DEVELOPING A NEW DRUG DEVELOPMENT PARADIGM

RESPONDING TO THE CHALLENGE OF CER AND RE IN THE US AND EUROPE

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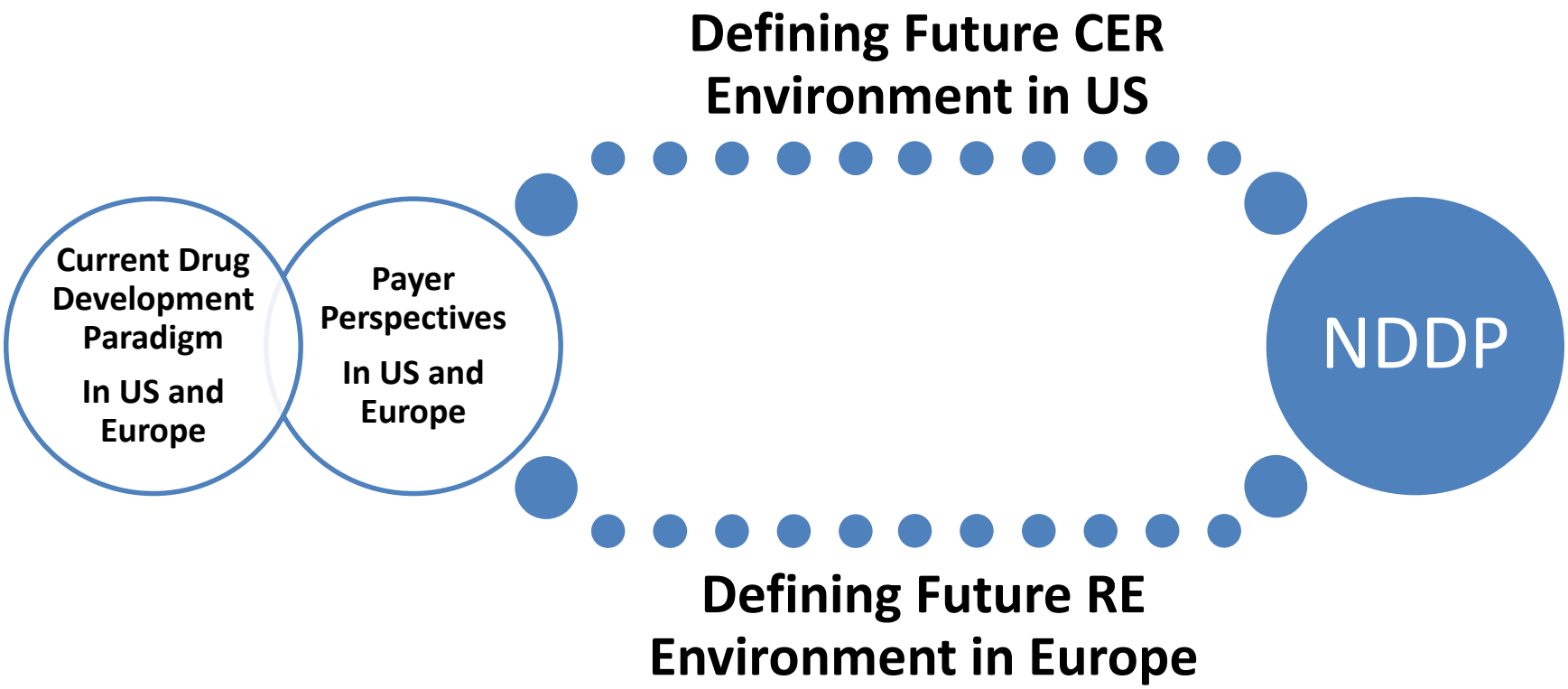
OVERALL PROCESS OF THE CMTP / OHE STUDY



AGENDA

- The future environment for relative effectiveness evidence in Europe
- A comparison of the European and US environments
- Implications for drug development and evidence generation

EXPLORING THE FUTURE OF RE FOR DRUGS IN EUROPE

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ELEMENTS AFFECTING THE FUTURE OF RE IN EUROPE?

Baseline factors

- Payers continue to face "austerity" pressures
- Decision making by Payer / HTA bodies remains at national / sub-national level
- Patient expectations continue to rise

Key Factors Assessed

- **New pharmaco-vigilance regulation (PAES and PASS)**
- **Adaptive Licensing (AL)**
- **Assessment of clinical evidence by HTA bodies/payers at launch**

Key Factors Assessed (continued)

- **Demand for post-launch RE studies by HTA bodies/payers**
- **Coordination between regulatory and HTA bodies**
- **Infrastructures to conduct RE research**
- **Methodologies to analyse RE evidence**
- Use of Patient Reported Outcomes (PROs)
- Relationship between FDA and EMA
- Personalised medicine
- Commissioning and funding RE studies

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EUROPE CRITICAL KEY FACTORS IDENTIFIED -- DEFINITIONS

TOP TWO CRITICAL KEY FACTORS	SECOND TWO CRITICAL KEY FACTORS
Regulatory change: *New pharmaco-vigilance regulation* enables the EMA to seek "efficacy" data in addition to "safety" (at first authorisation or post-authorisation) in order to inform a benefit-risk assessment of a medicine. *Adaptive Licensing:* prospectively planned, flexible approach to regulation with iterative phases of evidence gathering to reduce uncertainties followed by regulatory evaluation and license adaptation	Coordination between regulatory and HTA bodies: Interaction between regulatory and HTA bodies can in principle cover one or more of: • the offering of scientific advice both pre- and post-launch leading to • the possible coordination and/ or agreement on evidence requirements (e.g. type of study design and type of end points to be included)
HTA change: *Assessment of clinical evidence by bodies/payers at launch* identifying incremental effectiveness of a new medicine (compared to current practice) based on clinical trial data and modelling techniques *Demand for post-launch RE studies by HTA bodies/payers* Studies requested by HTA bodies/payers to demonstrate benefits in real world setting	Infrastructure and methods: The extent to which: • improvements in research infrastructures and in the availability of data are made • robust methodologies to analyse evidence produced by RE studies will be developed and agreed by key stakeholders

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THREE RESULTING SCENARIOS

Three scenarios, operating fundamentally on a logic of increasing Europe an co-ordination.….

- Scenario 1: Status quo Little regulatory change. No HTA agreement on methods for clinical assessment, and post-launch studies requested in some countries. Limited regulatory and HTA coordination either pre or post launch.
- Scenario 2 – Some changes Post-authorisation efficacy studies (PAES) implemented. Convergence of HTA methods for clinical assessment but HTA ability to request post-launch studies constrained by role of regulatory. Some regulatory and HTA coordination pre-launch
- Scenario 3 – Major changes; high-trust environment Integrated regulatory system, including AL, applied to a variety of drugs. Convergence of HTA methods for clinical assessment and coordination for demand of post-launch studies (often linked to conditional reimbursement schemes). Joint regulatory and HTA thinking for pre-and post- launch.

