

Real-World Evidence

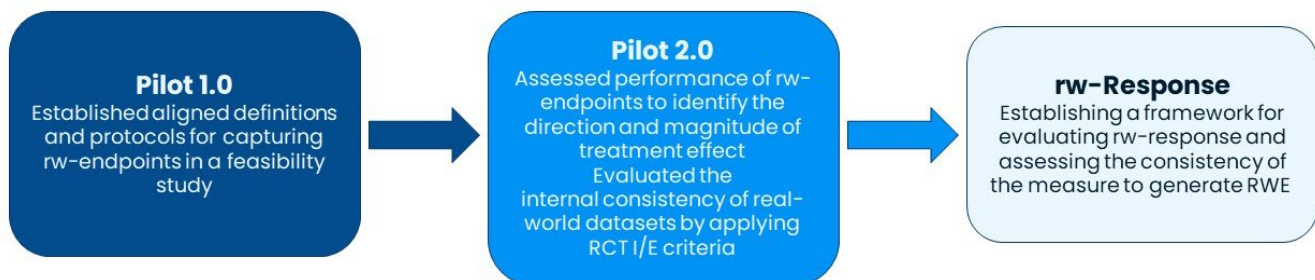
Pilot Projects

The Definition: Real-world evidence (RWE) is the clinical evidence derived from data on the uses and potential benefits and/or risks of a medical product outside of a traditional clinical trial. Clinical trials do not necessarily reflect the breadth of data that can be collected in a more diverse real-world data (RWD) setting. There is potential value of these data and evidence to supplement evidence from clinical trials to expand the population studied for the long-term benefits of a product.

The Problem: RWE can potentially fill evidence gaps about the performance of medical products used in the real-world setting, including populations that may not have been represented in clinical trials. However, traditional clinical endpoints may be difficult to obtain and evaluate from RWD, and the parameters and conditions of use of RWE have not been well defined. There is a need for better characterization of the role real-world endpoints may play in evaluating product effectiveness and an improved understanding of appropriate methodology to evaluate and assess the validity of RWE to support regulatory decision-making.

The Solution: Friends of Cancer Research (*Friends*) convened stakeholders to curate data to determine how endpoints generated from RWD correlate with overall survival and other key indicators of disease burden from clinical trials. The group used these data to help inform the development of a validation framework. *Friends* continues its work to solve this problem through a new RWE pilot project to evaluate, establish, and validate a uniform definition for real world endpoints that measure response (rw-response). These pilot projects help inform ongoing regulatory discussions on the use of RWE by proposing a standard approach for data collection, as well as provide vital information about the long-term value of a product including its safety and efficacy.

The Research Question: Can real-world endpoints be defined and aligned across multiple data sources to generate evidence on patient outcomes?



Why Is This Important? The RWE Pilot Projects establish aligned definitions and frameworks for measuring real-world endpoints, investigate how different elements of RWD can be leveraged to support drug development, and add to the collective evidence supporting the use of RWE in oncology research. RWD generates evidence that reflects a larger and more diverse patient population than is included in clinical trials and addresses timely clinical questions including use of different treatments in standard of care practice and long-term safety.

Who Is Involved?

Pilot 1.0: COTA, the U.S. Food and Drug Administration (FDA), Flatiron Health, IQVIA, Kaiser Permanente/Cancer Research Network (CRN), Mayo Clinic/OptumLabs, and National Patient Centered Cancer Research Network (PCORnet)/University of Iowa

Pilot 2.0: Aetion, American Society of Clinical Oncology (ASCO) CancerLinQ/ConcertoAI, CRN, COTA, FDA, Flatiron Health, IQVIA, Mayo Clinic, McKesson, National Cancer Institute (NCI) SEER-Medicare Linked Database, Mayo Clinic/OptumLabs, Syapse, Tempus

rw-Response Pilot: Ambra Health, ASCO, Columbia University, ConcertAI, COTA, FDA, Flatiron Health, Guardian Research Network, IQVIA, Ontada, Syapse, Tempus

RWE Project

Key Findings from Pilots 1.0 and 2.0

Pilot 1.0: Establishing Definitions and Protocols for Capturing rw-Endpoints

Pilot 1.0 Objective: Evaluate the performance of rw-endpoints across multiple data sets by focusing on a common question: *What outcomes can be evaluated for patients with advanced NSCLC (aNSCLC) who are treated with immune checkpoint inhibitors?*

Pilot 1.0 Design: Retrospective observational analysis of data collected from six healthcare data organizations from patients with aNSCLC treated with immune checkpoint inhibitors derived from electronic health record (EHR) and claims-based databases.

