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The Impact of Market Access on the Design of Clinical Trials

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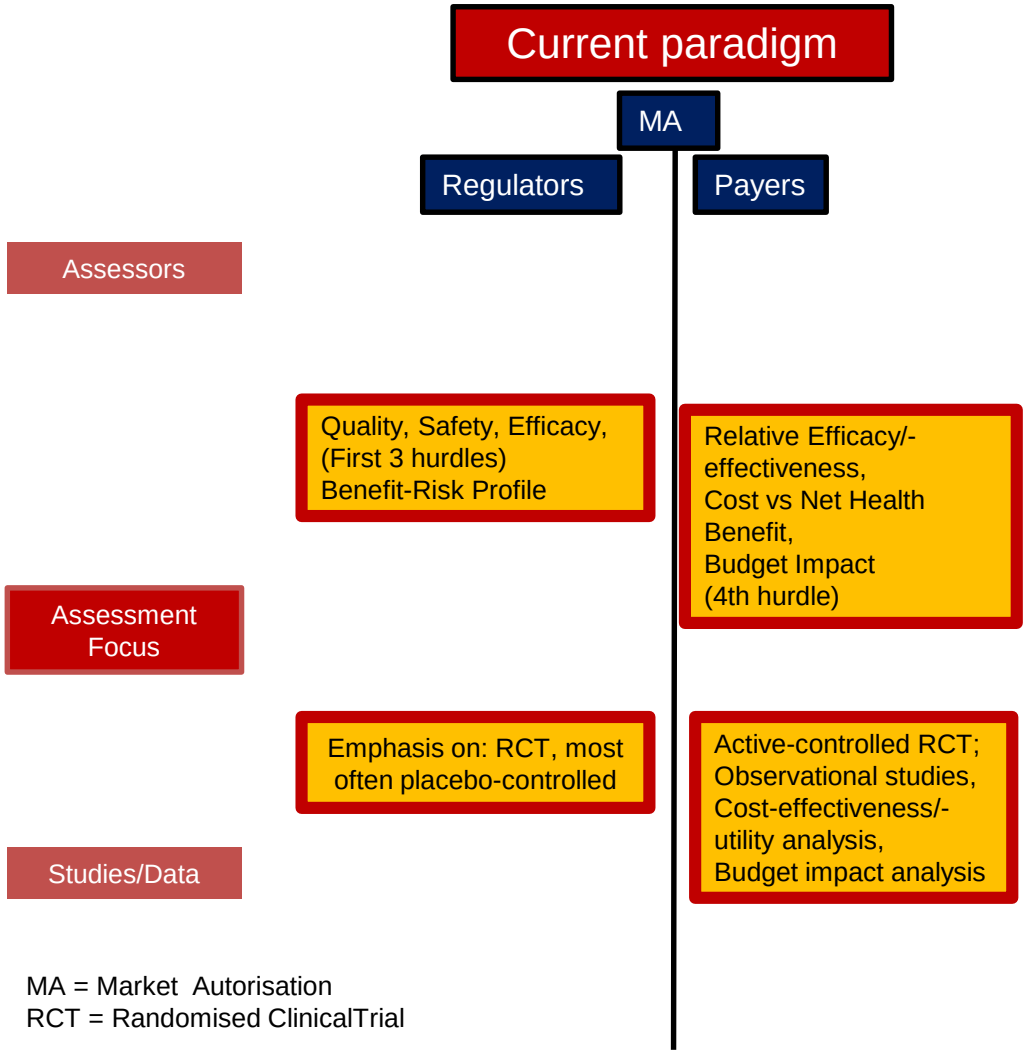
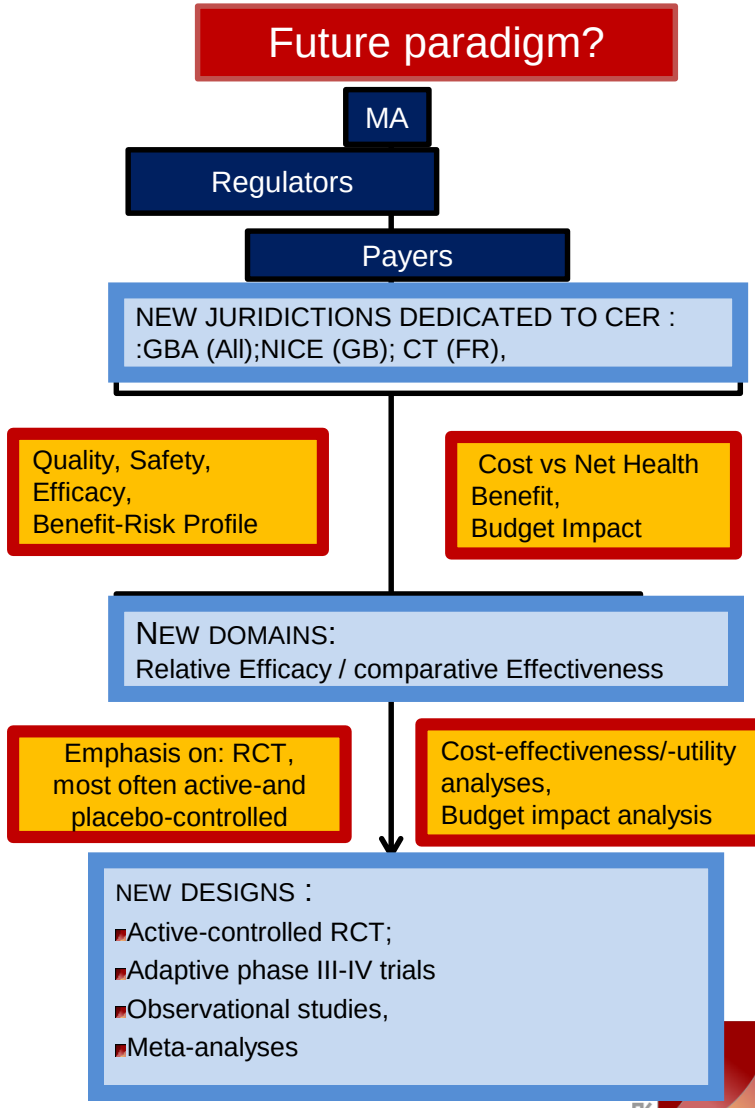
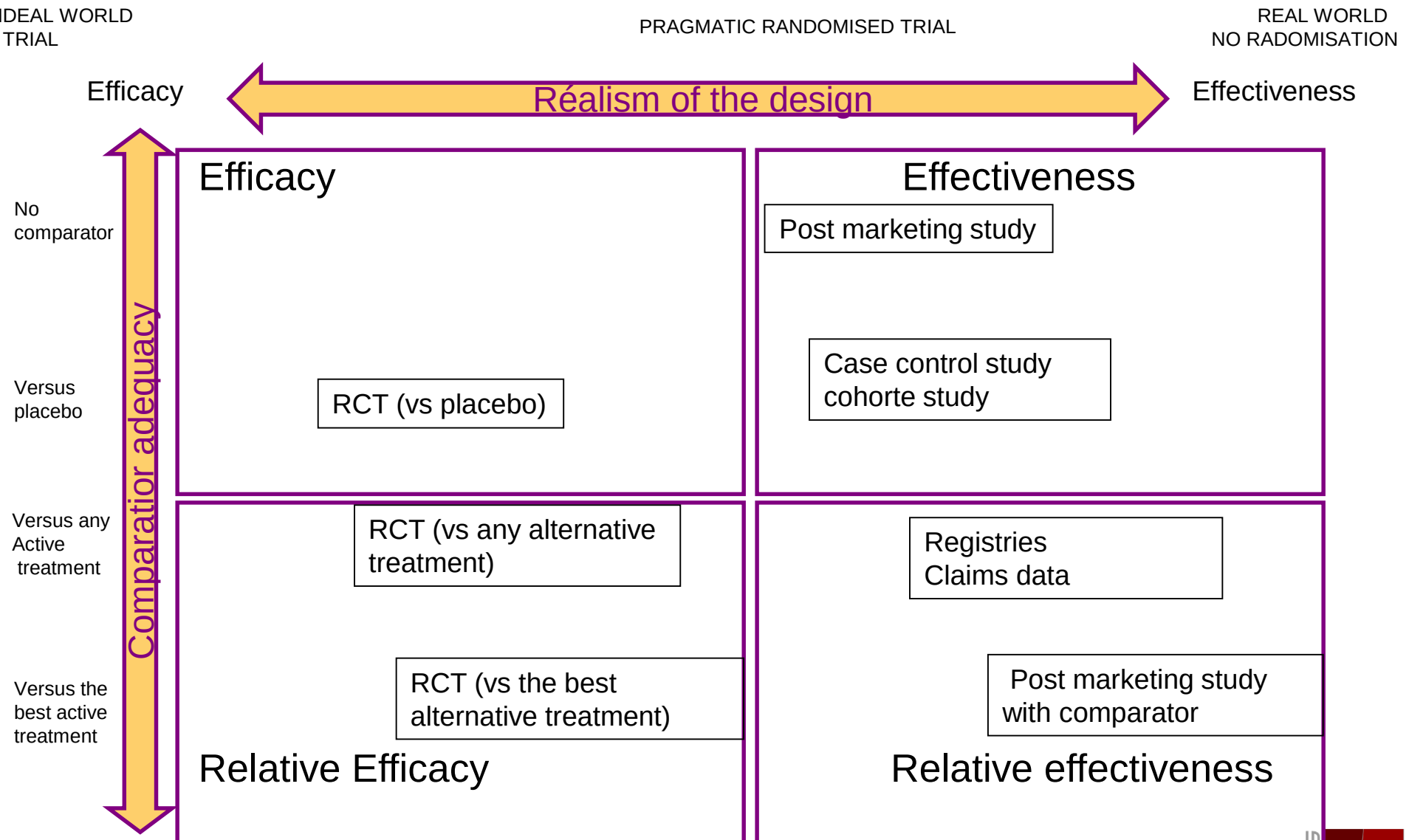
How to Help The Payer To Make a Decision ?

