HEALTH ECONOMICS
Health Econ. **21**: 742–756 (2012)
Published online 28 July 2011 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/hec.1741

SURROGATES, META-ANALYSIS AND COST-EFFECTIVENESS MODELLING: A COMBINED ANALYTIC APPROACH

NEIL HAWKINS[a,*], GERRY RICHARDSON[a,c], ALEX J SUTTON[b], NICOLA J COOPER[b], CHRIS GRIFFITHS[d], ANNE ROGERS[e] and PETER BOWER[e]

[a]*Centre for Health Economics, University of York, York, UK*
[b]*Department of Health Sciences, University of Leicester, Leicester, UK*
[c]*Hull York Medical School, York, UK*
[d]*Centre for Health Sciences, Barts & The London School of Medicine & Dentistry, London, UK*
[e]*Primary Care Research Group, University of Manchester, Manchester, UK*

SUMMARY

Estimates of cost-effectiveness analyses are typically obtained either directly from 'trial' based analyses or indirectly via surrogate endpoints in 'model' based analyses. Data from clinical trials that include both surrogate and final endpoints can be used in a joint analysis that combines these two approaches. This joint approach allows the inclusion of information regarding the effects of treatment on surrogate endpoints while relaxing the strong assumption of 'conditional independence' associated with indirect model-based analyses. An example cost-effectiveness analysis of Chronic Disease Self-Management Programme is used to compare the different approaches. It is shown that despite using a common data set, the different analytic approaches produce differing estimates of the cost-effectiveness of the intervention and the value of future research. The paper concludes by discussing the selection of the appropriate analytic approach. Copyright © 2011 John Wiley & Sons, Ltd.

Received 23 February 2009; Revised 7 February 2011; Accepted 18 March 2011

KEY WORDS: surrogate outcome; economic evaluation; Bayesian; Chronic Disease Self-Management Programme; randomised controlled trial

1. INTRODUCTION

Presuming the application of a Bayesian decision rule, economic evaluations of healthcare technologies are based on estimates of mean costs and effects—the final decision endpoints—for each treatment option. Precisely which costs are included and which scale is used to measure effects will depend on the preference of the decision-maker. The expected values of the means are used to identify the optimum treatment given current information, and the estimated joint distribution of the means are used to estimate the probability of correctly identifying the optimal treatment and the potential value of additional information in increasing this probability. Together, these analyses inform the related decisions of whether to adopt a treatment and whether further information is required (Vanness and Mullahy, 2006). The required estimates of the joint distribution of the means for the final decision endpoints are commonly derived from either 'trial' or 'model' based analyses.

In 'trial' based analyses, the final decision endpoints are predicted for each treatment option based on the direct relationship between treatment choice and final endpoints observed inferred from a clinical trial. Typically, a trial-based analysis will be based on a single trial, although rare examples of meta-analysis of cost-effectiveness estimates do exist (Cheng and Niparko, 1999; Bower *et al.*, 2003). Data from trials that included surrogate endpoints but not the final decision endpoints cannot be included in a trial-based analysis.

*Correspondence to: Centre for Health Economics, Alcuin 'A' Block, University of York, Heslington, York, UK, YO10 5DD. E-mail: nsh2@york.ac.uk

In 'model' based analyses, the final decision endpoints are predicted for each treatment option based on an indirect relationship operating via one or more surrogate endpoints (Elston and Taylor, 2009). The 'model' combines the predicted effect of treatment choice on the surrogate endpoints and the estimated relationship between the surrogate endpoints and the final decision endpoints. The relationship between treatment choice and the surrogate endpoints is typically estimated based on the relationship observed within clinical trials, either based on an individual trial or a meta-analysis of multiple trials. The relationship between the surrogate endpoints and mean costs and effects may be estimated from a variety of sources including data from clinical trials, observational studies and even clinical opinion (Elston and Taylor, 2009).

Two recent evaluations of asthma treatments provide practical examples of the two approaches. In the 'model' based evaluation, the effect of individual treatments on the surrogate endpoint of mean per cent symptom-free days was estimated from a meta-analysis of randomised controlled trials and relationships between mean per cent symptom-free days and mean costs, and quality-adjusted life years (QALYs) were estimated using data from a single trial. These relationships were combined to obtain treatment-specific estimates of incremental mean costs and QALYs (Doull *et al.*, 2007). The relationship between mean per cent symptom-free days and mean costs and QALYs was assumed to be identical for each treatment. In the 'trial' based analysis, mean costs and symptom-free days were estimated for each treatment arm included in a single trial. (Sullivan *et al.*, 2005)

In some cases, it may not be possible to obtain estimates of the final decision endpoints for all treatment options within a direct trial-based analysis. For example, it may be impracticable to encompass the relevant time horizon for a decision-maker, such as a patient's lifetime, within a clinical trial, or there may not be an available trial that includes all relevant treatment options. In these cases, an indirect model-based analysis will be necessary (Buxton *et al.*, 1997; Sculpher *et al.*, 2006).

Where there are no trials available that include all relevant treatment options, an indirect comparison based on the available trial evidence may be helpful. Although indirect comparisons could in principle be based on the final cost and effect endpoints, they are more usually applied to surrogate endpoints. Indirect comparisons require the assumption that treatment effects are exchangeable across trials, and this assumption is more likely to be met for surrogate endpoints than for final endpoints: the causal path between treatment and final endpoints will be longer than the path between treatment and surrogate endpoints, and as the causal path lengthens, there is increasing opportunity for differences between trials to modify relative treatment effects and potentially confound indirect comparisons. For example, the effects of asthma treatments on forced expiratory volume in 1 s may be similar across different countries, but the effects on mortality may well be influenced by local medical practise. These differences may bias indirect comparisons based on mortality. This source of potential bias will be a particular concern for cost endpoints.

However, balanced against the 'length' of the causal pathway and the scope for confounding, we should consider the scope for error in the measurement of surrogate endpoints. For example, if the methods used to measure forced expiratory volume in 1 s are not standardised between trials, differences in measurement between trials, particularly systematic differences between trials comparing different sets of treatments, may confound indirect comparisons. In contrast, the methods used to assess final endpoints, such as death, may be more consistent.

Although indirect model-based analysis via surrogate endpoints can be helpful (and some would argue essential) in meeting the needs of decision-makers, they require the assumption that all the important effects of treatment on the final decision endpoints are mediated, or predicted, by the surrogate endpoints. In other words, if we condition on the surrogate endpoints, the final decision endpoints are independent of treatment choice—a form of conditional independence. For example, in our example asthma model, mean costs (other than the treatment acquisition cost) and QALYs will depend only on estimated symptom-free days and not on treatment.

