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CRIS Discussion Paper Series – 2006.VII

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July 2006

ABSTRACT

Randomised controlled trials (RCTs) are the primary means by which pharmaceutical companies evaluate the therapeutic benefits of their products. The strength and relevance of the evidence provided from RCTs will determine whether a product can be marketed or not and the subsequent extent of its use. In order to gain access to a market, pharmaceutical companies must perform RCTs to produce safety and efficacy evidence to a level which satisfies the regulatory bodies responsible for granting product licences. However, the safety and efficacy evidence produced for that purpose may not be sufficient to ensure that a product is reimbursed and actually used in clinical practice. Health technology assessment and appraisal bodies, such as the National Institute for Clinical Excellence (NICE) and Hospital Drugs and Therapeutic Committees, critically appraise the nature and relevance of RCT evidence in order to make recommendations about the extent to which a product should be used. Individual clinicians will make treatment decisions based on their own assessment of the evidence, as well as taking into account the reviews performed by advisory bodies. Thus, those involved with product adoption decisions will have preferences for the types of evidence they want to see and, consequently, the extent to which these preferences are satisfied will influence the nature and extent of a treatment's use. It is therefore important for sponsors of drugs to consider decision-makers' preferences for RCT designs when planning their studies. The primary objective of this paper is to illustrate how discrete choice analysis (DCA) could be used for that purpose. The approach is illustrated using, as a case study, the design of trials to evaluate adjuvant bisphosphonates in the management of patients with primary operable breast cancer. Clinicians' preferences for evidence are determined and then used to identify a trial design likely to lead to the highest probability of prescribing the product (market share). However, evidence generation has a cost attached to it. Therefore the paper goes on to look at how physician preferences for evidence and the resulting predicted impact on product use can be combined with trial design costs in an overall investment appraisal framework. Within such a framework, it is shown how a company producing a technology could identify the profit maximising RCT strategy. Finally, a number of issues for consideration in future research are briefly discussed, including the circumstances under which private and public sector perspectives are likely to be aligned.

1. INTRODUCTION

Discrete choice analysis (DCA) is the name given to a set of multivariate data analysis techniques which can be used to predict decision-makers' choices between alternative products or services.[1-3] The techniques have been widely applied to assist with product design and marketing decisions in a number of industries.[4-6] In the commercial context, the primary interest has been to use DCA to estimate the probability that a decision-maker will choose a given product or service from the set of available alternatives. Since the probability of choosing a given product is assumed to depend upon the utility derived from its attributes compared with that of its alternatives, it is possible to use DCA to estimate the demand for both new and existing products given different defining characteristics.

In contrast to the commercial applications of DCA, where the primary interest is in modelling product demand, health economists have recently begun to use the technique for estimating the value of treatment processes and outcomes in preference, utility or monetary terms. The literature on health applications of DCA is now extensive.[7-26;26-58] But, to date, DCA has not been applied to assist with the design of randomised controlled trials (RCTs). However, the purpose of RCTs is such that DCA is likely to be of value in the RCT planning and design context because there is a relationship between the decision to adopt a health care intervention (demand for the intervention) and the design characteristics of the RCTs used to evaluate its benefits.

Randomised controlled trials (RCTs) are the primary means by which pharmaceutical companies evaluate the therapeutic benefits of their products.[59-63] The strength and relevance of the evidence provided from RCTs will determine whether a product can be marketed or not and the subsequent extent of its use. In order to gain access to a

market, pharmaceutical companies must perform RCTs to produce safety and efficacy evidence to a level which satisfies the regulatory bodies responsible for granting product licences. However, the safety and efficacy evidence produced for that purpose may not be sufficient to ensure that a product is reimbursed and actually used in clinical practice. Health technology assessment and appraisal bodies, such as the National Institute for Clinical Excellence (NICE) and Hospital Drugs and Therapeutic Committees, critically appraise the nature and relevance of RCT evidence in order to make recommendations about the extent to which a product should be used.[64] Individual clinicians will make treatment decisions based on their own assessment of the evidence, as well as taking into account the reviews performed by advisory bodies. Thus, those involved with product adoption decisions will have preferences for the types of evidence they want to see and, consequently, the extent to which these preferences are satisfied will influence the nature and extent of a treatment's use. It is therefore important for sponsors of drugs to consider decision-makers' preferences for RCT designs when planning their studies. The primary objective of this paper is to illustrate how discrete choice analysis (DCA) could be used for that purpose. The approach is illustrated using a discrete choice stated preference (SP) survey concerned with the design of trials to evaluate adjuvant bisphosphonates in the management of patients with primary operable breast cancer.

The remainder of the paper is divided into seven sections. In the following section, a discrete choice modelling approach to drug prescribing behaviour is set out in general form. This is followed in section 4.3 by an overview of the key components of a discrete choice SP survey. In section 4.4, the design of the adjuvant bisphosphonates case-study survey is presented. The results for the non-choice question components of the survey are presented in section 4.5. The results pertaining to the estimation of

the parameters of a binary discrete choice model are presented in section 4.6 where consideration is given to the qualitative and quantitative effects. Section 4.7 focuses on using the discrete choice model results for the design of RCTs. Specifically, the use of the results to determine designs which optimise the probability of product adoption and to operationalise an investment appraisal approach to RCT design are illustrated. The final section includes a discussion of the results and the implications for future research.

2. A DISCRETE CHOICE MODEL OF DRUG DEMAND

In this section, a discrete choice model of drug demand is set out in general form. A specific binary choice formulation of this model is used in the applied example which follows later in the paper.

2.1. Random utility theory of drug choice behaviour

Discrete choice models derive from random utility theory of choice behaviour.[1;3] Under this theory, the probability that a clinician will choose drug i from the set of alternative treatments available, J, is given by:

$$Pr(i \mid \mathrm{J}) = Pr(U_i > U_j) \quad \forall j \in J, j \neq i \qquad (1)$$

where U_i and U_j denote the utility which a clinician derives from using the different products, i and j. A clinician is assumed to choose the treatment option which maximises his or her utility. Assuming that the clinician is behaving as a perfect agent, this should also be the choice which maximises the utility of the patient receiving the treatment. Since the utility of a treatment is assumed to be derived from the characteristics that define it, equation (1) can be re-written as:

$$Pr(i \mid \mathrm{J}) = Pr\left(U_i(Z_i) > U_j(Z_j)\right) \quad \forall j \in J, j \neq i \qquad (2)$$

where Z_i and Z_j denote vectors of characteristics the levels of which define the treatment alternatives, i and j. Note that the vectors of attributes can include characteristics of the clinician e.g. the preferences of primary care physicians might differ from those of hospital specialists.

If a clinician's utility function was known and if all the relevant characteristics were observed, then perfect predictions could be made about a clinician's choice of treatment. Since this is not the case in practice, a discrete choice model of behaviour can be constructed based on the following identity:

$$Pr(i \mid \mathrm{J}) = Pr\left(U_i(Z_i) > U_j(Z_j)\right) = Pr\left(V_i(X_i) + \varepsilon_i > V_j(X_j) + \varepsilon_j\right) \quad \forall j \in J, j \neq i \qquad (3)$$

where V_i and V_j denote the observable components of utility, X_i and X_j are vectors of observable treatment characteristics and ε_i and ε_j are the unobserved random components of utility for products i and j respectively. The latter takes into account the difference between the true, U, and observed, V, utility. The right hand side of equation (3) can be re-arranged to give the following general (multinomial) expression for a random utility model of drug prescribing behaviour:

$$Pr(i \mid \mathrm{J}) = Pr\left(\varepsilon_j - \varepsilon_i < V_i(X_i) - V_j(X_j)\right) \quad \forall j \in J, j \neq i \qquad (4)$$

2.2. Discrete choice model formulations

In order to operationalise the above model, it is necessary to specify functional forms for both the observable and unobservable components of utility. For the deterministic

component of utility, it is common practice in discrete choice models to specify V as a function which is linear in the vector of unknown parameters, β', such that:

$$V_i = \beta' X_i = \beta_1 X_{1i} + ... + \beta_l X_{li} \qquad (5)$$

$$V_j = \beta' X_j = \beta_1 X_{1j} + ... + \beta_l X_{lj} \quad \forall j \in J, j \neq i$$

where $\beta_1 .....\beta_l$ are the coefficients to be estimated for each of the l attributes included in the model. In practice it has been observed that the linear additive model of equation (5) works well in most applied situations[1] and is a formulation that has been used frequently in recent health economics applications. This functional form for the observable component of utility will therefore be used in the analyses which follow.

For the unobservable component of utility, the disturbances ($\varepsilon_i, \varepsilon_j$) are assumed to be distributed randomly (hence the name random utility model). A number of alternative distributions can be assumed which give rise to different discrete choice model formulations.[1;2] The most frequently used approaches are the logit and probit models. It has been noted that in practice there is little difference between the results derived from those two approaches.[2] Since the probit model is used in the case-study which follows, it is described in more detail here. In the case of probit models, the unobserved components of utility are assumed to be distributed jointly normal. Using the probit discrete choice model formulation, the probability that a prescribing clinician will choose drug i from the set of alternative treatments available, J, is given by:

$$Pr(i \mid \mathrm{J}) = \int_{\varepsilon_i=-\infty}^{\infty} \int_{\varepsilon_1=-\infty}^{\varepsilon_i+V_i-V_1} \int_{\varepsilon_2=-\infty}^{\varepsilon_i+V_i-V_2} ..... \int_{\varepsilon_j=-\infty}^{\varepsilon_i+V_i-V_j} \Phi\left(\tilde{\varepsilon}\right) de_j ... de_2 de_1 de_i, \qquad (6)$$

where $\Phi(.)$ denotes the standardised cumulative normal distribution, $\tilde{\varepsilon}$ is a vector composed of each disturbance ε_i for all i in J and there are j alternatives in J. The probit model is estimated using maximum likelihood techniques. This gives rise to estimates for $\beta_1 \ldots\ldots \beta_l$ and consequently, through equation (6), the probabilities of choosing alternative products can be derived.

3. DISCRETE CHOICE STATED PREFERENCE SURVEYS

The parameters of a discrete choice model, such as that set out in equation (6), can be estimated using data pertaining to observed choice behaviour (revealed preference data), simulated choice behaviour (stated preference data) or a combination of the two.[1;3] Regardless of the source of data, the dataset needs to contain, for each alternative in the choice set, an indicator of the choice made together with the defining characteristics of the alternatives (the X s in the above equations).

To date, the approach typically adopted by health economists has been to use simulated choice data obtained from discrete choice stated preference surveys (often referred to as conjoint analysis).[48;65] Since the required data on actual drug choice behaviour would be difficult to obtain and, by definition, is not available for new products in development, the approach adopted in this paper is to use data generated from a discrete choice stated preference (SP) survey. The design stages of such surveys have been enumerated in detail elsewhere,[3;65] but generally they include the following components:

1) Determination of attributes, levels and scenarios

2) Elicitation of preferences

3) Data analysis and interpretation

These stages are discussed briefly in turn below.

3.1. Determination of attributes, levels and scenarios

When designing an SP survey, the attributes (characteristics) of interest need to be defined and levels (values) need to be assigned to them. A number of approaches to doing this have been identified, including the use of literature reviews, interviews and selection based on a specific research question.[3;65] The various approaches are not mutually exclusive and, in practice, a combination of them is often used. At a general level, it is postulated here that the probability of choosing a given health care intervention is a function not only of the demonstrated benefits, but also of the 'design' characteristics of the RCTs from which the evidence of product benefit is derived. Consequently, the design problem in the current context involves selecting attributes and levels from the set of RCT design characteristics enumerated in Table 1. In order to ensure that an SP survey is realistic, the literature suggests that attribute levels should be plausible and capable of being traded.[65]

Once the attributes and their levels have been determined, they are combined into scenarios or profiles to present to survey participants for evaluation. A scenario is a combination of attributes and levels that characterize the choice object of interest in the study, in this case RCTs. The number of possible scenarios (the full factorial design) defined by the chosen number of attributes and levels can be very large and is given by:

$$S = \prod L_i^{A_i}$$

where S denotes all possible combinations of attribute levels and A_i denotes the number of attributes possessing the number of levels L_i. An SP survey with a very large number of scenarios would be impractical due to the cognitive burden which the presentation of a large number of scenarios would place on survey participants. Therefore a practical problem to overcome is how to reduce the number of scenarios whilst ensuring that the parameters of the model can be reliably estimated. A common approach to reducing the number of scenarios is to identify an orthogonal fraction using experimental design catalogues such as those available in computer programmes like SPEED.[66] Orthogonal arrays of scenarios are such that each attribute level appears an equal number of times and the attributes are uncorrelated.[3]

Table 1

Trial Design Attributes

1. Comparators

Can be chosen from one or more broad types, including:

i) Placebo
ii) Most commonly used
iii) Most effective
iv) Least cost
v) Most cost-effective.

Specification usually involves the choice of specific product formulations and modes of administration.

Most studies compare two treatments although more are possible.

2. Population

Specification usually involves choices about:

i) Age group
ii) Sex
iii) Ethnic origin
iv) Disease stage
v) Co-morbidities
vi) Previous treatments
vii) Concomitant treatments
viii) De novo or refractory patients.
ix) Sub-group comparisons

3. Setting

Specification usually involves choices about:

i) Single country, single centre
ii) Single country, multi-centre
iii) Multinational, single centre
iv) Multinational, multi-centre
v) Inpatient
vi) Outpatient
vii) Specialist centre
viii) Routine practice centre

4. Endpoints

Specification usually involves choices about:

i) Efficacy
ii) Effectiveness
iii) Side effects
iv) Adverse events
v) Quality of life
vi) Direct costs (NB includes product prices)
vii) Indirect costs
viii) Resource use
ix) Surrogate endpoints

5. Effect sizes

Specification usually involves choices about:

i) Clinical significance
ii) Statistical significance
iii) Primary endpoints
iv) Secondary endpoints

Table 4.1 (continued)

6. Duration of observation

Specification usually involves choices about:

i) Fixed period of observation
ii) Variable (e.g. in sequential designs).

Choices are linked closely to the choice of endpoints and the statistical properties of the study.

7. Acceptable error rates: α and β

Choices are linked closely to the choice of endpoints and the duration of follow-up.

Often chosen according to convention and based on the primary endpoint(s) i.e. $\alpha = 5\%$, $\beta = 10\%$

Do not have to be the same for each endpoint (and usually aren't).

Used in conjunction with the statistical properties of endpoints, the desired effect sizes and withdrawal rates to determine sample size.

8. Statistical methods

Specification usually involves choices relating to:

i) Objectives of the trial
ii) Nature of other trial parameters, most notably the disease area and endpoints (type of data)
iii) Method of randomisation.

3.2. Elicitation of preferences

Preferences are elicited by presenting the scenarios to respondents who are asked to rank or rate each of them, or to indicate their preference (choice) from sets of two or more profiles presented alongside each other (the discrete choice format). The preference elicitation approach preferred by health economists to date has been the discrete choice format since it reflects the random utility theory of choice behaviour (see above).[1;3;65] Further, health economists have tended to elicit preferences using binary (pairwise) choice tasks in which respondents select their preferred scenario from each of a number of pairs (the choice set). Typically, choice sets have been generated by randomly pairing (without replacement) the scenarios in the orthogonal array, although alternative approaches could be employed.

The choice sets usually incorporate some pairwise comparisons that form the basis of tests to identify inconsistent respondents. Inconsistent respondents are traditionally defined as those who do not make the choices one would expect them to make given the researcher's prior expectations about a positive or negative relationship between the attribute values and utility. Thus, to test for inconsistency defined in this way, the design needs to contain some pairwise combinations of scenarios for which the preferred scenario might be predicted *a priori*. These can fall naturally from the random generation of the choice sets or be generated manually. Using such tests, inconsistent respondents can then be identified at the analysis stage and dropped from the analysis along with non-trading subjects (see below).