Thomas Lönngren : Executive Director EMA Ministerial Conference "Innovation and Solidarity on Pharmaceuticals" Brussels –23 & 24 September 2010





Efficacy vs Effectiveness



Source: hight level pharmaceutical forum 2005-2008

Definitions

by the High Level Pharmaceutical Forum

- **Efficacy** is the extent to which an intervention **does more good than harm under ideal circumstances.**

- **Relative Efficacy** is the extent to which an intervention does more good than harm **compared to one or more alternative interventions under ideal circumstances**

- **Effectiveness** is the extent to which an intervention does more good than harm **when provided under the usual circumstances of health care practice**

- **Relative Effectiveness** is the extent to which an intervention does more good than harm when provided under the usual circumstances **compared to one or more intervention alternatives**

The Evolving Interface Between Regulators and HTA

Licensing: Benefits and Risks	Relative Efficacy Assessment	HTA: Cost and Health consequences

HLPF report: « distinction between […] relative effectiveness of medicinal products and health-economic assessments ».

« The REA(CER) paradigm »

Looking for a Compromise Between Timely Access and Robust Evidence

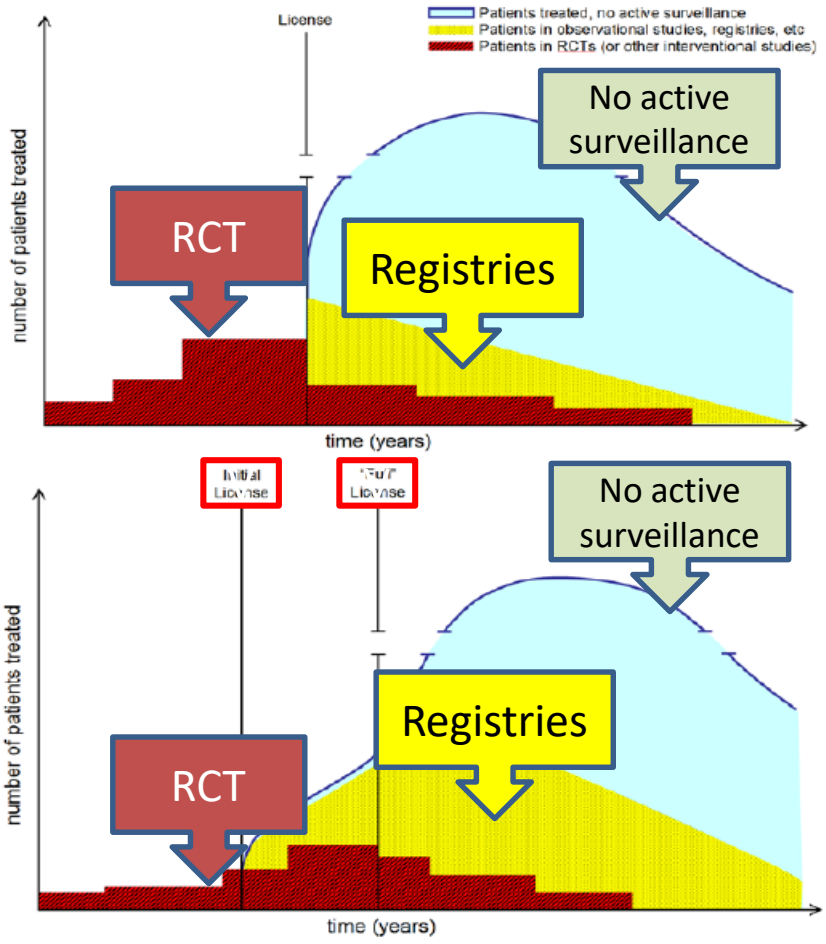
- Enrichment strategies : **The targeted approach** : one of the keys to lowering drug development costs. In lung cancer the FDA has been able to move from classifying the disease from what can be seen under the microscope to looking at the patient molecular profile and treating the cancer by specific subtype..
- Surrogate endpoints : Between 2010 and 2012, **94 new drugs** obtained traditional approval of the FDA, **45** of which were approved on the basis of a surrogate endpoint. Once a surrogate is well established, it can be used in traditional approval and accelerated approval is no longer required.
- Master Protocols : It is **not necessary to reinvent the wheel** every time a new clinical trial begins. Master protocols create a single clinical trial that can test many drugs at the same time. The lung cancer protocol Lung-map is a good example of a less costly paradygm for developping drugs.
- Flexible designs : **Single-arm studies** are accepted by the FDA when the patient population is small, the natural history of the disease well characterized, the drug's beneficial effects are large

REES
Réseau d'Evaluation en Economie de la Santé

Blurring the Distinction Between Pre and Post Commercialisation

- Additional approval pathways
  - Fast tracked : Drug intended to treat serious conditions and « **non clinical or clinical data »** demonstrates « **potential to address unmet needs ».**
  - Breakthrough therapy designation : Drug intended to treat serious conditions. « **Clinical evidence** demonstrates **a huge improvement on key endpoint over available therapy »**
  - Accelerated approval : Drug intended to treat serious conditions and **demonstrates an effect on surrogate endpoints**, which is **likely to predict clinical benefit** or demonstrates an effect on a clinical endpoint measured earlier than morbidity or mortality indicators.
  - Priority review : Drug intended to treat serious conditions and if **approved would provide a serious improvement** in effectiveness and safety.

