ADDIS: Aggregate Data Drug Information System for drug benefit-risk analysis and automated evidence synthesis

Tommi Tervonen

Faculty of Economics and Business, University of Groningen, The Netherlands

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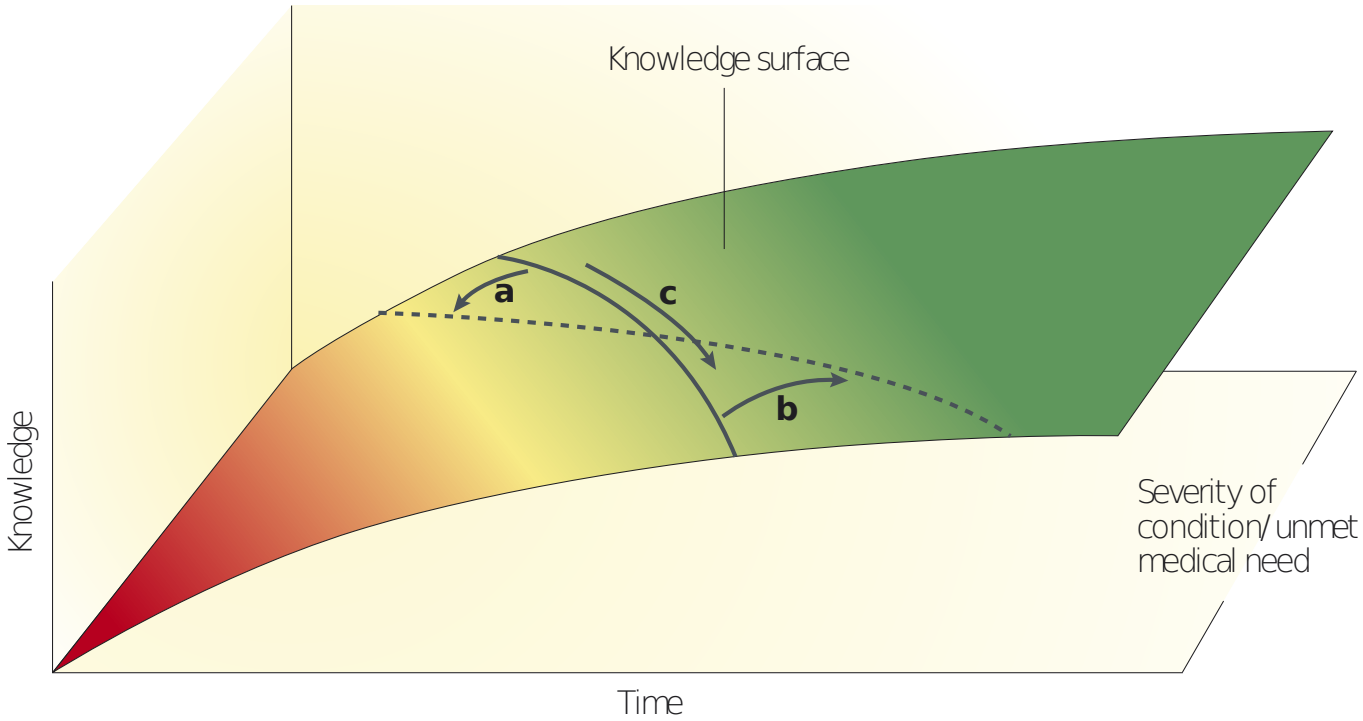
Introduction: evidence-based medicine (EBM)

- Evidence-based medicine aims to apply the best available evidence gained from scientific research to medical decision making
- A large share of decisions made by health care professionals are informed by evidence-based medicine, e.g. prescription, regulatory- and reimbursement policy decisions
- Although the scientific evidence is transparent and achieved with methodological rigour, the actual decisions are often unstructured, ad hoc and lack transparency as the treatment benefit-risk valuation is not explicit

Introduction: application of EBM in drug benefit-risk analysis

- For a drug to be granted marketing authorization, it must be proven efficant, safe, and have a sufficient benefit-risk (BR) profile compared to other drugs already in the market



Eichler & al., Nature Drug Disc, 2008

Project Escher

- Escher is a national research project of the Dutch Top Institute Pharma that aims to improve drug regulation through science
- 16 PhD students and 4 PostDocs working in 5 universities (RUG/UMCG, UU/UMCU, Erasmus MC) in collaboration with the industry (MSD, GSK, Amgen, WINap)

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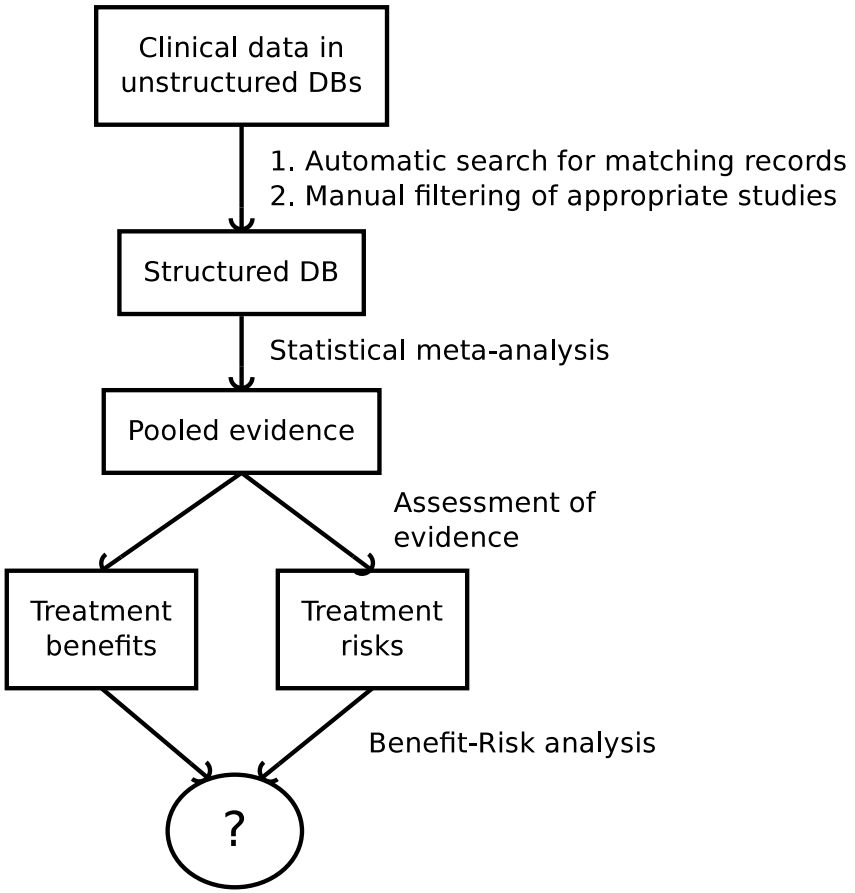
- 16 PhD students and 4 PostDocs working in 5 universities (RUG/UMCG, UU/UMCU, Erasmus MC) in collaboration with the industry (MSD, GSK, Amgen, WINap)
- Work package 3.2 (RUG/UMCG with Schering-Plough/Merck) aims to bridge the gap between aggregate clinical data and evidence-based drug regulation by having *useful* methods for benefit-risk analysis implemented in *usable* software (which would then be *used* in real-life decision making)

Useful/Usable/Used: Keen & Sol, IOS Press, 2008

Drug benefit-risk analysis

- BR analysis should include all relevant evidence, and therefore apply (network) meta-analysis



