

Request for Proposal

OPERAND

Observational Patient Evidence for
Regulatory Approval and uNderstanding
Disease

Table of Contents

Background and Program Objectives	1
Objective of the RFP	3
Study Objectives and Analyses	4
ROCKET Atrial Fibrillation and LEAD-2 Trials.....	5
Study Deliverables	6
Project Timelines.....	6
Eligibility and Funding	6
Submission and Response Requirements	7
Selection Criteria/Weighted Scoring	7
Submission and Selection Process and Timeline.....	9
References.....	10
Appendix A: Relationship of OPERAND to Related Activities	11

Background and Program Objectives

The Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard (MRCT Center), in collaboration with OptumLabs, is pleased to offer this funding opportunity to study the conditions under which it may be possible to replicate the findings of previously published randomized clinical trials (RCTs) with observational data. Such evidence would set the stage for improving confidence in estimates of treatment effectiveness for patient populations beyond those originally studied in RCTs.

Recent interest in real world evidence (RWE) studies has been driven by the desire to bring innovative products to patients more quickly than the traditional drug development path involving RCTs. This desire has been expressed through regulatory mandates included in the *Prescription Drug User Fee Act* (PDUFA) VI¹ and the 21st Century Cures Act.² Specifically, the FDA has deemed RWE one of the topics of high importance to be funded under (PDUFA) VI³ ultimately culminating in the publication of draft guidance for RWE applications by the end of FY 2021. In addition, the 21st Century Cures Act mandates (section 3022) that FDA propose a framework and enact a program to evaluate RWE to support approval of new indications and to satisfy post-approval requirements. It is clear from these recent mandates that FDA has committed to facilitating the use of RWE and considering its use for regulatory approvals, at least for some applications.

While prospectively planned clinical trial data remains the cornerstone of regulatory submissions, to date RWE has not been routinely utilized or accepted for drug approval due to a number of challenges: lack of final regulatory guidance on its use to support regulatory decision-making for medical products (although a draft guidance specific to devices has been issued);⁴ absence of a rigorous, standardized methodology to define, abstract, analyze, and submit RWE; and the fact that RWE—unlike prospective trial data—is not acquired for the purpose of drug approval, leading to potential data quality and bias issues.

The program entitled **Observational Patient Evidence for Regulatory Approval and uNderstanding Disease (OPERAND)** is designed to better inform the use of RWE from retrospective observational studies in medicine and regulatory decision-making. We propose a program that will first use retrospective observational data to determine if such data can confirm previously published RCT results and, if successful, extend the use of the data for other potential applications. The methodology developed and utilized must be compelling to regulatory approvers, payers, and policy makers.

The OPERAND initiative has three components—Design, Application, and Scale.

1. *Design* involved the assembly of a Technical Expert Panel (TEP) including representatives from the FDA, ISPOR, PhRMA, NPC, academia, pharmaceutical representatives, MRCT Center, and OptumLabs. At an in-person meeting at the MRCT Center, the study design was discussed and finalized, and subsequently further refined.

¹ and ² <https://www.congress.gov/bill/114th-congress/house-bill/34/text>

³ <https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm446608.htm>

⁴ <http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm513027.pdf>

2. *Application* is the subject of this RFP. The goal of the Application phase of OPERAND is to demonstrate the technical feasibility of replicating the average treatment effects of two RCTs that were previously used by the FDA for marketing approval of pharmacological agents. This work has two components with the second component being conditional on the first. The first component is the trial replication activity itself. Following completion of this work the TEP will review the results and decide whether to proceed with the second component. The second phase of the work would evaluate the ATE in the population actually treated (i.e., within the original indication but without the stringent inclusion/exclusion criteria of the trials).
3. *Scale* is intended to broaden the number of clinical trial replications to a large number of additional trials. Pending successful completion of the Application phase, Scale will be the subject of a future RFP.

While there are examples of individual RCTs that have been replicated using observational database analyses,⁵ no replication of a large number of trials across several different therapeutic areas simultaneously has yet been published. Such an effort is needed to shed light on a number of critical questions particularly relevant in retrospective analyses, including quality of data sources, bias (and ways to mitigate it), and variability in observational database studies. One important issue is the potential of reducing missing variable bias through data linkage—in particular, by linking claims data with electronic medical records, sociodemographic variables, and other data such as insurance benefit design to control for confounders that are missing in analyses based on claims data alone. Data linkage may also enable more accurate characterization of the inclusion/exclusion criteria used to define study populations.