As far as the author is aware, there is no formula for estimating the sample sizes required for binary choice SP surveys. Consequently, there is no firm statistical basis for the sample sizes used in previously reported studies. However, a notable feature

of discrete choice surveys is that each respondent can provide as many as *n* observations to the dataset, where *n* is the number of choice sets included in the survey. Thus, a relatively small number of respondents can provide a sufficiently large number of observations for valid statistical analyses to be performed. Finally, preference elicitation surveys have been administered to respondents in a variety of ways including the use of mail, phone, web and interactive computer elicitation techniques with adequate responses having been reported for each.[65]

3.3. Data analysis and interpretation

The statistical method used to analyse SP data depends upon the approach used to elicit preferences. For the discrete choice approach, which is of primary interest here, probit regression has been widely used by health economists for estimating the parameters of discrete choice models. A number of probit estimators are available in statistics programmes such as Stata Version 7.0 (Stata).[67] However, in previously published studies, researchers have tended not to specify the statistics programmes or the precise estimation commands they have used.

A standard probit estimator relies on the assumption that the explanatory variables and the error term are independently and identically distributed and that they are uncorrelated. These assumptions are likely to be inappropriate in the case of discrete choice data obtained from SP surveys since multiple observations are obtained from each respondent. Stata provides two alternative probit estimation commands which are appropriate for such repeated measurement panel data: probit (cluster) and xtprobit (pa, robust).[67] Both estimators, which are essentially equivalent, take into account the potential for a respondent's responses to be correlated. Both approaches also generate robust standard errors.

An estimation issue which arises in the literature is whether or not discrete choice regression models should be specified with a constant term. Examples of both approaches can be found. The answer to this issue appears to lie in the way in which the choice exercise is framed. For example, in a study which looked at preferences for miscarriage management, the scenarios presented to respondents were labeled "surgical treatment" and "medical treatment."[43] Since these labels convey information which might be used by respondents to decide which option was preferred, the authors estimated a model with a constant term. The authors interpreted the negative constant as indicating a general preference for surgical over medical management when all the attributes for the two interventions are the same.

In contrast, models have been estimated without constants where the labeling of the choices conveys no properties of the alternatives. For example, in a study looking at preferences for in vitro fertilization services, the choice alternatives were labeled "clinic A" and "clinic B" and the authors estimated a model without a constant term.[68] Thus, contemporary practice is to omit constants when the choice task involves generically labeled alternatives and vice-versa.

A linear additive form of the utility function has typically been assumed by health economists on the grounds that research has shown that alternative models seldom result in a better fit than the linear additive model.[69] It has recently been pointed out that a simple regression error specification test (RESET) could be applied to determine whether there are problems associated with the linear functional form of discrete choice models.[70] However, in health economics applications, only one study could be found that reports a test for model mis-specification.[36]

In the health economics literature, it has become common practice to estimate models based only on a subset of respondents who are deemed to be consistent traders. Inconsistent respondents (as defined above) and non-trading respondents are typically dropped from the analysis and the results obtained from the full sample are not usually reported. A non-trading respondent is defined as one who always selects a choice scenario with a higher level of a particular (dominant) attribute irrespective of the levels of the remaining attributes. Such respondents are identified at the analysis stage by looking for choice patterns consistent with this behaviour. However, it has been noted that whether or not analyses should be performed on the full sample or only on consistent traders depends upon the objectives of the study.[8] In this study, analyses are reported for both the full sample as well as subsets of consistent traders.

Finally, health economics researchers have primarily been interested in using the regression coefficients for deriving utility scores and, where a cost attribute is included, estimates of willingness-to-pay (WTP).[65] This has enabled, for example, alternative service configurations to be ranked in terms of their utility scores. To date, health economists applying discrete choice stated preference surveys have not derived predicted choice probabilities from their models, although these are the primary interest here.

4. CASE STUDY OF ADJUVANT BISPHOSPHONATES

4.1. Adjuvant bisphosphonates in the management of breast cancer

Breast cancer is the most common form of female cancer in England and Wales where, in 1998, there were 34,822 newly diagnosed cases representing an incidence rate of 130.83 per 100,000 females. The incidence of breast cancer increases sharply with age and, overall, has been rising since the early 1970s. During the same period, mortality from breast cancer has fallen. Currently, the survival rate at 5 years post-diagnosis is 75.9%. In 2000, there were 11,340 deaths from breast cancer in England and Wales.[71]

National guidance exists for the management of patients with breast cancer.[71] Management is centred on multidisciplinary teams composed of breast surgeons, oncologists (clinical and medical), radiologists, pathologists and breast care nurses. The precise nature of initial treatment depends upon the clinical staging of the disease at diagnosis, but typically involves a combination of surgery, chemotherapy, radiotherapy and hormone replacement therapy. After completion of initial treatment, patients are monitored on an ongoing basis to ensure early detection of disease recurrence (relapse). In patients who relapse, most have metastatic (distant) disease which often affects both organs (visceral metastases) and bone (osseous metastases). The prognosis for patients with metastatic disease is poor, with the aim of treatment being palliative rather than curative.

The case study presented here is concerned with the preventive use of a class of drugs known as bisphosphonates which inhibit bone resorption (destruction). Clinical research has shown that bisphosphonates reduce the incidence of hypercalcaemia and pathological bone fractures in patients with established bone metastases from breast

cancer. Moreover, bisphosphonates have been shown to reduce the risk of bone metastases in patients with relapsed breast cancer without obvious bone involvement. In view of these proven benefits, the National Institute for Clinical Excellence in England and Wales (NICE) has recently recommended that bisphosphonates be used in the management of patients with bone metastases.[71] It has been estimated that currently about one third of patients with bone metastases receive bisphosphonate treatment at an approximate annual cost in England and Wales of £3.9 million. The annual cost could rise to as much as £25.6 million per annum if there is adherence to the recent guidance. The annual cost per patient for one of the more researched oral bisphosphonates (sodium clodronate) is about £2,200 and, once initiated, is recommended to be continued as long as skeletal disease remains an important problem.[72]

Whilst bisphosphonates have been recommended by NICE as a *treatment* for patients with bone metastases[71], the benefits of adjuvant bisphosphonates as a therapeutic strategy for the prevention of metastatic bone disease in patients with primary operable breast cancer has yet to be definitively established. A trial performed by Diel et al (1998) showed that, after 2 years treatment and 3 years of follow-up, the incidence of both osseous and visceral metastases was significantly lower for patients treated with the oral bisphosphonate clodronate compared with the control group.[73] Moreover, a statistically significant reduction in all cause mortality was observed. More recently, a larger and more representative prevention trial has demonstrated similar benefits.[74] Specifically, patients treated with clodronate experienced a statistically significantly lower rate of bone metastases compared with the placebo controls during a 2 year treatment period. This trend was observed at the end of a 5.5 years follow-up period although the difference was not statistically significant. A

significant reduction in all cause mortality was observed at the end of the long-term follow-up period. Whilst the evidence is suggestive of benefits associated with early bisphosphonate use, the indication remains under investigation and a further large trial of adjuvant clodronate is currently being conducted.[75]

Given that the early (preventive) use of bisphosphonates is a new indication, it was felt that it would make a practical case study for assessing the potential use of discrete choice analysis in the design of RCTs. This is primarily because it permits the use of a binary choice model formulation (see below). Consequently, a stated preference experiment has been designed to generate choice data taking the potential preventive use of adjuvant bisphosphonate therapy in primary operable breast cancer as an applied case study. However, it is important to note that the analyses which follow are exploratory and illustrative i.e. they are not intended as a definitive application of the method in this disease area.

4.2. Binary choice model formulation

In the case study which follows, a clinician is assumed to be faced with a binary choice situation in which he or she has to decide between two alternative bisphosphonate prevention regimens, i or j. Such binary choice behaviour is a special case of the multinomial choice situation described above since decision makers are assumed to be faced with exactly two alternative courses of action: $J = \{i, j\}$. Thus, for the binary choice probit model, equation (6) becomes:

$$Pr(i \mid \mathrm{J}) = \Phi(V_i - V_j) = \Phi\left(\beta'\left(X_i - X_j\right)\right) \qquad (7)$$

which is estimated using maximum likelihood techniques.

Thus, in this case study we are interested in predicting the probability of product adoption given different product benefit and trial design characteristics, X_i , X_j associated with the use of adjuvant bisphosphonates. The approach uses stated preference data generated from a discrete choice experiment the key design components of which are described below.

4.3. Determination of attributes and attribute levels

The design problem involves selecting, from the generic RCT design characteristics previously enumerated in Table 1, attributes and levels of specific relevance to the bisphosphonates case-study. These were determined by reviewing adjuvant bisphosphonate RCT publications[73-75] and discussing a preliminary (pilot) survey design with physicians with specialist knowledge of breast cancer management. The specific attributes and levels chosen for the analysis and how they relate to the generic characteristics in Table 1 are discussed in turn below and are summarised in Table 2.

Table 2

Attributes and Levels for the Stated Preference Survey

ATTRIBUTES X_k	**LEVELS**
Endpoint	
The primary measure of effectiveness used in the trial	Patients without metastatic bone disease[1] Patients alive without disease recurrence[2]
Effectiveness	
Difference in % of patients achieving primary endpoint at the end of the trial: (bisphosphonate *minus* current practice)	1% 10% 25% 40%
Uncertainty	
Width of 95% confidence interval for the effectiveness outcome	Level 1 : ± 0.01 x % Effectiveness Level 2 : ± 0.25 x % Effectiveness Level 3 : ± 0.75 x % Effectiveness Level 4 : ± 0.99 x % Effectiveness
Duration	
The duration of observation of patients enrolled in the trial	2 years 4 years 8 years 10 years
Population	
Disease stage at diagnosis for patients enrolled in the trial	Stage III only[1] Stages I, II and III[2]
Cost	
Additional cost of using adjuvant bisphosphonate prevention (compared with current practice) per 100 patients treated	£0 £450,000 £900,000 £1,800,000

Notes.

1. Binary variable coded 0 for analysis.
2. Binary variable coded 1 for analysis.

Endpoint. A large number of outcome measurements (endpoints) are usually made in RCTs. However, it is usual practice to select one outcome measure (the primary endpoint) which is used as the primary basis for discriminating between treatments under investigation and for determining the sample sizes required for the study. In order to explore the impact of the choice of primary endpoint on the decision to use adjuvant bisphosphonates, a categorical attribute with two levels was used. The first level, 'patients without metastatic bone disease', was chosen to reflect a primary hypothesis relating to adjuvant bisphosphonates, namely that the incidence of bone metastases is reduced as a result of their use.[73;74] The second level, 'patients alive without disease recurrence' was chosen to reflect the fact that disease free survival is arguably a more relevant primary endpoint, as reflected in the protocol of a recently designed and ongoing trial.[75] The first level was coded '0' for analysis and the second level was coded '1' for analysis.

Effectiveness. A challenge in designing this survey was to choose levels for the effectiveness attribute that would be plausible when combined with the levels of the endpoint, study population and duration attributes. It was also necessary to ensure that trading would take place (by not choosing attribute levels too close together) and that predictions of product adoption could encompass possible improved effectiveness of future treatments (by not restricting the levels to previously observed ranges). The effectiveness attribute was included as a continuous variable representing the absolute difference in the percentage of patients achieving the primary endpoint at the end of the trial (% effectiveness for bisphosphonate minus % effectiveness for current treatment practice). Four positive levels were chosen (1%, 10%, 25% and 40%) which means that only statistically significant improvements in effectiveness in favour of bisphosphonate prevention are considered in the analysis.

Allowing for the considerations mentioned above, the choice of attribute levels was informed by interpolating, for different annual time points, effectiveness outcomes from results reported for two recent trials[73;74] (see Appendix 1). From this interpolation, the smallest statistically significant difference observed was 2% (95% confidence interval: 0.33% to 3.67%) and the largest was 18% (95% confidence interval: 11.75% to 24.25%). The highest upper limit of the 95% confidence interval was 27.05% and the smallest was 0.23%. In order to facilitate respondents' interpretation, the effectiveness attribute values were also presented as 'number needed to treat' (NNT).

Uncertainty. A continuous variable attribute was included to assess the impact, on the adoption decision, of the degree of precision surrounding the point estimate of effectiveness for the primary endpoint. This was achieved by presenting 95% confidence intervals for the effectiveness outcomes which were calculated using the formula:

$$95\%\ CI = \pm\ P\left(Effectiveness\ (\%)\right)$$

where P , which denotes 'proportion', took on four values: 0.01, 0.25, 0.75 and 0.99. These levels of precision were the values used for the uncertainty variable at the analysis stage. The upper value was chosen to ensure that a high degree of uncertainty could be accommodated in the design without violating the assumption about the statistical significance of the results (see below). In otherwords, the constraint that P could not exceed unity ensured that the 95% confidence intervals did not straddle zero. The lower limit was chosen to accommodate a very low degree of uncertainty. The selection of the intermediate values was arbitrary, being equidistant from the upper and lower values. In addition to presenting respondents

with the 95% confidence intervals expressed as percentages, they were also presented in terms of NNT for the reasons stated for the effectiveness attribute above.

Duration. In order to assess the impact of duration of subject follow-up on the decision to use adjuvant bisphosphonates, duration of observation was included in the design as a continuous variable attribute with four levels: 2, 4, 8 and 10 years. These values were chosen to ensure that the range encompassed the periods of observation in two reported trials. Diel et al reported a median period of follow-up of 3 years, although some subjects were observed for as long as 7 years.[73] In the Powles et al trial, the median period of follow-up was 5 years with a maximum of 9.5 years.[74] The lowest level was chosen because it represents the duration of bisphosphonate prevention medication given in both trials.

Population. Patients with primary operable breast cancer can be classified into three stages of disease at diagnosis (Stages I, II and III) which reflect how advanced the disease is at presentation. Recent studies permitted the enrolment of patients from each of these three stages, although one study enrolled only subjects who were deemed to be at high risk of developing bone metastases.[73] In order to explore the impact of choice of study population on the decision to use adjuvant bisphosphonates, a categorical attribute with two levels was included in the survey design. The first level represented contemporary trial design practice of enrolling any patient with primary operable breast cancer i.e. with Stages I, II or III disease at diagnosis. The second level was chosen to depict an arguably less representative trial in which only patients with Stage III disease at diagnosis were enrolled. Since this population has more advanced disease, such a trial would depict a desire on the part of a study sponsor to demonstrate a therapeutic benefit in a shorter period of time. *A priori*, one would expect respondents to prefer a trial which is more representative of the actual

population being treated hence the first level was coded ‘1’ for analysis and the second level was coded ‘0’.

Cost. In order to assess the impact of the cost of using bisphosphonates on the decision to use them, cost was included in the design as a continuous variable attribute with four levels: £0, £450,000, £900,000 and £1,800,000. For consistency with the measurement of effectiveness, the levels were defined as the additional cost of using adjuvant bisphosphonate prevention (compared with current practice) per 100 patients treated. Moreover, in the introduction to the discrete choice task, it was pointed out that the cost related to the period of the trial and that the value could reflect different product formulations and durations of medication. The level £450,000 reflects the approximate UK price for the oral clodronate dosing regimen used in the Powles et al trial.[72;74] The other levels were chosen to provide a wide range of cost possibilities which could reflect, for example, different pricing policies, dosing regimens or duration of bisphosphonate prevention medication.

Other RCT design attribute considerations. Not all the RCT design characteristics presented in Table 1 appeared explicitly as attributes in the case-study survey design although all but study setting were covered in the survey questionnaire in some way. Those that were not included as attributes are considered briefly in turn below.

Comparators. The choice of comparator is an important aspect of RCT design. Since adjuvant bisphosphonate prevention is not currently standard practice, the issue of comparing explicitly against an alternative prevention regimen does not arise. The choice of comparator was not therefore included as an attribute in the discrete choice survey. Instead, in the introduction to the discrete choice tasks, respondents were asked to assume that the evidence presented came from trials where standard practice

was permitted in both arms of the trial, including the use of bisphosphonates, as appropriate, in the event of relapse (see questionnaire in Appendix 2). These assumptions reflect the practice actually adopted in recent trials. Thus, the comparators were assumed to be standard practice plus placebo versus standard practice plus bisphosphonate prevention.

Statistical properties. The survey did not include any attributes pertaining to the statistical properties of the hypothetical RCT designs, such as sample sizes, probabilities of type I and type II errors or the statistical methods used to analyse the data. However, in the introduction to the discrete choice tasks, respondents were asked to assume that the results presented to them were statistically significant at the conventional 5% level and, more generally, that the trials were well conducted (see survey questionnaire in Appendix 2).

Setting. No reference was made to the setting of the study, such as whether the trial was conducted in a number of centres or in a number of countries. Since the respondents are likely to be familiar with RCTs conducted in this context, it is reasonable to suppose that they would expect such studies to be multinational, multicentre trials.