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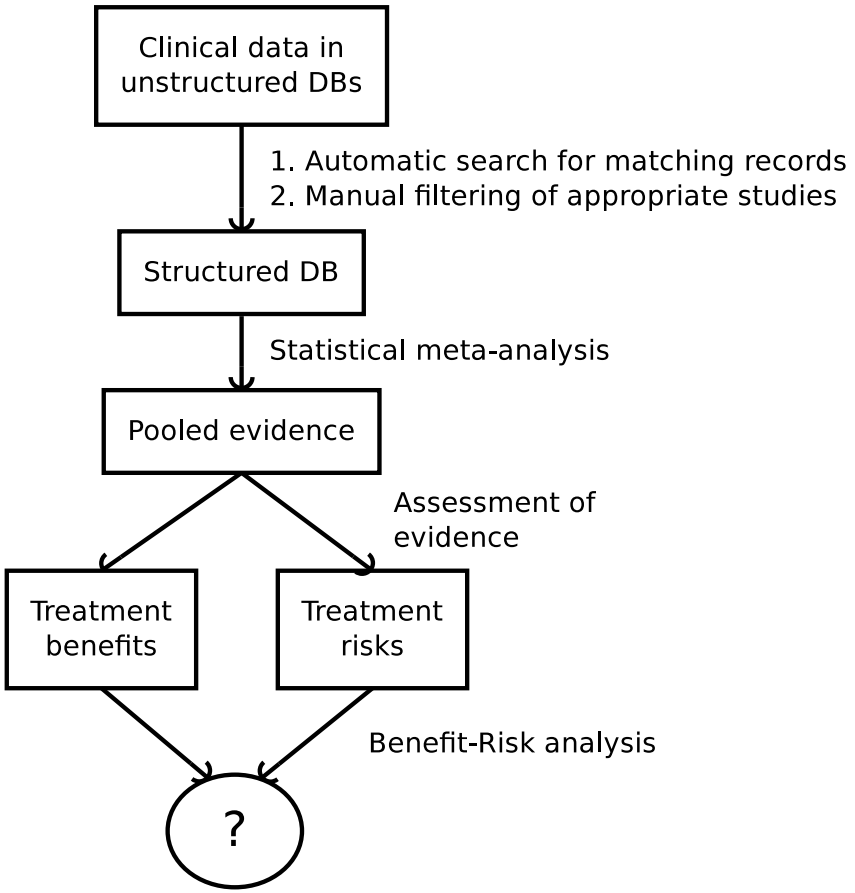
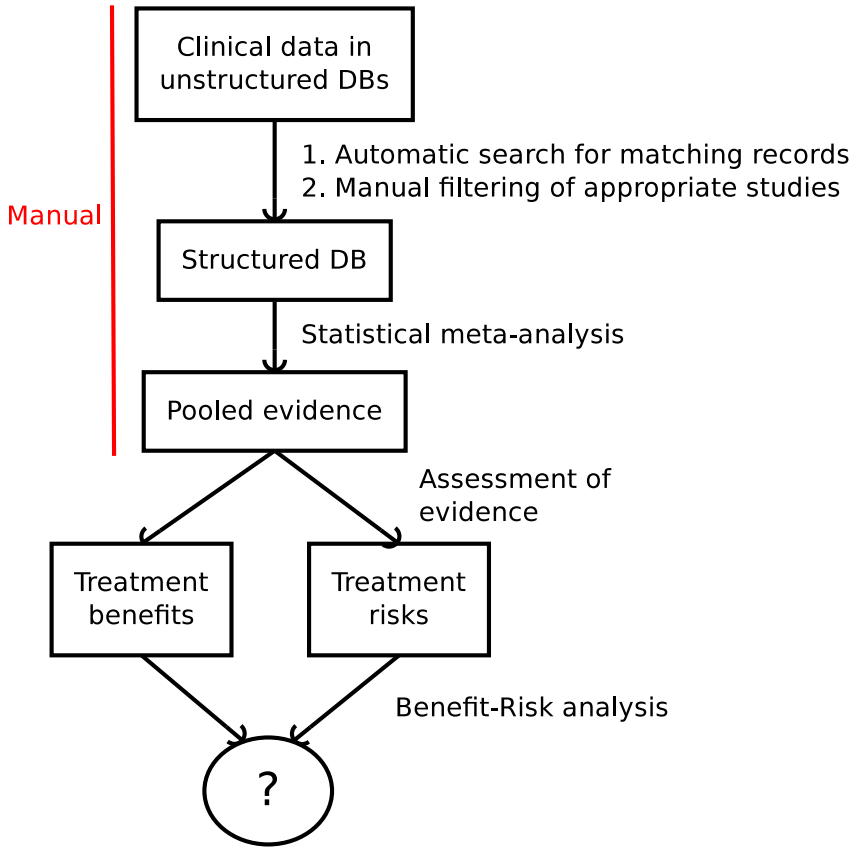


Drug benefit-risk analysis

Problems

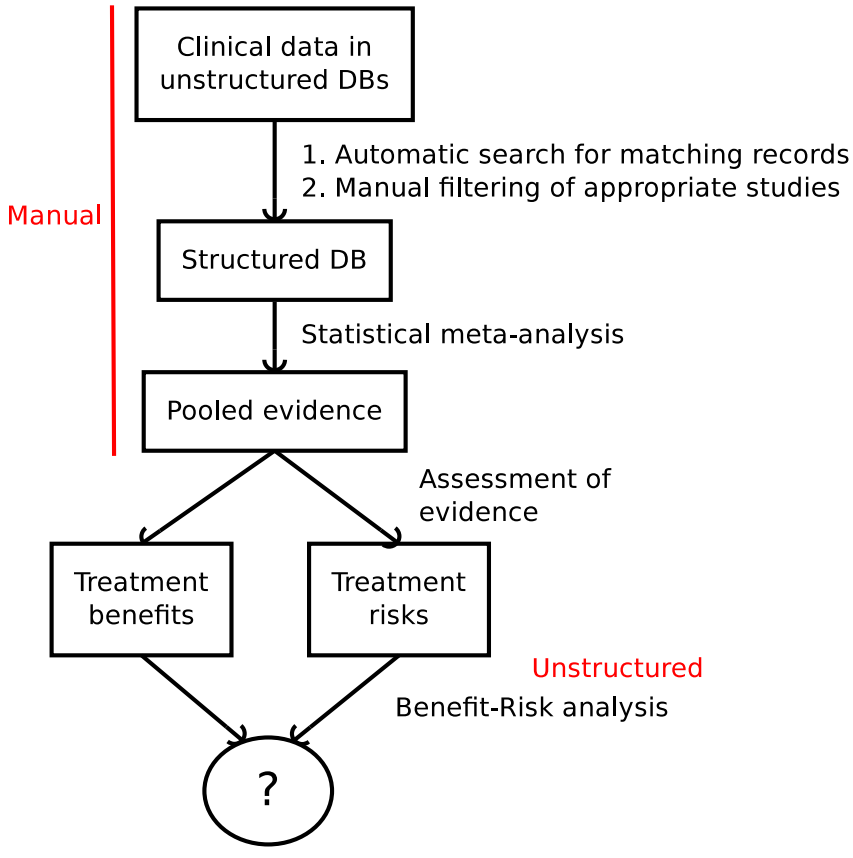
1. Inclusion of all relevant evidence in the meta-analysis is not guaranteed



Drug benefit-risk analysis

Problems

1. Inclusion of all relevant evidence in the meta-analysis is not guaranteed
2. The BR analysis is unstructured and non-transparent



Case study of BR analysis

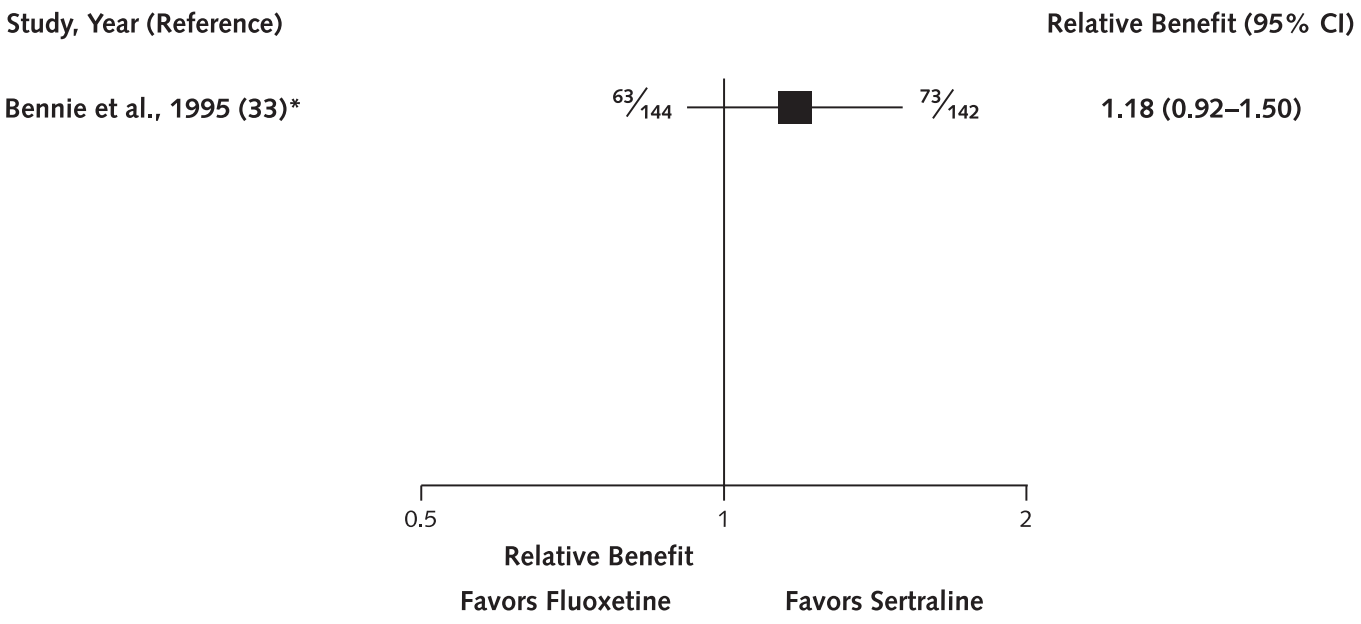
- Hansen & al. (Ann Intern Med, 2005) assessed safety and efficacy of four second generation antidepressants and concluded that there are "no significant differences among the drugs"
- In general, the assessment of antidepressants is hard; placebo effect is always present causing high uncertainty on the results
- Q's:
  1. How can the benefit-risk assessment of second-generation antidepressant be structured based on evidence from the clinical trials?
  2. Can we come up with something better than "no significant differences"?

