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# The Impact of Market Access on the Design of Clinical Trials

Prof. Robert Launois

**28, rue d'Assas**

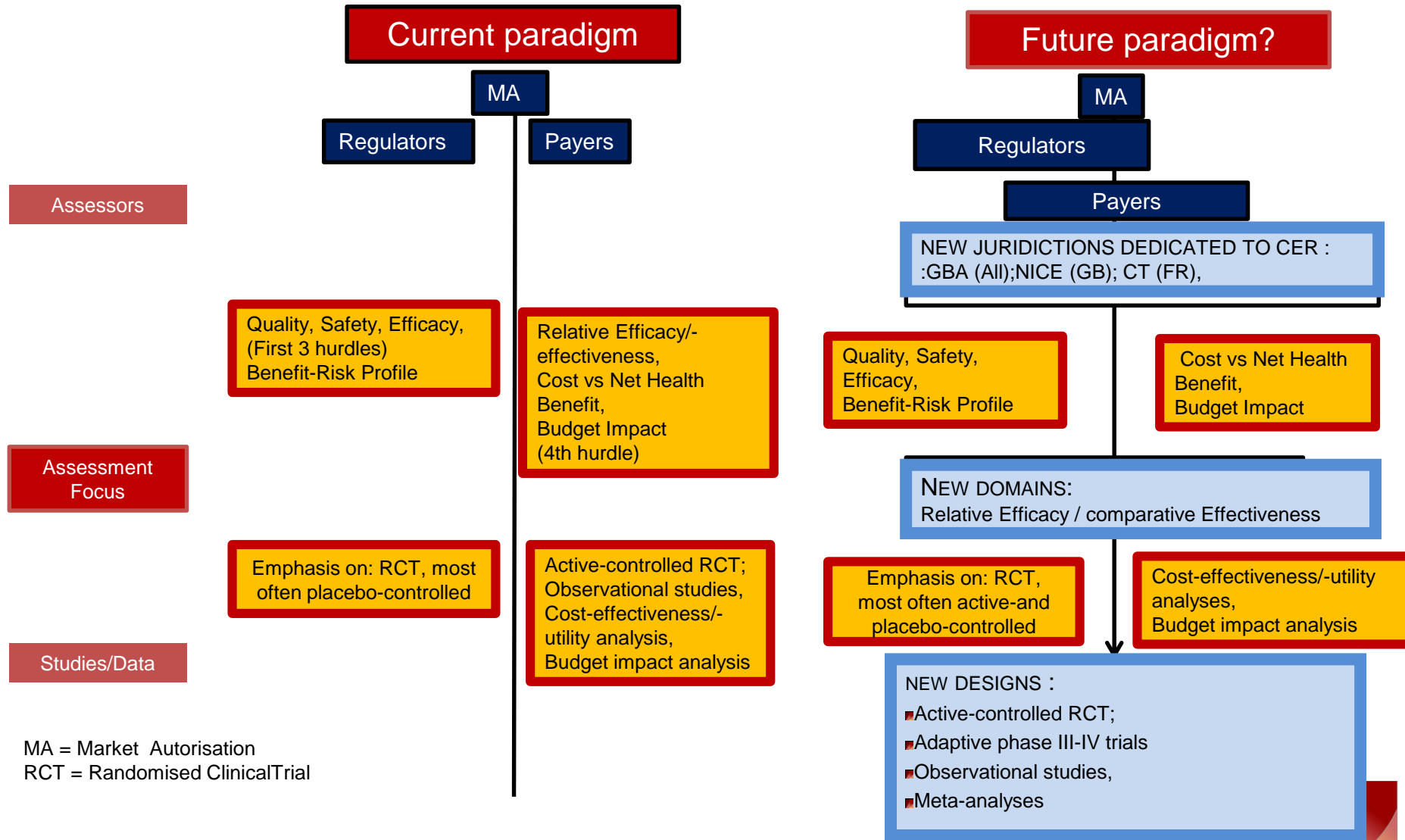
**75006 Paris – France**

Tel . 01 44 39 16 90 – Fax 01 44 39 16 92

E-mail : [reesfrance@wanadoo.fr](mailto:reesfrance@wanadoo.fr) - Web : [www.rees-france.com](http://www.rees-france.com)

