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A comparison of direct, indirect and joint analyses of cost-effectiveness.

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Introduction

An economic evaluation of a healthcare technology may be based on a direct analysis of the effect of treatment choice on the final endpoints of costs and effects or an indirect analysis operating via intermediate endpoints. In some cases, a joint model which combines both indirect and direct estimates of costs and effects may also be feasible. In this paper we present a framework for comparing and evaluating different analytic approaches.

In order to compare different approaches, we need to understand the, possibly conflicting, needs of decision-makers. In this paper we assume that the decision-maker's objective is to maximise health gain subject to budget constraint. Unbiased estimates of the expectation (taking into account uncertainty) of the incremental mean costs and effects for each treatment option, $E(\delta c_t)$ and $E(\delta q_t)$, are sufficient to make reliable adoption decisions based on current evidence. However, if the decision makers also wishes to consider the need for (and feasibility of) further research to reduce decision uncertainty, unbiased estimates of the joint distribution of incremental costs and effects, $P(\delta c_t = c \cap \delta q_t = q)$, are also required[1]. It has been argued that decision-makers should always take into account the need for further research, particularly as an unconditional decision to adopt a technology may preclude further research. In addition, there is a need to include all relevant treatments, otherwise the analysis may be invalid as the optimum treatment may be missed[2]. We would also expect, a priori, that the more *applicable* information we are able to include in an analysis, the greater the reliability of the final decision.

The direct, or "trial based", analysis can only include data from studies that include measures of the final outcomes of cost, including all relevant resource use, and effect, on an appropriate scale for decision-making. Direct analyses cannot incorporate additional data from studies of the effect of treatment on intermediate endpoints.

In an indirect, or "model based", analyses, the effect of treatment choice on intermediate endpoints is estimated - typically using clinical trial data - and expected costs and effects are then estimated conditional on the intermediate endpoints using a treatment model parameterised from a variety of sources. This form of analysis requires an assumption of conditional independence; that either the expectations or joint distribution of costs and effects are independent of treatment choice (*T*) conditional on a function (*m)* representing the 'model' based on the intermediate endpoints *I*:

$$E(\delta c_t), E(\delta q_t) \perp T \mid m(I)$$

or

$$P(\delta c_t = c \cap \delta q_t = q) \perp T \mid m(I)$$

Indirect analyses can incorporate additional data from studies of the effect of treatment on intermediate endpoints. Indirect analysis may be necessary when there are insufficient data to allow a direct analysis.

In a joint analysis, the effect of treatment choice on costs and effects is estimated both directly and indirectly via intermediate endpoints. Joint analysis requires study data including measures of both the final outcomes of cost and effects and the intermediate endpoints. It allows the incorporation of additional data from studies of the effect of treatment on intermediate endpoints. The analysis does not require an assumption of conditional independence, as costs and effects that are not conditional on the intermediate endpoint will be included via the direct component of the analysis.

In this paper, we compare the results of direct, indirect and joint analysis of the Chronic Disease Self Management Programme (CDSMP). This intervention, developed in the US, forms the basis of the Expert Patient Programme (EPP), a peer led self management programme that has recently been rolled out throughout the UK and will be available to 100,000 individuals

with chronic conditions by the year 2012[3]. This paper presents a methodology for introducing data of different types from different sources into a cost-effectiveness decision model. However, analyses of these data are ongoing and the results and conclusions of these analyses should not be used as evidence in favour of the CDSMP or the Expert Patient Programme.

These preliminary analyses are based on a synthesis of individual patient data from two trials that include measures of both costs and QALYs and the intermediate endpoint of patient reported self-efficacy (SE). In addition, the effect of incorporating additional aggregate data from a series of trials of the effect of EPP on mean self-efficacy into the indirect and joint analyses is investigated. The estimated incremental cost-effectiveness ratio (ICER), cost-effectiveness acceptability curves (CEAC), expected value of perfect information (EVPI) and the likely implications for decisions regarding treatment adoption and the need for further research are compared for each analytic approach.