Thus, the final design was based on the six attributes as decribed above. These were used to produce hypothetical RCT design scenarios using the method described below.

4.4. Generation of the discrete choice RCT design scenarios

The number of RCT design scenarios which can be defined given the attributes and levels shown in Table 2 is $4^4 \times 2^2 = 1024$ (the full factorial). In order to construct a cognitively manageable number of binary choice questions, an orthogonal fraction

was obtained using SPEED experimental design software.[66] This resulted in a set of 16 RCT profiles as shown in Table 3. A key property of this fraction of profiles is that the attributes are not correlated, and that the levels appear the same number of times.

In order to generate the binary choice questions to present to respondents, a method described by Louviere, Hensher and Swait (2000) was used.[3] This involves pairing each of the 16 RCT profiles shown in Table 3 with a different RCT profile randomly selected from a duplicate set. This process resulted in 16 choice sets. The differences between the attribute levels for each choice set are shown in Table 4. In order to minimise the problem of multicollinearity, the differences in attribute levels must not be significantly correlated. The absence of statistically significant correlations at conventional levels confirms that the resulting experimental design is reasonably orthogonal.

Table 3

Orthogonal 16 Profile Fraction of the Full Factorial Design

	ENDPOINT	EFFECTIVENESS	UNCERTAINTY	DURATION	POPULATION	COST
Profile from fractional Design	**Primary endpoint:**	**Difference in % achieving primary endpoint at the end of the trial**	**Uncertainty (95% CI = ± value in cell x X_2)**	**Duration of observation (years)**	**Disease stage at diagnosis**	**Additional cost of preventive strategy (£ per 100 patients)**
	X_1	X_2	X_3	X_4	X_5	X_6
1	DFS	10	0.75	10	Stage III	1,800,000
2	MBD	10	0.01	8	Stage III	900,000
3	DFS	10	0.25	4	Stage I,II & III	450,000
4	MBD	10	0.99	2	Stage I,II & III	0
5	DFS	25	0.75	8	Stage I,II & III	0
6	MBD	25	0.01	10	Stage I,II & III	450,000
7	DFS	25	0.25	2	Stage III	900,000
8	MBD	25	0.99	4	Stage III	1,800,000
9	MBD	40	0.75	4	Stage I,II & III	900,000
10	DFS	40	0.01	2	Stage I,II & III	1,800,000
11	MBD	40	0.25	10	Stage III	0
12	DFS	40	0.99	8	Stage III	450,000
13	MBD	1	0.75	2	Stage III	450,000
14	DFS	1	0.01	4	Stage III	0
15	MBD	1	0.25	8	Stage I,II & III	1,800,000
16	DFS	1	0.99	10	Stage I,II & III	900,000

DFS = patients alive without disease recurrence. MBD = patients without metastatic bone disease.

Table 4
16 Choice Sets for the Stated Preference Survey

Choice set	Endpoint X_1	Effectiveness X_2	Uncertainty X_3	Duration X_4	Population X_5	Cost X_6
1. Profile 1 versus Profile 15	1	9	0.50	2	-1	0
2. Profile 2 versus Profile 5	-1	-15	-0.74	0	-1	900000
3. Profile 3 versus Profile 16	0	9	-0.74	-6	0	-450000
4. Profile 4 versus Profile 14	-1	9	0.98	-2	1	0
5. Profile 5 versus Profile 7	0	0	0.50	6	1	-900000
6. Profile 6 versus Profile 9	0	-15	-0.74	6	0	-450000
7. Profile 7 versus Profile 1	0	15	-0.50	-8	0	-900000
8. Profile 8 versus Profile 11*	0	-15	0.74	-6	0	1800000
9. Profile 9* versus Profile 8	0	15	-0.24	0	1	-900000
10. Profile 10 versus Profile 12	0	0	-0.98	-6	1	1350000
11. Profile 11 versus Profile 3	-1	30	0.00	6	-1	-450000
12. Profile 12 versus Profile 10	0	0	0.98	6	-1	-1350000
13. Profile 13 versus Profile 6*	0	-24	0.74	-8	-1	0
14. Profile 14* versus Profile 13	1	0	-0.74	2	0	-450000
15. Profile 15 versus Profile 4	0	-9	-0.74	6	0	1800000
16. Profile 16 versus Profile 2	1	-9	0.98	2	1	0

Notes.

Left option in choice set possibly dominant if signs in the cells are: X_1 = +; X_2 = +; X_3 = -; X_4 = +; X_5 = +; X_6 = -.

Right option in choice set possibly dominant if signs in the cells are: X_1 = -; X_2 = -; X_3 = +; X_4 = -; X_5 = - ; X_6 = +.

* Denotes the choices a respondent would make if behaving in line with prior expectations. The choice sets in which they appear, together with an expectation that a respondent should choose the same option from the identical choice sets 10 and 12, are used in the construction of tests for inconsistent respondents as described in the text.

Figure 1

Example Binary Choice Question

Trial Design Characteristics	Bisphosphonate Prevention A	Bisphosphonate Prevention B
Primary endpoint	Patients alive without disease recurrence	Patients without metastatic bone disease
Difference in % of patients achieving primary endpoint at the end of the trial (bisphosphonate *minus* placebo)	10% [NNT = 10]	1% [NNT = 100]
95% confidence interval on the primary endpoint	2.50% to 17.50% [NNT = 5.71 to 40.00]	0.75% to 1.25% [NNT = 80.00 to 133.33]
Duration of observation	10 years	8 years
Disease stage at diagnosis for patients enrolled in the trial	Stage III only	Stages I, II and III
Additional cost of using adjuvant bisphosphonates per 100 patients treated (bisphosphonate *minus* placebo)	£ 1,800,000	£ 1,800,000

Which adjuvant bisphosphonate prevention option would you prefer for patients presenting with primary operable breast cancer (Stage I to Stage III)?	Prefer Prevention A	Prefer Prevention B
	✓	

In the study questionnaire presented to respondents, the choice sets were formed into 16 binary choice questions. Respondents were asked to consider each choice and then indicate which alternative they would prefer based on the profile descriptions presented. Figure 1 provides an example of one of the choice questions presented to physicians in the stated preference survey. The study questionnaire is presented in full in Appendix 2.

4.5. Formulation of non-choice questions

A number of additional (non-choice) questions were included in the survey instrument. These covered a number of factors including:

i) Characteristics of the respondent: specialty, grade and budget responsibilities

ii) Patient caseload by stage of disease at diagnosis

iii) Respondent views on the relative importance of different decision-makers in the product adoption decision (to assess the extent to which the sample covered the important decision-makers)

iv) The importance of different trial design characteristics (to assess whether or not important attributes were omitted from the design)

v) The importance of different endpoints (to assess whether or not important endpoints were omitted from the design)

vi) The difficulty of completing the questionnaire and the time taken by both the respondent and interviewer (to assess the practicality of the survey).

In addition to the above, respondents were invited to make comments on any aspect of the survey. The format of the non-choice questions can be seen in the full survey instrument which is presented as Appendix 2.

4.6. Sample selection and survey administration

A priori, a number of decision-makers and other influences can be hypothesized to affect the product adoption decision. One issue is whether to sample individuals or a collective decision-making unit. In this study, it was decided to focus on a sample of senior physicians selected primarily from the specialties which, *a priori*, are the most actively involved in the management of patients with this condition and, consequently, the choice of adopting the new treatment regimen or not.

The population from which the sample was selected was identified from a proprietary database containing details of UK physicians including their specialty and contact details[76] A search of the database was performed in order to identify clinicians involved in the management of breast cancer. The results of the search are summarised in Table 5.

Table 5

Stated Preference Survey Sample

Specialty[1]	Population[2]	Invited to participate	Agreed to participate[3]	Completed the questionnaire[3]
Medical oncologist	32	21	18 (85.71%)	14 (66.67%)
Clinical oncologist	284	58	18 (31.03%)	16 (27.59%)
Surgical oncologist	28	22	19 (86.36%)	17 (77.27%)
Radiologist	33	9	5 (55.56%)	2 (22.22%)
Other	17	15	10 (66.67%)	5 (33.33%)
Total	394	125	70 (56.00%)	54 (43.20%)

Notes.

1. Specialists were senior registrar grade or higher and actively involved in breast cancer management.
2. Identified from The Medical Directory, FT Business Ltd, 1999.[76]
3. Percentages are the response rates relative to the number invited to participate.

In this survey, the questionnaire was administered using a telephone-mail-telephone technique which involved the following three steps:

i) Calling potential respondents to enlist involvement and, if willing to participate, to arrange a telephone follow-up interview

ii) Mailing the questionnaire to participants to review the materials and complete the responses, and

iii) Follow-up telephone interviews to record responses on paper.

A professional market research agency was commissioned to implement the survey, although they were not involved with the design of the questionnaire, the processing of the data, the statistical analysis or the interpretation of the results. All completed questionnaires were mailed to the author who processed and analysed the data.

Prior to the implementation of the full survey, simulations based on pilot data (4 completed questionnaires) were used to assess the results with different sample sizes. In this way, a sample in excess of 25 respondents was deemed necessary although a target of 100 was set within the data collection budget available. A final sample of 54 was achieved (see Table 5 and the results section below).

4.7. Model specification and estimation

In order to estimate a binary choice probit model of the demand for bisphosphonates as postulated in equation (7) above, the following linear additive utility function was assumed:

$$\Delta V = \beta_1\ \Delta ENDPOINT + \beta_2\ \Delta EFFECTIVENESS + \beta_3\ \Delta UNCERTAINTY + \beta_4\ \Delta DURATION + \beta_5\ \Delta POPULATION + \beta_6\ \Delta COST + \varepsilon \quad (8)$$

where ΔV is the difference in utility between the two bisphosphonate prevention regimens, $\Delta ENDPOINT$ is the difference in the primary endpoint, $\Delta EFFECTIVENESS$ is the difference in the effect size demonstrated, $\Delta UNCERTAINTY$ is the difference in the degree of uncertainty surrounding the demonstrated effectiveness, $\Delta DURATION$ is the difference in the duration of observation, $\Delta POPULATION$ is the difference in study population and $\Delta COST$ is the difference between the incremental cost associated with bisphosphonate use. $\beta_1 - \beta_6$ are the parameters to be estimated, and ε is the unobservable error term for the model which reflects the unobservable factors in the utility function. Given that the choice alternatives presented to respondents are couched in 'generic' terms (i.e. Prevention A and Prevention B), models were estimated without a constant.

The explanatory variables are measured as the differences between the levels of the attributes appearing in the 16 choice questions (prevention A minus prevention B) as shown in Table 4. ΔV is measured as a binary variable which takes on the value '1' if prevention A is chosen (the left hand side of the choice sets) and '0' if prevention B is chosen (the right hand side choice).

Models were estimated using the probit (cluster) command in Stata version 7 (Stata).[67] A regression error specification test (RESET) was applied to each model in order to determine whether there were problems associated with the functional form of the model.[70] Any model failing the RESET test at conventional levels of significance ($p < 0.05$) would be regarded as being mis-specified.

Models were estimated for the full sample of respondents and for two sub-groups of 'consistent traders' identified using the definitions of inconsistent and non-trading respondents given below.

Consistent traders sub-group A. In this survey, a test for consistency fell naturally from the random pairing of the choice scenarios since two choice sets contained the same profiles (see choice sets 10 and 12 in Table 4 and Appendix 2). One would expect a respondent who is consistent with their answers to select the same scenario for both of these choices. An advantage of this definition over the conventional approach described below is that it is not necessary to have prior expectations about the qualitative effects to perform this test. In this study it is therefore regarded as the primary test of consistency. Respondents who failed to choose the same scenario for choice sets 10 and 12 were dropped for this sub-group analysis together with non-trading respondents. Non-trading respondents were identified at the analysis stage by examining those individuals who exhibited any one of the choice patterns shown in Table 6.

Consistent traders sub-group B. A sub-group analysis was also performed based on a conventional test of consistency. Table 4 shows four choice sets for which the preferred scenarios might be predicted given the expected signs of the coefficients. Respondents who failed to make choices in line with those that might be expected for

choice sets 8, 9, 13 or 14 were dropped for this sub-group analysis together with non-trading respondents who were identified in the same way as for sub-group A above.

No other sub-group analyses were performed (e.g. separate analyses by specialty) due to the relatively small sample sizes to which such analyses would give rise.

Table 6
Choice patterns used to define non-trading respondents[1]

Choice set	Endpoint	Effectiveness	Uncertainty	Duration	Population	Cost
1	1	1	1	1	0	
2	0	0	0		0	1
3		1	0	0		0
4	0	1	1	0	1	
5			1	1	1	0
6		0	0	1		0
7		1	0	0		0
8		0	1	0		1
9		1	0		1	0
10			0	0	1	1
11	0	1		1	0	0
12			1	1	0	0
13		0	1	0	0	
14	1		0	1		0
15		0	0	1		1
16	1	0	1	1	1	

1. Non-trading respondents were deemed to be those who exhibited the choice patterns specified in the columns of Table 6. A ‘1’ in a column indicates that bisphosphonate prevention option A was chosen and ‘0’ indicates the choice of option B.

5. RESULTS: NON-CHOICE QUESTIONS

In this section, the results of the non-choice question components of the stated preference survey are presented. Many of the results tables referred to in this section can be found in Appendix 3. Such tables are denoted Table A3.1, A3.2 etc.

5.1. Study population and sample

The survey response rate, by specialty, is shown in Table 5. A total of 394 specialists were identified of which 125 (31.73%) were invited to participate in the survey. Of those invited to participate, 55 (44.00%) refused and 70 (56%) accepted. Of those agreeing to participate, questionnaires were obtained from 54 providing an overall response rate of 43.20%. Therefore a sample of 54 questionnaires was obtained within the budget constraint and the completion rate for those who responded was 100%.

5.2. Respondent characteristics

The composition of the 54 respondents in terms of their specialty and title are shown in Table A3.1. The sample included 17 surgical oncologists (31.48%), 14 medical oncologists (25.93%) and 16 clinical oncologists (29.63%). Forty respondents (74.07%) were senior registrar grade or higher. At the time the survey was conducted, only one of the respondents was not involved in the day-to-day management of patients with breast cancer. The annual number of new cases of breast cancer seen by the respondents is summarised, by specialty, in Table A3.2. For the sample as a whole, the average number of new cases seen each year is 176.37 (SD = 142.42). The estimated distribution of new cases by stage of disease at diagnosis is shown in Table A3.3. Only 14 respondents (25.93%) indicated having any involvement with the

management of budgets related to the treatment of patients with breast cancer (Table A3.4). The nature of that responsibility, exactly as articulated by the respondents, can be found in Table A3.15.

5.3. Survey completion

Apart from the optional open-ended questions, there were no missing responses. It can be seen from Table A3.5 that only 2 respondents found the questionnaire "very difficult" to complete. 22 respondents (40.74%) found the questionnaire "moderately difficult" to complete, 18 (33.33%) found it "slightly difficult" to complete and 12 (22.22%) found it "not difficult" to complete. Respondents spent an average of 26.76 minutes (SD = 13.11) reviewing the materials and preparing their responses for the telephone interview (Table A3.6). The telephone interviews lasted an average of 11.41 minutes (SD = 4.56). Therefore in total respondents spent an average of 38.17 minutes (SD = 13.32) participating in this survey.

Of the 54 respondents, 48 (88.89%) indicated a willingness to participate in future research. This required their personal details to be disclosed (Table A3.7). The same number indicated that they would like to see the results of the study (Table A3.8). Finally, 30 respondents (55.56%) provided comments on the questionnaire (Table A3.9). The comments, exactly as articulated by the respondents, can be found in Table A3.16.

5.4. Influences on the decision to use adjuvant bisphosphonates

Respondents were asked to rate the importance of a predetermined list of specialties on a 3 point ordinal scale:

i) High degree of influence on the decision to adopt bisphosphonates (coded 1 for analysis)

ii) Some influence on the decision to adopt bisphosphonates (coded 2 for analysis)

iii) No influence on the decision to adopt bisphosphonates (coded 3 for analysis).

The results of the analysis of the responses to this question using the above coding are shown in Table A3.10. Medical oncologists (mean rating 1.15, SD = 0.41), radiotherapists (1.35, SD = 0.55) and surgical oncologists (1.80, SD = 0.59) were viewed as the specialties with the highest degree of influence on the decision to use bisphosphonates.

