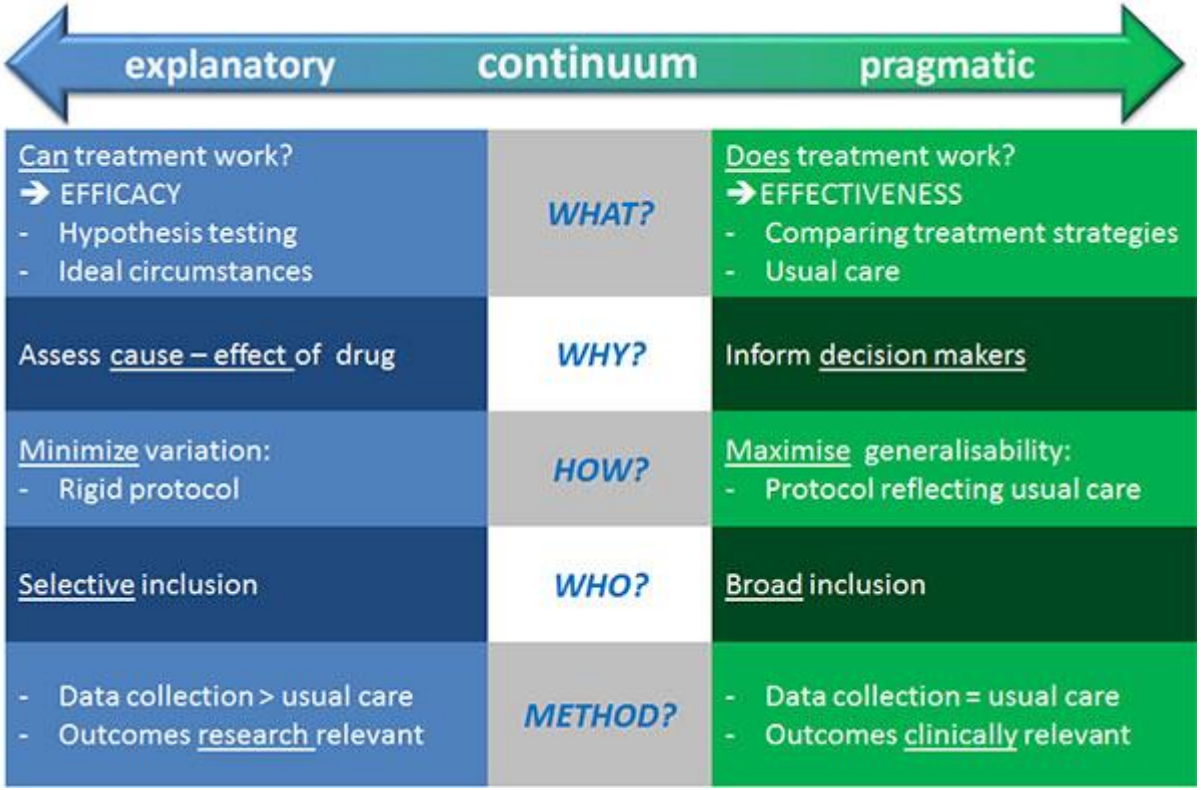


THE REAL WORLD

CLINICAL TRIAL

PRAGMATIC TRIAL

PRAGMATIC TRIAL CONTINUUM



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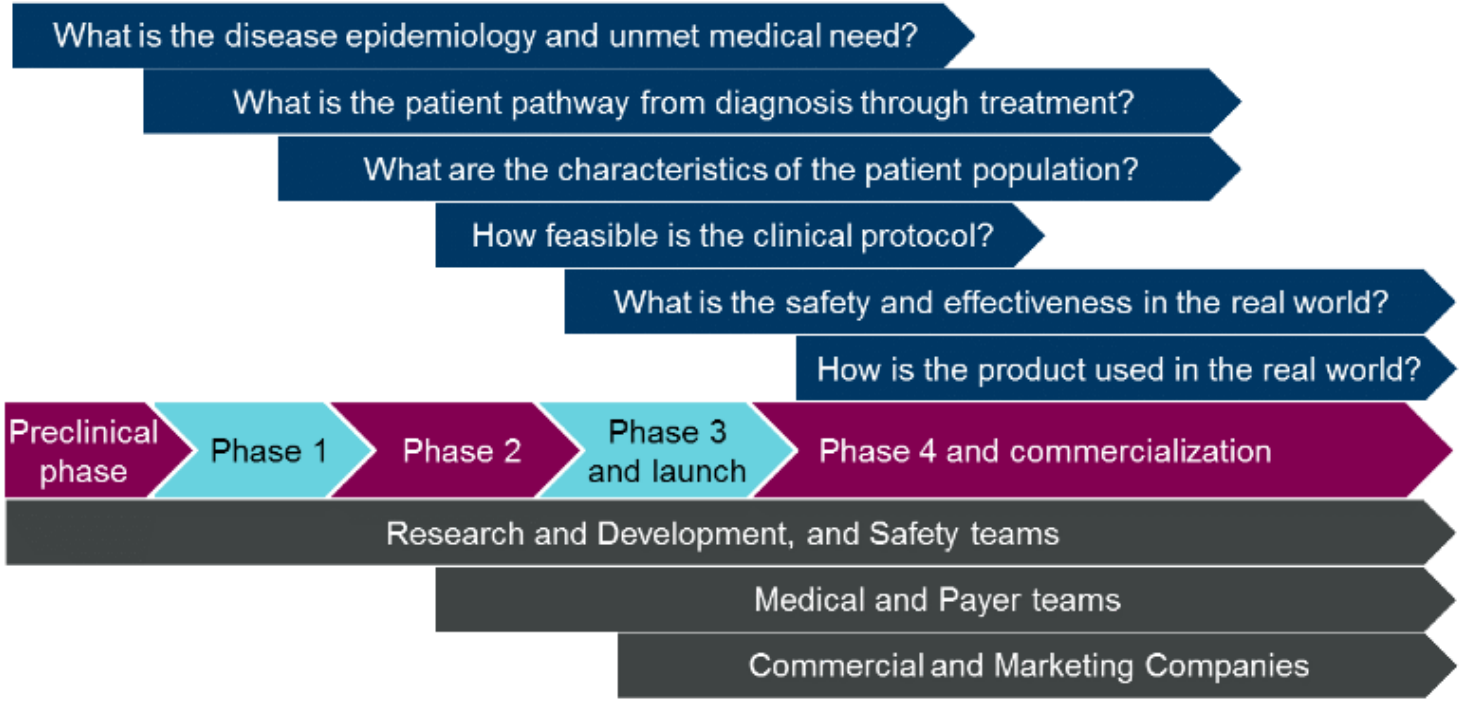
RWE: ADDING VALUE

- Identify/demonstrate unmet need
