

The Effect of Comparative Effectiveness Research on Drug Development Innovation: A 360° Value Appraisal

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clinical | commercial | consulting | capital



*“...the companies that will survive and thrive in this new environment will be those that embrace **Comparative Effectiveness Research** as the next logical step in the progression of requiring evidence and recognize it as a necessary input for a value-driven healthcare system.”*

– Eli Lilly Executive

Agenda



CER Explained

CER Convergence

CER Value

CER Cases

CER Explained

Evolutionary rather than revolutionary

CER Explained

New application of traditional concept



CER is a key emerging area that decision-makers utilize when evaluating healthcare products – a signal for biopharmaceutical companies to adapt their drug development strategy

CER Background

- Pharmaceutical companies are increasingly seeing their products subjected to health technology assessments (HTAs) by public and private payers
- The cornerstone of HTA value appraisal is CER, a 'real-world' comparison of new product with the existing standard of care

CER Definition

- Defined by the IOM as 'the comparison of effective interventions among patients in typical patient care settings, with decisions tailored to individual patient needs'
- Relative Efficacy (RE) is a related concept focused on clinical trial evidence

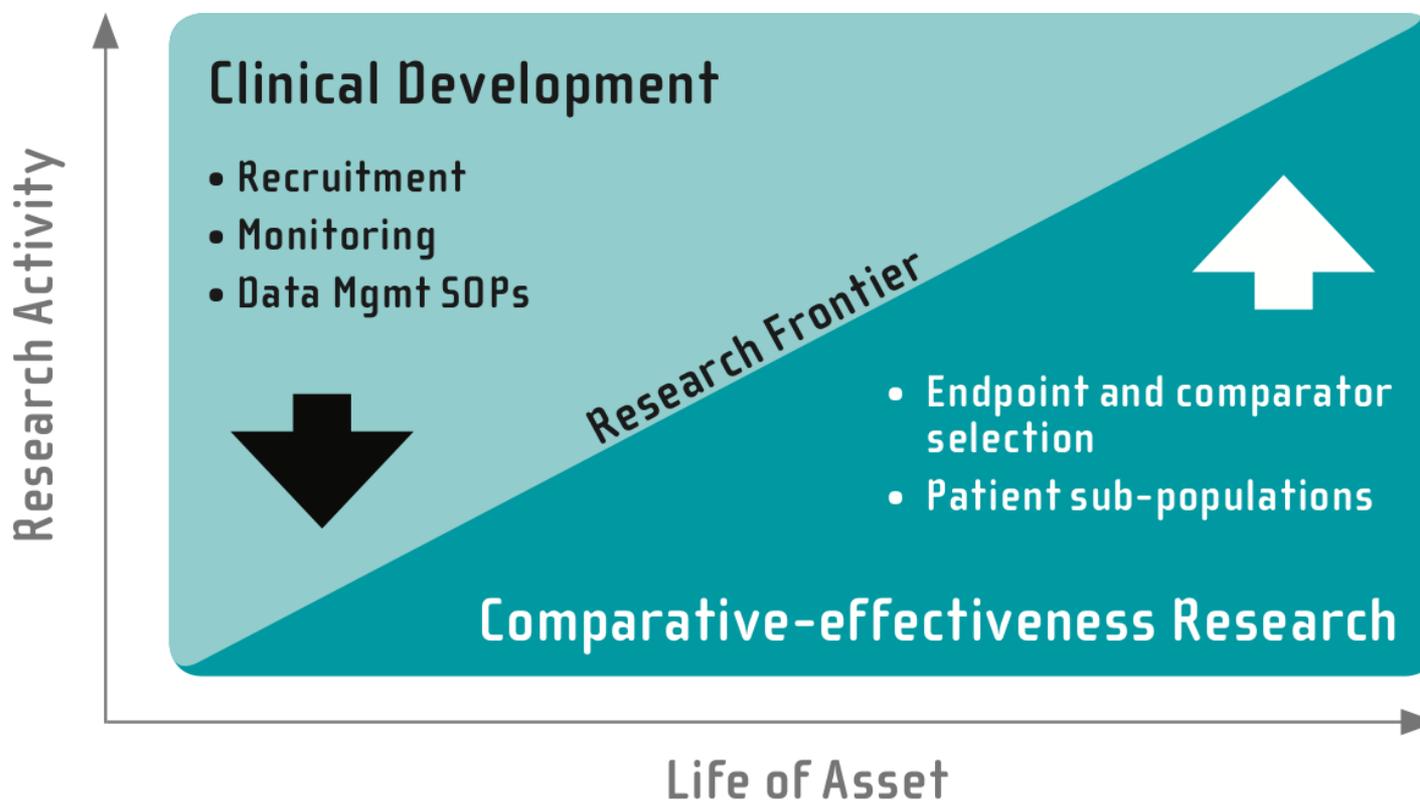
CER Application

- CER weighs the benefits and harms of various modalities used to prevent, diagnose, treat, or monitor clinical conditions to determine which works best for particular types of patients and in different settings and circumstances

CER Explained

From early phase to late phase

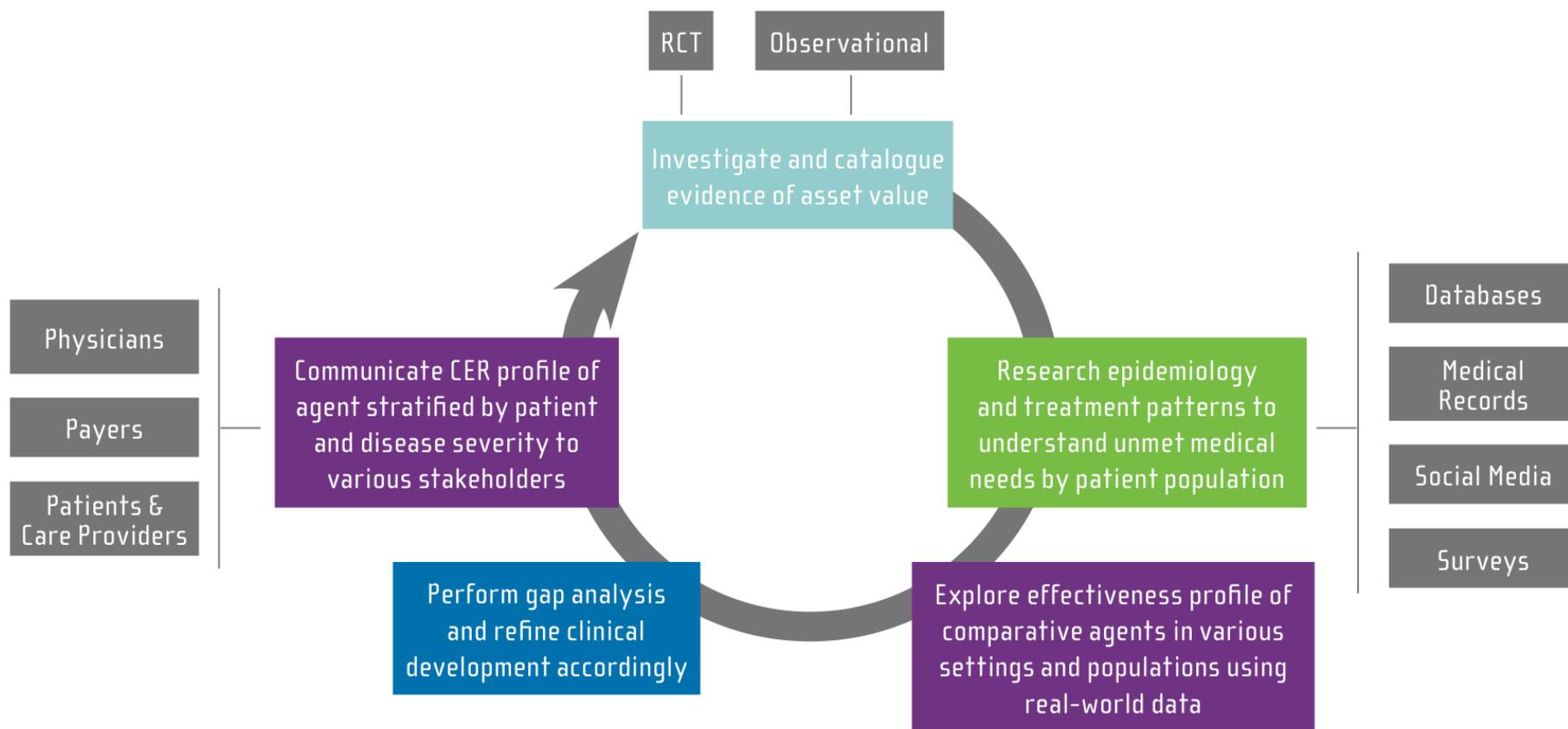
Early in an asset's lifecycle, CER can guide development strategy and valuation. Later, it can help identify new indications and subpopulations with residual unmet need.



CER Explained

Evidence Development Cycle

CER encompasses investigating the real-world practice patterns, understanding patient populations, comparing the relative effectiveness of products, and communicating the results



CER Convergence

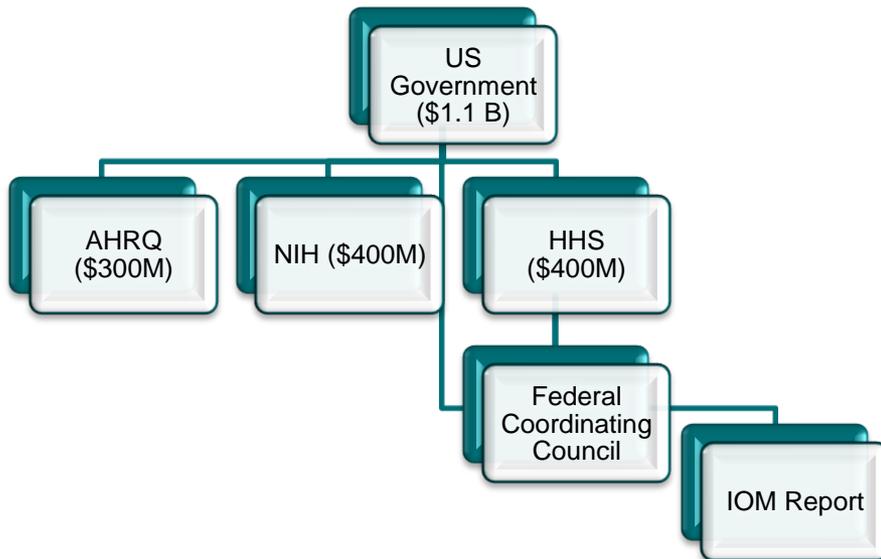
Will a common pathway emerge for key stakeholders?

