Regulators and HTA: do we have the same need ?

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Agenda

- Decision on clinical value and place in clinical practice at EU level ?
- REA carried out across countries on an international basis ? How should this be done and who should be involved ?

Clinical value and place in clinical practice at EU level

- Clinical value at EU level: should be assessed immediately after MA, need to find alignment on definition of value
- Place in clinical pratice at EU level: different question, should be assessed when medicine is on the market, to be handled with PM activities

Evidence standards regulators vs. HTA/payers: definition of value

- Level of acceptable uncertainty
- External validity (efficacy vs. effectiveness)
- Perception of clinical relevance
- Absolute vs. relative efficacy
- Methodological issues (validity of QoL instruments, composite endpoints, surrogates, Bayesian stats, …)

Letter from a group of payers to EMA :

"we would like to comment on the content…"

- The assessment is based on a 'wrong' or an inappropriate premise (e.g. with respect to a comparator drug).
- Concern about the increasing use of surrogate endpoints like the Progression Free Survival
- The use of **composite endpoints** […] is controversial.

The difficulty: the EU dilemma

- *One* standard for drug approval
- *One* application, *one* assessment
- *One* decision valid in 27 EU + 3 EFTA countries

- "single payer", but:
- *30*+ different HTA methodologies and interpretations
- *30*+ independent decisions about whether the medicine should be paid for

Variation in acceptance of SO across disease areas and HTAs

Disease	SO	HAS	NICE	IQWiG	AHRQ	CADTH/ CDR	PBAC	SMC
Diabetes	HbA1c				N/A			
CVD	BP			N/A	N/A			
	LDL			N/A	N/A			
Oncology	TTP			N/A	N/A			
	TTF			N/A	N/A	N/A	N/A	N/A
	PFS			N/A				
Osteo-porosis	BMD		N/A	N/A	N/A		N/A	
HIV	Viral load CD4 count		N/A	N/A	N/A			

Accepted | Accepted with reservations | Not accepted | No comment given | N/A: No appraisal reporting outcome identified

SO = Surrogate outcome
Heron Evidence Development Ltd. Sedelnikova M, Lock K, Modha R.; Used with

Interaction - regulators and HTA/payers Opportunities today ?

- Alignment of regulatory and HTA/payers evidence requirements
  - Parallel scientific advice
  - Mutual input on clinical guidelines
  - Relative efficacy/effectiveness assessment
- Alignment of post-marketing research activities

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PM benefit and risk assessment

- Today: PM activities not regulated (exception: RMP, Conditional MA)
- Tomorrow: new pharmacovigilance regulation, towards the notion of benefit and risk management plan
- Which objectives ?
- Which methodology to assess PM efffectiveness studies ?
- Could it be carried out across countries ?
- Who should be involved ?

Which objectives ?

- Change patient population
- Change of endpoints
- Change position of the product
- Compare strategies, efficacy/effectiveness
- Proactive assessment of (potential) safety concerns

…taking on board that if efficacy is universal, effectiveness is (partly) local

Which methodology ?

- Key question: is it possible to draw « local » conclusions from a multinational study ?
  - RCT (superiority, non inferiority, 3 arm trials)
  - Pragmatic clinical trials
  - Network meta analysis (indirect comparisons)
  - Observational studies

Health Care databases suitable for assessment of B and R

- Pt level of information about Tt received
- Accurate measurement of outcome of interest
- Well measured key covariates
- Clear timing (Tt assignment, outcome)
- Understanding how pts entering and leaving the database
- Subgroups of treated and controls broadly comparable

From Rubin DB, Stat Med 2010

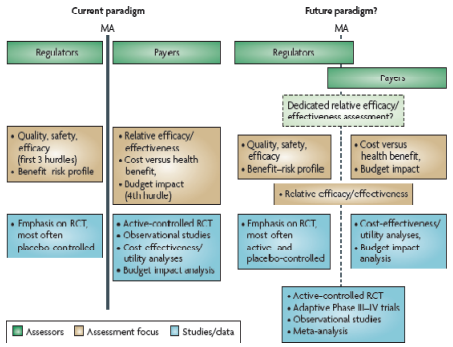
Could it be carried out across countries ?

- Broadly yes for RCT or pragmatic trials
- Broadly no for observational studies
- Both are important (different objectives)

Who should be involved ?

- Insurance claims/payor databases
- Electronic medical records (primary care practitionners)
- Survey databases (information collected through interviews)
- Pharma industry
- Academic networks

Change of paradigm



From Eichler et al, NRDD, 2010

Acknowledgments

- Hans Georg Eichler