Relative effectiveness across Europe: Do Member States diverge in clinical outcomes from treatment?

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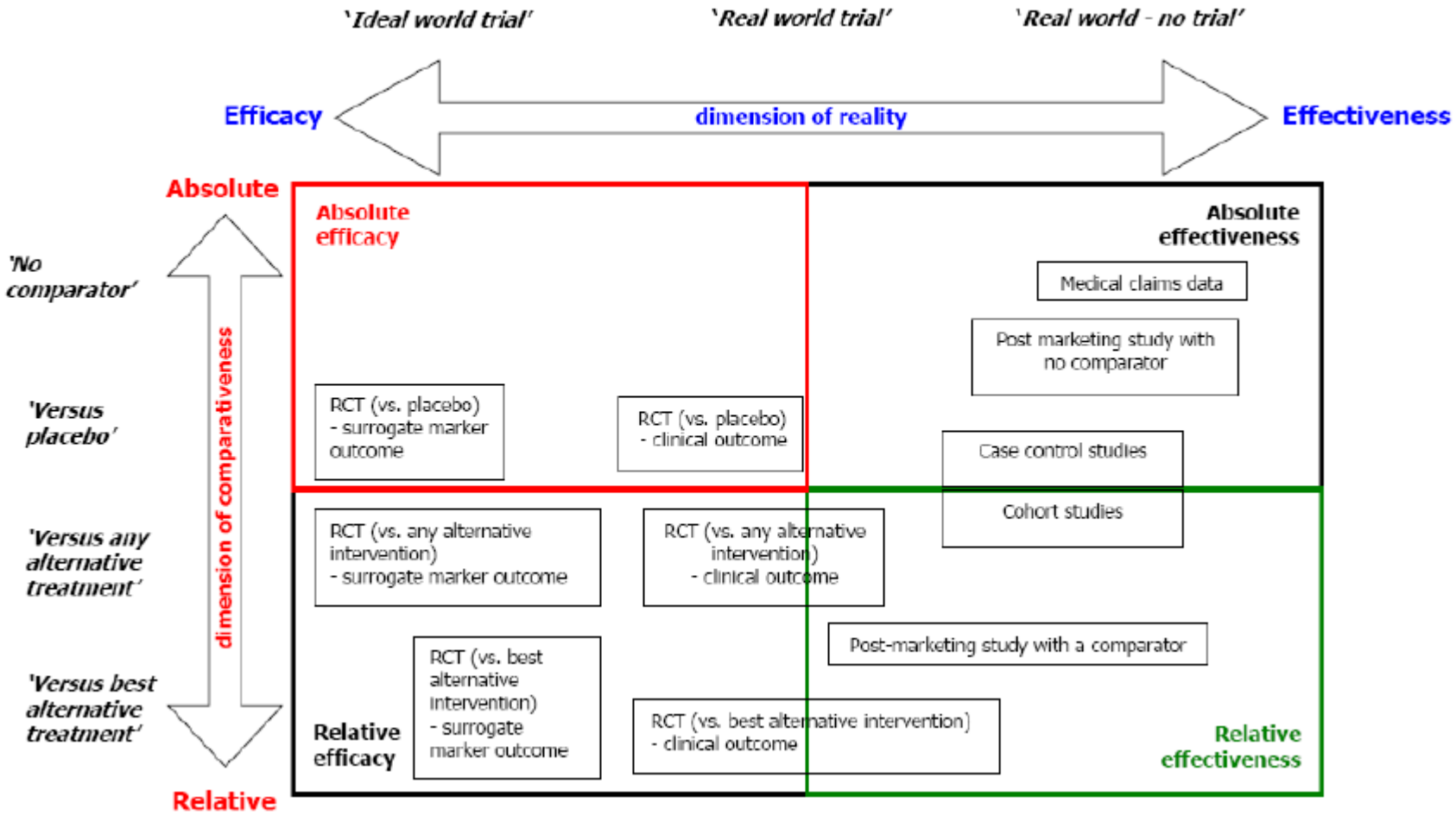
Introduction (1)



Source: High Level Pharmaceutical Forum 2008

Introduction (2)

- Increasing interest in the US and Europe on the relative effectiveness and comparative effectiveness to assess the 'real' added therapeutic value of a medicine.
- Europe: Is it feasible to have a Pan-European assessment of relative effectiveness of medicines?
- If so, the industry model would evolve towards a "live licence" approach with increasing post-marketing research.
- EU collaborative initiatives to date:
  - EMA evaluates relative efficacy.
  - MEDEV could potentially assess relative effectiveness.
  - EUnetHTA Joint Action (2010-12): Work Package 5 aims to develop a common methodology to assess relative effectiveness of pharmaceuticals.
  - The Swedish initiative (2009): co-operative cross border collection of observational data in some disease areas.