CER Convergence

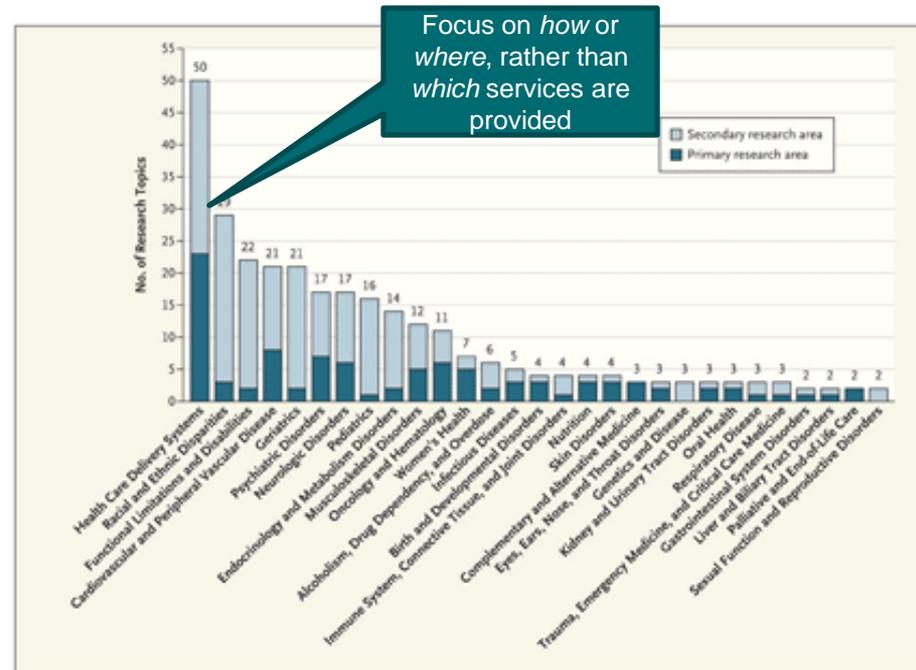
CER in the U.S.

Rising health care expenditures exceeding \$2.2 trillion, or 16% of GDP, are impetus for federal health care reform policies

The American Recovery and Reinvestment Act of 2009 appropriated \$1.1B for CER out of the \$787.2 Congressional Economic Stimulus Bill



IOM recommended CER review of the top 100 topics most important to the health of the US population



CER Convergence

CER as a public good



Recent attention on CER provides decision-makers with a unique opportunity and responsibility to build innovative and sustainable CER structures



“In presenting the outlines of this concept, Janet Woodcock drew an analogy to the interstate highway system and national electricity grid. Such large public works require sustained government support because the market is unlikely to provide the interconnecting pieces necessary for the whole to work efficiently.”

“The analogy aptly suggests the scale of the federal research infrastructure that would be needed to close the **enormous gap in clinical evidence in decision making**...One can imagine, for example, the challenge of using grants to build the interstate highway system. The result would probably be stretches of highway where the gains to local interests are clear, but with no interstitial linkages.”

CER Convergence

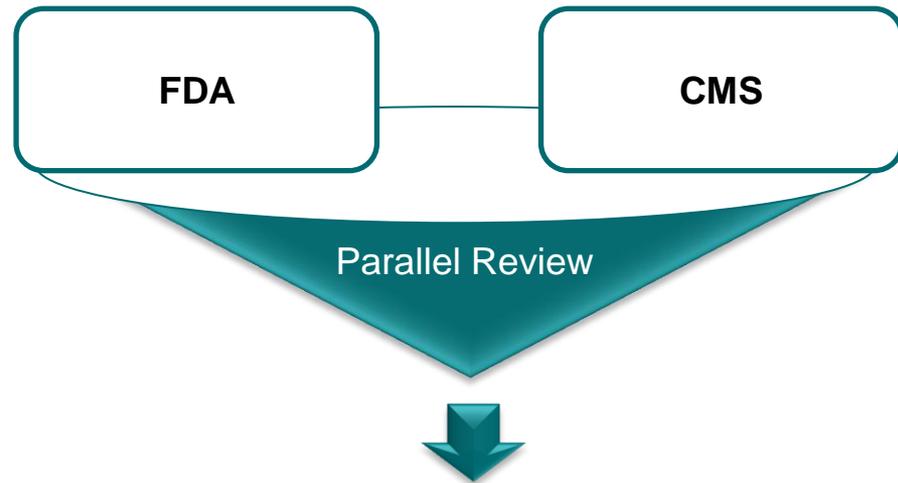
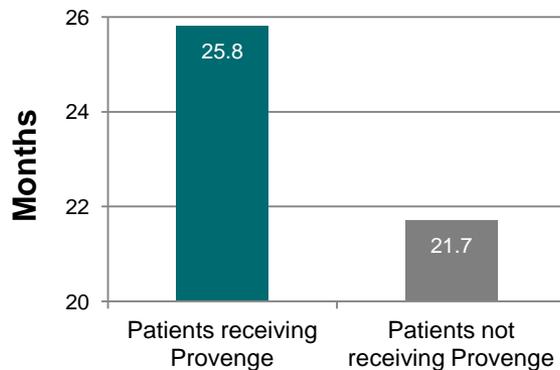
CER in concert

Will coordination between agencies will streamline government efforts and improve efficiency in reviewing the same medical technology?

Provenge Case

Expected Provenge cost is \$93,000

Median Survival



- Enhanced Communication between regulators, reimbursement authorities, and manufacturers
- Reduce administrative burden
- Provide more rapid access to new technologies
- Provide feedback to companies about study design and endpoints needed to justify reimbursement

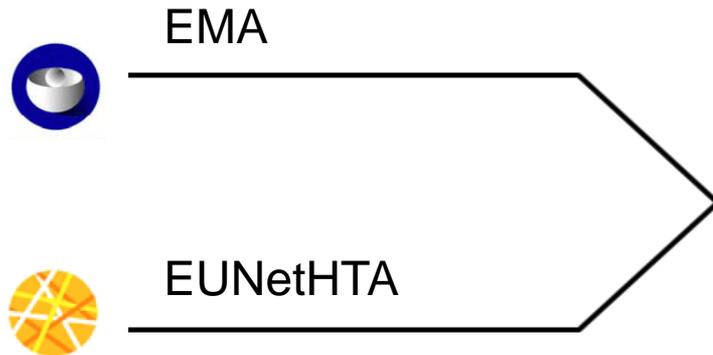
A proposed “parallel review” process between the FDA and the CMS would mark a landmark change in market access in the U.S.

CER in the Global Marketplace

CER in concert



Collaboration between Europe's approval and review boards may result in increased transparency, scientific advice and efficiency in evaluating pharmaceutical products



Outcomes

- **Aim:** Improve the availability and best use of data in relative effectiveness assessments
- **Increased Availability and Transparency of Data:**
 - EMA information not usually available to HTA decision-makers or payers
 - Collaborative talks center on EMA providing detailed data to HTAs such as EPARS, which are published by the EMA, and reflect scientific conclusions reached by the Agency's evaluation process
- **Scientific Advice:**
 - HTA bodies complained they do not get the right studies from pre-licensing development programs
 - Idea to create a single drug development program to meet the needs of regulators and payers
 - Three pilot projects in Europe have been completed involving HTA authorities, industry, and regulators. Results TBD
- **Future dialogue about disease-specific guidelines:**
 - For example, what is an appropriate assessment tool for an anti-depressants in the eyes of HTA bodies and regulators?

CER Convergence

CER in the U.K.

Risk-based pricing deals that hinge on clinical evidence are becoming more prevalent, highlighting the relevance of CER in Europe

Glaxo offers NHS rebate if latest cancer drug fails to outperform Pfizer rival

26 December 2010

“...price is driven by value and value is driven by evidence, and therefore we can start to construct different sorts of arrangements where we can balance this off.”

“The Government...outlined plans for a radical shake-up of its drugs policy and the introduction of a “value-based” pricing model...”

“... The model would allow companies to agree an initial “contingent” price for a medicine that could then be revised in the light of clinical evidence as to the drug's effectiveness.”

The Telegraph



+



CER Convergence

CER in the U.S.

Partnerships are an efficient CER mechanism stakeholders can construct in a mutual effort to understand the real-world value of treatment options

FEBRUARY 3, 2011, 9:29 AM ET

AstraZeneca and WellPoint the Latest to Focus on Value in Care

AstraZeneca and WellPoint's HealthCore subsidiary have teamed up to study which treatments for chronic and other diseases give the best value for money. AZ says it will use the data to help make R&D decisions and in talks with payers about covering available drugs...

The partnership is part of a movement toward greater use of comparative-effectiveness research, which is designed to compare multiple treatment options to find the best and most cost-effective. This expands upon the traditional clinical trials drug companies are required to run to gain regulatory approval...

THE WALL STREET JOURNAL.

AstraZeneca



+

WELLPOINT



CER Value

Think differently to differentiate

CER Value

Methods to alter existing R&D approach

Drug and device developers must adjust their existing approach to research and development:

1

Adapt experimental research design methods to address multiple stakeholder demands

2

Demonstrate real-world value through a suite of post-market observational research methods

3

Create a transparent CER evaluation protocol based on standard principles



Results can help patients, clinicians, policymakers, and purchasers make more informed decisions , thereby improving care

CER Value

Stakeholder assessment

CER requires drug and device developers to adapt their research by assessing the competing needs of multiple stakeholders

Biopharma Industry

- Synching innovation with public health
- Quality delivered
- Benefit-risk 'signals' vs. background 'noise'

Patients

- Safety and effectiveness
- Quality of life improvements
- Convenience of care

Physicians

- Evidence based recommendations to accommodate unique characteristics and circumstances of each patient
- Interventions/strategies that produce favorable outcomes

Payers

- Real-world data to evaluate treatments and manage utilization control techniques accordingly
- Real-time information to ensure evidence-based treatment

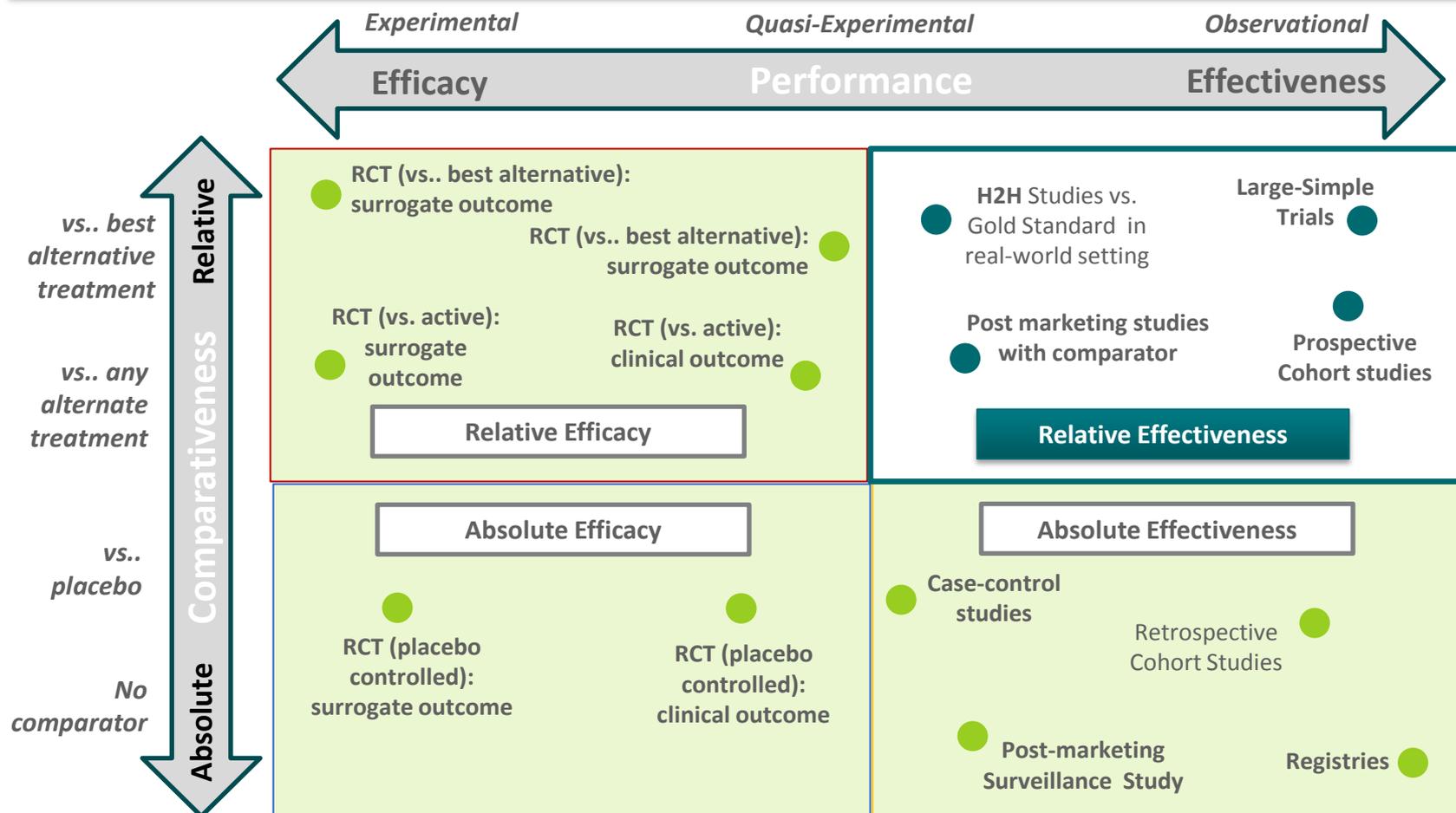
Policymakers

- Financing medical care judiciously
- Minimizing the impact to the federal budget
- Improving public health

