Reimbursement based on surrogate endpoints in cardiovascular diseases

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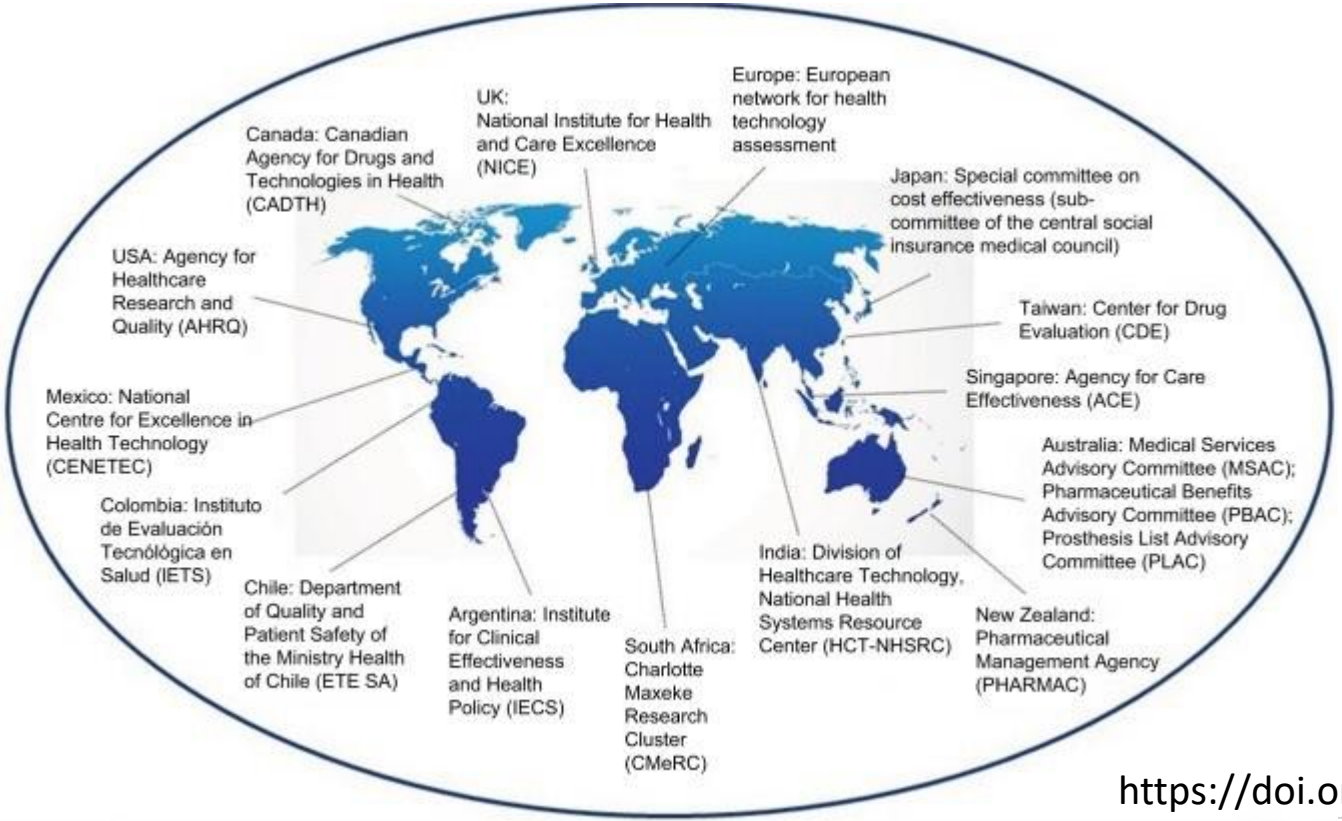
Conflicts of Interest

- No relevant CoI to declare
- Member of ESC Clinical Practice Guidelines Committee
- Member of Value in Health Advisory Board

Content

- Health Technology Assessment and Reimbursement
- The Economic Evaluation Framework
- Economic evaluation and RCTs with target outcomes
- Surrogate outcomes as drivers of economic analyses: issues
- Developments in use of surrogate outcomes in registration decisions
- Developments in use of surrogate outcomes in reimbursement decisions

