ADDING VALUE AND EXPERTISE FOR SUCCESSFUL MARKET ACCESS

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Lundbeck PROGRESS IN MIND

Market Access - price & reimbursement

- Situation today within psychiatric and neurological diseases
  - Increased requirements for reimbursement of new drugs in Europe
  - Treatment guidelines often recommend generics as first choice

HTA agencies / payer* evidence requirements

To make rational decision on price and reimbursement, HTA / payers need evidence of:

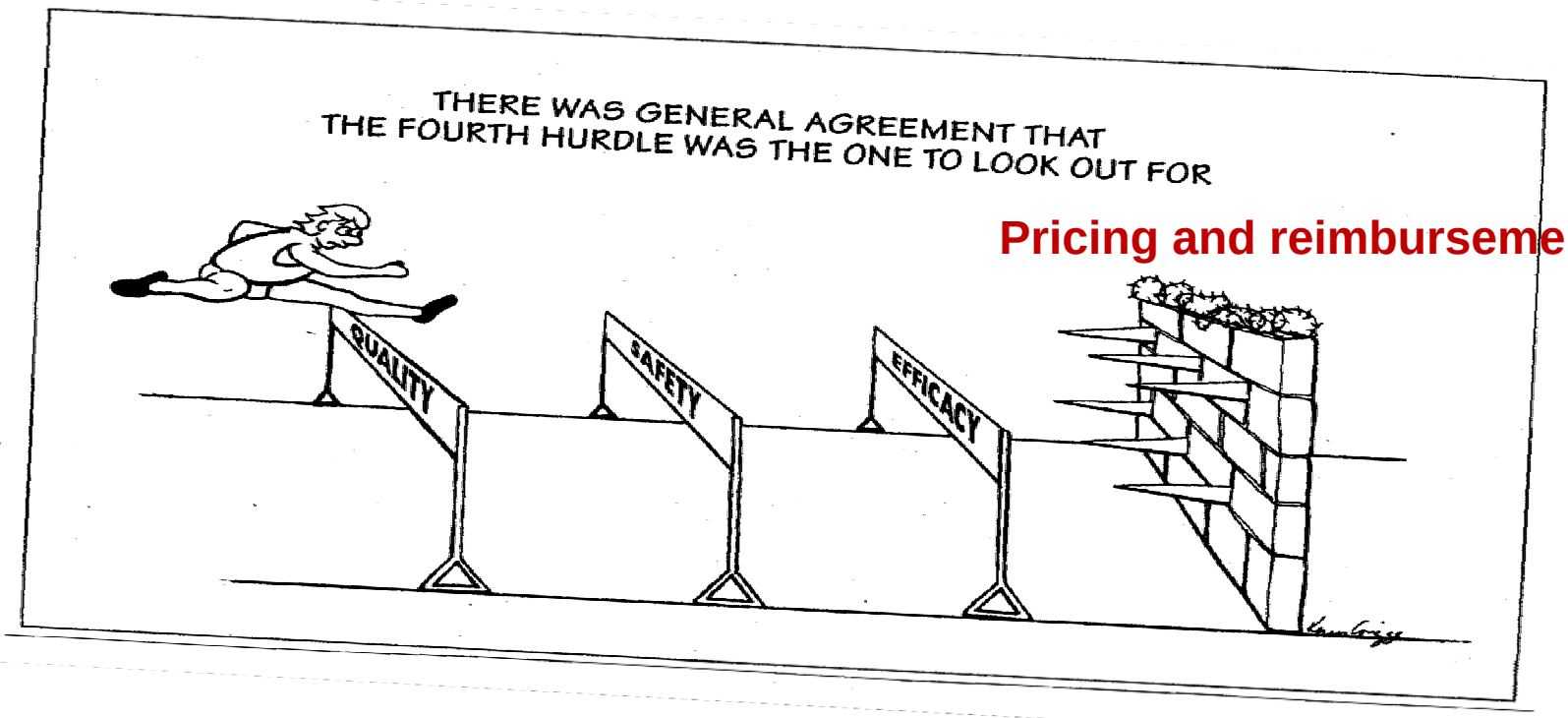
- Relative Effectiveness
  - the extent to which the drug does more good than harm compared to one or more treatment options in clinical practice
- Cost-Effectiveness
  - an assessment of relative effectiveness, with the added element of considering resource utilization and costs

