Economic evaluation and approaches to uncertainty analysis

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Webinar series

1. Impact modelling for early economic evaluation

2. Measuring delivery costs for early economic evaluation

3. Early economic evaluation for HIV prevention products in development

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Webinar structure

- Quick recap on impact modelling and costs

- What is economic evaluation?
  - Key analytical components of an economic evaluation
    - Consider HIV prevention-specific EE issues

- Uncertainty

- Limitations

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Impact modelling recap

- A model is any simplification of a system
- Health impact models:

  - predict disease/infection

  - estimate the differential impact of a variety of interventions on the disease/infection

- In early development, efficacy is an unknown variable
- Models in early development provide an explicit framework for priority setting and communication

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Costs recap

- Cost = value of all resources required to deliver an intervention
- Cost data are essential to understand the 'value for money' of an intervention
- Costs are useful for manufacturers and donors in 'early' development to make decisions around product characteristics, production and pricing (will affect uptake and RoI)
- Established methods for costing– need some adaptation to account for 'early' EEs
  - Expert elicitation, modelling and uncertainty analysis

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What is an economic evaluation?

- The use of analytical methods to identify, measure, value and compare the costs and consequences of alternative interventions systematically

Costs A → Program A → Consequences A

Choice

Costs B → Program B → Consequences B

Drummond et al (2005)
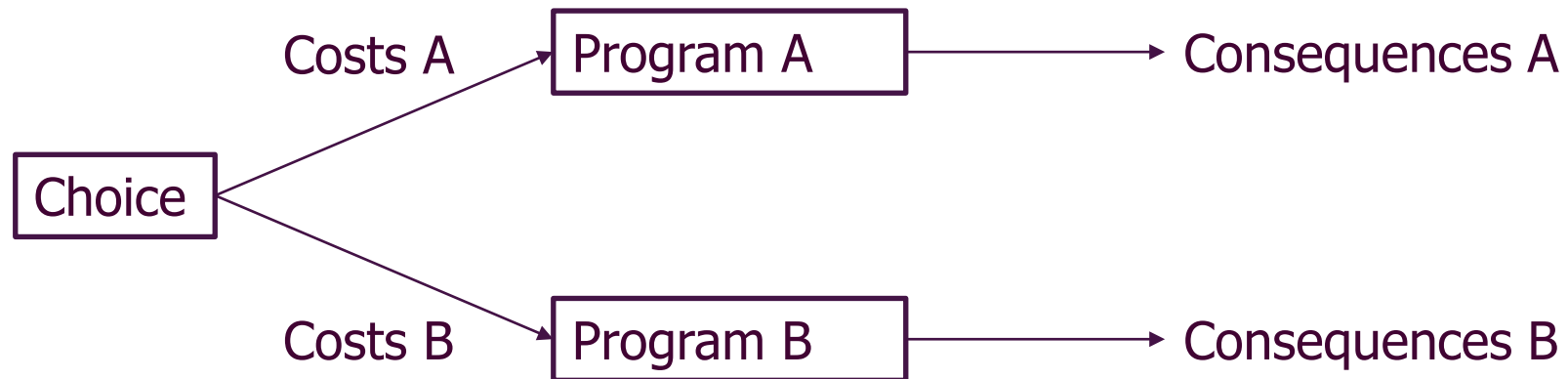
Why are economic evaluations important?

In late stage of development/after introduction, it can inform allocation of resources at policy junctures:

- Adoption (where, when, how, who): allocation of resources for family planning services
- Scale up (or down): scale up of male circumcision initiatives
- Discontinuation: end of product 'life'

Empirical evidence suggests that in recent years the use of early economic assessments was rarely published: their specific purpose to support internal decisions.

In early R&D (preclinical up to Phase II), economic evaluations can:

- Inform R&D decisions,
- Establish market potential and feasible pricing,
- Ensure that reimbursement/recommendation requirements are met

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Main applications of early economic evaluations

1. **Inform R&D decisions**

   - Identification of potentially successful projects across a portfolio by offering **benchmarks for the minimum performance required** and a forecast of market potential, as opportunity assessment

   - An early economic model can be used to determine **which efficacy or clinical profile has to be attained for a given price** so that the product has the potential of being cost-effective

   - Economic modeling in early stages can **identify parameters to which the estimated cost-effectiveness is particularly sensitive**, so that these key items can be prioritized for data collection

Annemans et al (2010) Hartz et al (2008)

Main applications of early economic evaluations

2. Establish market potential and feasible pricing

- Preliminary evaluation of the cost-effectiveness at **different pricing scenarios, target populations, delivery models** and indications can be carried out to inform initial pricing

- Price will usually range between minimum ROI requirements of developers and manufacturers and the maximally attainable price defined by willingness-to-pay of payers

- Early evaluations can highlight any deviation from the desired price range, providing an opportunity to optimize manufacturing processes (lowering CoGS), improve aspects of the product profile (reducing delivery costs or increasing adherence)

3. Ensure that reimbursement/recommendation requirements are met, paving the way for reimbursement decisions

- Setting up reimbursement data early helps to **identify gaps in the evidence** needed that can then be addressed further in the product development

Hartz et al (2008)

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MATRIX and EEEs

Innovative approach to advance early-stage HIV prevention technologies:

- Nine technologies in the pipeline
- Products represent a combination of:
  - new delivery systems: long-acting implants/injectables like bio-degradable implants or subcutaneous depots, as well as vaginal films/inserts;
  - multiple indications: HIV prevention and HIV prevention plus STI prevention and/or family planning,
  - diverse active pharmaceutical ingredients (ARV and non-ARV based APIs).

- Early-stage economic evaluation performed as part of MATRIX has been designed to inform:
  - Benchmark-driven management of the R&D portfolio
  - Evidence-based clinical development planning

https://matrix4prevention.org/

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How to set up an EE

- Define the decision problem the EE will inform
- Choose a suitable EE design
- Consider population and setting
- Define intervention
- Choose a comparator
- Estimate costs
- Define and measure outcomes
- Calculate incremental cost-effectiveness ratio (ICER)
- Understand time horizons
- Consider uncertainty
- Interpret results in light of decision problem

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Comparators

- Economic evaluation: incremental approach to measuring costs and effects
- Comparison of an intervention with 'something else'
  - Standard of care
  - Another intervention
  - Do-nothing comparator
- Key analytical decision!
- Important implications for comparability across settings

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Costs

- Understand scope of intervention
- Define perspective
- Think about direct costs and consequential costs
- Define time horizon and discount rates
- Separate start-up activities and recurrent activities
  - Estimate useful life of start-up activities

Outcome measures

Intermediate outcomes:
- Person reached

Disease area specific:
- Case of HIV averted

Multi-dimensional health units (non-disease area specific):
- DALYs/QALYs averted/gained

Financial return on investment (ROI)
- Monetary units (USD, GBP, etc)

Choice depends on policy decision

Economic evaluation types

Costing

Cost-effectiveness

Cost-utility

Cost-benefit

Intermediate outcomes:
- Person reached

Disease area specific:
- Case of HIV averted

Multi-dimensional health units
(non-disease area specific):
- DALYs/QALYs averted/gained

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Disability-adjusted life years (DALYs)

- DALY: health outcome measure with two main components
  - Quality of life reduced due to a disability
  - Lifetime lost due to premature mortality
- Allows for comparisons across all disease areas

DALY

Disability Adjusted Life Year is a measure of overall disease burden, expressed as the cumulative number of years lost due to ill-health, disability or early death

= YLD Years Lived with Disability + YLL Years of Life Lost

Healthy life — Disease or Disability — Early death — Expected life years
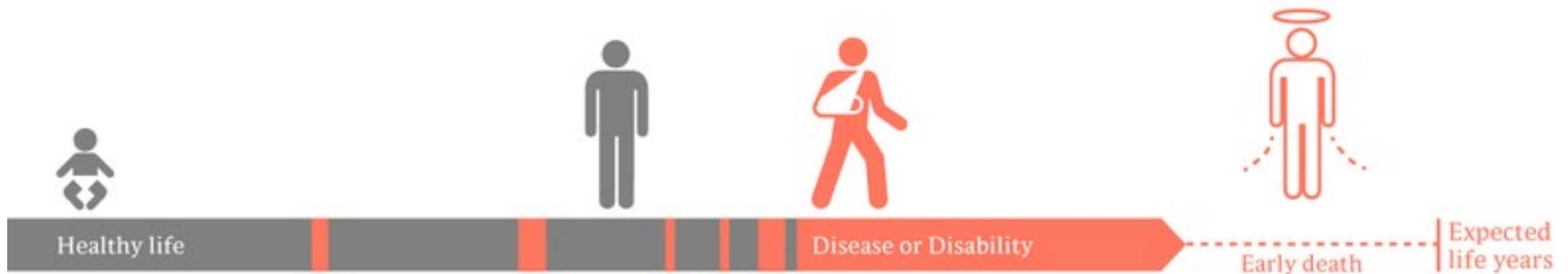
ICERs