- Explore root causes and/or stratify disease
- Inform R&D decisions
- Expand indications

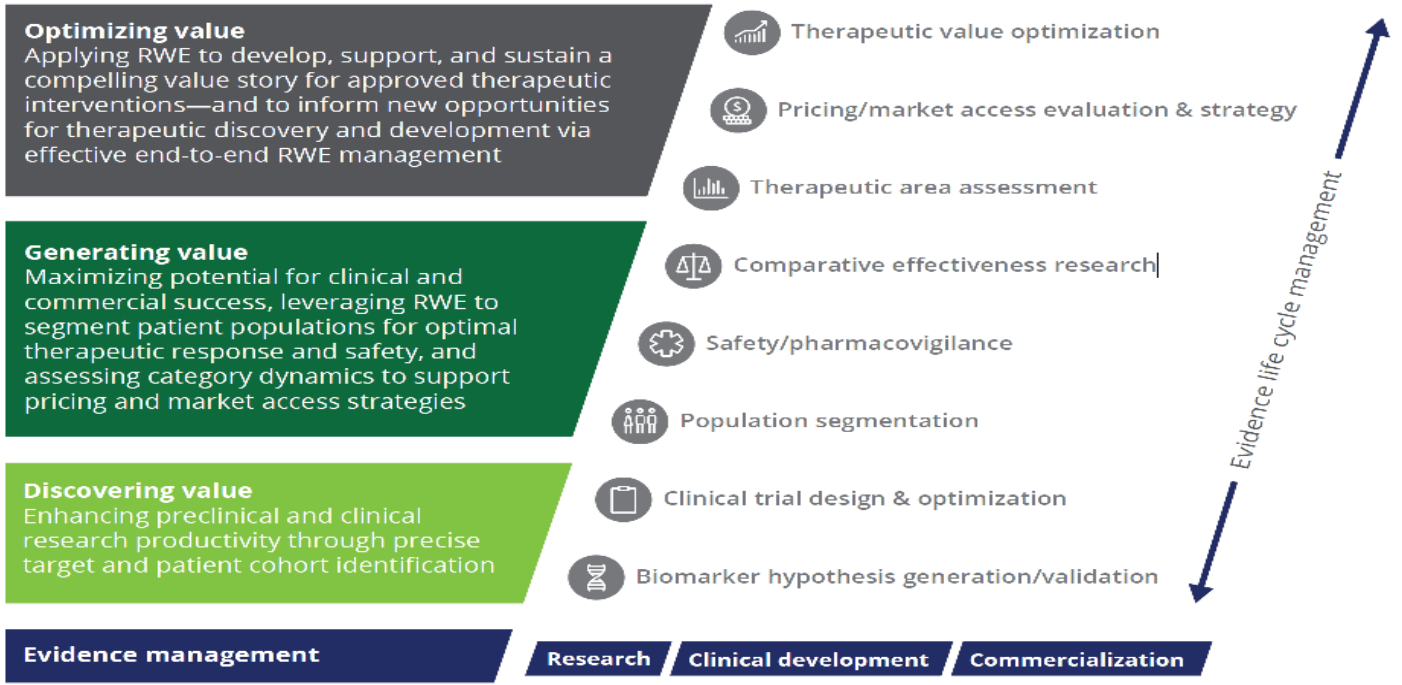
- Facilitate innovative trial designs (retro+, hybrid, etc.)
- Collect outcome data from new sources
- Efficient site selection
- Targeted patient recruitment