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SOME CHANGE SCENARIO "MOST LIKELY"

Regulatory:

- Post-authorisation efficacy studies (PAES) implemented
- CMA used as now in limited cases

HTA bodies/payers:

- Convergence of methods for clinical assessment
- Ability to request post-launch studies constrained by regulatory PAES role

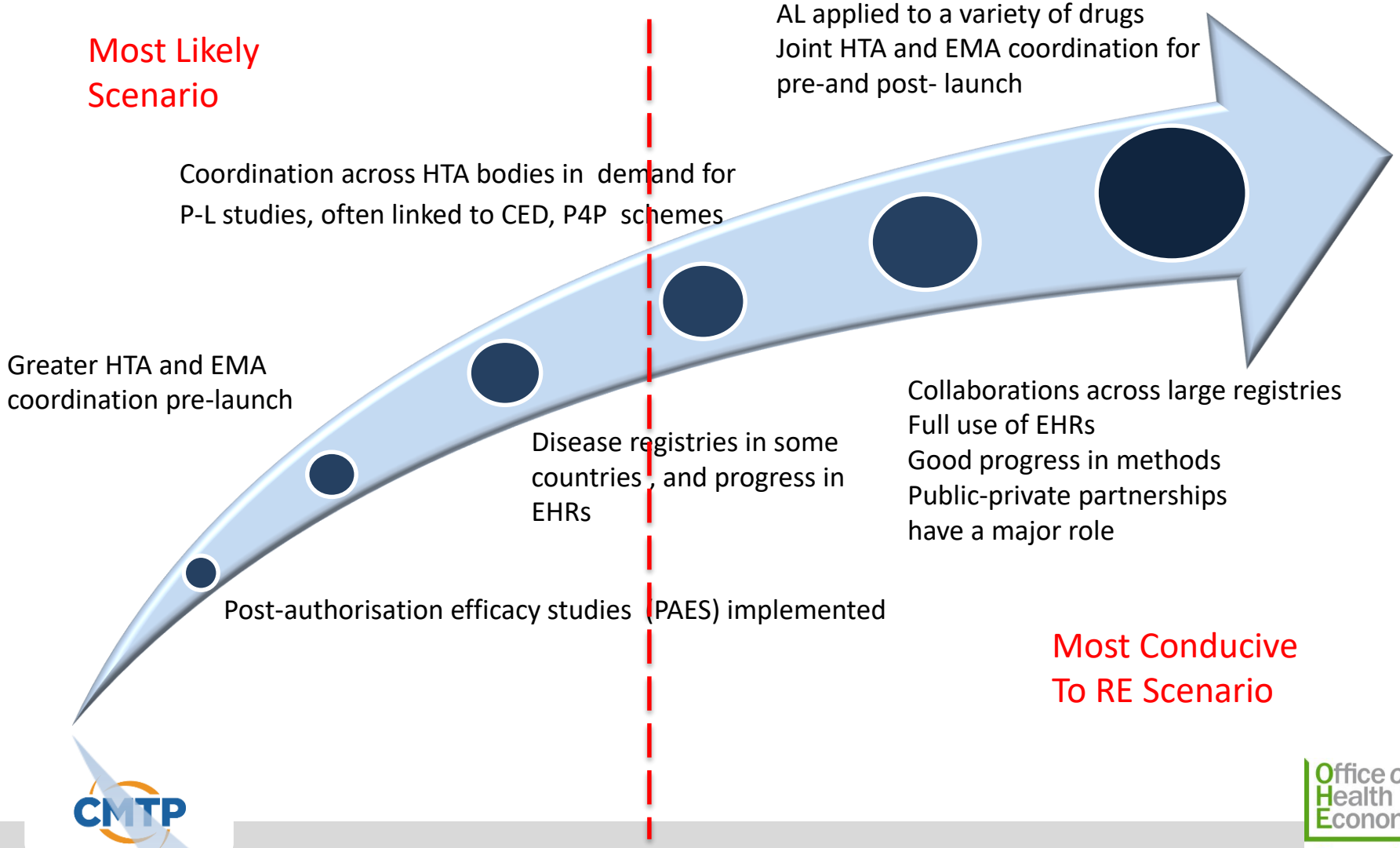
Regulatory and HTA bodies/payers dialogue:

- Some coordination pre-launch but not post-launch

Infrastructures and methods:

- Increased use of disease registries in some countries
- Progress in EHRs
- Limited methods development
- Industry is responsible for financing and conducting studies
- Limited opportunity to identify subgroups/biomarkers pre-launch

MOVEMENT TOWARD HARMONIZATION IN EUROPE



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COMPARING THE CER/RE EVIDENCE ENVIRONMENTS IN THE US AND EUROPE

Adrian Towse and Donna Messner

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US CRITICAL KEY FACTORS IDENTIFIED -- DEFINITIONS

TOP TWO CRITICAL KEY FACTORS	SECOND TWO CRITICAL KEY FACTORS
Integration of Health Systems: Extent to which hospitals, multispecialty care delivery and other services, and coverage become integrated into a comprehensive system for delivering care to members	Big Data: Advancements in technology and techniques to facilitate analysis and utilization of rapidly growing, large repositories of unstructured or semi-structured health information (incl. lab data, information on biospecimens, genomic or biomarker data, etc.)
EHR: Degree to which electronic health records are standardized, in terms of both nomenclature and interoperability, allowing accessibility for research purposes	Role of patients: The degree to which the activities of organized patient groups will impact drug development and expectations for CER

THREE RESULTING SCENARIOS

Three scenarios, operating fundamentally on a logic of increasing health care integration…

  - in a fully integrated system, the provider bears financial risk for most health care services of a patient

- Higher integration scenario – high level of integration; prevalence of risk-based payment models moving towards capitated
- Moderate integration scenario – moderate level of integration; many patients in integrated systems but many still not
- Status quo scenario -- low integration. Fragmentation of payment methods; traditional fee-for-service model widespread. ACOs with incentive bonuses for quality metrics

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MODERATE INTEGRATION SCENARIO "MOST LIKELY"

- Integration: Pop in integrated systems doubled (others in fragmented sys)
  - Within integrated systems, risk for care shifted to HC system away from traditional payers
  - More incentive to look at the long-term outcomes and costs for drugs; but ability to use their own data is partial
  - Contracting with ACOs largely on quality metrics; includes measures of cost
- EMR: Some interoperability in large systems or states; more standardization, but records of a many patients still not captured
- Big Data: Many data sources still poor quality, but increased opportunities
- Patient role: Organized patient groups build networks (PCORI PPRN)
  - work with investigators, statisticians to mitigate bias;
  - collect relevant clinical and patient-reported outcomes from a high proportion of their memberships;
  - embed clinical trials within registries (especially in the rare disease space)