- Incremental cost-effectiveness ratio (ICERs)
- Key metric used in EE
- Compares incremental costs/effects of intervention and comparator

$$\frac{\text{Cost (interventions)} - \text{Cost (comparator)}}{\text{Effectiveness (intervention)} - \text{Effectiveness (comparator)}}$$
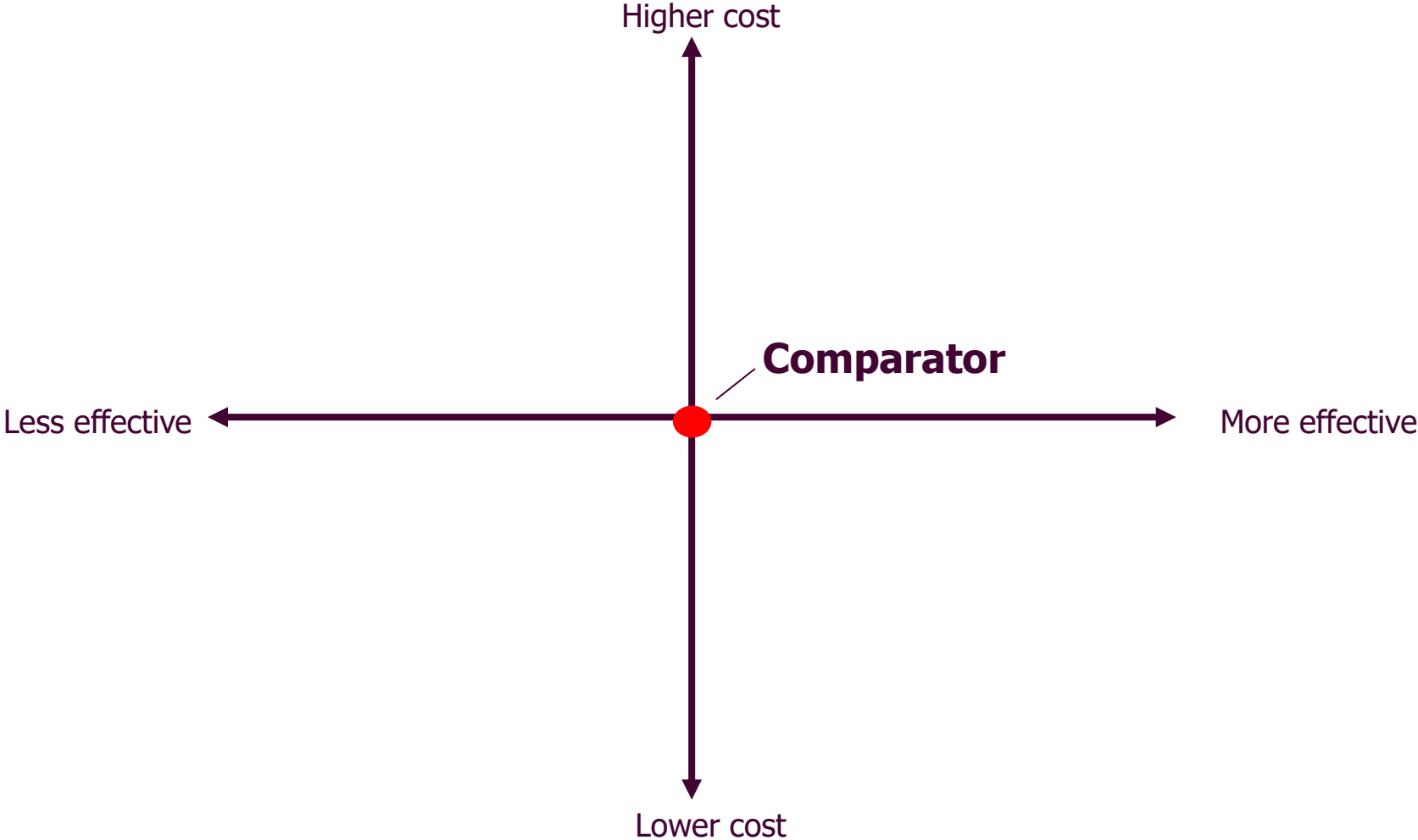
- Commonly expressed as 'incremental per DALY averted'
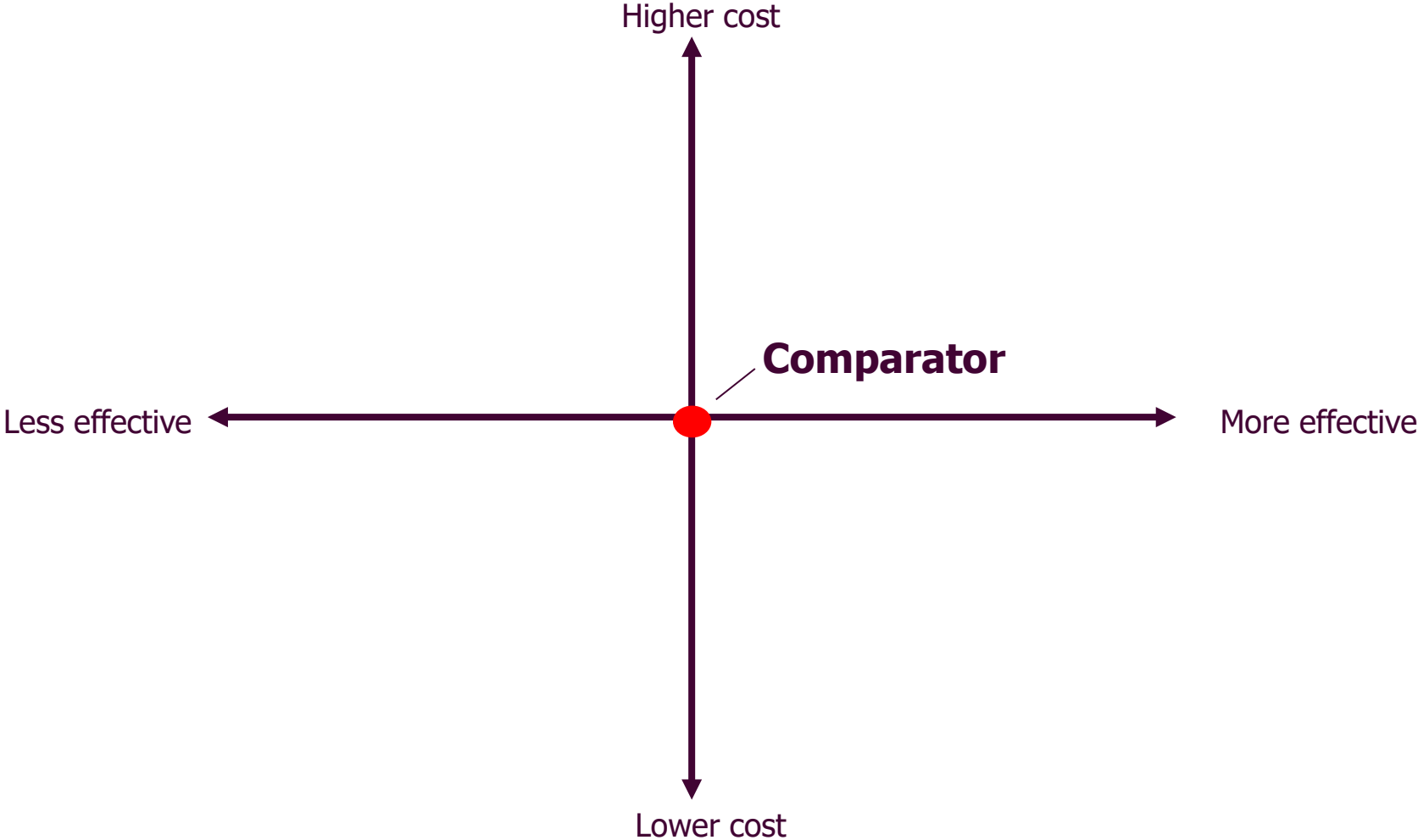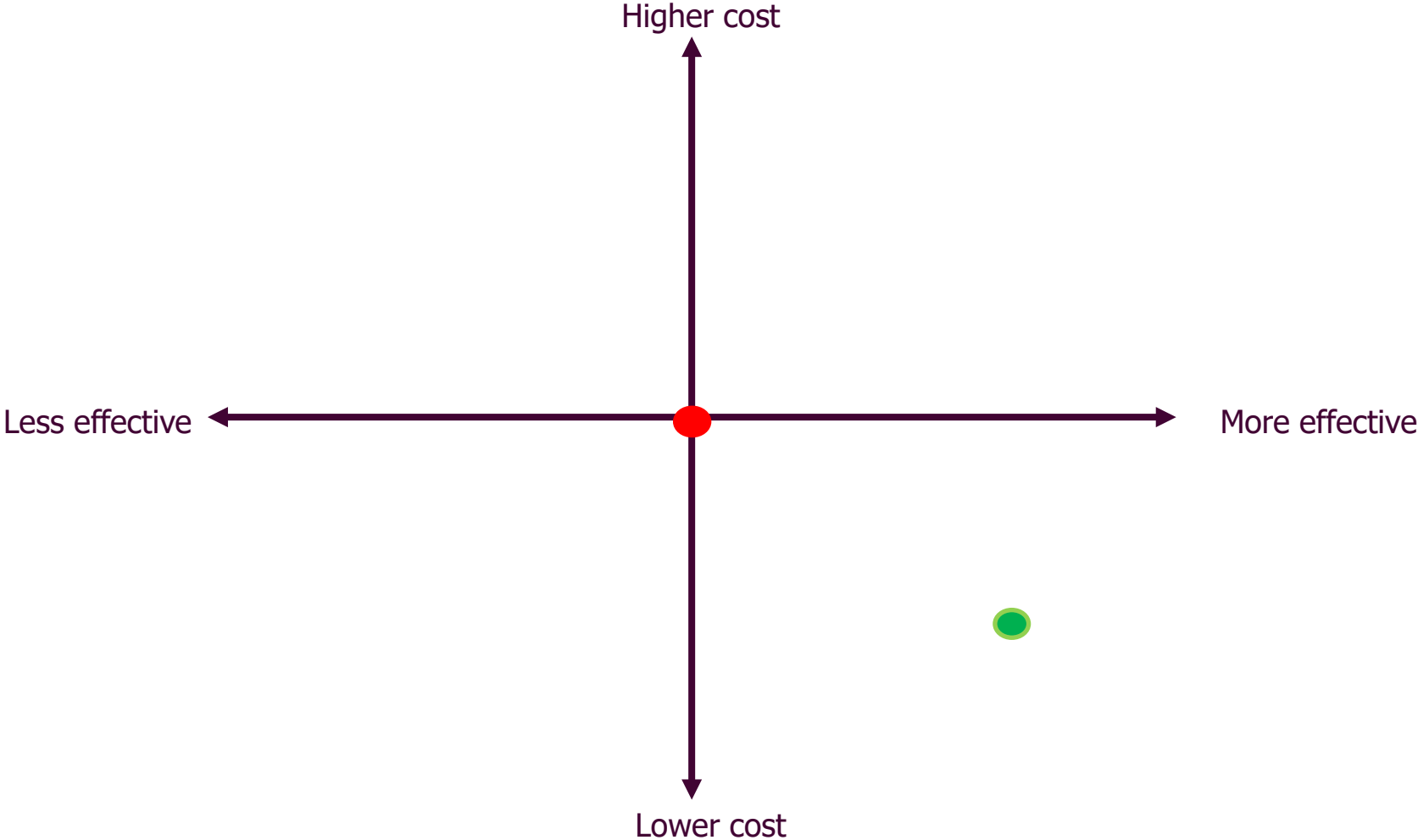
Cost-effectiveness plane
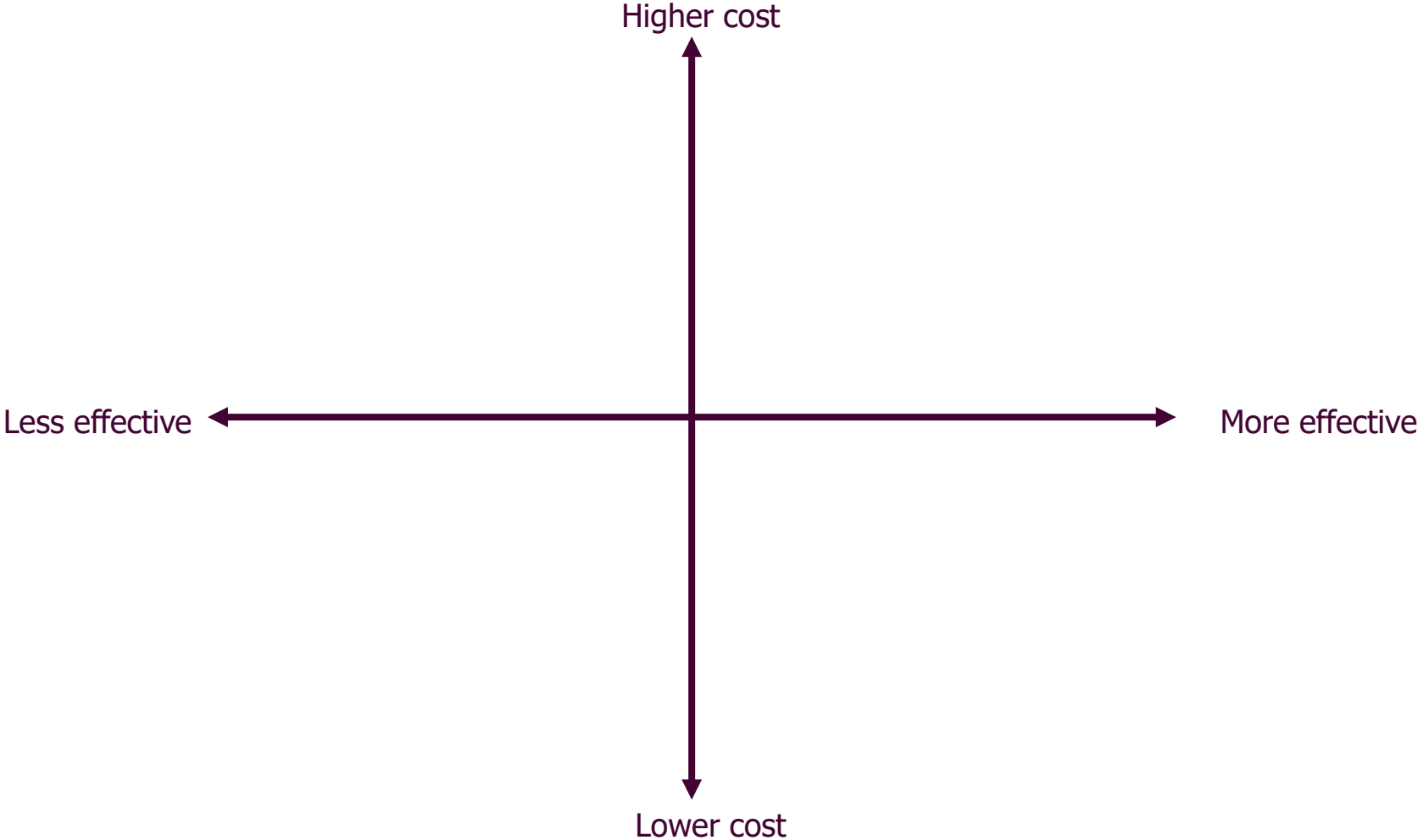
Higher cost