36 respondents (66.67%) indicated that important influences on the decision to use bisphosphonates were missing from the list of specialties provided (Table A3.11). These are shown, exactly as articulated by the respondents, in Table A3.17. The missing influences cited were other specialties (16 citations, 33.33% of all citations), nurses (14, 29.17%), patients / relatives / patient support groups (11, 22.92%), managers / policy makers (6, 12.50%) and the media (1, 2.08%).

5.5. Importance of adjuvant bisphosphonate trial design characteristics

Respondents were asked to rate the importance of a predetermined list of trial design characteristics on a 4 point ordinal scale:

i) Very important characteristic (coded 1 for analysis)

ii) Quite important characteristic (coded 2 for analysis)

iii) Characteristic of little importance (coded 3 for analysis)

iv) Characteristic not important (coded 4 for analysis).

The results of responses to this question using the above coding are shown in Table A3.12. The results confirm the importance of the six trial design characteristics included in the discrete choice exercise. Four of these characteristics (primary endpoint, statistical significance, effect size and study population) had a mean rating close to 1 (very important) and two (duration of observation and comparators) had a mean rating between 1 (very important) and 2 (quite important). The other characteristics included in this question (lead investigators, countries in which the trial is conducted and organisation sponsoring the trial) had mean ratings tending towards 3 (of little importance). The choice of primary endpoint (mean rating 1.15, SD = 0.49), statistical significance (1.22, SD = 0.46) and effect size (1.26, SD = 0.44) were the three most important design characteristics.

5.6. Importance of bisphosphonate trial endpoints

Respondents were asked to rank a predetermined list of bisphosphonate trial primary endpoints in order of importance with 1 being the most important endpoint and 8 being the least important. The results of responses to this question using the above coding are shown in Table A3.13. The two endpoints used in the discrete choice exercise, percentage of patients alive without disease recurrence and percentage of patients without metastatic bone disease, were ranked as the most important and third most important endpoints respectively. The former had a mean ranking of 2.43 (SD = 1.80) and the latter 3.91 (SD = 1.94). The additional cost associated with the use of adjuvant bisphosphonates was ranked as the least important endpoint (mean 6.81, SD = 1.59).

Six respondents (12.97%) indicated that important endpoints were missing from the list provided (Table A3.14). These are shown, exactly as articulated by the respondents, in Table A3.18. It can be seen that 5 of the 11 omissions cited could be referred to as 'clinical' endpoints (e.g. serum calcium levels) and the remainder as 'economic' endpoints (e.g. cost per QALY).

6. RESULTS: DISCRETE CHOICE MODEL ESTIMATION

In this section, the results of the discrete choice model probit regression analysis are presented in terms of the qualitative and quantitative effects.

6.1. Qualitative effects

For each of the three models estimated, the signs on the attribute coefficients suggest identical qualitative effects (see Table 7). These are summarised below.

1) ***Choice of primary endpoint.*** The coefficient for this attribute (Endpoint) has a positive sign which implies a preference for disease free survival over the incidence of metastatic bone disease as the primary endpoint in adjuvant bisphosphonate trials. Consequently, this suggests that a product is more likely to be chosen if a trial demonstrates an improvement in the proportion of patients alive without disease recurrence compared with one that shows an improvement in the incidence of metastatic bone disease.

2) ***Effectiveness.*** For the effectiveness attribute (Effectiveness), the coefficient has a positive sign suggesting that the probability of adopting a product is an increasing function of the level of effectiveness demonstrated, regardless of the choice of primary endpoint.

3) ***Degree of uncertainty surrounding the point estimate of effectiveness***. The sign on the coefficient of the uncertainty variable (Uncertainty) is negative which indicates that the preference for a product decreases as the degree of uncertainty surrounding the point estimate of effectiveness increases.

4) ***Duration of observation***. The positive sign on the coefficient for this attribute (Duration) suggests a preference for trials of longer durations. In other words, the probability of adopting a product is an increasing function of the duration of evaluation of its benefits.

5) ***Study population***. A product whose benefits are demonstrated in a trial which enrolls patients with all stages of primary operable breast cancer is more likely to be chosen than one whose enrolment is restricted to subjects with Stage III disease at diagnosis. This is indicated by the positive sign on the study population coefficient (Population).

6) ***Incremental cost of adjuvant bisphosphonate use***. The negative coefficient for the cost attribute (Cost) suggests that the lower the incremental cost of using a bisphosphonate prevention strategy the more likely it is to be chosen.

To summarise the above findings, the qualitative effects (signs for the attribute coefficients) are in line with the author's prior expectations which provides evidence of the theoretical validity (internal consistency) of the estimated models.

6.2. Quantitative effects

Table 7 shows the primary results of this analysis. A Ramsey regression error specification test (RESET) suggests there is no problem with the functional form of any of the three models. The null hypothesis that all of the coefficients are simultaneously zero can be rejected on the basis of the Wald test ($p < 0.01$ in each case). Independently, attributes are statistically significantly different from zero at the 5% level or better with the exception of the duration variable which is borderline significant in both the 'full sample model' and the 'consistent traders sub-group A' model ($p = 0.06$ in both cases). These results indicate that each of the RCT design attributes included in the analysis is important in the decision to adopt adjuvant bisphosphonate treatments and that most respondents were willing to trade off different RCT design characteristics.

Table 7
Probit Regression Results[1,2]

RCT Design Attributes	(1) Full Sample	(2) Consistent Traders: Sub-group A[3]	(3) Consistent Traders: Sub-group B[4]
Endpoint	0.2787***	0.2700***	0.3185***
	[0.0522]	[0.0630]	[0.0625]
Effectiveness	0.0457***	0.0390***	0.0464***
	[0.0061]	[0.0068]	[0.0068]
Uncertainty	-0.6210***	-0.6653***	-0.7844***
	[0.0746]	[0.0987]	[0.0725]
Duration	0.0255*	0.0301*	0.0482***
	[0.0134]	[0.0159]	[0.0136]
Population	0.2419***	0.2675***	0.3292***
	[0.0563]	[0.0651]	[0.0704]
Cost	-5.43e-07***	-5.86e-07***	-5.95e-07***
	[5.97e-08]	[7.36e-08]	[6.97e-08]
Observations	864	608	656
Respondents	54	38	41
Log likelihood	-399.35	-285.18	-290.39
Wald chi2 (6)	238.95	163.01	241.27
Prob > chi2	0.0000***	0.0000***	0.0000***
Ramsey chi2(1)	0.30	0.10	0.01
Prob > chi2	0.5861	0.7485	0.9060
Correct predictions	79.28%	79.93%	81.10%

Notes.

1. Models were estimated using the probit (cluster) option available in Stata Version 7.0.[67] This estimator takes into account the potential non-independence of the observations and generates robust standard errors (shown in brackets).
2. Significance levels are denoted as follows: * significant at 10%; ** significant at 5%; *** significant at 1%
3. Inconsistent respondents were defined as those who did not choose the same scenario for choices 10 and 12 (n=10). Non-trading respondents were defined as those who exhibited dominant preferences for any attribute (n=7). Dropping these respondents left a sample of 38 consistent traders (one respondent was both inconsistent and a non-trader).
4. Inconsistent respondents were defined as those who did not choose the options expected for choices 8,9,13 or 14 (n=6). Non-trading respondents were defined as those who exhibited dominant preferences for any attribute (n=7). Dropping these respondents left a sample of 41 consistent traders.

The primary interest in this analysis is with using the regression results to compare the predicted probabilities of product adoption contingent upon alternative RCT designs. These can be computed using the regression results from Table 7 and Equations (7) and (8). Therefore sponsors of RCTs could use the regression results from product-specific stated preference surveys in a number of ways, including to:

1) Evaluate the impact of different RCT designs on the probability of product adoption;

2) Determine a technically feasible design which maximises the *expected* predicted probability of product adoption, and

3) Operationalise an investment appraisal approach to RCT design.[77]

Each of these uses is illustrated briefly in section 4.7 below.

7. USING DISCRETE CHOICE MODEL RESULTS IN RCT DESIGN

A number of potential uses of discrete choice modelling results in the context of RCT design are considered below. It must be emphasised that although this analysis is based around a case study of adjuvant bisphosphonate trials, the material presented below is purely illustrative. The main body of the text focuses on the results. The formulae, working assumptions and example calculations are presented in Appendix 4.

7.1. Impact of RCT designs on the probability of product adoption

One potential use of DCM results is to compare and rank alternative RCT designs in terms of the predicted probabilities of product adoption to which they give rise. Specifically, given a set of candidate designs, sponsors of RCTs could use the results

to select the design which gives the highest predicted probability of product adoption, $\Pr(A \mid \mathrm{J})$. This is equivalent to choosing the design with the highest decision-maker preference or utility score, ΔV_{AB}.

Table 8 and Figure 2 illustrate this application of the results by comparing the predicted probabilities of each of seven hypothetical candidate designs against a hypothetical baseline (existing) treatment. The differences in utility, ΔV_{AB}, are calculated by substituting the regression coefficients from the full sample model (Table 7) and the *differences* in the values of the RCT design attributes into Equation (8). The predicted probabilities are calculated by substituting the resulting utility values into Equation (7). An example calculation is provided in Appendix 4.

In Table 8, designs 1 to 6 differ from the baseline design only in terms of the level (value) of one RCT design attribute. This is done in order to illustrate how the impact on $\Pr(A \mid \mathrm{J})$ of changing the value of only one RCT design characteristic can be evaluated. For example, Design 1 differs from the baseline in terms of the choice of primary endpoint. This gives rise to a predicted probability of adoption of approximately 0.61. With a design identical to the baseline, the predicted probability would be 0.50. In contrast, hypothetical RCT Design 7 is defined as having the "best" attribute values shown in Table 2. This means that this design has "better" design characteristics than the baseline for all attributes except study population (which is the same). Consequently, Design 7 has the highest predicted probability amongst the RCT designs compared in Table 8. The ranking of the designs in descending order of their predicted probabilities is shown in the last row of Table 8.

Table 8: Impact of RCT Designs on the Probability of Product Adoption

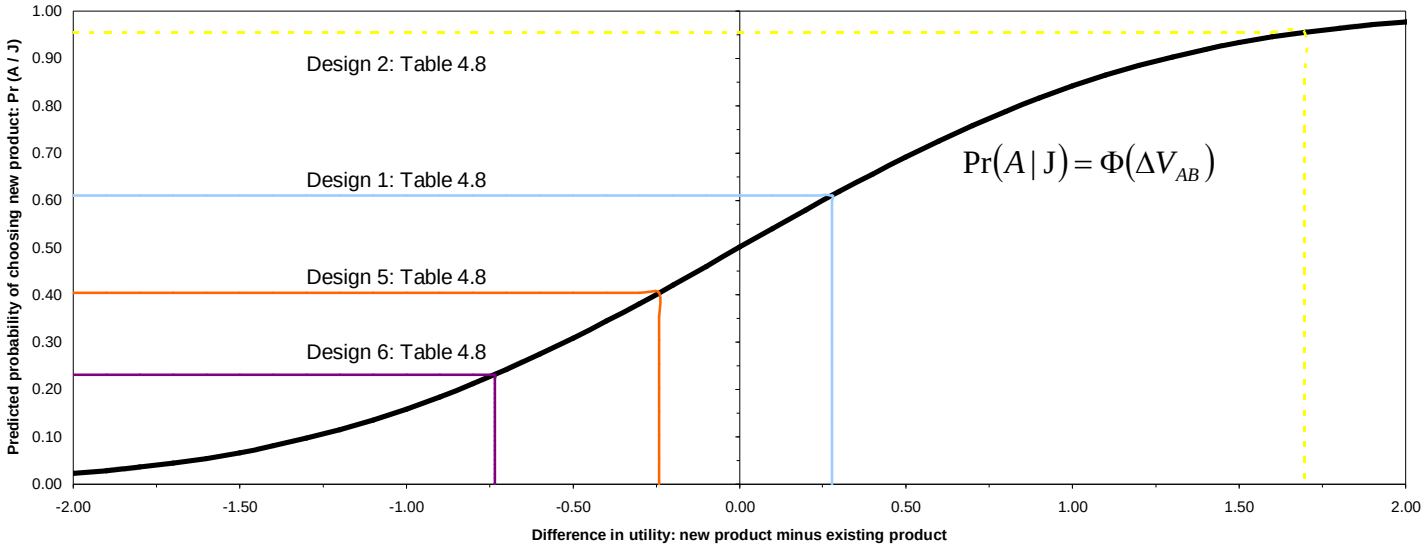
Attribute	(1) Baseline product evidence	(2) New Product RCT Design 1	(3) New Product RCT Design 2	(4) New Product RCT Design 3	(5) New Product RCT Design 4	(6) New Product RCT Design 5	(7) New Product RCT Design 6	(8) New Product RCT Design 7
Endpoint	Patients without metastatic bone disease	Patients alive without disease recurrence	Patients without metastatic bone disease	Patients without metastatic bone disease	Patients without metastatic bone disease	Patients without metastatic bone disease	Patients without metastatic bone disease	Patients alive without disease recurrence
Effectiveness	2.90%	2.90%	40.00%	2.90%	2.90%	2.90%	2.90%	40%
Uncertainty	0.23% to 5.57% [0.92]	0.23% to 5.57% [0.92]	0.23% to 5.57% [0.92]	2.87% to 2.93% [0.01]	0.23% to 5.57% [0.92]	0.23% to 5.57% [0.92]	0.23% to 5.57% [0.92]	39.60% to 40.40% [0.01]
Duration	2 years	2 years	2 years	2 years	10 years	2 years	2 years	10 years
Population	Patients with Stages I to III disease at diagnosis	Patients with Stages I to III disease at diagnosis	Patients with Stages I to III disease at diagnosis	Patients with Stages I to III disease at diagnosis	Patients with Stages I to III disease at diagnosis	Patients with Stage III disease at diagnosis	Patients with Stages I to III disease at diagnosis	Patients with Stages I to III disease at diagnosis
Cost	£450,000	£450,000	£450,000	£450,000	£450,000	£450,000	£1,800,000	£0
Difference in utility (new minus existing product) ΔV_{AB}		0.2787[1]	1.6955[1]	0.5651[1]	0.2040[1]	-0.2419[1]	-0.7331[1]	2.9876[1]
Predicted probability $\Pr(A \mid \mathrm{J})$		0.6098[2]	0.9550[2]	0.7140[2]	0.5808[2]	0.4044[2]	0.2318[2]	0.9986[2]
Preference ranking of RCT design based on predicted probabilities	**6**	**4**	**2**	**3**	**5**	**7**	**8**	**1**

Footnotes to table can be found on next page.

Table 4.8 (continued)

1. ΔV_{AB} is derived using the regression results and Equation (2). A denotes the new product and B denotes the existing product.
2. Derived by substituting the value ΔV_{AB} into Equation (1).
3. Figures in parentheses are the levels of the uncertainty attribute, which expresses the 95% confidence interval as a proportion of the point estimate of effectiveness.
4. See Appendix 4 for an example calculation.

Figure 2
Predicted probabilities of choosing a new product based on different RCT designs



Whilst it is informative to compare selected candidate RCT designs in this way, this approach does not identify an optimal (predicted probability maximising) design because all possible combinations of attribute values are not considered. Moreover, the calculations do not allow for the fact that the 'Effectiveness' and 'Uncertainty' attribute values are, prior to the conduct of a trial, uncertain. Thus, of more practical value is to identify a trial design which maximises the *expected* predicted probability of product adoption. How this can be done is illustrated in section 4.7.2 below.