* For simplicity the HTA (Health Technology Assessment) agency / payer is defined as the agency (agencies) making the decision on the price and reimbursement of a new drug

Agenda

- The increased complexity of drug development
- How do we interact with HTA agencies and payers to negotiate price and reimbursement
- Key areas where statisticians can add value
  - Comparative Efficacy Research
  - Epidemiological Studies
  - Cost-Effectiveness
- Recommendations

The increased complexity of drug development

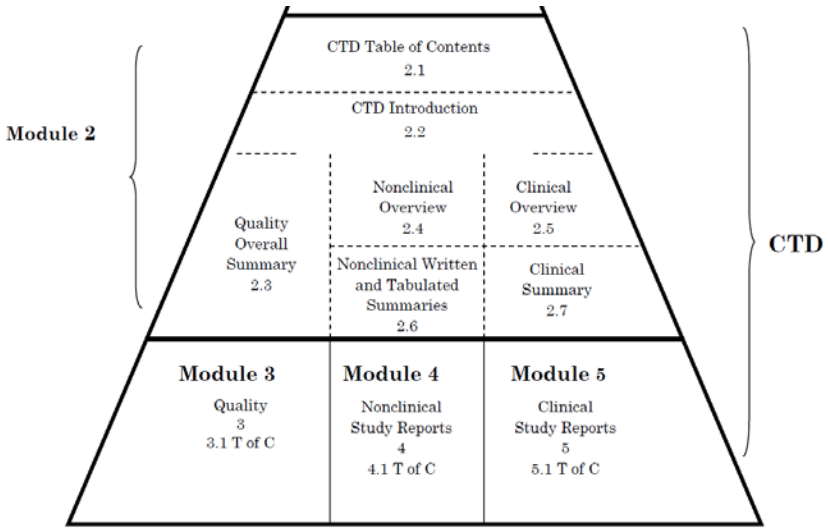


Market access alignment foundation

Europe	US
Registration	
In EU, EMA approval does not guarantee market access	FDA approval guarantees US market access
Pricing & reimbursement to negotiate use and place in therapy	
Mainly country central or regional authorities deciding on pricing and reimbursement	Price level set freely but private and state health plans [e.g. Medicare (65+), and Medicaid (low income)] determine formulary access, negotiate on price
Market Access value platform	
Evidence-based with focus on comparative therapeutic value and cost-effectiveness	Evidence-based, but legally restricted to data in prescribing information

Interacting with HTA agencies and payers

Regulatory submission dossier



HTA / payer submission dossier*

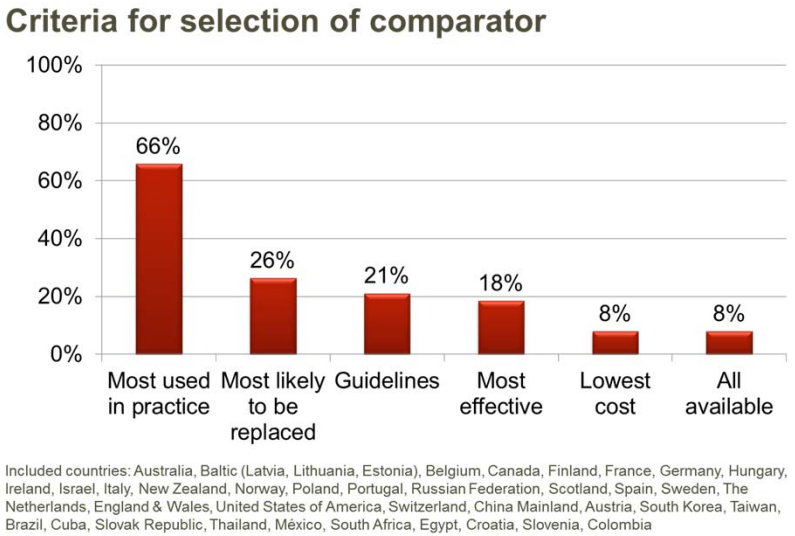
- Differences between countries in process, content & methodology requirements
- **Clinical value** is key in all countries
  - Validity and results of relevant RCTs
    - Individually and meta-analysis results
  - Comparative efficacy/effectiveness
    - Head-to-Head RCT
    - Indirect & mixed treatment comparisons
  - Results of non-RCTs / observational trials
  - Adverse events
- **Cost effectiveness**