Case study: data from meta-analysis

Study, Year (Reference)	Fluoxetine	Sertraline
Bennie et al., 1995 (33)*	$^{63}/_{144}$	$^{73}/_{142}$

Hansen & al., Ann Intern Med, 2005

Case study: data from meta-analysis



Hansen & al., Ann Intern Med, 2005

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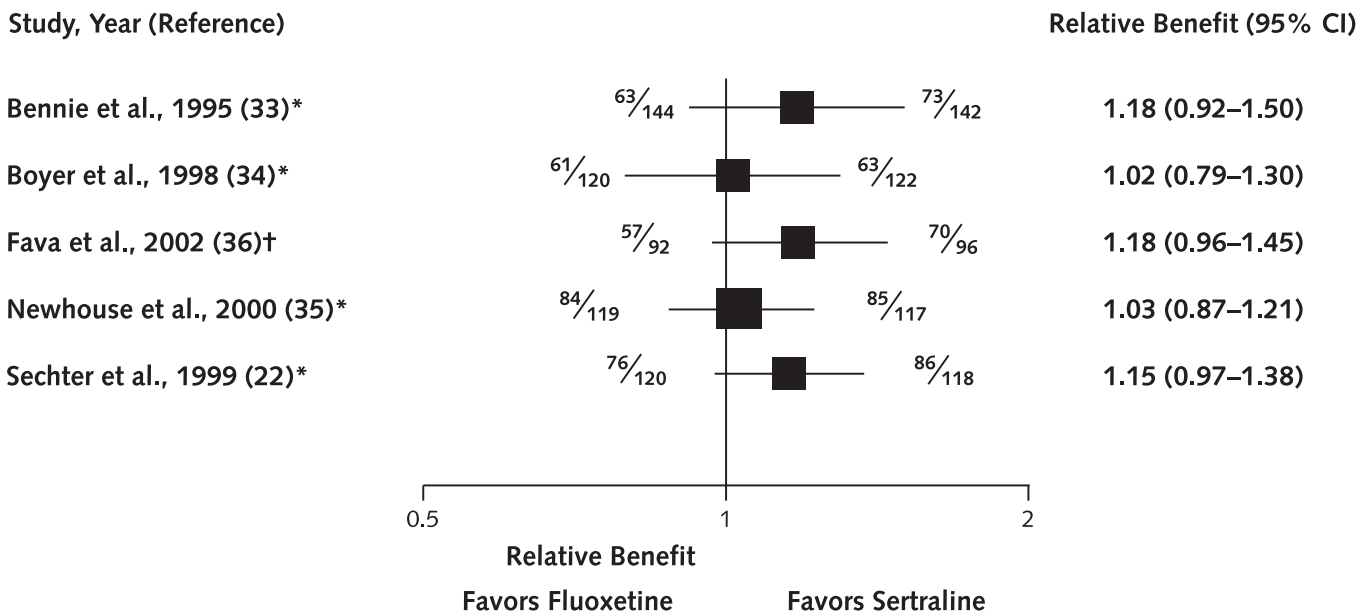

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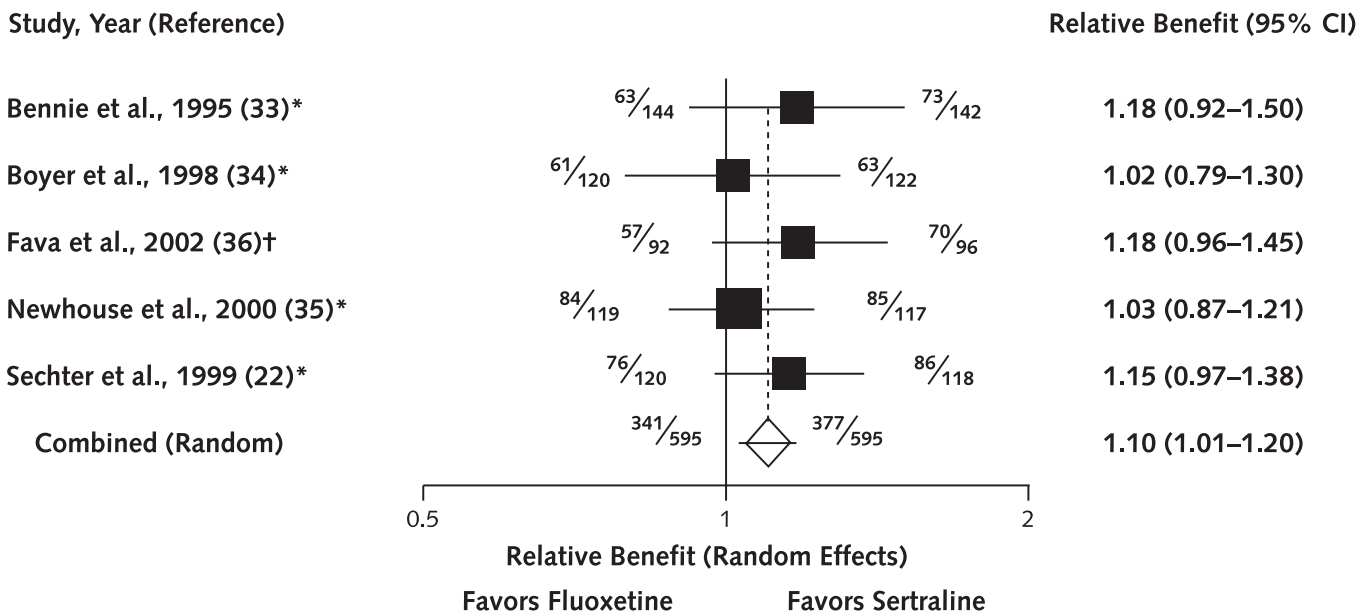

Hansen & al., Ann Intern Med, 2005

Approach

- Separate clinical data (measurements) from the value judgements (MCDA)
- Include all data present in the original analysis (imprecise measurements)
- Provide metrics for decision uncertainty
- Enable model generation for re-applicability