Less effective ← → More effective

Lower cost

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Cost-effectiveness plane

Higher cost

Less effective ← → More effective

Comparator

Lower cost

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Cost-effectiveness plane

Cost-effectiveness plane

Higher cost

Less effective ← → More effective

Lower cost

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Cost-effectiveness plane

Higher cost

Less effective

More effective

Lower cost

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Cost-effectiveness plane

Higher cost

Less effective — More effective
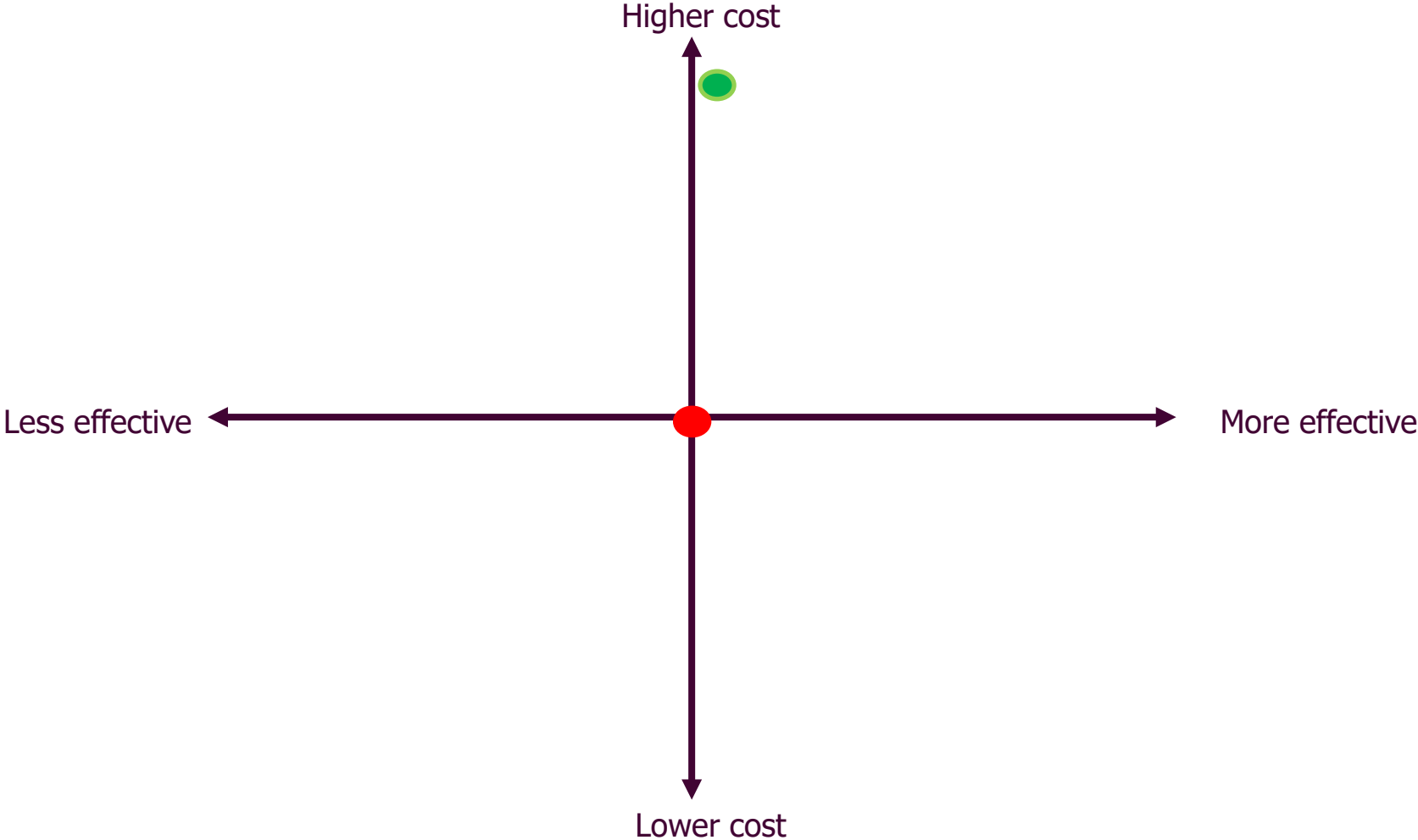
Lower cost