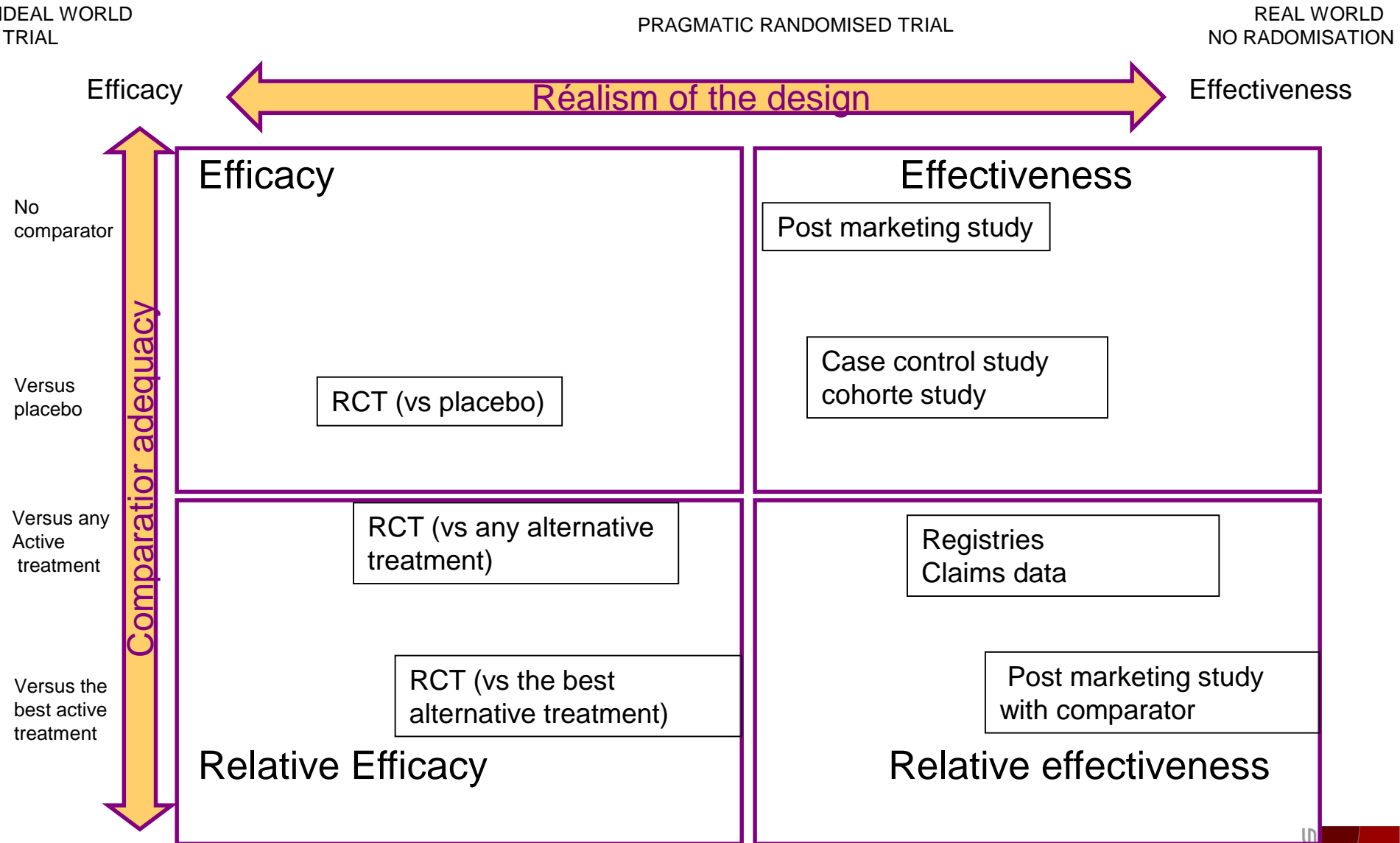
# How to Help The Payer To Make a Decision ?