If this assumption of conditional independence is not warranted, including only those effects of treatment that are mediated by surrogate endpoints may lead to biased estimates of mean costs and QALYs and also the underestimation of uncertainty. For example, $CD4^+$ counts have been used as a surrogate for survival in HIV

DOI: 10.1002/hec

trials. Although certain drugs improve $CD4^+$ count, and $CD4^+$ count is a good measure of survival, other adverse effects of these drugs may actually reduce survival (Ellenberg, 1994). In this instance, the $CD4^+$ count surrogate does not reliably capture the effect of treatment on final endpoint (Fleming and DeMets, 1996). A reliance on surrogate endpoints may lead to the effect of inappropriate adoption decisions being compounded as the value of future research is underestimated.

The strong assumptions embedded in model-based analysis create a tension between the desire to include a wide range of treatment options (and information) and the concerns as to the validity of the resulting estimates. On occasion, these concerns may lead to a direct trial-based analysis with a narrow scope and evidence base being preferred over a broader indirect model-based analysis.

Some clinical trials include measures of both surrogate and final decision endpoints. In this paper, we demonstrate how data from these trials can be used in an analysis that combines both direct 'trial' based and indirect 'model' based approaches. Vis-à-vis, direct information regarding the effect of treatment on the final decision endpoints and indirect information regarding the effect of treatment on surrogate endpoints are combined within a joint analysis. This joint approach allows the inclusion of information regarding surrogate endpoints while relaxing the strong assumptions of conditional independence associated with indirect model-based analyses.

The remainder of this paper is structured as follows. Section 2 presents the motivating example of the Chronic Disease Self-Management Programme (CDSMP). Section 3 outlines the direct, indirect and joint models developed for the motivating example. Section 4 reports the results and compares and contrasts the findings from the three analytic approaches. We show in this example that, despite being based on a common set of trial data, the three methods of analysis potentially lead to different decisions regarding the adoption of CDSMP and the value of further research. Section 5 includes a description of the underlying assumptions for each method of analysis and considers how the most appropriate method might be selected. Section 6 concludes the paper.

2. EXAMPLE: CHRONIC DISEASE SELF-MANAGEMENT PROGRAMME

Recently, interventions to support patients in their self-care of chronic diseases have been developed. An example is CDSMP, which has been developed in the US. This forms the basis of the Expert Patient Programme, 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 (Department of Health, 2006).

The CDSMP intervention is designed to increase patients' level of self-efficacy, defined as their confidence in their ability to manage their condition (Bandura, 1977). It is hypothesised that improving patients' self-efficacy will lead to improvements in health outcomes (Lorig *et al.*, 2001a; Lorig *et al.*, 2003). The decision problem is to determine whether the addition of the CDSMP programme to current treatment is cost-effective and should be adopted and also whether further research should be required or commissioned.

2.1. Available data

The systematic procedure used to identify the data is described elsewhere (Richardson, 2007). Individual patient data (IPD) were available from two UK randomised trials comparing the CDSMP intervention with 'no intervention' (Griffiths *et al.*, 2005; Richardson, 2007). For these trials, the final decision endpoints of QALYs and total costs (over a 6-month period) were estimated. These trials also included measurement of the surrogate endpoint self-efficacy and a covariable, baseline EuroQol-5D (EQ-5D).

In addition, six non-UK randomised trials were identified that compared CDSMP (or similar) with 'no intervention' (Richardson, 2007; Richardson *et al.*, 2005). For these trials, only summary statistics for the effect of treatment on the surrogate endpoint (self-efficacy) were available. Henceforth, these are referred to as the 'additional surrogate' data. Details of all included trials are provided in the Table I.

DOI: 10.1002/hec

Table I. Summary of studies included in the analysis

Study	Country	Study design	Date	*N*	Type of data available	Change in self-efficacy mean	Standard error
Kennedy *et al.* (2007)	UK	RCT	2006	629	IPD	0.52	0.21
Griffiths *et al.* (2005)	UK	RCT	2005	476	IPD	0.23	0.13
Lorig *et al.* (2001b)	US	Before and after	2001	489	AD	0.50	2.40
Lorig *et al.* (2001a)	US	Before and after	2001	430	AD	0.31	1.67 2.53
Siu *et al.* (2007)	Hong Kong	RCT	2007	148	AD	0.57	0.39
Fu *et al.* (2003)	China	RCT	2003	954	AD	0.63	0.21
Lorig *et al.* (2003)	US	RCT	2003	327	AD	0.44	0.30

RCT, randomised controlled trial; IPD, individual patient data; AD, aggregate data.

3. METHODS

In general, a cost-effectiveness analysis can be described in terms of two components: prediction and parameter-estimation models. The prediction model is used to estimate the joint distribution of mean costs and effects for each treatment option for a future patient. The parameter-estimation models are used to obtain estimates for the parameters required for the prediction models. Typically, these estimates are obtained by fitting the parameter-estimation models to the data from clinical trials or observational studies.

In a direct trial-based analysis, the trial can be seen as a direct experimental model of a future patient. For example, the prediction model of mean costs and QALYs for future patients consists of the appropriate coefficients from a linear regression (the parameter-estimation model) predicting the costs and QALYs observed in the trial.

In an indirect model-based analysis, mean costs and effects for a future patient are predicted based on the effect of treatment choice on a surrogate endpoint. An example would be a Markov model that combines the effect of treatment on the probability of being in discrete states with estimates of the costs and QALYs associated with each state (prediction model). The transition parameters for the Markov model and state associated costs and QALYs may be estimated from survival analysis of trial data (parameter-estimation model).

We describe the direct, indirect and joint analyses of the CDSMP intervention in terms of these two components: prediction and parameter-estimation models. The parameter-estimation models are a series of linear regressions that predict costs, QALYs and the surrogate endpoint (in the indirect and joint analysis) for individuals observed in clinical trials. Costs were modelled as following a log-normal distribution. The effects of treatment and other variables were assumed to be additive on the untransformed scale. As the parameter-estimations models are linear additive, the prediction models need only condition on treatment choice and do not need to take account of the values of other patient level covariables for the estimation of mean costs and QALYs.

In each analysis, the direct cost of the CDSMP intervention, estimated at £198, was added to the estimated non-treatment costs to arrive at the total treatment cost. This estimate of the intervention cost is a weighted average of the treatment cost reported in each trial £250 for the national evaluation (Department of Health, 2005; Richardson, 2007), £123 for the other UK-based trial (Griffiths *et al.*, 2005)). Using the latter estimate would clearly increase the cost-effectiveness of the intervention, but this analysis is not included here.

For the indirect and joint analyses, two sets of results are reported: (i) based only on the IPD available from two trials; and (ii) including the data on the surrogate endpoint from the six additional trials.