* Most HTA agencies / payers have a template with specified structure & format

COMPARATIVE EFFICACY RESEARCH

Comparative efficacy

- Selection of comparator(s)
  - Variability between countries regarding views on appropriate comparator
  - Data from clinical practice is helpful in identifying relevant comparators
  - Comparison with off-label or unlicensed drugs is sometimes requested
  - Sequence of therapy, 1st or 2nd line



Included countries: Australia, Baltic (Latvia, Lithuania, Estonia), Belgium, Canada, Finland, France, Germany, Hungary, Ireland, Israel, Italy, New Zealand, Norway, Poland, Portugal, Russian Federation, Scotland, Spain, Sweden, The Netherlands, England & Wales, United States of America, Switzerland, China Mainland, Austria, South Korea, Taiwan, Brazil, Cuba, Slovak Republic, Thailand, México, South Africa, Egypt, Croatia, Slovenia, Colombia

Use a systematic literature review to identify relevant RCTs for relevant comparators

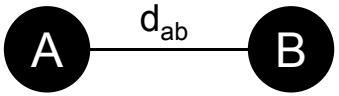
- Define research protocol
  - Objective
  - Population
    - Inclusion and exclusion of trials
    - Any sub-populations of interest
  - Comparators
  - Endpoints
  - Data source (e.g. obs, lsmeans)
  - Limitations and biases
- Search
- Review
- Data extraction

- Incomplete block design
  - (mean, sd, n) per study & treatment
  - Two-way ANOVA w/ sparse data and known (but varying) variance

Study	Treatment						
	A	B	C	D	E	F	G
1	X,X,X	X,X,X					
2		X,X,X	X,X,X	X,X,X			
3	X,X,X		X,X,X				
4	X,X,X	X,X,X	X,X,X				
5	X,X,X	X,X,X		X,X,X			
6		X,X,X	X,X,X				
7	X,X,X		X,X,X				
8	X,X,X	X,X,X	X,X,X				
9			X,X,X	X,X,X	X,X,X		
10						X,X,X	X,X,X
11			X,X,X		X,X,X		
12				X,X,X	X,X,X	X,X,X	

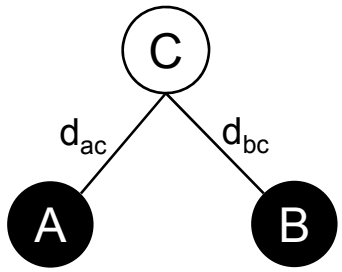
Comparative efficacy: Direct comparison

- Direct comparison of AvB
  - Meta-analysis of head-to-head trials
  - Similarity in trials e.g. design, treatment/dose, population, stat method ..
  - Heterogeneity in treatment effects (i.e. variability between trials results)
  - Choice of stat model: Assume $Y_{i,t} \sim N(\mu_{i,t}, \sigma_{i,t}^2)$, study i and treatment t
    - Fixed effect model: $\mu_{i,t} = \alpha_i + \beta_t$
    - Random effect model: $\mu_{i,t} = \alpha_i + \beta_t + \varepsilon_{i,t}$, $\varepsilon_{i,t} \sim N(0, \tau^2)$



