Observational Patient Evidence for Regulatory Approval and Understanding Disease (OPERAND)

Barbara E. Bierer, MD
MRCT Center
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What is the role of real-world data in regulatory decision making?

Program Objective

Improve the confidence in observational data to generate evidence supporting treatment effectiveness and safety for patient populations beyond those studied in randomized clinical trials (RCTs).

Approach

• Two project teams simultaneously and independently replicate two clinical trials using the OptumLabs Data Warehouse (OLDW).
  ▪ OLDW is a comprehensive, real-world data set with over 200 million de-identified lives across administrative claims and electronic health record (EHR) information.
• Focus on testing methodologies and setting standards to support the reliability of evidence generated.
• Engage diverse experts in government, academia, and industry to advise the program.

Potential impact

• Validation of using observational data to complement evidence from RCTs.
• Innovation in clinical trial design, thereby bringing new treatments to market faster and more efficiently.
• Inform policy on the use of real-world evidence to support regulatory approvals of new drug indications and to satisfy post-approval safety surveillance requirements.
Program overview

Phase 1  
**Completed**  
Program design, funding, recruitment of expert panel, and trial selection.

Phase IIA  
**Preliminary Analysis Completed**  
Two academic institutions each replicate the same two previously published RCTs of pharmacological products that were used as the basis of marketing approval by the U.S. Food and Drug Administration.

Phase IIB  
**In Analysis**  
Further analysis of treatment effects in the broader patient population actually treated.

Phase III  
**Pending**  
Extend the replication effort to a larger group of trials to generate a bolus of evidence on the reliability (and limits) of evidence.
### Phase I: Program design and initiation

**Focus:** Planning. Technical expert panel, funding. Trial design, RFP

| Planning | • Multiple meetings between MRCT Center and OptumLabs to establish outcomes, methods and partners  
|          | • Both entities have close collaborators. Independence essential |
| TEP      | • Recruited a technical expert panel (TEP) made up of representatives from industry, academic, professional and trade associations, and FDA colleagues.  
|          | • Discuss and review plan, outcomes, and process  
|          | • Participate in meetings at critical stages of program |
| Funding  | • Contributions from industry solicited to cover costs of research program  
|          | • Common contract for each donor, no rights to approve or suppress  
|          | • Funders became Operating Committee |
| RFP      | • Trials selected, RFP developed and sent to OptumLab partners.  
|          | • Responses reviewed by OptumLabs and MRCT Center, then by TEP and Operating Committee |
| Immediate steps | • Two teams chosen, each independent of one another, without any communication between them  
|          | • Observational study and planned analyses pre-registered  
|          | • Each team given access to data in private sandbox |
Phase IIA design: Trial Replication

**Focus:** On-label effectiveness in defined subgroups

| Number of Teams & Trials | Two academic institutions will independently replicate two identical target trials:  
1. ROCKET for atrial fibrillation  
2. Lead-2 for Type 2 diabetes control |
|--------------------------|--------------------------------------------------------------------------------|
| Data                     | (a) Claims data alone and (b) Claims + EHR, each used for sensitivity analyses  
Data will be restricted to inclusion and exclusion criteria of pivotal RCT and on-label indication for Phase IIA |
| Methodology              | Bootstrapping methods along with bias analysis will be used to understand variability in treatment effect estimates |
| Documentation            | Research team must document assumptions and choices made when emulating trials |
| Approach                 | To ensure comparability, the teams will:  
• Be given a common clinical question and the study RCT protocol  
• Be given defined set of anticipated methods  
• Have flexibility to use their own methods in certain areas  
• Initially, be restricted to inclusion/exclusion criteria |
### OPERAND Collaborative

#### Co-Leads

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<tr>
<th>OPTUM Labs</th>
<th>MULTI-REGIONAL CLINICAL TRIALS</th>
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#### Sponsors

- Amgen
- AstraZeneca
- Merck
- Optum
- Pfizer
- Sanofi
- UCB BioSciences, Inc.

#### Research Partners Selected

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<th>Brown University</th>
<th>Harvard Pilgrim Health Care Institute</th>
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#### Technical Expert Panel

Sponsor representatives

+ 9 representatives from academia, pharmaceutical companies, professional societies, etc.

FDA participant as observer
Measures of Replication

Regulatory agreement
Defined as statistically significant result with directional equivalence between the RCT and observational study.

Estimate agreement
Defined as the point estimate of the observational study falling within the 95% confidence interval of the ATE from the RCT using the reported standard errors of the RCT to define the confidence interval.
Preliminary Results: Distribution of estimates from ROCKET AF Trial and the replication study
Program governance

**Operating Committee**
- Oversight of integrated program
- Establish strategy and priorities
- Approve business plan & communications
- Voting power to make decisions for the program

**Technical Expert Panel**
- Establish research and scientific priorities, protocols and plan
- Review research & scientific activities
- Select grant recipients

**Research Teams Selected**
- Design and implement research & translation projects
- Provide clinical & care translation insight
- Publish research

**Program Management**
- Develop execution strategy
- Manage grant program
- Manage ongoing program work

**Financial Sponsors**
- MRCT
- OptumLabs

**Subject Matter Experts from multiple stakeholder groups**

**Sponsor representatives**

**Subject Matter Experts from multiple stakeholder groups**

**Sponsor representatives**

**Brown University**

**Harvard Pilgrim Health Care Institute**
Thank You

Barbara E. Bierer, MD
Faculty Director, MRCT Center
Professor of Medicine, Harvard Medical School
Senior Physician, Brigham and Women’s Hospital
bbierer@bwh.harvard.edu

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