Real World Pragmatic Studies: Pharma Perspective and a Recent Example

Transforming Clinical Trial Design and Execution

Cynthia Huang Bartlett, MD

Senior Medical Director, Breast Cancer Portfolio

Pfizer Oncology

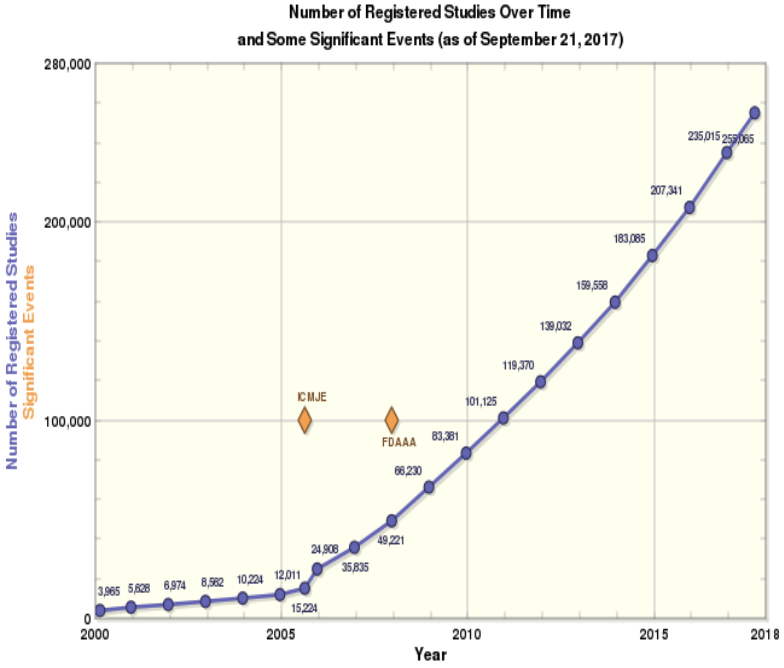
Pfizer Innovative Health

Pfizer Oncology

Disclaimer

The views and opinions expressed in this presentation are those of the author and do not necessarily reflect the views or position of my employer, Pfizer Inc.

Exponential Increase of Numbers of Clinical Trials But …



Source: https://ClinicalTrials.gov

- Time Consuming, tedious, inefficient
- Artificial
- Done in “trial-friendly” centers
- Low participation hence poor representation?
- May require real world evidence to confirm / clarify /reimburse

Pharmaceutical Companies Have Mastered the Design and Implementation of Explanatory Trials But Still New to the Pragmatic Trials

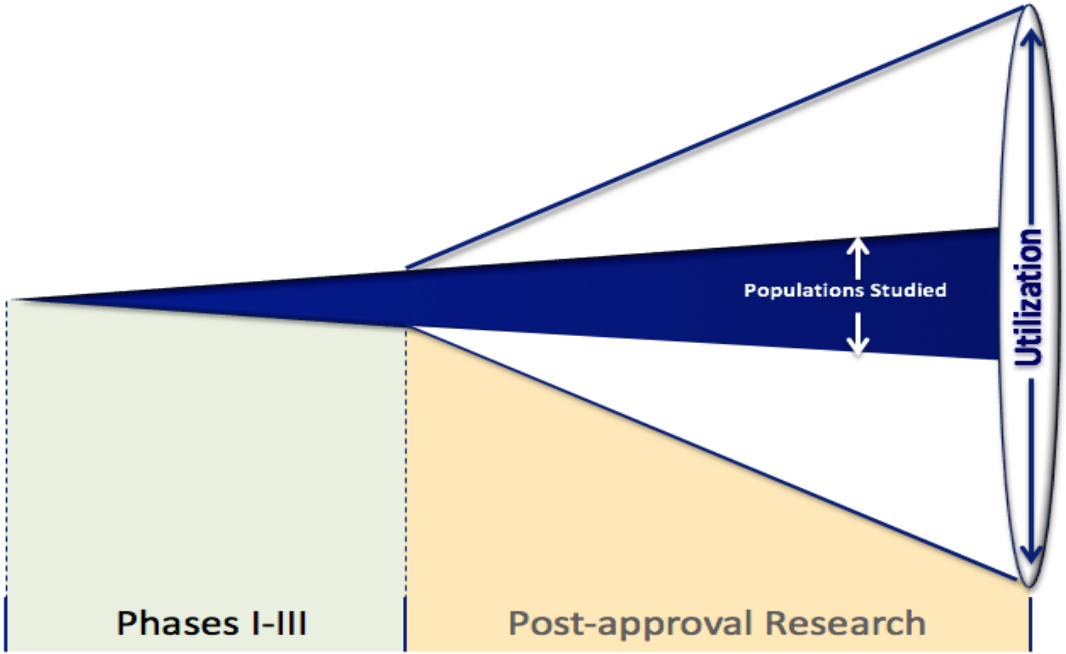
Explanatory trials – "can the drug work"?	Pragmatic trials – "does it work in my clinic?"
• Estimate efficacy –benefit produced under ideal conditions (safety as risk/benefit) • How and why the intervention works?	• Estimate effectiveness –benefit under routine clinical practice • Answers practical questions about risk/benefit (cost) versus competing interventions

Can pragmatic studies serve for registration? Label expansions? How and when?