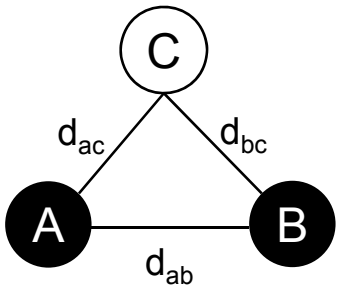
Comparative efficacy: Indirect comparison

- Indirect comparison of AvB
  - Two meta-analysis of AvC trials and BvC trials
  - Usual issues with meta-analysis still applies
  - Indirect (d_{ab}) = d_{ac} - d_{bc}



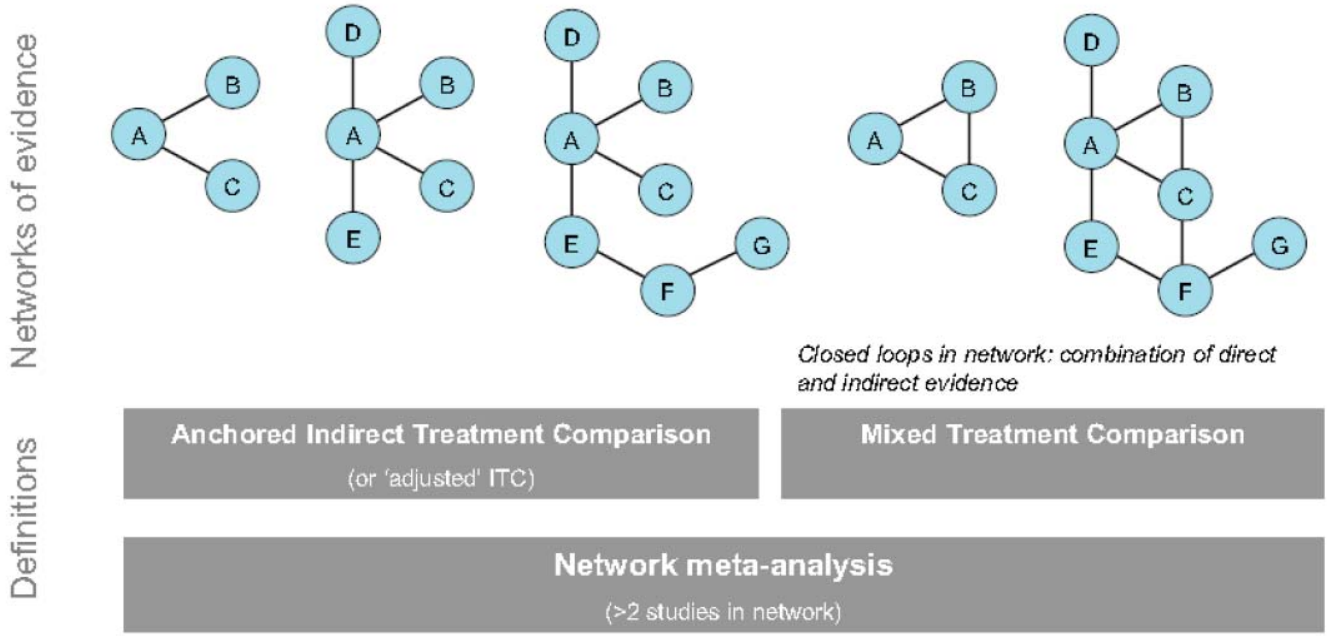
Comparative efficacy: Mixed treatment comparison

- Mixed treatment comparison / network meta-analysis
  - Combined estimate of direct and indirect treatment difference from 2-arm trials (AvB, AvC, BvC) and 3-arm trials (AvBvC)
  - Usual issues with meta-analysis still applies
  - Underlying assumption that direct (d_{ab}) & indirect (d_{ac} - d_{bc}) effects are consistent in 2-arm trials



Extending to general networks with several comparators

ISPOR Indirect Treatment Comparisons Good Research Practices Task Force



International Society for Pharmacoeconomics and Outcomes Research (ISPOR):
https://www.ispor.org/workpaper/interpreting-indirect-treatment-comparison-and-network-meta-analysis-studies-for-decision-making.pdf