Introduction (3)

- One challenge for a Pan-European approach is the potential variation of relative effectiveness between (and also within) countries.
- Potential sources underlying this variation:
  1. At individual level: clinical and demographic patient's characteristics, compliance.
  2. At institutional level: differences in clinical practice, local P&R systems and comparators, service delivery and organisation, resources available, private/public status, etc.
  3. At national level: national P&R system and comparators, features of the healthcare systems, population health, national guidelines/regulations, country' economy (%GDP spent in health care), etc.

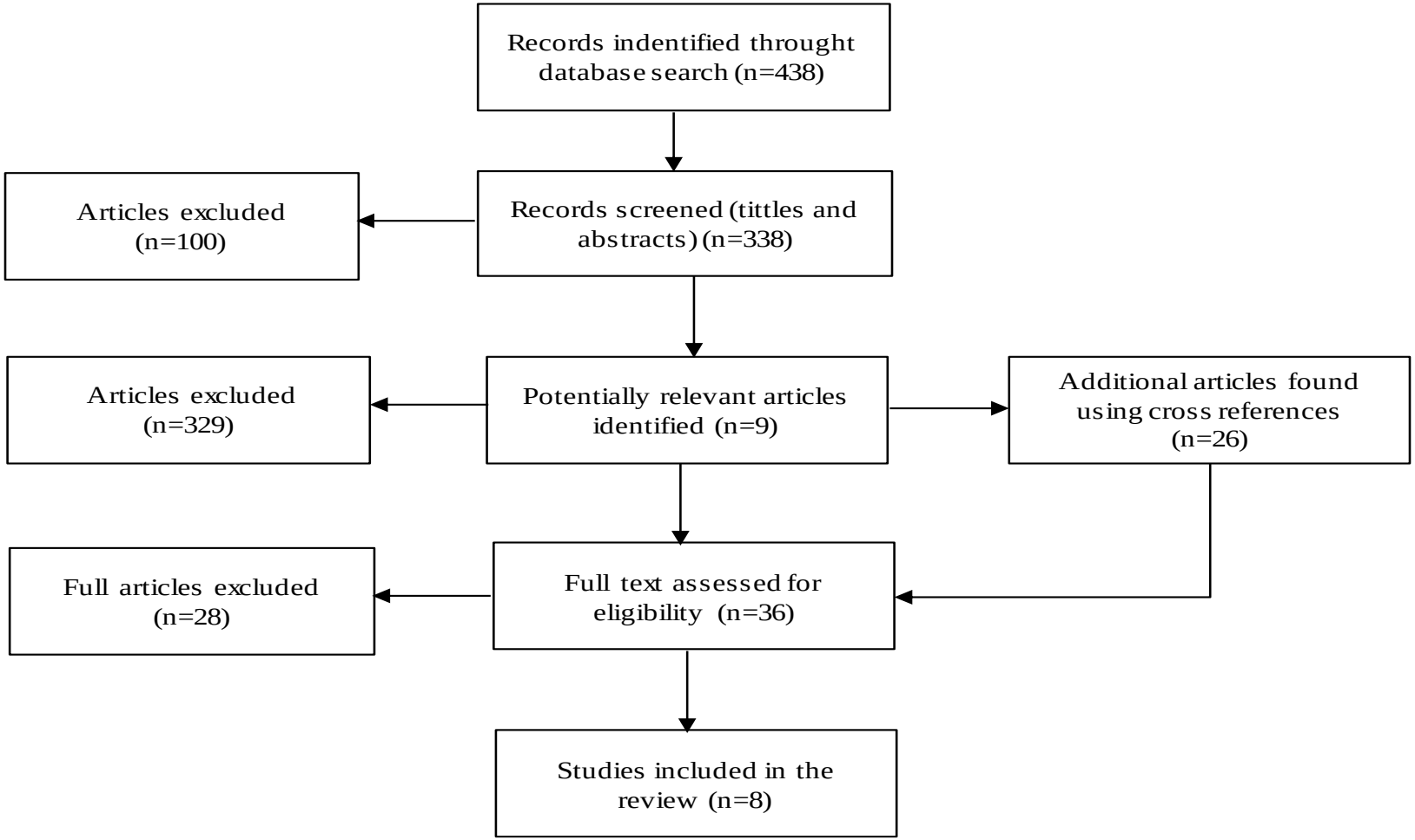
Objectives

- To understand the extent of likely variation, if any, in underlying relative effectiveness of medicines in two or more of the 27 EU Member States (MS).
- To identify any study discussing the transferability and generalisability of clinical effectiveness in any disease area across different EU jurisdictions.

Method

- Systematic literature review of medical and health economics literature in four databases: Medline, Embase, EconLit, and Health Management Information Corsontium (HMIC).
- Logical combinations of keywords related to effectiveness, generalisability, external validity, transferability, Europe and review were searched in titles and abstracts.
- Papers published in English language between 2000 and May 2010 were considered.
- Inclusion criteria: clinical studies and cost-effectiveness studies discussing differences in relative effectiveness across MS in any disease area.

