



Pragmatic Phase III Trials

Maria Koehler MD PhD

Pfizer Oncology Strategy and Innovation

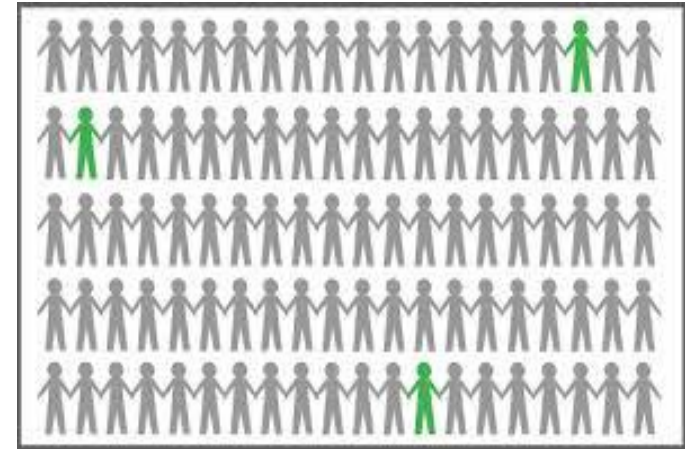
NY, NY

DISCLOSURE

I am an employee of Pfizer Inc, USA

Current Randomized Clinical Trials

- Standard for regulatory purpose
- Time Consuming, tedious, inefficient
- Artificial
- Done in “trial-friendly” centers
- Low participation hence poor representation?
- May require RWE to confirm / clarify /reimburse



Vision:

use real world studies for regulatory purpose for specific scenarios (BTD drugs, subsequent indications, label updates, combinations within approved indication)

but must solve

- Data quality
- Endpoints assessable in real world
- EHR vs CRF and real world practice vs strict trial assessments

Beyond Label or in Label?

Decision Makers need high quality evidence about:

- **Effectiveness**
 - Outcomes when the product is used in the real world
- **Incremental clinical impact**
 - How does the product compare to the treatment(s) that patients usually receive?
- **Cost and Value**
 - How much will it cost to adopt the new product?
 - How much benefit for added cost?

Explanatory vs Pragmatic Trials

- **Explanatory trials – “can the drug work”?**
 - Estimate efficacy –benefit produced under ideal conditions (safety as risk/benefit)
 - How and why the intervention works?
- **Pragmatic trials – “does it work in my clinic?”**
 - 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?

Design

Explanatory Trials

- Maximize the chance to reveal a biological effect of a new treatment
 - Treatment or placebo
- Randomization necessary
- Safety: limited information
- Blinding compulsory
 - Treatment assignment
 - Independent Evaluator

Pragmatic Trials

- Identify differences between competing treatments
 - New vs established therapy
- Randomization necessary but may be a “block”
- Safety known to a various degree
- Blinding may not be possible

Setting

Explanatory Trial

- Carefully controlled environment
- Expert clinician/researchers

Pragmatic Trial

- “Real world”
- Variety of settings
 - Private practice/academic
 - Rural/urban
 - HMO
 - Practicing clinicians

Patient Population

Explanatory Trial

- Strict entry criteria
- Homogenous population:
 - Minimize extraneous patient factors (comorbidities) that influence outcome
 - “Clinical trial friendly” individuals
- Trained Trialist

Pragmatic Trial

- Defined patient groups (presentation vs diagnosis)
- Real World Heterogeneity
 - Minimize exclusion criteria
 - Diverse patient populations
 - Comorbidities acceptable
 - Heterogeneous practice settings
 - HMO
- Practicing clinician

Structure

Explanatory Trial

- Complexity is standard
 - Multiple sub-aims, subpopulations
- Within established research infrastructure
- Time horizon dictated by the duration needed to measure an effect

Pragmatic Trial

- Simplicity
- Lower cost (eventually)
- Feasibility
 - Must be acceptable to practitioners
- Timeliness
 - The clinical question is waiting!

Outcomes

Explanatory Trial

- Intermediate
- Reflecting disease processes that support biological plausibility
- Mortality
- Morbidity
- Safety
- “What do researchers and clinicians care about”

Pragmatic Trial

- Broad range of functional and efficacy outcomes, e.g.,
- Quality of life
- Symptom severity
- Satisfaction
- Costs
- Mortality
- Morbidity
- “What do patients care about?”
- “What should we pay for?”