Health Technology Assessment and reimbursement

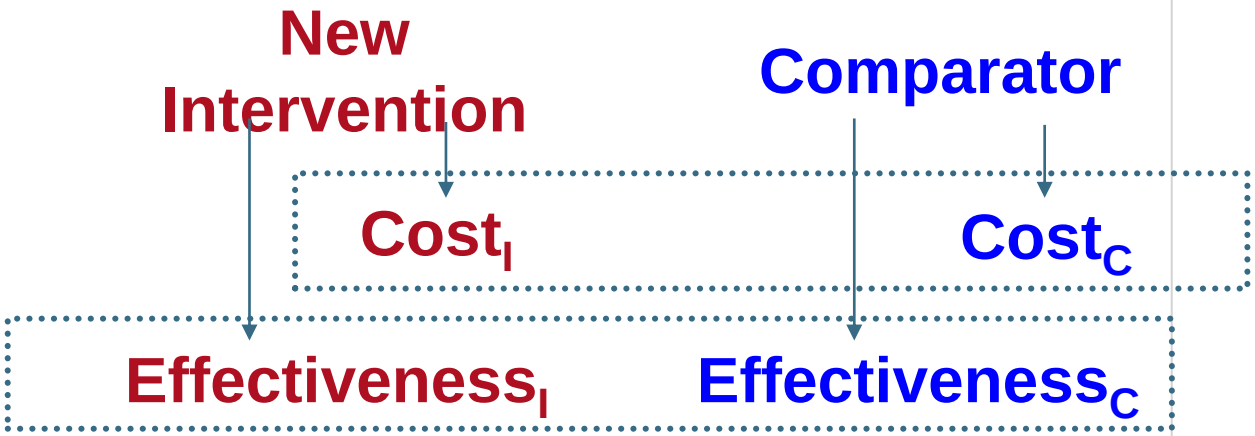


Economic evaluation/ consideration of benefits and costs used to guide reimbursement decisions and/or price negotiations

https://doi.org/10.2147/AMEP.S175683

Economic evaluation: an objective way of making choices

"The comparative analysis of alternative courses of action in terms of both their costs and their consequences" (Drummond et al, 2015)



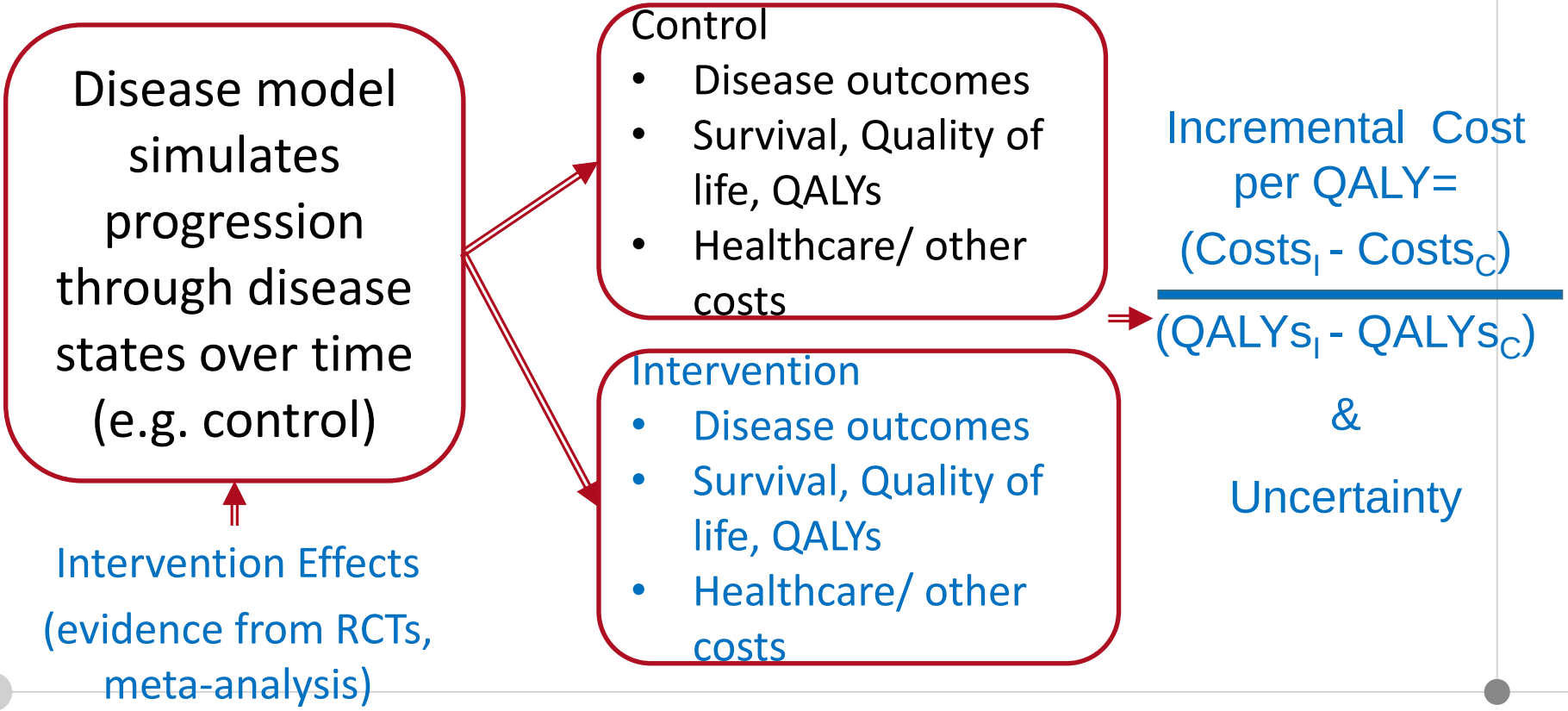
$$\text{Incremental cost-effectiveness ratio (ICER)} = \frac{Cost_I - Cost_C}{Effect_I - Effect_C}$$