CER Value

Study design evaluations

Study designs can be evaluated along the performance and comparativeness continuum and should incorporate relative effectiveness



CER Value

Initiatives snapshot

CER can show the product value through a suite of post-market observational research methods



INITIATIVES TO DEMONSTRATE REAL-WORLD VALUE:

STROBE (Risk-Benefit)

- 22-point checklist of factors to include in an accurate and complete report of an observational study

OMOP (Risk-Benefit)

- Public-private methods development and testing consortium taking a 2 tiered approach

ISPE (Observational/Pharmacoepidemiologic)

- Address protocol development, responsibilities, study conduct, communication, adverse event reporting, and archiving
- An earlier FDA document had similar objectives

Sentinel Initiative (Safety)

- Focused on real world long-term safety and risk data based on retrospective analysis of claims data

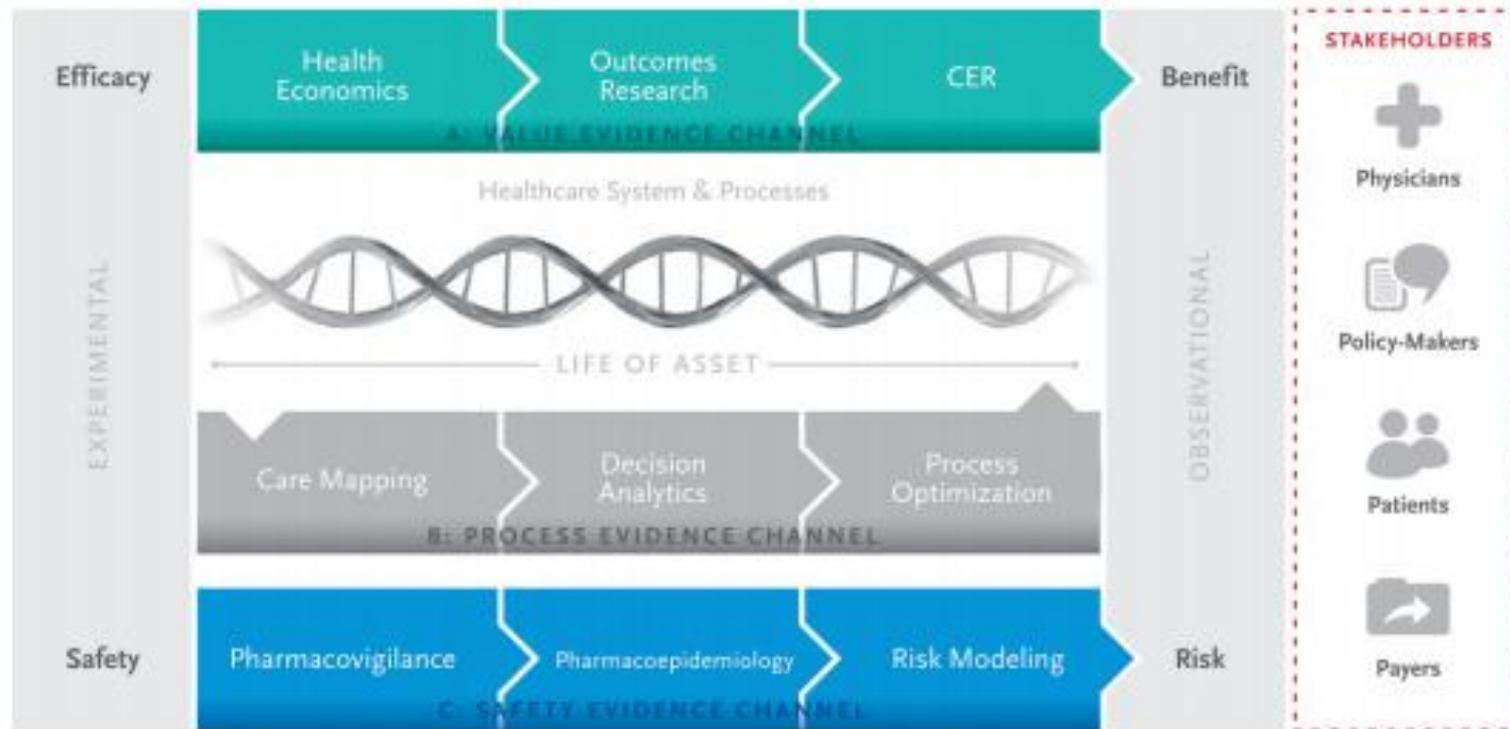
CMS (Evidence of Value)

- Manifested by its national coverage decisions that recommend 'coverage with evidence development'

CER Value

Evidence conversion

Stakeholders in the new health landscape will require customized clinical and commercial evidence derived from patient-level analysis of real-world data



Post-launch, efficacy and safety are translated into benefit and risk

CER Value

Evidence standardization

Despite progress in developing strategies to enhance value, it is essential to create a transparent CER evaluation protocol based on standard principles



- CER should focus on a holistic notion of evidence development, encompassing a variety of treatment process and outcome metrics, measured by alternative research designs.

- CER analysts aim to measure product performance under conditions of uncertainty in order to provide information on the public health impact of adoption of biopharmaceuticals (short and long-term)

- A 'comparative effectiveness' balance sheet' for biopharmaceutical products can be conceptualized as a snapshot of positive and negative product attributes that is updated periodically

- The idea is to get a scorecard of what matters to stakeholders at that particular time, and use this as a framework for product valuation and construction of the CER balance sheet.

CER Value

Horizon scanning

Healthcare reform is the catalyst for CER evolution and refinement.

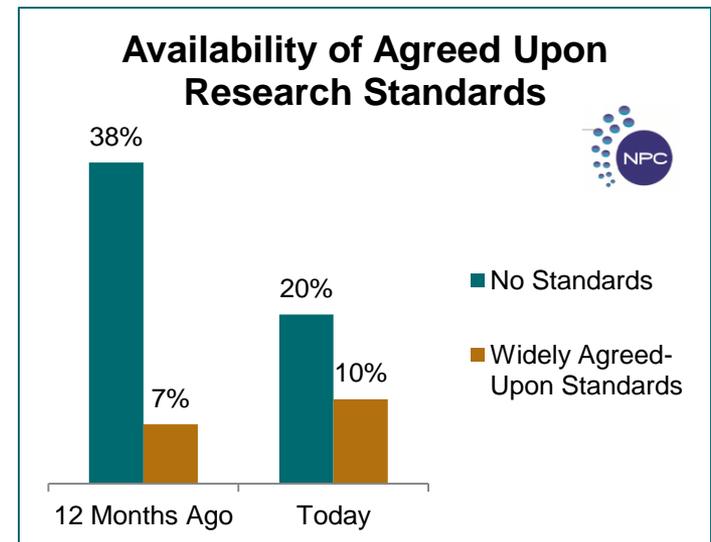
“The Pink Sheet”

April 04, 2011

IoM Recommends Standards For Systematic Reviews Of CER

The IOM is looking towards PCORI to oversee standards on how to conduct systematic reviews of CER and making recommendations on what those standards should be including:

- 21 standards with 82 elements to ...”address issues such as bias, conflict of interest of the research team, and gaining user and stakeholder input...”



“Currently, CER evaluation is much like the wild, wild West. While a few organizations have made some strides, there is little in the way of publicly available, comprehensive evaluation criteria.”

- WellPoint Chief Pharmacy Officer

CER Cases

Real-world Examples of Real-world Research

CER Case Study: CATIE

Clinical antipsychotic trials of intervention effectiveness



Background

Treatments

- The CATIE Schizophrenia Study is comparing the effectiveness of six medications approved for market use by the U.S. Food and Drug Administration:
 - ziprasidone (Geodon)
 - olanzapine (Zyprexa)
 - quetiapine (Seroquel)
 - risperidone (Risperdal)
 - clozapine (Clozaril)
 - perphenazine (Trilafon)*
- The CATIE Alzheimer's Disease Study is comparing the effectiveness of four FDA-approved medications for these symptoms:
 - olanzapine (Zyprexa®)
 - quetiapine (Seroquel®)
 - risperidone (Risperdal®)
 - citalopram (Celexa®)

Study Description

- The Clinical Antipsychotic Trials of Intervention Effectiveness project (CATIE) is a randomized control trial that evaluated the clinical effectiveness of atypical antipsychotics in the treatment of schizophrenia and Alzheimer's disease

Outcomes & Implications

- The results conclude that the older (first generation) antipsychotic medication perphenazine was less expensive and no less effective than the newer (second generation) medications used in the trial during initial treatment, suggesting that older antipsychotics still have a role in treating schizophrenia

CER Case Study: GeCCO

Genotype guided comparison of clopidogrel & prasugrel Outcomes



Background

Disease

- About 25 percent of people worldwide are born with a version of the *CYP2C19* gene that produces a cytochrome P450 2C19 enzyme that is not fully functional
- Patients who are "extensive metabolizers" of clopidogrel were born with a normally functioning version of the *CYP2C19* gene have comparable outcomes to those patients taking prasugrel, a newer, higher cost drug with metabolism less dependent on genetic variations

Treatments

- Prasugrel has shown greater efficacy but higher bleeding risk than clopidogrel in head-to-head clinical trials, but to date none of the studies limited the patient population to those who extensively metabolize clopidogrel, which could substantially impact the results

Study Description

- Genotype Guided Comparison of Clopidogrel & Prasugrel Outcomes (GeCCO) is a head-to-head prospective, observational study comparing clopidogrel (Plavix) and prasugrel (Effient)
- The trial will study more than 14,000 extensive metabolizers of clopidogrel were born with a normally functioning version of the *CYP2C19*

Outcomes & Implications

- The study will compare effectiveness of the two drugs by measuring the rate of cardiovascular deaths, nonfatal heart attacks and nonfatal strokes over a six-month period
- The study could have important patient safety ramifications and significant cost implications for health plans that pay for these drugs. Clopidogrel, the third largest selling drug in the United States with \$4.9 billion in 2008 sales, could face generic competition when its patent expires in late 2011, creating additional savings opportunities

CER Case Study: CATT

Comparison of AMD treatment trials



Background

Disease

- AMD is a disease that damages the macula. The macula is the area of the retina responsible for central vision. AMD is a leading cause of blindness among older Americans. Nearly two million Americans are visually impaired by AMD, while more than seven million are at increased risk of vision loss from the disease