Cost-effectiveness plane

Cost-effectiveness plane

Higher cost

Less effective — More effective

Lower cost

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Cost-effectiveness plane

Higher cost

Cost-effectiveness threshold

Less effective

More effective

Lower cost

Cost-effectiveness plane

Higher cost

Cost-effectiveness threshold

Less effective

More effective

Lower cost

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Cost-effectiveness plane

Higher cost

Cost-effectiveness threshold

Less effective

More effective

Lower cost

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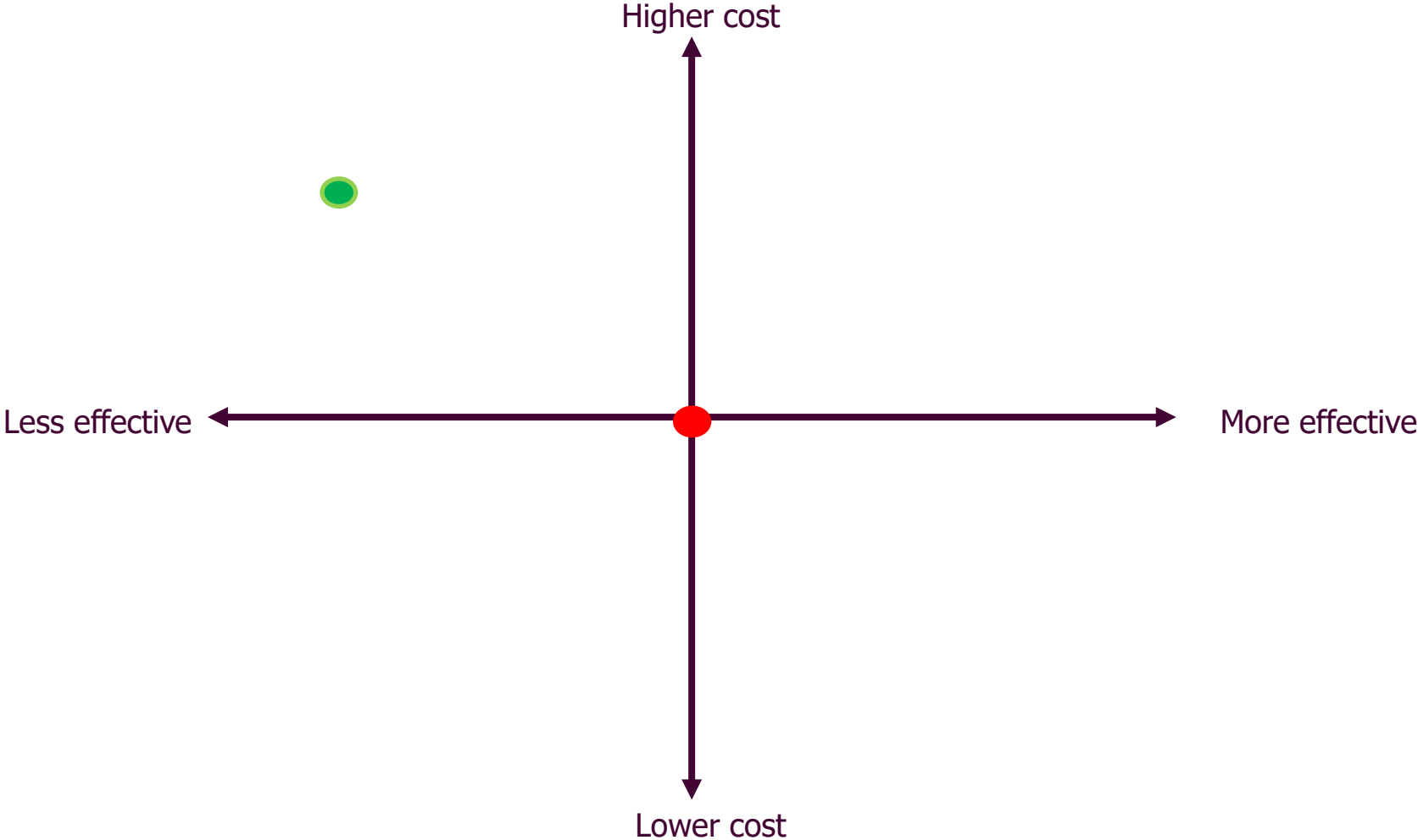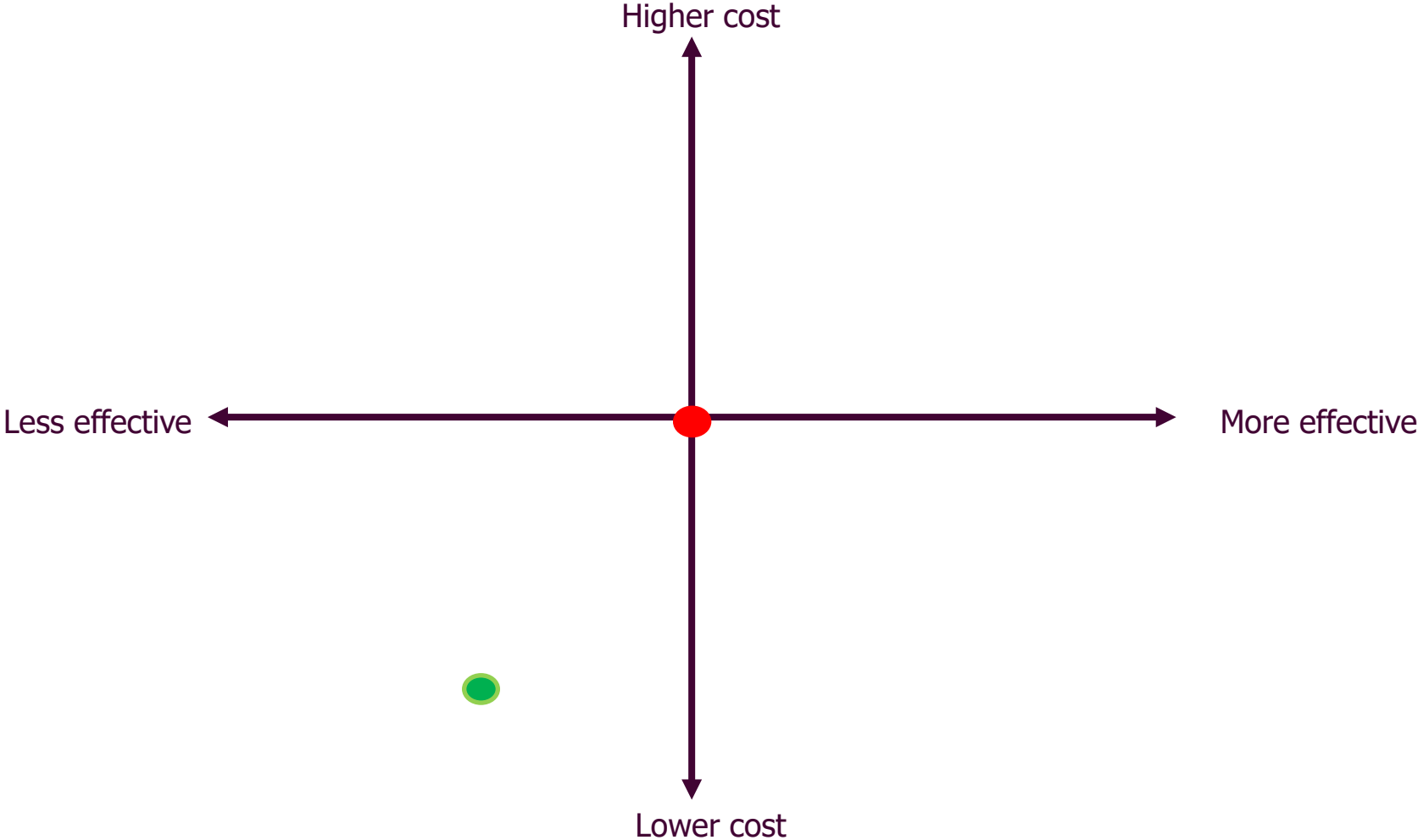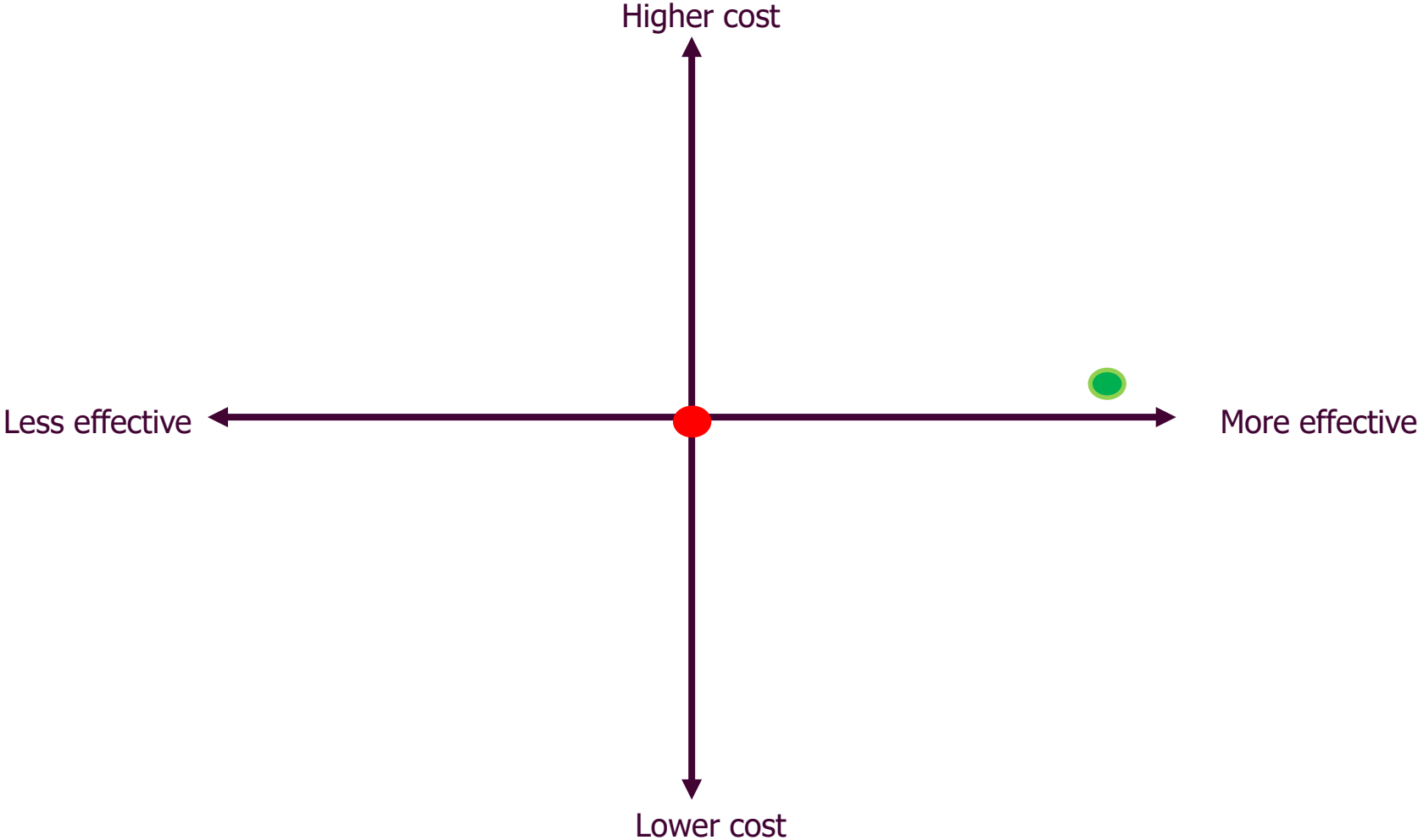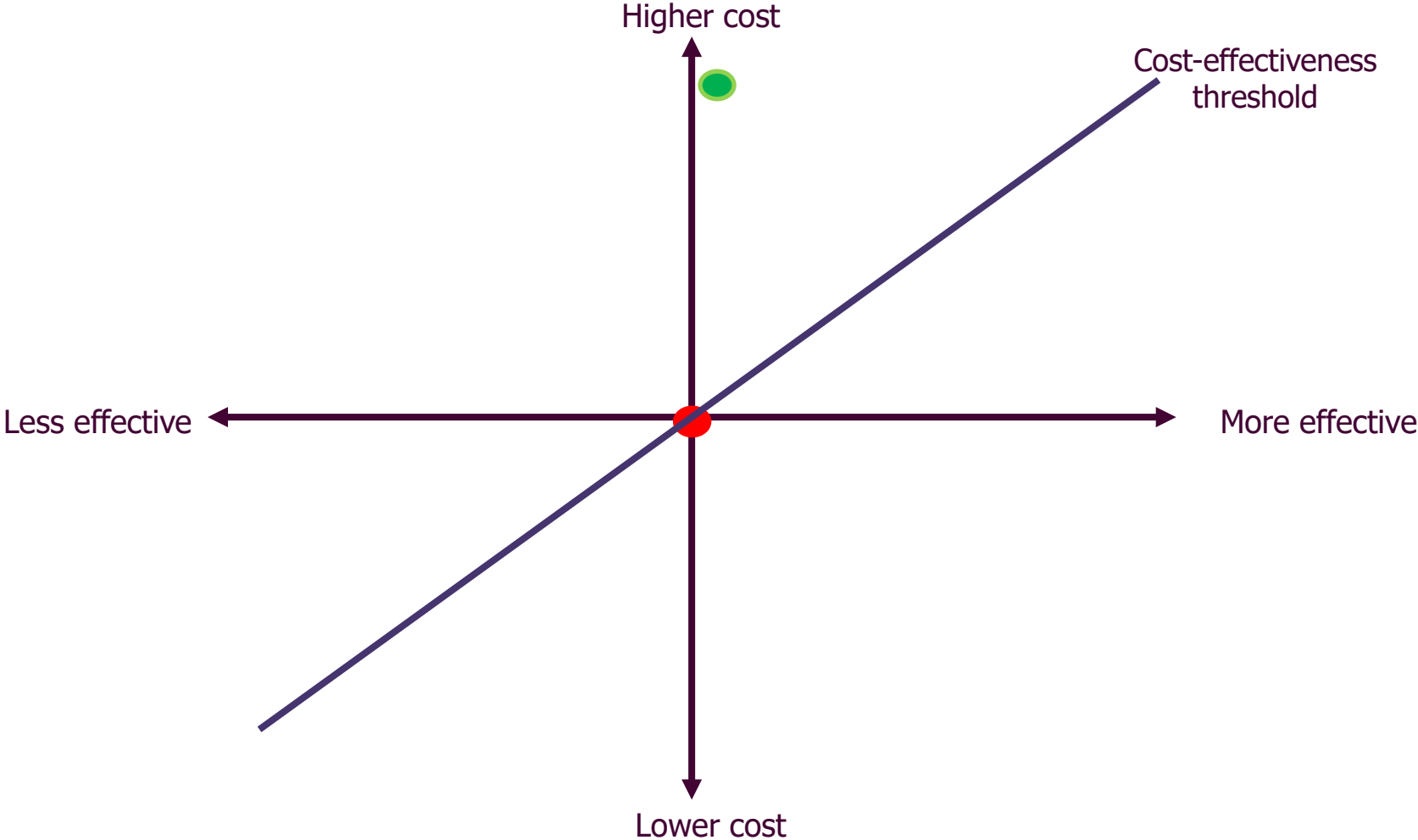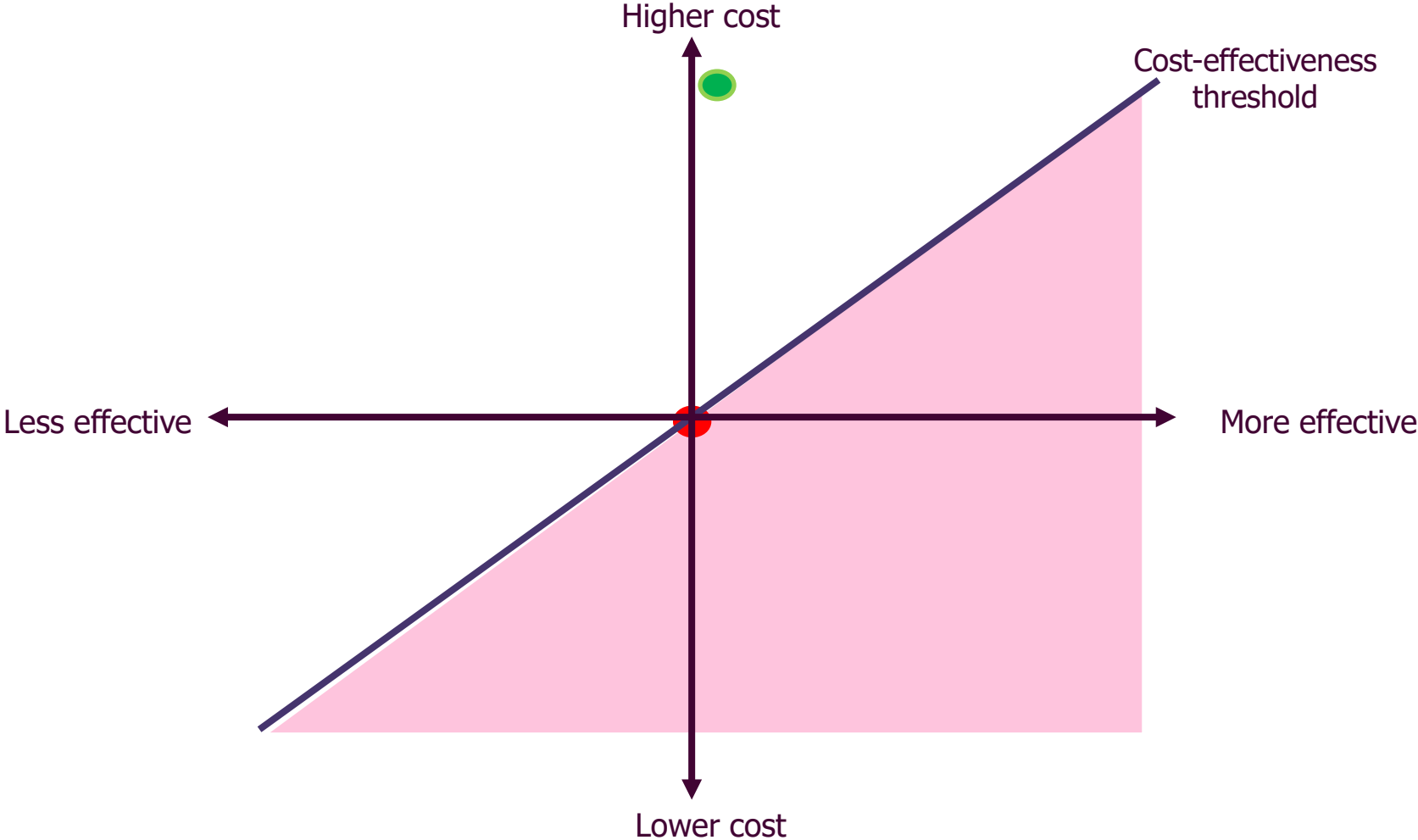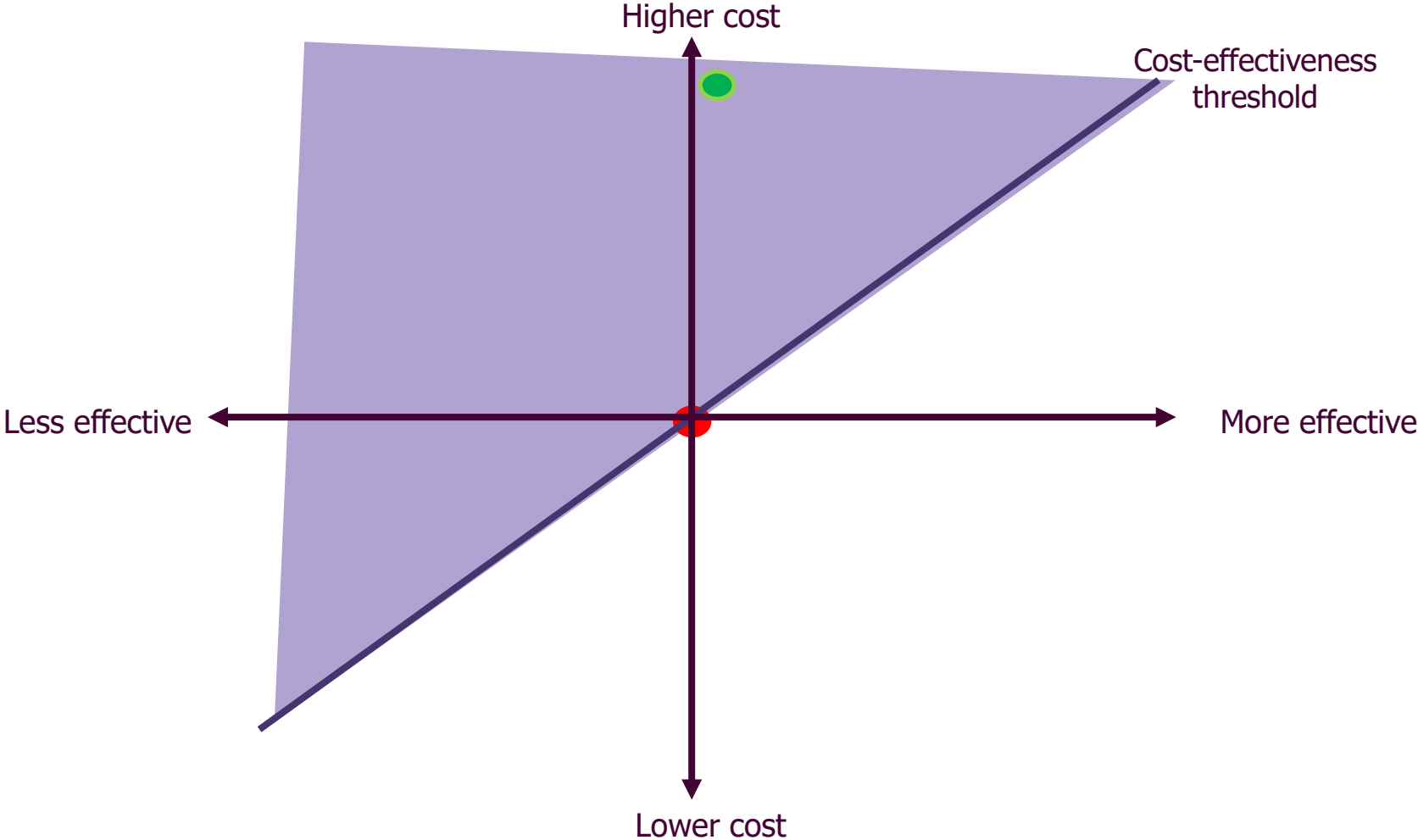
Cost-effectiveness thresholds