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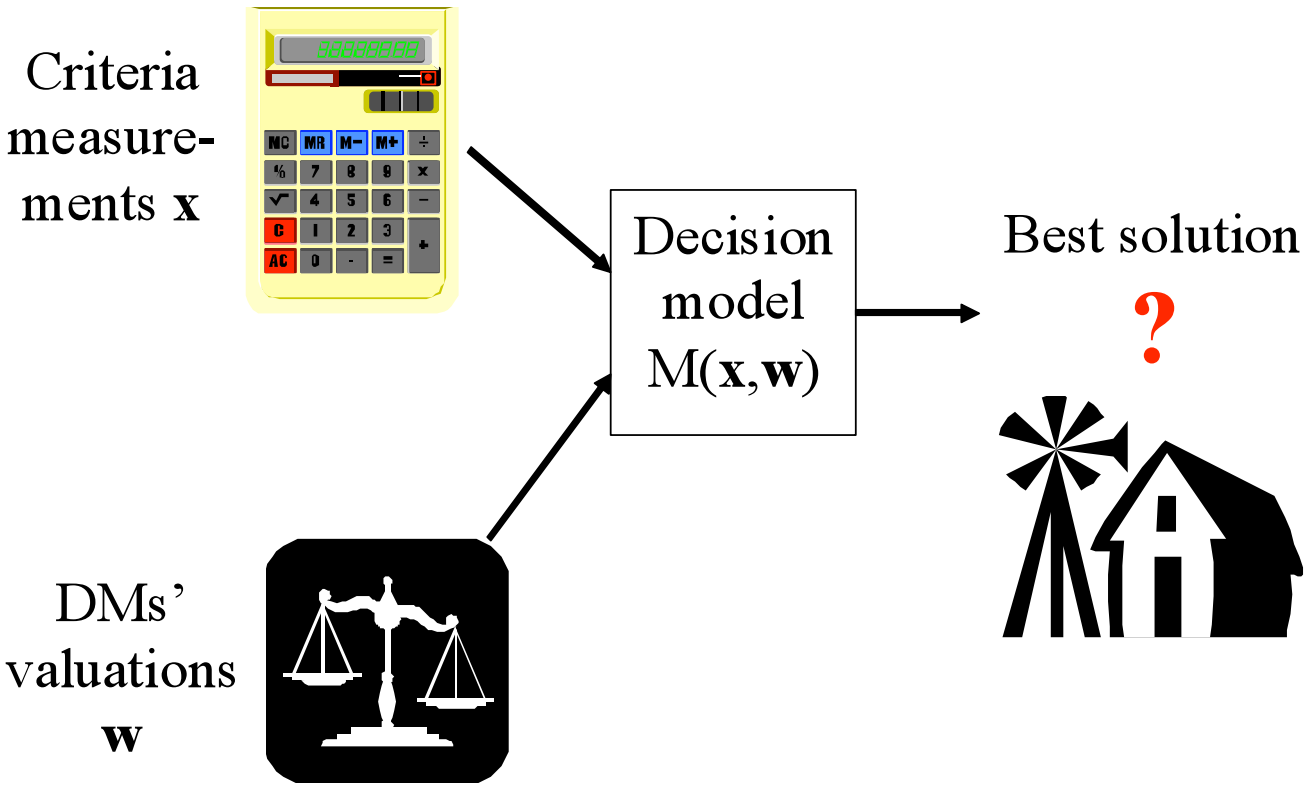
- Include all data present in the original analysis (imprecise measurements)
- Provide metrics for decision uncertainty
- Enable model generation for re-applicability
- We chose to apply Stochastic Multicriteria Acceptability Analysis (SMAA)

SMAA(-2)

- SMAA(-2) is a multi-criteria decision aiding (MCDA) method for ranking a set of alternatives evaluated on basis of a set of criteria
- Preference information expressed with a weight vector and a value function of a commonly accepted shape (in practice often linear one)
- Uncertain or imprecise criteria values are represented by stochastic variables that map the deterministic value functions to value distributions

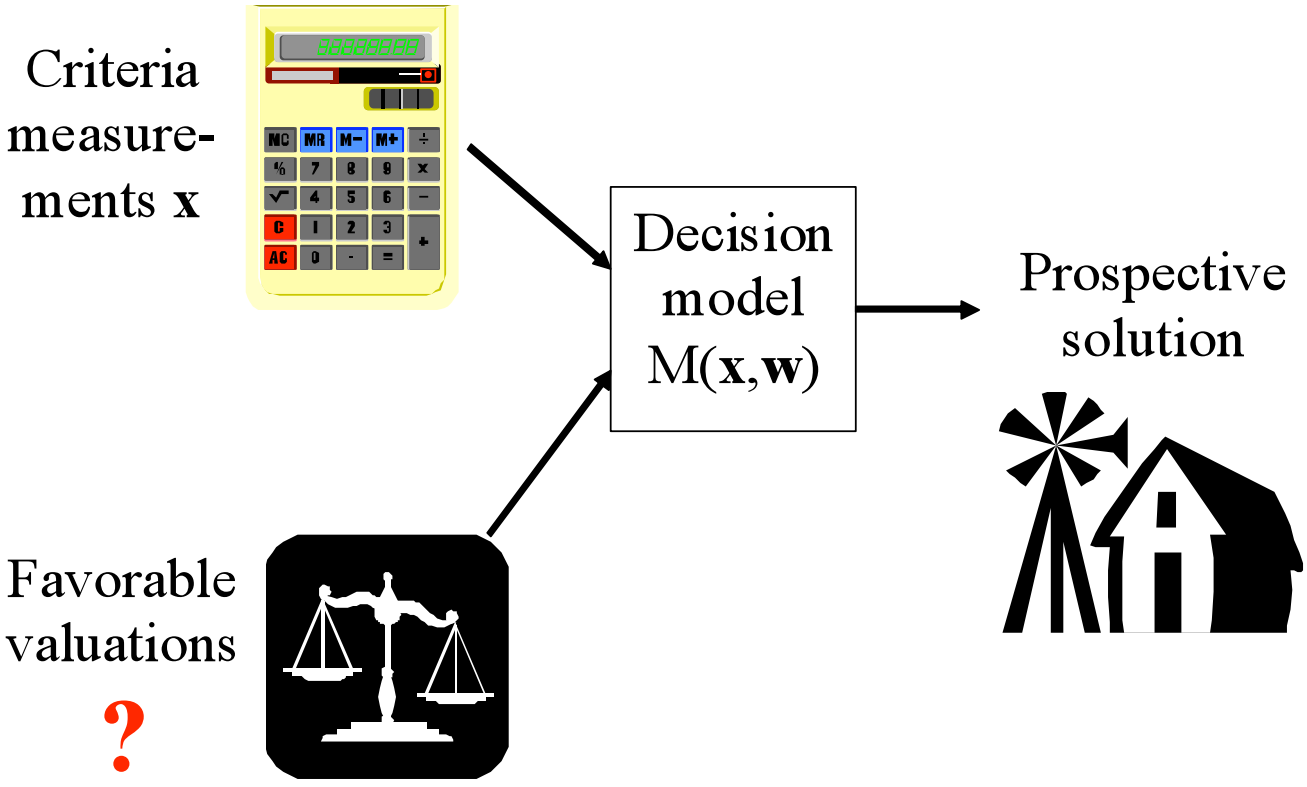
Lahdelma & Salminen, EJOR, 1998 / Tervonen & Figueira, JMCDA, 2008

Traditional MCDA



Lahdelma & Salminen, Springer, 2010

Inverse approach



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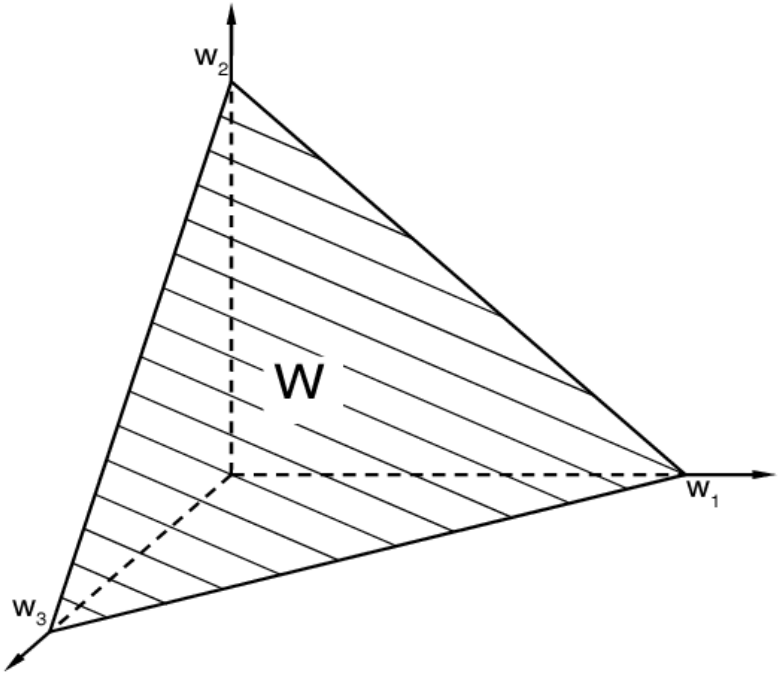
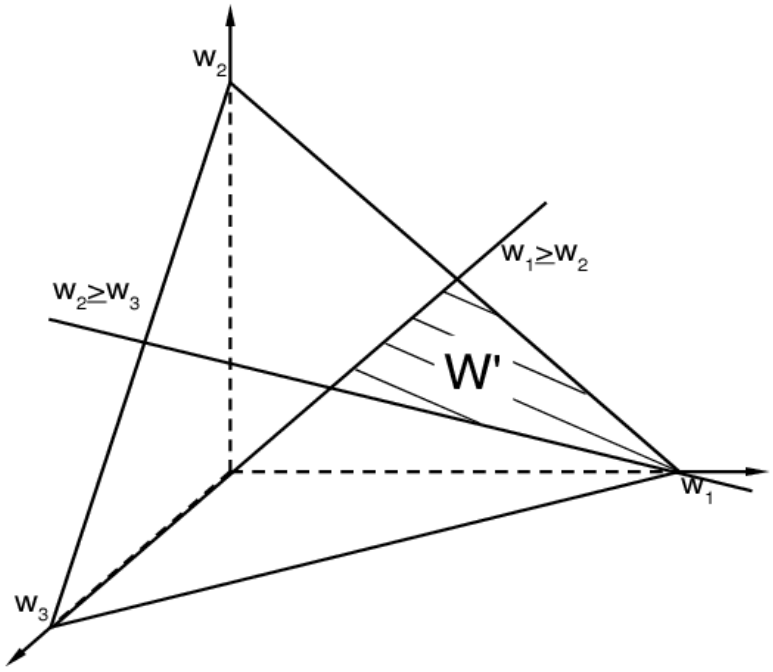
Weight space