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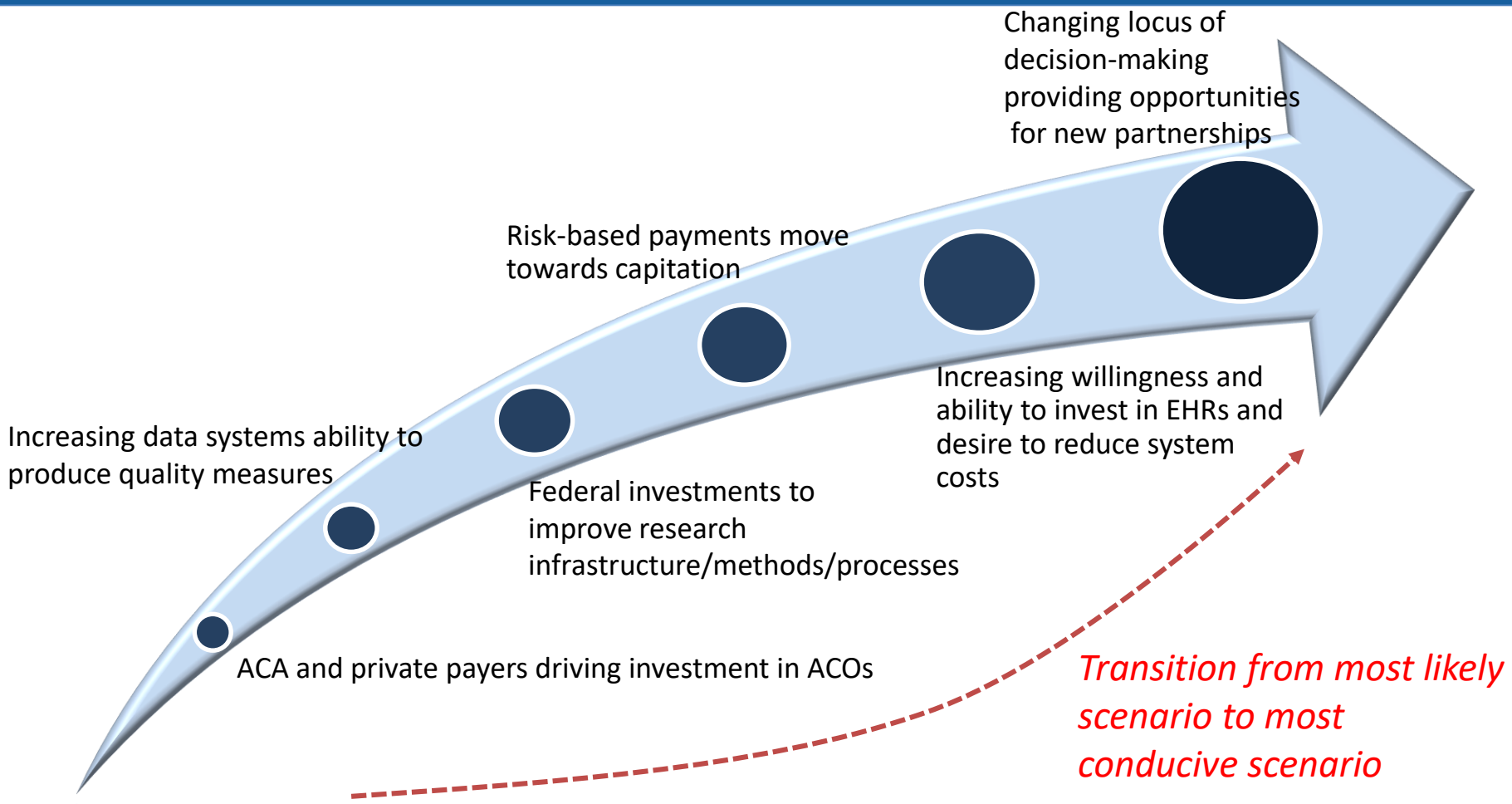
MOVEMENT TOWARD INTEGRATION OF HEALTH SYSTEM IN THE US



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SIMILARITIES BETWEEN US AND EU MOST LIKELY SCENARIOS FOR COMPARATIVE EFFECTIVENESS RESEARCH (CER) AND RELATIVE EFFECTIVENESS (RE) EVIDENCE

- Cost pressures require increasing focus on efficiency and on value.
- Payers/Health Technology Assessment (HTA) bodies will impose greater demands for CER/RE evidence for access, preferential tier placement/favorable pricing; how does this:
  - work in my population?
  - compare with existing alternatives?
  - affect resource use/ cost?
- Payers/HTA bodies will still require Randomized Controlled Trial (RCT) or Pragmatic Controlled Trial (PCT) -based evidence for initial market access.
- Progress on the development of Electronic Health Records (EHRs), patient/disease registries and on creating a more data rich environment.
- Food and Drug Administration (FDA) and European Medicines Agency (EMA) both seeking to achieve earlier licensing of products.
- Policies and incentives to achieve better vertical integration within health systems, together with greater data and evidence sharing between systems.

DIFFERENCES BETWEEN US AND EU MOST LIKELY SCENARIOS FOR COMPARATIVE EFFECTIVENESS RESEARCH (CER) AND RELATIVE EFFECTIVENESS (RE) EVIDENCE

- The US makes greater progress than the EU in creating a data rich environment and exploring the potential of Big Data: conducive for conduct of RCTs in only select systems; largely for higher quality observational research
- Greater US policy focus on and investment in increased capacity to conduct CER. In the US payers/providers conduct Real World Evidence (RWE) research. In the EU, industry is expected to fund/collect RWE.
- EU reduces differences across (national) payer and HTA bodies evidence requirements.
- FDA has no interest in adaptive licensing while the EMA is seeking to implement this.
- EMA and HTA bodies demand active comparators. FDA does not demand active comparators
- Structured scientific interaction between EMA and HTA bodies. No formal process to account for payer evidence needs in early FDA advice.
- US focus on patient-centered research prominent. In EU patient influence is a less important driver.

Futurescapes: expectations in Europe for relative effectiveness evidence for drugs in 2020:
http://www.futuremedicine.com/doi/pdf/10.2217/cer.15.7
Futurescapes: evidence expectations in the USA for comparative effectiveness research for drugs in 2020:
http://www.futuremedicine.com/doi/pdf/10.2217/cer.15.6
The future of comparative effectiveness and relative efficacy of drugs: an international perspective:
http://www.futuremedicine.com/doi/pdf/10.2217/cer.15.8

THE NDDP PROJECT – IMPLICATIONS FOR DRUG DEVELOPMENT

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Get Real

Real-Life Data in Drug Development

Before phase3	During phase3	After Launch
Potential Value	Predict Value of new Medicine	Confirm Value
Background RWE on disease, treatments, care pathways, unmet need etc	Comparative Trials. Pragmatic Trials, giving information on effectiveness More Focussed Context for current care and outcomes to inform initial assessments Evidence Synthesis to combine all sources of information: RCT + PCT + OBS	Post Launch RWE on: use of new medicine, relative effectiveness, longer term outcomes

How much can be done pre-launch?

Or should we get to Post-Launch sooner?