We demonstrate that the indirect and direct analyses can be viewed as special cases of the joint analysis with certain parameters constrained to zero and use this treatment to examine the underlying assumptions and their corollaries for each of the methods of analysis. We also consider how the appropriate method of analysis might be selected.

Methods

Decision Problem

The CDSMP intervention is designed to increase patients level of self-efficacy, defined as their confidence in their ability to manage their condition.[4] It is hypothesised that improving patients' self-efficacy will lead to improvements in health outcomes[5, 6]. The decision problem is to determine whether the EPP programme is cost-effective compared to no intervention.

Two sources of data were available. Firstly, individual patient level data are available from two trials comparing the EPP interventions to 'no intervention'[7, 8]. These trials provided details of resource use sufficient to estimate costs and also repeated measures of utility derived from EQ-5D data allowing treatment effect to be expressed in terms of quality adjusted life years (QALYs). These trials also included measurement of the SE intermediate endpoint. These trials were used in all the analyses (direct, indirect and joint as described below).

In addition, there were eight trials that provided estimates of mean self-efficacy comparing EPP to 'no intervention'. However, these trials provided no estimates of costs or QALYs. Henceforth, these are referred as the additional data.

Methods of analysis

Estimates of incremental mean costs and effects for the EPP intervention compared to 'no intervention' were estimated using joint, direct and indirect analyses. The three analytic approaches are summarised in table 1. Each analysis has two main components, a within-study calibration model and an out-of-study prediction model.

The out-of-study prediction model is used to predict the incremental mean costs and effects for each treatment option for the future – next through the door – patients for whom we are trying to identify the optimum treatment, given budget restraints.

The within study calibration model predicts values for the costs, effects and other intermediate variables for the subjects included in the various studies based on their characteristics and model parameters; these parameter estimates are subsequently used in the prediction model. A Bayesian analysis was used to estimate the values of the model parameters; the likelihood functions used to incorporate the trial and additional aggregate data are also shown in table 1.

1. Direct Analysis

In the calibration model, the mean costs and qalys for subject *s* ($\mu_{c,s}$ and $\mu_{q,s}$), are estimated as a linear function of treatment indicator variables *T* and other covariables *X*.

The trial data are incorporated into the analysis using the following likelihoods, $c_s \sim N(\mu_{c,s}, \sigma_c^2)$ and $q_s \sim N(\mu_{q,s}, \sigma_q^2)$.

In the prediction model, the incremental mean costs and QALYs for a future patient are assumed to equal the value of the costs and QALYs conditional on treatment $\beta_{c|t}$ and $\beta_{q|t}$ parameters from the calibration model.

2. Indirect Analysis

In the calibration model, $\mu_{c,s}$ and $\mu_{q,s}$ are estimated as a linear function of the intermediate endpoint, rather than the treatment indicator, and other covariables and the mean value of the intermediate endpoint *I* for subject *s* ($\mu_{i,s}$) is estimated as a linear function of treatment and other covariables.

The trial data are incorporated into the analysis using the likelihoods, $c_s \sim N(\mu_{c,s}, \sigma_c^2)$, $q_s \sim N(\mu_{q,s}, \sigma_q^2)$ and $s_i \sim N(\mu_{s,i}, \sigma_s^2)$; and additional data on the mean change ($\overline{\delta I_t}$) and its associated standard error (s_t^2) in self-efficacy associated with treatment *T* are incorporated using the following likelihood function, $\overline{\delta I_t} \sim N(\beta_{i|t}, s_t^2)$.

In the prediction model, the incremental mean costs and QALYs for a future patient are assumed to equal the value the products of the $\beta_{i|t}$ and $\beta_{c|i}$ and the $\beta_{i|t}$ and $\beta_{q|i}$ parameters from the calibration model.

3. Joint Analysis

For the joint analysis, the calibration model is a combination of the calibration models from the direct and indirect analysis: $\mu_{c,s}$ and $\mu_{q,s}$ are estimated as a linear function of the intermediate endpoint, treatment and other covariables; $\mu_{i,s}$ is estimated as a linear function of treatment and other covariables.