Comparative efficacy – points to consider

- Is direct evidence from RCTs always more realiable?
- Direct evidence should always be presented
- Discuss similarity in trials going into meta-analyses
- Investigate heterogeneity
  - Presence of effect modifiers
  - Could be explained by adjusting for study level baseline characterics
  - Use random effect model to provide more conservative results in the presence of between study variability in treatment effects
- Examine inconsistency between direct and indirect effect in close loops
  - Can it be explained by an extreme observation in one trial?
  - Differences in treatment effect modifiers between comparisons?

Comparative efficacy - treatment effects in sub-groups

- Requirement varies considerably between HTA agencies / payers
- Germany (IQWiG / G-BA)
  - Require evaluation by subgroup and impose reimbursement restrictions based on disease or patients characteristics
    - Dossier should discuss, for each RCT, results with interaction test $p<0.2$
- UK (NICE)
  - Require evaluation of relevant sub-groups of patients in which clinical and cost-effectiveness may differ to overall population
- Sweden (TLV)
  - Evaluation in the entire licensed indication; rarely subgroup discussions

Example: Selincro® (nalmefene)

- Selincro (nalmefene) approved by EMA in 2013
  - Label: Reduction of alcohol consumption in adult patients with alcohol dependence who have a high drinking risk level (according to WHO), without physical withdrawal symptoms and who do not require immediate detoxification
  - Three double-blind RCTs: nalmefene vs placebo; + psychosocial support
  - Co-primary endpoints: Change in Total Alc Cons (g/day) & Heavy Drinking Days
- Two indications recognised in EMA guideline on alcohol dependence
  - Full abstinence goal (relapse prevention after detoxification)
    - Several drugs approved e.g. naltrexone, acamprosate
  - Intermediate harm reduction goal (without prior detoxification)
    - Selincro is currently the only drug approved

Example: Selincro® (nalmefene)

UK (NICE)

- Systematic literature review
  - Research protocol, data extraction ..
- Psychosocial support accepted as appropriate comparator
  - Clinical evidence based on head-to-head RCTs
- Meta-analysis of confirmatory trials, with/without supportive trials identified
- NICE concluded that the clinical effectiveness evidence was relevant to clinical practice in England

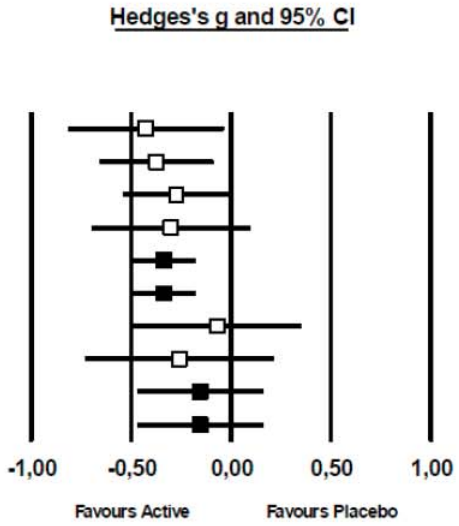
Germany (IQWiG / G-BA)

- Systematic literature review
  - Research protocol, data extraction ..
- G-BA specified naltrexone as the appropriate comparator
  - No head-to-head RCTs available
- Indirect comparison
  - Two meta-analysis of nalmefene vs placebo, and naltrexone vs placebo trials
  - Very limited relevant naltrexone trials identified as ‘off-label’ setting
- IQWiG concluded no added benefit proven

Example: Selincro® (nalmefene) - Germany (G-BA)