RWE derived from the analysis of claims data has been used for years following product approval to obtain safety data (e.g., FDA's Sentinel Initiative).⁶ For the current proposed project on RWE, we leverage the fact that the indication on the product label may not reflect the practice of medicine; medicines and biologics are often prescribed or utilized in a manner that differs from the one approved. Off-label use of products is common after regulatory approval is granted. Utilizing RWE can potentially expand the population of an approved product to a broader population within the same indication or encompass a new indication (label expansion).

Publications by ISPOR, ISPE, and the FDA have described guidelines for high quality epidemiological and outcomes research using observational databases.⁷ Much of the existing literature, particularly

⁵ Fralick M., Kesselheim A., Avorn J., Schneeweiss S. 2017. Use of Health Care Databases to Support Supplemental Indications of Approved Medications. *JAMA Internal Medicine*. Doi:10.1001/jamainternmed.2017.3919. Seeger J., Bykov K., Bartels D., Huybrechts K., Zint K., Schneeweiss S. 2015. Safety and Effectiveness of Dabigatran and Warfarin in Routine Care of Patients with Atrial Fibrillation. *Thrombosis and Haemostasis* 114(6):1277-89.

⁶ <https://www.fda.gov/Safety/FDAsSentinelInitiative/ucm2007250.htm>

⁷ Johnson, M., Crown, W., Martin, B., Dormuth, C., Siebert U. 2009. Good Research Practices for Comparative Effectiveness Research: Analytic Methods to Improve Causal Inference from Non-randomized Studies of Treatment Effects Using Secondary Data Sources. Report of the ISPOR Retrospective Database Analysis Task Force—Part III. *Value in Health* 12(8): 1062-1073. Public Policy Committee, ISPE. Guidelines for Good Pharmacoepidemiology Practice (GPP). *Pharmacoepidemiology and Drug Safety* 2016; 25:2-10. DOI:10.1002/pds.3891 <https://www.fda.gov/downloads/drugs/guidances/ucm243537.pdf>

with respect to epidemiological methods, has been informed from drug safety studies conducted with the Mini-Sentinel data and other claims databases. These studies have shown that, in general, strong observational research design incorporates pre- and post-measurement on both an intervention and control group, known as quasi experimental design. Beyond this, matching or weighting methods are generally recommended to balance on observable confounders—for example, propensity score matching, G-estimation or Inverse Probability Weighting from the epidemiology literature, or differences-in-differences methods from the economics literature. All the epidemiologic methods mimic the effect of RCTs in terms of balancing treatment and control groups. However, epidemiologic methods balance the cohorts only based on observed covariates. Methods from the econometrics literature, such as instrumental variables and differences in differences, also attempt to balance on the basis of unobserved variables associated with both the treatment and outcomes. OPERAND will enable evaluation of the sensitivity of study results to multiple methodologies as well as the range of variables available for covariate control (e.g., claims alone, claims plus EMR, claims plus sociodemographics, claims plus EMR plus sociodemographics).

Objective of the RFP

The primary goal of this request for proposal is to fund two academic institutions each to replicate the same two previously published randomized controlled trials of pharmacological products that were used as the basis of marketing approval by the U.S. Food and Drug Administration (FDA). Pending review of the trial replication work by the TEP, the research teams will then “open the aperture” to estimate the ATE for the populations actually treated within the original indication. All analyses will be conducted using the OptumLabs Data Warehouse (OLDW)—a database of more than 120 million lives of claims data linkable to over 50 million lives of electronic medical record data. Researchers will access the OLDW through a secure virtual sandbox provisioned with the OptumLabs Unified View, which includes integrated claims and clinical data. In order to protect confidentiality, despite de-identification, no patient-level data will be downloaded or leave the OptumLabs servers.

The two trials to be replicated are the ROCKET Atrial Fibrillation and the LEAD-2 studies (additional details below). The intention is for the two selected academic groups to utilize the same reference publications describing the trials, as well as the same data and core statistical methodologies as the starting point. This will help to clarify the basis for differences in analyses, if any, arising either from issues of transparency in clinical trial publications, variation in trial design interpretation by the different research groups, or the different assumptions made in the analyses. While using a set of core methods is required, the academic groups will be encouraged to utilize other statistical methodologies of their choosing, to enable evaluation of variability introduced by alternative methods. Pending a review of the findings, the intent is to then extend the analysis to the real-world population actually treated but still within the original indication and with the same comparator treatment as the study group. Finally, pending the results of this study, a future RFP would extend the replication effort to a significantly larger group of trials to quickly generate a bolus of evidence on the reliability (and limits) of evidence that it is possible to generate with high quality observational studies.