- Country-specific decision rule to inform on 'value for money'

  - Important criteria (but not only one)

- No gold standard for methods to estimate thresholds

  - Demand side (willingness to pay)

  - Supply side (opportunity cost/marginal productivity)

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HIV prevention EEE considerations

- Consequential costs
  - Low effectiveness = more HIV cases = more ART
- Varying morbidity
  - DALY weights different on ART/non-ART
  - Need to understand ART coverage
- Comparator
  - What will be the standard of care in the future?
  - Complexity with multiple products

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HIV prevention EEE considerations

- Time horizon

  - Costs accrued now save costs years/decades in the future

- Accounting for constraints in access

  - Need to include increases costs/reduced effectiveness or relaxing/not relaxing constraints

  - Example: Adherence counselling

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What is uncertainty?

- There is rarely (or ever) complete and perfect information (state of inherent uncertainty)
- But decisions still have to be made…
- Important to acknowledge areas of uncertainty in order to assess (and plan for) variability and risk
- Particularly important in EEEs, where there are many unknowns

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Types of uncertainty

- Methodological:
  - Lack of clarity on the appropriate model structure
    - Perspective, time horizon, discount rate
- Structural:
  - Limited evidence on the natural history of the disease
    - Transmission pathways, health states
- Parameter:
  - Uncertainty on true numerical values that populate model
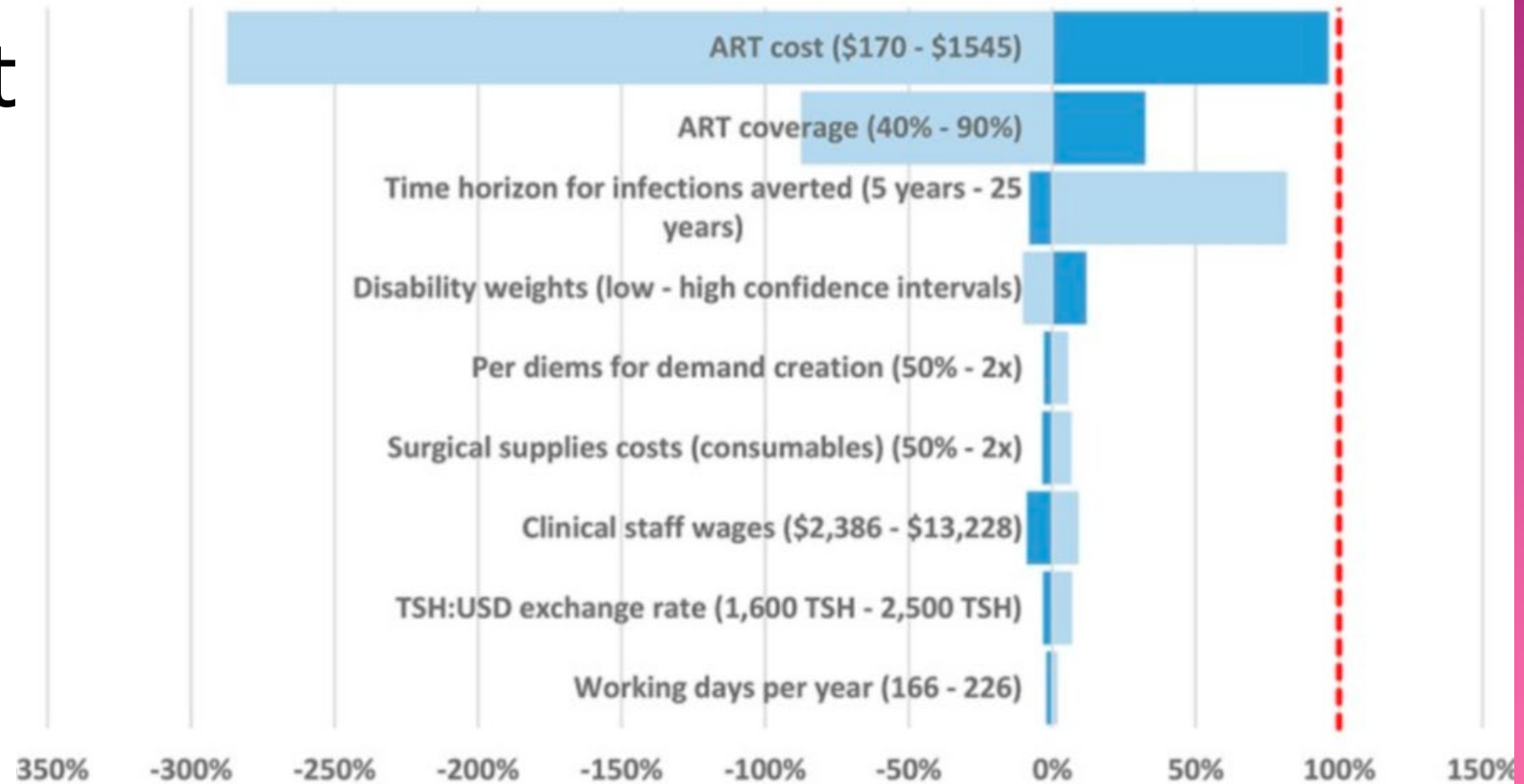   - Transition probabilities, DALY weights, prices

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Uncertainty Analyses

- Deterministic sensitivity analysis
  - Univariate or multivariate
- Probabilistic sensitivity analysis
- Scenario analysis
- Threshold analysis
- Value of information analysis (VOIA)

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Deterministic sensitivity analysis

- Tests the effect of variations to parameters on the ICER
  - Univariate
  - Multivariate

ART cost ($170 - $1545)

ART coverage (40% - 90%)

Time horizon for infections averted (5 years - 25 years)

Disability weights (low - high confidence intervals)

Per diems for demand creation (50% - 2x)

Surgical supplies costs (consumables) (50% - 2x)

Clinical staff wages ($2,386 - $13,228)

TSH:USD exchange rate (1,600 TSH - 2,500 TSH)

Working days per year (166 - 226)

350% -300% -250% -200% -150% -100% -50% 0% 50% 100% 150%

Torres-Rueda et al (2018)

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Probabilistic sensitivity analysis

- Statistical technique to assess parameter uncertainty across many/all parameters
- Considers variation of parameters simultaneously
- Montecarlo simulations to calculate ICERs when parameter values for many/all parameters are chosen at random
  - 1000s of runs of the model
- Requires understanding underlying distributions of different variables

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# Probabilistic sensitivity analysis