From RCT to Toolkit for Evidence Generation



Current scenario:

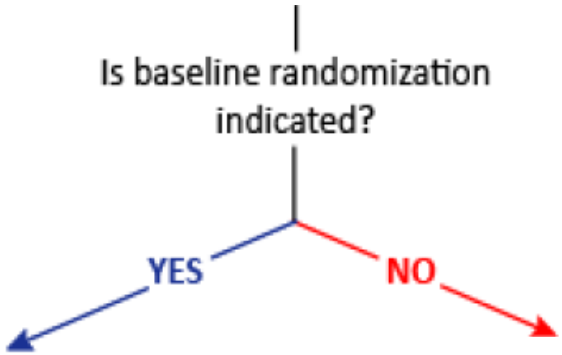
Post-licensing treatment experience of many patients does not contribute to evidence generation

Adaptive Licensing:

After initial license, patient experience is captured to contribute to real-world information

Hans-Georg Eichler CPT 2012

The Tool Kit for Evidence Generation



From the PCORI Methods Committee report

Is baseline randomization indicated?

YES-Prefer **baseline randomization** for:

- high validity in the presence of strong baseline confounding
- if no ethical issues prevent randomization
- if sufficient resources available
- if enough time available to await results

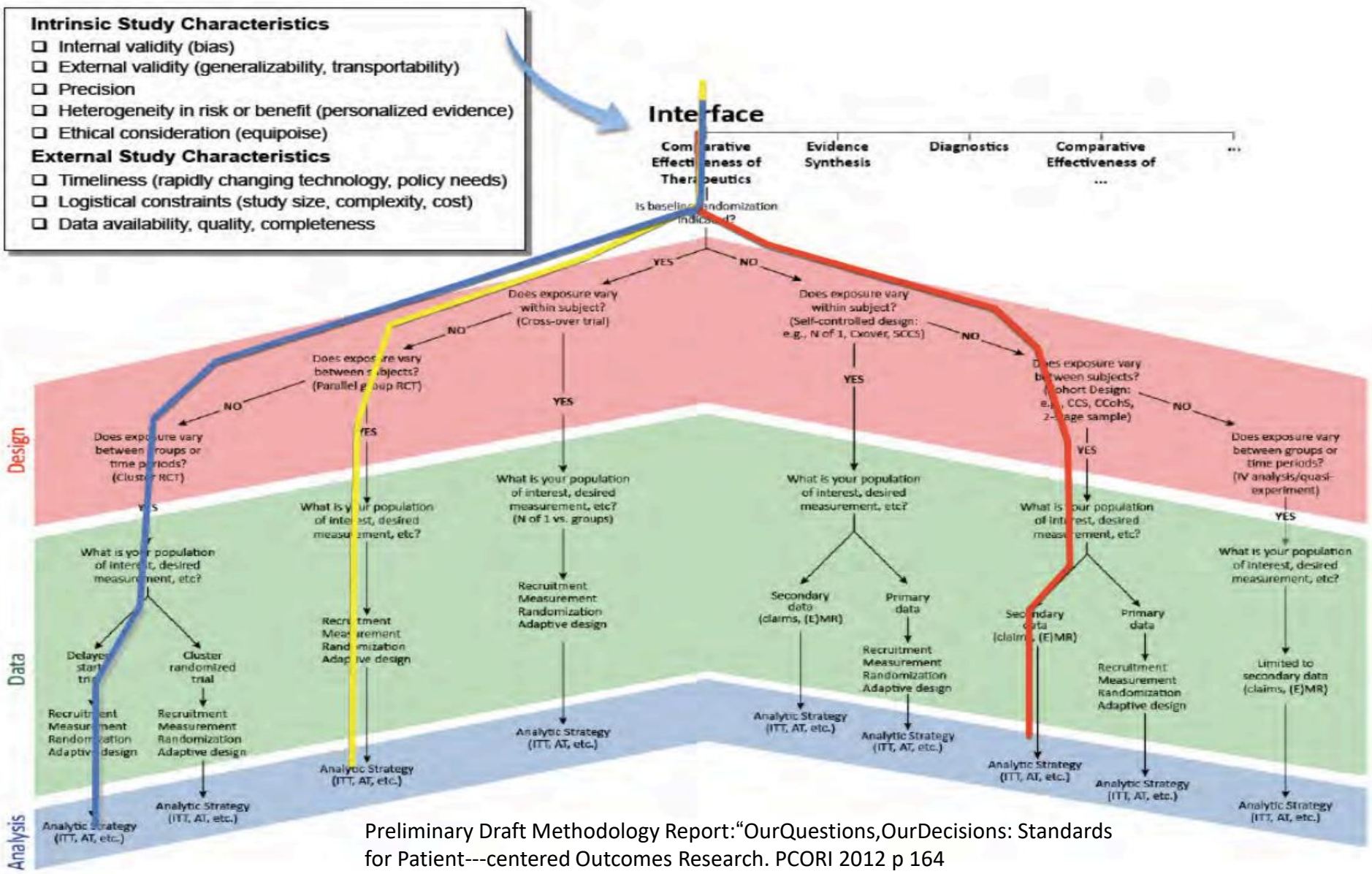
NO-Prefer **observational study** for:

- high representativeness for "routine care" by not perturbing the care system
- Need good reason to believe that confounding can be controlled through adjustment

Helpful references include:

Rothwell PM Lancet 2005
Miler FG & Joffe S NEJM 2001
Concato J PDS 2012

PCORI's Standards [2012]



Preliminary Draft Methodology Report:"OurQuestions,OurDecisions: Standards for Patient---centered Outcomes Research. PCORI 2012 p 164

Evolution of Post Marketing Activity

Benefits

RCT's in context of conditional approval

Payers requirements: coverage with evidence development→ relative (comparative) effectiveness

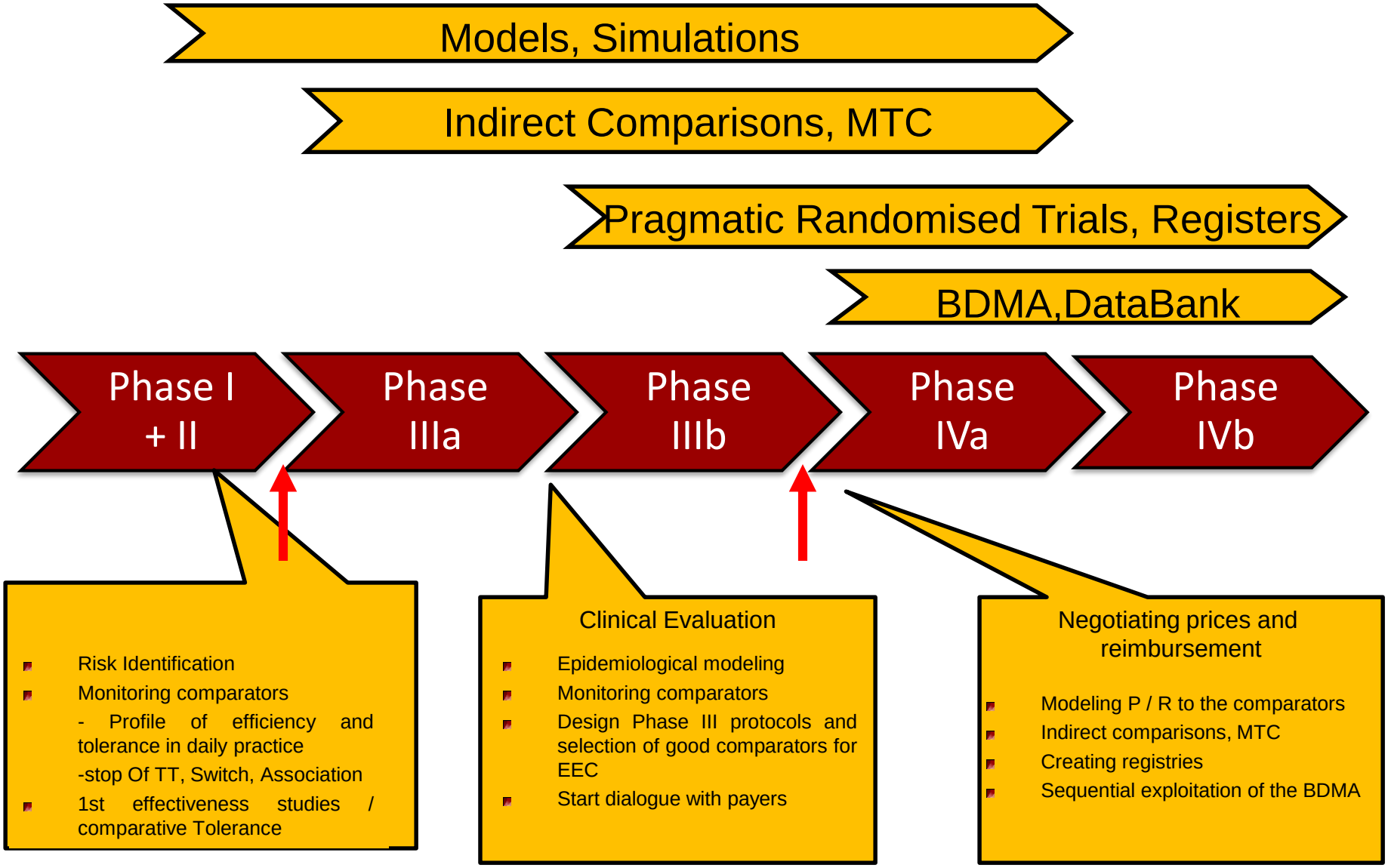
Risks

Spontaneous reporting

Active surveillance
EU:Risk Management Plans: Registries, Observational studies (eMedical Records)
LST's : Large Simple Trial