The trial data are incorporated into the analysis using the likelihoods, $c_s \sim N(\mu_{c,s}, \sigma_c^2)$, $q_s \sim N(\mu_{q,s}, \sigma_q^2)$ and $s_i \sim N(\mu_{s,i}, \sigma_s^2)$; and additional data using the likelihood function, $\overline{\delta I_t} \sim N(\beta_{i|t}, s_t^2)$.

The prediction model is also a combination of the direct and indirect prediction models; the incremental mean costs for a future patient is assumed to equal the sum of $\beta_{c|t}$ and product of the $\beta_{i|t}$ and $\beta_{c|i}$ parameters and QALYs the sum of $\beta_{q|t}$ and product of the $\beta_{i|t}$ and $\beta_{q|i}$ parameters

In all of the analysis the correlation between costs and QALYs are accounted for by including the following term, $\kappa(Q_s - \overline{Q})$, in the cost regression. All of the linear predictors in the calibration models included a study specific intercept terms so the estimated model parameters reflected within study variation and were not influenced by between study differences. All of the analyses currently assume fixed effects. They could be extended to random effects for any of the parameters.

In each analysis, the direct cost of the EPP intervention, estimated at £250[9], was added to the estimated non-treatment costs to arrive at the total treatment cost. This estimate of the intervention cost was employed in one of the trials [8]. However, the other trial for which individual patient data are available[7] estimated a lower intervention cost, and using the latter estimate would clearly increase the cost-effectiveness of the intervention.

Implementation

Parameters were estimated using Monte-Carlo Markov Chain methods implemented in the Winbugs 1.4 software.

Results

Parameter estimates

The mean estimated regression co-efficients and their 95% credibility intervals[1] are shown in table 2. The $\beta_{c|t}$ and $\beta_{q|t}$ parameters from the direct model indicate that EPP treatment is associated with higher non-treatment costs and QALYs than no-intervention. The $\beta_{i|t}$ parameters for the indirect and joint analyses indicate that the EPP programme is associated with an increase in patient reported self-efficacy. The costs and QALYs conditional on self-efficacy parameters, $\beta_{c|i}$ and $\beta_{q|i}$, indicate that increased self-efficacy is in turn associated with lower non-treatment costs and increased QALYs. Combining these two effects in the prediction model, the resulting estimate of the effect of EPP on QALYs from the indirect model is lower than the direct model, 0.002 compared to 0.009. In contrast, the estimated incremental non-treatment costs associated with EPP from the indirect model is lower than the direct model, £-6 compared to £12.

The incorporation of additional information increases the estimated mean increase in self-efficacy associated with EPP from 0.273 to 0.455.

Predicted cost-effectiveness

The cost-effectiveness acceptability curves for each analysis are shown in figure 2. The CEACs for the direct and joint analyses are almost identical. The CEAC for the indirect analysis is shifted to the right reflecting the lower estimated increase in QALYs for EPP. The incorporation of additional data shifts the CEACs for both the indirect and joint analysis to the left, reflecting the effect of the increased estimate of the effect of EPP on self-efficacy.

The direct 'trial based' and joint analyses produced similar ICERs of £29,111 and £28,333 for EPP, similar probabilities that EPP is optimal of 0.52 and 0.53, and similar EVPIs of £105 and £107. The inclusion of the additional

[1] analogous to the usual interpretation of a frequentist confidence interval

aggregate data on SE to the joint model reduced the ICER to £25,200, increased the probability that EPP is optimal to 0.62 and reduced the EVPI to £72.

The results of the indirect analysis different from the joint and direct analyses; the ICER is £122,000 for EPP, which reduces to £80,333 if the additional SE data are included. In both cases the probability that EPP is optimal is 0.00 and the EVPI is £0.

Likely recommendations

Assuming an acceptable cost-effectiveness threshold of £30,000; a decision maker making adoption decisions based on current data alone would adopt EPP based on the direct and joint analyses and would reject EPP based on the indirect analysis. Based on the joint or direct analysis, a decision-maker who was also concerned with need for further information might commission further research or make the adoption of EPP conditional in some way on the conduct of further research. Based on the indirect analysis, the decision-maker would decide that there is no value in future research.