Ergebnis des Indirekten Vergleichs

Model	Group by Prp.	Study	Outcome	Statistics for each study: Hedges's g	Standard error	Lower limit	Upper limit	p-Value	Sample size: Active	Placebo
	NMF	NMF02b	HDD	-0,427	0,198	-0,815	-0,039	0,0308	62	44
	NMF	NMF04b	HDD	-0,373	0,144	-0,655	-0,091	0,0096	85	114
	NMF	NMF05b	HDD	-0,274	0,137	-0,542	-0,005	0,0456	103	111
	NMF	NMF06b	HDD	-0,301	0,202	-0,698	0,095	0,1365	102	32
Fixed	NMF			-0,336	0,081	-0,495	-0,176	0,0000	352	301
Random	NMF			-0,336	0,081	-0,495	-0,176	0,0000	352	301
	NTX	NTX04	DD%, HDD%	-0,071	0,216	-0,494	0,351	0,7413	31	32
	NTX	NTX51	HDD%	-0,258	0,241	-0,730	0,213	0,2831	34	34
Fixed	NTX			-0,155	0,161	-0,469	0,160	0,3360	65	66
Random	NTX			-0,155	0,161	-0,469	0,160	0,3360	65	66



https://www.g-ba.de/downloads/92-975-614/2014-08-28_Modul4A_Nalmefen.pdf

Example: Selincro® (nalmefene) - Germany (G-BA)

Meta-Analyse	Effektstärke		Hetero-genität	Indirekter Vergleich Nalmefen vs Naltrexon	
	Hedges' g ± SE	p-Wert [95 % KI]	I^2 p-Wert	Hedges' g [95 % KI]	p-Wert
Nalmefen vs Placebo	-0,336 ± 0,081	p<0,001 [-0,495; -0,176]	0,0% p=0,916	-0,181 [-0,534; 0,172]	p=0,314
Naltrexon vs Placebo	-0,155 ±0,161	p=0,336 [-0,469; 0,160]	0,0% p=0,562		

SE: Standardfehler, KI: Konfidenzintervall

EPIDEMIOLOGICAL STUDIES

Use of epidemiological studies in HTA / payer interactions

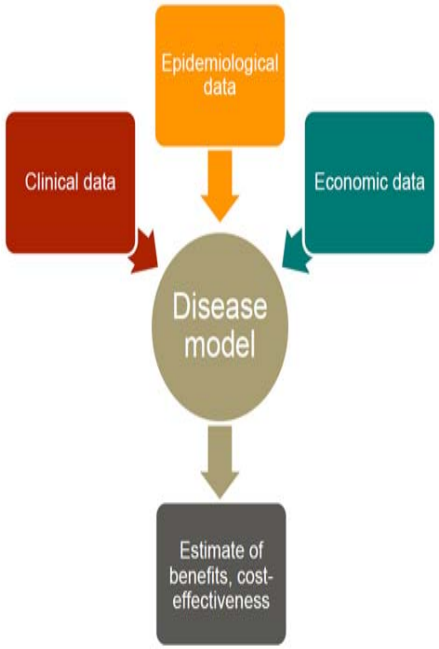
- Mapping treatment practices in routine care and unmet need
- Link between clinical endpoints (short-term) and ressource utilization / patients-related outcomes (long-term)
- Generating data for the cost-effectiveness model by calculating healthcare resource use according to health state in the population of interest
- Comparative effectiveness

- Observational data; assignment to treatment not randomised
  - Likely imbalance in observed and unobserved baseline characteristics
  - Handling of observed confounders: regression model, stratification, matching, propensity score

