Gaps in RWE Research - Lack of Proper Statistical Methods vs. Lack of Proper Use of Statistical Methods

Weili He, PhD; Hongwei Wang, PhD; Ivan Chan, PhD
AbbVie, Inc.
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Weili He, Hongwei Wang, and Ivan Chan are employees of AbbVie, Inc.
Outline

- Environment for Real-World Evidence (RWE) Research
- Key Considerations in Real World Data (RWD) and RWE research
- Key Challenges in RWD and RWE research
- Applying quantitative approaches in RWE research
- Conclusions
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Environment for RWE – US

- 21st Century Cures - FDA shall establish a program to evaluate the potential use of real world evidence (RWE) to support:
  - Help support the approval of new indication for an approved drug
  - Help support or satisfy post-approval study requirements
FDA PDUFA (Prescription Drug User Fee Act) VI on Enhancing Use of RWE for Use in Regulatory Decision-Making:

- **2018**
  - RWE benefits to patients, regulators & industry;
  - RWE availability, quality, and access challenges, and approaches to mitigate these;
  - Methodological approaches for the collection, analysis, and communication of RWE;
  - Appropriate contexts of use of RWE in regulatory decision-making regarding effectiveness.

- **2019**
  - Initiate, appropriate activities (e.g., pilot studies or methodology development projects) aimed at addressing key outstanding concerns and considerations.

- **2021**
  - Publish draft guidance on how RWE can contribute to the assessment of safety and effectiveness in regulatory submissions, for example in the approval of new supplemental indications and for the fulfillment of post-marketing commitments and requirements.
Environmental for RWE – US (Cont’d)

- FDA CDRH RWE Guidance (Issued on Aug. 31, 2017)
- Biotechnology Innovation Organization (BIO) is issuing a white paper for comment on incorporating RWE into regulatory decision with check lists for assessing data quality, conducting RW study and request the establishment of a framework with more clarity and guidance from FDA (2018)
- PhRMA RWE WG Meeting draft Points of Considerations on data methodology and data quality (2018)
Environment for RWE – EU

- EMA publishes multiple guidance on conducting post-authorization safety and efficacy studies and promoting the usage of RWE:
  - 2017 EMA Patient Registry Initiative to support research in understanding natural history of disease and characterizing the effectiveness and safety of products
  - 2016 EMA Guideline for post-authorization safety studies focusing on non-interventional study

- Increasing public private consortium in RWE research, such as
  - Adaptive pathway (AP)
  - IMI GetReal
  - European Health Data & Evidence Network (EHDEN) (ongoing)
EU IMI GetReal Project [https://www.imi-getreal.eu/]:

- Launched in October 2013, GetReal is a three-year, €2 Billion project of the Innovative Medicines Initiative (IMI), a EU public-private consortium consisting of pharmaceutical companies, academia, HTA agencies and regulators (e.g., NICE, HAS, EMA and ZIN), patient organizations and SMEs.

- GetReal aims to show how robust new methods of RWE collection and synthesis could be adopted earlier in pharmaceutical R&D and the healthcare decision making process.

- The three-year project completed in October 2016, with training and publications on RWE in public domain.
Environment for RWE – EU (Cont’d)

- EU IMI GetReal Project objectives and structure:
Outline

❖ Environment for Real-World Evidence (RWE) Research

❖ Key Considerations in RWD and RWE research

❖ Key Challenges in RWD and RWE research

❖ Applying quantitative approaches in RWE research

❖ Conclusions
Key Considerations in RWD and RWE research

- Considerations for generating RWE*
  - Regulatory context
    - New indication
    - Labeling revision
    - Safety revision
    - B/R profile knowledge
  - Clinical context
    - Prevalence of the disease
    - Population
    - Geographic factors
    - Clinical equipoise
    - Expected treatment effect size

Key Considerations in RWD and RWE research (Cont’d)

- Considerations for generating RWE* (Cont’d)
  - Data Considerations
    - Minimal missing data
    - Sufficient data reliability and validity
    - Establish data quality assurance procedures
  - Method Considerations
    - Interventional vs. observational
    - Prospective, retrospective, or hybrid
    - Appropriate analytic approach
    - Credibility established (protocol development and replication of results achieved/planned): pre-specify SAP, transparency, robustness of findings with agreed upon process, e.g., clinicaltrials.gov for RCTs

*A framework for regulatory use of real world evidence. Duke-Margolis Center for Health Policy, Sept. 2017*
Putting them all Together

- Defining the scientific question
- Identify suitable trial design
- Selection of RWD Sources that are “Fit for Purpose”
- Data standards/analytics
- Ensure compliance with FDA Regs e.g. Part 11 and GCP
- Submission of RWE for regulatory action
- Decision

* Source: Corrigan-Curay. Real World Evidence A Path Forward. FDA RWE Public Meeting, Sept. 13, 2017
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Key Challenges in RWD and RWE research

- Regulatory guidance documents still under development
- Data challenges
  - Availability of data and gaps in data collection
  - Data standards and methodologies for data collection
  - Interoperability of databases
  - Data quality and representativeness
  - Methods for linking data sources
- Process and infrastructure challenges
  - IT infrastructure and process maps to facilitate RWD/RWE research
  - Transparency, consistency, and reproducibility
  - Verifiability and robustness of RWE results/conclusions
  - Re-useable tools development, e.g., advanced analytics
Key Challenges in RWD and RWE research (Cont’d)