Integrated assessment of clinical outcomes (the good and the bad)→ relative effectiveness: EU PAES

No Single Approach Fulfill All Possible Needs for CER Information

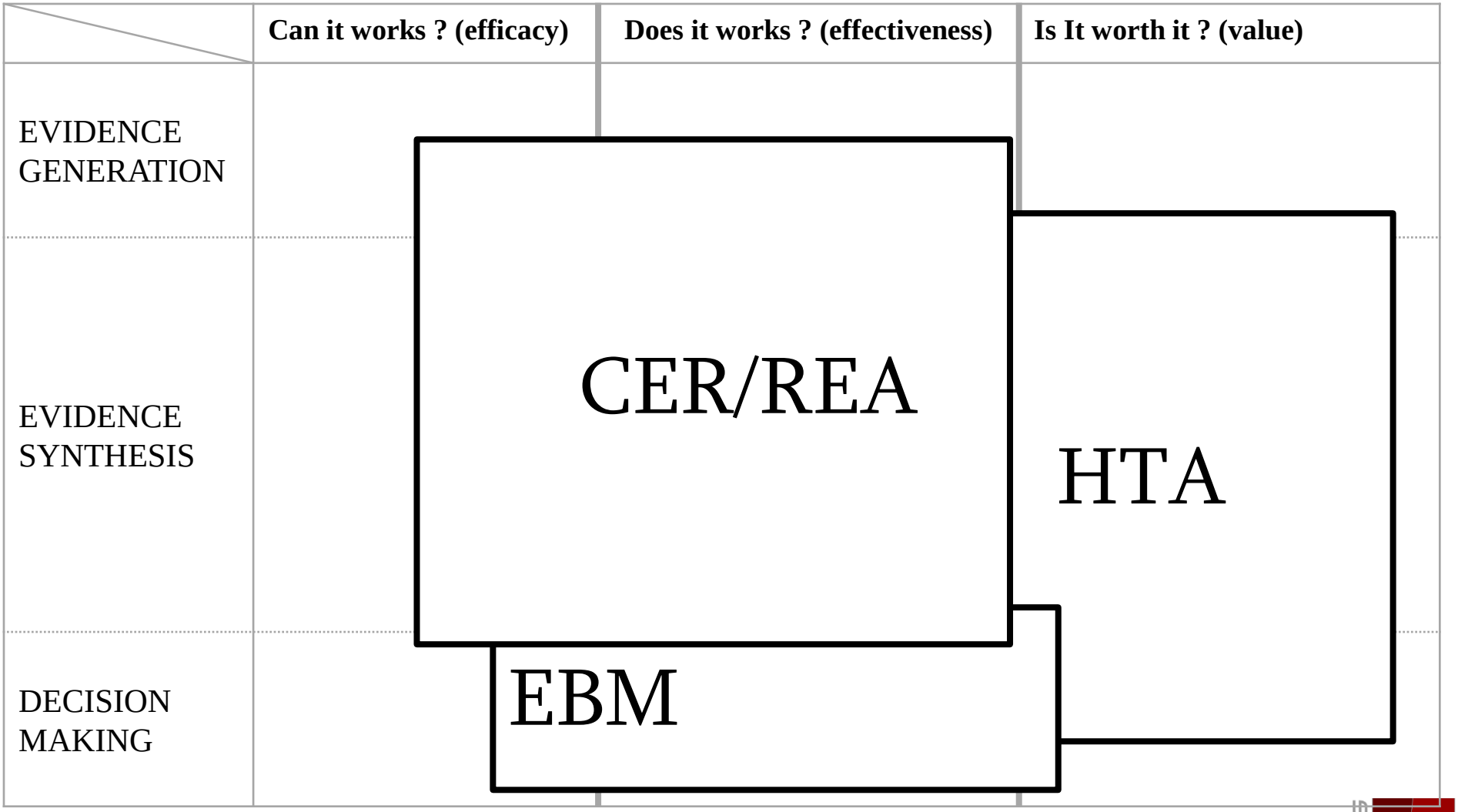


S.Schneeweiss Clinical Pharmacology & Therapeutic 2011

What will change with adaptive pathways?