Study Objectives and Analyses

For each trial, the initial objective is to mimic the inclusion/exclusion criteria, endpoint definitions, exposure windows, and other design features of each study as closely as possible. Then, using a series of multivariate methods described in this RFP, along with one or more methods selected by the awardee, average treatment effect (ATE) estimates will be produced and compared to those reported in the original publication.

1. Mimic the inclusion/exclusion criteria of the trial, as well as the primary endpoint, and follow-up period. Carefully document your definitions as one of the goals of OPERAND is to understand how differences in researcher decision-making may introduce variability into ATE estimates.
2. Define one or more measures of medication adherence (such as medication possession ratios) and use it as a control variable in your analyses.
3. Create three patient cohorts for each study: (1) using the full sample of patients with claims data, irrespective of whether they have linked EHR data, (2) the sample of claims that link with EHR data, and (3) the sample of patients with claims plus EHR data. (See discussion below on comparisons of these samples.)
4. Perform multivariate analyses to estimate ATEs using the following:
 - A single equation method such as generalized linear models (GLM) to introduce the treatment variable as a covariate. Please describe your criteria/method for selecting the other covariates included in the model.
 - Propensity score matching. We leave the specification of variables to be included in the propensity score model, as well as other decisions, such as the size of the calipers, to the research team but please describe these decisions and criteria fully.
 - Inverse probability weights. Same documentation requirements as the other two methods.
 - At least one other appropriate method at the discretion of the researcher (e.g., regression discontinuity methods, instrumental variables, differences in differences, G-estimation, targeted maximum likelihood estimation (TLME)). More than one method is encouraged.
5. Estimate separate sets of models for the three samples of patients. Linking to EHR will substantially reduce the sample but provide additional covariate controls. Use bootstrapping methods for all ATE estimates from the observational data to evaluate the effects of alternative methods and data samples on estimation bias (relative to the published RCT ATE) and standard errors.
6. How do the ATE estimates from the 3 samples compare?
7. Compare the results from the multivariate analyses to the published estimates of ATE using two methods:
 - 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.
8. Are the results similar? If not, why do you think they differ? Do you have greater confidence in some of the observational results than others? Why or why not?

Results from the trial replication analyses will then be reviewed by the TEP which will make a recommendation with respect to proceeding with the analysis of treatment effects in the broader patient population actually treated.

ROCKET Atrial Fibrillation and LEAD-2 Trials

The ROCKET Atrial Fibrillation study (NCT00403767) was chosen by the OPERAND Operating Committee as an example of a study where the endpoint (stroke or non-CNS systemic embolism) could be measured in claims data. The LEAD-2 study (NCT00318461) was an example of a study where the endpoint was a clinical value (HbA1c). Since the OLDW contains both claims and EHR data the combinations of the two data types influence the inclusion/exclusion criteria, endpoints, and control variables in complex ways. We recommend starting with the claims cohort first and then matching to the subset of patients who also have EHR data. For the purposes of this RFP, we are interested in comparing analyses from three main samples for each study: (1) Patients with claims irrespective of EHR status, (2) the subset of patients with claims who link to the EHR, but the sample includes variables only from the claims subset, (3) patients with both claims and EHR. Some additional considerations:

- Although ejection fraction is an inclusion/exclusion criterion for the ROCKET AF trial we recommend conducting the primary analysis without using this variable as it will substantially reduce the sample size and previous research has indicated that there may be questions with the consistency with which reliable ejection fraction values have been identified by natural language processing. Research teams may elect to include ejection fraction as an inclusion/exclusion criterion in the linked claims plus EHR analyses as a sensitivity analysis.
- For the LEAD-2 study, it is likely that additional HbA1c values can be obtained from the EHR for patients missing HbA1c values in the claims data. This will expand the number of patients with HbA1c endpoint data beyond the HbA1c results found in the claims files alone.
- For both the ROCKET and LEAD-2 studies, the subset of patients with linked EHR data will have additional covariate controls of interest such as blood pressure values, BMI, and lipid panels. We are interested in understanding whether the inclusion of such clinical covariates materially shifts the ATE estimates obtained from using the two claims samples.