Parameters were estimated using Markov Chain Monte Carlo methods implemented in the OPENBUGS (Thomas A, O Hara B, Ligges U, and Sturtz S. Making BUGS Open. R News 6: 12–17) software. A Bayesian approach has a number of potential advantages: a bivariate distribution can be easily assigned to costs and QALYs to reflect their correlation (although in the current analysis, the bivariate model was found to be unstable and was not used in the final analysis), non-normal distributions can be assigned to costs; the various components of the estimation models can be jointly estimated; and any missing cost and QALY values will be

DOI: 10.1002/hec

sampled from the posterior distribution. All the BUGS code used to fit the models described in the following text is available from the first author on request.

3.1. Direct analysis

In the descriptions that follow, the J trials for which individual patient data are available are indexed by subscript j ($j = 1 \ldots\ldots J$), and the I_j individual subjects within the j^{th} trial are indexed by the subscript i ($i = 1 \ldots I_j$).

The individual patient QALY data from each subject in each trial ($q_{i,j}$) are assumed to be normally distributed:

$$q_{i,j} \sim N\left(\mu_{\mathrm{q}_{i,j}}, \sigma^2_{\mathrm{q}_j}\right) \quad i = 1\ldots.I_j,\ j = 1\ldots.J \tag{1}$$

The variance ($\sigma^2_{\mathrm{q}_j}$) is allowed to vary between trials.

The expected QALYs for each subject ($\mu_{\mathrm{q}_{i,j}}$) are estimated as a linear regression including a study-specific intercept (α_{q_j}), treatment indicator ($T_{i,j}$) and the covariable baseline EQ-5D ($E_{i,j}$). β_{q} is the regression coefficient associated with the treatment effect, and hence provides the average difference in QALYs between EEP and control interventions:

$$\mu_{\mathrm{q}_{i,j}} = \alpha_{\mathrm{q}_j} + \beta_{\mathrm{q}} T_{i,j} + \delta_{\mathrm{q}} E_{i,j} \quad i = 1\ldots.I_j,\ j = 1\ldots.J \tag{2}$$

The individual patient cost data ($c_{i,j}$) are assumed to follow a log-normal distribution (with treatment and other variables having an additive effect on mean cost):

$$\log\left(c_{i,j}\right) \sim N\left(\mu_{\mathrm{c}_{i,j}} - \frac{\sigma^2_{\mathrm{c}_j}}{2}, \sigma^2_{\mathrm{c}_j}\right) \quad i = 1\ldots.I_j,\ j = 1\ldots.J \tag{3}$$

Again, note the variance of the costs ($\sigma^2_{\mathrm{c}_j}$) is allowed to vary between trials. The expected costs for each subject ($\mu_{\mathrm{c}_{i,j}}$) are estimated in a similar regression to the one used for QALYs; only now the subscript c indicates that the parameters refer to cost. Note in this example, the same covariable (baseline EQ-5D) is specified, but alternative covariables could be included.

$$\mu_{\mathrm{c}_{i,j}} = \alpha_{\mathrm{c}_i} + \beta_{\mathrm{c}} T_{i,j} + \delta_{\mathrm{c}} E_{i,j} \quad i = 1\ldots.I_j,\ j = 1\ldots.J \tag{4}$$

Here, the coefficient of primary interest is β_{c}, which is the regression coefficient associated with the mean difference in cost between treatment arms.

The predicted incremental mean QALYs (Δq) and costs (Δc) for a future patient receiving CDSMP are then assumed to equal the value of the costs and QALY treatment coefficients:

$$\Delta q = \beta_{\mathrm{q}}$$

$$\Delta c = \beta_{\mathrm{c}}$$

3.2. Indirect analysis

The individual subject data on the surrogate, $S_{i,j}$ are assumed to be normally distributed with mean $\mu_{\mathrm{s}_{i,j}}$ and trial-specific variance $\sigma^2_{\mathrm{s}_j}$:

$$S_{i,j} \sim N\left(\mu_{\mathrm{s}_{i,j}}, \sigma^2_{\mathrm{s}_j}\right) \quad i = 1\ldots.I_j,\ j = 1\ldots.J \tag{5}$$

The mean effects, $\mu_{\mathrm{s}_{i,j}}$, are predicted in a linear regression including a study-specific intercept, treatment indicator and other covariables.

$$\mu_{\mathrm{s}_{i,j}} = \alpha_{\mathrm{s},j} + \beta_{\mathrm{s}} T_{i,j} + \delta_{\mathrm{s}} E_{i,j} \quad i = 1\ldots.I_j,\ j = 1\ldots.J \tag{6}$$

DOI: 10.1002/hec

The individual subject QALY and cost data are included using the likelihood functions given in Equations (1) and (3), respectively.

In the indirect analysis, QALYs for each subject are estimated as a linear regression similar to Equation but are dependent on the surrogate endpoint ($S_{i,j}$)—level of self-efficacy—rather than the treatment indicator:

$$\mu_{q_{i,j}} = \alpha_{q_j} + \gamma_q S_{i,j} + \delta_q E_{i,j} \quad i = 1....I_j,\ j = 1....J \tag{7}$$

where γ_q is the regression coefficient, which estimates the mean change in QALYs for each unit change in the surrogate endpoint.

Equation (4) is similarly modified for the indirect analysis:

$$\mu_{c_{i,j}} = \alpha_{c_j} + \gamma_c S_{i,j} + \delta_c E_{i,j} \quad i = 1....I_j,\ j = 1....J \tag{8}$$

where γ_c is the regression coefficient, which estimates the mean change in costs for each unit change in the surrogate endpoint. These two parameter-estimation models do not include terms for the effect of treatment on costs and QALYs as the treatment effect is captured solely via its effect on the surrogate endpoint.

In a second analysis, data from the $k = 1...K$ additional surrogate data trials reporting the mean difference in the surrogate endpoint between trial arms, $\Delta\overline{S}_k$, and its associated variance, s_k^2 can be included using the following likelihood function:

$$\Delta\overline{S_k} \sim N\left(\beta_s, s_k^2\right). \quad k = 1...K \tag{9}$$

Note that the mean of this normal distribution, β_s, is the same parameter as in Equation (6). Different likelihood functions, which contain common parameters have been used recently in other contexts (Jackson *et al.*, 2006; Sutton *et al.*, 2008) for synthesising individual and aggregate data.

The predicted incremental mean costs and QALYs for a future patient are then estimated as the products of the effect of treatment on the surrogate endpoint and the effect of the surrogate endpoint on costs and QALYs:

$$\Delta c = \beta_s . \gamma_c \tag{10}$$

$$\Delta q = \beta_s . \gamma_q \tag{11}$$

3.3. Joint analysis

The joint analysis is a combination of the direct and indirect analyses. The likelihoods for costs, QALYs and surrogate outcomes are specified as before (Equations (1), (3) and (5)). Like the indirect model, the surrogate endpoint is predicted in a linear regression including a treatment indicator (Equation (6)).