- Focus on licencing → Focus on patient access
- Magic moment → Life cycle management
- Big population → small population
- RCT only → all designs
- Prevision → Monitoring
- Open utilisation → Managed utilisation

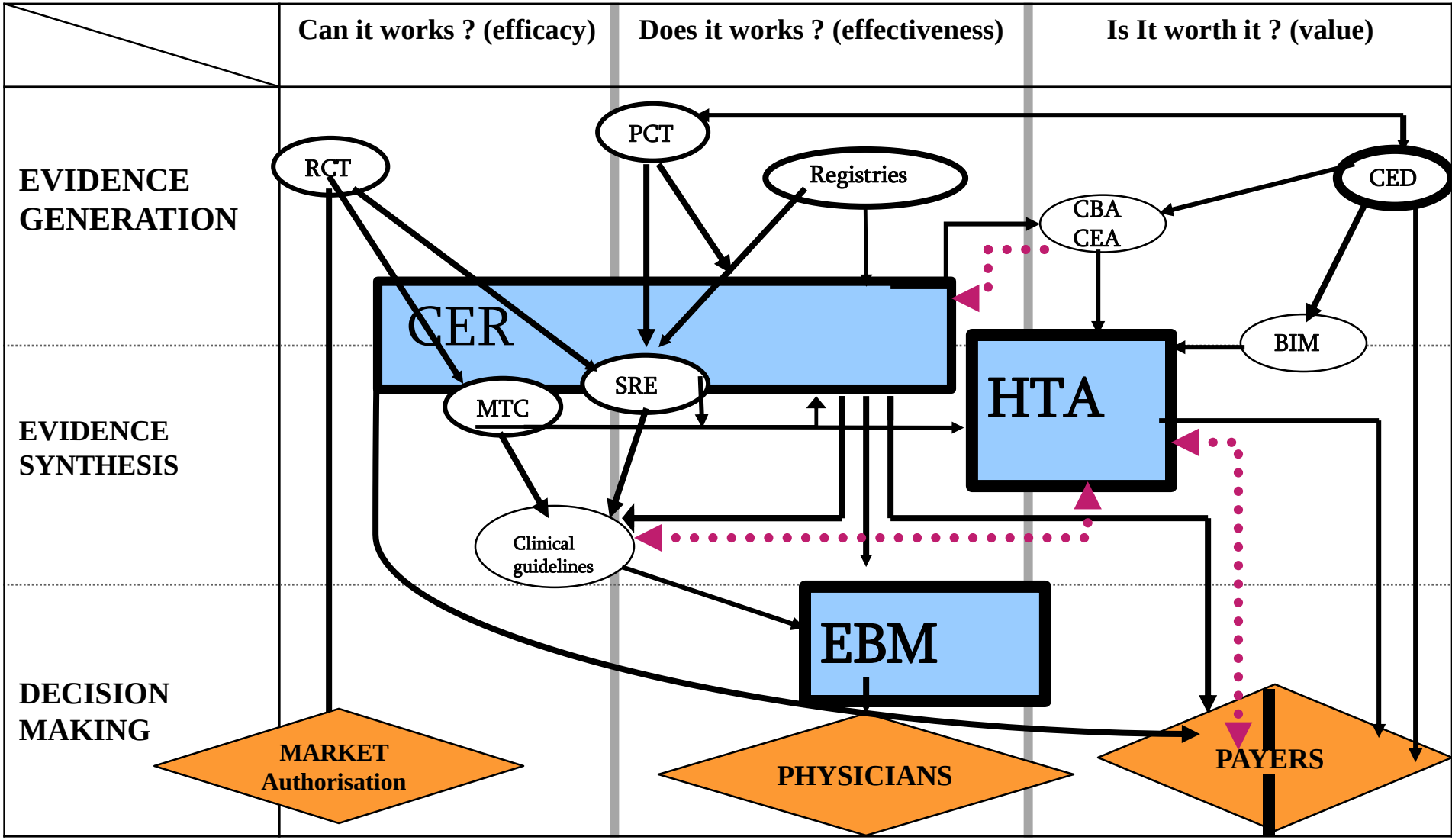
An Organising Framework



Bryan Luce et al International Working Group for HTA advancement 2010

REA (Relative Effectiveness Assessments) ; EBM : Evidence Based Medecine; HTA : Health Technology Assessment .