The manuscripts reporting the design and results for these two studies can be found at the following links:

1. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *New England Journal of Medicine* 2011 Sep 8;365(10):883-91. <https://www.nejm.org/doi/full/10.1056/NEJMoa1009638>
2. Nauck M, Frid A, Hermansen K, Shah N, Tankova T, Mitha I, Sdravkovic M, During M, Matthews D, LEAD-2 Study Group. Efficacy and Safety Comparison of Liraglutide, Glimepiride, and Placebo, All in Combination with Metformin, in Type 2 Diabetes. *Diabetes Care*, 32(1):84-90, 2009. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2606836/>

Study Deliverables

This research project is expected to produce the following deliverables:

1. Detailed project design including statistical analysis plan by completing the OptumLabs Detailed Research Agreement (DRA) template. The original project design will be registered in advance and archived on a study registration site, along with the individual analysis plans of the selected academic institutions.
2. Documentation outlining assumptions, additional methodology, and interim results.
3. Draft and final written report that includes a description of the project design and key analytic findings for the initial trial replication work. Assuming the TEP recommends additional analysis of a broader patient cohort, the final report will be extended to include the project design and key analytic findings for the patient groups treated beyond those studied in the original RCTs. The report should also include recommendations for additional analyses, as well as the Scale component of OPERAND.
4. A PowerPoint slide deck summarizing the study results to be presented at various national conferences on RWE in the Fall of 2019, as well as the 2019 OptumLabs Research & Translation Forum and potentially the MRCT Center Annual Conference. It is also expected that the study results will be submitted for publication in peer-reviewed journals jointly by OptumLabs, MRCT Center, & the selected research partners.

Project Timelines

The sponsors are seeking project proposals that can be feasibly completed within 9 months of contract execution, with estimated completion of the trial replication component by September 2019 and, assuming the extension to the broader treated population is approved, completion of those analyses by December 2019. Project completion means delivery of a PowerPoint slide deck and final written report summarizing the study results. While we expect the study results will be disseminated via high-impact publications and conferences, we are interested in ways to accelerate other translation channels, such as payer policy and health care delivery system guidelines, etc. Thus, proposals that are designed with translation end points in mind and that align with our timeline for delivery are desirable.

Eligibility and Funding

This funding opportunity is being offered to OptumLabs Partners with expertise in pharmacoepidemiology and health services research, observational studies using claims data, and pharmacological comparative effectiveness research with medical claims and/or electronic medical record data. Only OptumLabs Partners are eligible to submit proposals. Parties not under an active master agreement with OptumLabs are eligible to participate as a collaborator on the project, but will be required to team with an OptumLabs Partner who has full research status related to the use of OLDW.

The total funding award being offered is \$150,000 plus a credit for an OLDW project sandbox and reimbursement for one (1) OptumLabs SAS Server license. The \$150,000 award may cover direct project costs inclusive of no more than 10% indirect institutional costs (i.e., Of the \$150,000 budget,

\$15,000 can be indirect cost whereas the remaining \$135,000 must be direct costs). Organizations should propose a budget in accordance with a project to be completed within the timeline.

Submission and Response Requirements

Please use the OptumLabs Research Application which is included as an attachment to submit your proposal; we outline areas of important emphasis below.

1. A description of your proposed project, including:
 - a. Overview of the population, including a description of study cohorts/comparison groups or other subgroups of interest
 - b. List of key variables of interest
 - c. Description of planned analyses for each objective
 - d. Discussion of potential translation opportunities of study outcomes
2. Project Feasibility - summary of required project resources
 - a. Team staffing (staff bios)
 - b. Proposed detailed budget that includes a breakdown of costs associated with this project
 - c. Resources
 - d. Project timeline by major study deliverables listed above
 - e. Deliverables
3. Information about your project team capabilities, distinctive competencies and why it is uniquely qualified to succeed
 - a. Describe team expertise, including specialties/areas of expertise (e.g., methodologist/statistician)
 - b. Team experience with Claims data and optionally EHR data - or Optum, Humedica or OptumLabs data more specifically, if applicable. Specifically describe experience working with large-scale data sets to perform complex data scrubbing, preparation, and transformation using multi-step processes. Include detail on the programming languages, statistical techniques, and business intelligence tools employed.
 - c. References
 - d. List other relevant work that your institution has handled previously or is engaged in currently