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



MA = Market Authorisation  
RCT = Randomised Clinical Trial

# 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 paradigm for developing 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**

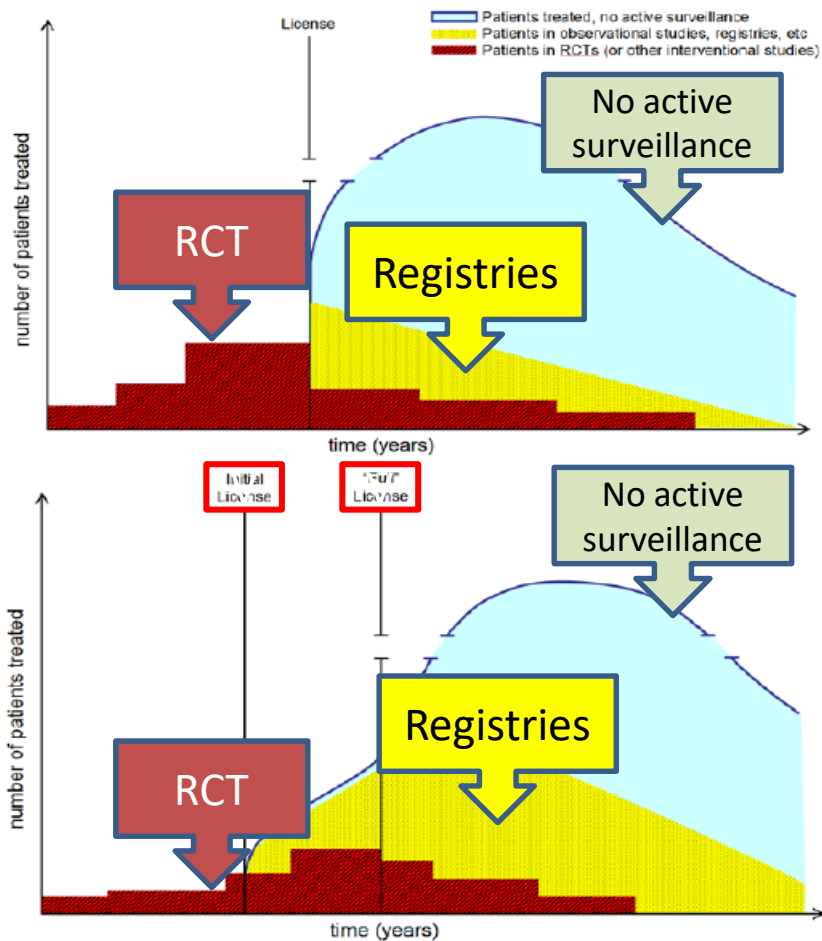


# Blurring the Distinction Between Pre and Post Commercialisation

## ✦ 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

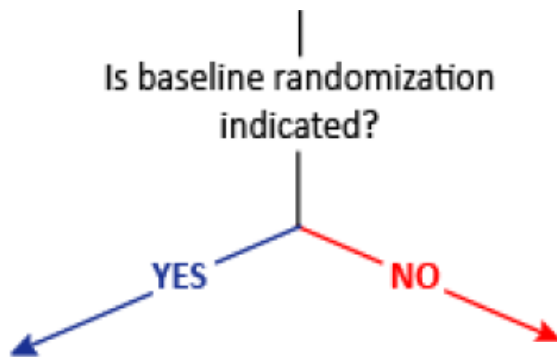
## Adaptive Licensing:

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





# The Tool Kit for Evidence Generation



## 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

Miller FG & Joffe S NEJM 2001

Concato J PDS 2012

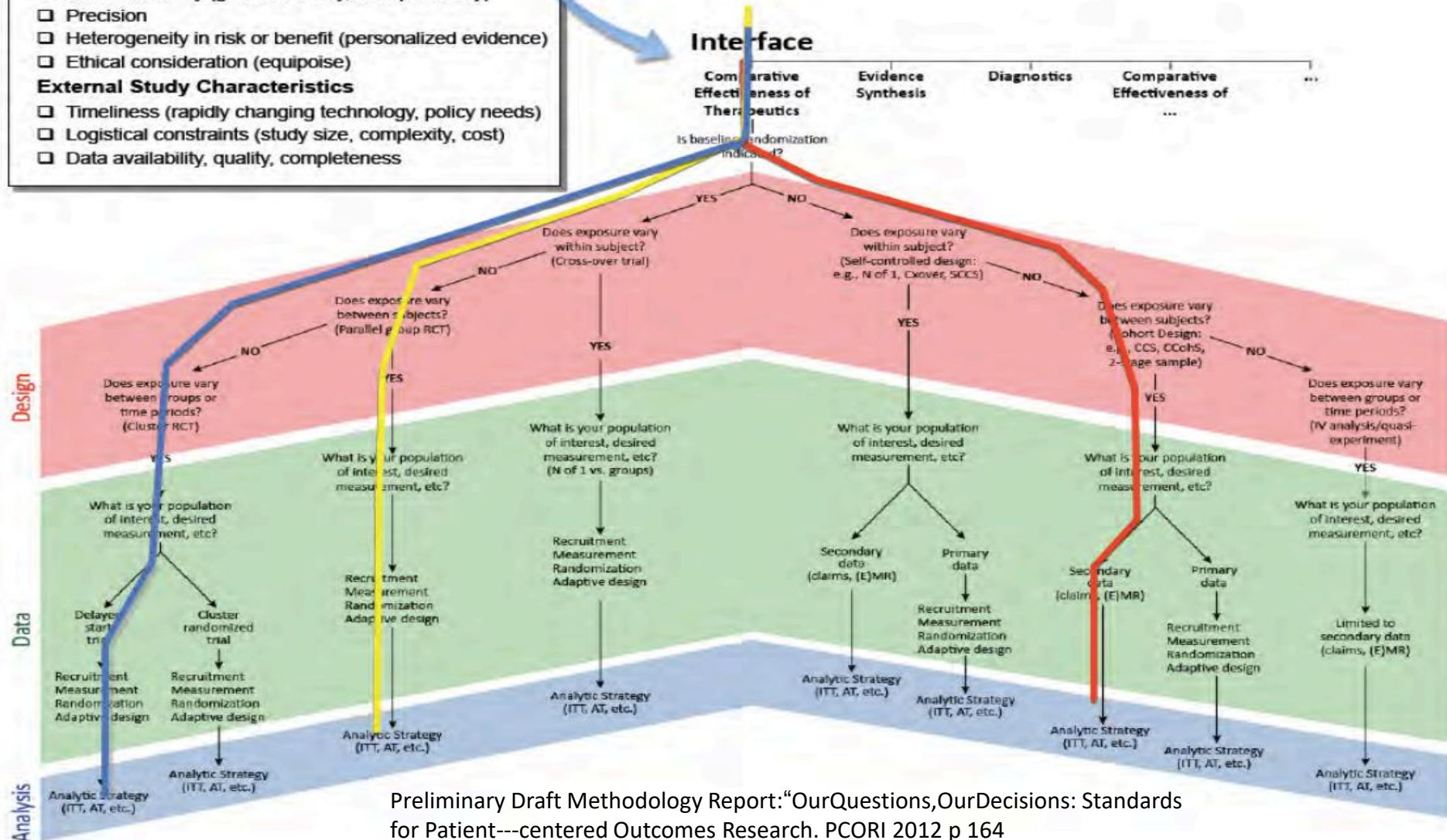
# PCORI's Standards [2012]

## Intrinsic Study Characteristics

- Internal validity (bias)
- External validity (generalizability, transportability)
- Precision
- Heterogeneity in risk or benefit (personalized evidence)
- Ethical consideration (equipoise)

## External Study Characteristics

- Timeliness (rapidly changing technology, policy needs)
- Logistical constraints (study size, complexity, cost)
- Data availability, quality, completeness