QALYs and costs for each subject are estimated as linear regressions; this time including both the surrogate endpoint and the treatment indicator.

$$\mu_{q_{i,j}} = \alpha_{q_j} + \beta_q T_{i,j} + \gamma_q S_{i,j} + \delta_q E_{i,j} \quad i = 1....I_j,\ j = 1....J \tag{12}$$

$$\mu_{c_{i,j}} = \alpha_{c_j} + \beta_c T_{i,j} + \gamma_c S_{i,j} + \delta_c E_{i,j} \quad i = 1....I_j,\ j = 1....J \tag{13}$$

Again, an additional analysis was conducted including the additional surrogate data as per the indirect analysis.

The predicted incremental mean costs and QALYs for a future patient are then estimated as the effect of the surrogate endpoint on costs and QALYs (γ_c and γ_q) plus the product of the effect of treatment on the surrogate endpoint (β_s) and the effect of the surrogate endpoint on costs and QALYs (γ_c and γ_q):

$$\Delta c = \beta_c + \beta_s . \gamma_c \tag{14}$$

$$\Delta q = \beta_q + \beta_s . \gamma_q \tag{15}$$

DOI: 10.1002/hec

Table II. Comparison of the three analytic approaches

	Analysis		
	Direct	Indirect	Joint
Within-study parameter-estimation model	$\mu_{c_{i,j}} = \alpha_{c_j} + \beta_c T_{i,j} + \delta_c E_{i,j}$ $\mu_{q_{i,j}} = \alpha_{q_j} + \beta_q T_{i,j} + \delta_q E_{i,j}$	$\mu_{c_{i,j}} = \alpha_{c_j} + \gamma_c S_{i,j} + \delta_c E_{i,j}$ $\mu_{q_{i,j}} = \alpha_{q_j} + \gamma_q S_{i,j} + \delta_q E_{i,j}$ $\mu_{c_{i,j}} = \alpha_{c_j} + \gamma_c S_{i,j} + \delta_c E_{i,j}$	$\mu_{c_{i,j}} = \alpha_{c_j} + \beta_c T_{i,j} + \gamma_c S_{i,j} + \delta_c E_{i,j}$ $\mu_{q_{i,j}} = \alpha_{q_j} + \beta_q T_{i,j} + \gamma_q S_{i,j} + \delta_q E_{i,j}$ $\mu_{c_{i,j}} = \alpha_{c_j} + \gamma_c S_{i,j} + \delta_c E_{i,j}$
Likelihood-IPD	$\log(c_{i,j}) \sim N\left(\mu_{c_{i,j}} - \frac{\sigma^2_{c_j}}{2}, \sigma^2_{c_j}\right)$ $q_{i,j} \sim N\left(\mu_{q_{i,j}}, \sigma^2_{q_j}\right)$	$\log(c_{i,j}) \sim N\left(\mu_{c_{i,j}} - \frac{\sigma^2_{c_j}}{2}, \sigma^2_{c_j}\right)$ $q_{i,j} \sim N\left(\mu_{q_{i,j}}, \sigma^2_{q_j}\right)$ $S_{i,j} \sim N\left(\mu_{s_{i,j}}, \sigma^2_{s_j}\right)$	$\log(c_{i,j}) \sim N\left(\mu_{c_{i,j}} - \frac{\sigma^2_{c_j}}{2}, \sigma^2_{c_j}\right)$ $q_{i,j} \sim N\left(\mu_{q_{i,j}}, \sigma^2_{q_j}\right) S_{i,j} \sim N\left(\mu_{s_{i,j}}, \sigma^2_{s_j}\right)$
Likelihood-summary statistics		$\Delta \overline{S}_k \sim N(\beta_s, s^2_k)$	
Out-of-study prediction model	$\Delta q = \beta_q \Delta c = \beta_c$	$\Delta q = \beta_s . \gamma_q \Delta c = \beta_s . \gamma_c$	$\Delta q = \beta_q + \beta_s . \gamma_q \Delta c = \beta_c + \beta_s . \gamma_c$
Constraints	Data on surrogate endpoints is not relevant and cannot be incorporated ($\gamma_c, \gamma_q = 0$)	Costs and QALYs are conditionally independent of treatment given self-efficacy ($\beta_c, \beta_q = 0$)	None. Data on surrogate endpoints can be incorporated without implicit assumption that costs and QALYs are conditional independent of treatment given self-efficacy

IPD, individual patient data; QALYs, quality-adjusted life years.

All three models are summarised in Table II.

If sufficient data had been available, particularly multiple trials including surrogate and final endpoints, other model specifications could have been compared. For example, the relationship between surrogate and final endpoints could be modelled as a random effect to account for the heterogeneity between trials.

4. RESULTS

The estimated incremental cost-effectiveness ratio (ICER), cost-effectiveness acceptability curves (CEAC) and expected value of perfect information (EVPI) are compared for each analytic approach. The subsequent implications for recommendations regarding treatment adoption and the need for further research are described (Barton et al., 2009).

4.1. Cost-effectiveness

The estimated regression coefficients and their 95% CI[1] for each of the analyses are shown in Table III.

The direct analysis indicates that CDSMP treatment is associated with higher non-treatment costs (£63) and QALYs (0.009) than no intervention. Including the treatment cost, the direct analysis gives an ICER of £29 311.

The indirect analysis indicates that the CDSMP programme is associated with an increase in patient-reported self-efficacy (0.377) and that increased self-efficacy is in turn associated with decreased non-treatment costs (£−11 per unit change) and increased QALYs (0.009 per unit change). When these are combined, CDSMP treatment is associated with lower non-treatment costs (£−4) and higher QALYs (0.003) than no intervention leading to an ICER of £55 644 when the treatment cost is included.

In the joint analysis, the CDSMP programme is associated with an increase in patient-reported self-efficacy (0.365), and increased self-efficacy is associated with lower non-treatment costs (£−11 per unit change) and

[1]Analogous to the usual interpretation of a frequentist CI.