Selection Criteria/Weighted Scoring

Responses to this RFP will be reviewed and scored by the OPERAND Technical Expert Panel (TEP) which is made up of representatives from the project sponsors, the FDA, academia, MRCT Center, OptumLabs, other industry experts, PhRMA, NPC, and ISPOR. The TEP is an advisory group that provides input on study design and translation of findings into policy development. The recommendations of the TEP will be presented to the Operating Committee which is a smaller decision-making body that provides oversight of project activities and deliverables, including:

- Selecting the grant award recipients
- Providing input and feedback on study deliverables (listed below)

- Accelerating translation opportunities (e.g., interface with external organizations like Duke-Margolis Center, FDA involvement, publication and conference/workshop participation).

OptumLabs and the MRCT Center will facilitate periodic meetings with the project teams and, as appropriate, the Operating Committee once the project is initiated in order to enable timely feedback of work in progress and preliminary outcomes.

Selection criteria have been developed in collaboration with the Sponsors, MRCT Center, and OptumLabs, and include a weighted algorithm of component scores across a set of strategic priorities, including but not limited to:

- Project Feasibility – data, timeline, and budget
- Project Team Capabilities
 - Subject matter expertise in retrospective database studies of pharmacological treatments including statistical methods from epidemiology, health services research, or econometrics.
 - Experience using large claims-based data asset
 - Knowledge of OptumLabs Data
- Project Impact
 - Novelty/innovation in discretionary methods
 - Experience in publishing in high impact journals

Rating Category	Rating Factor	Weight
Project Feasibility	Experience with retrospective health care comparative effectiveness studies (claims and EHR), timeline, and budget	0.25
Project Team Capabilities	Team Experience in subject area	0.10
	Knowledge of OptumLabs Data	0.20
Project Impact	Knowledge of statistical methods	0.25
	Degree of novelty/innovation in discretionary methods	0.10
	Experience in publishing in high impact journals	0.10
		1.00

Submission and Selection Process and Timeline

Partners considering responding to this proposal are invited to submit questions about this RFP by December 13th by emailing them to Emily Dayalji (emily.dayalji@optum.com). OptumLabs will address the questions via webinars to be hosted on December 14th and December 20th.

Respondents' proposals must be submitted, via email, to Emily Dayalji (emily.dayalji@optum.com) and Hayat Ahmed (HAhmed@BWH.Harvard.edu), no later than Thursday, January 17, 2019.

Proposal review and award selection – the Operating Committee comprised of representatives from MRCT, OptumLabs, the FDA, and the OPERAND Sponsors will score the submissions based on the enclosed **scoring** rubric and selection criteria (see Appendix A). All respondents will be notified of the selection decision on or before Friday, February 15.

- Request for Proposals Open
 - Formal announcement of Request for Proposal December 10
 - Partner respondents submit RFP questions December 13
 - Overview of RFP – Q&A sessions December 14 & December 20
 - RFP application deadline January 17

- Review and Selection
 - Committee member review and scoring January 17 – February 5
 - Grant notification February 15

