

# What Is Considered Clinically Meaningful?

## *EU Regulatory Perspective*

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# Regulatory Dilemma ...

**Efficacy**

**Clinical Relevance**

**Comparative Effectiveness**

**Relative Efficacy**

**Benefit-Risk-Assessment**

**Early Access**

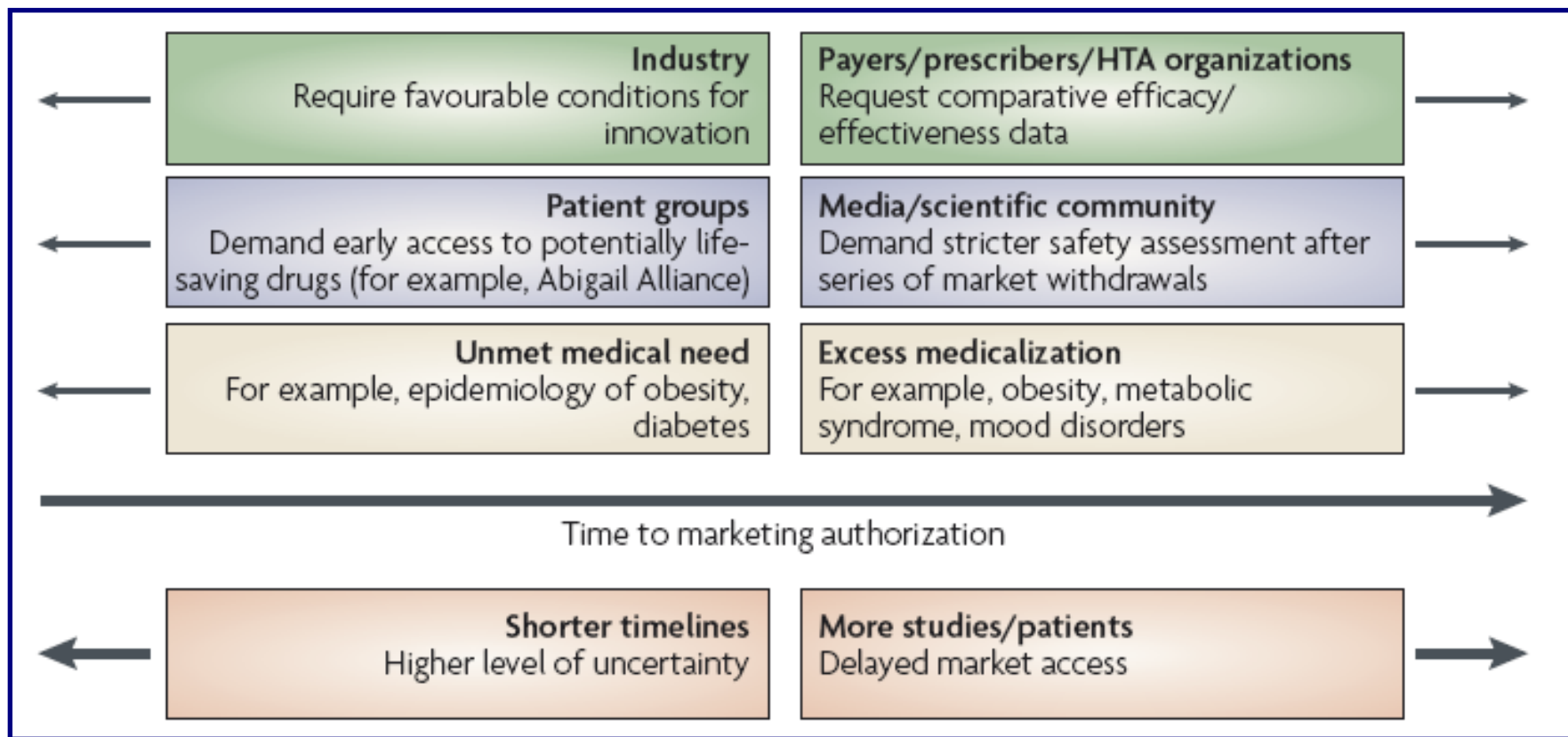
**Risk Management**

**Effectiveness**

**Cost Effectiveness**

# Regulatory Dilemma ...

from: Eichler HG et al., NRDD 2008



# Note for Guidance / Scientific Advice

- **Short-term Studies**
  - Placebo control
  - Three-arm-studies with active control and placebo
  - Duration
- **Maintenance/Long-term Studies**
  - Randomized withdrawal design (relapse prevention)