Discussion

Alternate analytic frameworks

In the example presented, the indirect analysis produced different results compared to the joint and direct analyses. Decision-makers would be likely to reach different conclusions regarding adoption and the need for further research based on the indirect analysis.

In addition, the indirect and joint analyses allow the inclusion of additional data on the effect of treatment on the intermediate endpoint. In the case of the joint analysis this led to a reduction in uncertainty at the acceptable threshold of £30,000. The inclusion of additional data did not lead to a reduction in uncertainty at all thresholds, as the expected mean costs and QALYs also changed.

Both the indirect and direct models can be seen as special cases of the joint model. In the direct model, the effects of the intermediate endpoint, on costs and QALYs are not included ($\gamma_{c|i}$ and $\gamma_{q|i}$ are constrained to zero). In the indirect model, the effects of treatment on costs and QALYs, independent of the intermediate endpoint, are not included ($\beta_{c|t}$ and $\beta_{q|t}$ are constrained to zero).

The indirect model is likely to produce more certain estimates of cost and effects as the $\beta_{c|t}$ and $\beta_{q|t}$ are constrained to zero and no uncertainty regarding the parameters is included in the prediction model. The removal of this uncertainty is also likely to increase the correlation between estimated costs and effects. However, this will not always lead to a reduction in decision uncertainty at a given threshold as the estimates of expected costs and effects may also change.

The central questions arising from these observations are: how should we select the 'appropriate' analytic approach when we have a choice of analytic

frameworks; and what are the implications for the interpretation of our results, especially when we do not have a choice.

Direct Analysis

Direct analysis appears to be an attractive option as it does not require any assumptions regarding the effect pathway or any assumptions of conditional independence. However, direct analysis requires, and is restricted to studies, that include appropriate measures of cost and effect and does not allow the incorporation of additional data on intermediate endpoints. In addition, if the assumption of conditional independence is valid, the direct model may overestimate uncertainty in costs and effects.

Indirect Analysis

If studies including measures of all relevant costs and effects over the appropriate time horizon do not exist, an indirect analysis via intermediate endpoints may be required. In addition, an indirect model allows the incorporation of additional data on intermediate endpoints. The incorporation of additional data may be necessary to include all relevant comparators in a model. The indirect model does, however, require an assumption of conditional independence.

In an indirect model, if we believe that the expectations, averaging over uncertainty, of $\beta_{c|t}$ and $\beta_{q|t}$ are zero, the estimates of expected mean cost and effect from our model can be regarded as unbiased. This may be a reasonable assumption, especially if there is no evidence to the contrary. This is sufficient if we are only interested in adoption decisions based on current evidence.

However, unless we believe with certainty that $\beta_{c|t}$ and $\beta_{q|t}$ **actually** are zero, rather than have an **expectation** of zero, the estimates of decision uncertainty and EVPI from the indirect model will be biased. This is a much stronger assumption and harder to justify.

Joint Analysis

A joint analysis allows the incorporation of additional data on intermediate endpoints and does not require an assumption of conditional independence. It does however require study data that includes appropriate measures of cost and effect and measures of the intermediate endpoint. Joint models also potentially allow the assumption of conditional independence implicit in indirect models to be tested, helping model selection.

Selection

The empirical estimates of decision uncertainty or value of information should not be used as the basis for selecting the appropriate analytic approach. As we have seen in the EPP example, both the direct or indirect models were associated with lower decision uncertainty depending on the acceptable cost-effectiveness threshold. Similarly, the decision to include additional data should not depend on whether the additional data reduces estimated uncertainty.

The choice between analytic frameworks, should be influenced by our belief in the true value of the $\beta_{c|t}$ and $\beta_{q|t}$ parameters, if we believe these are zero or have an expectation of zero, the estimates from the indirect model may be appropriate, if not then the direct model or joint models are appropriate.