Results (1)


Records indentified throught database search (n=438)
Records screened (tittles and abstracts) (n=338)
Articles excluded (n=100)
Potentially relevant articles identified (n=9)
Articles excluded (n=329)
Additional articles found using cross references (n=26)
Full text assessed for eligibility (n=36)
Full articles excluded (n=28)
Studies included in the review (n=8)

Results (2)

- No observational studies met the search criteria.
- Eight cost-effectiveness studies were the base of this review and we focused on their clinical data. However, these studies mostly report results on relative *efficacy* (from randomised controlled trials).

Results (3)

Study	Type	Disease area	Intervention	Setting	Findings
Barbieri et al., 2005	Review of CE studies.	Non-specific.	Medicines in any disease area.	UK, Spain, Germany, France, Italy.	Three studies reported heterogeneity on relative effectiveness but no sources of this variation were further explored. Significant but not systematic differences in CE results due to unit costs and resource use.
Cook et al., 2003	CEA from the 4S trial.	Cholesterol	Simvastatin vs placebo	Denmark, Finland, Iceland, Norway, Sweden.	Mortality rate across countries no different to the overall mortality rate. Therefore health outcomes were pooled.
Hakkart-vanRoijen, 1998	CEA	Psoriasis	Multinational clinical trials with two arms: Tapered vs abrupt discontinuation of cyclosporin.	UK, Spain, Turkey, Canada	Not statistically significant differences in the main outcome (total days of systematic therapy-free days , STDFs) across the four countries because the small number of patients in each of them.

Results (4)

Study	Type	Disease area	Intervention	Setting	Findings
Manca and William 2006	Methodological paper CEA	Non-specific. Case study in cardiovascular disease.	Non-specific. Case study ATLAS trials and WOSCOPS study	Non-specific.	The authors proposed an algorithm to assist the choice of appropriate analytical strategy to adapt CE results from different countries.
Manca et al., 2007	CEA from the ATLAS trial.	Chronic heart failure.	Low v high dose ACE lisinopril.	17 countries from a group of 16 European countries, US, Canada, and Australia.	Both patient and country-level factors explained variability in differential survival and costs across countries. Country-level factors: life expectancy, private and public health expenditure, alcohol and tobacco. Patient factors: age, sex and left ventricular function.
Sculpher et al., 2008	Review of CE studies	Any	Non-specific.	Any	Most cited factors underlying variation in CEA: unit costs, variations clinical practice, geographical setting, healthcare resources.

Results (5)

Study	Type	Disease area	Intervention	Setting	Findings
Wilke et al., 1998	CEA	Aneuysmal subarachnoid hemorrhage (SAH).	RCT with four arms: three doses of tirilazad and a vehicle-only arm.	5 countries from a group of 9- EU countries, New Zeland , and Australia.	Factors underlying differences in mortality rates across countries: severity and patient characteristics.
Vemer et al., 2010	CE modelling study.	Smoking-related	Four arms: three cessation therapies and an unaided arm.	Holland, Belgium, UK, Germany, Sweden, France	Between country variability in CE results mainly due to three factors: discount rates, incidence and mortality of smoking-related diseases, and utility values used to estimate QALYs. Other six analysed factors showed lower or null effect on the heterogeneity of the results: demography, smoking prevalence, all-cause mortality, costs of disease, resources used for SCTs, unit costs of SCTs.

Discussion (1)

- Literature testing for heterogeneity in relative efficacy and relative effectiveness across European countries is very scarce.
- The degree of heterogeneity in relative effectiveness remains an unresolved empirical issue.

Discussion (2)

Regarding relative *efficacy*:

- Many multicountry studies are underpowered to test for heterogeneity as they are designed to estimate the overall treatment effects.
- There is an underlying *assumption* relative efficacy is constant and generalisable across settings.
- Consensus on reporting country level data from these studies would be desirable.
- Regression techniques as Multilevel Models using RCTs data are useful tools to explore between country variations in treatment effects.

Discussion (3)

- In the cost-effectiveness literature, heterogeneity of clinical data (mostly relative efficacy) is rarely explored as it is assumed to be transferable across jurisdictions.
- However, two factors introducing variation in relative efficacy were identified:
  - Patients' and disease characteristics
  - Countries' total heath expenditure as percentage of their GDP
- Clinical practice variation is one of the most cited factors when analysing heterogeneity of cost effectiveness results but only from the cost side (with no further exploration on relative efficacy or relative effectiveness).

Discussion (4)

Regarding relative *effectiveness*:

- Between country heterogeneity on relative effectiveness is more likely to occur but no studies were found. This may be because:
  - Registry data is costly to collect.
  - When collected, there is not easy access to it for research purposes.
  - Methodological challenges of these studies: e.g. not harmonised measures, selection bias, multidrug exposure, etc.
- More efforts are needed to produce prospective and retrospective observational studies, for example, collecting and analysing registry data if MS are interested in the clinical effect in routine medical practise of the medicines they pay for.