The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no [115303], resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.
www.imi.europa.eu

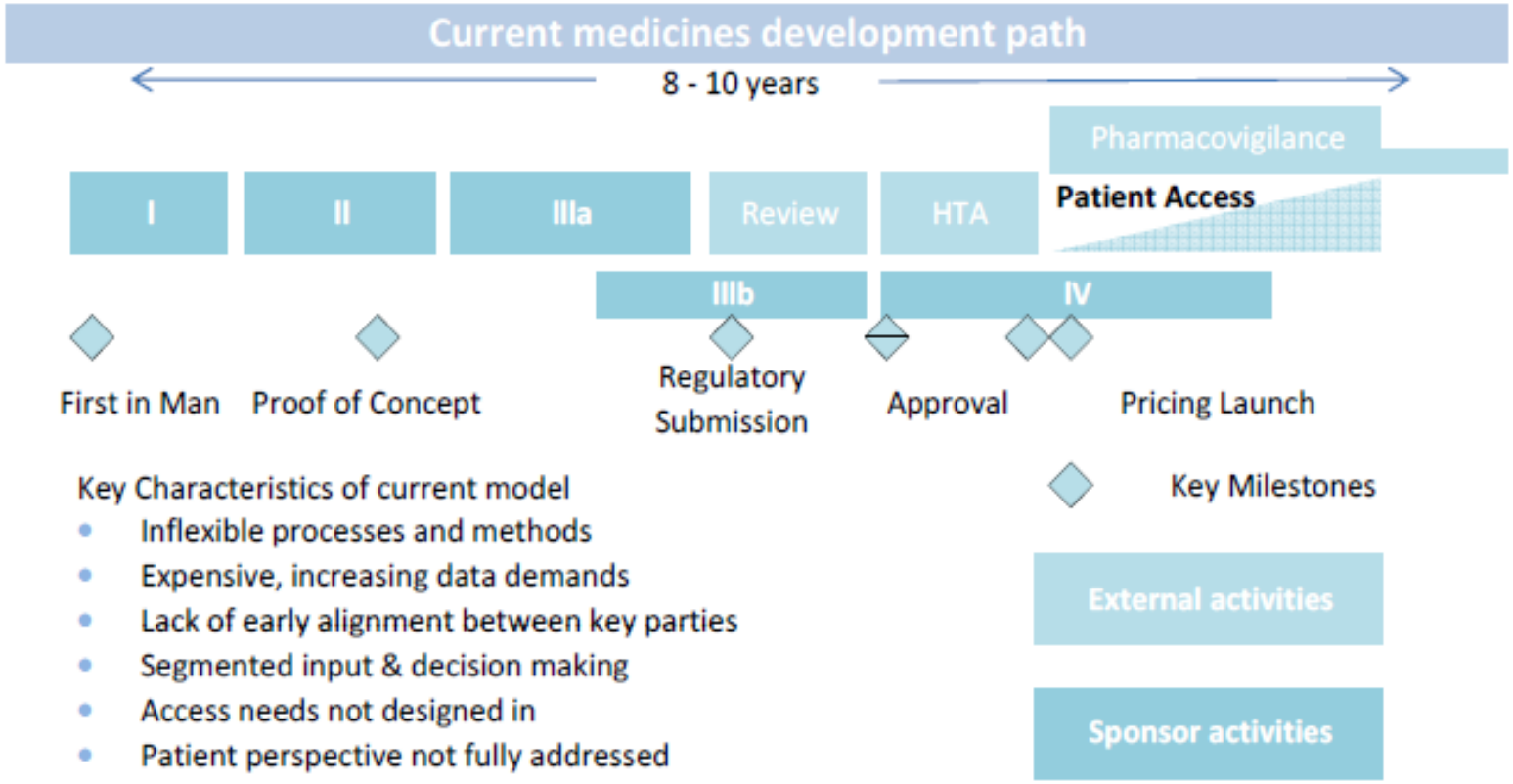
SOME RECENT CALLS FOR CHANGE

PROPOSALS FOR REFORM

- Barker urges industry to move to a “learn and confirm” model
- Orloff et al. argued for a radical redesign to reduce development costs with (i) more use of biological, pharmacological, and statistical modelling and simulation to fine tune study requirements, and (ii) adaptive trial design
- The President’s Council of Advisors on Science and Technology (PCAST) Report recommended reengineering the clinical trials system
- Califf et al. also focused on the need for clinical trials to be integrated into the health care delivery system rather than research and delivery being regarded as separate enterprises.
- EHRs provide a means for both identifying patients for recruitment into clinical trials and for following patients in clinical trials reducing the costs of implementing trial protocols.

PROBLEMS WITH THE CURRENT DRUG DEVELOPMENT PARADIGM

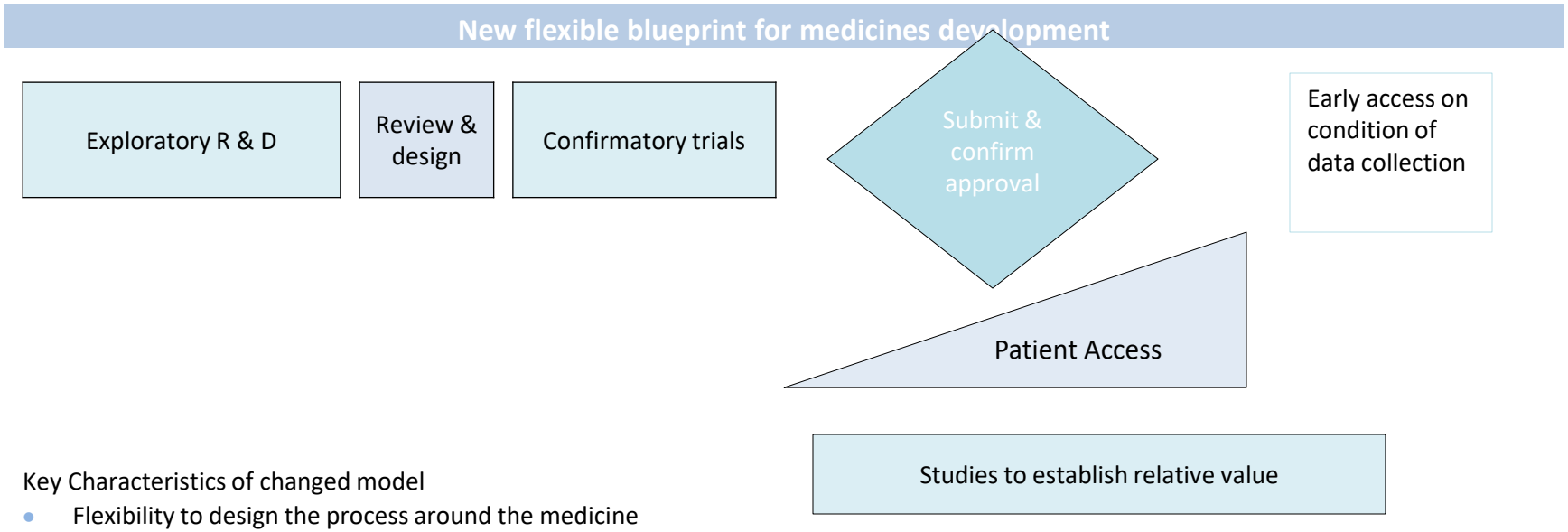
2030 The future of Medicine - Avoiding a Medical Meltdown
Dr. Richard Barker, MA, FRSM