7.2. Identifying a design that maximises the expected probability of product adoption

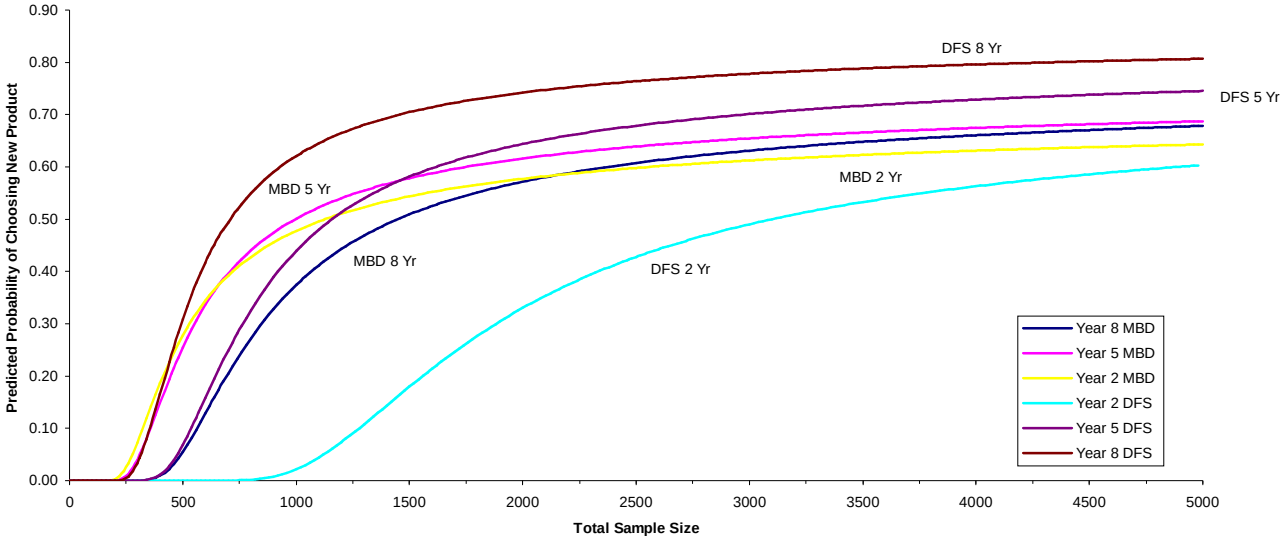
At the planning stages of an RCT, the predicted probability of product adoption given by Equation (7) is uncertain since the results of a trial are unknown. Specifically, for the case study presented in this paper, the uncertainty surrounding the predicted probabilities stems from the uncertainty surrounding the results of trials with respect to the 'Effectiveness' and 'Uncertainty' attributes. Since it is desirable to consider alternative RCT designs in a way which allows for this uncertainty (i.e. in terms of *expected* predicted probabilities), it is necessary to calculate the *expected* values for the 'Effectiveness' and 'Uncertainty' outcomes for any trial design under consideration. The expected values are then used for the calculation of predicted probabilities using Equation (7).

Making use of an approach previously described by Backhouse (1998)[77] and Detsky (1985;1990),[78;79] expected 'Effectiveness' and 'Uncertainty' outcomes have been calculated to produce the illustrative results presented in Figure 3 (see Appendix 4 for formulae, working assumptions and example calculations). Figure 3 shows expected predicted probabilities, over a range of trial sample sizes, for six hypothetical RCT

designs when compared against the baseline treatment presented in Table 8. In order to simplify the exposition, the six designs differ from the baseline only in terms of i) the choice of primary endpoint (patients without metastatic bone disease (MBD)) or patients alive without disease recurrence (DFS)) and / or ii) the duration of the trial (2, 5 or 8 years). It can be seen that, upto a total sample size of approximately 440 subjects (220 per arm), a trial of 2 years duration with MBD as the primary endpoint gives rise to the highest expected predicted probability. Thereafter, a trial with 8 years of follow-up and DFS as the primary endpoint has the highest expected predicted probability of adoption. This is the design which maximises the expected predicted probabilities given the working assumptions. It should be emphasised that these results are purely illustrative and are sensitive to the assumptions made in their derivation, particularly the distributions of the prior expected outcomes (see Appendix 4).

A problem with this approach to RCT design is that, whilst an expected predicted probability maximising design can be identified, it may not be optimal from a commercial (profit maximising) perspective. This is because it does not take account of costs and time to market and hence the timing of revenues. It is therefore necessary to extend this analysis to consider the cost and revenue implications of alternative RCT designs.

Figure 3
Expected Predicted Probabilities for RCTs of 2, 5 and 8 Years Duration



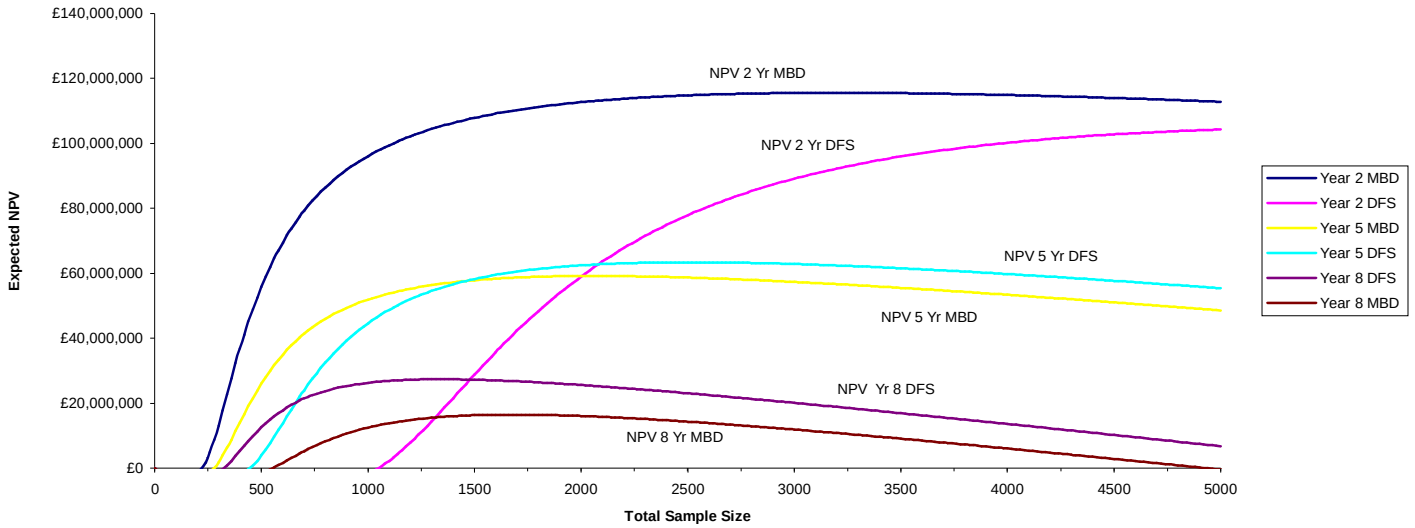
7.3. Using DCM results within an investment appraisal framework

Backhouse (1998) has shown how pharmaceutical companies could take profit considerations into account when making decisions about the design of their RCTs.[77] In this section, the hypothetical trial designs considered in section 4.7.2 above are used, together with the same assumptions, as a basis for illustrating how a commercially optimal (expected net present value maximising) design can be identified. In order to do this, a number of additional simplifying assumptions are made about the costs of performing the bisphosphonate trials, market size, product uptake and the time horizon for the commercial appraisal. The assumptions made can be found in Appendix 4 together with the formulae used and example calculations.

Figure 4 shows the expected net present values (NPV), as a function of sample size, for each of the six hypothetical RCT designs considered in section 4.7.2 above. For each individual trial, the optimal sample size is that for which the expected NPV curve is at its maximum. It can be seen that, for all sample sizes up to at least 5000 subjects in total, a trial of 2 years duration with MBD as the primary endpoint gives rise to the highest expected NPV. The expected NPV maximising design occurs at a total sample size of approximately 3200 subjects (1600 per arm) and has an NPV of about £115 millions. A notable feature of this finding is that it serves to illustrate that a design which maximises expected NPV is not necessarily the design which maximises the expected predicted probability of product adoption.

Once again, it is important to emphasise that the calculations presented in this paper are for illustrative purposes only and that the findings are sensitive to the various assumptions that need to be made for this type of analysis.

Figure 4
Expected Net Present Values for RCTs of 2, 5 and 8 Years Duration



8. DISCUSSION AND CONCLUSION

The results from this exploratory study suggest that the application of discrete choice modelling to stated preference data provides a promising method for incorporating the preferences of decision-makers into the design of RCTs. Specifically, this paper illustrates how such empirical analyses of decision-makers' preferences for RCT design characteristics can be used to estimate the probabilities of product adoption contingent upon different designs. It has been shown how the probabilities can be used to determine preference maximising and profit maximising RCTs. The findings also suggest that the approach is both practical and theoretically valid in this context. Few respondents had difficulty understanding and completing the questionnaire, there was no missing data and the total time respondents spent on the survey was less than one hour. All but six participants expressed both a willingness to participate in any further stages of the research and an interest in seeing the results. The qualitative effects for the RCT design attributes included in the analysis are in line with prior expectations, each was found to be a statistically significant determinant of the decision to adopt a new product and most respondents were prepared to make trade-offs between them.

Despite the promising results, a number of issues need to be considered in future research and practical applications. Firstly, this analysis utilised preferences elicited from clinicians from different specialties involved in the management of patients with breast cancer. This implies that other decision-makers are not involved in the product adoption decision and that each specialty represented in the sample carries equal weight. If these assumptions do not hold, then the predicted probabilities of product adoption will be unreliable. Respondents in this survey confirmed the importance to the product adoption decision of the specialties that made-up most of the sample. But

they also indicated that the influence of other parties should be considered, notably patients and other specialties involved in the management of breast cancer. If the preferences of physicians and patients are aligned, then the results which focus on the former will be robust. There would be practical challenges in applying this type of survey to patients because they may not be familiar with the terminology and practices of RCT design. This would be a valuable area for future research.

It is notable that very few respondents indicated that the influence of decision-making and advisory bodies such as formulary committees and NICE were important. Nevertheless, how such groups formulate their decisions and the preferences underlying them is both a fundamental and topical issue.[80;81] Therefore the potential for applying discrete choice analysis to members of such bodies would be a worthwhile line of future investigation since it offers a feasible means of explicitly quantifying the preferences of key stakeholder groups.

Secondly, the example application chosen for this study lent itself readily to the use of a simple binary choice model of drug prescribing. This is because adjuvant bisphosphonates are not currently established as a therapeutic strategy for the prevention of metastatic bone disease and so the choice problem could be simplified to the decision to use them or not contingent upon the RCT designs and results. Clearly, many treatment choice situations will be less straightforward as physicians are often presented with more than two possible courses of action. In such situations, it may be necessary to construct more complex multinomial models[1] of drug prescribing behaviour which would in turn require more complex stated preference choice surveys for their application.[3] Moreover, the results from a survey conducted for one product indication will not be generalisable to another which could, for example, lead to a large number of studies required for a sponsor of multiple

technologies. So the number, size and complexity of stated preference surveys would necessitate consideration being given to the potential benefits and costs associated with the research effort.

Thirdly, the stated preference survey presented respondents with a series of binary choices for which they were required to indicate a preference for one of the two adjuvant bisphosphonate prevention options. Respondents were not given the opportunity to indicate that they would prefer an alternative other than the two presented in any given choice set. In other words, they were not given the opportunity to 'opt-out'. A review of applications of discrete choice experiments to health care programmes confirms that this approach is consistent with previous practice.[82] However, it has recently been pointed out that the inclusion of an opt-out option may better mimic the circumstances under which actual choices are made and may therefore give rise to more reliable estimates of product or service adoption.[83] But there are also disadvantages of including opt-out alternatives. Subjects may choose the opt-out alternative simply to avoid making difficult trade-offs and it may not be possible to derive the attribute levels (characteristics) of the opt-out option.[83] Both of these factors could significantly reduce the number of observations available for analysis. Furthermore, research conducted outside the health field suggests that estimates of attribute weights and demand can be sensitive to the format of the opt-out alternative presented to respondents.[84] Clearly, further research is required into the issue of obtaining reliable predictions of actual choice behaviour from discrete choice stated preference surveys. In this respect whether and how to include an opt-out alternative is one of a number of aspects to address.

Fourthly, the model parameters were estimated using discrete choice stated preference survey data which is currently the most common approach used in health economics

applications. An alternative would be to use revealed preference data[81] i.e. data pertaining to actual rather than simulated choices. However, it may not be practical to obtain or construct a dataset containing the necessary RCT and product adoption variables and such data will clearly not be available for new products. It should also be noted that it may not be practical to conduct stated preference surveys amongst some decision-makers e.g. NICE appraisal committee members.

Finally, although aspects of this paper have illustrated the potential use of DCA within a private sector investment appraisal framework, this should not detract from the potential value, in other contexts, of modelling product adoption decisions as a function of RCT design. For example, a useful line of future research would be to explore the conditions under which the private sector perspective on optimal RCT designs would be aligned with the societal perspective adopted by NICE. NICE considers both clinical effectiveness and cost in formulating its advice and its preferred measure for gauging value is the cost per quality adjusted life-year (QALY) (the incremental cost-effectiveness ratio).[80] Approaches to producing optimal trial designs from the societal perspective using cost-effectiveness criteria have been proposed.[85;86] The extent to which the private and societal perspectives will yield equivalent optimal designs will depend upon the importance of the cost-effectiveness ratio in product adoption decisions. Little is known about this relationship and although a recent paper used discrete choice modelling to produce insights from recommendations made by NICE, the extent of the impact of the recommendations on actual product usage was not explored.[81] In this study, measures of both clinical effectiveness and cost were considered as separate variables but the cost per quality adjusted life year gained was not explicitly evaluated by respondents. However, in considering whether important endpoints were missing from the analysis, only two

respondents mentioned the absence of cost per QALY information which raises questions about the alignment of physician and NICE decision-making criteria. Further research into how cost per QALY data could be presented in stated preference surveys would be a beneficial area for further research because it is not a measure that is widely understood amongst many stakeholders.

In conclusion, more sophisticated survey designs and statistical analysis methods may be required in future applications in order to correctly model the treatment decision-making situation of interest. Nevertheless, the results from this analysis suggest that DCA offers a practical and valid method by which sponsors of RCTs could take the preferences of decision-makers into account when planning their studies. Therefore further research into the application of the technique in this context would seem to be worthwhile.

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Appendix 1

Effectiveness Outcomes Interpolated From Clinical Trials

	Clodronate[1]	Placebo[1]	Difference[2]	Lower 95%CI[3]	Upper 95%CI[3]
% Patients without metastatic bone disease					
From Powles et al (2002)					
Year 1	99.00	97.00	2.00	0.33	3.67
Year 2	96.20	93.30	2.90	0.23	5.57
Year 3	94.00	89.00	5.00	1.67	8.33
Year 4	91.00	87.50	3.50	-0.21	7.21
Year 5	89.00	84.50	4.50	0.45	8.55
Year 6	86.00	83.50	2.50	-1.81	6.81
Year 7	84.50	82.00	2.50	-1.97	6.97
Year 8	83.00	80.00	3.00	-1.65	7.65
From Diel et al (1998)					
Year 1	100.00	92.00	8.00	3.58	12.42
Year 2	98.00	88.00	10.00	4.28	15.72
Year 3	97.00	82.00	15.00	8.20	21.80
Year 4	92.00	78.00	14.00	6.03	21.97
Year 5	88.00	75.00	13.00	4.31	21.69
Year 6	78.00	75.00	3.00	-6.57	12.57
Year 7	78.00	75.00	3.00	-6.57	12.57
% Patients alive					
From Powles et al (2002)					
Year 1	98.00	98.00	0.00	-1.68	1.68
Year 2	92.70	92.40	0.30	-2.85	3.45
Year 3	90.00	87.00	3.00	-0.82	6.82
Year 4	86.50	84.00	2.50	-1.75	6.75
Year 5	82.90	79.30	3.60	-1.09	8.29
Year 6	81.00	76.50	4.50	-0.40	9.40
Year 7	78.50	73.00	5.50	0.37	10.63
Year 8	78.00	72.00	6.00	0.82	11.18
Year 9	74.00	65.50	8.50	3.02	13.98
Year 10	74.00	60.00	14.00	8.43	19.57
From Diel et al (1998)					
Year 1	100.00	82.00	18.00	11.75	24.25
Year 2	95.00	78.00	17.00	9.44	24.56
Year 3	90.00	72.00	18.00	9.31	26.69
Year 4	80.00	65.00	15.00	5.03	24.97
Year 5	80.00	63.00	17.00	6.95	27.05
Year 6	75.00	60.00	15.00	4.54	25.46
Year 7	75.00	60.00	15.00	4.54	25.46

1. Data points were interpolated from the survival curves reported in Powles et al (2002)[74] and Diel et al (1998).[73]
2. Clodronate % minus placebo %.
3. Confidence intervals for the differences in % effectiveness were calculated using the formula provided by Armitage & Berry (1995) pp 128-130.[87]

Appendix 2

The Stated Preference Survey Questionnaire

8 March 2002

Dear [Doctor]

The Use of Conjoint Analysis in the Design of Clinical Trials

Thank you very much for agreeing to take part in this research.