Treatments

- Lucentis (ranibizumab) was approved by the U.S. Food and Drug Administration (FDA) in June of 2006 for the treatment of advanced, or wet, AMD. The approval was based on evidence from clinical trials showing that Lucentis slows the rate of progression of vision loss from wet AMD
- Avastin (bevacizumab) was approved by the FDA in 2004 as an intravenous treatment for patients with advanced colorectal cancer and therefore has been available off-label to treat wet AMD. Avastin is thought to remain in the eye longer than Lucentis and therefore possibly allow for less frequent injections

Study Description

- Comparison of AMD Treatments Trial (CATT) is a multicenter clinical trial to compare the relative safety and effectiveness of two drugs currently used to treat advanced age-related macular degeneration (AMD)
- The trial determined the relative safety and effectiveness of treating wet AMD in 1,200 patients. This clinical trial will be conducted at 47 clinical centers across the country

Outcomes & Implications

- It is hoped the results of this study will improve the treatment of wet AMD. Reducing the frequency of treatments without compromising effectiveness would reduce the treatment burden for patients and produce a potential cost savings
- The initial study results conclude that Lucentis and Avastin had equal effects on visual acuity when administered according to the same schedule. This means that providers and payers will now have to rationalize the cost of using Lucentis when a low-cost, effective alternative exists

Appendix

CER Strategies to Enhance Value

Criticisms



Risks and benefits of innovative medical treatments are the subject of intense societal debate, particularly concerning the methods and approaches, as it remains a topic that is paradoxically undefined

- **“The current process of drug approval lacks a systematic approach to benefit-risk analysis, leading to inconsistency, lack of transparency and an inability to challenge or defend decisions.”**

-Boston Consulting Group, February 2006

- **“...in both the pre-approval and post-marketing setting, the risk-benefit analysis that currently goes into regulatory decisions appears to be ad hoc, informal, and qualitative...”**

-The Future of Drug Safety, The Institute of Medicine, 2007

- **“It is a frustrating aspect of BR evaluation that there is no defined and tested algorithm or summary metric that combines benefit and risk data . . . that might permit straightforward quantitative comparisons of different treatment options.”**

-The Council for International Organizations of Medical Sciences, CIOMS

Adapting Experimental Research Design QUINTILES®

Study design overview

Several types of studies can address stakeholder requirements. It is key to judiciously choose a study type, as each has its advantages and disadvantages

Type of Study	Advantages	Disadvantages
Active-controlled superiority-showing randomized controlled trial (RCT)	<ul style="list-style-type: none"> High internal validity May provide relevant relative efficacy (RE) information if comparator deemed appropriate 	<ul style="list-style-type: none"> Often requires large sample size Only one comparator can usually be studied
Two-arm non-inferiority-showing RCT	<ul style="list-style-type: none"> May be the only alternative available for demonstration of efficacy if placebo-controlled RCT considered unethical Provides limited RE information 	<ul style="list-style-type: none"> May lack assay sensitivity and therefore internal validity
Active-and placebo-controlled RCT	<ul style="list-style-type: none"> Most informative trial design High internal validity 	<ul style="list-style-type: none"> Non achievable if placebo control considered unethical Often requires large sample size
Pragmatic clinical trial	<ul style="list-style-type: none"> High external validity Demonstrates relative effectiveness 	<ul style="list-style-type: none"> Lower signal-to-noise ration than conventional RCTs Requires larger sample size May mask small true differences between treatments
Common reference indirect comparison based on RCT information (network meta-analysis)	<ul style="list-style-type: none"> Relatively easy and less expensive than RCTs Useful in the absence of head-to-head RCTs 	<ul style="list-style-type: none"> Essentially non-randomized methodology May be subject to unknown confounding variables
Observational Studies	<ul style="list-style-type: none"> May be conducted retrospectively or prospectively Less expensive and time-consuming than RCTs Large patient numbers can be observed 	<ul style="list-style-type: none"> Non-randomized information Subject to high risk of confounding variables

CER in the Global Marketplace

CER internationally



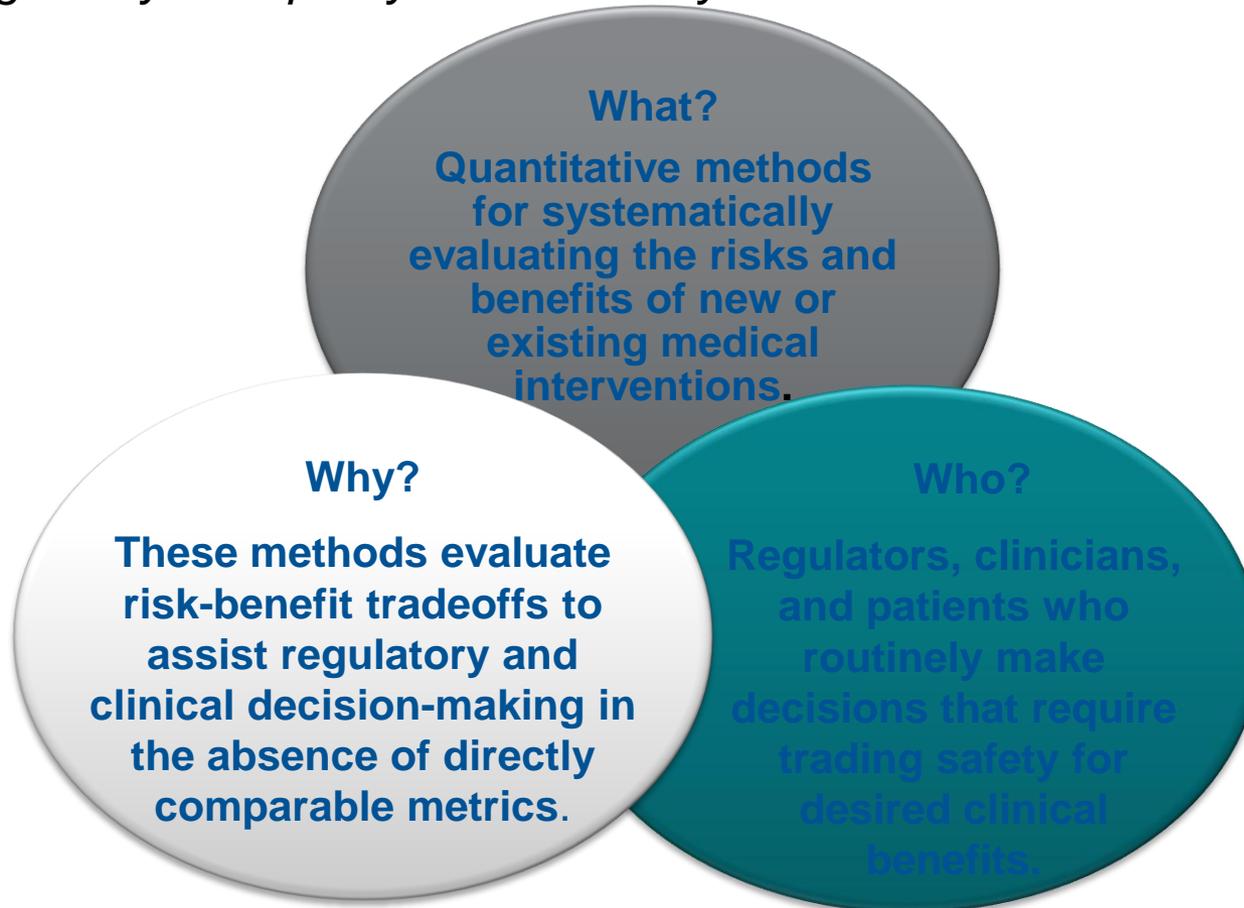
Various agencies influence CER globally to measure cost-effectiveness in healthcare

Key Drug Review and Decision-Making Bodies in Select Countries, 2009

Country		Review Body	Function/Role	Evaluation Tendencies	Relation to Government
<i>Denmark</i>		DKMA	Coverage/Regulatory	Budget Impact	Integrated
<i>England</i>		NICE	Coverage/Regulatory	Health Economics	Arms-Length
<i>France</i>		HAS CEPS	Coverage/Advisory Pricing/Regulatory	Budget Impact	Integrated Integrated
<i>Germany</i>		IQWiG	Coverage/Advisory	Health Economics	Arms-Length
<i>Netherlands</i>		CHF	Coverage and Pricing/Advisory	Health Economics	Integrated
<i>Sweden</i>		TLV	Coverage and Pricing/Regulatory	Health Economics	Arms-length
<i>Australia</i>		PBAC	Pricing/Advisory	Health Economics	Independent

Introduction to Risk Benefit Assessment (RBA)

Risk and benefit assessment and monitoring are significant contributors to promoting safety and quality in the delivery of health care.



Source: William L. Holden. Benefit-risk analysis: a proposal using quantitative methods

Introduction to RBA

Problem Statements



The problem statements in risk benefit assessment center around drug development strategies, regulatory approval, and risk management.

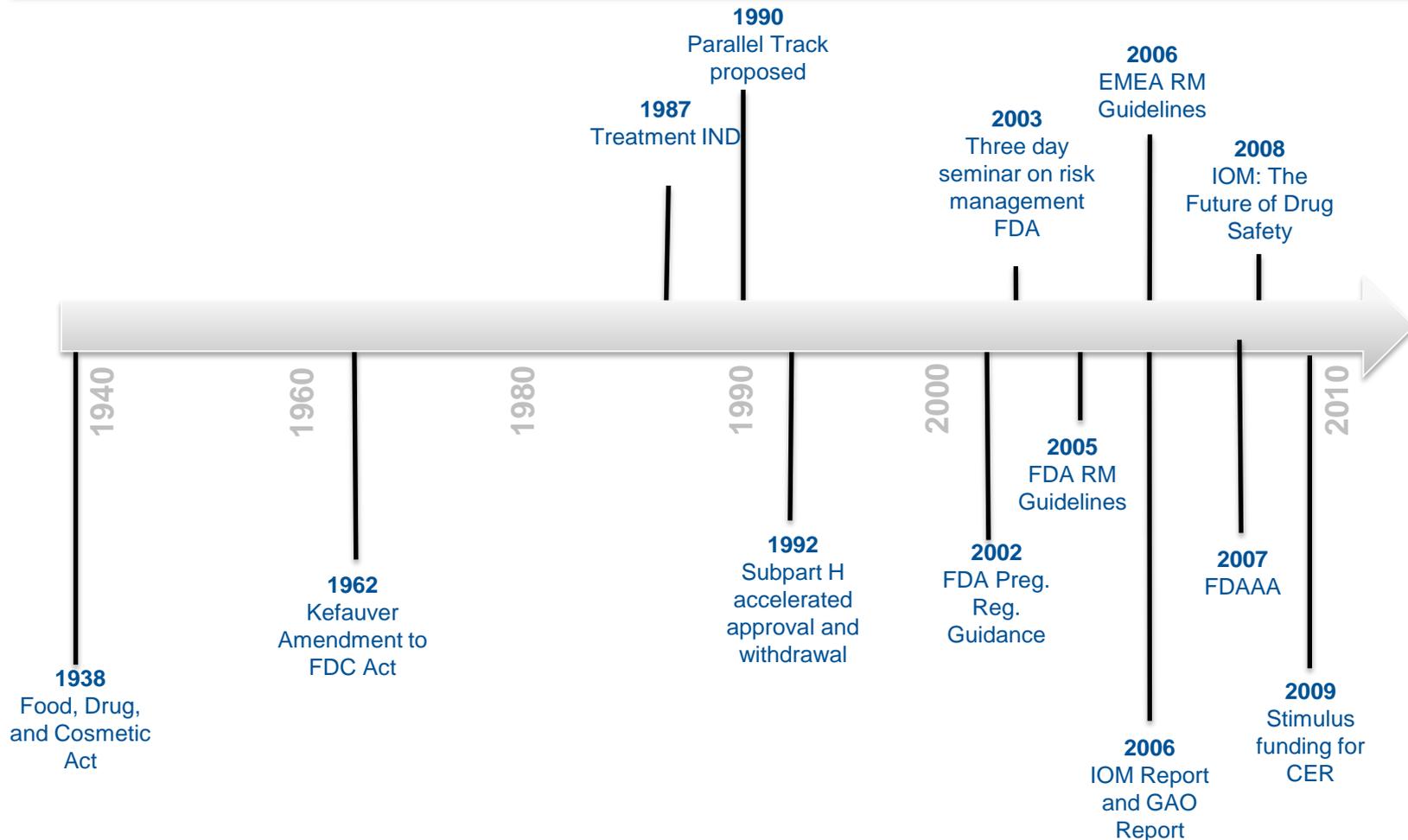
Area	Questions
Development Strategies	<ul style="list-style-type: none">▶ When does one conclude that the increased benefit of a new therapy outweighs the potential increased risk?▶ How does one appropriately measure the trade-off between the benefit and risk of a specific therapy?▶ How can this information lead to better-informed product-development decisions in cases where early data indicate the possibility of an adverse event?
Regulatory Approval	<ul style="list-style-type: none">▶ How does one determine if risks outweigh benefits and require product labeling/removal decisions?
Risk Management	<ul style="list-style-type: none">▶ How does one know when to require post-marketing risk/benefit management plans?