DOI: 10.1002/hec

Table III. Results

	Analysis									
	Direct		Indirect		Joint		Indirect + additional data		Joint + additional data	
	Mean	(95%CI)	Mean	(95%CI)	Mean	(95%CI)	Mean	(95%CI)	Mean	(95%CI)
Regression coefficients										
Costs on treatment (β_c)	63	20, 105			65	25, 103			64	22, 106
QALYs on treatment (β_q)	0.009	0.000, 0.018			0.007	−0.003, 0.016			0.007	−0.002, 0.016
Costs on self-efficacy (γ_c)			−11	−20, −3	−11	−20, −2	−11	−20, −3	−11	−20, −2
QALYs on self-efficacy (γ_q)			0.009	0.007, 0.011	0.009	0.007, 0.011	0.009	0.007, 0.012	0.009	0.007, 0.011
			0.38	0.07, 0.67	0.37	0.08, 0.64	0.43	0.33, 0.53	0.43	0.33, 0.53
Self-efficacy on treatment (β_s)										
Incremental non-treatment costs	63	20, 105	−4	−10, 0	60	20, 99	−5	−9, −1	59	−17, 101
Incremental total cost	261	218, 303	194	188, 198	258	218, 297	193	189, 197	257	215, 299
Incremental QALYs	0.009	0.000, 0.018	0.003	0.001, 0.007	0.01	0.001, 0.020	0.004	0.003, 0.005	0.011	0.002, 0.019
ICER (£ per QALY)	29 300		55 600		25 800		48 800		24 100	
Probability that EPP is optimum at a cost-effectiveness threshold of £30 000	0.52		0.03		0.61		0.00		0.67	
EVPI at a cost-effectiveness threshold of £30 000 (£)	104		1		83		0		59	

QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio; EPP, expert patients programme; EVPI, expected value of perfect information.

DOI: 10.1002/hec

increased QALYs (0.009 per unit change). In addition, independent of the effects mediated through self-efficacy, CDSMP treatment is associated with higher non-treatment costs (£65) and QALYs (0.007) than no intervention. Including the treatment cost gives an ICER of £25 786.

The incorporation of additional surrogate data into the indirect and joint analyses increases the estimated mean increase in self-efficacy associated with CDSMP from 0.35 to 0.428. This reduces the ICER in the indirect analysis to £48 760 and in the joint analysis to £24 064.

4.2. Value of information

The cost-effectiveness acceptability curves for each analysis are shown in Figure 1 and the EVPI in Figure 2. The CEACs for the direct and joint analyses are almost identical with similar probabilities that CDSMP is optimal at a threshold of £30 000 of 0.52 and 0.61. The EVPIs are also similar at £104 and £83 per patient. In contrast, the indirect analysis produces a probability that CDSMP is optimal at a threshold of £30 000 close to 0. The EVPI is also close to £0.

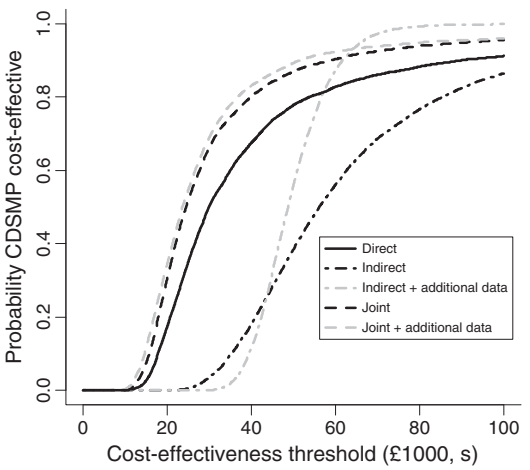

Figure 1. Cost-effectiveness acceptability curves for each analysis. CDSMP, Chronic Disease Self-Management Programme

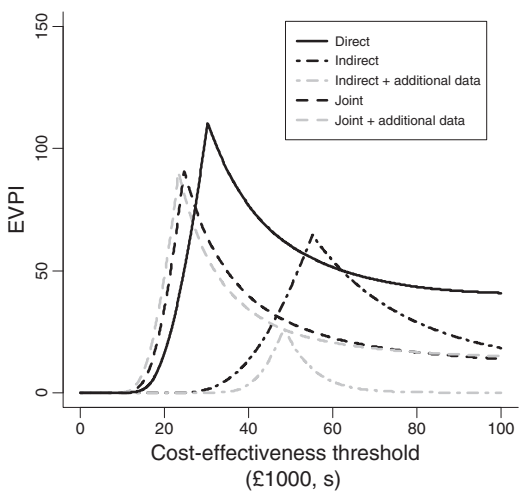

Figure 2. Expected value of perfect information (EVPI) for each analysis

DOI: 10.1002/hec

The incorporation of additional surrogate 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 CDSMP on self-efficacy, and therefore improves estimates of cost-effectiveness. For the joint model, the probability that CDSMP is optimal increases to 0.67, and the EVPI reduces to £59. For the indirect model, the probability that CDSMP is optimal and the EVPI remain close to 0.

4.3. Likely recommendations

The value of a QALY is open to some debate. However, the National Institute for Health and Clinical Excellence (NICE) have suggested a threshold for the cost per QALY of between £20 000 and £30 000. (NICE, 2004) Interventions with a cost per QALY below £20 000 are likely to be judged as an acceptable use of the National Health Service resources, whereas those above £30 000 require strong additional evidence of, for example, wider societal costs/benefits. If we use the higher end of this range and assume an acceptable cost-effectiveness threshold of £30 000, a decision-maker making adoption decisions based on current data alone would adopt CDSMP based on the direct and joint analyses but would reject it 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 CDSMP 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.

5. DISCUSSION

We have shown that given a common dataset, comprising the two trials for which IPD was available, the direct trial-based and indirect model-based analyses lead to different recommendations regarding the adoption of CDSMP and the need for further research. Under the direct trial-based analysis, CDSMP would be deemed possibly cost-effective and further research of potential value, whereas under the indirect model-based analysis, CDSMP would be deemed not cost-effective and further research of little value. The conflicting results were due to the effects of treatment on costs and QALYs that were independent of the effects mediated by the surrogate endpoint. In addition, we showed that a wider body of trial data regarding the effect of treatment on the surrogate could be included in the indirect model-based analysis.

We also presented results from a joint analysis that combined the independent effects of treatment on costs and QALYs, treatment on surrogate endpoint, and surrogate endpoint on costs and QALYs. This analysis produced similar results to the direct trial-based analysis. Like the indirect model-based analysis, it allowed the inclusion of additional data regarding the surrogate endpoint but did not require a strong assumption of conditional independence.

Given the conflicting results between the different analytic approaches, which is most appropriate?—we consider the advantages and disadvantages of each.

5.1. Advantages and disadvantages

The direct trial-based approach is simple, being based on the empirical relationship between treatment and final endpoints. However, a disadvantage of this approach is that additional data on surrogate endpoints cannot be incorporated. Although in principle, multiple trials could be combined in a direct trial-based analysis, this is rarely carried out in practise, and the methodology has been little discussed.

