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Leveraging Real-World Evidence in Clinical Trial Design: Statistical Challenges and Opportunities

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Disclaimer

I confirm that, the opinions and thoughts discussed in this presentation are subject to my own independent views and are not subject to the opinions of the organization that I represent.

Agenda

- The Paradigm Shift in Clinical Evidence
- Real-World Data & Real-World Evidence
- Why Integrate RWE into Clinical Trials?
- Statistical Challenges in RWE Integration
- Methodological Frameworks
- Regulatory Landscape: FDA & EMA Perspectives
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- Technological Advances Shaping RWE
- The Future of Clinical Trial Design
- Ethical Considerations
- Challenges in RWE Integration
- Conclusion

The Paradigm Shift in Clinical Evidence

Traditional RCTs

- Gold standard methodology
- Strict inclusion criteria
- Homogeneous populations
- High cost & lengthy timelines
- Limited generalizability

RWE Integration

- Reflects real-world practice
- Diverse patient populations
- Enhanced external validity
- Accelerated timelines
- Improved cost-efficiency

Real-World Data & Real-World Evidence

Real-World Data (RWD)

Patient health status data routinely collected from:

- Electronic health records
- Medical claims databases
- Product registries
- Patient-generated data

Real-World Evidence (RWE)

Clinical evidence derived from systematic analysis of RWD

- Observational studies
- External control arms
- Post-market surveillance
- Comparative effectiveness

➢ 21st Century Cures Act: FDA framework for evaluating RWE in regulatory submissions

Why Integrate RWE into Clinical Trials?

Enhanced Generalisability	Accelerated Timelines	Cost Efficiency	Regulatory Support
• Broader patient populations mirror real-world clinical practice beyond restrictive trial criteria	• External control arms reduce recruitment burden and shorten study duration significantly	• Optimized control arms and reduced operational costs whilst maintaining scientific rigor	• FDA & EMA frameworks increasingly accept RWE for approval decisions and labelling claims

Statistical Challenges in RWE Integration

Confounding & Selection Bias

Treatment assignment not randomized, systematic differences between trial participants and real-world patients affect outcomes

Data Heterogeneity

Variability across healthcare systems, diagnostic criteria, medical practices, and data collection methodologies

Unmeasured Confounders

Unobserved factors, physician preference, patient behaviors, disease severity, remain after covariate adjustment

Temporal Bias

Evolving standards of care render historical RWD less comparable to contemporary prospective trial data

Methodological Frameworks

Propensity Score Methods

Propensity Score: Conditional probability of receiving treatment given baseline characteristics

01

Matching

Pair real-world patients with trial participants having similar propensity scores

02

Stratification

Group patients into quintiles based on scores to balance characteristics across strata

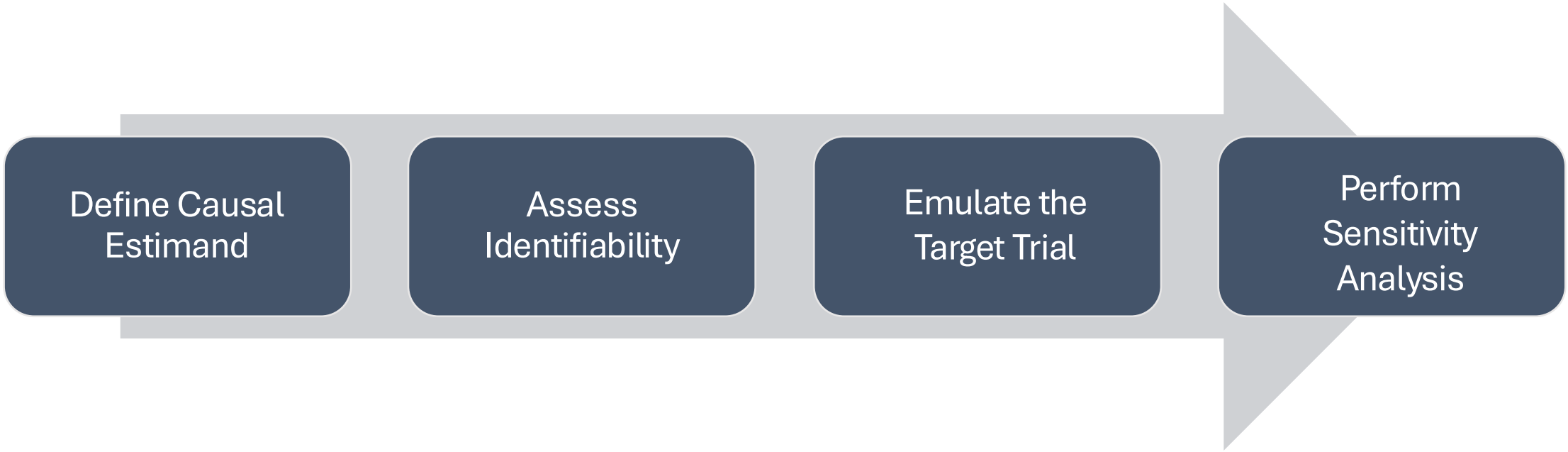
03

Weighting (IPTW)

Create pseudo-population where treatment groups are comparable via inverse probability weights

Methodological Frameworks

Causal Inference Framework: The Causal Roadmap



Methodological Frameworks

Bayesian Hierarchical Models & Dynamic Borrowing

Bayesian Additive Regression Trees (BART)

- Non-parametric flexible modeling
- Captures non-linear and interaction effects
- Identifies heterogeneous treatment effects
- No need to specify functional form

Dynamic Borrowing via Power Priors

Power Prior Parameter (α):

α = 0 → ignore external data

α = 1 → full borrowing

0 < α < 1 → partial, data-dependent borrowing

ProPP Method

Propensity-score weighted Power Prior: First applies PS weighting to address measured confounding, then uses power priors for unmeasured confounding

Regulatory Landscape: FDA & EMA Perspectives

FDA Real-World Evidence Programme	EMA Position on RWE
• Framework established 2018 • Support for regulatory decisions • Post-market surveillance • Extrapolation to broader populations	• Emphasis on rare diseases • Expanded access programmes • Observational studies framework • Post-authorisation safety studies

RWE as *complementary tool*, not replacement for RCTs

Reflection paper encourages RWE integration in drug development

Key Message: Regulatory acceptance is growing, with clear guidance for methodological rigour

Opportunity in Trial Design

RWE offers powerful advantages for accelerating and enhancing drug development programmes.