Key Characteristics of current model

- Inflexible processes and methods
- Expensive, increasing data demands
- Lack of early alignment between key parties
- Segmented input & decision making
- Access needs not designed in
- Patient perspective not fully addressed

A FLEXIBLE BLUEPRINT FOR MEDICINES DEVELOPMENT



Key Characteristics of changed model

- Flexibility to design the process around the medicine
- Reduced bureaucracy
- Alignment on approach between regulators and innovators
- Single flow of learning, not fragmented
- Patients perspective and access needs designed in

Source: Barker, R. 2030 The Future of Medicine: Avoiding a Medical Meltdown. 2010

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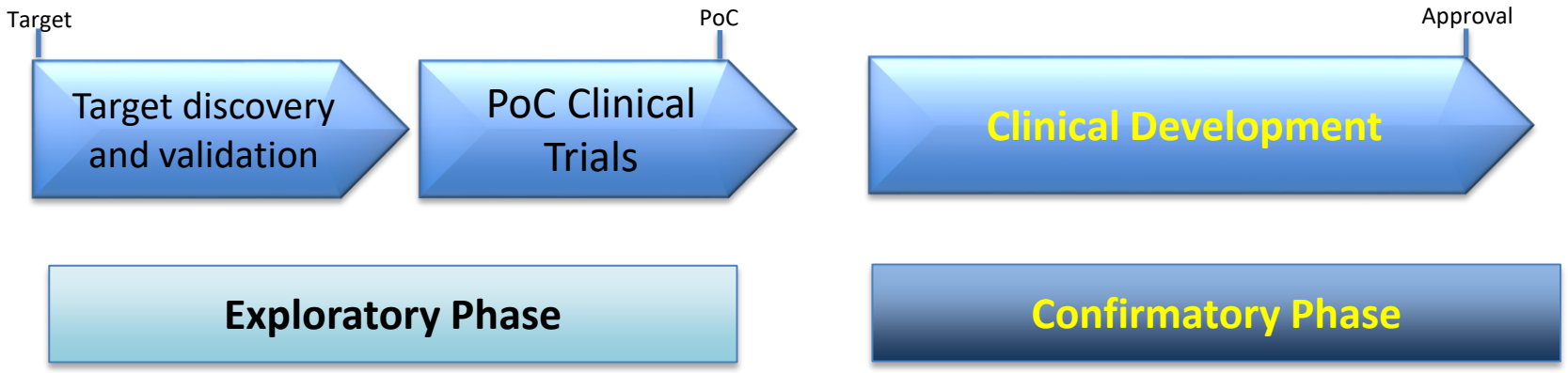
A NOVEL MODEL FOR CLINICAL DEVELOPMENT



- **Apply biomarkers, modeling and simulation and advanced statistical methodology**
- **Demonstrate PoC and establish dose selection**

- Apply innovative tools and clinical trial designs such as adaptive or seamless studies
- Identify target patient populations and confirm optimal dose; establish the benefit/risk ratio

Orloff et al. Nature Reviews Drug Discovery 2009

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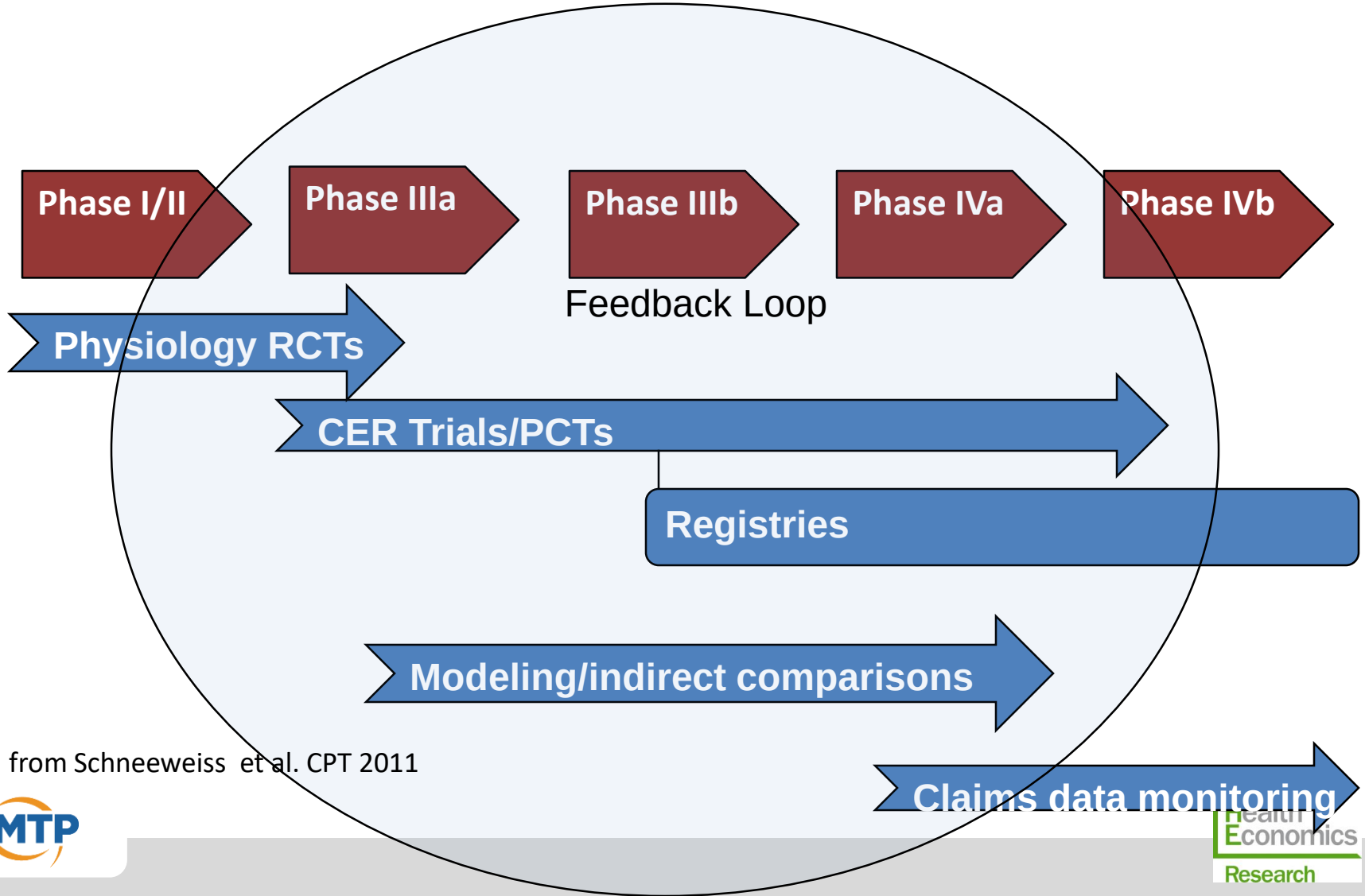
A STRATEGY FOR CER AND MARKET ACCESS