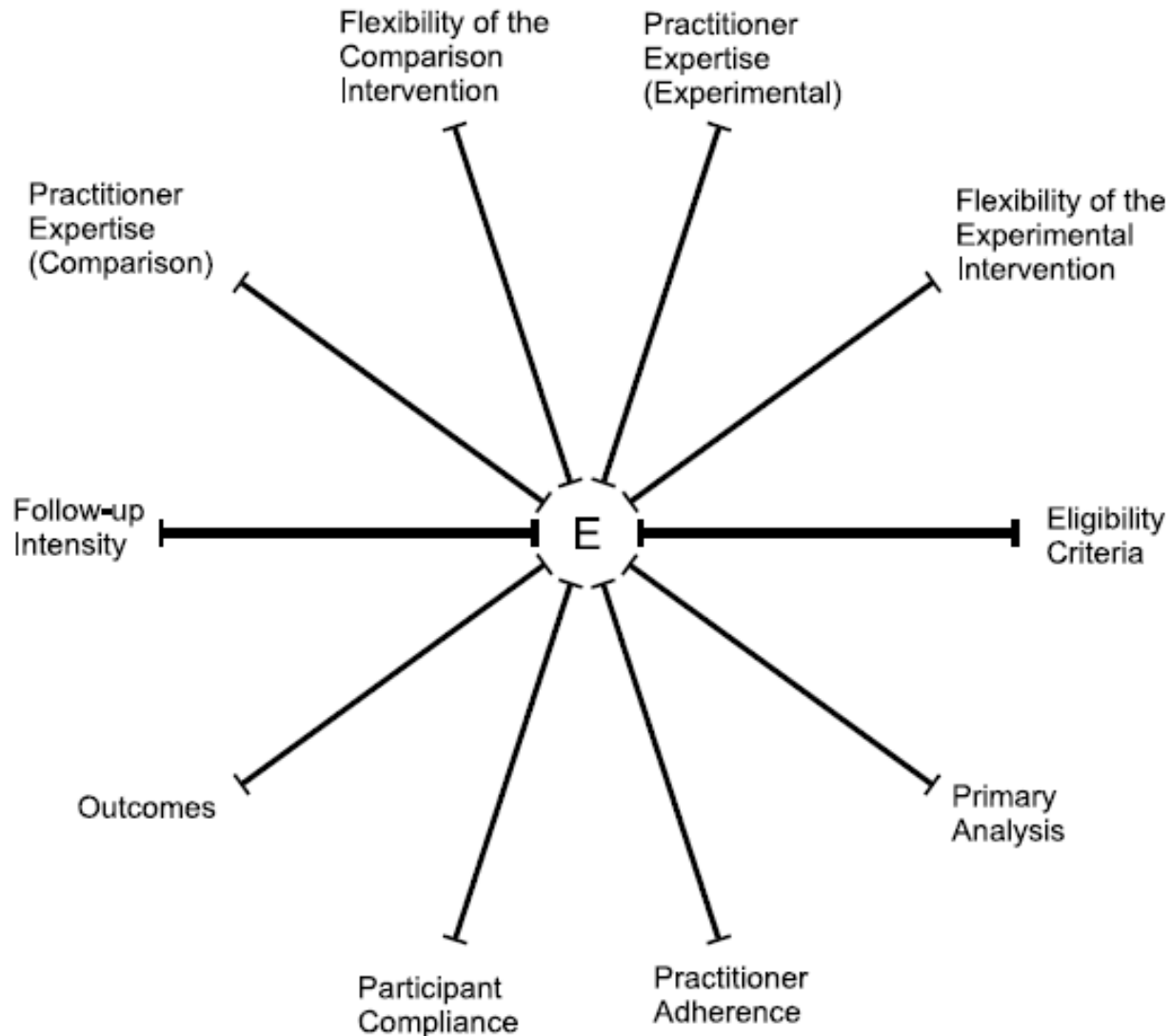
Pragmatic does not mean “anything goes”

Still have to **fiercely minimise bias**

1. **Selection** - Randomization & allocation concealment
2. **Cross-over**: FDA prefers no switching: pragmatic studies unlikely can reinforce that
3. **Performance** – similar conditions both groups
4. **Detection bias** – blinded outcome
5. **Attrition bias** – collecting data on dropout and intention to treat analysis

There are strict rules: PRECIS

- The Pragmatic-Explanatory Continuum Indicator Summary (PRECIS)
 - the pragmatic trial features include the recruitment (investigators and participants), the intervention and its delivery, follow-up, and the analysis of outcomes.
- Requires a judgement on key aspects of trial design
- Illustrated by a PRECIS wheel
 - Many trials deemed to be pragmatic with regard to at least one of these dimensions, but few are truly pragmatic on all dimensions.