External Control Arms

Synthetic control groups from RWD enable single-arm trials in rare diseases where randomization is unethical

Hybrid Control Approaches

Augment small control groups with RWD to increase statistical power whilst reducing placebo assignments

Broadening Trial Reach

Include diverse populations from Expanded Access program typically excluded from traditional RCTs

Case Study

External Control Arms in Oncology

- CAR-T Cell Therapy Development

> Successfully demonstrated treatment effectiveness using historical data and external databases as synthetic controls

- Single-arm trial design where randomization not feasible
- RWE contextualized results without randomized control group
- Accelerated regulatory pathway for innovative therapy

Case Study

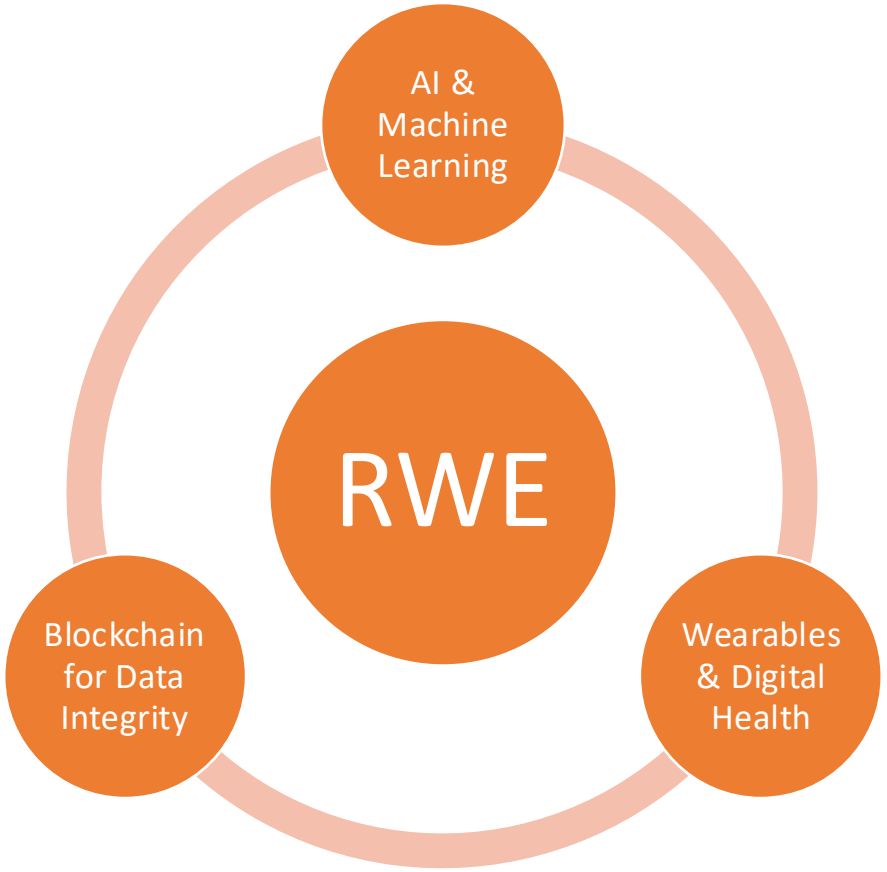
Rare Disease Trials

- MPS II Trial (Hunter Syndrome)

> Registry data and clinical records provided external control, enabling evaluation despite limited patient population

- Synthetic control group from historical data
- Natural disease progression insights
- Drug effectiveness assessment in small population

Technological Advances Shaping RWE



The Future of Clinical Trial Design

RWE represents a transformative shift towards patient-centric, efficient drug development

Faster Development

Accelerated timelines through synthetic controls and hybrid designs

Greater Generalizability

Real-world outcomes reflecting diverse patient populations

Adaptive Approaches

Continuous innovation through interdisciplinary collaboration

Ethical Considerations

Data Privacy Protection

Robust safeguards ensuring patient confidentiality throughout data collection and analysis

Informed Consent

Clear protocols for data usage permissions in real-world evidence generation

Bias Mitigation

Rigorous assessment and adjustment for inherent biases in observational datasets

Challenges in RWE Integration

Data Quality & Consistency

Inconsistent definitions, missing values, and varied formats across healthcare systems complicate harmonization.

Regulatory Hurdles

Frameworks for evaluating RWE quality and reliability still evolving, particularly for novel treatments

Statistical Complexity

Advanced methodologies required to properly adjust for confounding and selection bias demand specialised expertise

Conclusion

- **RWE Transforming Drug Development**
  RWE offers faster, more generalizable drug development, overcoming RCT limitations like high costs and slow timelines.

- **Challenges in RWE Integration**
  RWE faces issues like bias and data heterogeneity, requiring advanced statistical methods for valid conclusions.

- **Future Innovations and Collaboration**
  AI, wearables, and real-time data collection will improve trials, but ongoing collaboration is needed to address data quality and regulatory challenges.

ANY QUESTIONS?

Thank You!