CER Strategies to Enhance Value



Drug safety timeline

Over the past ten years, risk and benefit assessment has seen a number of new changes in the form of regulations and guidelines



CER Explained

Rationale for CER Readiness

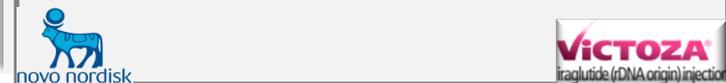


Four case studies highlight the importance of integrating CER in the clinical process early & effectively

Anticipate CER Studies Early Before Another Group Initiates

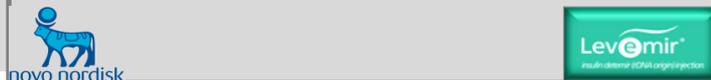


Pharmaceutical Organizations are Integrating CER Into Their Clinical Development Programs

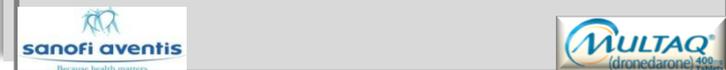


Conduct CER Effectively

Choose Comparators that are Relevant to Your Stakeholders (Patients, Providers, Payers, Regulators)



Condition the Market for Innovative Endpoints to Reinforce their Relevance to Stakeholders (Patients, Providers, Payers, Regulators)



CER in the Global Marketplace

CER in the U.S.



The U.S. Government's emphasis on evidence is illustrated through recent changes in healthcare - the ARRA provided \$1.1 billion in CER to promote high quality care through diverse initiatives

Activity	ARRA CER Initiatives for FDA
<i>Development of a Clinical Trial Repository</i>	<ul style="list-style-type: none"> ▪ Support the software development life-cycle phases of requirements and design analysis, development/enhancement, testing, training, and implementation
<i>Convert Legacy Data</i>	<ul style="list-style-type: none"> ▪ Convert legacy data from clinical studies relevant to specific questions of comparative efficacy to a standard format harmonizing terminologies as needed and storing the standardized data in the data repository
<i>Implement Modern Analytical Tools</i>	<ul style="list-style-type: none"> ▪ Support comparative effectiveness research using the clinical study data repository. ▪ Provide integration and implementation support for selected tools
<i>PACES</i>	<ul style="list-style-type: none"> ▪ Facilitate comparative analysis pilots to conduct advanced and robust analysis for detecting clinical trends to understand which interventions are most effective for which patients under specific circumstances ▪ Establish Partnership in Applied Comparative Effectiveness Science for Medical Products (PACES) ▪ Host public scientific workshops to discuss analytic tools, methods, and best practices for analyzing data across multiple clinical studies

HTA Influence and Development

- Policy makers are beginning to use HTA for evidence-based decision making.
- Formal contract systems is still under development and academic institution work is under research grants rather than government contracts.
- Overall, HTA is still in nascent stage and there is still significant growth ahead.

HTA Influence and Development

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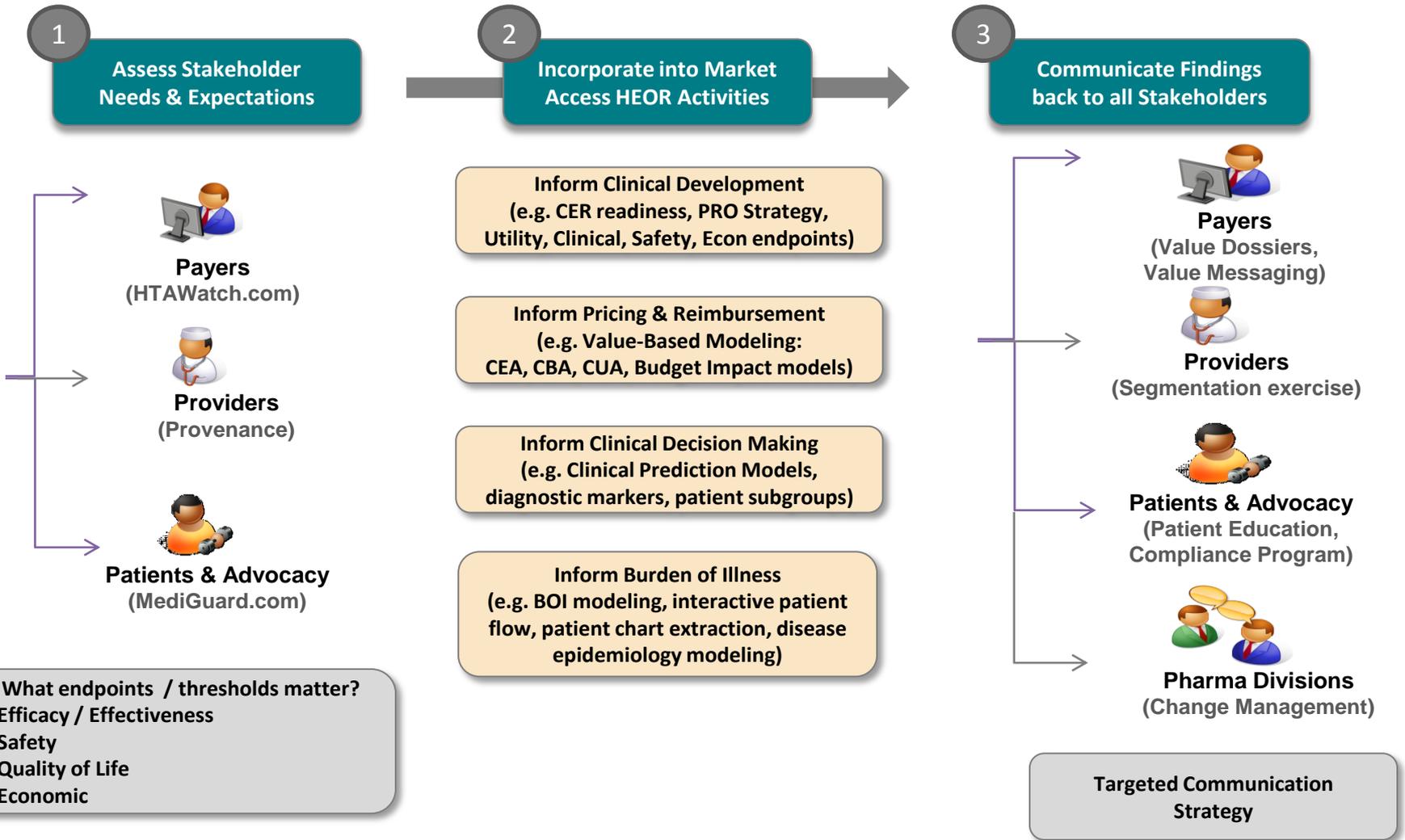
HTA Growth Opportunities

- Lack of coordination
 - HTA is scattered among various administrative areas within government agencies
 - No national HTA commission and lack of consistency among policies.
- Overall need to restructure the HTA framework
- HTA should be conducted for different types of technology
 - Need oversight of all relevant stakeholders to conduct HTA while following coherent guidelines.
- HTA should be free from conflict of interests (ie, be publically funded)

Process of Incorporating Stakeholder Needs

From Sanofi Kickoff

Substantiating product value across multiple HEOR activities and various



CER Study 1: A comprehensive framework for analyzing heterogeneity of treatment effects in comparative effectiveness research

Specific Aims: (1) To test an analytic framework for subgroup analysis using the CER example of therapy to be determined; (2) To apply the framework to thoroughly examine published CER studies that resulted in policy decisions affecting a subgroup.

Will empirically test the value of: **pre-specifying** the subgroups and analytic protocol for testing heterogeneity of treatment effect (HTE), **differentiating exploratory versus confirmatory** subgroup analyses, testing for interactions, **displaying graphically** the HTE results, **validating** subgroup results.

CER Study 2: Systematic Assessment of the Benefits and Risks of a therapy (TBD): A Multicriteria Decision Analysis using the Analytic Hierarchy Process

Specific Aim:

To conduct a **multi-criteria decision analysis** to do a benefit-risk assessment of the thiazolidinediones in individuals with type 2 diabetes relative to sulfonylureas and metformin, using the Analytic Hierarchy Process. (Dolan, 1989; Tsaty, 1994; Singh, 2006; Dolan, 2008)

The Analytic Hierarchy process can flexibly address a range of decisions that involve both **quantitative data** and **subjective input**. The methodology can also be **applied to evaluate medications in the pre-approval period**, with appropriate accounting for uncertainty around the estimates of long term safety. Investigators will: define the decision context; assemble and organize outcome information; make comparisons among the alternatives; combine the results of the judgments; and perform sensitivity analyses.

Clinical Design Strategy 1: Optimal Clinical Trial Designs for Estimating Treatment Effects in Subpopulations

Specific Aim: To develop **statistical methods and software** that will enable investigators and regulators to determine, for a given scenario, the **best trial designs and analyses** for generating evidence about treatment effectiveness in different subpopulations.

Will consider three categories of studies: 1) where the subpopulations of interest are known before the study starts, and there are relatively **few**; 2) where the subpopulations of interest are known before the study starts, and there are **more than a few** such subpopulations of interest; and 3) where the subpopulations of interest are **unknown** before the study starts.