# Evolution of Post Marketing Activity

## Benefits

RCT's in context of conditional approval

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

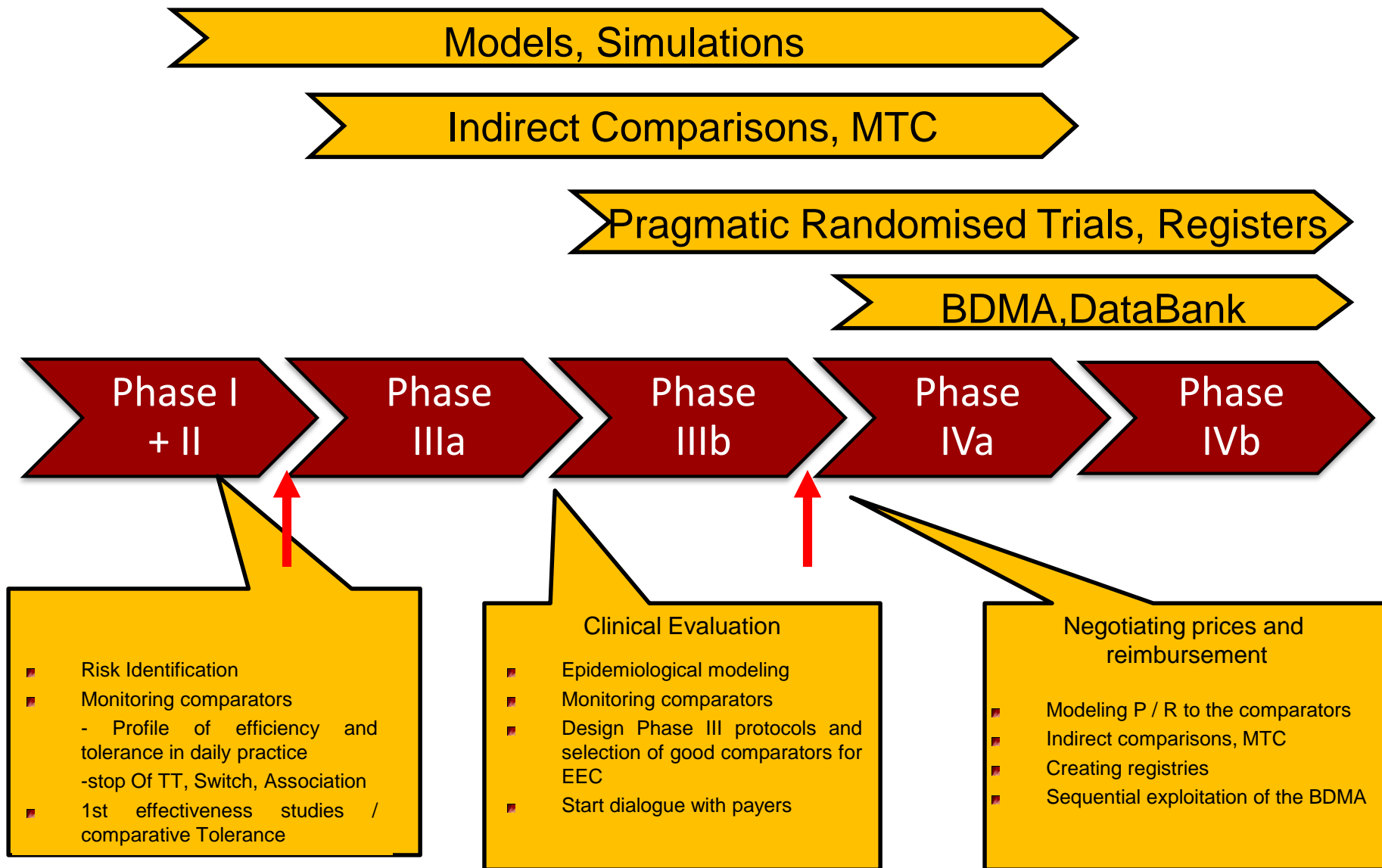