Adapted from Schneeweiss et al. CPT 2011

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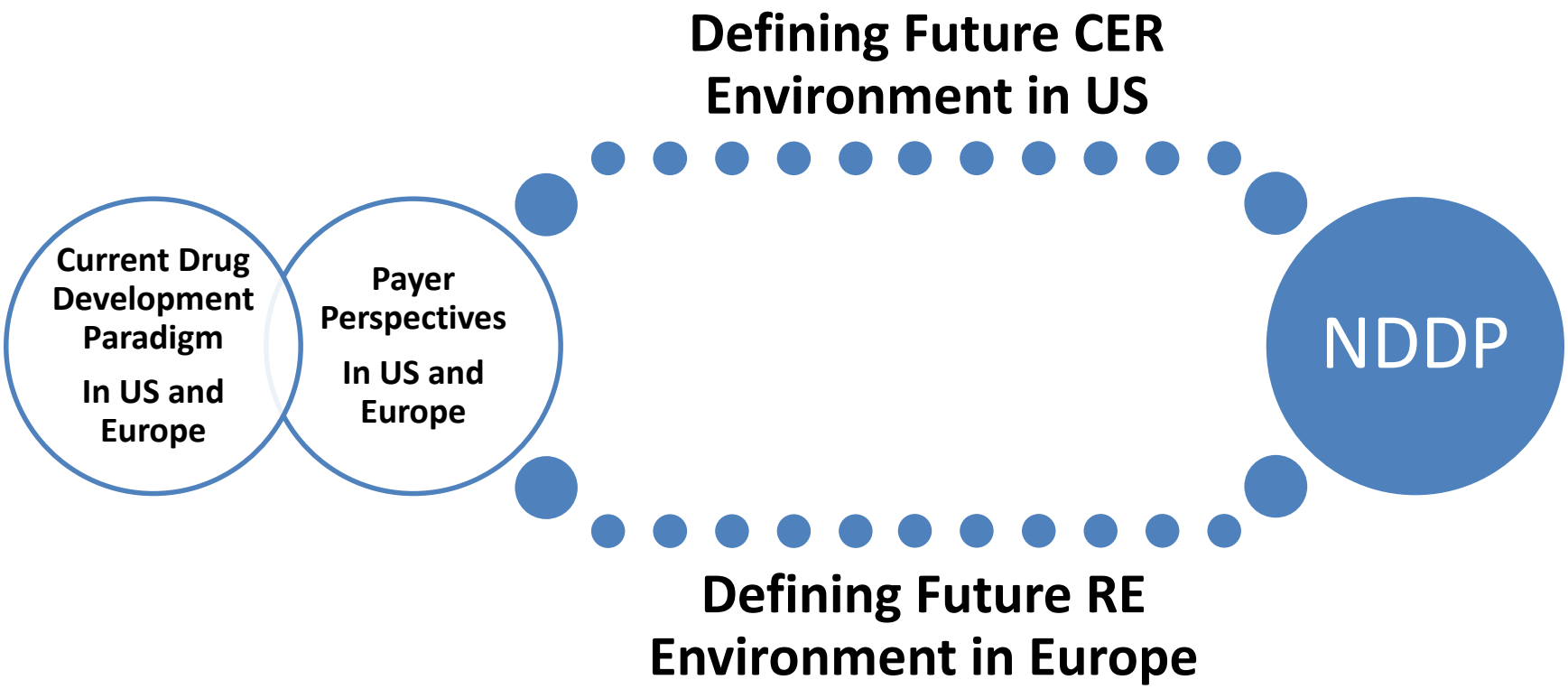
OVERALL PROCESS



WHAT IS NEW ABOUT THE ENVIRONMENT WE DESCRIBE?

- Greater acceptability of enrichment designs and surrogate endpoints for regulatory approval
- Patient-powered research networks and country-sponsored registries
- Selected pockets of healthcare systems and some countries with reliable mechanisms to track patients healthcare use across settings of care and longitudinally through clinically-rich electronic health records
- Greater harmonization between regulatory agencies and HTA bodies in Europe

DEFINITIONS

Term	Definition
Adaptive Design	A design that allows the modification of the trial and/or statistical procedures during the conduct of a trial, based on the review of interim data. The purpose of an adaptive design is to increase the probability of success without undermining the validity and integrity of the trial. (Chow et al. al. 2008)
Confirmatory Trials	As compared to the traditional approach to drug development that separates clinical development into sequential phases, an integrated model aims at improving the effectiveness of clinical development process by increasing flexibility and maximizing the use of accumulated knowledge. In this model, broader, more flexible phases leading to submission for approval are designated 'exploratory' and 'confirmatory' In the confirmatory phase, modern designs, tools and knowledge are applied to larger-scale studies with the goal of identifying the target patient population in which the drug is efficacious, establishing the benefit/risk ratio and confirming the optimal dose and dosing regimen. During this phase, innovative clinical trial designs such as adaptive or seamless studies compress timelines, improve dose and regimen selection, and reduce the number of patients assigned to non-viable dosing regimens.(Orloff et al. 2009)
Exploratory Research	See "Confirmatory Trials" for explanation of the model. During the exploratory phase of development, this model uses all available knowledge and tools, including biomarkers, modelling and simulation, as well as advanced statistical methodology. Trials are designed to determine proof-of-concept (Poc) and to establish dose selection to a level of rigour that will enhance the likelihood of success in the confirmatory phase.(Orloff et al. 2009)
Large Simple Trials	A prospective, randomized controlled trial that uses large numbers of patients, broad inclusion criteria, multiple study sites, minimal data requirements, and electronic registries. Its purpose is to detect small treatment effects, gain effectiveness data, improve external validity. (Peto et al. 1993)
Pragmatic Clinical Trial	PCTs are randomized controlled trials that can rigorously evaluate the risks, benefits, and costs of treatment interventions as they occur in "real-world" settings and for heterogeneous, "real-world" patients. Results can be very relevant to healthcare decision makers. (Chalkidou, et al. 2012).
Proof of Concept Studies	See "Confirmatory Trials" for explanation of the model. During the exploratory phase of this model, trials are designed to determine proof of concept (PoC) and to establish dose selection to a level of rigour that enhances the likelihood of success in the confirmatory phase. (Orloff et al. 2009)
Registry	An organized system that uses non-experimental study methods to collect uniform data (clinical or other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves one or more predetermined scientific, clinical, or policy purposes.
Sequential Cohort Studies	Sequential cohort design begins tracking utilization and resource use through administrative and electronic health record data as soon as a drug gains market access. (Schneeweiss et al. 2011). Sequential cohorts are defined for calendar intervals, such as quarters, in order to balance temporal selection bias that may occur with new use of a drug (e.g., it may be used only in most difficult to treat population at the outset).

PRODUCT ARCHETYPE # 1: BREAKTHROUGH DRUG

A new breakthrough drug of relatively high cost that is effective in a small population of patients who suffer from a common disease but have a specific biomarker identified by a companion diagnostic test

"Supportive data in broader population may be observational (if rigorous) with a strong, plausible biologic case for a broader population."