Hypothesis Testing

One option to inform model selection is to perform a test of the hypothesis that the true values of $\beta_{c|t}$ and $\beta_{q|t}$ are zero . If we accept this hypothesis, the indirect model should be accepted over the joint model. This should be equivalence test of the alternate hypothesis (H_1) that $\beta_{c|t}$ or $\beta_{q|t}$ lie in a defined range ($\theta_L < \beta < \theta_U$). If we use a non-equivalence test, we are likely to adopt indirect models when we have little data, even if $\beta_{c|t}$ and $\beta_{q|t}$ deviate significantly from zero, due to lack of power, and reject them when we have large amounts of data, even if $\beta_{c|t}$ and $\beta_{q|t}$ are close to zero. However, if we do adopt an equivalence test, we have to define an acceptable range over which it is acceptable for $\beta_{c|t}$ to deviate from 0. If this range is narrow, there will in

any event be little difference between the joint and indirect analyses if selected.

Conclusions

Where there is sufficient data to allow for a trial based analysis, we would suggest considering a joint modelling approach. This potentially allows a larger evidence base relating to intermediate endpoints to be incorporated without requiring assumptions of conditional independence.

If an indirect analysis via an intermediate endpoint is required, the validity of the assumption of conditional independence should be carefully considered; are the intermediate variables included in an indirect analysis likely to capture all of the effect of treatment on costs and effects? If not, do we believe the bias operates in a particular direction?

Even if we believe our estimates are unbiased, failure to take into account the uncertainty around the assumption of conditional independence, may lead to the overall uncertainty in the final decision being underestimated and to erroneous conclusions as to the need for further research.

373 **Table 1: Comparison of the three analytic approaches**

	Analysis: Direct	Indirect	Joint
Within-study Calibration Model	$\mu_{c,s} = \alpha_c + \beta_{c\|t}T_s + \delta_{c\|x}X_s + \kappa(Q_s - \overline{Q})$ $\mu_{q,s} = \alpha_q + \beta_{q\|t}T_s + \delta_{q\|x}X_s$	$\mu_{c,s} = \alpha_c + \gamma_{c\|i}I_s + \delta_{c\|x}X_s + \kappa(Q_s - \overline{Q})$ $\mu_{q,s} = \alpha_q + \gamma_{q\|i}I_s + \delta_{q\|x}X_s$ $\mu_{i,s} = \alpha_s + \beta_{i\|t}T_s + \delta_{i\|x}X_s$	$\mu_{c,s} = \alpha_c + \beta_{c\|t}T_s + \gamma_{c\|i}I_s + \delta_{c\|x}X_s + \kappa(Q_s - \overline{Q})$ $\mu_{q,s} = \alpha_q + \beta_{q\|t}T_s + \gamma_{q\|i}I_s + \delta_{q\|x}X_s$ $\mu_{i,s} = \alpha_s + \beta_{i\|t}T_s + \delta_{i\|x}X_s$
Likelihood -IPD	$c_s \sim N(\mu_{c,s}, \sigma_c^2)$ $q_s \sim N(\mu_{q,s}, \sigma_q^2)$	$c_s \sim N(\mu_{c,s}, \sigma_c^2)$ $q_s \sim N(\mu_{q,s}, \sigma_q^2)$ $I_s \sim N(\mu_{i,s}, \sigma_i^2)$	$c_s \sim N(\mu_{c,s}, \sigma_c^2)$ $q_s \sim N(\mu_{q,s}, \sigma_q^2)$ $I_s \sim N(\mu_{i,s}, \sigma_i^2)$
Likelihood -Additional data		$\overline{\delta I_t} \sim N(\beta_{i\|t}, s_t^2)$	$\overline{\delta I_t} \sim N(\beta_{i\|t}, s_t^2)$
Out-of-study Prediction Model	$\delta c_t = \beta_{c\|t}$ $\delta q_t = \beta_{q\|t}$	$\delta c_t = \beta_{i\|t}.\gamma_{c\|i}$ $\delta q_t = \beta_{i\|t}.\gamma_{q\|i}$	$\delta c_t = \beta_{i\|t}.\gamma_{c\|i} + \beta_{c\|t}$ $\delta q_t = \beta_{i\|t}.\gamma_{q\|i} + \beta_{q\|t}$
Constraints	Data on intermediate endpoints is not relevant and cannot be incorporated ($\gamma_{c\|i}, \gamma_{q\|i} = 0$)	Requires implicit assumption that costs and QALYs are conditional independent of treatment given self-efficacy ($\beta_{c\|t}, \beta_{q\|t} = 0$)	None. Data on intermediate endpoints can be incorporated without implicit assumption that costs and QALYs are conditional independent of treatment given self-efficacy

