The Use of RWD/RWE to Inform Clinical Trial Design

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Outline

- Retrospective data
- Prospectively study design and external data
- Useful frameworks for real-world evidence studies in regulatory setting
- Take home message

Check out new FDA home page!
https://www.fda.gov

Medical Products Regulated by Center for Biologics Evaluation & Research

Vaccines, Blood & Biologics

- Vaccines (preventative and therapeutic)
- Gene therapies
- Human tissues, engineered cellular products
- Whole blood, plasma and blood products
- Biologics related devices
- Live biotherapeutic products
- Xenotransplantation products
- Allergenics

Retrospective Data: Definition & Sources

Retrospective data include existing data that have been recorded for reasons other than the current study.

Attribute	Traditional Sources	New Source: Real-World Data
Examples	Prior rand. clinical trials, registries	Claims, EHRs, prescriptions
Purposes	Research plan prospectively specified study protocols	Billing and clinical management
Outcome Definitions Collection Methods, Timing	Use the same definitions, methods and schedules to collect data per study protocols	Provider's own methods to collect data during medical encounters of patients; outcome definition TBD
Data Quality	Data monitored per protocol	Quality varies across providers
Auditability	Legally auditable for clinical trials with source data, e.g., EHRs.	Not auditable b/c EHRs & claims are the source data

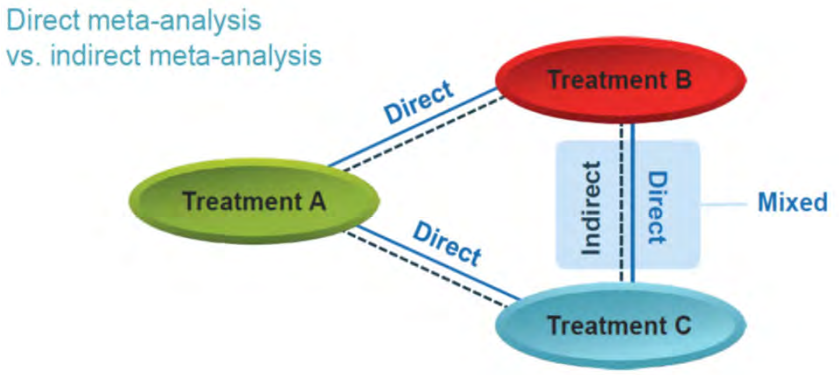
Retrospective Data: Methods & Uses

- Methods
  - Existing statistical literature are about meta-analysis and network meta-analysis of traditional sources. (Efthimiou 2016)
  - Network meta-analysis of RWD have emerged. (Briere 2018, Jenkin 2018)
- Uses
  - RWD useful for other aspects of clinical study design, e.g., site selection, recruitment, attrition, visit scheduling (Martina 2018)
  - Inform treatment effect size in sample size calculation (Cook 2017)
  - Understand subgroup heterogeneity (Madigan 2013)
  - From efficacy to effectiveness (Katkade 2018)

Existing Statistical Methods: Meta-Analysis & Network Meta-Analysis

Meta-Analysis & Network Meta-Analysis

Estimand: Average relative treatment effect size between competing treatments in targeted population



- **Indirect comparison**
  – when only two (or one pair of) treatments are being compared indirectly
- **Mixed treatment comparisons**
  – a generalization of indirect comparisons with more than two (or multiple pairs of) treatments being compared indirectly

Steps

https://www.rtihs.org/news-and-events/webinar-introduction-network-meta-analysis

Meta-Analysis Assumptions
Transitivity, heterogeneity & inconsistency

- Treatment Effect (TE) = ∆Treatment-Control
- Effect Modifier (EF) = Factor that modifies ∆TE size across studies

1. Transitivity (aka Similarity or Exchangeability)
   - Similarity of patients and study design
   - Distribution of EF between comparisons are **not systematically different**
2. Homogeneity
   - Measure of variance between studies
   - Studies are "**similar enough**" to be pooled for analysis
3. Consistency
   - Agreement between direct & indirect evidence for a given pair of treatments
   - Direct and indirect evidence can be pooled

Retrospective Data Gaps

Selection

- Evaluate the effectiveness of **pre-registration** and improve.
- **Independent investigator** conducts evidence synthesis or at least data selection to minimize potential bias
- Promote surging interest of **sharing control data** in recent years
- Extend current good practices of evidence synthesis guidelines to include RWD by types (e.g., EHR, claims, etc.) for better uptake

Analysis

- Alternative models accounting for difference between RWD and historical RCT data or obs. study.
- NMA methods more tailored to different types of RWD (e.g., EHR, claims, etc.) for better uptake