- **Endpoints**
  - Rating-scales
  - ***Means vs. Responders/Remitters***

# Short-term Studies in Schizophrenia

- **Parallel, double blind, randomized and controlled trials necessary**
  - in general 6 week duration
- **Choice of control**
  - Placebo
  - Active comparator
  - Choices must be justified by the applicant
- **Three-arm or multi-arm studies in at least one trial**
  - Assay sensitivity

# Study Designs in Schizophrenia

- Three adequate and well controlled designs possible:
  - Placebo control                      Superiority
  - Active control                         Superiority or Non-Inferiority
- Non-Inferiority Design tested in most cases
  - New drug is not inferior by more than some predefined amount                      →
  - Non-Inferiority Margin
    - ?? To be informed by historical data on a stable difference between verum and placebo
    - ?? Clinically how much difference from placebo is needed

# Assessment of Efficacy in Short-term Studies of Schizophrenia

- **Statistical Significance and Clinical Relevance needed**
- **Endpoints:**
  - Primary: e.g. differences in PANSS
  - Secondary: CGI
- **Difference between Baseline and Post-Treatment-Score**
- **30 % individual Improvement on Standard Ratings is Considered Clinical Relevant**

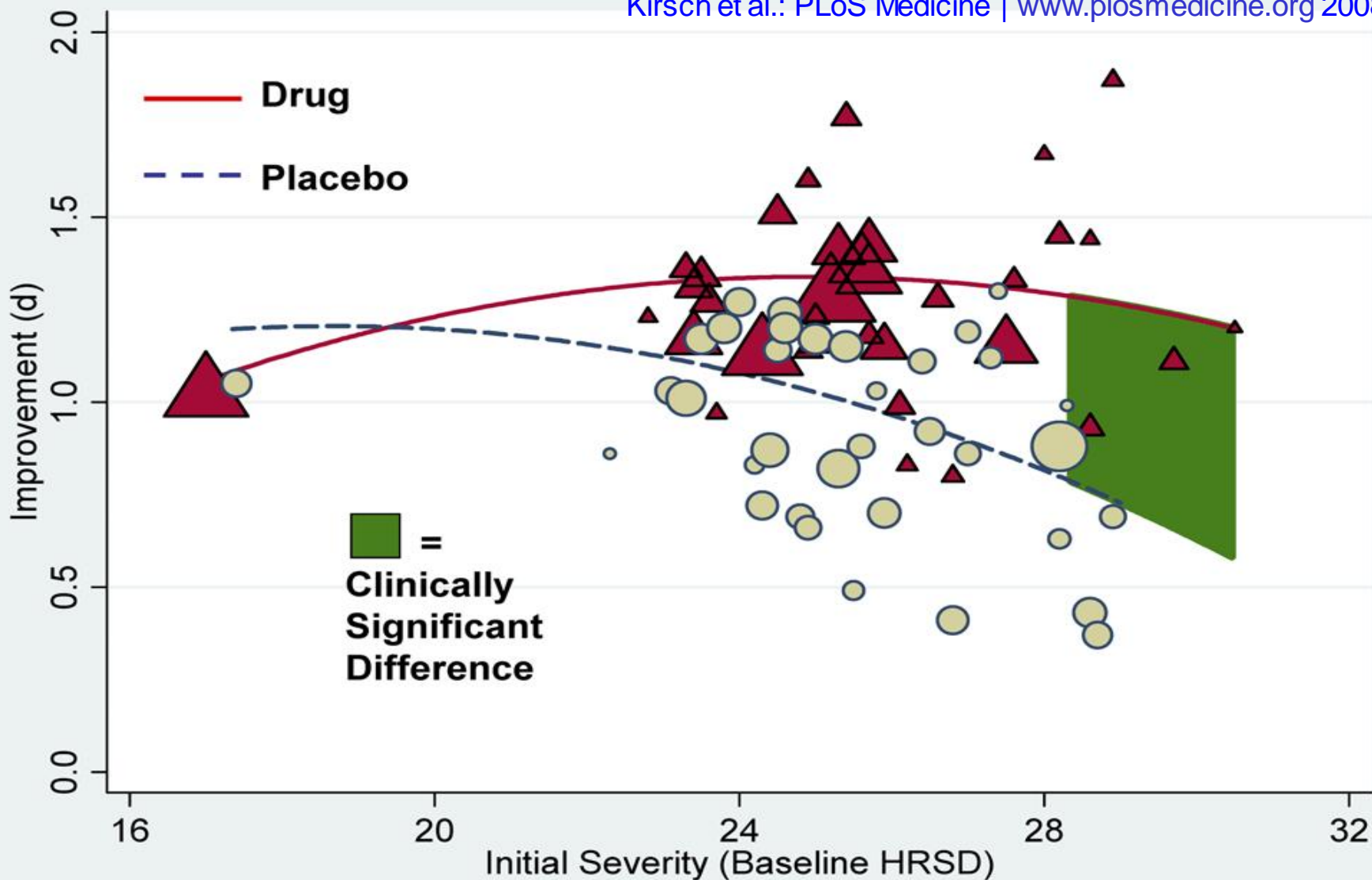
# Responder Analysis: 30% improvement in PANSS-Scores