## Risks

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

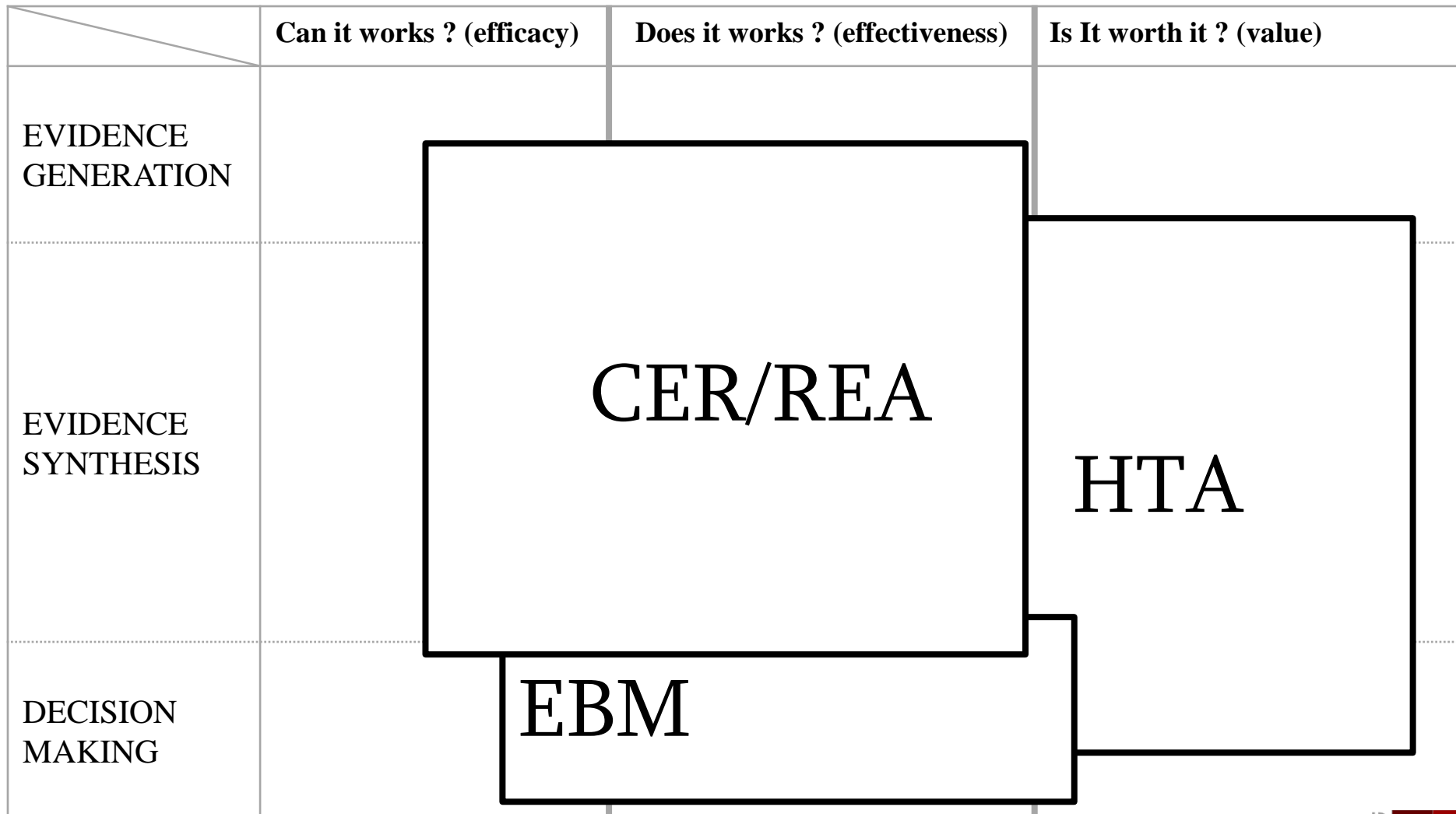
# No Single Approach Fulfill All Possible Needs for CER Information