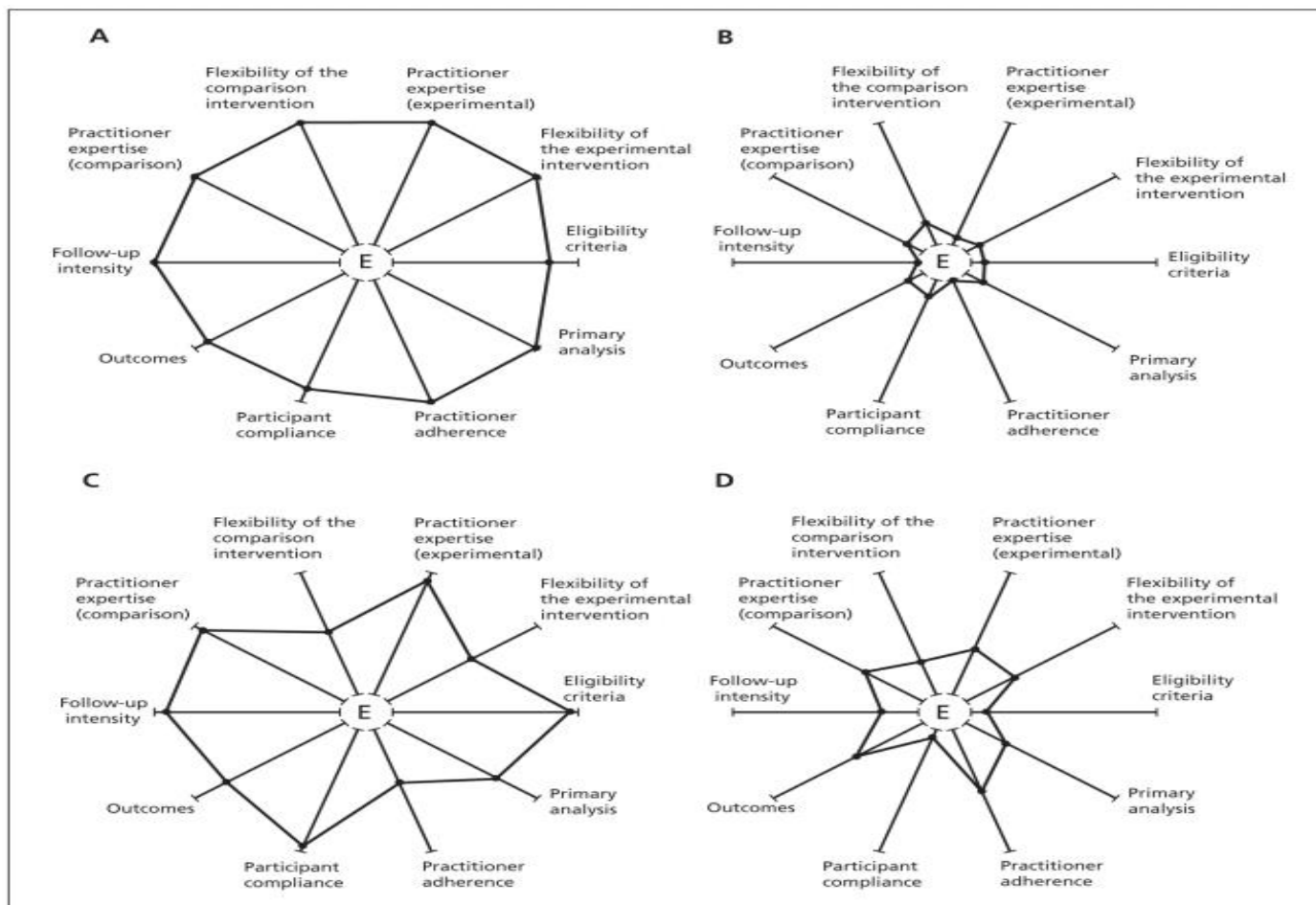


A blank pragmatic - explanatory continuum indicator summary (PRECIS) “wheel.”

[CMAJ. 2009 May 12; 180\(10\): E47–E57.](#)

doi: [10.1503/cmaj.090523](https://doi.org/10.1503/cmaj.090523)

PRECIS examples of a randomized controlled trials



A: self-supervised and directly observed treatment of tuberculosis. **B:** PRECIS summary of the North Am Symptomatic Carotid Endarterectomy Trial of carotid endarterectomy in symptomatic ppts with high-grade carotid stenosis. **C:** PRECIS summary of a randomized trial of low-dose acetylsalicylic acid therapy for the prevention and treatment of pre-eclampsia **D:** PRECIS summary of a randomized trial of low-dose ASA for the prevention of pre-eclampsia in women at high risk.