In the responder analyses significantly more responders were observed in all paliperidone groups (56%, 51% and 61% in the 6 mg, 9 mg and 12 mg groups, respectively,  $p < 0.001$  for all doses) compared to the placebo group (30%).

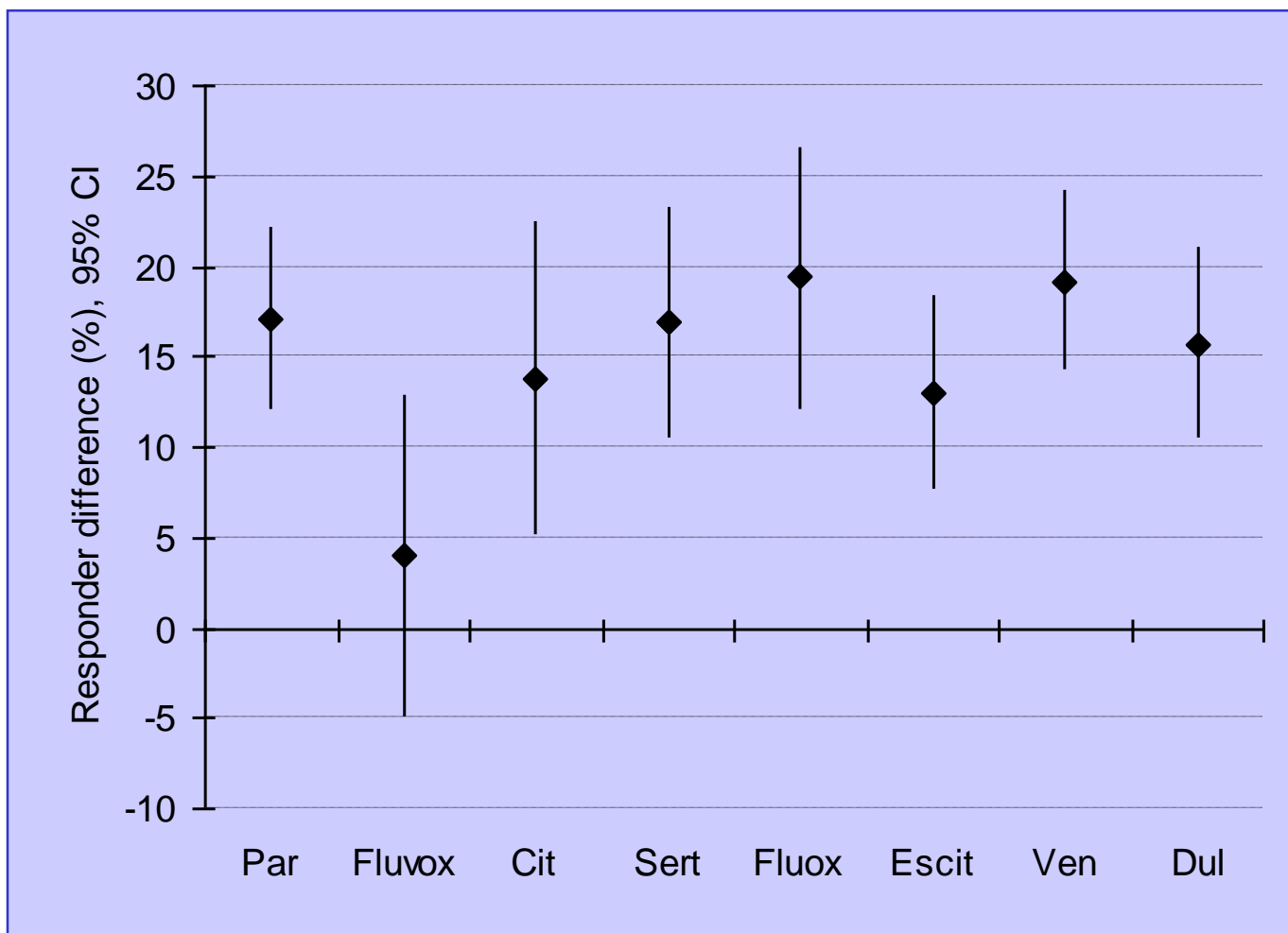
In the responder analyses significantly more responders were observed in both paliperidone groups (50%,  $p = 0.025$  and 51.4%,  $p = 0.012$  in the 6 mg and 12 mg groups, respectively) compared to the placebo group (34.3%).

In the responder analyses significantly more responders were observed in all paliperidone groups (40%, 46% and 53% in the 3 mg, 9 mg and 15 mg groups, respectively,  $p \leq 0.001$  for all doses) compared to the placebo group (18%).