The indirect approach has the advantage that data from trials reporting surrogate outcomes can be incorporated, commonly allowing a wider range of data to be included. This may be necessary to allow the inclusion of relevant comparators. However, the drawback of this approach is the implicit assumption that if we know the value of the surrogate endpoint for an individual, the expected costs and effects are conditionally independent of treatment. In other words, the surrogate endpoint, within the model structure, provides all the

DOI: 10.1002/hec

information required to inform the adoption and research decisions. Although if this assumption is valid, the indirect model-based analysis will lead to increased precision over a direct trial-based analysis (Day and Duffy, 1996).

The joint model includes data on both surrogate and final endpoints and does not require the conditional independence assumption of the indirect model. It will capture effects of the treatment on final endpoints not mediated by the surrogate or included in the model structure. However, it does require the availability of trials including both the surrogate and final endpoints.

5.2. The role of hypothesis testing

Both the indirect and direct models can be seen as special cases of the joint model. In the direct model, the independent effects of treatment on costs and QALYs mediated by the surrogate endpoint are not explicitly included (γ_c and γ_q are constrained to zero, see Table II). However, these effects will be captured by the β_c and β_q coefficients. In the indirect model, the effects of treatment on costs and QALYs independent of the surrogate endpoint are not included (β_c and β_q are constrained to zero) and will not be captured by the analysis.

This relationship between the direct and the indirect models suggests a role for hypothesis testing to infer which model is appropriate. A test suggesting that the true values of β_c and β_q, from the joint analysis are zero would support the adoption of the indirect model. This should be an equivalence test of the alternate hypothesis (H_1) that β_c or β_q lie in an acceptable range. However, if the acceptable range selected for this equivalence test is narrow, there will be little difference anyway between the results of the joint and indirect analyses (if selected). If a test of non-equivalence is used rather than a test of equivalence, an indirect model may be adopted when there is little data because of lack of power to reject the null hypothesis (even though β_c and β_q deviate markedly from zero) and rejected when there are large amounts of data (even though β_c and β_q are close to zero).

5.3. Conceptual models

Rather than relying on blind hypothesis testing, it may be more useful to develop a conceptual model mapping the causal pathway from treatment choice to final endpoints to assess adequacy of the surrogate endpoints in representing the important effects of treatment on the final endpoints (Fleming and DeMets, 1996; Greenland *et al.*, 1999).

An example conceptual model of the effects of CDSMP on costs and QALYs is shown in Figure 3. This indicates that there may be important effects of CDSMP on the final endpoints that are not captured by the surrogate endpoint of self-efficacy. The development of a conceptual model at the start of the modelling process also reduces the risk of the availability of data inappropriately defining the analysis (Sculpher *et al.*, 2000).

The development of a conceptual model might also be useful in identifying potential sources of bias in the regression modelling (VanderWeele *et al.*, 2008; Hernán *et al.*, 2002). Some of the potential sources of bias are illustrated using our example conceptual model:

(i) Confounding due to omitted variables
For example, education level may influence both the treatment-seeking behaviour and the self-efficacy score leading the self-efficacy score to be endogenous (a variable that is related to and determined by other variables in the model). If this variable is not included in the analysis, the resulting confounding may lead to a biased estimate of the predictive relationship between the self-efficacy score and costs and QALYs.

(ii) Reverse causality or simultaneity
For example, subjects experiencing greater quality of life because of exogenous factors may also record higher self-efficacy scores. Reverse causality can lead to biased estimate of the predictive relationship between variables. The effects of reverse causality can be accounted for using approaches such as structural modelling and G-estimation (Flanders and Augestad, 2008).

DOI: 10.1002/hec

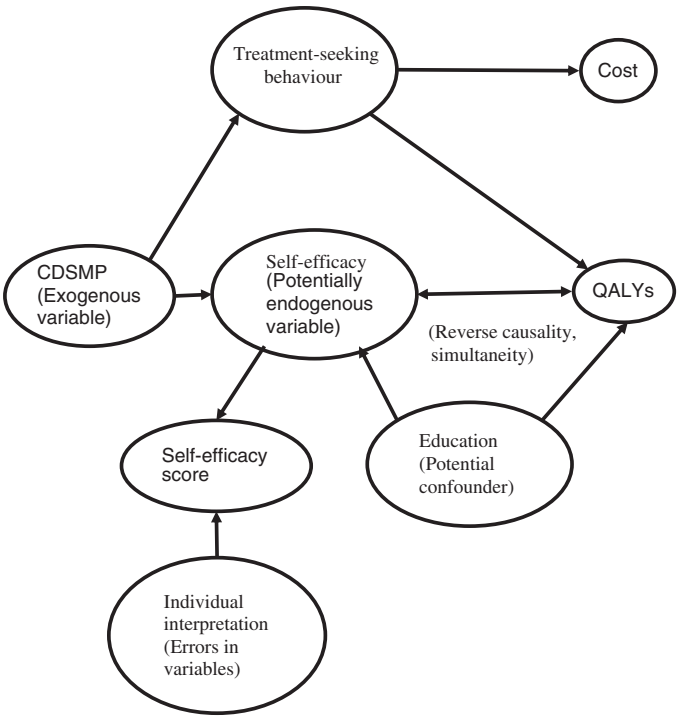

Figure 3. Conceptual treatment model. CDSMP, Chronic Disease Self-Management Programme; QALYs, quality-adjusted life year

(iii) Regression dilution due to errors in variables
For example, the self-efficacy score may be measured with error. This random error associated with a predictor variable may lead to regression dilution, where the absolute magnitude of the relationship between variables is underestimated. This can be accounted for by statistical models that take account of errors in variables. These methods require some estimate of the magnitude of measurement error, often derived from the analysis of repeated measures within individuals (White *et al.*, 2001).

(iv) Controlling for intermediate variables
For example, part of the effect of the CDSMP intervention on cost may be mediated by a change in treatment-seeking behaviour. If we were to include treatment-seeking behaviour as a predictor variable in our model, we would obtain a biased estimate of the effect of CDSMP on the final endpoints. This effect has been termed iatrogenic (Bulterys and Morgenstern, 1993) or overadjustment (Schisterman *et al.*, 2009) bias. Intermediate variables pose a particular problem when they act as both intermediate variables and confounders (Robins, 1989), and a variety of analytic solutions have been proposed (Robins, 2008).

(v) Omission of intermediate pathways
For example, patients participating in the CDSMP may gain process utility increasing QALYs without changing self-efficacy scores. If we measure process utility, we can include this additional surrogate in our analysis. Qu and Case (2007) described the use of path analysis to estimate the direct and indirect effects of treatment, where there are multiple surrogate endpoints.

Omitted variables, reverse causality and measurement error lead to what econometricians term as endogeneity. This occurs when the predictor variables are correlated with the error or disturbance term as defined by the 'true' model generating the observed data.