Key considerations in economic evaluations

- **Comparator**: usual/current care
- **Timeframe**: long enough for key differences to emerge
- **Health measure**: comprehensive to allow comparison between interventions and disease areas (quality-adjusted life year, QALY)
- **Perspective**: Healthcare/Payer, Societal

➢Net effects of health technologies on overall health and costs, not just direction but also size of effects, are crucial for decisions on coverage and reimbursement.

Economic evaluation in CVD typically requires LONGTERM perspective and therefore MODELING



What is good value (cost-effective) health technology in different jurisdictions?

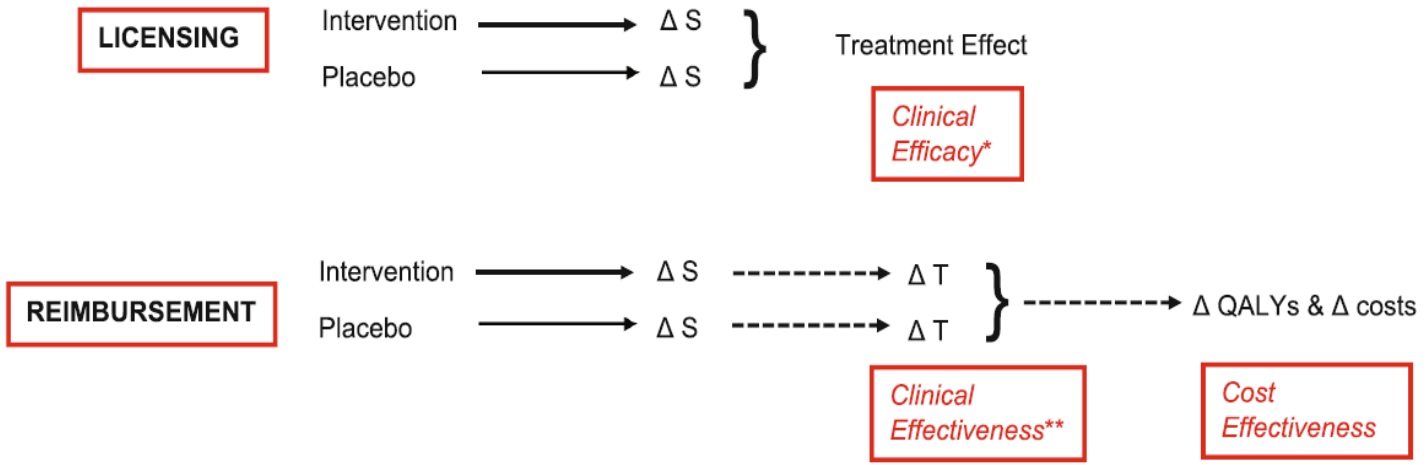
- Incremental cost per QALY thresholds in use:
  - UK (NICE): £20,000 - £30,000 plus modifiers based on QALY shortfalls
  - Ireland (HIQA): €20,000 - €45,000
  - Spain: €30,000
  - Canada: $20,000 - $100,000
  - US: $50,000 - $150,000
- World Health Organisation (WHO) (developing countries): if ICER of intervention
  - < GDP/capita: very cost-effective
  - between 1x & 3x GDP/capita: cost-effective
  - > 3x GDP/capita: not cost-effective