Retrospective Data Landscape Summary

Topic	Description	Comments
Heterogeneous Data Sources	• Level: Aggregated Data vs. Individual Patient Data • Purpose: RCT (masked vs not), single-arm, registry, claims	How to account for differences e.g., definitions, uncertainties, potential confounders, data collection frequencies
Challenges	• Different data generated *not* for research purposes • Unmeasured confounders	• When is “similar enough”? • RWD ≠ historical RCT (quality) • Selection bias
Analysis Methods	Lit. review → Meta-Analysis (MA) → Network Meta-Analysis → Multivariate Network MA	Evolving research areas
Data quality	Numerous existing guidelines for various purposes	Fit-for-purpose requirements

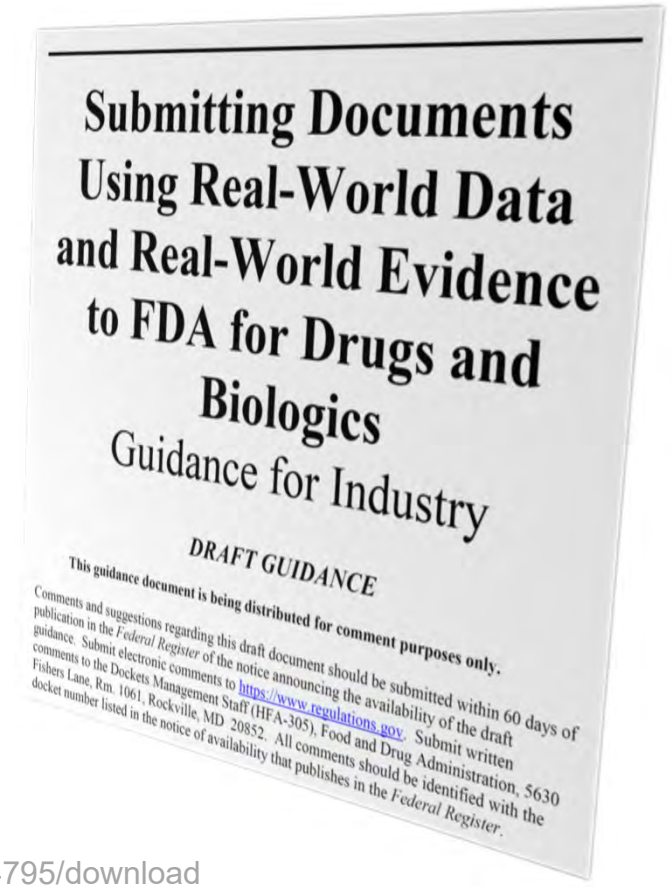
RWD and RCT Data Are Different

Characteristics	RWD	Traditional Historical Control Data
Typical sources	Claims, EHRs	Prior RCT control subjects, registries
Purposes	Billing, administrative	Establishing efficacy and/or safety
Data standard, structure & quality?	Variable depending on source	Standardized, well structure data, monitoring and audit for quality
Access & control similar to RCT data?	Varied but different	1. obs./registry data: more limited 2. prior trials controls: comparable
Definition of endpoint & covariates	Specific to sources / contexts	Prospectively specified
Validation of variable definitions	Required	1. obs./registry data: required 2. prior trials controls: maybe

Bottomline: Compared to clinical trial data, evaluating a study with RWD would require sufficient evidence for 1) data quality, 2) definition of analysis variables & 3) validation of definitions.

Regulatory Submissions

- RWE clinical studies & RCTs may follow similar steps.
- **Encourage early discussions** with FDA for RWD/RWE on:
  1. Data sources, standards, & quality
  2. Definition of analysis endpoints & covariates
  3. Validation of the defined endpoints & covariates



Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drugs and Biologics

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

https://www.fda.gov/media/124795/download

External (Historical) Data Control vs. Borrowing

External Data = Data from sources outside of the prospective study, including data collected in the past (i.e., historical data)

Types of Combining External Data and Prospective Study Data

External **Control**	External **Borrowing**	Synthetic Evidence
Control vs. single-arm study	Augmenting control arm in RCTs	Combine historical & concurrent data

Levels of Pooling External Data and Concurrent Control Patient Enrollment

Design	Treat. : Ctrl.	Enroll Control Patients?	Pooling External Data
RCT	1:1	Yes	No pooling
External **Borrowing**	N:1	Yes (fewer)	Dynamic pooling
External **Control**	1:0	No (single-arm)	Complete pooling

External Control & Borrowing Methods

Types

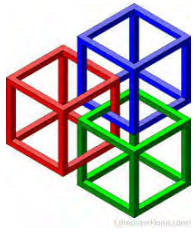
Test-then-pool	Uncertain *a priori* ext. data sufficiently similar to current control arm (Viele 2014)
Power Priors	Assigns a 'weight' to the historical data somewhere in between complete and no pooling (Psioda and Ibrahim 2018)
Hierarchical Modeling	External data more similar to current control data, more "weight" assigned to the external data (Pennello and Thompson 2007)