Will construct candidate clinical trial designs aimed at making inferences about specific subpopulations. Will include **group sequential designs with no adaptation**, and group sequential designs that incorporate the following types of **pre-specified adaptations** at interim analyses: **changes in the sample size, changes in the randomization probabilities, and changes in the subpopulations sampled.**

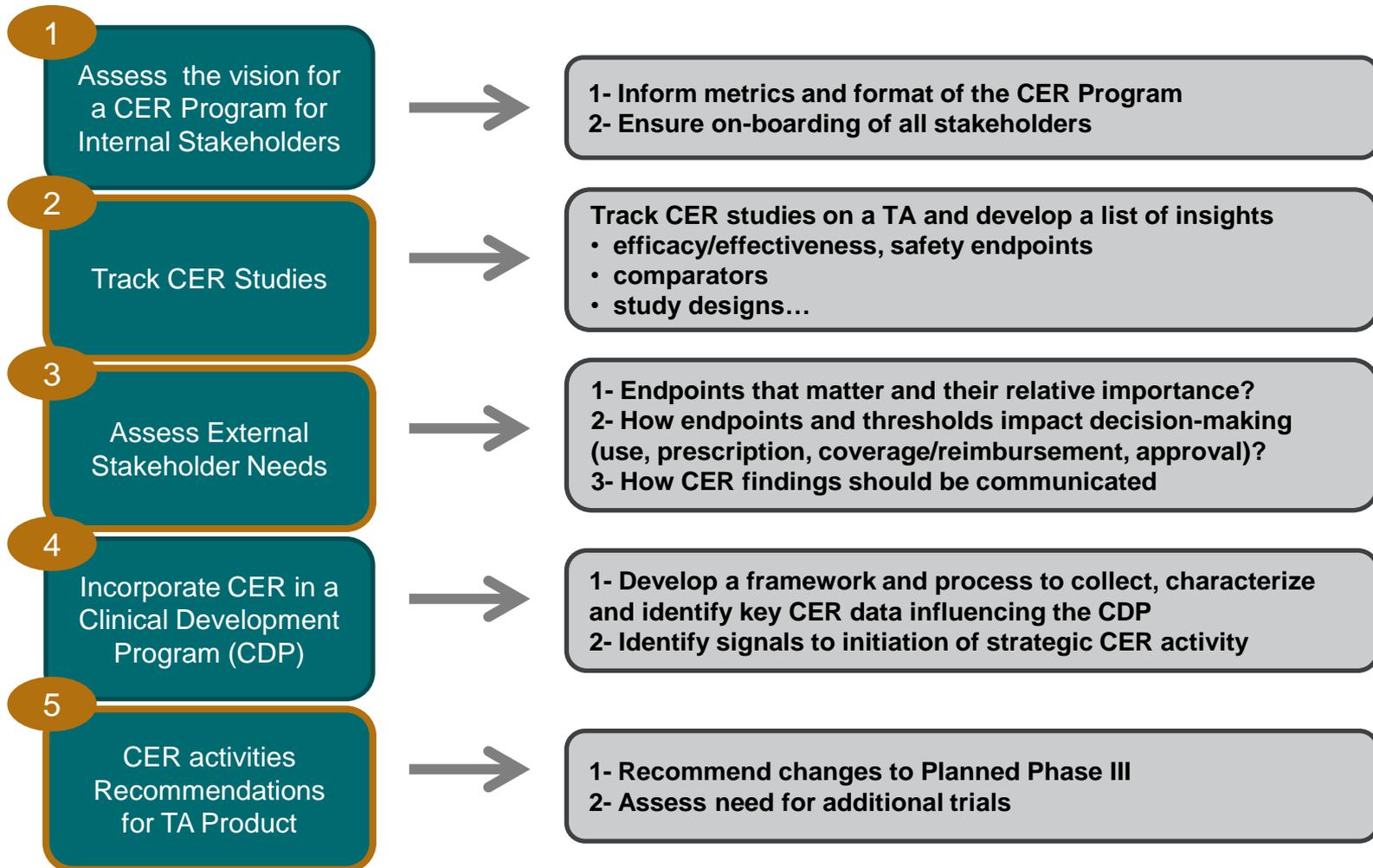
Clinical Design Strategy 2: Improved Design of Randomized Trials with Use of Information from Historical Controls

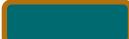
Specific Aim: To develop **mixture prior models** for use when incorporating **historical control data** with a concurrent control that is part of a randomized controlled trial (RCT).

Flexible Bayesian nonparametric models allows one to include more relevant data sources than is possible when using other models; the **mixture approach will be more robust to data-source-specific departures from a common, exchangeable hierarchical model.**

We will **develop and test this model**, using the RCTs in JANUS and data from other databases. We will carry out **simulation** studies to test these mixture prior models and **compare the method to alternative formulations** for incorporating historical data. We will use patient-level data in FDA database, along with complementary data warehoused in these other databases.

Conceptual CER Program Framework



 TA-specific steps

- The CER program is to be used by a multidisciplinary team of "internal stakeholders":
 - The clinical team
 - The market access team
 - The marketing and commercial team
- Through primary research we will attempt to understand each stakeholder's expectations and needs for a CER program to help improve drug development.
 - How do you think CER will impact you moving forward?
 - How would you like to apply the CER program?
 - What information are you most interested in collecting and in what format?
 - How would you like to be involved in the CER program?
 - What avenues of collaboration do you anticipate with the other internal stakeholders?
- For example the market access team might identify and develop economic, clinical and/or PRO clinical endpoints to be included in a Phase III trial. The clinical team might then adapt its study design and target population to best capture the information most relevant to all stakeholders. The marketing and commercial team would then need to communicate findings from the CER program back to all stakeholders to optimize the value message of the compound.

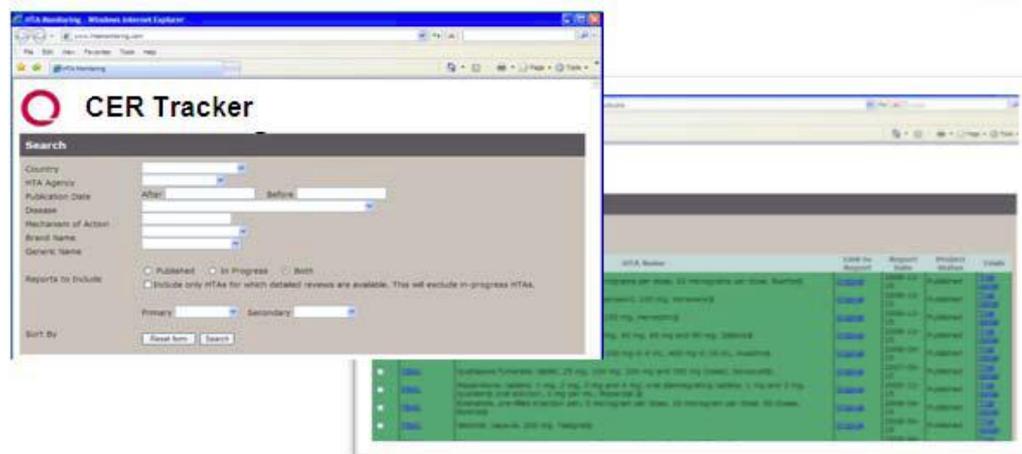
Through a systematic secondary research effort, we propose to track CER studies within a specific therapeutic area to identify parameters such as endpoints, comparators, study design, impact on various stakeholders, and funding sources.

1. Within specific therapeutic areas we would monitor relevant drug classes to understand which are holding up to their comparator in a real-world setting and how compounds with multiple indications are evaluated.
2. We will also identify the planned CER studies using The Institute of Medicine (IOM) 100 areas recommended for CER evaluation as well as the PICORI and the AHRQ governmental sites.
3. We will compare the key fields to the manufacturer's product pipeline and provide recommendations as to the near future areas to focus CER efforts on as well as an evaluation of the risks involved in not actively pursuing a CER Program in the areas identified.
4. We will also identify a series of signals to would indicate the need for initiating CER.

Gain Insight into CER Studies and CER Initiatives



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Can inform CER strategy

CER TRACKER

1. Library of tracked CER studies
2. Search capabilities with user friendly interface
3. Value-added interpretation (quality scoring)
4. Implications to stakeholders

EYE on CER

1. Track public CER initiatives
2. Track Pharma CER initiatives
3. Track CER US and ex-US
4. Trends and patterns

Observational Studies and CER

– **Observational Studies to Take on a Larger Role**

Predicted that CER, at least on the federal level, will be more about observational studies, systematic reviews, database studies and other broad types of analysis than head-to-head trials (“CER Policy Does Not Equate To Head-To-Head Trials, UBC’s Luce Says,” “The Pink Sheet,” July 5, 2010).

– **Evaluation of Observational Studies**

Cambridge, Mass.-based Outcome Sciences – a provider of patient registries, technologies and studies to evaluate real-world outcomes, with seed funding from the National Pharmaceutical Council – released in April a framework for evaluating observational CER studies known as GRACE (Good Research for Comparative Effectiveness) (“PCORI Should Take Lead On Public CER Inventory, Pharma Groups Tell HHS,” “The Pink Sheet,” Aug. 23, 2010). Health insurer WellPoint also released guidelines on how it will evaluate CER, including observational studies (“WellPoint’s CER Guide Describes How It Will Determine Usefulness Of Studies,” “The Pink Sheet,” May 24, 2010).

- **Increasing Respect for Observational Studies**

Minimize bias including “confirmation bias is one of our biggest enemies, or analyzing to a foregone conclusion.” For instance, Harrell suggests there could be a masking of outcomes data while analysis is ongoing to approximate what is going on during RCTs. Harrell also stressed the importance of pre-filed statistical analysis plans. “It’s very, very uncommon in observational research to actually have detailed analyses that are actually signed and dated,” he said. “This has to change and could change immediately.

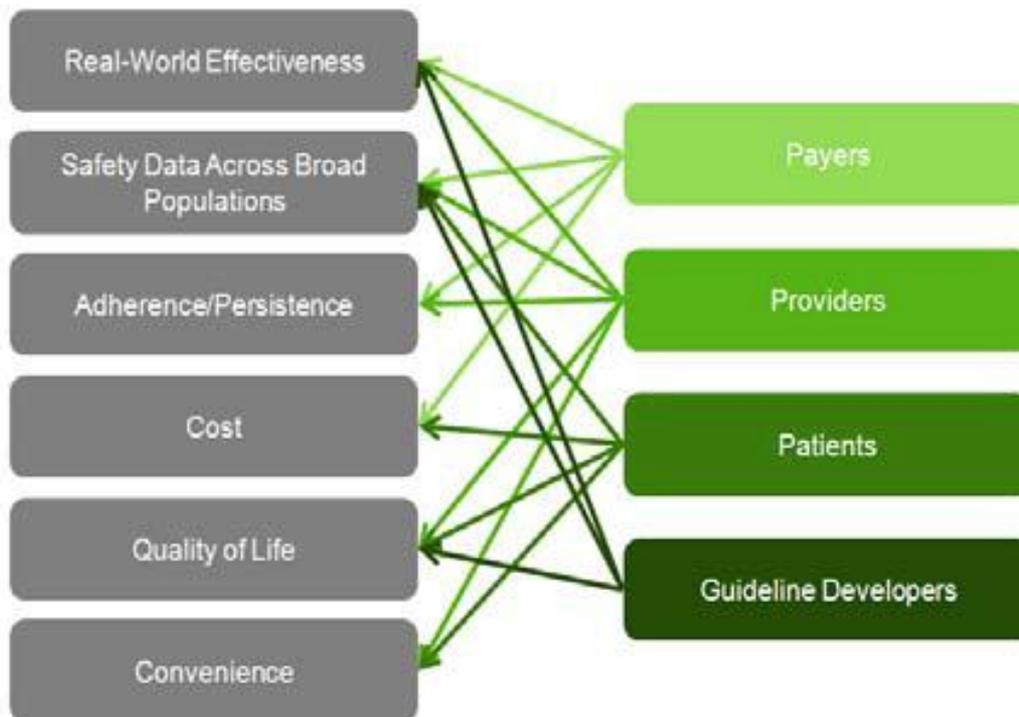
We will conduct primary research with external stakeholders to assess:

- The relative importance of safety and effectiveness endpoints, economic and humanistic endpoints for each stakeholder as well as thresholds of interest/clinically meaningful difference
- How would endpoints or a combination of endpoints (Quintiles to develop scenarios to be tested) impact stakeholder decision-making (use, prescription, coverage/reimbursement, approval) ?
 - e.g. if long-acting insulin were to be clinically superior to other OAD in terms of A1c control with no weight gain and similar hypoglycaemic event risk from an AHRQ sponsored study, how would that impact your current decision making?
- How should CER findings be communicated to each stakeholder for optimal impact?
- How do stakeholders consider evidence from manufacturer-funded CER studies as opposed to government-funded research?
- How do stakeholders envision CER influencing their decisions in the near and long-term future?