Roland BMJ 1998, 316, 253
Scott Ramsey MD, U. Washington

Opportunity to Use Real World Data/Evidence For Registration

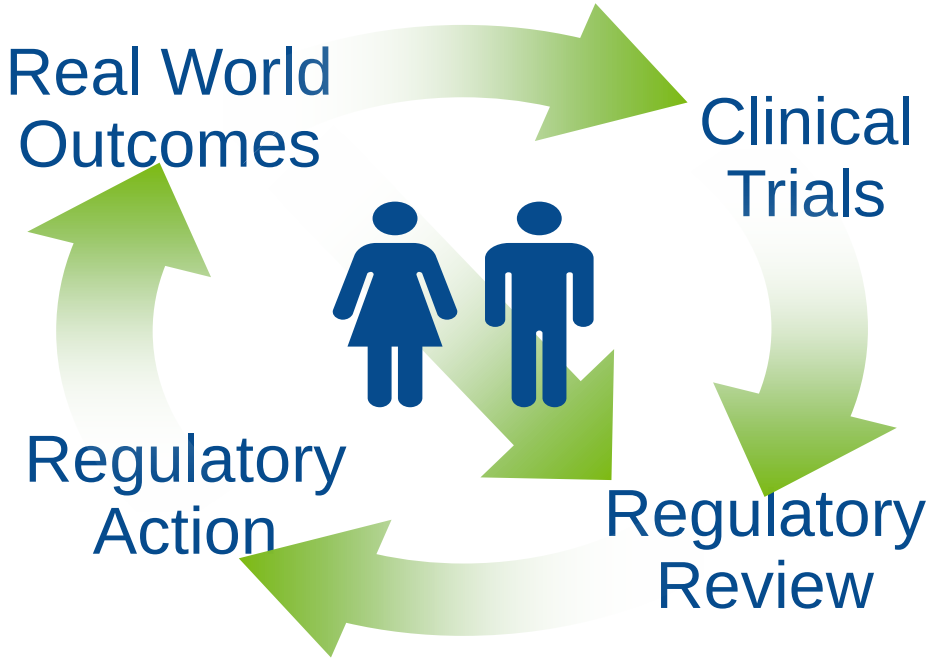
Utilization Outpaces Trial Evidence: → **Evidence Gap**



- Differing age groups (elderly, pediatrics)
- Race, ethnicity & gender variances
- Unstudied co-morbid conditions
- Differing concomitant drugs (including OTC)
- Lifestyle variances including smoking, dietary habits
- Differences in disease severity
- Varying levels of compliance

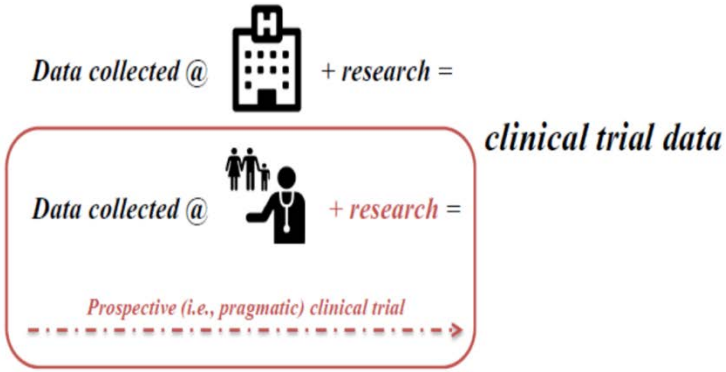
Regulatory Consideration of RWE is Evolving…