Control vs. Borrowing Methods

External control	External borrowing	Considerations
• Bayesian approaches • Treatment modeling, ex: propensity score (PS) • Various matching metrics & methods	Bayesian dynamic borrowing, ex: – Hierarchical models – Power priors – Commensurate priors – Robust MA priors PS-based augmentation with multiple controls	• Simulation-based sample size estimation • Large & diverse control pool • Prespecify analysis plan • Balance assessments

External Data and Study Design: Gaps

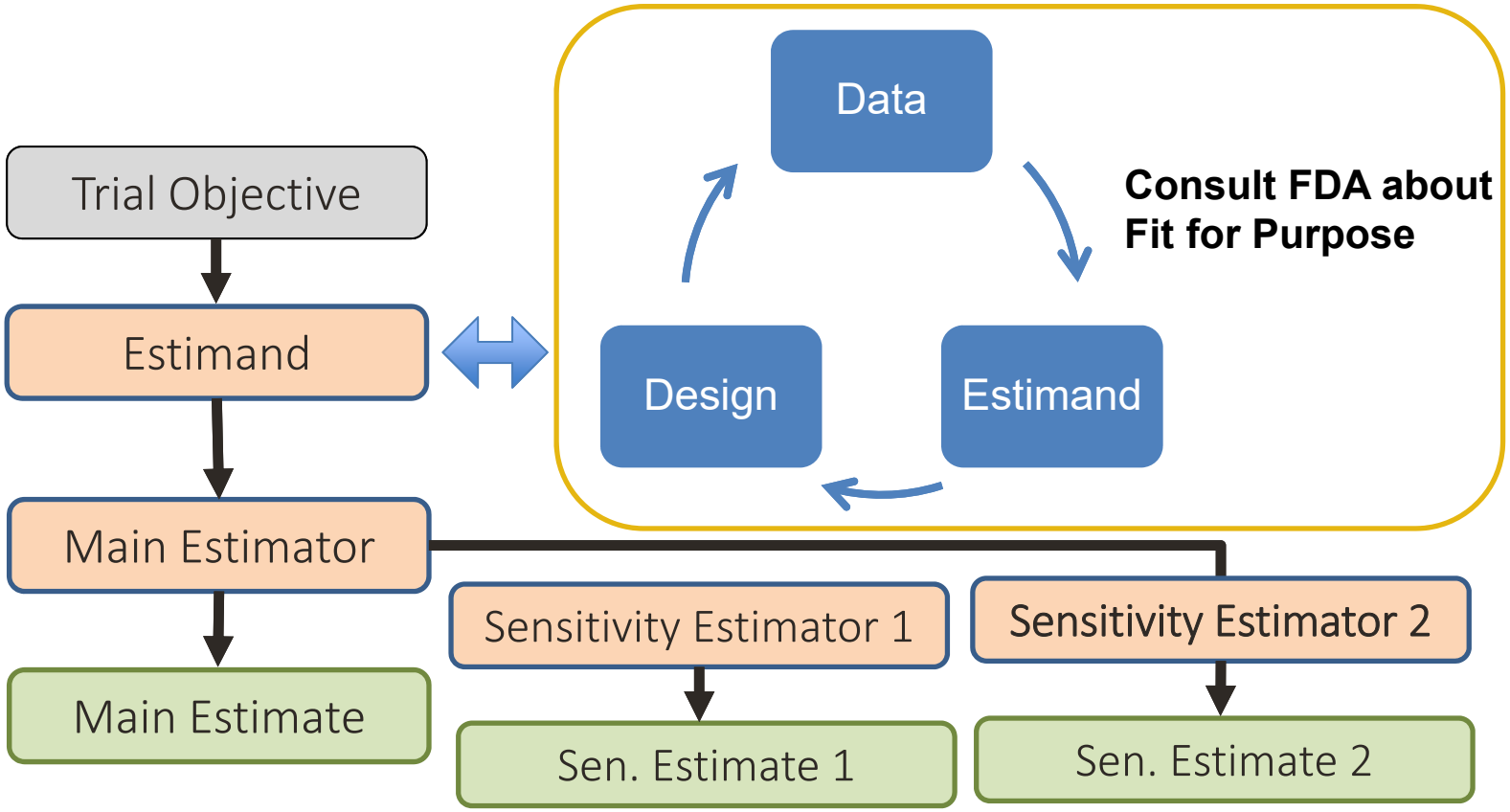
- Comparability assessment
  - Metrics using covariates & exposure
  - Adjust for time-dependent covariates in control
- Rubin causal models
  - Limited overlapping with control
  - Sample size calculation and trial simulations
- Other causal inference approaches
  - Treatment vs. outcome modeling approach
  - Doubly robust methods
- Borrowing from multiple sources for control
- Combining RWD + prior RCT data
  - Weighted average
  - Meta-analytic
  - Data fusion