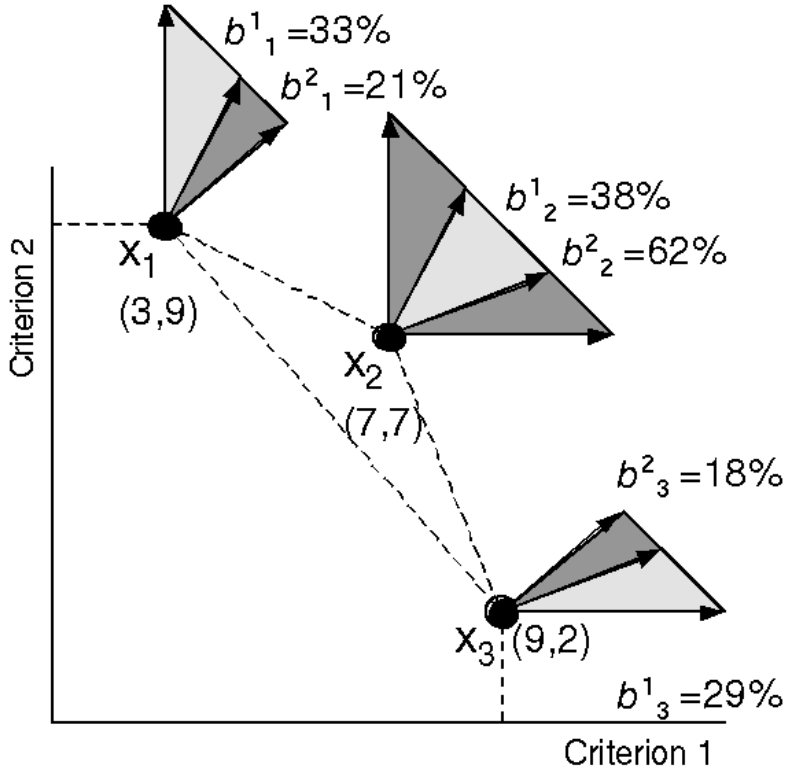
- Total lack of preference information is represented by a uniform joint probability distribution of the weight space



- If some preference information is available, the weight space can be restricted with linear constraints

Rank acceptability index

Describes the share of different weights and criteria measurements ranking an alternative on a certain rank



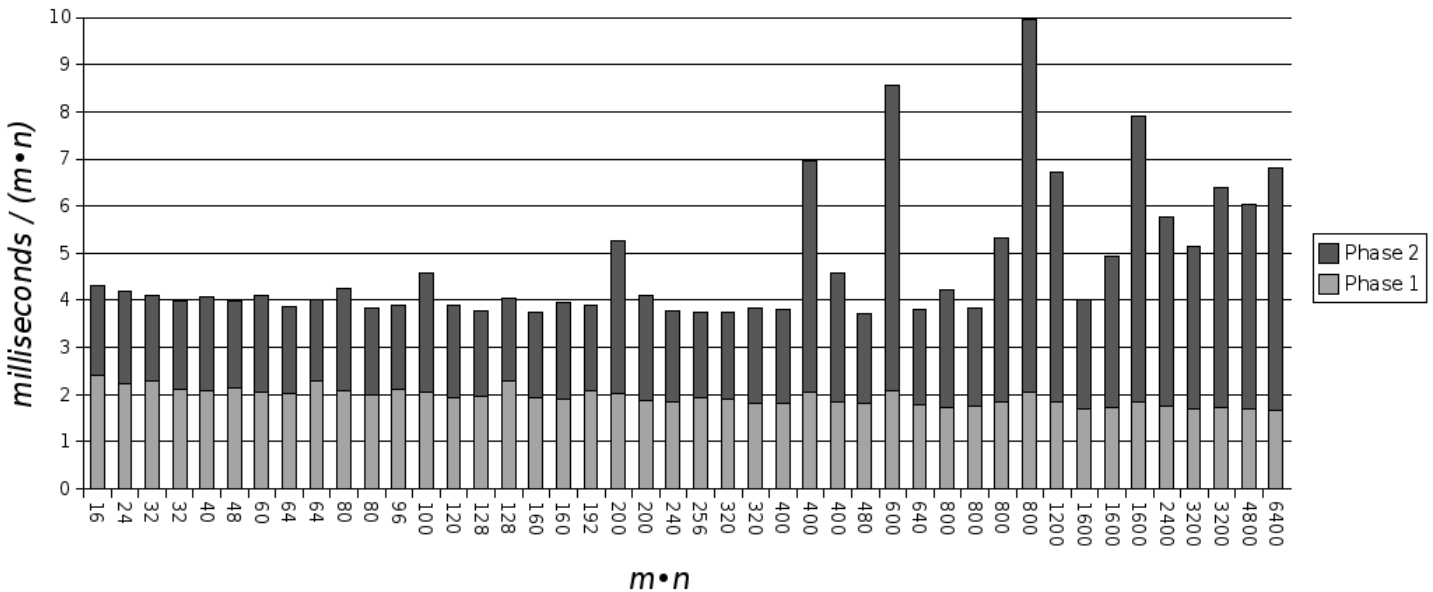
$$b_i^r = \int_{\xi \in \chi} f_\chi(\xi) \int_{w \in W_i^r(\xi)} f_W(w)\, dw\, d\xi$$

Central weight vector & confidence factor

- **Central weight vector** describes the preferences of a typical DM supporting this alternative with the assumed preference model
  - CW's are used for inverse approach: instead of asking preferences and giving results, answers the question "which preferences support an alternative to be the most preferred one?"
- **Confidence factor** is the probability for an alternative to be the preferred one with the preferences expressed by its central weight vector
  - CF measures whether the criteria measurements are accurate enough to discern the efficient alternatives

Computation

- Analytical techniques based on discretizing the integrals with respect to each dimension are infeasible, so the integrals are estimated through Monte Carlo simulation
- 10000 simulations provide sufficient accuracy for the indices
- Algorithm has less-than squared mean complexity and is very fast in practice



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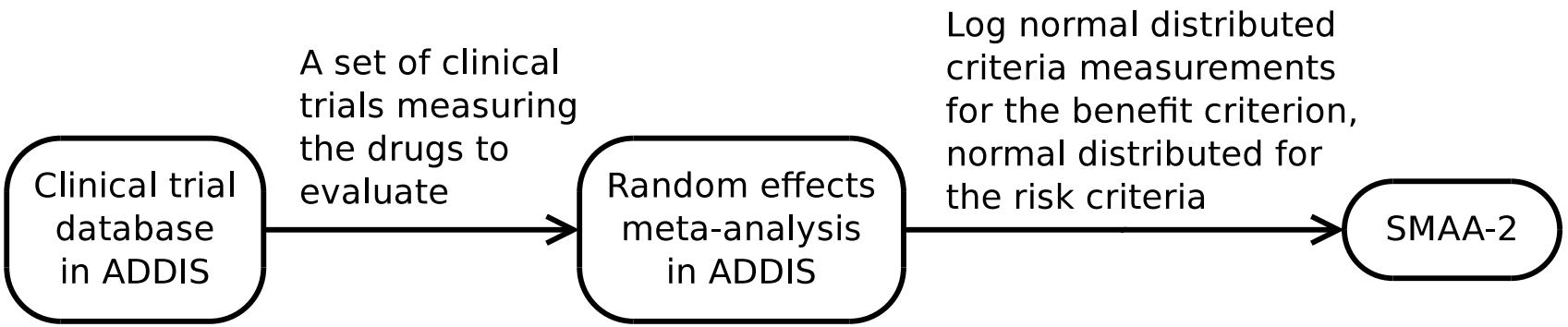
Tervonen & Lahdelma, EJOR, 2007

MCDA Model Generation



Tervonen, URPDM'2010

When cannot the MCDA-BR-model be generated?