Economic evaluation and RCTs with target outcomes

- Impact of intervention on target patient-relevant outcomes
- Large, include economic outcomes, and could inform economic evaluations:
  - Inform Disease model structure based on key outcomes
  - Inform Survival, Quality of life and Costs
- Treatment effects applied on key outcomes are CLOSER to survival/QALYs/costs

➢ **Minimize bias on “economic” outcomes and economic evaluation**

Comparison of role of surrogate endpoints in licensing and reimbursement, Weir & Taylor 2022



S: surrogate endpoint
T: final patient-relevant outcome
Δ: baseline-follow up change
QALYs: quality adjusted life years

---------→ extrapolation of Δ S to Δ F and to Δ QALYs & Δ costs

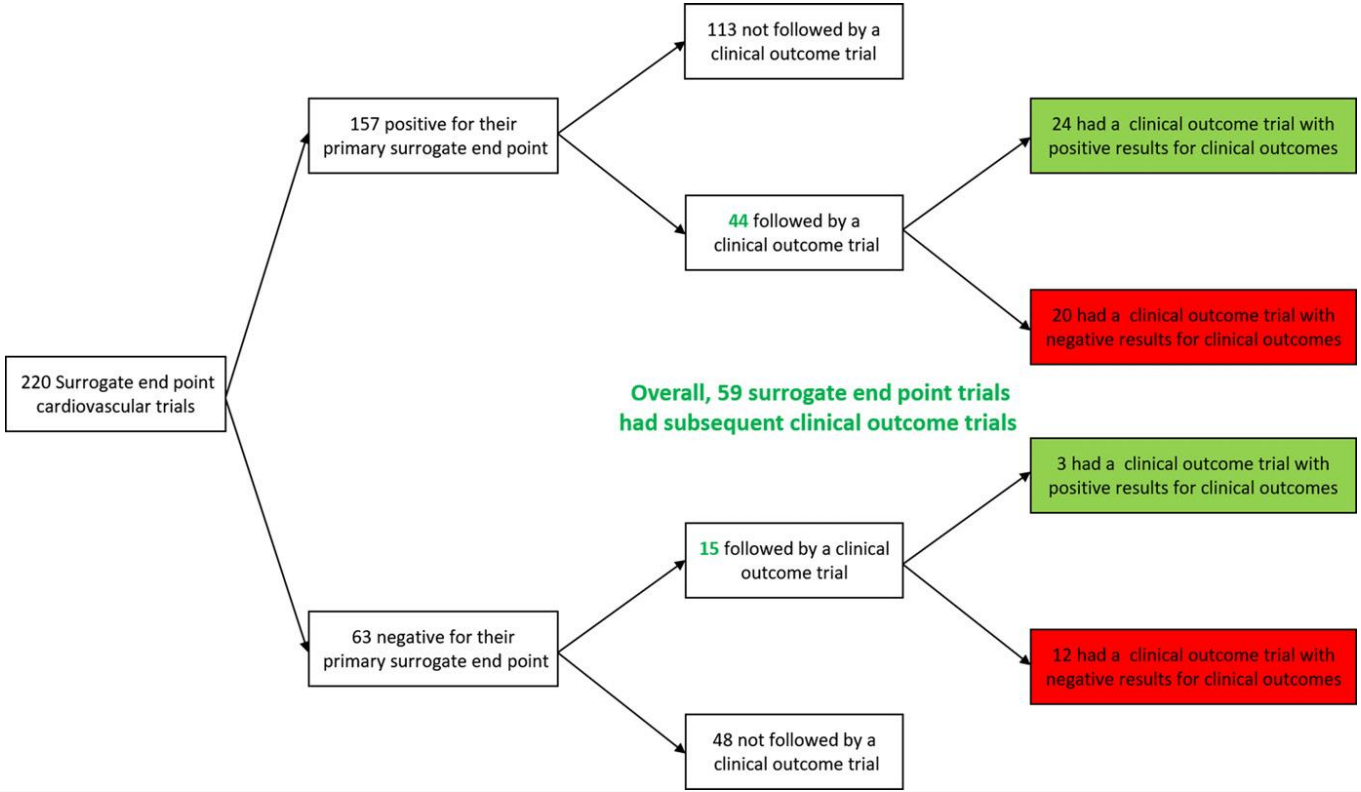
*efficacy: the therapy produces a superior outcome (S)
*effectiveness: the therapy produces the desired outcome (T) result