References

- Anglemyer A, Horvath HT, Bero L Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials(Review). The Cochrane Collaborative: John Wiley & Sons, Ltd., 2014.
- Benson K., Hartz AJ. "A Comparison of Observational Studies and Randomized, Controlled Trials." N Engl J Med 2000. Jun 22;342(25):1878-86.
- Concato J, Shah N., Horwitz RI. "Randomized Controlled Trials, Observational Studies, and the Hierarchy of Research Designs." N Engl J Med. Jun 22;342(25):1887-92.
- Fralick M., Kesselheim A., Avorn J., Schneeweiss S. 2017. Use of Health Care Databases to Support Supplemental Indications of Approved Medications. JAMA Internal Medicine. Doi:10.1001/jamainternmed.2017.3919.
- Hannan E. "Randomized Clinical Trials and Observational Studies: Guidelines for Assessing Respective Strengths and Limitations." JACC: Cardiovascular Interventions 1(3):211-217, 2008.
- Hernandez-Diaz S., Varas-Lorenzo C., Garcia Rodriguez LA. 2006. Non-steroidal anti-inflammatory drugs and the risk of acute myocardial infarction. Basic Clin Pharmacol Toxicol. 98(3):266-274.
- Ioannidis JP. 2005. Why most published research findings are false. PLoS Med. 2(8):e124,
- Kwok CS, Loke YK. 2010. Meta-analysis: the effects of proton pump inhibitors on cardiovascular events and mortality in patients receiving clopidogrel. Aliment Pharmacol. Ther. 31(8):810-823.
- Johnson, M., Crown, W., Martin, B., Dormuth, C., Siebert U. 2009. Good Research Practices for Comparative Effectiveness Research: Analytic Methods to Improve Causal Inference from Non-randomized Studies of Treatment Effects Using Secondary Data Sources. Report of the ISPOR Retrospective Database Analysis Task Force—Part III. *Value in Health* 12(8): 1062-1073.
- Madigan D., Ryan P., Schuemie M., Stang P., Overhage J., Hartzema A., Suchard M., DuMouchel W., Berlin J. Evaluating the Impact of Database Heterogeneity on Observational Study Results. 2013. American Journal of Epidemiology 178(4):645-651.
- Public Policy Committee, ISPE. Guidelines for Good Pharmacoepidemiology Practice (GPP). Pharmacoepidemiology and Drug Safety 2016; 25:2-10. DOI:10.1002/pds.3891
- Seeger J., Bykov K., Bartels D., Huybrechts K., Zint K., Schneeweiss S. 2015. Safety and Effectiveness of Dabigatran and Warfarin in Routine Care of Patients with Atrial Fibrillation. Thrombosis and Haemostasis 114(6):1277-89

Other Resources

1. <https://www.focr.org/sites/default/files/pdf/RWE%20-%20Project%20PRE-MEETING%20DRAFT.pdf>
2. <http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm513027.pdf>
3. <http://www.nejm.org/doi/full/10.1056/NEJMs1609216>

Appendix A: Relationship of OPERAND to Related Activities

The Duke-Margolis Center for Health Policy, in close coordination with both FDA and the National Academies, has formed an RWE Collaborative to further contribute to ongoing RWE data, methods, and policy development at the national level. Both MRCT Center and OptumLabs participate in the advisory group for this effort and will contribute research, evidence, and expertise to collaborative projects alongside other participating organizations. In turn, a representative from the Duke-Margolis Center participates on the OPERAND TEP. Close coordination between OPERAND, the Duke-Margolis RWE Collaborative, and other ongoing stakeholder activities will help magnify and reinforce positive progress in this space.

Another important effort is the Aetion study being funded by the FDA. The ultimate goal of both Aetion and OPERAND is to generate empirical evidence about the ability to replicate average treatment effects from published trials as a measure of the reliability of treatment effect estimates from observational data. The Aetion project intends to use the Aetion analytic platform to evaluate treatment effects in approximately 30 trials using studies that have outcomes captured in claims data. In contrast, for trials with claims-based outcomes (e.g., occurrence of stroke or AMI), OPERAND will systematically evaluate how ATE estimates vary by statistical method, as well as the introduction of controls for measures from electronic medical records (blood pressure, BMI, lipid levels, etc.). In addition, at least some of the trials evaluated in OPERAND will have endpoints measurable only in EMRs (e.g., blood pressure levels), thus expanding the potential application of evidence from observational studies beyond claims-based studies.

OPERAND will also measure differences in how different academic organizations interpret the inclusion/exclusion criteria and endpoints of the same trials, as well as their implementation decisions even when using the same methods (particular features selected for propensity score matching, size of the calipers, etc.)

In contrast to the Aetion study, OPERAND is interested in trial replication only as the first step. We also want to examine the treatment effects for the broader populations actually treated. Again, we plan to “expand the aperture” systematically beginning with the narrow inclusion/exclusion criteria and expanding to the patient population treated with the medication, to enable us to understand how the ATE changes as the inclusion/exclusion criteria are loosened. Ultimately, this empirical data will contribute to regulatory decision-making in examining the ability to estimate ATEs for new indications to either substitute for, or complement, RCTs. While the extension is not part of the Phase II work, after consideration of TEP review and recommendations, it may be a major component of Phase III.

OPERAND and the Aetion study will share common methodology for comparing the estimates of ATEs from statistical analyses of observational data to those of the published trials to decide when the results are “close enough” to be considered a “replication.” These methods are described below. The OPERAND team is grateful to the FDA and the Aetion investigators for sharing the comparison methods as we believe that using common methodology and approach will help to unify the evidence from the two studies into a broader body of comparative evidence.