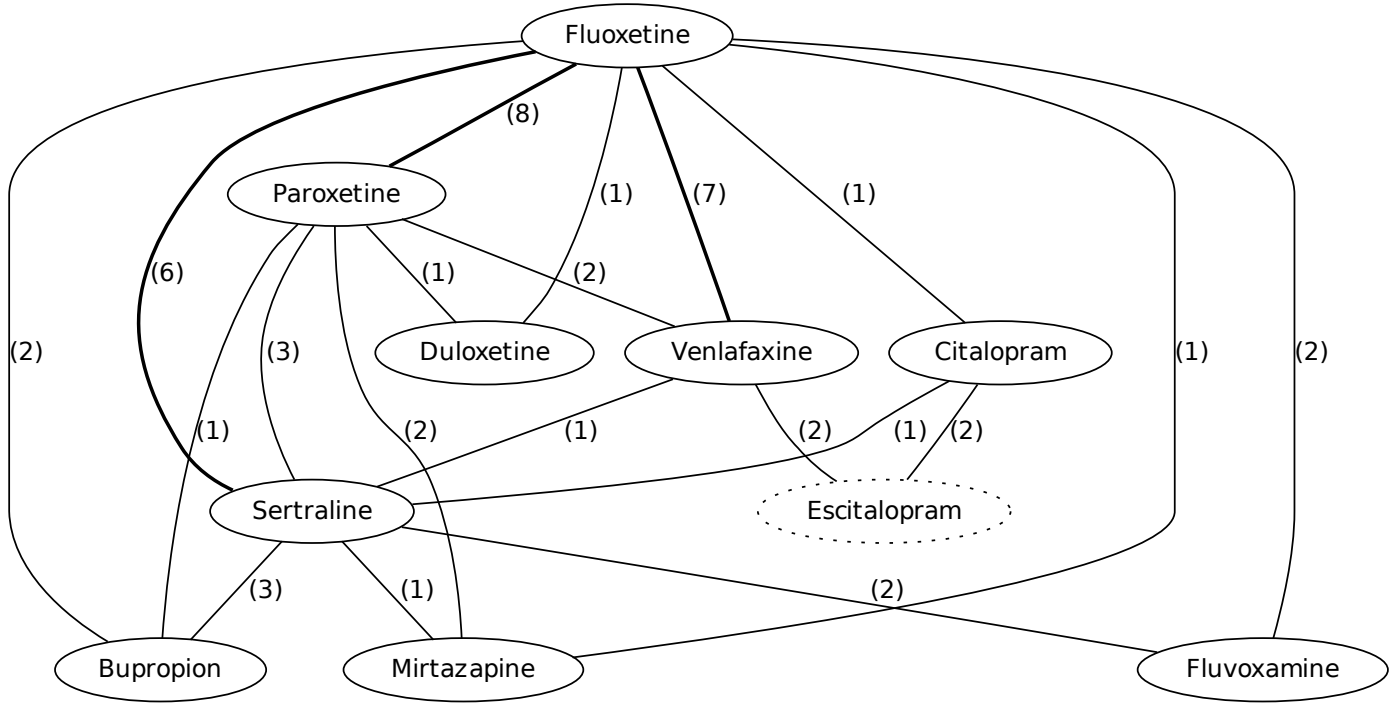
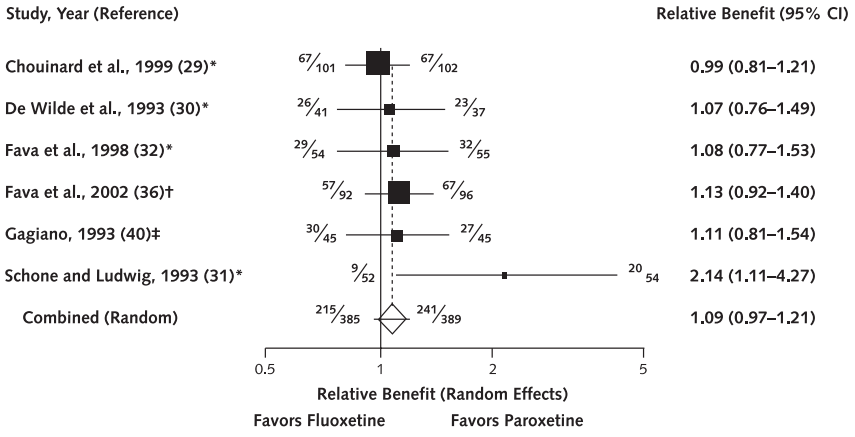
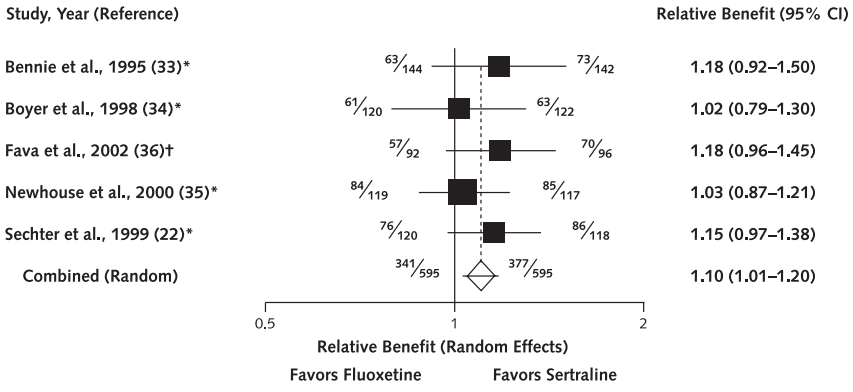
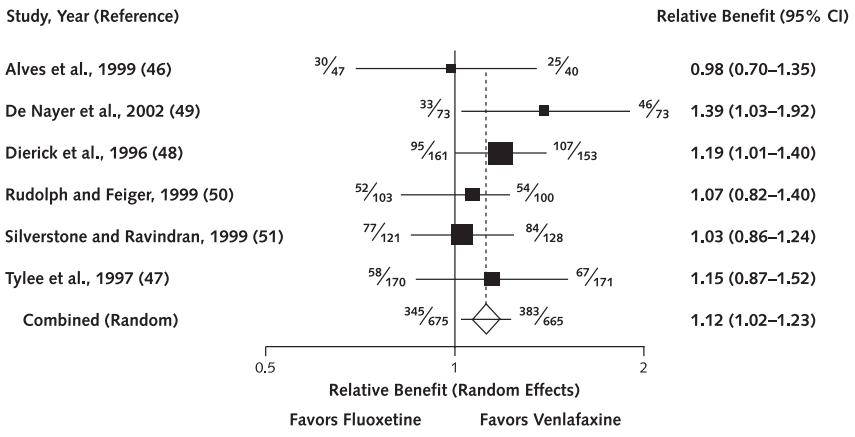


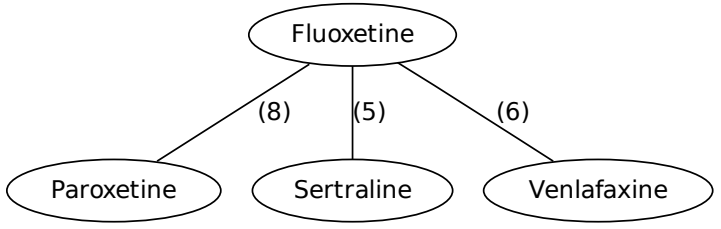
Figure: Evidence network of studies comparing efficacy of 2nd gen antidepressants