I am a part-time PhD student at the University of Nottingham. As part of my research I am conducting a survey to assess how a technique known as conjoint analysis might be used to take into account the views of health care professionals when designing clinical trials. The work is not being conducted on behalf of any sponsoring organisation or company.

The research will include interviews with specialists like you and I have asked Accent Marketing and Research to conduct these interviews on my behalf.

I should be grateful if you would assist me with this research by spending about 10 minutes reading the enclosed material. Then on the (insert date), one of Accent's researchers will telephone you to collect your responses to each of the questions. Hence, this material does not need to be returned to me.

The questionnaire does not require you to provide any personal or patient information. Furthermore, Accent will not pass on the names of those who participate in this research to me unless you give your consent for this to happen.

A copy of the results of this survey will be available for all those who have taken part in this research.

If you have any questions relating to the enclosed, please do not hesitate to contact me.

Thank you in advance for your help with this research.

Yours sincerely,

Martin E Backhouse

Enc.

INTRODUCTION

Clinical research has shown that bisphosphonates reduce the incidence of hypercalcaemia and pathological bone fractures in patients with established bone metastases from breast cancer. Moreover, bisphosphonates have been shown to reduce the risk of bone metastases in patients with relapsed breast cancer without obvious bone involvement. However, the effectiveness of adjuvant bisphosphonates as a preventive therapeutic strategy for patients with primary operable breast cancer has yet to be definitively established.

In the choices which follow, you are asked to imagine that **you alone** are deciding which adjuvant bisphosphonate therapy to use based on the trial evidence which is presented. For each choice, you will be asked to compare two alternatives (labelled 'Bisphosphonate Prevention A' and 'Bisphosphonate Prevention B'), which differ only in terms of the following trial design characteristics and results:

- **Primary endpoint:** the main measure chosen to compare the effectiveness of adjuvant bisphosphonate therapy against no such therapy (placebo) in patients with primary operable breast cancer.
- **Difference in % of patients achieving the primary endpoint:** the effectiveness of adjuvant bisphosphonate therapy measured as the <u>difference</u> between the % of patients experiencing the primary endpoint in the 'bisphosphonate' and 'no bisphosphonate' arms of the trial i.e. adjuvant bisphosphonate % ***minus*** no adjuvant bisphosphonate %. The results are also shown in the form of the number of patients that would need to be treated with bisphosphonates in order for one patient to benefit from treatment i.e. number needed to treat (NNT).
- **95% confidence interval on the primary endpoint:** a measure of the uncertainty surrounding the point estimate of the primary endpoint outcome. A range of % difference values is presented within which there is a 95% chance that the true difference will lie. The 95% confidence interval is also shown in the form of the number of patients that would need to be treated with bisphosphonates in order for one patient to benefit from treatment i.e. number needed to treat (NNT).
- **Duration of observation:** the duration of the trial in years (not the duration of adjuvant bisphosphonate therapy). It is assumed that all subjects are followed for this period of time. The primary endpoint results are those observed at the end of this follow-up period.
- **Disease stage at diagnosis:** the eligible study population defined in terms of the stage of primary operable breast cancer at diagnosis (Stages I to III).
- **Additional cost of using adjuvant bisphosphonates:** the ***additional cost*** of using adjuvant bisphosphonates compared with not using them i.e. adjuvant bisphosphonate cost ***minus*** no adjuvant bisphosphonate cost. The cost figure presented is the difference per **<u>100 patients</u>** for the period of the trial. In the choices which follow, no information is provided about the duration of adjuvant bisphosphonate therapy i.e. the cost information can reflect different agents and different durations of bisphosphonate treatment.

In making your choices you should assume that:

1) The efficacy results presented are statistically significant at the 5% level.

2) The evidence comes from well-designed, randomised, double-blind placebo controlled trials in patients with primary operable breast cancer.
3) The evidence is the only evidence that is available to make your decision.
4) The alternatives differ only in terms of the characteristics which are presented.
5) Subjects in both arms of the trial received surgery, chemotherapy, hormonal therapy and radiotherapy as required.
6) In the event of relapse, appropriate local or systemic therapies (including bisphosphonates) were administered as required to subjects in both arms of the trial.
7) The adjuvant bisphosphonates were well tolerated i.e. no significant side effects were observed.

PART A

In this part of the questionnaire you are presented with 16 choices. In each case, you are asked to choose **only one** of the two adjuvant bisphosphonate treatment strategies for patients with primary operable breast cancer. Please indicate your choice by marking a ✓in the appropriate box as shown in the following example:

Example:

Trial Design Characteristics	Bisphosphonate Prevention A	Bisphosphonate Prevention B
Primary endpoint	Patients alive without disease recurrence	Patients without metastatic bone disease
Difference in % of patients achieving primary endpoint at the end of the trial (bisphosphonate *minus* placebo)	10% [NNT = 10]	1% [NNT = 100]
95% confidence interval on the primary endpoint	2.50% to 17.50% [NNT = 5.71 to 40.00]	0.75% to 1.25% [NNT = 80.00 to 133.33]
Duration of observation	10 years	8 years
Disease stage at diagnosis for patients enrolled in the trial	Stage III only	Stages I, II and III
Additional cost of using adjuvant bisphosphonates per 100 patients treated (bisphosphonate *minus* placebo)	£ 1,800,000	£ 1,800,000

Which adjuvant bisphosphonate prevention option would you prefer for patients presenting with primary operable breast cancer (Stage I to Stage III)?	Prefer Prevention A	Prefer Prevention B
	✓	

Now please complete the following choice questions making sure that you choose one option for each of the 16 choices.

CHOICE 1

Trial Design Characteristics	Bisphosphonate Prevention A	Bisphosphonate Prevention B
Primary endpoint	Patients alive without disease recurrence	Patients without metastatic bone disease
Difference in % of patients achieving primary endpoint at the end of the trial (bisphosphonate *minus* placebo)	10% [NNT = 10]	1% [NNT = 100]
95% confidence interval on the primary endpoint	2.50% to 17.50% [NNT = 5.71 to 40.00]	0.75% to 1.25% [NNT = 80.00 to 133.33]
Duration of observation	10 years	8 years
Disease stage at diagnosis for patients enrolled in the trial	Stage III only	Stages I, II and III
Additional cost of using adjuvant bisphosphonates per 100 patients treated (bisphosphonate *minus* placebo)	£ 1,800,000	£ 1,800,000

Which adjuvant bisphosphonate prevention option would you prefer for patients presenting with primary operable breast cancer (Stage I to Stage III)?	Prefer Prevention A	Prefer Prevention B

CHOICE 2

Trial Design Characteristics	Bisphosphonate Prevention A	Bisphosphonate Prevention B
Primary endpoint	Patients without metastatic bone disease	Patients alive without disease recurrence
Difference in % of patients achieving primary endpoint at the end of the trial (bisphosphonate *minus* placebo)	10% [NNT = 10]	25% [NNT = 4]
95% confidence interval on the primary endpoint	9.90% to 10.10% [NNT = 9.90 to 10.10]	6.25% to 43.75% [NNT = 2.29 to 16.00]
Duration of observation	8 years	8 years
Disease stage at diagnosis for patients enrolled in the trial	Stage III only	Stages I, II and III
Additional cost of using adjuvant bisphosphonates per 100 patients treated (bisphosphonate *minus* placebo)	£ 900,000	£ 0

Which adjuvant bisphosphonate prevention option would you prefer for patients presenting with primary operable breast cancer (Stage I to Stage III)?	Prefer Prevention A	Prefer Prevention B

CHOICE 3

Trial Design Characteristics	Bisphosphonate Prevention A	Bisphosphonate Prevention B
Primary endpoint	Patients alive without disease recurrence	Patients alive without disease recurrence
Difference in % of patients achieving primary endpoint at the end of the trial (bisphosphonate *minus* placebo)	10% [NNT = 10]	1% [NNT = 100]
95% confidence interval on the primary endpoint	7.50% to 12.50% [NNT = 8.00 to 13.33]	0.01% to 1.99% [NNT = 50.25 to 10000.00]
Duration of observation	4 years	10 years
Disease stage at diagnosis for patients enrolled in the trial	Stages I, II and III	Stages I, II and III
Additional cost of using adjuvant bisphosphonates per 100 patients treated (bisphosphonate *minus* placebo)	£ 450,000	£ 900,000

Which adjuvant bisphosphonate prevention option would you prefer for patients presenting with primary operable breast cancer (Stage I to Stage III)?	Prefer Prevention A	Prefer Prevention B

CHOICE 4

Trial Design Characteristics	Bisphosphonate Prevention A	Bisphosphonate Prevention B
Primary endpoint	Patients without metastatic bone disease	Patients alive without disease recurrence
Difference in % of patients achieving primary endpoint at the end of the trial (bisphosphonate *minus* placebo)	10% [NNT = 10]	1% [NNT = 100]
95% confidence interval on the primary endpoint	0.10% to 19.90% [NNT = 5.03 to 1000.00]	0.99% to 1.01% [NNT = 99.01 to 101.01]
Duration of observation	2 years	4 years
Disease stage at diagnosis for patients enrolled in the trial	Stages I, II and III	Stage III only
Additional cost of using adjuvant bisphosphonates per 100 patients treated (bisphosphonate *minus* placebo)	£ 0	£ 0

Which adjuvant bisphosphonate prevention option would you prefer for patients presenting with primary operable breast cancer (Stage I to Stage III)?	Prefer Prevention A	Prefer Prevention B

CHOICE 5

Trial Design Characteristics	Bisphosphonate Prevention A	Bisphosphonate Prevention B
Primary endpoint	Patients alive without disease recurrence	Patients alive without disease recurrence
Difference in % of patients achieving primary endpoint at the end of the trial (bisphosphonate *minus* placebo)	25% [NNT = 4]	25% [NNT = 4]
95% confidence interval on the primary endpoint	6.25% to 43.75% [NNT = 2.29 to 16.00]	18.75% to 31.25% [NNT = 3.20 to 5.33]
Duration of observation	8 years	2 years
Disease stage at diagnosis for patients enrolled in the trial	Stages I, II and III	Stage III only
Additional cost of using adjuvant bisphosphonates per 100 patients treated (bisphosphonate *minus* placebo)	£ 0	£ 900,000

Which adjuvant bisphosphonate prevention option would you prefer for patients presenting with primary operable breast cancer (Stage I to Stage III)?	Prefer Prevention A	Prefer Prevention B

CHOICE 6

Trial Design Characteristics	Bisphosphonate Prevention A	Bisphosphonate Prevention B
Primary endpoint	Patients without metastatic bone disease	Patients without metastatic bone disease
Difference in % of patients achieving primary endpoint at the end of the trial (bisphosphonate *minus* placebo)	25% [NNT = 4]	40% [NNT = 2.5]
95% confidence interval on the primary endpoint	24.75% to 25.25% [NNT = 3.96 to 4.04]	10.00% to 70.00% [NNT = 1.43 to 10.00]
Duration of observation	10 years	4 years
Disease stage at diagnosis for patients enrolled in the trial	Stages I, II and III	Stages I, II and III
Additional cost of using adjuvant bisphosphonates per 100 patients treated (bisphosphonate *minus* placebo)	£ 450,000	£ 900,000

Which adjuvant bisphosphonate prevention option would you prefer for patients presenting with primary operable breast cancer (Stage I to Stage III)?	Prefer Prevention A	Prefer Prevention B

CHOICE 7

Trial Design Characteristics	Bisphosphonate Prevention A	Bisphosphonate Prevention B
Primary endpoint	Patients alive without disease recurrence	Patients alive without disease recurrence
Difference in % of patients achieving primary endpoint at the end of the trial (bisphosphonate *minus* placebo)	25% [NNT = 4]	10% [NNT = 10]
95% confidence interval on the primary endpoint	18.75% to 31.25% [NNT = 3.20 to 5.33]	2.50% to 17.50% [NNT = 5.71 to 40.00]
Duration of observation	2 years	10 years
Disease stage at diagnosis for patients enrolled in the trial	Stage III only	Stage III only
Additional cost of using adjuvant bisphosphonates per 100 patients treated (bisphosphonate *minus* placebo)	£ 900,000	£ 1,800,000

Which adjuvant bisphosphonate prevention option would you prefer for patients presenting with primary operable breast cancer (Stage I to Stage III)?	Prefer Prevention A	Prefer Prevention B

CHOICE 8

Trial Design Characteristics	Bisphosphonate Prevention A	Bisphosphonate Prevention B
Primary endpoint	Patients without metastatic bone disease	Patients without metastatic bone disease
Difference in % of patients achieving primary endpoint at the end of the trial (bisphosphonate *minus* placebo)	25% [NNT = 4]	40% [NNT = 2.5]
95% confidence interval on the primary endpoint	0.25% to 49.75% [NNT = 2.01 to 400.00]	30.00% to 50.00% [NNT = 2.00 to 3.33]
Duration of observation	4 years	10 years
Disease stage at diagnosis for patients enrolled in the trial	Stage III only	Stage III only
Additional cost of using adjuvant bisphosphonates per 100 patients treated (bisphosphonate *minus* placebo)	£ 1,800,000	£ 0

Which adjuvant bisphosphonate prevention option would you prefer for patients presenting with primary operable breast cancer (Stage I to Stage III)?	Prefer Prevention A	Prefer Prevention B

CHOICE 9

Trial Design Characteristics	Bisphosphonate Prevention A	Bisphosphonate Prevention B
Primary endpoint	Patients without metastatic bone disease	Patients without metastatic bone disease
Difference in % of patients achieving primary endpoint at the end of the trial (bisphosphonate *minus* placebo)	40% [NNT = 2.5]	25% [NNT = 4]
95% confidence interval on the primary endpoint	10.00% to 70.00% [NNT = 1.43 to 10.00]	0.25% to 49.75% [NNT = 2.01 to 400.00]
Duration of observation	4 years	4 years
Disease stage at diagnosis for patients enrolled in the trial	Stages I, II and III	Stage III only
Additional cost of using adjuvant bisphosphonates per 100 patients treated (bisphosphonate *minus* placebo)	£ 900,000	£ 1,800,000

Which adjuvant bisphosphonate prevention option would you prefer for patients presenting with primary operable breast cancer (Stage I to Stage III)?	Prefer Prevention A	Prefer Prevention B

CHOICE 10

Trial Design Characteristics	Bisphosphonate Prevention A	Bisphosphonate Prevention B
	Patients alive without disease recurrence	Patients alive without disease recurrence
Difference in % of patients achieving primary endpoint at the end of the trial (bisphosphonate *minus* placebo)	40% [NNT = 2.5]	40% [NNT = 2.5]
95% confidence interval on the primary endpoint	39.60% to 40.40% [NNT = 2.48 to 2.53]	0.40% to 79.60% [NNT = 1.26 to 250.00]
Duration of observation	2 years	8 years
Disease stage at diagnosis for patients enrolled in the trial	Stages I, II and III	Stage III only
Additional cost of using adjuvant bisphosphonates per 100 patients treated (bisphosphonate *minus* placebo)	£ 1,800,000	£ 450,000

Which adjuvant bisphosphonate prevention option would you prefer for patients presenting with primary operable breast cancer (Stage I to Stage III)?	Prefer Prevention A	Prefer Prevention B

CHOICE 11

Trial Design Characteristics	Bisphosphonate Prevention A	Bisphosphonate Prevention B
Primary endpoint	Patients without metastatic bone disease	Patients alive without disease recurrence
Difference in % of patients achieving primary endpoint at the end of the trial (bisphosphonate *minus* placebo)	40% [NNT = 2.5]	10% [NNT = 10]
95% confidence interval on the primary endpoint	30.00% to 50.00% [NNT = 2.00 to 3.33]	7.50% to 12.50% [NNT = 8.00 to 13.33]
Duration of observation	10 years	4 years
Disease stage at diagnosis for patients enrolled in the trial	Stage III only	Stages I, II and III
Additional cost of using adjuvant bisphosphonates per 100 patients treated (bisphosphonate *minus* placebo)	£ 0	£ 450,000