Dimensions for Assessing the Level of Pragmatism in a Trial

Table 1. Nine Dimensions for Assessing the Level of Pragmatism in a Trial, as Proposed in the Pragmatic–Explanatory Continuum Indicator Summary 2 (PRECIS-2) Tool.*

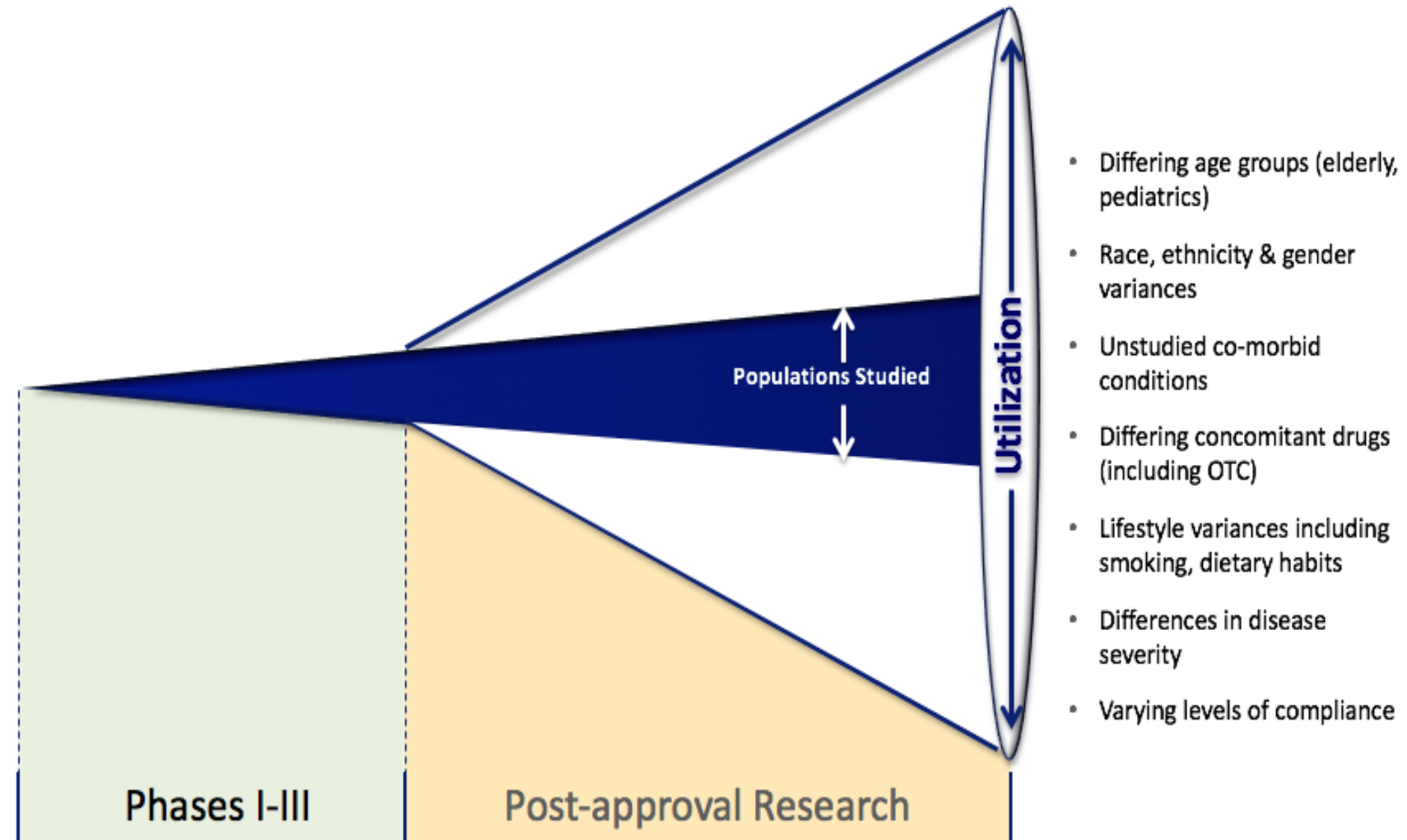
Dimension	Assessment of Pragmatism
Recruitment of investigators and participants	
Eligibility	To what extent are the participants in the trial similar to patients who would receive this intervention if it was part of usual care?
Recruitment	How much extra effort is made to recruit participants over and above what would be used in the usual care setting to engage with patients?
Setting	How different are the settings of the trial from the usual care setting?
The intervention and its delivery within the trial	
Organization	How different are the resources, provider expertise, and organization of care delivery in the intervention group of the trial from those available in usual care?
Flexibility in delivery	How different is the flexibility in how the intervention is delivered from the flexibility anticipated in usual care?
Flexibility in adherence	How different is the flexibility in how participants are monitored and encouraged to adhere to the intervention from the flexibility anticipated in usual care?
The nature of follow-up	
Follow-up	How different is the intensity of measurement and the follow-up of participants in the trial from the typical follow-up in usual care?
The nature, determination, and analysis of outcomes	
Primary outcome	To what extent is the primary outcome of the trial directly relevant to participants?
Primary analysis	To what extent are all data included in the analysis of the primary outcome?