- Study design challenges
  - Substantial variabilities in study designs and lack of consensus when conducting RW study to address specific type of research questions, e.g., comparative effectiveness, non-medial switch of biologic products, patient journey, disease progression, path to diagnosis, biomarkers and subgroup identification, etc.
  - Some of the above design challenges are recognizable and remediable, but some others may defy solely analytic solutions due to major design flaws
Key Challenges in RWD and RWE research (Cont’d)

- Study design challenges (Cont’d)
  - Other design challenges*
    - Establish causal relationship
    - Design matches research questions
    - Control for bias and confounding at both design stage and analytic stage
    - Sufficient statistical precision and mitigation of multiplicity
    - Statistical significance and clinical important effect size
    - Completeness of data and not intervening with routine clinical practice
    - Address unobserved confounders
    - Ascertainment of target population and key outcomes, e.g., may not be definable and need approximation
    - Different needs of key stakeholders

* Goodman, Schneeweiss. Using design thinking to differentiate useful from misleading evidence in observational research. JAMA, Vol 317 (7)
Key Challenges in RWD and RWE research (Cont’d)

- Study design challenges (Cont’d)
  - Need to ensure
    - right population
    - exposure assessment (start time, duration, discontinuation, switch, adherence concurrent medication)
    - Intervention
    - right outcome measures (often different from those of RCTs)
    - safety issues
    - Appropriateness of Blinding/unblinding
    - Data ascertainment and minimization of systemic biases and confounding
    - Fulfilling the needs of different stakeholders
Key Challenges in RWD and RWE research (Cont’d)

- Study design challenges (Cont’d)
  - Need to avoid
    - Immortal time bias\(^1\): A span of cohort follow-up, because of exposure definition, the outcome under study could not occur
    - Reverse causation\(^2\): Confounding by indication
    - Adjusting for intermediate variables in the exposure to outcome pathway\(^3\)

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Key Challenges in RWD and RWE research (Cont’d)

- Methodology challenges
  - Existing analysis methodologies require deeper understanding of practical usages and appropriate applications, e.g.:
    - Propensity score based methods (matching, stratification, weighting, adjusting) versus multivariate regression models
    - Network meta-analysis / Indirect treatment comparison
    - Machine learning and Predicative modeling
    - Natural language processing for unstructured data
    - Assess and reduce measurement errors and understanding the impact of data limitations for making inferences
  - Statistical techniques suffer from the same limitation that they cannot overcome unquantifiable or poorly recorded confounders
  - Model fit, sensitivity analysis, Internal validity, external validity, reproducibility, pre-specification
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Applying quantitative approaches in RWE research

Assessment of data aspects:

- Data sources, quality, and accuracy:
  - Feasibility assessment and availability of key data elements
  - Longitudinal nature of the data source
  - Data elements, measure of exposure, potential confounding factors
  - Accuracy of data being captured (e.g. diagnosis, intervention, outcome)
  - Data allowing for comparative analysis
  - Generalizability of the results (spectrum between RCTs and RW setting)

- Endpoints:
  - Endpoints in RW setting may be different from RCTs
  - Need to validate routine care RWD endpoints in given indication
  - Need to develop algorithm for endpoints that are not captured in precise way and/or in different places in medical records
Applying quantitative approaches in RWE research (Cont’d)

Assessment of data aspects (Cont’d):

- **Missing data:**
  - Assess level of missing data, including whether or not certain data fields are not designed to capture or level/magnitude of missing data for key data elements at patients’ level
  - Methods for missing data imputation and sensitivity analysis to assess robustness
  - Missing at random assumption may not hold, e.g., survival effect

- **Linking or pooling different databases:**
  - Use appropriate approaches for linking different databases, accounting for differences in coding and reporting and using suitable and adequate patient identifiers
  - For pooling, use appropriate methods to prevent double-counting of patients across different data sources
  - Relatively small proportion of patients may be linkable and heterogeneity when pooling
Applying quantitative approaches in RWE research (Cont’d)

Assessment of study design and methodology aspects:

➢ Causal evidence
  ✓ Design studies that establish causal evidence, working within constrains of data source, cohort entry criteria, operational definition of data elements, temporal anchors, exposures, methodological approaches, outcomes, follow up, covariates.

➢ Bias minimization
  ✓ Apply analytic approaches that identify and minimize known biases and confounding factors
  ✓ Acknowledge and quantify, if possible, biases with the study design and analytic approaches, and discuss strengths and limitations of the research
Applying quantitative approaches in RWE research (Cont’d)

Assessment of utility of advance analytics in medical research:

- Advanced analytics such as machine learning and artificial intelligence is evolving rapidly and no one-size fits all solution
- Many of these techniques still remain untapped in medical research which requires customization to accommodate the volume, variety and velocity of big data
- Best practice sharing, establishing research partnership, user-friendly tool development, and cases studies can unlock the potentials and advance their wide adoption
Conclusions

- RWD/RWE research is evolving rapidly and is playing an increasingly important role
- Quantitative approaches play a critical role in the conduct of RWE research from conceptualization, design, analyses, interpretation to communication
- With growing knowledge and evolving regulatory environment, statisticians as quantitative scientists should be in the forefront in shaping up RWE research strategy, leading the methodologic development and execution
Thank you !