Meta-analysis limitations









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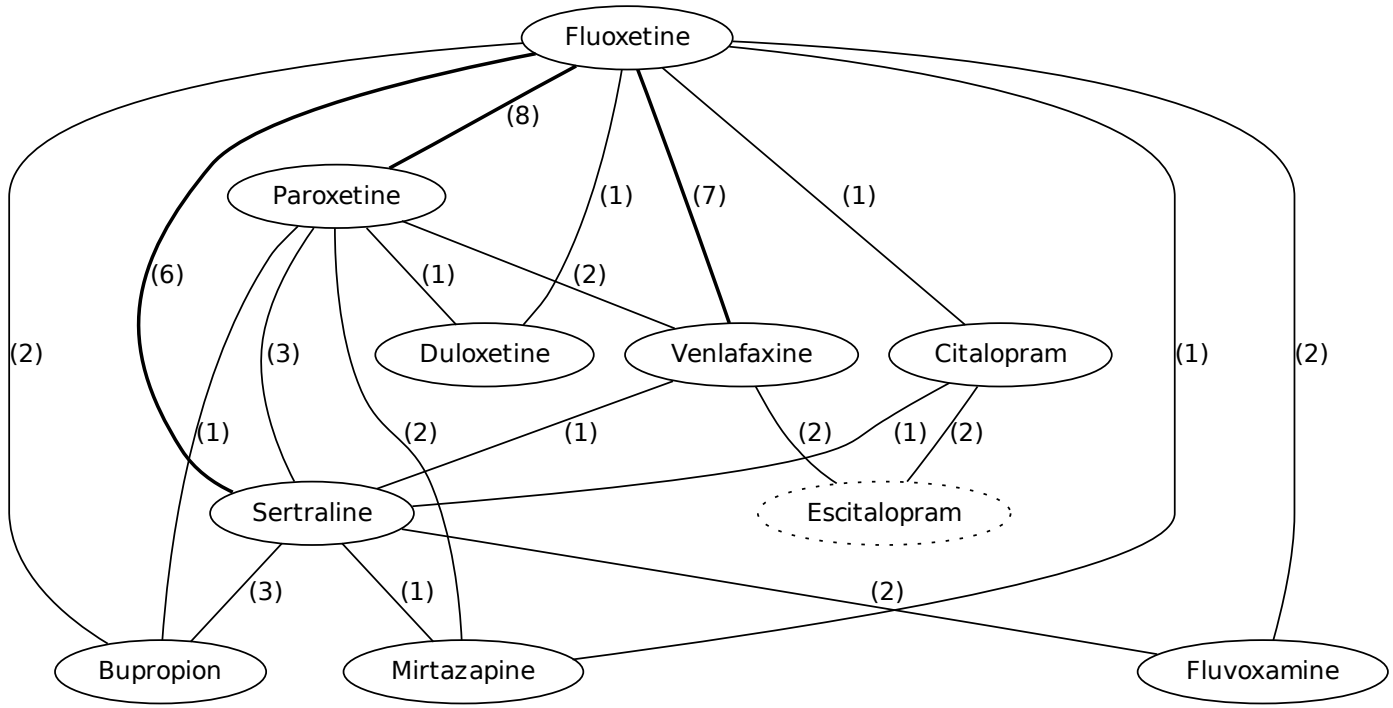

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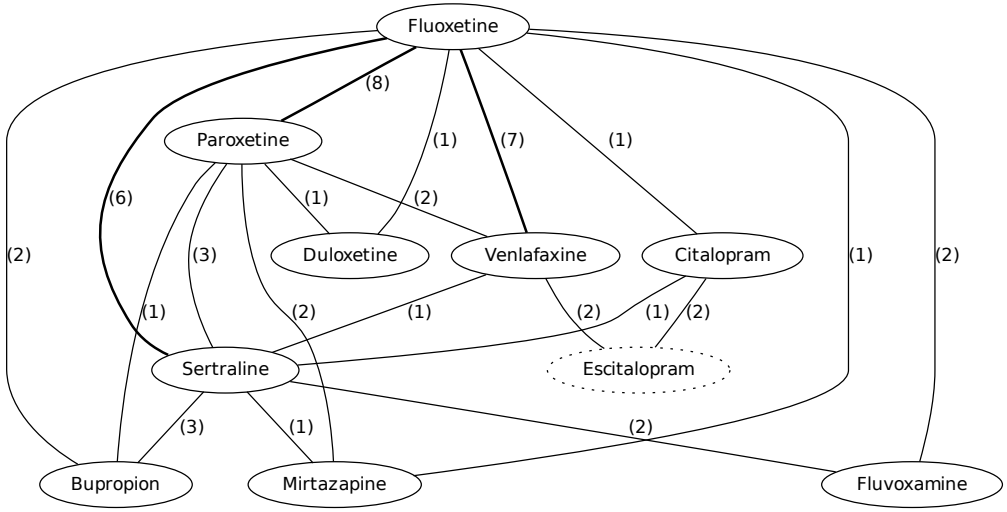
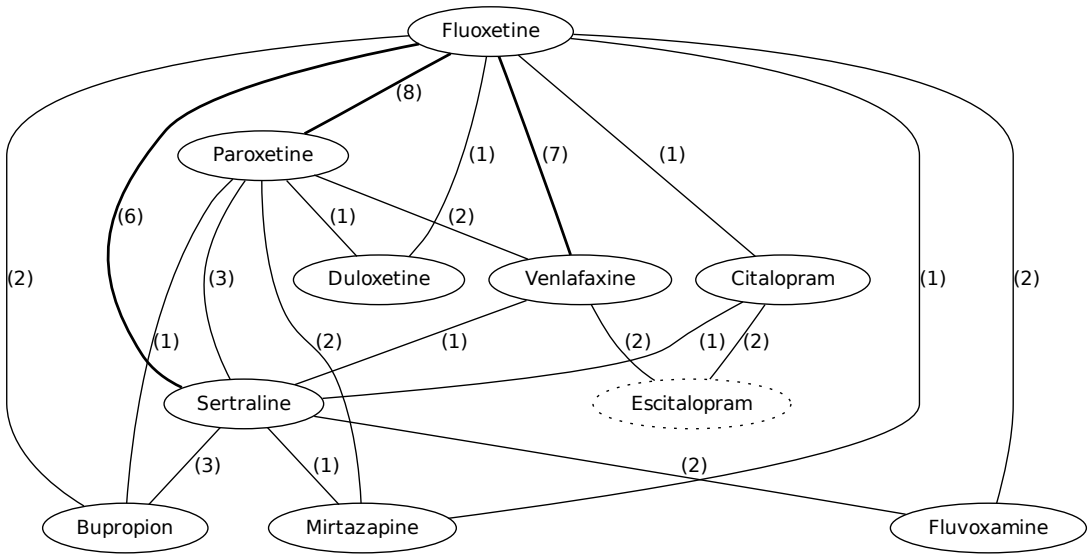


- Uncertainty about fluoxetine not represented explicitly
- What happens if we choose another baseline?
  - Other studies included $\rightarrow$ possibly different results
- Not all drugs can be included (escitalopram)
- We're "double counting" multi-arm trials