As stakeholders have different perspectives, responsibilities, and incentives for decision making; the need for evidence varies

Stakeholders

Patients with a specific TA
Patient advocacy group members
Payers (e.g. Managed Care Organizations)
Payers (e.g. Pharmacy Benefit Managers)
Front-line providers
Key Opinion Leaders with clinical guideline involvement
Regulators (e.g. ex-FDA persons with knowledge of the TA)



1. What economic, clinical and humanistic endpoints and effectiveness thresholds would impact their use/ coverage/ reimbursement/ approval of a drug for the metabolic therapeutic areas?
2. Would they stop taking/drop coverage a drug that did not fare well in a CER study?
3. How do they value direct real-world drug comparisons in your health care decision making process?
4. Are manufacturer-funded CER studies a source of CER data they consider favourably?

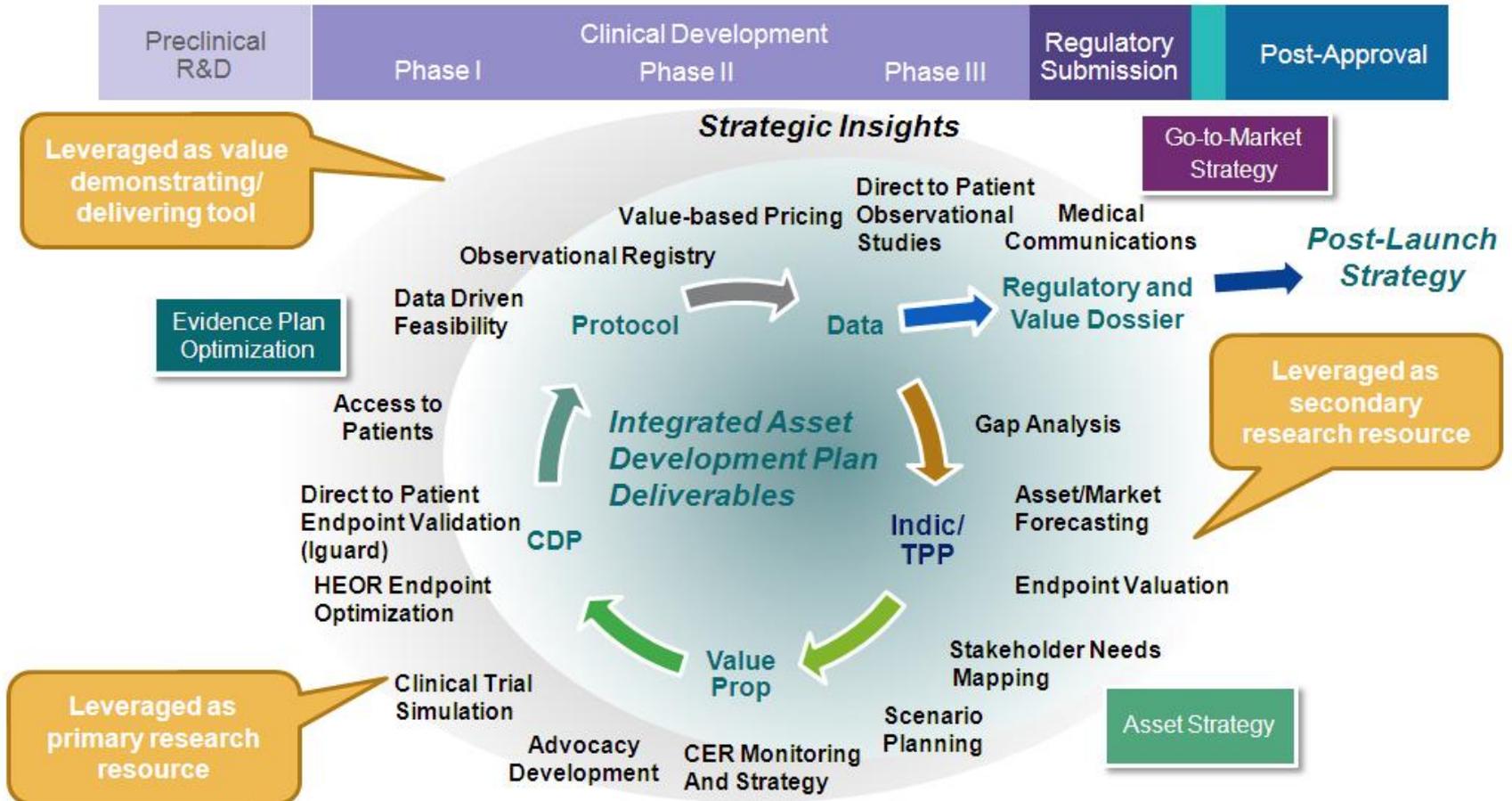
Integrate CER into the Drug Development

Quintiles has developed an integrated perspective on the types of information and analysis that should be used at each stage of the clinical development process. This should include leveraging CER needs to inform

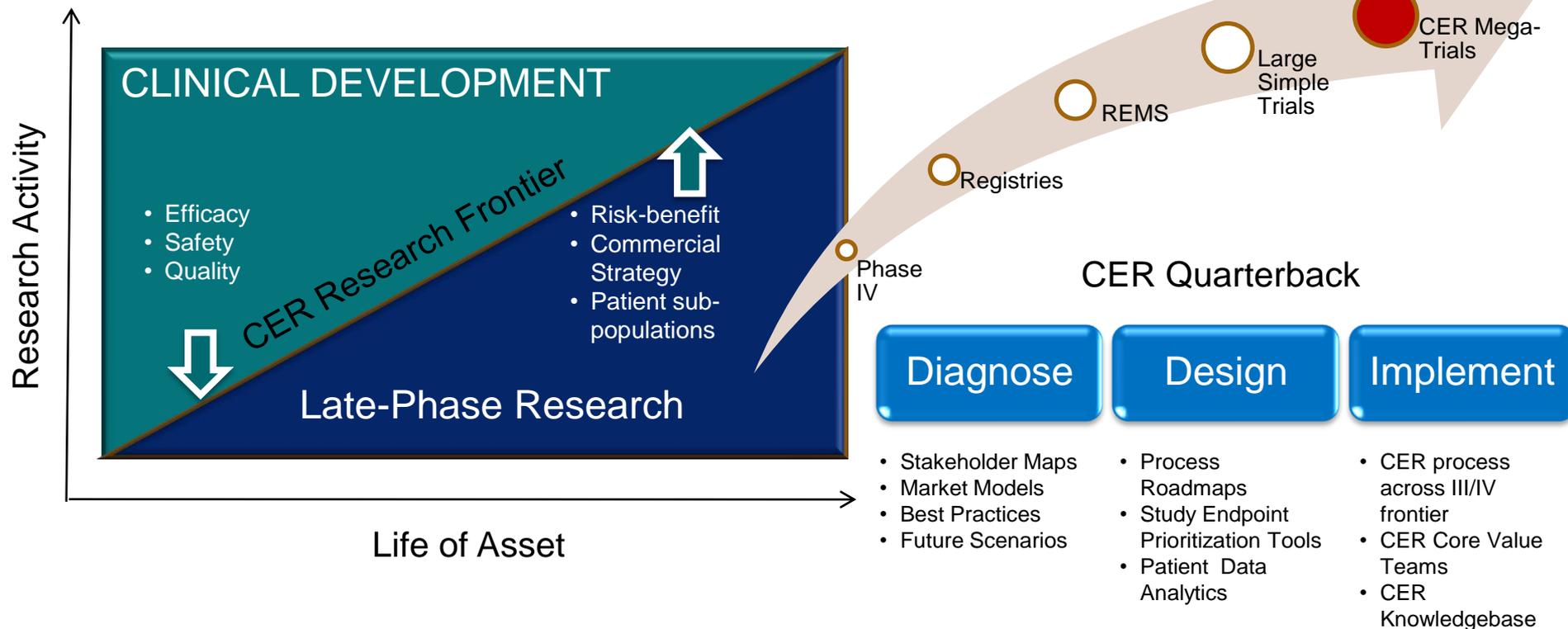
- key value differentiators
- target product profile development
- product value proposition
- specific Clinical Development Plan (CDP)
- protocol development

Goal: integrate key CER findings and data into clinical development planning and decision making milestones and deliverables to ensure optimal comparative data is provided to stakeholders at time of launch and beyond

Integrate CER into the Drug Development



CER is evolving into a fundamental strategy focused on substantiating the proof of a product's value, thereby amplifying and extending the commercial value of an asset. Consulting can lead the transfer of knowledge and sharing of resources across the "CER Research Frontier."



Recommendations on CER Activities Needed – Gap Analysis

What is already in place, what is missing to implement the optimal CER drug development strategy?

- Consider study design: what endpoints can be included within current/planned Phase II or Phase III trials?
- Consider other data sources (registry, claims...) and timing to implement new study
- What are competing interests?

How can we ensure collaboration across internal stakeholders?

- Include internal communication of the tool and its application to internal stakeholders through a mechanism for collaboration to ensure a unified CER approach. Develop a framework for each group to interact.

How can we communicate our CER findings to all relevant stakeholders through a CER communication plan?

- Develop a roadmap to generate and disseminate CER evidence to each external stakeholder working with all internal stakeholders. Help get internal feedback on the CER drug development tool and diagnostic.