* Information in the table is adapted from Loudon et al.²²

Practical Issues

- Pragmatic trials are valuable and relevant for clinical practice
 - **The current health care climate is “right” but not “ripe” for pragmatic trials**
- A continuum not a dichotomy (explanatory/pragmatic)
- Should clinical trials that change practice be pragmatic?
- Should pragmatic trials have a larger role in formulating the label claims for contemporary medicines?

Utilization outpaces trial evidence: ➡ evidence gap



Real World Data (RWD) sources?

What evidence do RWD provide?

Regulatory developments in RWD area
(examples)

Can pragmatic studies be simplified by using
electronic health records?

Trend 1. Evolution of Longitudinal RWD sources

Real World Data is healthcare data not collected through RCT and used for decision making^{1,2}



- +
 - Large/low cost
 - Tx patterns/ costs
 - Follow-up across healthcare settings (inpt/outpt/ER)
- - 6 mo lag
 - No clinical information
 - Coding
- Set up for research
 - Deeper clinical information for condition of interest
 - Expensive, usually indirect access
 - Smaller #s
 - Biased sample

1. "Using Real-World Data for Coverage and Payment Decisions: The ISPOR Real-World Data Task Force Report," Value in Health, Volume 10, November 5, 2007.

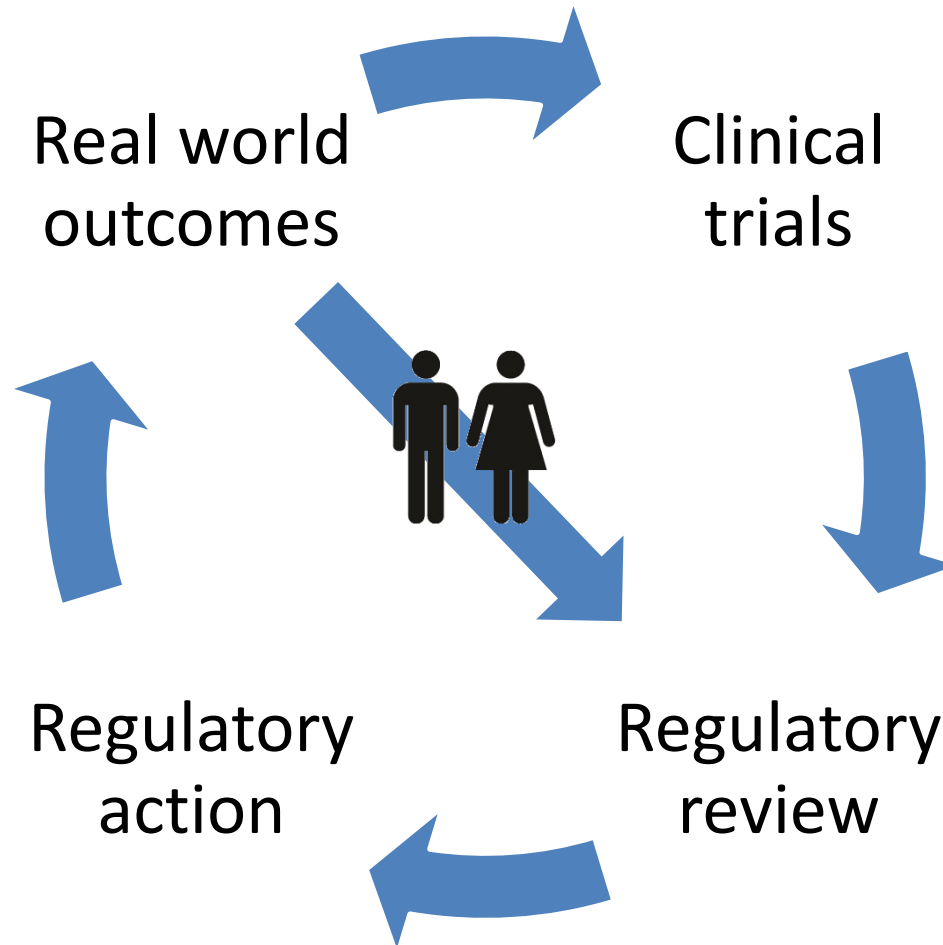
2. Annemans, L., Aristides, M., Kubin, M. "Real-Life Data: A Growing Need," ISPOR Connections 2007.