Surrogate outcomes as drivers of economic analyses: issues

- Typically smaller RCTs with limited ability to inform patient-relevant target outcomes and economic outcomes
  - External data needed
- Require modeling the relationship between SURROGATE and TARGET outcomes: direction and size of effects
- Key Question: How ‘surrogate outcomes’ influence long-term health outcomes

➢ **Substantially increased uncertainty as to value of intervention to patient**

Two Decades of Cardiovascular Trials With Primary Surrogate Endpoints: 1990–2011, Bikdeli et al. 2017



Relationship between surrogate and target outcomes: issues

- Effects on target outcomes may not materialise
- Adverse effects more likely to be missed
- Predicted effect size on target outcomes may be incorrect
  - surrogate endpoints RCTs more likely to report positive treatment effects (Ridker and Torres 2005: 67% vs 54%; Ciani et al. 2013: 62% vs. 37%; P = 0.01).
  - surrogate endpoints RCTs found treatment effects 46-47% larger than target outcomes RCTs (Ciani et al. 2013 ratio of ORs or RRs 1.46, p=0.03).

➢ **“Surrogate endpoint bias”**

See also review by Manyara et al 2023 for a summary of issues

Developments in use of surrogate outcomes in reimbursement decisions

- Regulatory agencies increasingly consider evidence using surrogate outcomes (40% HTA agencies with guidance, Grigore et al. 2020) and offer accelerated approval to promising new technologies based on surrogate outcomes (e.g. FDA, EMA). Guidance on acceptable surrogates is evolving.
- Strategies for **surrogate outcome validation**: evidence levels and strength of relationship (Ciani 2023), Biomarker-Surrogacy Evaluation Schema (Lassere et al 2008)
- Proposals for only **validated surrogate outcomes to be accepted** (Bruce et al 2019, Hey et al. 2020)
- **Conditional authorisation** on acquiring further, target outcomes data (EU Pharmaceutical Regulation 2023)

Surrogate outcomes and reimbursement decisions: current situation

- Higher level of uncertainty in economic evaluations based on surrogate outcomes
- More limited reimbursement decisions:
  - Restricted approvals (e.g. high risk subgroups)
  - Price discounts
  - Risk-sharing agreements (e.g. NICE patient access schemes, Cancer Drug Fund)
  - Outcome-based ontracts
  - Broader coverage for rare diseases, severe condition/no alternative treatment (e.g. QALY shortfall modifiers for NICE cost-effectiveness threshold)

Summary

- Reimbursement decisions require assessment of net health effects and net costs of technologies
- Assessment Framework is unchanged for surrogate outcomes
- However, substantially higher level of uncertainty in assessments of value of technologies evidenced by surrogate outcomes
- More restricted reimbursement options in place and further evidence sought
- Assessment framework same for CVD and non-CVD interventions: interpretation of disease severity and level of innovation/unmet need important