"If diseases are common, we expect more rigor."
(Demand for RCTs in broader population may depend on therapeutic area & available treatments)

***HTA bodies** – would expect 'prospective' observational study*
***Payers** – would likely restrict coverage to population with predictive marker. May use own data to evaluate "indication creep."*
***ACO** – would consider partnership to study in broader population.*

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PRODUCT ARCHETYPE # 1
BREAKTHROUGH DRUG

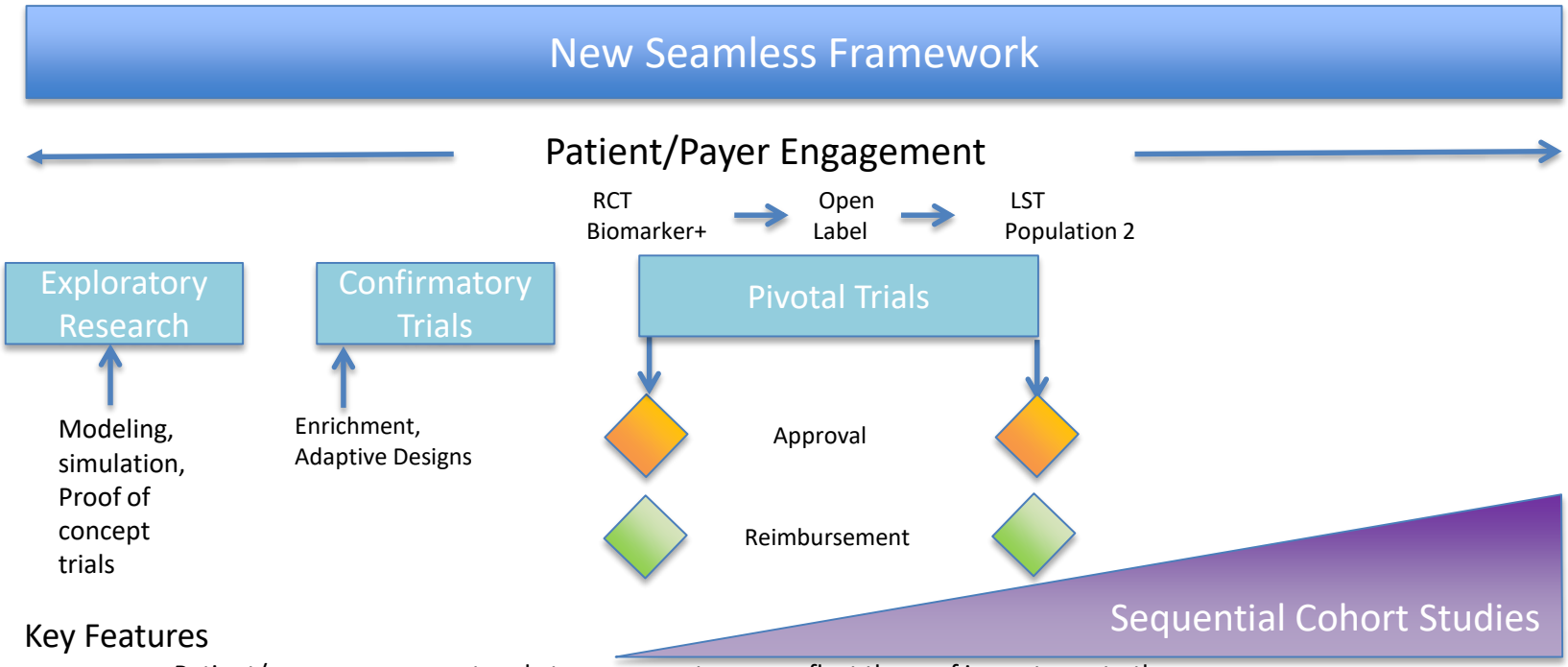
A new drug that is a breakthrough for treating patients who suffer from a common disease, but has been studied only in a small population that has a specific predictive biomarker identified by a companion diagnostic test.

Example:

Lipid-lowering drug studied in patients with familial hyperlipidemia
Ultimate potential use would be statin users in the general population

NEW DRUG DEVELOPMENT PARADIGM FOR 2020: MOST LIKELY SCENARIO FOR CER/RE

Archetype 1: Breakthrough drug studied only in small population with biomarker



Key Features

- Patient/payer engagement early to ensure outcomes reflect those of importance to them
- Smaller targeted trial brings drug to market earlier
- Bayesian/adaptive designs to improve efficiency of trial development throughout the life cycle with clear decision points after each round of evidence development
- Second trial in broader population is large simple trial with focused question
- EMA requirements for post-authorization efficacy studies can be built into the second trial
- Sequential cohort studies initially used to track off-label use; data used to design second trial

Sponsor Activities

Partnerships

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DRUG DEVELOPMENT PROGRAM FOR BREAKTHROUGH DRUG STUDIED ONLY IN A SMALL POPULATION WITH BIOMARKER: MOST LIKELY SCENARIO

Study Design	Phase of Drug Development	Goal
Modeling studies/Enrichment, Adaptive Design Trials	Exploratory Research/Confirmatory Trials	Define the populations in which impact on outcomes is greatest;
Observational Studies/Registry	Exploratory Research	Understand patterns of use in broader population, begin to understand subgroups for additional indications; Patient registry opportunity to explore associations of biomarker with outcomes identify population for enrollment
RCT	First pivotal trial in biomarker positive population	Early market access with small targeted trial measuring surrogate outcome
Observational Studies	Post-regulatory for narrow population	Partner with payers/patient advocacy groups to help them ensure use is consistent with label; better design second trial
LST	Second pivotal trial	Streamlined data collection to enable access to broader population, safety, hard outcomes
Sequential Cohort Studies	Post-regulatory for broader population	Continue partnerships to better define resource/outcome impact for pricing differential

PRODUCT ARCHETYPE # 2: "ME-TOO" NEW DRUG IN CROWDED, COMPETITIVE MARKET

A new drug in a crowded, competitive market for a common chronic disease with a demonstrated effectiveness similar to its competitors. The manufacturer has identified several potential subgroups where the drug may be more effective; however, those subgroup analyses were underpowered and not planned a priori. Of the subgroups examined post hoc, one group was patients who did not improve on their initial therapies

US payers: new drugs with similar effectiveness as competitors would be tiered at the same level

Prefer RCT data with prospectively identified subgroups sufficiently powered to be considered for premium pricing: "Won't accept underpowered subgroup analysis from pharmaceutical industry other than hypothesis generating for more pharma studies."