Trend 2. Focus on Patient-Centered Outcomes

- FDA's Patient-Focused Drug Development initiative under **PDUFA V** focuses on patient perspective (1).
- Innovations to address patient needs are increasingly patient centered (wearables, apps)
- Real world approach can facilitate patient centeredness by:
 - Focusing on **broader populations** and patient relevant outcomes vs RCTs
 - **Promoting precision medicine** in general practice
 - Better informing and **engaging patients** through patient portals for EHRs
 - Supporting **better coordination** of health information
 - **Facilitating identification** of patients and ease participation in clinical trials
 - **Accelerating access** to needed medications

Why real world data are important?

“the most useful source of knowledge will come from randomization in the context of clinical practice” Califf



Cost of clinical trials are increasing threefold the rate of inflation

FDA focus of real world evidence

Use of Electronic Health Record Data in Clinical Investigations

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to <http://www.regulations.gov>. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Cheryl Grandinetti at 301-796-2500, (CDER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010, or CDRH Program Operations Staff at 301-796-5640.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

May 2016
Procedural

- EHR data in prospective clinical investigations of human drugs and biological products medical devices, and combination products.
- Can data from healthcare systems supplement new approvals or label expansions ?

1. Dr. Woodcock, Director Center for Drug Evaluation and Research (1)
“do a trial inside the healthcare system utilizing the data collection methods of the healthcare system....Could support expanded labeling (current off-label uses!)”
2. RWD for label change in multiple rare diseases (2)
3. Label Enhancements (High-dose influenza vaccine versus standard dose (Medicare claims))

F:\0228148
6/12/16

1. Available at: <https://healthpolicy.duke.edu/events/enhancing-application-real-world-evidence-regulatory-decision-making>
2. Available at: <http://www.raps.org/Regulatory-Focus/News/2016/03/10/24517/Real-World-Evidence-Can-it-Support-New-Indications-Label-Expansions/>

PDUFA VI Commitment Letter

Raising importance of RWD

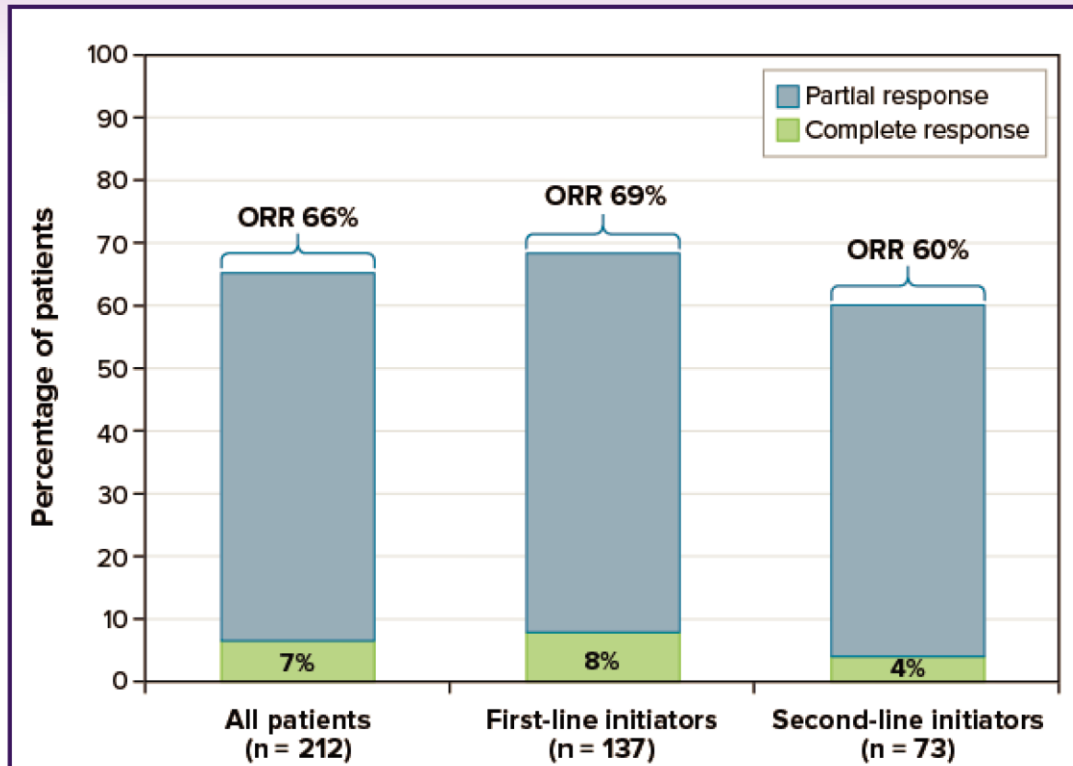
FDA commitment: “use of RWE in regulatory decision making” and separately for “use of RWE for fulfillment of postmarketing regulatory commitment”

