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

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
• Finding appropriate RWE options
• RWD adding value to the drug development lifecycle
• Evidence synthesis and network meta-analysis
• Regulations and international standards impacting RWD/Observational research
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

**Pharma**
- Understand the market
- Differentiate the product
- Address data gaps

**Healthcare Providers**
- Maximum treatment safety and effectiveness
- Reduced treatment costs

**Payers/HTA**
- Evidence of positive clinical, humanistic and economic outcomes

**Patients**
- Minimal side effects
- Cure the disease
- Improve quality of life
- Affordable care
(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

Planning
- Establish a cross-functional RWE planning team
- Identify RWE needs
- Evaluate available RWE
- Identify RWE gaps
- Develop a prioritized RWE study and publications plan
- Define a research question

What is the potential of RWE across the product lifecycle?

Generation
- Choose an appropriate study design and/or real world data source
- Develop the study protocol and statistical analysis plan
- Publicly register the study where applicable
- Conduct the study

How do I access high-quality real world data?

Communication
- Complete the study report
- Develop publications in accordance with the publications plan
- Consider communication aids and promotional material in accordance with local regulatory guidelines

What are the challenges associated with communicating RWE?
FINDING RWE OPTIONS

Development Stage
- Early (strategy)
- Mid (operational)
- Late (submissions)

Category
- Population
- Intervention/Comparator
- Outcome
- Study Design
(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
THE REAL WORLD
PRAGMATIC TRIAL
### PRAGMATIC TRIAL CONTINUUM

<table>
<thead>
<tr>
<th>Question</th>
<th>Continuum</th>
<th>Purpose</th>
<th>Protocol</th>
<th>Inclusion</th>
<th>Data Collection</th>
<th>Outcomes</th>
<th>Usual Care</th>
<th>Usual Care</th>
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<tr>
<td>➔ EFFICACY</td>
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<td>Usual care</td>
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<td>Hypothesis testing</td>
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<td>Ideal circumstances</td>
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<td>Assess cause – effect of drug</td>
<td>WHY?</td>
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<td>Inform decision makers</td>
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<td>Minimize variation:</td>
<td>HOW?</td>
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<td>Maximise generalisability</td>
<td>Protocol reflecting usual care</td>
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<td>Rigid protocol</td>
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<td>Selective inclusion</td>
<td>WHO?</td>
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<td>Broad inclusion</td>
<td></td>
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<td>Data collection &gt; usual care</td>
<td>METHOD?</td>
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<td>Outcomes research relevant</td>
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• Setting the scene: RWE definitions
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• **RWD adding value to the drug development lifecycle**
• Evidence synthesis and network meta-analysis
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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

What is the disease epidemiology and unmet medical need?
What is the patient pathway from diagnosis through treatment?
What are the characteristics of the patient population?
How feasible is the clinical protocol?
What is the safety and effectiveness in the real world?
How is the product used in the real world?

Preclinical phase  |  Phase 1  |  Phase 2 and launch  |  Phase 3 and commercialization
Research and Development, and Safety teams  |  Medical and Payer teams  |  Commercial and Marketing Companies
END-TO-END EVIDENCE MANAGEMENT

**Optimizing value**
Applying RWE to develop, support, and sustain a compelling value story for approved therapeutic interventions—and to inform new opportunities for therapeutic discovery and development via effective end-to-end RWE management.

- **Therapeutic value optimization**
- **Pricing/market access evaluation & strategy**
- **Therapeutic area assessment**
- **Comparative effectiveness research**
- **Safety/pharmacovigilance**
- **Population segmentation**
- **Clinical trial design & optimization**
- **Biomarker hypothesis generation/validation**

**Generating value**
Maximizing potential for clinical and commercial success, leveraging RWE to segment patient populations for optimal therapeutic response and safety, and assessing category dynamics to support pricing and market access strategies.

**Discovering value**
Enhancing preclinical and clinical research productivity through precise target and patient cohort identification.

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**Evidence management**

**Research** | **Clinical development** | **Commercialization**

Source: Deloitte analysis.
## Examples of Data for RWE

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