Yamamoto et al. (2022)
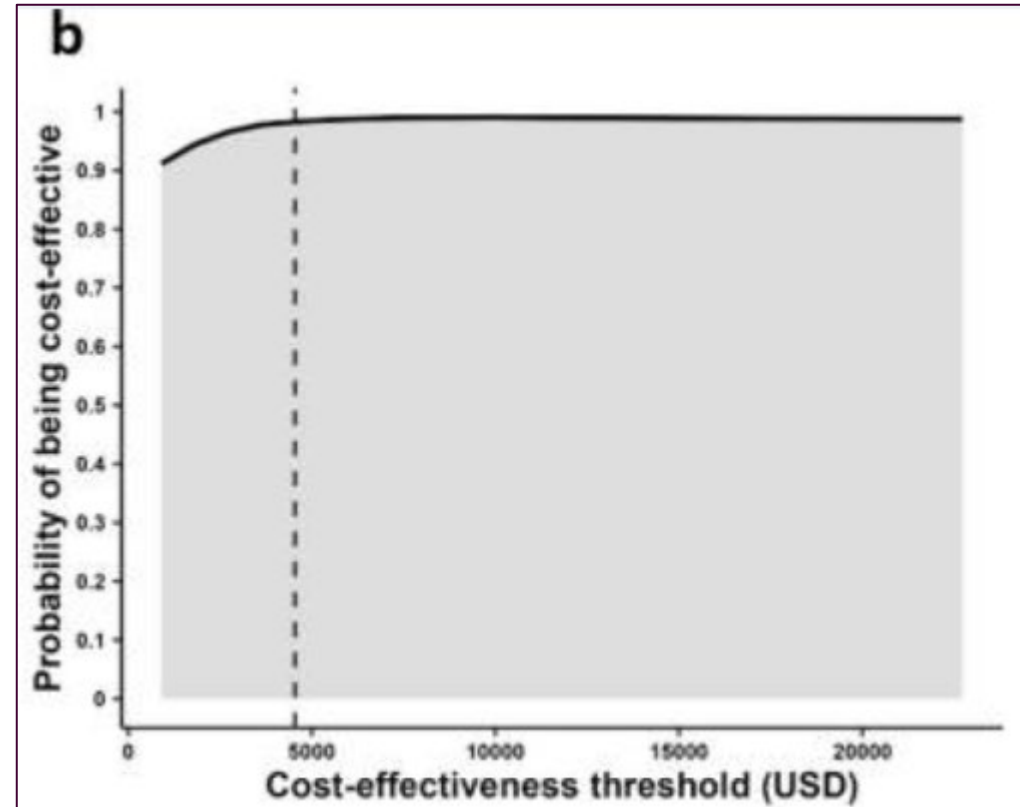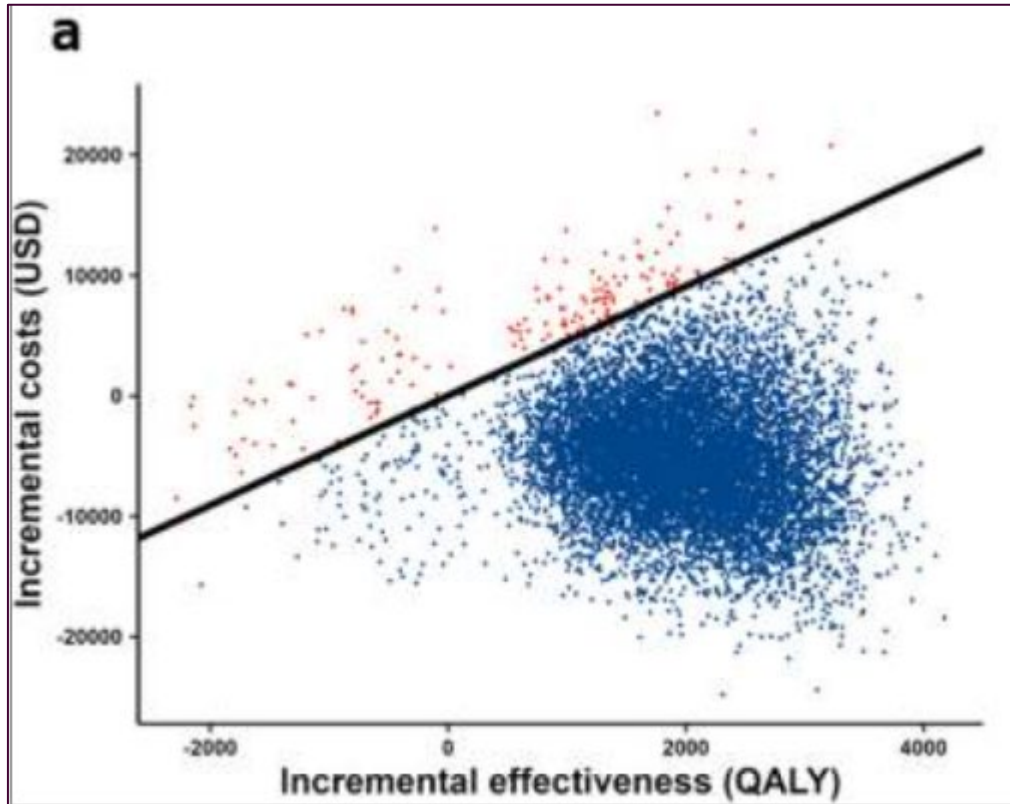
Scenario analysis

- Exploring impact of a group of assumptions that represents one or several 'scenarios'
- Requires systematically changing a set of parameters to reflect scenario
- Best case and worst case scenarios (common)
- Other examples: high/low uptake, short/long duration of protection

Hallett et al. (2011)

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Scenario analysis

- Before the dapivirine ring was introduced

- Scenario analyses reflecting a variety of future SOC and implementation strategies, assuming a range of effectiveness and coverage, fixing the product price at US$7 per ring and 12 rings per year.
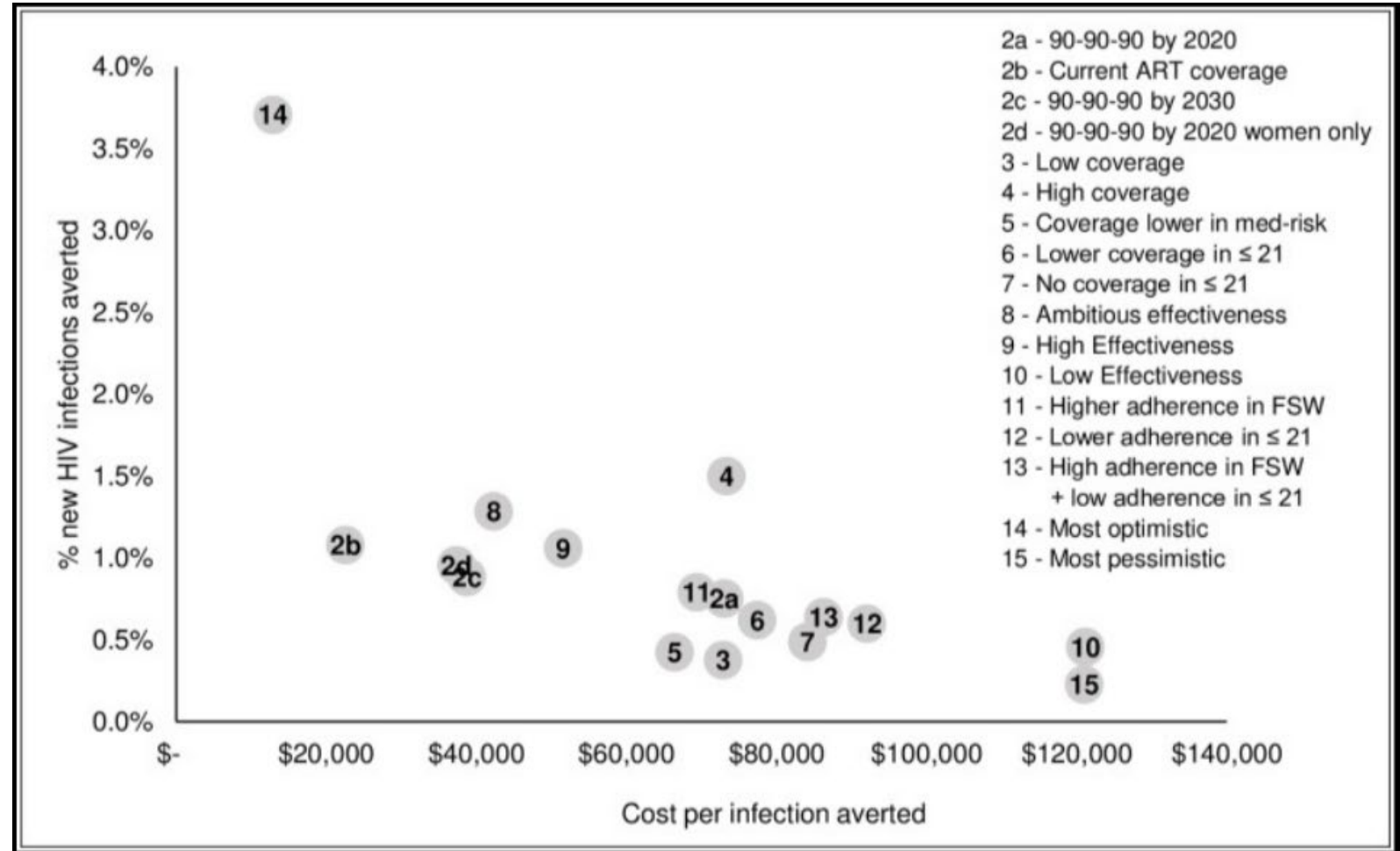
Incremental cost per HIV infection averted by use of the dapivirine ring in South Africa (2018–2035).

Threshold analysis

- A type of scenario analysis focusing on key variables that contribute most to overall outcome
- Key question: how much would a parameter have to change before the decision changes?
- Examples:
  - Product is 65% effective: what is the maximum it could cost to be CE?
  - Product costs $100 pp/year: what is the minimum effectiveness it would need to have to be CE?

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Value of information (VOI) analysis

- Quantitative approach to assess potential benefits of reducing uncertainty
- Is it worthwhile to collect additional information relative to the decision problem?
- Obtaining more information has a cost (e.g. trials)
- Cost compared to potential economic benefit (expected value of perfect information, EVPI)
- EVPI: compares net benefit between a decision made with 'perfect' certainty and one with current levels of uncertainty

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Early economic evaluation: limitations

- Limited clinical data
- Lack of clarity on costs of delivery

  - Esp. new modalities
- Need to rely on assumptions

  - Importance of uncertainty analysis
- Regulatory uncertainty
- Product evolution

  - Key for iterative processes of re-estimation

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Summary

- Economic evaluations are a systematic way to compare costs and outcomes of interventions
- They can be used to inform key decisions early in the development pipeline
- Data requirements include cost and effectiveness data (model-heavy)
- Essential to characterise and estimate uncertainty

Thank you!

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