6. Enhancing Use of Real World Evidence for Use in Regulatory Decision-Making

As we participate in the current data revolution, it is important that FDA consider the possibilities of using so-called “real world” data as an important tool in evaluating not only the safety of medications but also their effectiveness. To accomplish this will require an understanding of what questions to ask, including how such data can be generated and used appropriately in product evaluation, what the challenges are to appropriate generation and use of these data, and how to address such challenges. Towards this end, FDA will do the following:

- a. By no later than the end of FY 2018, FDA will complete one or more public workshop(s) with key stakeholders, including patients, biopharmaceutical companies, and academia, to gather input into issues related to Real World Evidence (RWE) use in regulatory decision-making. The workshop(s) should address, among other things, the following topics:
 - Benefits to patients, regulators, and biopharmaceutical companies of RWE in regulatory decision making;
 - RWE availability, quality, and access challenges, and approaches to mitigate these;
 - Methodological approaches for the collection, analysis, and communication of RWE; and
 - Appropriate contexts of use of RWE in regulatory decision-making regarding effectiveness.
- b. By no later than the end of FY 2019, FDA will initiate (or fund by contract), appropriate activities (e.g., pilot studies or methodology development projects) aimed at addressing key outstanding concerns and considerations in the use of RWE for regulatory decision making.
- c. By no later than the end of FY 2021, considering available input, such as from activities noted above, FDA will 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 postmarketing commitments and requirements. FDA will work toward the goal of publishing a revised draft or final guidance within 18 months after the close of the public comment period.

Proof of Concept: Example of Concordance of RWD and RCT Outcomes



- Retrospective chart review of 212 patients in US/Canada
- ORR: 66% vs. 61-74% in 4 P3
- 1-year survival in first-line 85% vs. 84% in RCT of tx naive
- Median PFS 9.5 mos vs. 7.7-10.9 mos

Available at: <http://www.focr.org/sites/default/files/pdf/Blueprint2016%20-%20Panel1.pdf>

Sutter S. Pink Sheet June 27, 2016. Available at: <http://www.focr.org/news/pink-sheet-real-world-evidence-may-find-home-breakthrough-pathway>

The Salford Lung Study

Maintained Scientific Rigor

- Interventional
- Randomised
- Controlled

Study as near to “real world” as possible **using a pre-license medicine**

- embraced heterogeneity of patient population
 - normalised the patient experience
 - pragmatic – “usual care”
 - relevant endpoints collected
-
- Answered “Does it work for my patient” and submitted for label



The Salford Lung Study is the first of its type in the world

Maintains scientific rigor: randomised, active control, robust primary endpoint

Salford Lung Study results show COPD patients treated with Relvar® Ellipta® achieve superior reduction in exacerbations compared with 'usual care'

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Sept 2016

Effectiveness of Fluticasone Furoate– Vilanterol for COPD in Clinical Practice

Jørgen Vestbo, D.M.Sc., David Leather, M.B., Ch.B., Nawar Diar Bakerly, M.D.,
John New, M.B., B.S., J. Martin Gibson, Ph.D., Sheila McCorkindale, M.B., Ch.B.,
Susan Collier, M.B., Ch.B., Jodie Crawford, M.Sc., Lucy Frith, M.Sc.,
Catherine Harvey, D.Phil., Henrik Svedsater, Ph.D., and Ashley Woodcock, M.D.,
for the Salford Lung Study Investigators*

Validation of real world data approach

Pfizer breast cancer pilot study

Question:

- Can similar clinical conclusions be drawn from real world data compared to standard clinical trials?