DOI: 10.1002/hec

One technique used to correct for endogeneity is instrumental variable analysis. An instrumental variable is a factor associated with exposure to an intervention but independent of other factors associated with exposure and associated with outcomes only via its association with exposure (an assumption known as the 'exclusion restriction'). Indeed, the presence of endogeneity can be tested statistically using the Durbin–Wu–Hausman test (Hausman, 1978), which compares instrumental variable and ordinary least squares estimates.

In a well-designed randomised controlled trial, treatment allocation satisfies these requirements because it is random and therefore independent of the characteristics of participants. Estimates from the analysis of a randomised trial or the corresponding results of the direct modelling will therefore not be subject to the biases previously listed, whereas the results of an indirect analysis may be. In a joint analysis, the effects of the biases listed previously will be captured in the term describing the direct relationship between treatment and costs and QALYs. However, estimates from an indirect model will be biased if the relationship between the surrogate and the final endpoints are subject to the biases previously mentioned.

5.4. Assessment of surrogate endpoints

The decision to adopt an indirect model-based analysis requires a judgement as to the adequacy of the surrogate endpoints included. A number of quantitative measures and qualitative criteria describing the validity of surrogate endpoints have been suggested.

Quantitative measures include the Prentice criteria (Prentice, 1989) (the conditional distribution of the final endpoint given the surrogate endpoint alone is the same as the conditional distribution of the clinical outcome given the surrogate marker and treatment), the proportion of treatment effect explained by a single surrogate (Freedman *et al.*, 1992) or relative effect (Buyse and Molenberghs, 1998). Interestingly, like the joint analyses presented in this paper, they are based on analysis of data sets including both the surrogate and final endpoints.

Qualitative criteria have been described by Bucher *et al.* (1999) and Elston and Taylor (2009). Bucher *et al.* (1999) suggested a number of criteria for determining whether a surrogate end point should be used as the basis for decision-making. Bucher suggested that in addition to a strong, independent and consistent association between the surrogate and final endpoints, there should be either evidence from randomised trials in either the same or other drug classes indicating that improvement in the surrogate endpoint has led to improvement in the final decision endpoint. In addition, Bucher suggested that the effect on the surrogate should be large, precise and lasting, and the risk benefit ratio is likely to be in favour of the proposed treatment.

Elston and Taylor (2009) described three levels of evidence: level 1 comprises evidence that treatment effects on the surrogate corresponds to effects on the final endpoint arising from clinical trials showing that a change in the surrogate outcome with treatment is associated with a commensurate change in final endpoints; level 2 comprises evidence of consistent relationship between surrogate endpoint and final endpoint arising from observational studies demonstrating an association between the surrogate and final endpoints; and level 3 comprises evidence of biological plausibility of the relationship between surrogate and final endpoints arising from pathophysiologic studies and understanding of disease processes.

In general, the literature on surrogacy has focussed on whether the surrogate endpoint can replace the final endpoints within individual trials for the purposes of inference (Johnson *et al.*, 2006; Weir and Walley, 2006). However, in cost-effectiveness analysis, we are interested in estimating mean costs and effects for future patients based on the available evidence. As such, rather than aspiring to determine whether the final endpoints can be 'replaced' by the surrogate endpoints, we should be concerned with estimating what the surrogate endpoint fails to tell us about the final endpoints in addition to what it does tell us.

The joint analysis presented in this paper avoids a 'take it or leave it' approach to surrogacy as it 'weights' the information on a surrogate according to the strength of its relationship to final endpoints. If the surrogate predicts the majority of the effect of treatment on costs and effects, additional information on the surrogate will have a large effect on the final estimates; if the surrogate only predicts a small proportion of the effect of treatment, additional information on the surrogate will have limited impact.

DOI: 10.1002/hec

6. CONCLUSIONS

Where clinical trials do not include final endpoints or all comparators, extrapolation from a surrogate measure of treatment effect to final decision endpoints is a common component of cost-effectiveness analyses. However, we do need to carefully evaluate whether analysis based on surrogate endpoints will produce unbiased estimates of the expectation and the variance of the final decision endpoints. Paradoxically, as in the example presented in this paper, the use of poor surrogates can lead to uncertainty being underestimated. Failure to account for uncertainty about the structural form of our analyses and adequacy of our surrogates will bias estimates of the value of further research.

We recommend that wherever possible, clinical trials should include measures of both surrogate and final decision endpoints. This will allow a joint analysis that provides useful empirical information about the adequacy of surrogate endpoints. Where trial data including both surrogate and final endpoints are available, these should be used to evaluate the sufficiency of the surrogate endpoint; we advise caution in the use of hypothesis testing for this. Finally, we recommend the development of a conceptual model as the first stage of an evaluation.

REFERENCES

Bandura A. 1977. Self-efficacy: toward a unifying theory of behavioral change. *Psychological Review* **84**: 191–215.

Barton GR, Briggs AH, Fenwick EAL. 2009. Optimal cost-effectiveness decisions: the role of the cost-effectiveness acceptability curve (CEAC), the cost-effectiveness acceptability frontier (CEAF), and the expected value of perfection information (EVPI). *Volume in Health* **11**(5): 886–897.

Bower P, Byford S, Barber J, Beecham J, Simpson S, Friedli K, Corney R, King M, Harvey I. 2003. Meta-analysis of data on costs from trials of counselling in primary care: using individual patient data to overcome sample size limitations in economic analyses. *BMJ* **326**: 1247.

Bucher H, Guyatt GH, Cook DJ, Holbrook A, McAlister F. 1999. Users' guides to the medical literature: XIX. Applying clinical trial results. A. How to use an article measuring the effect of an intervention on surrogate end points. *JAMA* **282**: 771–778.

Bulterys M, Morgenstern H. 1993. Confounding or intermediate effect? An appraisal of iatrogenic bias in perinatal AIDS research. *Paediatric and Perinatal Epidemiology* **7**: 387–394.

Buxton M, Drummond MF, Van Hout B, Prince RL, Sheldon TA, Szucs T, Vray M. 1997. Modelling in economic evaluation: an unavoidable fact of life. *Health Economics* **6**: 217–227.

Buyse M, Molenberghs G. 1998. Criteria for the validation of surrogate endpoints in randomized experiments. *Biometrics* **54**: 1014–1029.

Cheng A, Niparko J. 1999. Cost utility of the cochlear implant in adults. *Archives of Otolaryngology - Head & Neck Surgery* **125**: 1214–1218.

Day N, Duffy SW. 1996. Trial design based on surrogate end points–application to comparison of different breast screening frequencies. *Journal of the Royal Statistical Society. Series A* **159**: 49–60.

Department of Health. 2005. Self care–A real choice: Self care support–A practical option.

Department of Health. 2006. Our health, our care, our say: a new direction for community services.