Peer-reviewed, prospective observational cohort studies may be acceptable, with these caveats:

- *Observational study should follow individuals from original drug trial , compare patients on competitor drugs*
- *Subgroup findings should be consistent with the existing biological argument and supportive of existing knowledge*

Those not accepting observational studies concerned about manufacturers providing the evidence, publication bias and underpowered subgroup analysis

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PRODUCT ARCHETYPE #2: NEW DRUG IN A CROWDED, COMPETITIVE MARKET

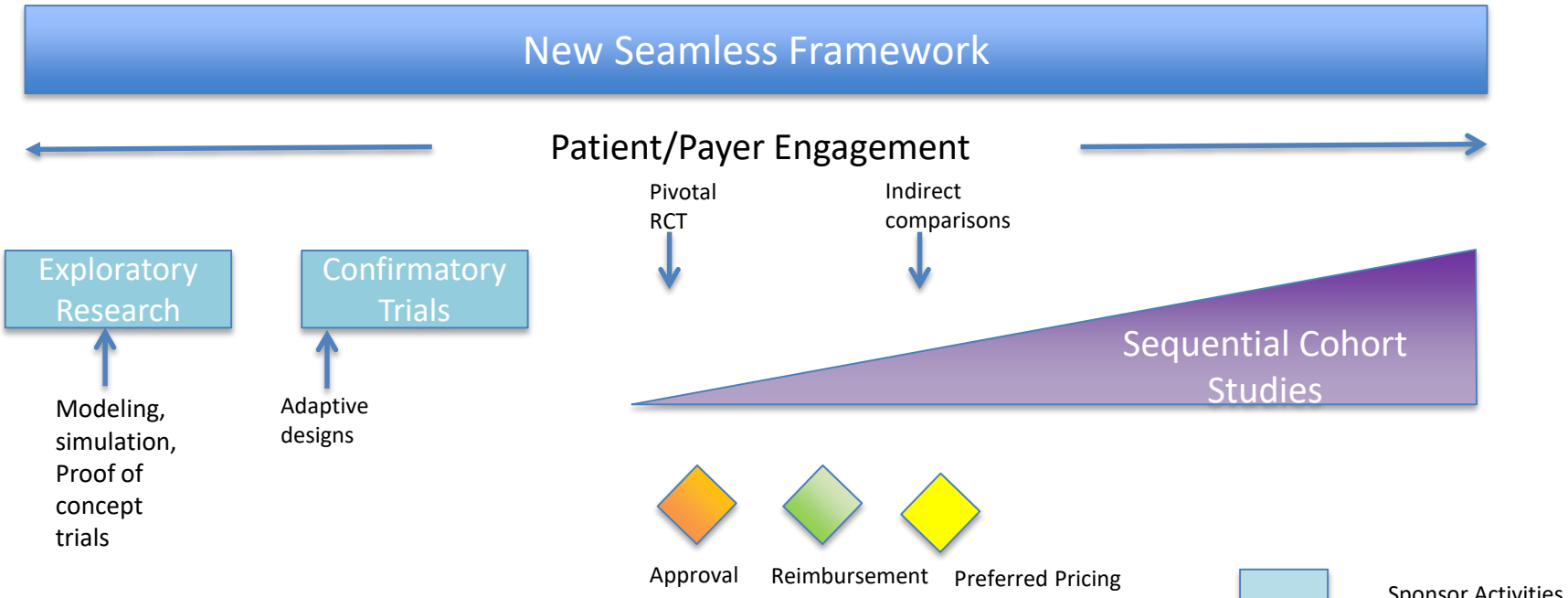
A new drug in a crowded, competitive market (including generic alternatives) for a common chronic disease with a demonstrated efficacy similar to its competitors. The manufacturer has identified several potential subgroups where the drug may be more effective; however, those subgroup analyses were underpowered and not planned a priori. Of the subgroups examined post hoc, one group was patients who did not improve on their initial therapies.

Example:

Rheumatoid Arthritis drug that has the potential to demonstrate superior efficacy in patients who have failed treatment with market leader

NEW DRUG DEVELOPMENT PARADIGM FOR 2020: MOST LIKELY SCENARIO FOR CER/RE

Archetype 2: Crowded competitive market, studied in large population, with potential superiority in subgroup



Key Features

- Patient/payer engagement early to ensure outcomes reflect those of importance to them
- Adaptive designs not just for dosing, but for subgroups with clear decision points after each round of evidence development
- Use of observational data helpful to identify subgroups
- Some potential to partner with payers/health systems for adaptive access in collecting observational data demonstrating improved use of health care outcomes/resources/cost
- EMA requirements for some post-authorization efficacy studies met through observational data

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DRUG DEVELOPMENT PROGRAM FOR A DRUG IN A CROWDED COMPETITIVE MARKET, STUDIED IN LARGE POPULATION, WITH POTENTIAL SUPERIORITY IN SUBGROUP: MOST LIKELY SCENARIO

Study Design	Phase of Drug Development	Goal
Modeling/simulation indirect comparisons	Exploratory Research	Identify appropriate comparators; target effect sizes;
Adaptive designs, RCTs	Confirmatory trials	Begin to understand subgroups with potential for larger effect sizes
RCT (LST?)	Pivotal trial	Come to market with the broadest potential target group
Open label follow up	Post-regulatory	Follow patients originally randomized and compare with observational cohorts to populate indirect comparison models
Indirect comparisons	Post-regulatory	Meet diverse payer needs for different comparators
Sequential Cohort Studies	Post-regulatory	Adaptive access partnerships to identify subgroups for improved tier placement, premium pricing; meet EMA PAES

WHAT TYPE OF CER/RE SHOULD DRUG COMPANIES INVEST IN BY 2020, AT WHAT STAGE OF DRUG DEVELOPMENT?

Payers will still demand randomized studies

-Patient registries will enable better design of trials, faster enrollment, drug companies can help facilitate their development

-Adaptive designs will be more acceptable and will improve efficiency of early phase drug development

-Indirect comparisons will be acceptable when there is biologically plausibility in a crowded market

-A complementary mix of observational studies/modeling to inform trial design and RCT/LSTs should be planned throughout the drug development cycle

WHAT TYPE OF CER/RE WILL EXTERNAL ENTITIES (E.G., FEDERAL, HTA BODIES, HEALTH PLANS) BE INVESTING IN OR EXPECTING BY 2020 THAT WILL IMPACT THE BUSINESS MODEL FOR DRUG DEVELOPMENT?

Federal bodies will invest in methods standards that will help improve quality of observational research;

Health plans/HTA bodies will want pragmatic trials that include: 1) active comparators compared to relevant treatment options; 2) in populations of end users; 3) with clinically meaningful endpoints that answers the question, "How does this new drug impact our bottom line?"

Health plans and some countries in Europe will be collecting more post-market observational data to better understand this.

Drug companies will need to be proactively partnering with health systems, patient and clinician organizations that maintain registries, and state-run registries to enable more efficient, randomized real world trials.

IN MOVING TO THE NDDP, WHAT ARE THE CHALLENGES FOR INDUSTRY?

- **Learn** to do large, cheap simple trials
- **Participate in the development of data policies and architecture** to support more efficient large simple trials
- **Understand when payers are aligned** about a gap in evidence that needs filling
- **Determine the product archetype** in advance; does it target "too broad" a market (archetype 2) or "too narrow" (archetype 1) based on the developmental decisions/compromises that need to be made
- **Define** the questions that need to be answered at each phase of development – the archetype will help drive an evidentiary strategy
- **Conduct more exploratory modeling** Have more discipline about killing projects and more realism about the target population

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