Recommendations on CER Activities Needed – Success Metrics

Create a CER Risk Assessment Tool

- Identify 5 to 10 attributes that would dictate the risk of a CER study being performed after launch by a governmental or private organization. These might include:
 - The growing public health importance of a disease (e.g. diabetes epidemic in the US)
 - Recent European activities/recommendation on a drug or therapeutic class (e.g. NICE rulings)
 - Therapeutic area identified by the Institute of Medicine (IOM) or AHRQ as a priority for CER assessment
 - Therapeutic drug classes with recent safety concerns, REMS programs

Develop Success Metrics to assess impact of CER implementation into the drug development plan

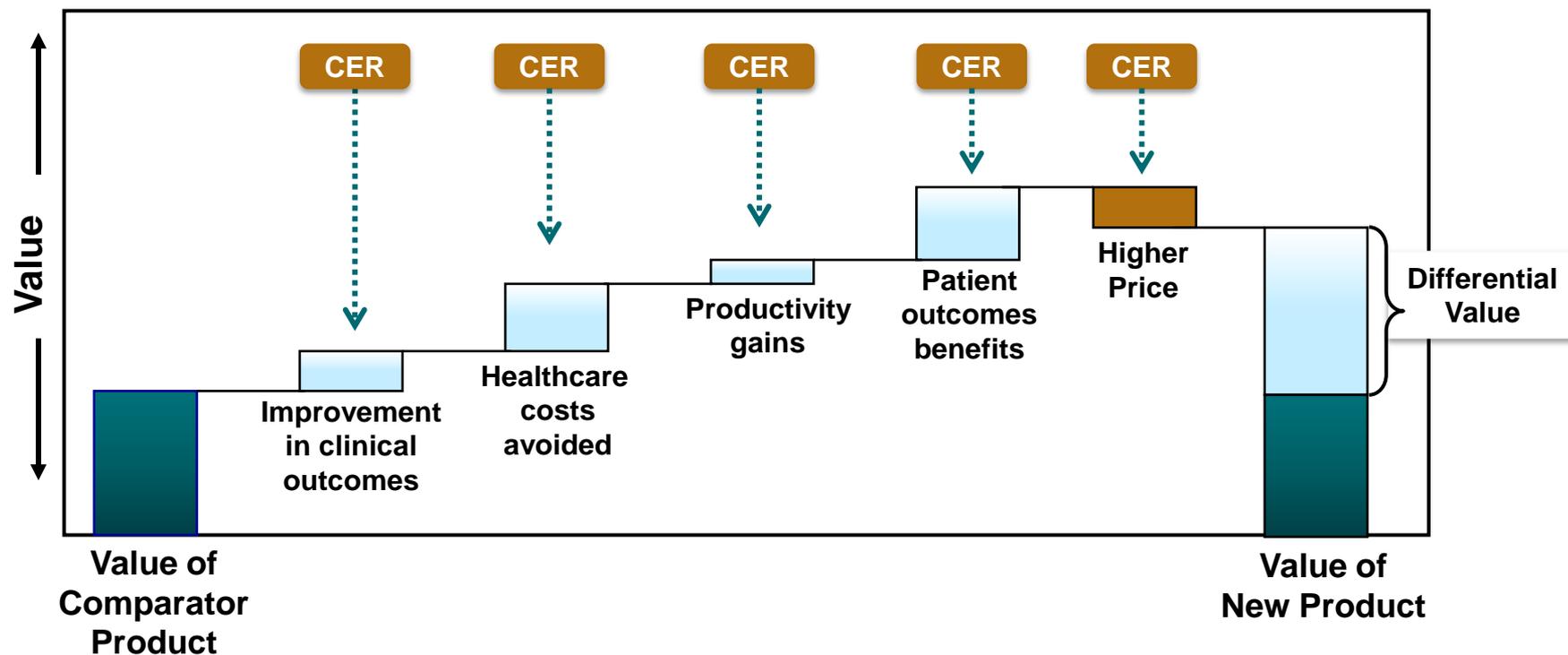
- Identify metrics to evaluate the impact of the CER strategic plan. These metrics should be relevant to internal funding sources and might include cost savings due to incorporating CER early in the development as opposed to funding CER research post-launch (comparison will be along 2 distinct but comparable TAs). Compare drug update with and without a CER strategic plan (comparison will be along 2 comparable drugs)

Demonstrating Real World Value

Economic value differentiator



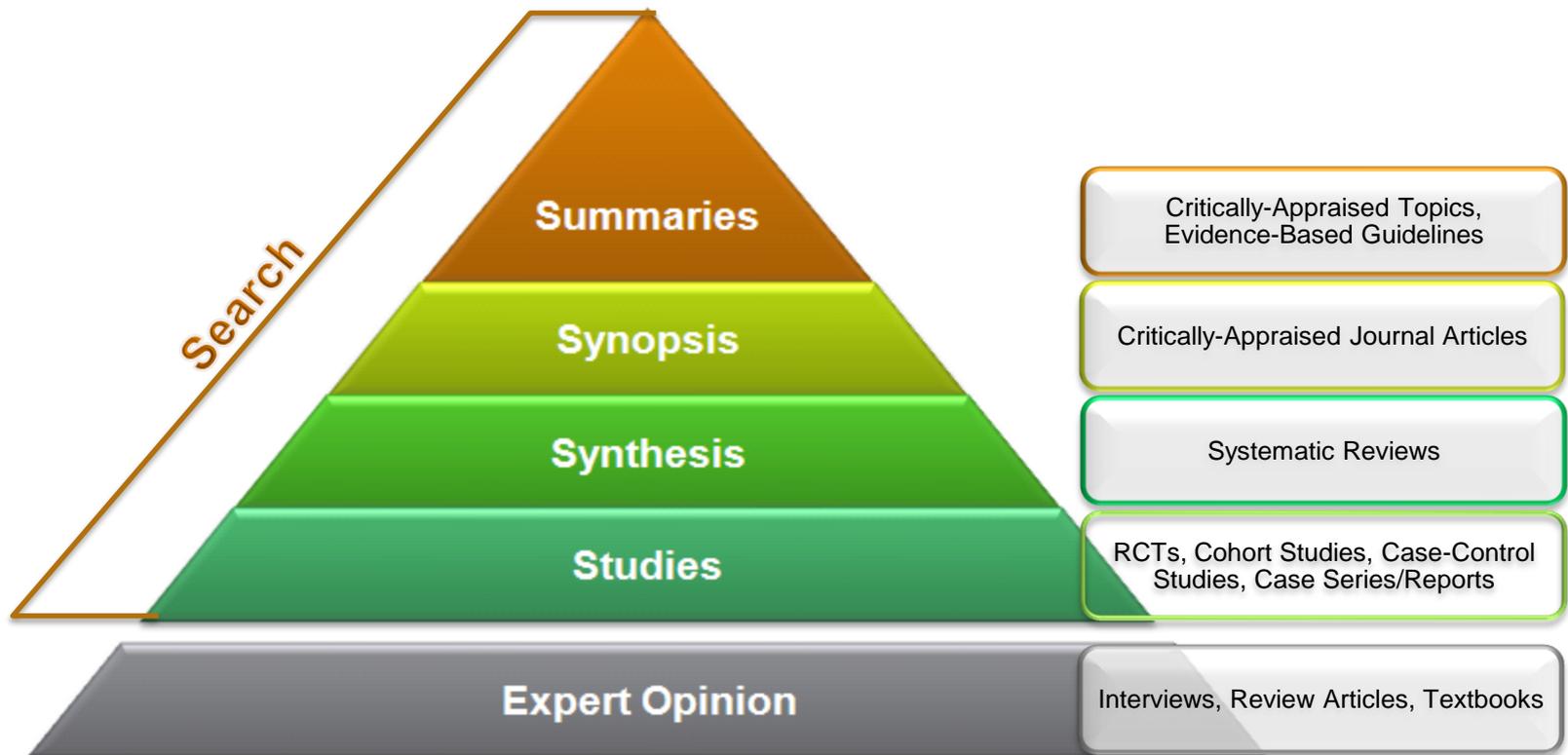
CER plays an important role in establishing a compendium of evidence that can be used to differentiate a new product's value



CER Value

Evidence Pyramid

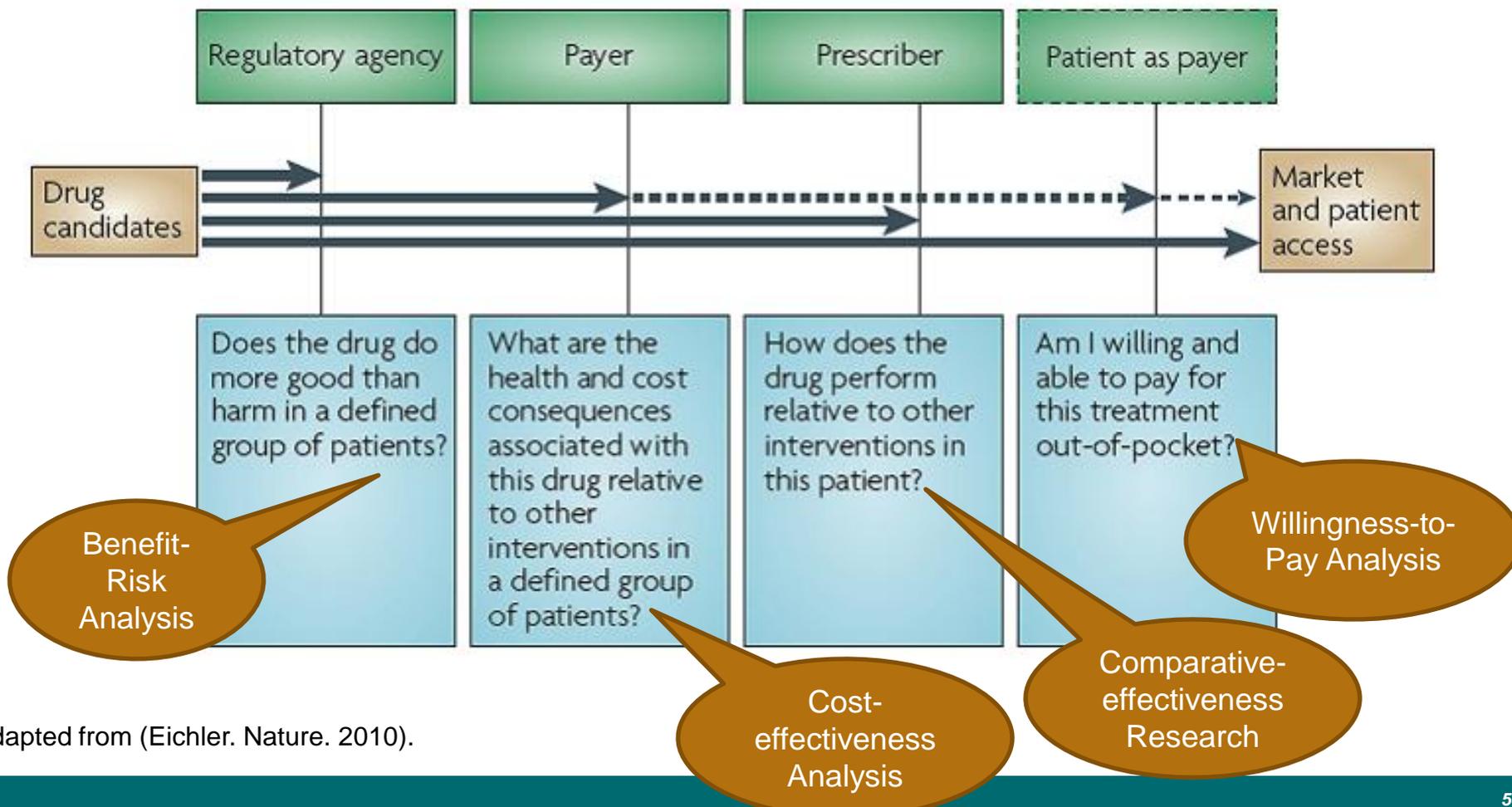
The level of evidence required for CER is dependent on the available data and the target audience



CER Explained

Role in market access

The road to market access for pharmaceutical products is moderated by several stakeholders with the patient serving as the final decision-maker



Adapted from (Eichler. Nature. 2010).

CER Convergence

CER in the U.S.



The foundation of CER in the U.S. began to develop in the 1970s with HTAs and continues to mature and gain traction in multiple sectors



1970s

HTA

1980s

Effectiveness
Research

1990s

Outcomes
Research

2000s

EBM and CER

“Acting” CER Bodies

- Agency for Healthcare Research and Quality (AHRQ)
- U.S. Preventive Service Task Force
- Department of Veterans Affairs and DoD
- Medicare / Medicaid
- Stimulus and Healthcare Reform Bills
 - The public/private Patient-Centered Outcomes Research Institute (PCORI)
- Cochrane Collaboration
- Blue Cross/Blue Shield
- Center for Medical Technology Policy
- Institute for Clinical and Economic Review
- ECRI
- Hayes, Inc
- Oregon Drug Effectiveness Review Project
- AMCP Format for Formulary Submission
- Academia