- Positioning and economic value analysis
- Safety monitoring
- Precision targeting
- Design combined offerings

RWE THROUGHOUT THE LIFECYCLE



END-TO-END EVIDENCE MANAGEMENT



Source: Deloitte analysis.

EXAMPLES OF DATA FOR RWE

Data source	Data owners/curators	Typical coverage (patient records)	Typical time to data access
Administrative claims databases	HealthCore, Japanese Medical Claims Database, NHS, Optum, Truven,	> 10 million	Immediate
Electronic health/medical records	CPRD, Evidera, NorthWest eHealth, Optum, Parexel, PCORnet, QuintilesIMS	2–10 million	Immediate
Clinical registries	American College of Cardiology, SwedeHeart, CALIBER, CancerLinQ, Health Data Insight, Severe Asthma Registry	< 2 million	Within 1 year
Prospective studies and hybrid approaches	CROs/AROs, academic partnerships	> 1000	Over 1 year
Patient-generated data (e.g. social media or patient-powered research networks)	PatientsLikeMe, Carenity, PCORnet	> 100 000	Immediate[13]

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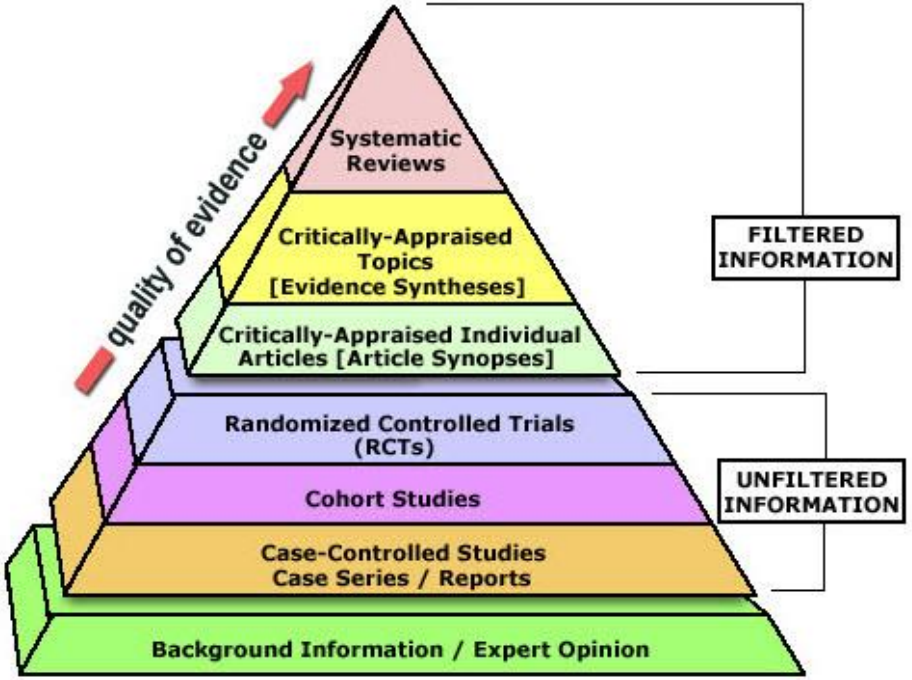
HIERARCHY OF EVIDENCE



EVIDENCE SYNTHESIS

- The process of retrieving, evaluating and summarising the findings of all relevant studies on a certain subject area.
- Estimate the effect between two interventions - a systematic review of relevant RCTs and synthesis of the RCT results using meta-analytical techniques (in a pairwise meta-analysis).
- Multiple treatments available for the same disease - network meta-analysis (NMA), an extension of the usual meta-analysis, may be used.