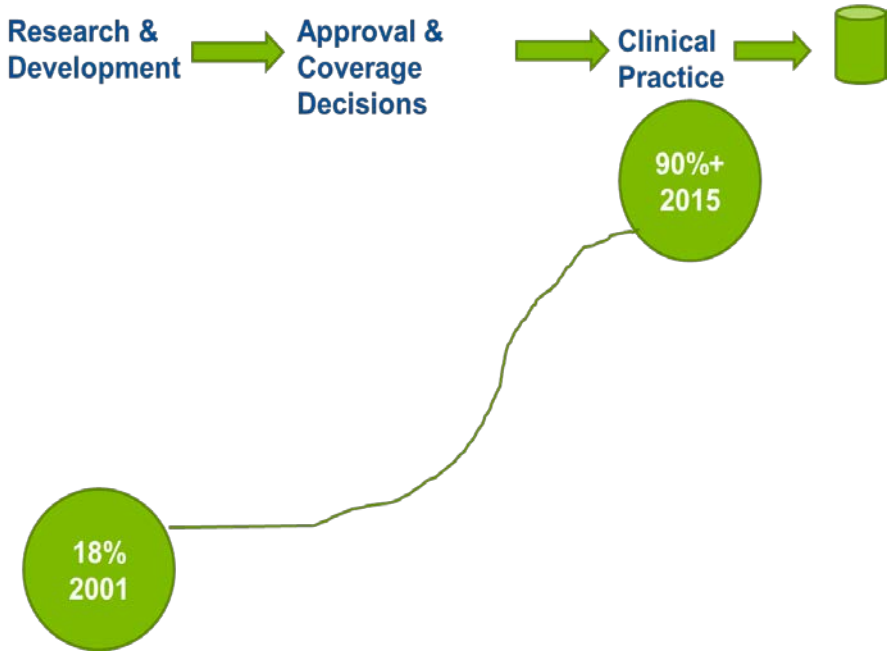
> ***The most useful source of knowledge will come from randomization in the context of clinical practice*** **– Rob Califf, FDA Commissioner**



Sean Khozin, MD,MPH; FDA

Technology Enables the Convergence of Real World Data and Clinical Trial Data





Rapid adoption of EHR system BUT there are many platforms

There Are Challenges Ahead

Data Source

- Data sources fragmented, in development, not designed for use by pharma/research
- Limited ex-US data available; Privacy requirements differ across markets and data sources
- Data quality and availability is inconsistent
- Manual abstraction of unstructured data is slow and expensive
- Interoperability of EHR

Endpoints and Assessment in Real World

- Define and validate real world endpoints
- Real world practice vs strict trial assessment interval

Study Operational Challenges

- Electronic health record (EHR) vs CRF and harmonization
- Different EHR platforms and rate of adoption
- Existing standard process may be modified

Key Considerations for Designing And Implementing A Prospective, Randomized, Pragmatic Studying in the Real World Setting Using EHR Data

A Case Study

Pfizer
Innovative
Health

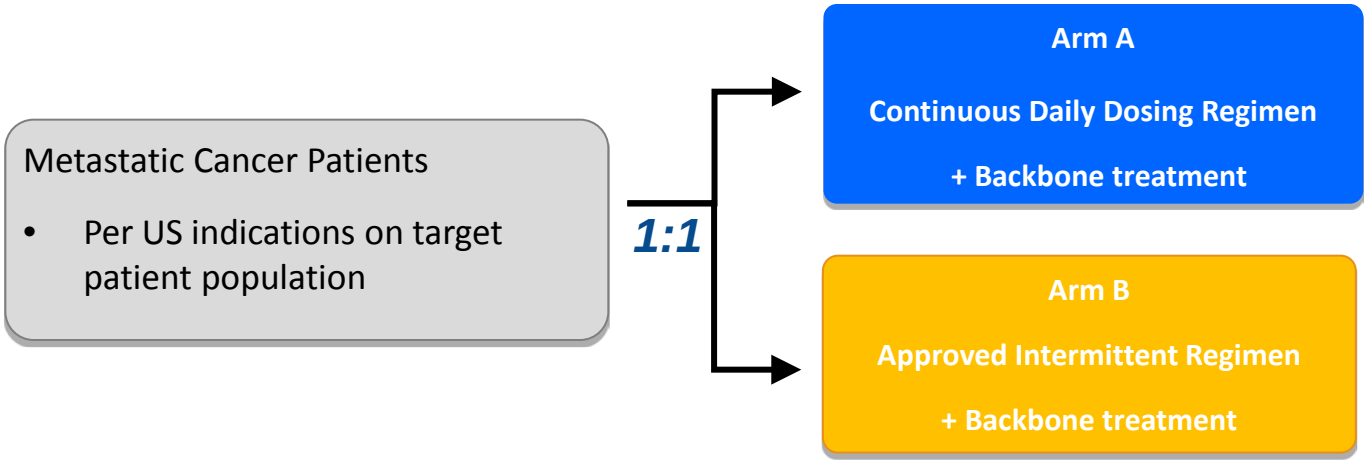
Pfizer
Oncology

Background: Two Different Dosing Regimens

- In oncology, it is a common practice in the real world setting to further optimize treatment regimen post-approval to meet the diverse needs of broad patient groups
- Drug A is the standard care of care of treating metastatic X cancer. Real-world experience showed that >65,000 patients treated in the United States and confirmed the favorable tolerability profile
- Drug A was dosed with an intermittent schedule (3 weeks on and 1 week off). This regimen is well established and accepted by oncologists.
- Continuous daily dosing (CDD) at lower starting dose may offer another option, allowing tailor the dosing strategies by patient preference
- PK/PD modeling suggest that two regimens have similar PK profile.
- Preliminary safety data from an ongoing Phase 2 study shown comparable safety profiles between the two regimens