Doull I, Price D, Thomas M, Hawkins N, Stamuli E, Tabberer M, Gosden T, Rudge H. 2007. Cost-effectiveness of salmeterol xinafoate/fluticasone propionate combination inhaler in chronic asthma. *Current Medical Research and Opinion* **23**: 1147–1159.

Ellenberg J. 1994. Selection bias in observational and experimental studies. *Statistics in Medicine* **13**: 557–567.

Elston J, Taylor RS. 2009. Use of surrogate outcomes in cost-effectiveness models: a review of United Kingdom health technology assessment reports. *International Journal of Technology Assessment Healthcare* **25**: 6–13.

Flanders W, Augestad LB. 2008. Adjusting for reverse causality in the relationship between obesity and mortality. *International Journal of Obesity (London)* **32**: S42–S46.

Fleming T, DeMets DL. 1996. Surrogate endpoints in clinical trials: are we being misled? *Annals of Internal Medicine* **125**: 605–613.

Freedman L, Graubard BI, Schatzkin A. 1992. Statistical validation of intermediate endpoints for chronic diseases. *Statistics in Medicine* **11**: 167–178.

Fu D, Fu H, McGowan P, Shen YE, Zhu L, Yang H, Mao J, Zhu S, Ding Y, Wei Z. 2003. Implementation and quantitative evaluation of chronic disease self-management programme in Shanghai, China: randomized controlled trial. *Bulletin of the World Health Organization* **81**: 174–182.

DOI: 10.1002/hec

Greenland S, Pearl J, Robins JM. 1999. Causal diagrams for epidemiologic research. *Epidemiology* **10**: 37–48.
Griffiths C, Motlib J, Azad A, Ramsay J, Eldridge S, Feder G, Khanam R, Munni R, Garrett M, Turner A, Barlow J. 2005. Randomised controlled trial of a lay-led self-management programme for Bangladeshi patients with chronic disease. *The British Journal of General Practice* **55**: 831–837.
Hausman JA. 1978. Specification tests in econometrics. *Econometrica* **46**: 1251–1271.
Hernán M, Hernández-Díaz S, Werler MM, MitcheII AA. 2002. Causal knowledge as a prerequisite for confounding evaluation: an application to birth defects epidemiology. *American Journal of Epidemiology* **155**: 176–184.
Jackson C, Best N, Richardson S. 2006. Improving ecological inference using individual-level data. *Statistics in Medicine* **25**: 2136–2159.
Johnson K, Freemantle N, Anthony D, Lassere MN. 2006. LDL-cholesterol differences predicted survival benefit in statin trials by the surrogate threshold effect (STE). *Journal of Clinical Epidemiology* **62**: 328–336.
Kennedy A, Reeves D, Bower P, Lee V, Middleton E, Richardson G, Gardner C, Gately C, Rogers A. 2007. The effectiveness and cost effectiveness of a national lay-led self care support programme for patients with long-term conditions: a pragmatic randomised controlled trial. *Journal of Epidemiology and Community Health* **61**: 254–261.
Lorig KR, Ritter P, Stewart AL, Sobel DS, Brown BW, Bandura A, Gonzalez VM, Laurent DD, Holman HR. 2001a. Chronic disease self-management program: 2-year health status and health care utilization outcomes. *Medical Care* **39**: 1217–1223.
Lorig KR, Sobel DS, Ritter PL, Laurent D, Hobbs M. 2001b. Effect of a self-management program on patients with chronic disease. *Effective Clinical Practice* **4**: 256–262.
Lorig KR, Ritter PL Gonzalez VM. 2003. Hispanic chronic disease self-management: a randomized community-based outcome trial. *Nursing Research* **52**: 361–369.
NICE. 2004. *Guide to the methods of technology appraisal. N0515*. National Institute for Clinical Excellence: London.
Prentice R. 1989. Surrogate endpoints in clinical trials: definition and operational criteria. *Statistics in Medicine* **8**: 431–440.
Qu Y, Case M. 2007. Quantifying the effect of the surrogate marker by information gain. *Biometrics* **63**: 958–963.
Richardson G. 2007. The cost-effectiveness of interventions to support self care. *PhD thesis*. University of York, UK.
Richardson G, Gravelle H, Weatherly H, Ritchie G. 2005. Cost-effectiveness of interventions to support self-care: a systematic review. *International Journal of Technology Assessment in Health Care*. **21**: 423–432.
Robins JM. 1989. The control of confounding by intermediate variables. *Statistics in Medicine* **8**: 679–701.
Robins JM. 2008. Causal models for estimating the effects of weight gain on mortality. *International Journal of Obesity* **32**: S15–S41.
Schisterman E, Cole SR, Platt RW. 2009. Overadjustment bias and unnecessary adjustment in epidemiologic studies. *Epidemiology* **20**: 488–495.
Sculpher M, Fenwick E, Claxton K. 2000. Assessing quality in decision analytic cost-effectiveness models. A suggested framework and example of application. *Pharmacoeconomics* **17**: 461–477.
Sculpher MJ, Claxton K, Drummond M, McCabe C. 2006. Whither trial-based economic evaluation for health care decision making? *Health Economics* **15**: 677–687.
Siu AM, Chan CC, Poon PK, Chui DY, Chan SC. 2007. Evaluation of the chronic disease self-management program in a Chinese population. *Patient Education and Counseling* **65**: 42–50.
Sullivan S, Lee TA, Blough DK, Finkelstein JA, Lozano P, Inui TC, Fuhlbrigge AL, Carey VJ, Wagner E, Weiss KB. 2005. A multi-site randomized trial of the effects of physician education and organizational change in chronic asthma care: cost-effectiveness analysis of the Pediatric Asthma Care PORT. *Archives of Pediatrics & Adolescent Medicine* **159**: 428–434.
Sutton AJ, Kendrick D, Coupland CAC. 2008. Meta-analysis of individual- and aggregate-level data. *Statistics in Medicine* **27**: 651–666.
VanderWeele T, Hernan MA, Robins JM. 2008. Causal directed acyclic graphs and the direction of unmeasured confounding bias. *Epidemiology* **19**: 720–728.
Vanness D, Mullahy J. 2006. Perspectives on Mean-Based Evaluation of Health Care. In *Elgar Companion to Health Economics*, Jones AM (ed.). Edward Elgar Publishing: Cheltenham.
Weir C, Walley RJ. 2006. Statistical evaluation of biomarkers as surrogate endpoints: a literature review. *Statistics in Medicine* **25**: 183–203.
White I, Frost C, Tokunaga S. 2001. Correcting for measurement error in binary and continuous variables using replicates. *Statistics in Medicine* **20**: 3441–3457.

DOI: 10.1002/hec