374 **Table 2: Example Results**

	Analysis:									
	Direct		Indirect		Indirect + additional data		Joint		Joint + additional data	
	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)
Regression co-efficients										
Costs on treatment (β_{ct})	12	(-65,89)					10	(-66, 85)	11	(-64,89)
QALYs on treatment (B_{qr})	0.009	(0.00,0.018)					0.007	(-0.002,0.016)	0.007	(0.002,0.016)
Costs on self-efficacy (γ_{ct})			-21	(-36, -5)	-21	(-37,-6)	-21	(-36,-4)	-21	(-36,-5)
QALYs on self-efficacy (γ_{qt})			0.008	(0.005, 0.010)	0.008	(0.005,0.010)	0.007	(0.005,0.010)	0.007	(0.005,0.010)
Self-efficacy on treatment (β_{st})			0.273	(0.048, 0.497)	0.455	(0.372,0.537)	0.268	(0.048,0.496)	0.455	(0.373,0.542)
Incremental Non-Treatment Costs	12	(-65,89)	-6	(-14,0)	-9	(-17,-3)	5	(-71,80)	2	(-73,79)
Incremental Total Cost	262	(185,339)	244	(236, 250)	241	(233,247)	255	(179,330)	252	(177,329)
Incremental QALYs	0.009	(0.00,0.018)	0.002	(0.00, 0.004)	0.003	(0.002,0.005)	0.009	(0.00,0.018)	0.010	(0.001,0.019)
ICER (£ per QALY)	29,111		122,000		80,333		28,333		25,200	
Probability that EPP is optimum at a cost-effectiveness threshold of £30,000	0.52		0.00		0.00		0.53		0.62	
EVPI at a cost-effectiveness threshold of £30,000 (£)	107		0.00		0.00		105		73	

Figure 1: Forms of evaluation

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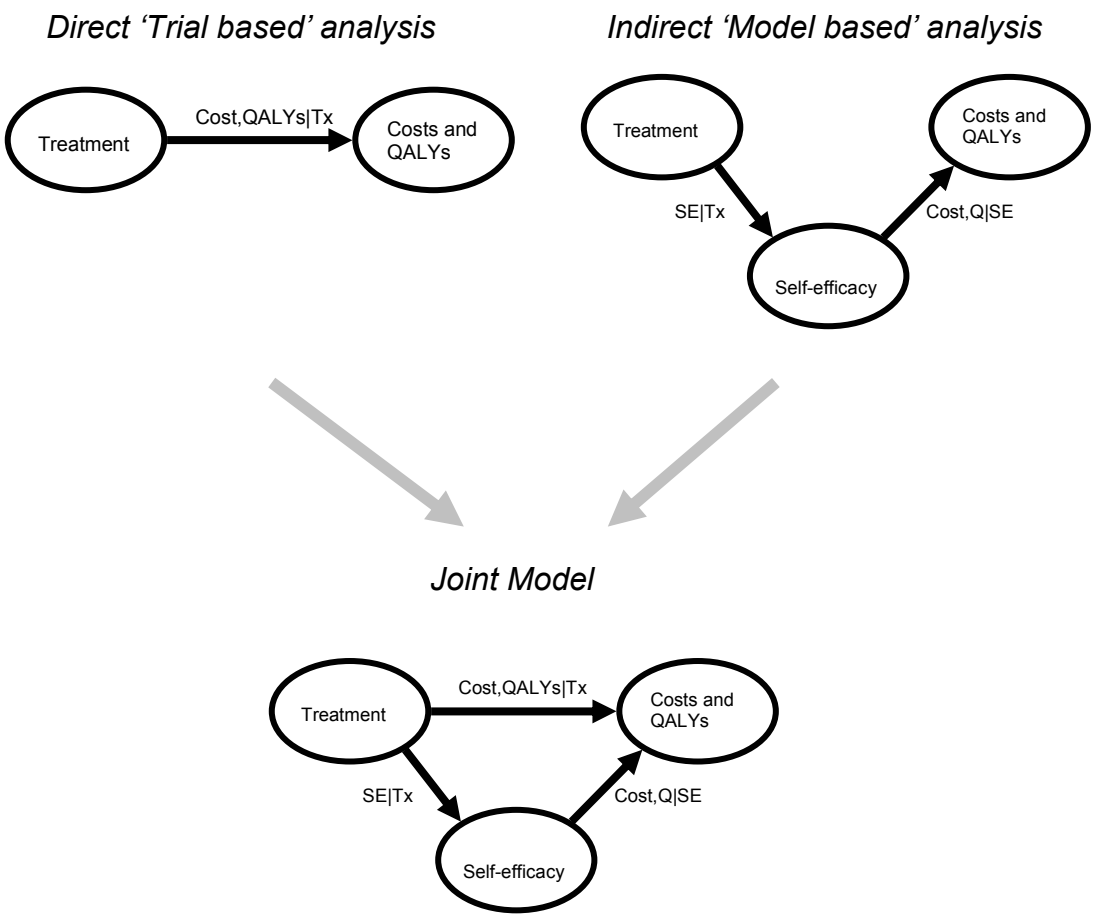