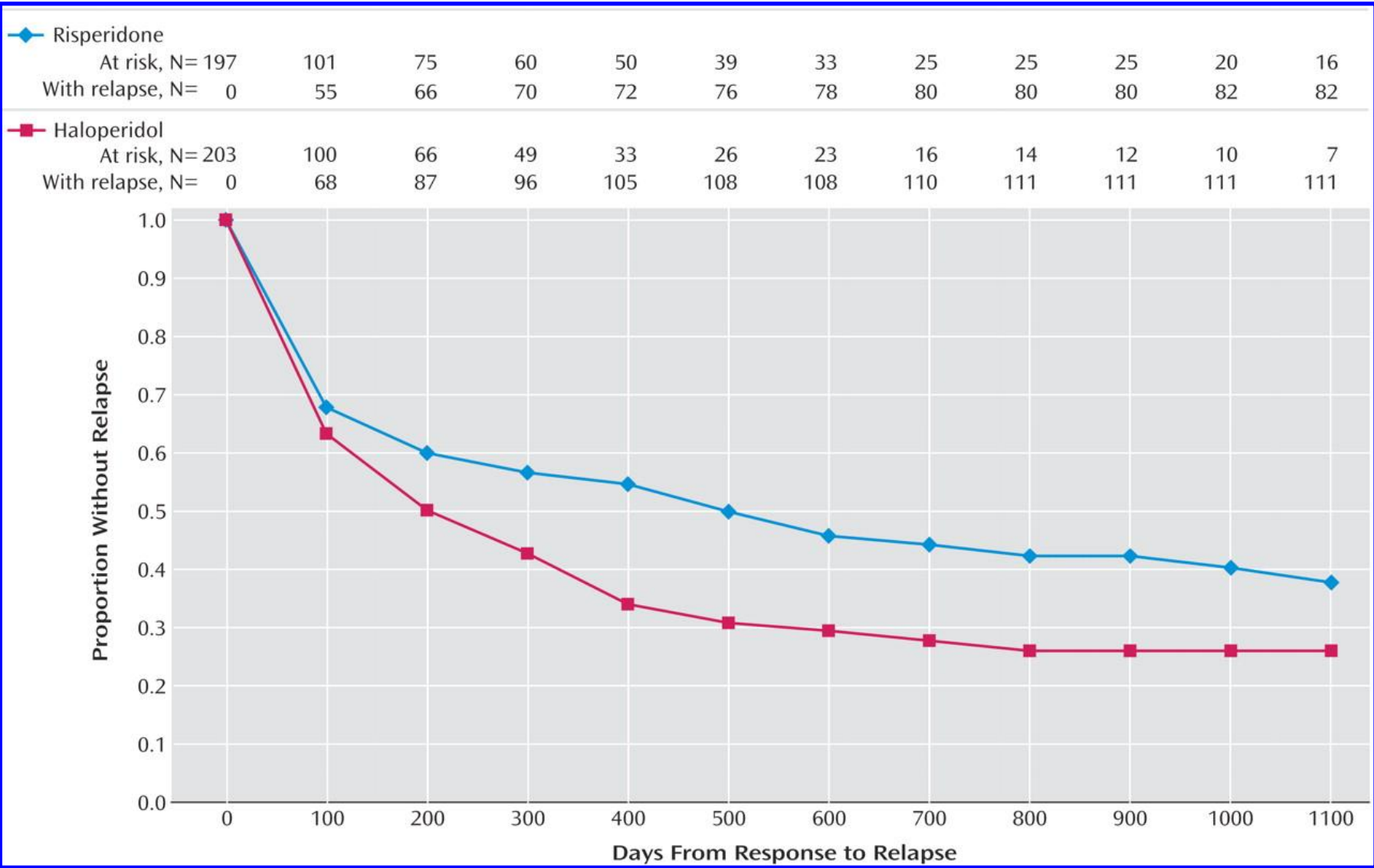




## Overall difference in percentage of responders between active drug and placebo (Melander H. et al.)



# Randomized Withdrawal Study



# Schizophrenia: *Negative* or *Cognitive* Symptoms as Target for a Drug Treatment Claim

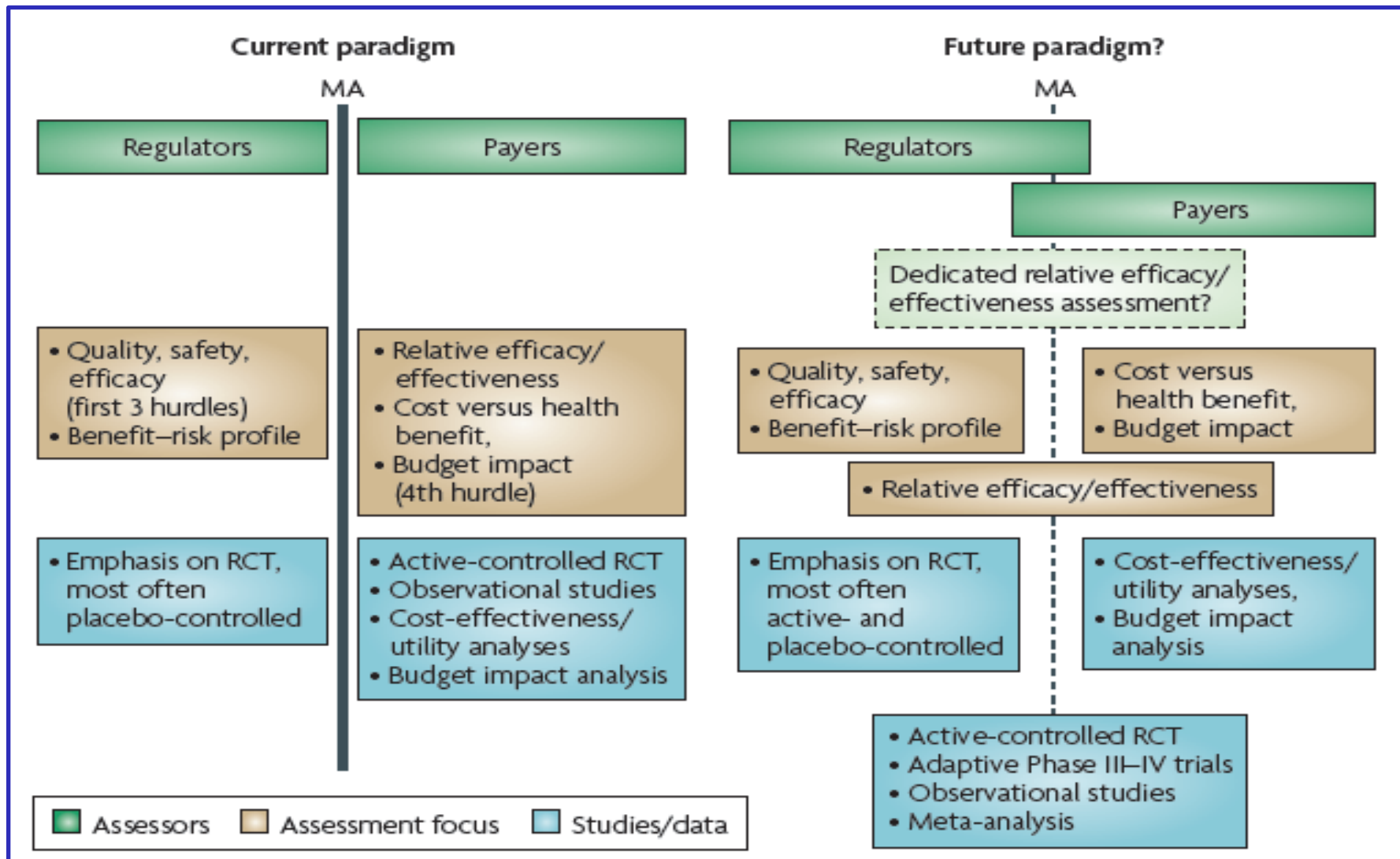
- **Both are considered as domains**
  - with an unmet medical need
  - which are not „pseudospecific“, but phenomenologically distinct from other symptoms
- **Overlap between these domains**
  - More data needed
  - Overlap would weaken possibility of separate claims
- **Do negative or cognitive results respond differently to standard antipsychotics**
  - In both domains results are disappointing

# Schizophrenia: **Cognitive** Symptoms as Target for a Drug Treatment Claim

- **Population:**
  - Distinct „Cognitive Impairment“ in patients with schizophrenia should be further established
  - Generalizable to community
- **Phase of the illness:**
  - In stable residuum
- **Domain:**
  - Spectrum of cognitive symptoms as a single target clearly preferred (MATRICS; CNTRICS; CANTAB; BACS a.o.)
  - Not enough data to focus on specific subtypes/targets
- **Co-Primary Endpoint:**
  - **Functional outcome mandatory**

# Possible Challenges ...

from: Eichler HG et al., NRDD 2010



# Summary: Clinical Relevance

- **Statistical significance and clinical relevance needed**
- **Estimation of relevance considers**
  - **Effect size of verum vs placebo in mean change from baseline**
  - **Difference in response and remission rates**
  - **Number needed to treat vs number needed to harm**
  - **Maintenance of effect**
    - **Relapse prevention (randomized withdrawal design)**
- **Key discussion point for benefit risk assessment in European Public Assessment Report**