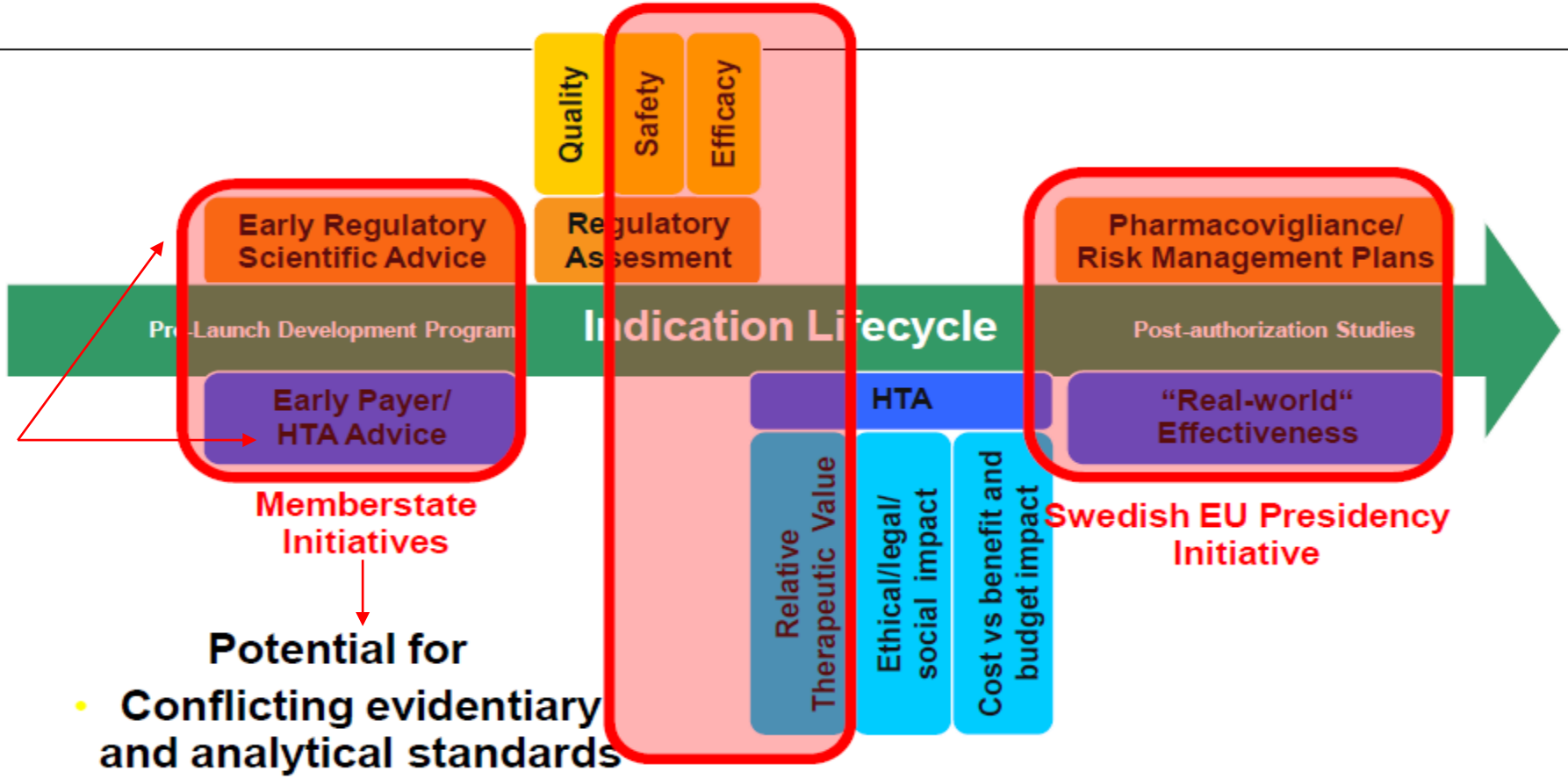
What Kind of Evidence : CER, EBM, HTA?



REA: Relative Effectiveness Assessments, HTA Health technology assessment ; EBM : Evidence based medecine RCT : Ramdomized clinical trial ; PCT pragmatic clinical trial ; MTC : Mix treatment comparison- ; SRE: Systematic review of evidencee ; CED : Coveragel e with evidence development; Relations controversées

Adapté de Bryan Luce et al International Working Group for HTA advancement 2010

The EUnetHTA Project: A Chance or a Threat For HealthEconomic ?



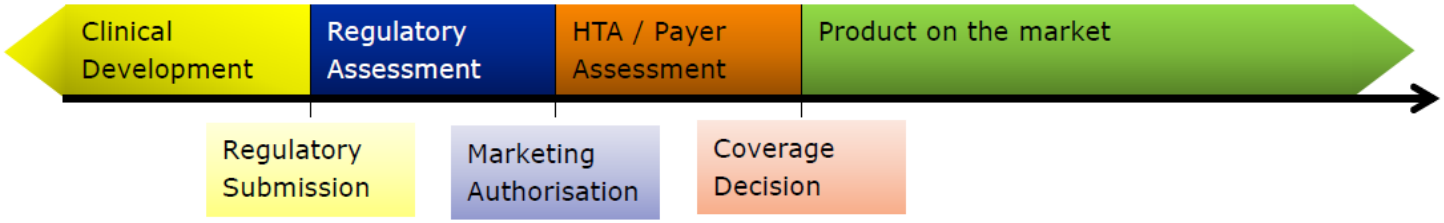
Blurring the Distinction Between Pre and Post Commercialisation

- Conditional marketing autorisation Orphan medicinal products, autorisation intended to be converted into regular autorisation once all data are available
- Autorisation under exceptional circumstances Orphan drugs used in rare patient populations, normally it would never be possible to collect full data.
- Accelerated review For drugs of major interest in terms of public health

A System Approach

Comprises the entire life-span:

Development → licensing → coverage → utilization → monitoring



Adaptive Licensing → Adaptive Pathways