Objective:

- Compare real world SOC data to SOC data obtained in standard clinical trials

Design:

- Using electronic health records for retrospective data on patient characteristics and treatment in the real world with letrozole alone as initial therapy for metastatic breast cancer
- Compare the findings to matched patients/data from a randomized controlled trial performed by Pfizer : letrozole data from control arm of the label directed studies

Flatiron Database

1.1 million patients with various cancers in US



**Filter database and extract EHR based on agreed criteria ie:
Metastatic breast cancer treated with letrozole as initial therapy**



Identified cohort of patients

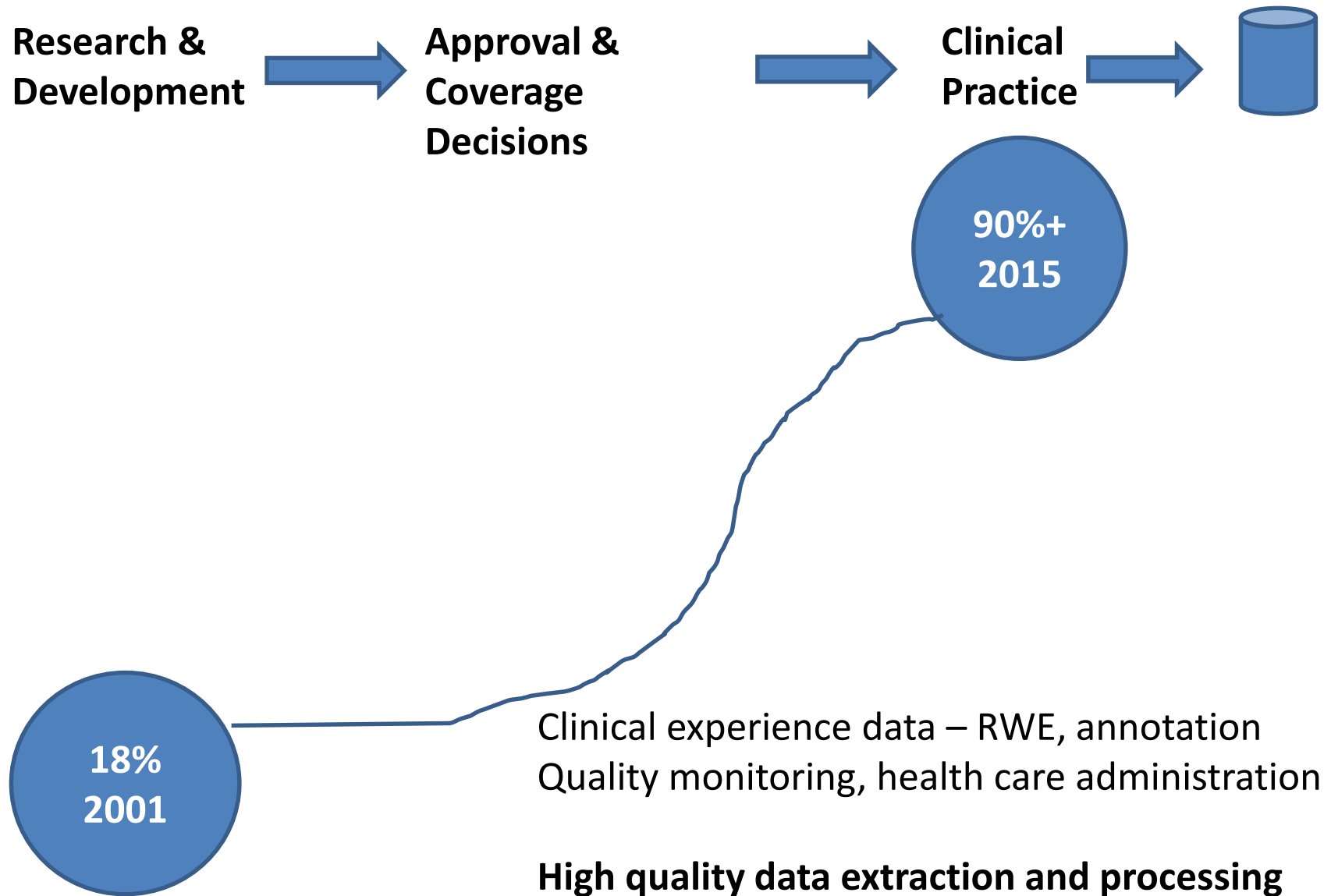
Example of data collected:

- Baseline characteristics
- Breast cancer diagnosis
- Biomarkers (ER/PR, HER2, BRCA)
- Details of letrozole therapy
- Details of therapies taken after 1st line letrozole
- Reason for therapy discontinuation
- Safety events and date of onset
- Date of death
- Real-world progression events and dates



Matching and Statistical Analyses

Electronic Health Records Adoption in USA



Are we ready for (EHR-based) Pragmatic Randomized Trials for Regulatory Submission ?

Pragmatic Randomized Trials leveraging EHRs are proposed to be used for regulatory purpose specifically for:

- Drugs with exceptional activity ie. strongly favorable benefit: risk ratio
- Subsequent indications in the same tumor (different combination regimen, or line of therapy)
- Confirmatory trials after accelerated approvals
- Different dose / schedule regimens or alternative populations