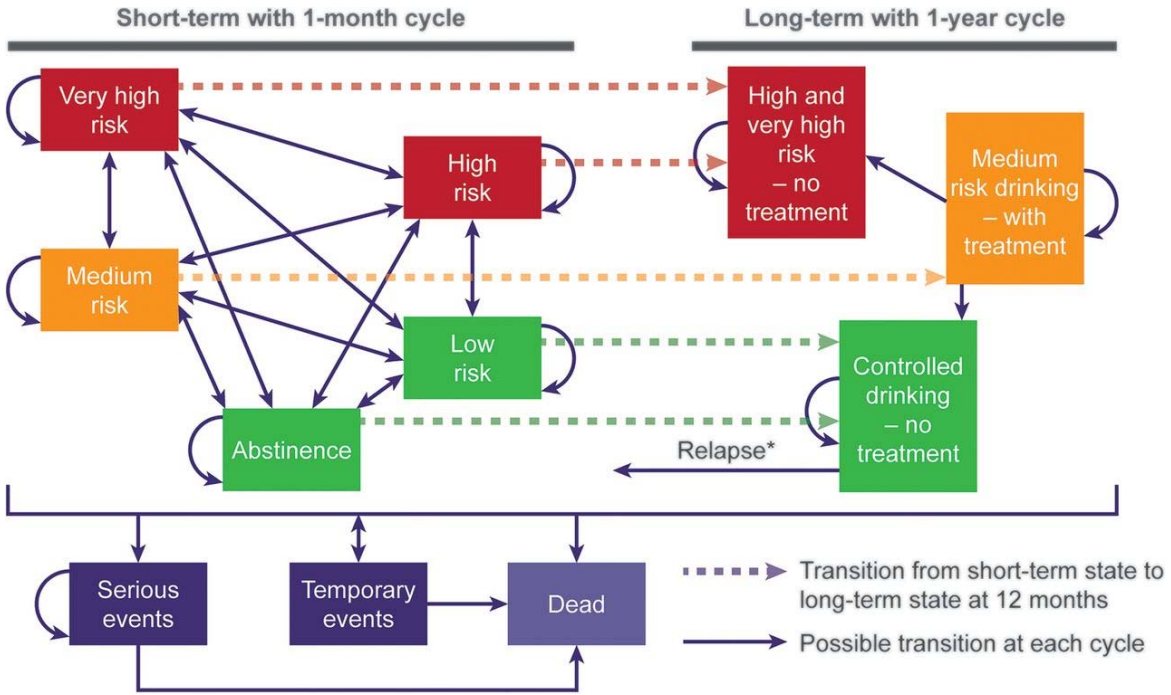

COST-EFFECTIVENESS

Cost-effectiveness

- Cost-effectiveness based on:
  - relative efficacy/effectiveness and resource utilization and costs
- Often requires an element of modelling
- Cost-effectiveness based on data from multiple sources
  - Extrapolate from short-term trial data to long-term outcomes
  - Investigate cost-effectiveness by patient subgroups
  - Explore sensitivity of results to changes in assumptions or inputs



Example: Selincro® - Cost-effectiveness model NICE



Alcohol-attributable harmful events included in the model:
Temporary events
-Transport injuries
-Injuries other than transport
-Lower respiratory infections
Serious
-Ischaemic heart disease
-Ischaemic stroke
-Liver cirrhosis
-Pancreatitis

Resource use
-GP, Specialist visit

Cost per event and ressource

*At each cycle, patients in the controlled drinking state could relapse into the drinking state they were in at the start of the model (high or very high drinking risk levels states in the short-term phase of the model), and hence to the original treatment they were successful with.

http://bmjopen.bmj.com/content/4/9/e005376.full

Example: Selincro® - Cost-effectiveness model NICE

- Short-term phase (first year): RCT data used for transition probabilities
- Long-term phase (years 2–5): Cycle length of 1 year based on the availability of reliable clinical data particularly with regard to the maintenance of effect and probability of relapse to heavy drinking
- Risk of experiencing alcohol-attributable harmful events

$$Personal\ Risk\ Disease(i)_{(T1)}Patient_{(z)} = General\ Population\ Risk\ Disease\ (i) * RRDisease(i)\,(x_{T1})Patient_{(z)}$$

$RRDisease(i)(x_{TI})Patient_{(z)}$ is the relative risk of disease (i) given an alcohol consumption at time T_1 of x grams for a Patient z with alcohol dependence, versus general population.

RECOMMENDATIONS

Recommendations

- Statisticians should be involved early in the market access strategy to
  - Plan and perform comparative efficacy research
  - Ensure proper design and analysis of epidemiological studies
  - Provide input and challenge the many assumptions / extrapolations in cost-effectiveness modelling
- Start early to avoid delays
- Take part in re-negotiation process