Which adjuvant bisphosphonate prevention option would you prefer for patients presenting with primary operable breast cancer (Stage I to Stage III)?	Prefer Prevention A	Prefer Prevention B

CHOICE 12

Trial Design Characteristics	Bisphosphonate Prevention A	Bisphosphonate Prevention B
Primary endpoint	Patients alive without disease recurrence	Patients alive without disease recurrence
Difference in % of patients achieving primary endpoint at the end of the trial (bisphosphonate *minus* placebo)	40% [NNT = 2.5]	40% [NNT = 2.5]
95% confidence interval on the primary endpoint	0.40% to 79.60% [NNT = 1.26 to 250.00]	39.60% to 40.40% [NNT = 2.48 to 2.53]
Duration of observation	8 years	2 years
Disease stage at diagnosis for patients enrolled in the trial	Stage III only	Stages I, II and III
Additional cost of using adjuvant bisphosphonates per 100 patients treated (bisphosphonate *minus* placebo)	£ 450,000	£ 1,800,000

Which adjuvant bisphosphonate prevention option would you prefer for patients presenting with primary operable breast cancer (Stage I to Stage III)?	Prefer Prevention A	Prefer Prevention B

CHOICE 13

Trial Design Characteristics	Bisphosphonate Prevention A	Bisphosphonate Prevention B
Primary endpoint	Patients without metastatic bone disease	Patients without metastatic bone disease
Difference in % of patients achieving primary endpoint at the end of the trial (bisphosphonate *minus* placebo)	1% [NNT = 100]	25% [NNT = 4]
95% confidence interval on the primary endpoint	0.25% to 1.75% [NNT = 57.14 to 400.00]	24.75% to 25.25% [NNT = 3.96 to 4.04]
Duration of observation	2 years	10 years
Disease stage at diagnosis for patients enrolled in the trial	Stage III only	Stages I, II and III
Additional cost of using adjuvant bisphosphonates per 100 patients treated (bisphosphonate *minus* placebo)	£ 450,000	£ 450,000

Which adjuvant bisphosphonate prevention option would you prefer for patients presenting with primary operable breast cancer (Stage I to Stage III)?	Prefer Prevention A	Prefer Prevention B

CHOICE 14

Trial Design Characteristics	Bisphosphonate Prevention A	Bisphosphonate Prevention B
Primary endpoint	Patients alive without disease recurrence	Patients without metastatic bone disease
Difference in % of patients achieving primary endpoint at the end of the trial (bisphosphonate *minus* placebo)	1% [NNT = 100]	1% [NNT = 100]
95% confidence interval on the primary endpoint	0.99% to 1.01% [NNT = 99.01 to 101.01]	0.25% to 1.75% [NNT = 57.14 to 400.00]
Duration of observation	4 years	2 years
Disease stage at diagnosis for patients enrolled in the trial	Stage III only	Stage III only
Additional cost of using adjuvant bisphosphonates per 100 patients treated (bisphosphonate *minus* placebo)	£ 0	£ 450,000

Which adjuvant bisphosphonate prevention option would you prefer for patients presenting with primary operable breast cancer (Stage I to Stage III)?	Prefer Prevention A	Prefer Prevention B

CHOICE 15

Trial Design Characteristics	Bisphosphonate Prevention A	Bisphosphonate Prevention B
Primary endpoint	Patients without metastatic bone disease	Patients without metastatic bone disease
Difference in % of patients achieving primary endpoint at the end of the trial (bisphosphonate *minus* placebo)	1% [NNT = 100]	10% [NNT = 10]
95% confidence interval on the primary endpoint	0.75% to 1.25% [NNT = 80.00 to 133.33]	0.10% to 19.90% [NNT = 5.03 to 1000.00]
Duration of observation	8 years	2 years
Disease stage at diagnosis for patients enrolled in the trial	Stages I, II and III	Stages I, II and III
Additional cost of using adjuvant bisphosphonates per 100 patients treated (bisphosphonate *minus* placebo)	£ 1,800,000	£ 0

Which adjuvant bisphosphonate prevention option would you prefer for patients presenting with primary operable breast cancer (Stage I to Stage III)?	Prefer Prevention A	Prefer Prevention B

CHOICE 16

Trial Design Characteristics	Bisphosphonate Prevention A	Bisphosphonate Prevention B
Primary endpoint	Patients alive without disease recurrence	Patients without metastatic bone disease
Difference in % of patients achieving primary endpoint at the end of the trial (bisphosphonate *minus* placebo)	1% [NNT = 100]	10% [NNT = 10]
95% confidence interval on the primary endpoint	0.01% to 1.99% [NNT = 50.25 to 10000.00]	9.90% to 10.10% [NNT = 9.90 to 10.10]
Duration of observation	10 years	8 years
Disease stage at diagnosis for patients enrolled in the trial	Stages I, II and III	Stage III only
Additional cost of using adjuvant bisphosphonates per 100 patients treated (bisphosphonate *minus* placebo)	£ 900,000	£ 900,000

Which adjuvant bisphosphonate prevention option would you prefer for patients presenting with primary operable breast cancer (Stage I to Stage III)?	Prefer Prevention A	Prefer Prevention B

PART B

1. What is your area of specialisation (please tick one of the following):

Medical Oncologist	☐	Radiologist	☐
Surgical Oncologist	☐	Radiotherapist	☐
General Practitioner	☐	Pharmacist	☐
Other	☐	Please specify:…….	

2. Approximately how many **new cases** of breast cancer do you see each year? ☐☐☐

3. Of the **new cases** of breast cancer that you see each year, approximately what percentage have the following stages of disease at diagnosis:

Per cent of new cases with **Stage I** disease at diagnosis = ☐☐☐%

Per cent of new cases with **Stage II** disease at diagnosis = ☐☐☐%

Per cent of new cases with **Stage III** disease at diagnosis = ☐☐☐%

Per cent of new cases with **Stage IV** disease at diagnosis = ☐☐☐%

Please check that the total adds to 100% **=** ☐☐☐%

4. In deciding whether to start using adjuvant bisphosphonates in patients with primary operable breast cancer, please indicate with a ✓ the degree of influence that you think each of the following specialties would have on the decision:

Specialty	High degree of influence	Some influence	No influence
Radiologist			
Medical Oncologist			
Radiotherapist			
Surgical Oncologist			
Pharmacist			
General Practitioner			

5. Are there any important decision-makers or influences missing from the list provided in Question 4 ? (please tick Yes or No) :

   Yes ☐

   No ☐

   If Yes, please specify: …….
   ……..
   ……..
   ……..
   ……..

6. When considering the evidence from a clinical trial relating to the use of adjuvant bisphosphonates in patients with primary operable breast cancer, please indicate with a ✓ the importance to you of the following trial design characteristics:

Trial characteristic	**Very important**	**Quite important**	**Of little importance**	**Not important**
Primary endpoint				
Comparator				
Study population				
Duration of follow-up				
Size of effect demonstrated				
Statistical significance of results				
Organisation sponsoring the trial				
Countries in which the trial is conducted				
Lead investigators				

7. If you were designing a clinical trial to inform you whether to use adjuvant bisphosphonates in patients with primary operable breast cancer, please rank the following endpoints in order of importance from 1 (the most important endpoint to you) to 8 (the least important endpoint to you):

Side effects	☐
% patients alive without disease recurrence	☐
Quality of life experienced by patients	☐
% patients alive	☐
Cost of patient management with bisphosphonates	☐
% patients without metastatic bone disease	☐
% patients without non-skeletal metastases	☐
% patients not experiencing skeletal morbidity	☐

8. Are there any important endpoints missing from the list provided in Question 7 ? (please tick Yes or No) :

   Yes ☐

   No ☐

   If Yes, please specify: …….
   ……..
   ……..
   ……..
   ……..

9. Do you have any responsibility for managing budgets related to the treatment of patients with breast cancer? (please tick Yes or No):

   Yes ☐

   No ☐

   If Yes, please provide a brief description of your responsibilities:
   ……..……
   ……..
   ……..
   ……..…
   ……..

10. Did you find this questionnaire:

Very difficult to complete	☐
Moderately difficult to complete	☐
Slightly difficult to complete	☐
Not difficult to complete	☐

11. Please provide any comments you would like to make about this questionnaire below:

……
……
……
……
……
……
……
……
……

12. How long has it taken you to complete this questionnaire? ☐☐☐ minutes

Please check that you have answered all the questions and then return this questionnaire in the envelope provided.

Thank you for completing this questionnaire.

Appendix 3

Results of the Non-choice components of the Stated Preference Survey: Questionnaire Part B

Table A3.1

Question 1: What is your area of specialisation?

Specialty	Title					
	Professor	Consultant	Senior Registrar	Registrar	Other	Total
Medical oncologist	1	5	3	3	2	14
Surgical oncologist	1	15	0	1	0	17
Clinical oncologist	0	11	0	4	1	16
Other	0	4	0	0	3	7
Total	2	35	3	8	6	54

Table A3.2

Question 2: Approximately how many new cases of breast cancer do you see each year?

Specialty	Summary of new cases		
	Mean	Standard deviation	Frequency
Medical oncologist	156.86	112.25	14
Surgical oncologist	144.29	65.36	17
Clinical oncologist	224.38	188.82	16
Other	183.57	203.32	7
Total	176.37	142.42	54

Table A3.3

Question 3: Approximately what percentage of new cases have the following stages of disease at diagnosis?

Stage	Observations	Mean	Standard deviation	Min	Max
% Stage I	54	38.24	22.63	0	90
% Stage II	54	30.19	15.42	0	60
% Stage III	54	15.83	11.89	0	50
% Stage IV	54	12.04	14.84	0	80
Stage I	54	69.66	65.54	0	360
Stage II	54	55.04	44.59	0	213
Stage III	54	30.24	50.02	0	340
Stage IV	54	21.43	29.12	0	170

Table A3.4

Question 9: Do you have any responsibility for managing budgets related to the treatment of patients with breast cancer?

Specialty	Budget responsibility?		
	Yes	No	Total
Medical oncologist	5	9	14
Surgical oncologist	5	12	17
Clinical oncologist	4	12	16
Other	0	7	7
Total	14	40	54

Table A3.5

Question 10: How difficult was this questionnaire to complete?

Specialty	Difficulty of questionnaire to complete				
	Very difficult	Moderately difficult	Slightly difficult	Not at all difficult	Total
Medical oncologist	0	4	6	4	14
Surgical oncologist	1	6	9	1	17
Clinical oncologist	0	7	3	6	16
Other	1	5	0	1	7
Total	2	22	18	12	54

Table A3.6

Question 12: How long have you spent on this questionnaire?*

Variable	Observations	Mean	Standard deviation	Min	Max
Reviewing time	54	26.76	13.11	0[1]	60
Interview time	54	11.41	4.56	0[2]	26.32
Total time	54	38.17	13.32	19	80

* Times are in minutes.
1. The minimum of zero was caused by one respondent reporting no preparation prior to interview.
2. The minimum of zero was caused by one respondent mailing responses but not participating in the interview.

Table A3.7

Are you happy to have your personal details disclosed?

Specialty	Disclosure of personal details		
	Yes	No	Total
Medical oncologist	12	2	14
Surgical oncologist	15	2	17
Clinical oncologist	14	2	16
Other	7	0	7
Total	48	6	54

Table A3.8

Would you like to be sent a copy of the results of this survey?

Specialty	Receive copy of the survey?		
	Yes	No	Total
Medical oncologist	9	5	14
Surgical oncologist	17	0	17
Clinical oncologist	15	1	16
Other	7	0	7
Total	48	6	54

Table A3.9

Question 11: Do you have any comments on the questionnaire?

Specialty	Comments on questionnaire?		
	Yes	No	Total
Medical oncologist	5	9	14
Surgical oncologist	13	4	17
Clinical oncologist	8	8	16
Other	4	3	7
Total	30	24	54

Table A3.10

Question 4: Degree of influence of different specialties on the decision to use adjuvant bisphosphonates?

Specialty	Observations	Mean	Standard deviation	Min	Max
Medical oncologist	54	1.15	0.41	1	3
Radiotherapist	54	1.35	0.55	1	3
Surgical oncologist	54	1.80	0.59	1	3
Pharmacist	54	2.57	0.57	1	3
Radiologist	54	2.63	0.56	1	3
GP	54	2.63	0.52	1	3

Table A3.11

Question 5: Are there any important decision makers or influences missing from the list in Question 4?

Specialty	Missing influences?		
	Yes	No	Total
Medical oncologist	7	7	14
Surgical oncologist	11	6	17
Clinical oncologist	11	5	16
Other	7	0	7
Total	36	18	54

Table A3.12

Question 6: Importance to you of the following design characteristics of an adjuvant bisphosphonates trial

Variable	Observations	Mean	Standard deviation	Min	Max
Primary endpoint	54	1.15	0.49	1	4
Statistical significance	54	1.22	0.46	1	3
Effect size	54	1.26	0.44	1	2
Study population	54	1.44	0.57	1	3
Duration	54	1.50	0.50	1	2
Comparator	54	1.57	0.57	1	3
Lead investigator	54	2.57	0.69	1	4
Countries	54	2.59	0.69	1	4
Sponsor	54	2.80	0.68	1	4

Table A3.13

Question 7: Ranking of importance of adjuvant bisphosphonate trial endpoints

Variable	Observations	Mean	Standard deviation	Min	Max
Disease free survival	54	2.43	1.80	1	8
Alive	54	3.78	2.45	1	8
No metastatic bone disease	54	3.91	1.94	1	7
Quality of life	54	4.11	2.09	1	8
Side effects	54	4.63	1.88	1	8
No skeletal morbidity	54	4.98	2.05	1	8
No other metastases	54	5.35	1.82	2	8
Cost	54	6.81	1.59	3	8

Table A3.14

Question 8: Are there any important endpoints missing from the list in Question 7?

Specialty	Missing endpoints?		
	Yes	No	Total
Medical oncologist	1	13	14
Surgical oncologist	1	16	17
Clinical oncologist	4	12	16
Other	1	6	7
Total	7	47	54

Table A3.15

Budget responsibility as articulated by respondents

Respondent	Comment
13	For the surgical side of things but not for the drugs.
14	As lead clinician I have some input into where our significant expenditure should be.
15	I start the treatment and see the patient through to when they die.
16	Not directly but we all have some influence. We have the North Trent Breast Care Group which we all have input in and decisions taken through this.
19	I'm the lead clinician for cancer. Separately responsible for prioritising money for the cancer agenda trust.
20	I'm Director of Surgery with a budget of £15millions. Also I'm the lead Cancer Clinician for the hospital. The hospitals overall budget is £115millions.
27	Indirectly in an advisory capacity re drugs and radiation therapy.
31	I sit on the Network Committee and we make decisions about where the money will go.
35	I was Head of Department and made some decisions regarding drugs to be used. Otherwise decisions are joint with other consultants.
36	I'm Clinical Director of Royal Free University College. I Chair the Breast Tumour Board for North London Network.
40	Answered no but made the comment: "Only priority setting at consultant meetings."
42	I sit on the Joint Hospital Board. Decide which drugs we will use.
43	Formulary sub-committee. Chairman of Cancer Network Systems, Network Therapeutics Group: dealing with all new cancer drugs.
44	Answered no but made the comment: "but on consultants' committee."
46	Answered no but made the comment: "but we have to prescribe responsibly within evidence based guidelines."
50	I'm involved in the Hospital Pharmacy Committee and the High Cost Drug Committee.