Multiple Existing and Relevant Frameworks

- FDA CDER & CBER Program for RWE Program (2018)
- FDA CDRH RWE to Support Regulatory Decision-Making (2017)
- E9(R1) on Estimand (ICH 2018)
- Rubin causal model (Rubin 1974)
- Roadmap of Statistical Learning (Petersen & van der Laan 2014) Keynote!
- ISPOR good practices for RWD studies (Berger 2017)
- MDIC Data Quality and Method Framework (drafted 2019)
- IMI GetReal Review of Networked Meta-Analysis Methodology (Efthimiou 2016)

E9(R1) Estimand & RWD Fit-for-Purpose



EXAMPLE

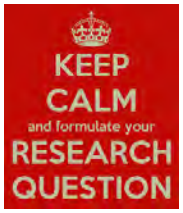
Examples

FDA

Condition	Product	Control	1° Endpoint	Methods
1) B-cell precursor acute lymphoblastic leukemia (ALL) in 1st or 2nd complete remission with minimal residual disease (MRD) ≥ 0.1% *(Gökbuget et al. 2018)*	2018 Blincyto: 1st approved therapy for MRD positive for ALL	Pooled historical data set from Europe & the US	Complete remission	① 189 single-arm treated subjects vs. 694 control by stabilized IPTW with covariates: age, sex, duration between initial diagnosis & salvage therapy, region, prior HSCT, prior # of salvage therapies, 1° refractory & in 1st salvage, refractory to last salvage therapy.
2) **Male** with hormone receptor (HR)-positive, HER2-negative advanced or metastatic breast cancer	2019 Ibrance: Expanded to from F to M patients	Pooled historical data set from Europe & US	Safety profile	② *"Based on limited data from postmarketing reports and electronic health records, the safety profile for men treated with IBRANCE is consistent with the safety profile in women treated with IBRANCE."*
3) Symptomatic heart disease due to severe native calcific aortic stenosis at high or greater risk for open surgical therapy *(Thourani 2016)*	2016 SAPIEN 3 transcatheter aortic valve replacement	938 patients in the open-heart surgery arm of PARTNER 2A trial	All-cause death, all stroke, aortic insufficiency ≥ moderate at 1yr	③

Observed Event Rate		Propensity Score Quintile Pooled Proportion Difference (ATT Method*) [90% CI]†	Margin
SAPIEN 3 (N=1069)	PIIA-SAVR (N=936)		
13.0%	23.2%	-9.2% [-12.4%, -6.0%]	7.5%

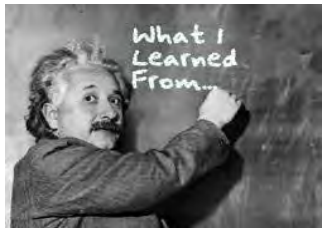
① Not from label; Gökbuget et al. (2018)
② IBRANCE label (April 2019) go.usa.gov/xmpHe
③ SAPIEN 3 label SSED (August 2016) go.usa.gov/xmp6g



Selected Future Research Questions

- **Complex treatment patterns** (switching various drugs) common in patient journeys
- How to define estimand with complex treatment patterns?
- What are key considerations?
- How to design, analyze, and interpret?

- **Fit-for-purpose** criteria and evaluation for data sources
- How to quantitatively characterize quality of a data source (e.g., validity, reliability)
- What are key considerations in selection of RWD sources for various regulatory purposes?
- Unavailable data ≠ missing data



Take-Home Message

- Evaluation of validation evidence for RWD/RWE is context-specific.
- Real-world data are fit-for-use to address the regulatory question. Thus, FDA encourages sponsors to discuss their RWE study early.
- Adequate study design, conduct, and analysis can provide scientific evidence to address the regulatory challenges, which otherwise could not be addressed.
- Many exciting research and application opportunities awaiting ahead to address unmet medical needs!
- Stay-tuned for the pair of landscape assessment papers of the ASA BIOP RWE Scientific Working Group.

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ASA BIOP RWE Scientific Working Group

Industry	Organization	Academic/FDA [£]	Organization
Weili He*¥	AbbVie	Martin Ho*¥	CBER
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* Working Group co-chairs

£ Liz Stuart (JHU) participates as non-member

¥ Workstream co-leads

§ Bill & Melinda Gates Medical Research Institute

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Questions and/or comments?

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