Study Objectives

- **Primary Objective**
  - To estimate the treatment effect size of two different regimens in the real world setting
- **Secondary Objectives**
  - To establish non-inferiority of efficacy between the two dosing regimens
  - To compare safety profiles of the two dosing regimens



Key Consideration 1: Selecting An Appropriate Primary Endpoint

Real-world Endpoint vs Conventional Study Endpoint (RECIST)

- Oncology drug tumor response assessment traditionally uses RECIST (Response Evaluation Criteria In Solid Tumors)*

But in real world, we need to use a real world endpoint

- **Real-world Progression-Free Survival (rwPFS)** is defined as the time from the date of the randomization to the date of the first documentation of *real world* progression (rwP) or death on study due to any cause in the absence of documented rwP, whichever occurs first.

- **Real-world Response Rate (rwRR)** is defined as the proportion of patients with an *real world* complete response or real world partial response based on their best overall real world tumor response.

rwPFS has a wide range in which clinical and radiologic tumor assessment are allowed (every 8-16 weeks) and the expected large variability in real world, it may be challenging to establish non-inferiority. Therefore rwRR was elected as the primary endpoint.

* E.A. Eisenhauer, et al: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal of Cancer 45 (2009) 228–247

Primary Endpoint: rwRR vs RECIST* RR

	rwRR	RECIST-defined RR
Source evidence	include various EHR unstructured/structured data ie: clinical case notes, radiology and pathology reports, laboratory data	Clinical assessment plus imaging
Assessment interval	Per clinical practice, recommend intervals to help interpretation of randomized data	Predefined by protocol on assessment interval
Target lesion/non-lesion	NA Per investigator opinion that could reliably assess tumor response	Predefined , for example • At least longest dimension of lesion ≥1 cm by CT or MRI
Imaging modalities	Flexible and per standard of care	Well defined mainly CT or MRI or CT portion of CT-PET
Final determination	Clinician's overall assessment	Predefined

- Ongoing discussion with FDA on response assessment method

* E.A. Eisenhauer, et al: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal of Cancer 45 (2009) 228–247

Key Consideration 2: Safety Reporting

Challenge: safety data in common EHR systems are not captured according to CTCAE grading and must be abstracted from unstructured data fields

- **Proper Extraction**: Adverse events that are captured in EHR in both structured and unstructured database in routine clinical practice
- **Opportunity for Real time?** Direct access to EHR data to perform near real-time collection and ongoing review of adverse events .
- **Timely Serious Adverse Events (SAEs) Reporting**
- **Performing ongoing reconciliation** of safety and clinical study databases (e.g. SAE reconciliation) to ensure patient safety and clinical study data integrity .

Key Consideration 2: Ensure Timely Safety Reporting, Reduce Investigator Burden

	Proposed Study	Conventional Study
Data capture	Point of care using EHR source data, minimal or no conventional CRF use	CRF to capture trial data slower entry time of data and backlog
SAE	Investigators captures info in clinical notes, EHR system daily uploads to icloud and then partner company facilitates the reporting via a secured email link between company and investigators/sites	Investigators completed the SAE form and MedWatch form Fax to company and FDA
Laboratory based AE (such as neutropenia)	Use structured data, grading by CTC AE criteria will occur automatically; EHR system will upload nighty and then partner company will send data to company Inform investigator in real time	Investigators fill in AE form
Non-laboratory based AE	Investigators document in clinical notes types/severity of AE, FL exact data and send to company, collect Grade≥3	Investigators fill in AE form Report all grade AEs

Key Consideration 3: Innovation to Optimize Patient Trial Participation and Engagement

	Proposed Study	Conventional Trials
Clinic Visit	Per standard of care	Strictly defined per protocol
Study Population	Per indication, Minimal restrictions to allow for real world practice decisions.	More defined to optimize to determine efficacy and safety for new drug
Drug Dispense	Specialty pharmacy ships the drug to home	Clinic, hospital
PRO questionnaire in subset of patients	Patient self administrated at home on computer	At the clinic
Drug Compliance	Based on dispensing information from pharmacy	Patient diary and pill count consolidation at the clinic

Key Consideration 4: Extensive Effort on Data Modules

Harmonization

Conventional Trial	Inputs	Outputs
	CRF	CDICS
	Laboratory	MedDRA
	E consent	

Proposed Trial	Inputs	Outputs
	EHR	CDICS?
	Laboratory data in icloude	MedDRA
	Data directly from patients	

Acknowledge

- All the collaborators in Pfizer and Flatiron
- Principle Investigator