# 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

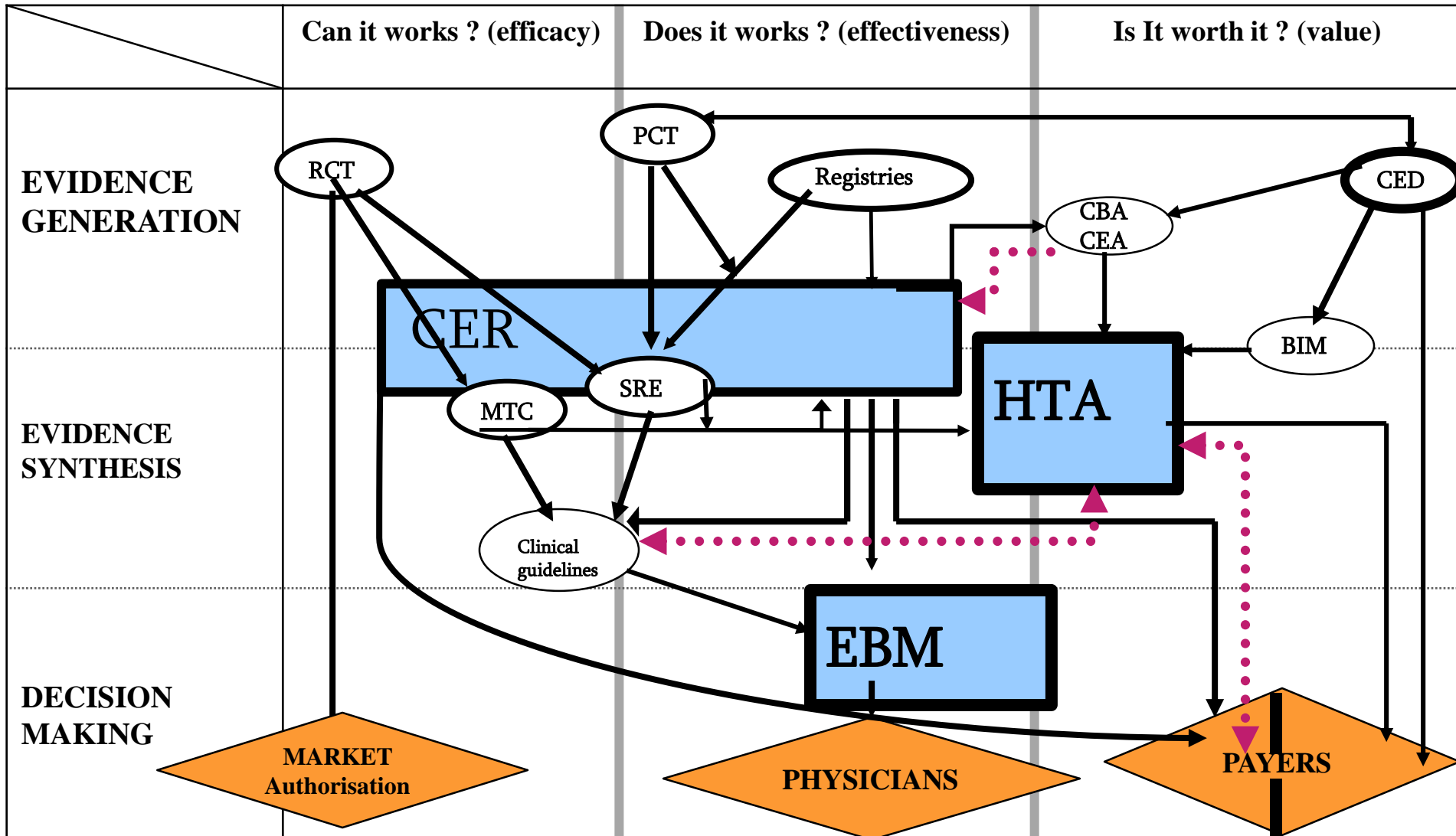
# An Organising Framework



Bryan Luce et al International Working Group for HTA advancement 2010

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

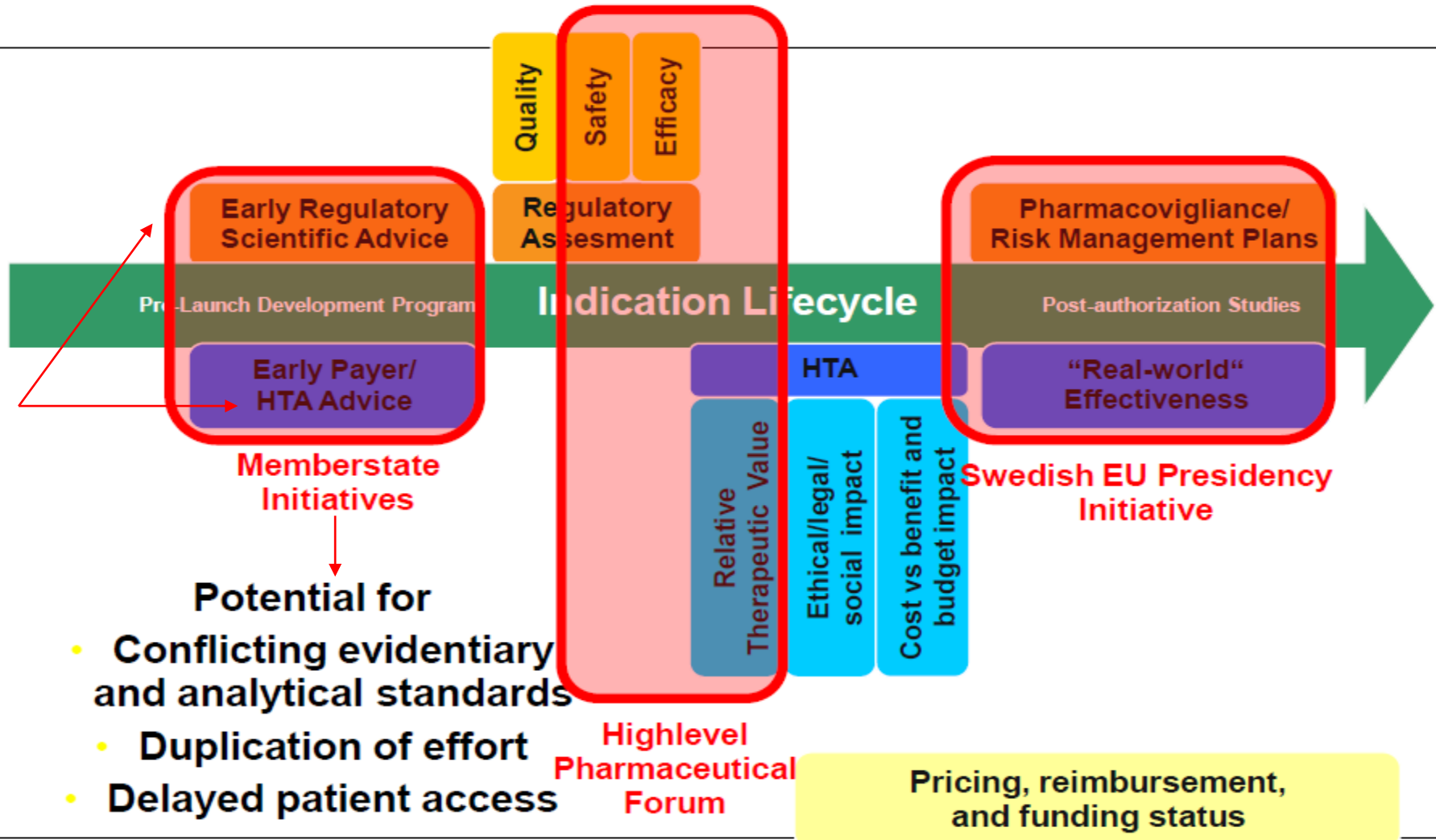
# What Kind of Evidence : CER, EBM, HTA?



REA: Relative Effectiveness Assessments, HTA Health technology assessment ; EBM : Evidence based medicine RCT : Randonized 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 ?