NETWORK META-ANALYSIS

- NMA is used to summarise relative treatment effects from RCTs that compare multiple competing interventions for the same condition
- Most NMAs are based on published aggregate data (AD), but this limits the ability to investigate the extent of network consistency and between-study heterogeneity.
- As individual participant data (IPD) are considered the gold standard in evidence synthesis, it may be possible to use this when conducting NMA.

WHY USE MA AND NMA

Meta-analysis:

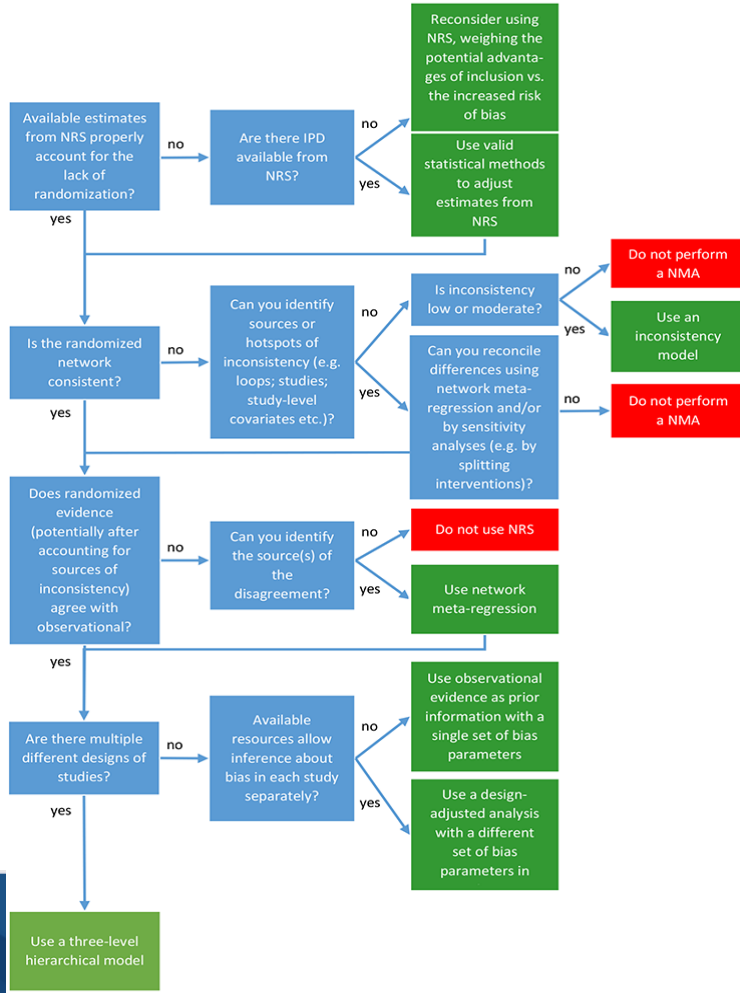
- **Summarises** the evidence on the effects of an intervention.
- **Assesses** reproducibility and generalisability of individual study findings.
- **Identifies** sources of heterogeneity in treatment effects

NMA in particular:

- **Increased precision and power** compared with a series of pairwise meta-analyses (synthesising both direct and indirect evidence on treatment comparisons in a single analysis).
- **Allows indirect comparison of** interventions that have not been compared directly in head-to-head trials.
- **Ranks treatments**
- **Reduces controversy** between individual studies.
- **Avoids selective use of data** in decision-making
- **Combines all of the evidence** in a joint analysis.

WHEN TO USE MA AND NMA

- Conflicting evidence
- Direct comparisons are not available
- Evidence only from comparisons with older or less effective treatments
- Bias in direct comparisons



NMA LIMITATIONS

- Not equivalent to direct evidence from RCTs
- Transitivity is assumed
- Difficulties in interpretation
- Complex to carry out
- Low return for effort

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RWE REQUIREMENTS

- After a medicinal product is approved, regulators expect that Marketing Authorization Holders (MAH) implement a pharmacovigilance system in order to continue monitoring the product's safety profile as they are used in clinical practice.
  - Spontaneous adverse reaction reporting
  - Interventional, phase IV clinical trials
  - Observational / Non-interventional studies - PASS

REGULATORY REQUIREMENTS

- Guideline on good pharmacovigilance practices (GVP) Module VIII – Post-authorisation safety studies
- GEP and GPP establish ethical and scientific standards for NIS
  - International Ethical Guidelines for Epidemiological Studies, CIOMS, 2017
  - https://cioms.ch/wp-content/uploads/2017/01/International_Ethical_Guidelines_LR.pdf
  - Guidelines for Good Pharmacoepidemiology Practices (GPP), ISPE, 2015
  - https://www.pharmacoepi.org/resources/policies/guidelines-08027/
- No harmonized regulatory framework across countries
  - CA notification, EC submission or notification, additional committees (Data Protection, Epidemiology etc.)

Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices

Guidance for Industry and Food and Drug Administration Staff

Document issued on August 31, 2017.

The draft of this document was issued on July 27, 2016

- RWD studies can provide information on a wider patient population, but an existing RWD source may have some inherent bias that could limit its value for drawing causal inferences between medical device exposures and outcomes.
- Careful study design, a study protocol and analysis plan should be created prior to accessing, retrieving, and analyzing RWD, regardless of whether the RWD are retro- or prospectively collected
- Protocols and analysis plans for RWD should address the same elements that a traditional clinical trial protocol and statistical analysis plan would cover.

CHECKLISTS FOR QUALITY ASSESSMENT

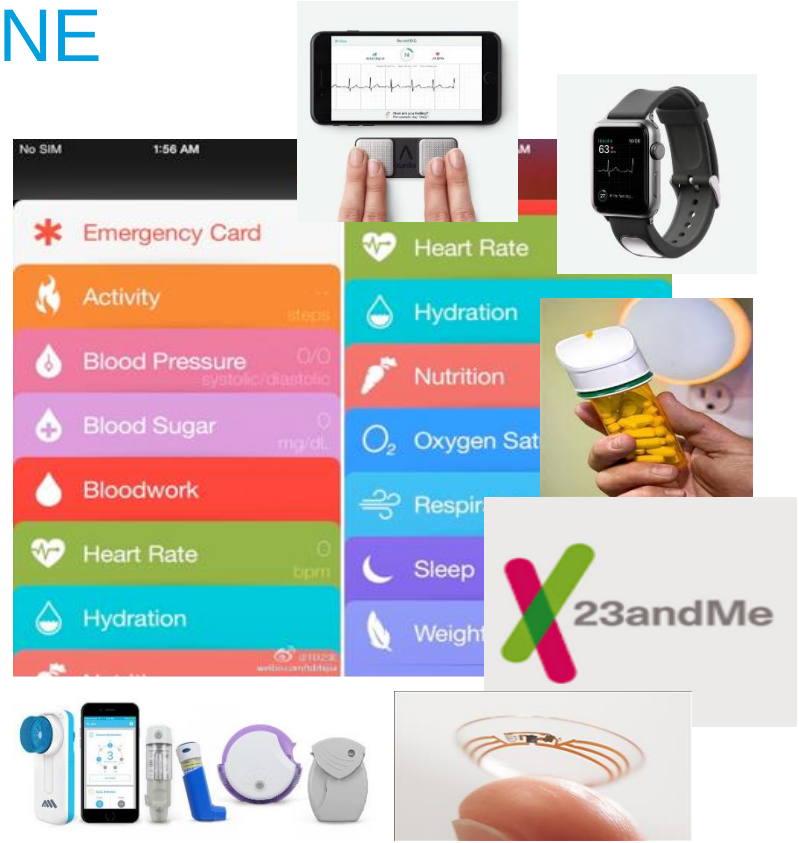
- Non-randomised study designs, controlled cohort, controlled before-and-after studies
  - GRACE Checklist
  - STROBE combined checklist for cohort, case-control and cross-sectional studies
  - ROBINS-I Assessment tool
  - ISPOR checklists for prospective observational and for retrospective database studies
  - Checklist for statistical methods to address selection bias in estimating incremental costs, effectiveness and cost-effectiveness (Kreif et al, 2013)
  - CASP cohort study checklist
  - Newcastle-Ottawa scale (case-control studies)

RWE CHALLENGES

Ecosystem	• Data silos and barriers to access • A consistent evidence throughout the patient's journey
Security and governance	• Lack of interoperability standards • Diverse regulations
Experience and Technology	• Lack of experience • Technology constraints

RWE MEETS DEEP MEDICINE

- Emerging strategic cross-sector and cross-country partnerships develop strategies to improve RWD standards, infrastructure and enable data use.
- A growing support for patients' data ownership, with data protection and privacy regulations restricting access.
- Technology remains the key enabler in extracting value from RWD.



THANK YOU