Pilot 1.0 Results:

- Despite differences in data sources, population characteristics were similar among the datasets.
- Aligned framework allowed for generation of rw-endpoints (e.g., TTD, TTNT, TTP) that correlated with OS.
- Several endpoints, such as TTD and OS, fell within the range of median times observed in clinical trials.

Correlation between rw-OS and rw-Endpoints

Data Set	rwOS vs rwTTNT		rwOS vs rwTTD	
	N	Correlation [95% CI]	N	Correlation [95% CI]
Data Set A	83	0.36	254	0.63
Data Set B			225	0.62 [0.54, 0.69]
Data Set C	96	0.70 [0.58, 0.79]	295	0.89 [0.86, 0.91]
Data Set D	1203	0.61 [0.57, 0.64]	4337	0.80 [0.79, 0.81]
Data Set E	358	0.62 [0.54, 0.68]	1456	0.77 [0.75, 0.79]
Data Set F	39	0.46 [0.33, 0.81]	142	0.80 [0.66, 0.85]

Data Set	rwOS vs rwPFS		rwOS vs rwTTP	
	N	Correlation [95% CI]	N	Correlation [95% CI]
Data Set D	4337	0.75 [0.74, 0.76]	2286	0.60 [0.57, 0.63]
Data Set F	142	0.84 [0.62, 0.86]	55	0.56 [0.21, 0.71]

Pilot 2.0: Collaboration to Identify the Challenge and Importance of Methodological Rigor in RWD to Support High-Quality RWE

Pilot 2.0 Objectives:

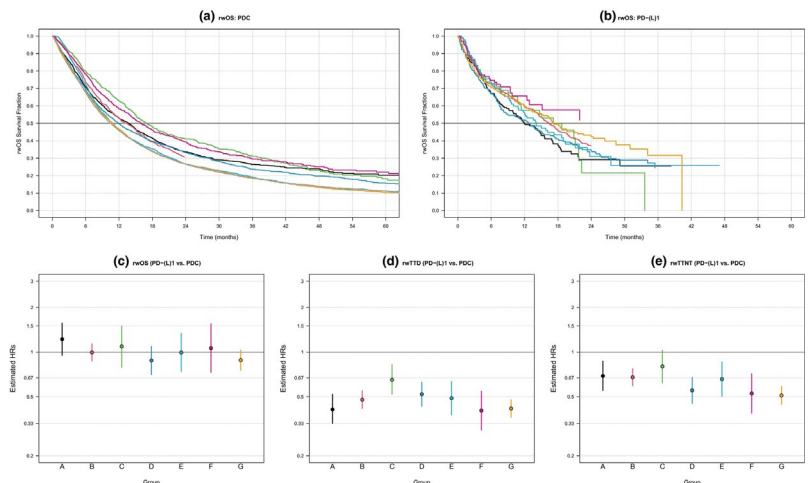
- Evaluate the potential opportunities and challenges of transforming RWD to RWE for clinical effectiveness through a common research protocol.
- Assess the performance of rwOS and the considerations necessary to assess directionality of treatment associations from data sets sourced from EHRs.

Pilot 2.0 Design: Retrospective observational analysis of data derived from EHR datasets from patients with aNSCLC treated with frontline platinum doublet chemotherapy (PDC), PD-(L)1 monotherapy, or in combination.

Pilot 2.0 Results:

- rwTTNT and rwTTD may be useful early clinical end points for use in prospective studies.
- There is a trend toward improved outcomes in patients receiving PD-(L)1 therapy over standard chemotherapy.
- The magnitude and consistency of treatment effect was more heterogeneous than in controlled clinical trials.
- Aligning the RWD patient population with key inclusion/exclusion (I/E) criteria from a clinical trial lacked statistical significance across all datasets between treatment and rwOS compared to the clinical trial, with varied estimated treatment effects across data sets.
- Sample size limitations, differences in the application of I/E criteria, and variability in missing data patterns across RWD sets may have contributed to variability of results.

Pilot 2.0 Results for rwOS, rwTTD, and rwTTNT



OS = Overall Survival, TTNT = Time to Next Treatment line, TTD = Time to Treatment Discontinuation, PFS = Progression free survival, TTP = Time to Treatment Progression

Learning from Previous Pilots: Building on the results from Pilot 1.0 and 2.0, *Friends* will expand work in rw-endpoints to conceptualizing a framework for assessing rw-response. The rw-Response Pilot will establish this framework and assess the consistency of the measure across data sources in an aligned real-world patient population with metastatic NSCLC.