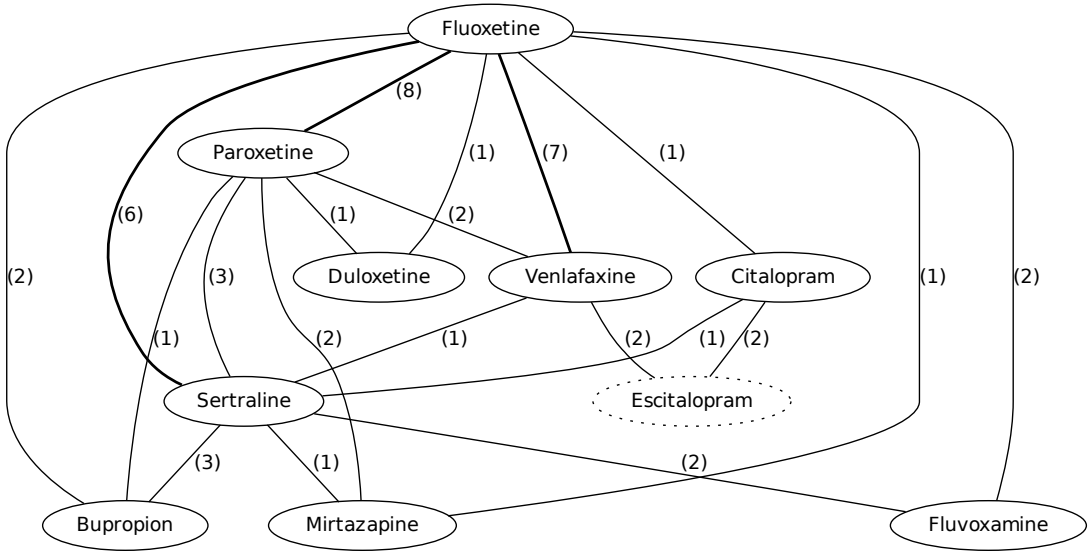
Solution: apply network meta-analysis



- Include **all** evidence in one mixed-treatment comparison (MTC) analysis

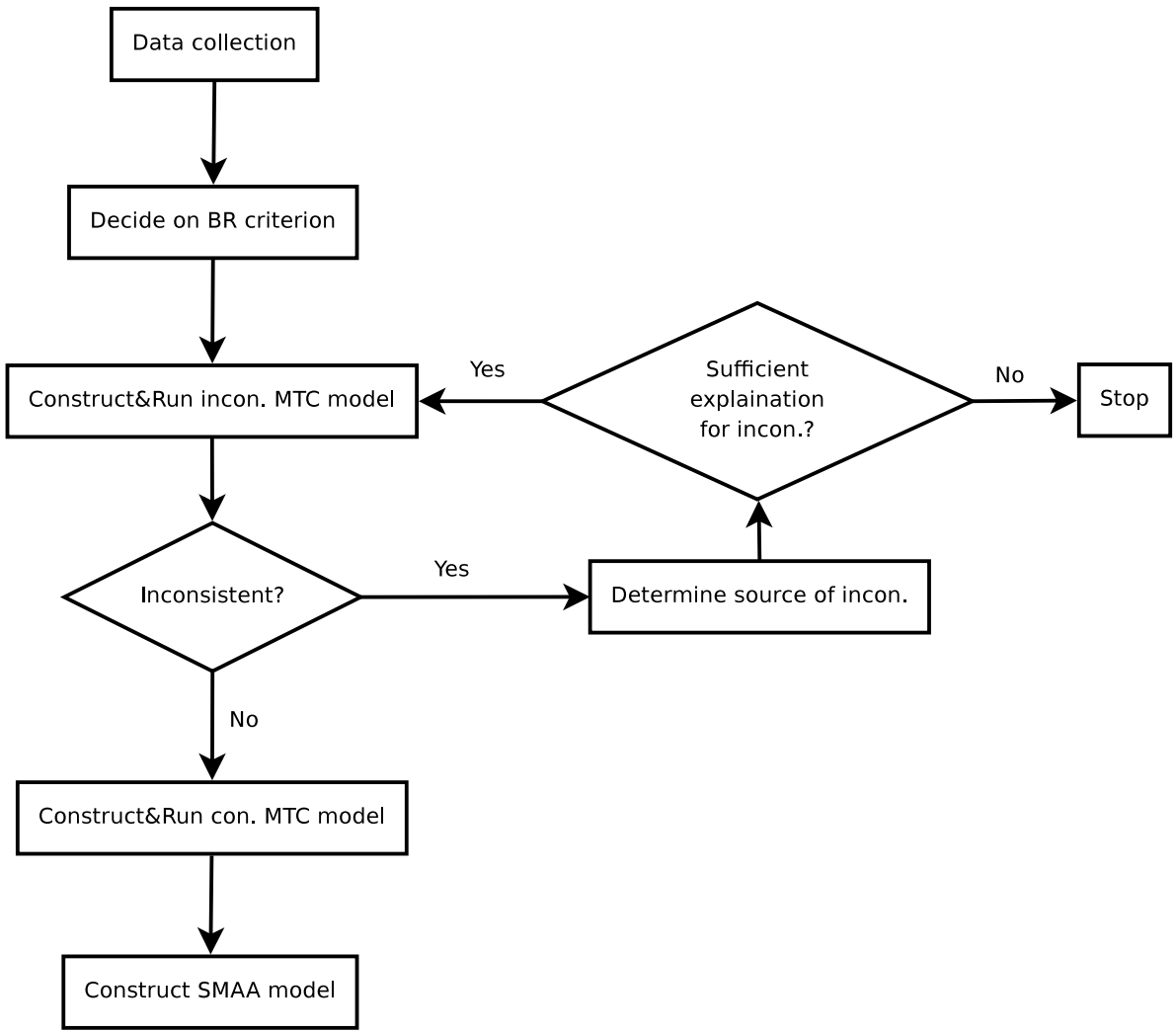
Van Valkenhoef & al., manuscript, 2010

Network meta-analysis problems



- Model considerably more complex (Bayesian instead of regression)
- Treatment network inconsistency must be evaluated
- No algorithms for generating MTC models exist(ed)

MTC/SMAA application

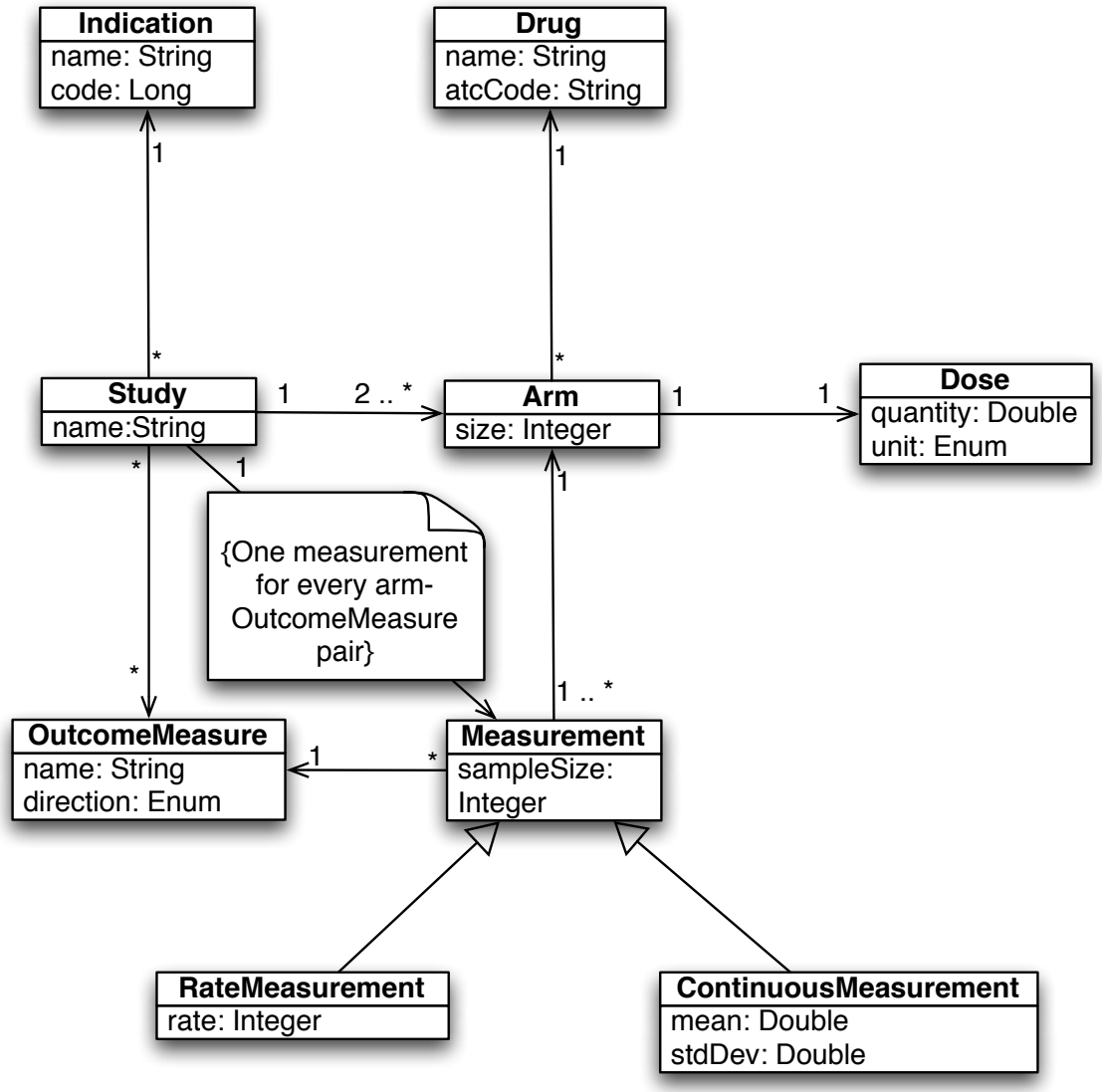


Zhao, MSc thesis @ KTH.se, 2010 (to appear)

Clinical trial data models

- Previous advances in clinical trial informatics have aimed for a comprehensive data model
- Comprehensiveness is conflicting with usefulness
- We provide a minimal data model to enable useful analyses

Minimal data model



Aggregate Data Drug Information System

- Import & store trial design & results
- Generation & computation of
  1. meta-analyses
  2. network meta-analyses
  3. SMAA benefit-risk models

Time for live demo!

ADDIS v0.9-SNAPSHOT from www.drugis.org

Conclusions

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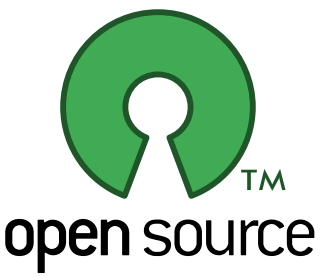
- Minimal data model is required for generation of useful analysis models
- The ADDIS software is open source, and implements already all this!



Obrigado pela sua atenção!