## Potential for

- **Conflicting evidentiary and analytical standards**
- **Duplication of effort**
- **Delayed patient access**







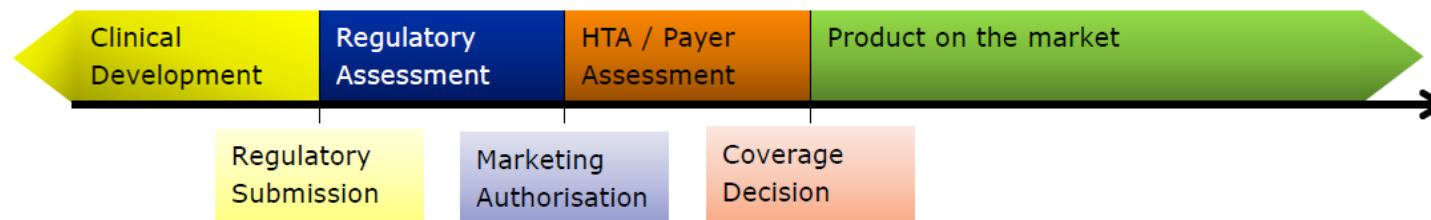
# Blurring the Distinction Between Pre and Post Commercialisation

- ✦ **Conditional marketing authorisation** Orphan medicinal products, authorisation intended to be converted into regular authorisation once all data are available
- ✦ **Authorisation 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