Figure 2: Cost-effectiveness acceptability curves (CEACs) for the direct, indirect, indirect including additional data, joint and joint including additional data analyses

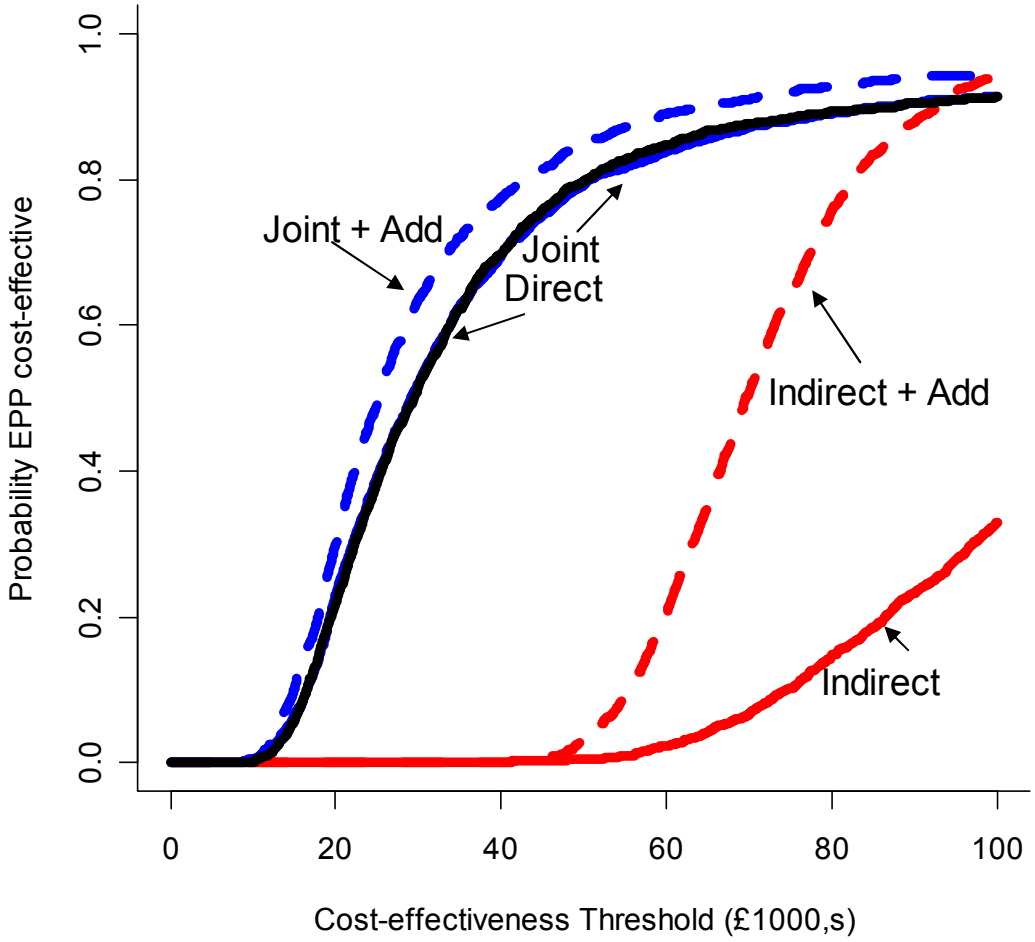
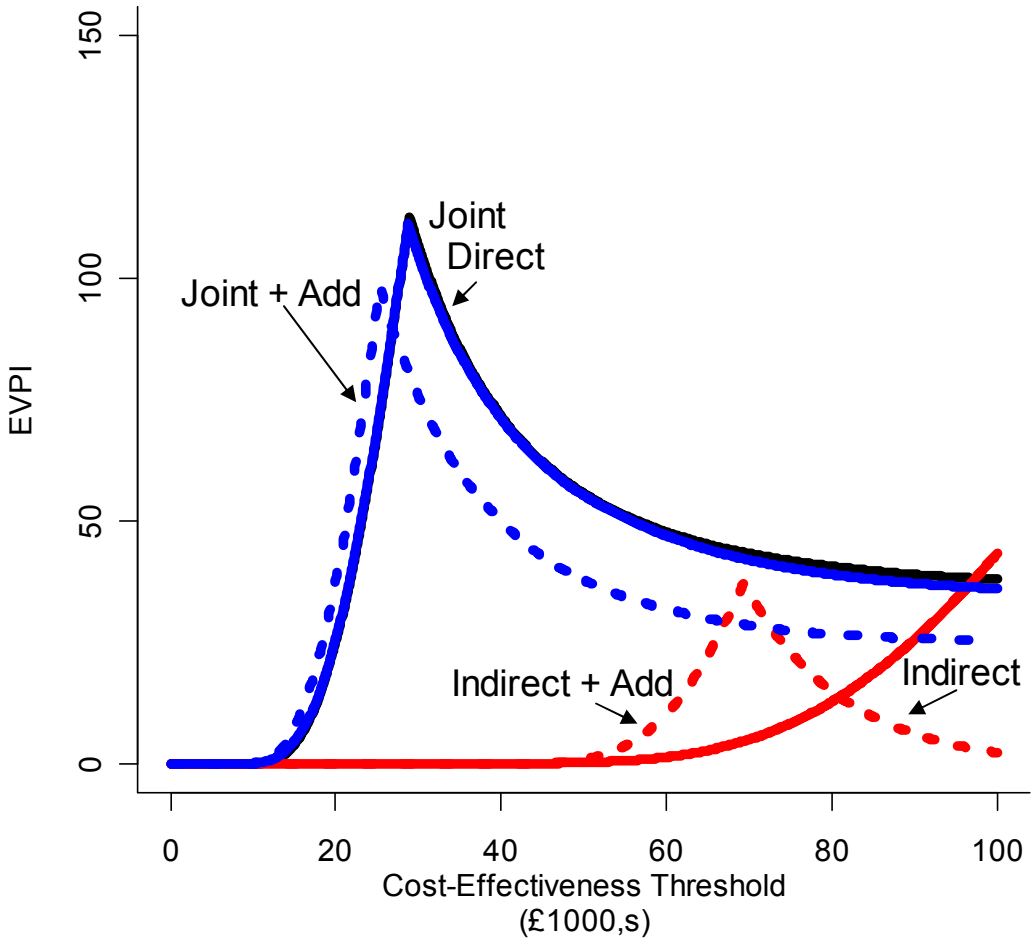


Figure 3: Expected value of additional information (EVPI) as a function of acceptable cost-effectiveness threshold for the direct, indirect, indirect including additional data, joint and joint including additional data analyses



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