Table A3.16

Comments on the questionnaire as articulated by respondents

Respondent	Comment
1	Interesting.
3	Only that I'm curious to see what endpoint. For me it's been a useful introduction to conjoint analysis from a learning point of view.
4	Certain of them not comparing like with like.
5	Didn't ask how often the patient needed treatment or the type i.e. whether it was tablet or iv. If iv then how often. The interval between treatments by this method is very important to the patient.
9	I found it more difficult to do Showcard 1 because there was no information on the number of patients in the trials.
10	The questionnaire could have been clearer in certain aspects. Each showcard has too much information in order to come up with a choice.
11	I was interested in some of the things being compared in that they don't seem really comparable.
13	It's a concept I hadn't actually appreciated.
16	First lot of questions not that easy: too much information to take in-surgeons are a bit thick! However, it was good – I think it's very important trying to get across what's important in clinical trials.
17	You seem to have covered everything.
19	No – it was quite interesting. I'm interested in bisphosphonates.
21	I found it a bit difficult with some of the choices reconciling them in my mind.
23	No but 10 minutes is unrealistic.
24	There were two problems for me: 1) We were asked to decide prevention strategy for all stages yet a lot of the data was only for Stage 3. 2) I wouldn't make a decision on a single set of data given like this. It was a very false way of looking at scientific data and I was very unhappy with it. I would be very happy for him to contact me to discuss this further.
27	The analysis of the data – it's the first time I've come across this type of vehicle at Showcard 1. I found it quite a useful exercise.
28	Only that on Showcard 2 we don't use this terminology (Stage I etc) – it's American but it didn't bother me unduly.
30	1. There is one important factor in the decision to use bisphosphonates which is not featured anywhere: the need for the staffing and infrastructure to give the treatments, especially if it is being done intravenously. 2. The way Showcard 1 was devised, I feel sure I have contradicted myself at times.
31	Some of the options in Showcards 1-16 don't look very feasible. Some of the scenarios are a bit difficult to understand how a trial can be designed this way. I can't get my head round why they've been written this way.

	Willing to participate in the next phase.

Table A3.16 (continued)

Respondent	Comment
32	I was intrigued by the format. I understand the research was about conjoint analysis but it seemed to be about the use of bisphosphonates which is a pretty controversial subject at the moment.
35	I didn't know what conjoint analysis was-I looked it up on the web. I found assigning values to the different characteristics listed was difficult.
36	Quite an interesting one.
37	I thought it was very well designed.
38	Some of the cost differences are very large-some had zero! It was fully comprehensive but the issue of patients alive without disease recurrence and patients without metastatic bone disease made it difficult to way up when you've got different endpoints.
40	I just found it difficult on the 1-16 choices, to make sure I'd noted the differences on each one. It was the number of choices.
41	It's a lot of fun. Quite challenging. Half the choice questions were very easy and half I didn't feel either option was acceptable but came down on one for the purpose of this exercise. 1) You know what % of stage III patients will be alive at a particular time point and that will naturally affect the way you look at it but you're told not to have any other information. 2) How desirable is the outcome? How likely is the outcome? Do you think your intervention is going to count on the outcome?
42	I've not done anything like this before. I found it very interesting.
44	It is not easy really. I have to think about the formulation of the questions and I can't come up with any bright ideas.
45	It took longer than 20 minutes. I was told it would take 10 minutes.
46	Good questionnaire. Have done this before.
50	Respondent wished to point out that 90% of breast cancer patients are treated by clinical oncologists and if they are called radiotherapists it could upset a lot of people. The situation is politically very sensitive. The economic analysis needs to be good.

Table A3.17

Missing decision makers or influences as articulated by respondents

Respondent	Comment
1	Pathologists.
2	Nurse specialist and the patient.
3	Nurse specialists or research nurses.
5	Patient.
6	Medical endocrinologist.
7	1. Clinical nurse specialists. 2. Pathologists.
8	Pathologist.

9	Breast nurse.
10	Breast care nurses.
11	Clinical nurse specialist – has some influence.

Table A3.17 (continued)

13	Breast care nurse.
17	Trust manager.
19	The respondent had originally indicated NICE but then deleted and changed the answer to no important decision-makers missing.
20	Palliative care people.
21	Orthopaedic surgeon.
23	Breast reconstruction surgeon.
24	Policy makers = managers.
25	Patient and relatives.
26	Breast care nurse.
27	The patient.
31	Pathologist.
34	1. Palliative medicine consultant. 2. Hospice consultant.
36	1. Patient support groups (some influence). 2. NICE (high degree of influence).
38	1. Plastic surgeon. 2. Palliative care consultants. 3. Breast care nurses/MacMillan nurses.
39	1. Breast care nurse. 2. Palliative care team i.e. MacMillan nurse. 3. Orthopaedic surgeon.
40	Patients.
41	1. The patient. 2. The media. 3. Specialist nurse.
42	Breast care sister.
43	NICE.
44	Breast care nurses.
46	Primary care Trusts as they have to fund increased costs.
47	The patient.
48	1. The patient. 2. The patient's relatives. 3. The breast care nurses.
49	1. Clinical chemist. 2. Rheumatologist
50	Answered no but made the comment: "You need to reframe radiotherapist as a clinical oncologist."

Table A3.18

Missing endpoints as articulated by respondents

Respondent	Comment
8	1.Serum calcium levels. 2.Number of pathological bone fractures.
31	1. Quality adjusted life-years 2. Cost per QALY
41	1. % of patients with spinal cord compression – this can go undetected. 2. Nothing about disability or time spent in hospital.
48	1. Health economics assessment. 2. Bone density assessment.
49	Cost of patient management without bisphosphonates.
50	1. Some management can reduce costs. 2. Endpoint 5 (cost): "Is this overall management cost? It's unclear."

Appendix 4

Technical Appendix

The purpose of this Technical Appendix is to set out the assumptions, equations and sources of data used for the illustrative analyses and results reported in section 7, "Using discrete choice model results in RCT design". Example calculations are provided. Although the examples draw on published data pertaining to a recently reported bisphosphonate trial[74], the calculations are illustrative and do not purport to solve an optimisation problem in this context.

1. Interpolation of effectiveness outcomes

In order to perform the illustrative calculations presented in this paper, effectiveness and uncertainty outcomes were interpolated, for three time points, from the survival curves reported in Powles et al (2002).[74] These are presented in Table A4.1 below.

Table A4.1

	Clodronate[1]	Placebo[1]	Difference[2]	Lower 95% CI[3]	Upper 95% CI[3]	Prior[4]
% Patients without metastatic bone disease						
Year 2	96.20	93.30	2.90	0.23	5.57	1-6
Year 5	89.00	84.50	4.50	0.45	8.55	1-9
Year 8	83.00	80.00	3.00	-1.65	7.65	1-8
% Patients alive[5]						
Year 2	92.70	92.40	0.30	-2.85	3.45	1-4
Year 5	82.90	79.30	3.60	-1.09	8.29	1-8
Year 8	78.00	72.00	6.00	0.82	11.18	1-11

4. Data points were interpolated from the survival curves reported in Powles et al (2002).[74]
5. Clodronate % minus placebo %.
6. Confidence intervals for the differences in % effectiveness were calculated using the formula provided by Armitage & Berry (1995) pp 128-130.[87]
7. The prior expectations for each outcome were assumed to be given by a uniform distribution in the range 1% to the upper limit of the 95% confidence interval (rounded up or down to the nearest whole number). Therefore, in the calculations, each value within the range is assumed to have an equal chance of representing the true difference in effectiveness.
8. Powles et al (2002) did not report disease free survival rates.[74] However, for the illustrative analyses performed in this chapter, the overall survival rates reported were used as if they were the disease free survival rates.

2. Choice of baseline design

It is important to note that the values of the predicted probabilities calculated for different trial designs depend upon the baseline values against which a new design is compared. Thus, such calculations require a 'baseline design' to be chosen. The calculations used to generate the results presented in Table 8 and Figures 2 to 4 are based on the following baseline design:

Table A4.2

Attribute	Baseline product evidence	Justification
Endpoint	Patients without metastatic bone disease	The primary endpoint in the Powles et al (2002) trial[74]
Effectiveness	2.90%	The statistically significant difference observed in the Powles et al (2002) study at the end of the treatment period (2 years).[74]
Uncertainty	0.23% to 5.57% [0.92]	The confidence interval was computed using the formula provided by Armitage & Berry (1995) pp 128-130[87]
Duration	2 years	The period (medication period) over which the statistically significant difference in the above measure of effectiveness was observed.
Population	Patients with Stages I to III disease at diagnosis	The Powles et al (2002) trial enrolled patients with primary operable breast cancer regardless of the stage of disease at diagnosis.[74]
Cost	£450,000	This level reflects the approximate cost of treating patients with oral clodronate for a 2 year period as allowed for in the Powles et al (2002) trial dosing regimen.[74]

This is the baseline design presented in column (1) Table 8. It is important to note that, despite being based on the Powles et al (2002) trial, the choice of this baseline is purely illustrative.

3. Example calculation of predicted probabilities of product adoption presented in Section 7.1, Table 8 and Figure 2

Consider the comparison between the baseline design and "New product RCT Design 7" shown respectively in columns (1) and (8) of Table 8. By substituting the regression coefficients from the full sample model (Table 7) and the *differences* in the values of the two RCT design attributes into Equation (8) we derive:

$$\Delta V_{AB} = \begin{bmatrix} (0.2787*1)+(0.0457*37.10)+(-0.6210*-0.91)+ \\ (0.0255*8)+(0.2419*0)+(-5.43e-07*-450000) \end{bmatrix} = 2.9876 \ .$$

Substituting the above utility value into Equation (7) gives the predicted probability of preferring RCT Design 7 (A) to the baseline design (B):

$$\Pr(A \mid \mathrm{J}) = \Phi(\Delta V_{AB}) = \Phi(2.9876) = 0.9986 \text{, and}$$

$$\Pr(B \mid \mathrm{J}) = 1 - \Phi(\Delta V_{AB}) = 1 - 0.9986 = 0.0014 .$$

All the results presented in Table 8 and Figure 2 were calculated in this way.

4. Example calculation of expected predicted probabilities of product adoption presented in Section 7.2, Figure 3

For the illustrative calculations used to produce Figure 3, it is assumed that trial sponsors would only consider studies of 2, 5 or 8 years duration and that they would only accept a study population which included subjects with all stages of primary operable breast cancer at diagnosis. It is further assumed that the new bisphosphonate treatment would be priced at parity with the existing treatment (equivalent to £450,000 per 100 patients treated) and that a total sample size above 5000 subjects would not be contemplated. These assumptions are made in order to limit the computational effort involved.

As an example calculation, consider the comparison between a design which differs from the above baseline only in terms of the period of follow-up (5 years instead of 2

years). The calculations are illustrated for a hypothetical trial which enrols a total of 1500 subjects (750 per arm). The calculation involves the following steps:

4.1. Calculation of expected effectiveness

For each sample size, *n*, we first need to calculate the *expected* values for the effectiveness attribute. Utilising an approach previously described by Backhouse (1998)[77] and Detsky (1985,1990)[78;78;79], the expected effectiveness, $E_n(\Delta X)$ likely to be demonstrated by a trial of sample size *n*, is given by the following formula:

$$E_n(\Delta X) = \sum_{\Delta X=-\infty}^{\infty} \Pr\left(D_n^{\phi} = \Delta X \middle| \Delta X\right).\Pr(\Delta X).\Delta X$$

where $\Pr\left(D_n^{\phi} = \Delta X \middle| \Delta X\right)$ is the conditional probability that a difference of ΔX will be established in a trial with significance level ϕ if that difference is in fact there (the power of a trial), and where $\Pr(\Delta X)$ is the prior probability of a true difference of ΔX.

For this illustrative calculation, $E_{n=1500}(\Delta X)$ =

(0.0781 * 0.1111 * (85.5%-84.5%) +
(0.1948 * 0.1111 * (86.5%-84.5%) +
(0.3874 * 0.1111 * (87.5%-84.5%) +
(0.6207 * 0.1111 * (88.5%-84.5%) +
(0.8216 * 0.1111 * (89.5%-84.5%) +
(0.9406 * 0.1111 * (90.5%-84.5%) +
(0.9869 * 0.1111 * (91.5%-84.5%) +
(0.9982 * 0.1111 * (92.5%-84.5%) +
(0.9999 * 0.1111 * (93.5%-84.5%) = **4.1953%**.

In the above calculation, the first number in each row is the power of the trial which is calculated using the formula described in Machin et al (1997) p19.[88] A two tailed test with significance level ϕ = 5% was assumed for all calculations. The second number in each row is the prior probability of the difference in effectiveness shown as the last number in each row. Thus, from Table A4.1, the assumed prior expectation of

difference in effectiveness is 1% to 9% with each value in that range assumed to have an equal prior probability: 1/9 = 0.1111.

4.2. Calculation of expected uncertainty

To calculate the expected uncertainty, 95% confidence intervals for the expected effectiveness outcome were computed using the formula provided by Armitage & Berry (1995) pp 128-130 referred to in the footnote to Table A4.2 above.[87] Based on this formula, the expected 95% confidence interval is: 0.7537% to 7.6369% (4.1953% ± 3.4416%). The expected uncertainty attribute value for this particular trial is therefore given by:

$$E_{1500} = \left[\left(7.6369 - 0.7537\right) / 4.1953\right] / 2 = 0.8203 .$$

This is the uncertainty value which enters the calculation below.

4.3. Calculation of expected predicted probability

By substituting the regression coefficients from the full sample model and the differences in the values of the two RCT design attributes into Equation (8) we derive:

$$E_{1500}\left(\Delta V_{AB}\right) = \begin{bmatrix} \left(0.2787 * 0\right) + \left(0.0457 * 1.2953\right) + \left(-0.6210 * -0.0997\right) + \\ \left(0.0255 * 3\right) + \left(0.2419 * 0\right) + \left(-5.43e-07 * -0\right) \end{bmatrix} = 0.1976$$

Substituting the above utility value into Equation (7) gives the *expected* predicted probability of preferring the RCT design as described above (A) to the baseline design (B):

$$E_{1500}\ \Pr\left(A \mid \mathrm{J}\right) = \Phi\left(E_{1500}\left(\Delta V_{AB}\right)\right) = \Phi\left(0.1976\right) = 0.5783 .$$

This value was used to plot, in Figure 3, the expected predicted probability for a trial of 5 years duration with total sample size of 1500 and the percentage of patients

without metastatic bone disease as the primary endpoint. Similar calculations were repeated across a large range of sample sizes and designs to produce Figure 3.

5. Example calculation of expected net present values presented in Section 7.3, Figure 4

Backhouse (1998) has shown how the net present value (NPV) for a trial can be calculated and used to determine optimal (NPV maximising) designs.[77] This is the approach adopted here. The example below builds on the example presented above.

5.1 Calculation of cost

In order to estimate the discounted cost of performing the trials PTC_n, the following simple cost function was assumed:

$$PTC_n = \sum_{t=0}^{H} \frac{F_t + V_t.n_t + FU_t.n_t}{(1+r)^t}$$

where F_t denotes the fixed cost of performing the trial, V_t denotes the variable cost per subject enrolled, FU_t denotes the follow-up cost per patient per year, n_t denotes the total trial sample size and *t* denotes the year in which the costs are incurred. In all calculations, the following assumptions are made:

F_t = £1,000,000, incurred in the first year (t = 0)

V_t = £3,000, incurred in the first year (t = 0)

FU_t = £1,000 incurred for each year of follow-up (t = 1 to 5)

H = 15 years, the time horizon for the NPV calculations

r = 0.15, the discount rate.

Based on the above assumptions, the cost calculation for the 5 – year trial illustrated in section 4 above is shown below in Table A4.3.

Table A4.3

Year	t	n	F_t	$V_t.n_t$	$FU_t.n_t$	TC_t	PTC_t
1	0	1500	£1,000,000	£4,500,000		£5,500,000	£5,500,000
2	1	1500			£1,500,000	£1,500,000	£1,304,348
3	2	1500			£1,500,000	£1,500,000	£1,134,216
4	3	1500			£1,500,000	£1,500,000	£ 986,274
5	4	1500			£1,500,000	£1,500,000	£ 857,630
6	5	1500			£1,500,000	£1,500,000	£ 745,765
						Total $PTC_{n=1500}$	**£10,528,233**

It should be emphasised that the assumed values used here are purely illustrative. They do not necessarily reflect the actual costs of performing such a trial.

5.2 Calculation of revenue

In order to estimate the discounted revenue associated with performing the trials, the following simple demand function was assumed:

$$E_n \Pr_t(A \mid \mathrm{J}).M_t$$

where M_t denotes the annual number of newly diagnosed cases of breast cancer assumed to be currently treated with the baseline product. The discounted revenue associated with a trial of given design and sample size, PTR_n, is given by:

$$PTR_n = \sum_{t=0}^{H} \frac{E_n \Pr_t(A \mid \mathrm{J}).M_t.P_t}{(1+r)^t}$$

where P_t denotes the cost per year per patient treated and all other variables are as described above.

In all calculations, the following variable values were assumed:

$M_t = 15{,}000$, assumed to be constant for the time horizon of this illustrative calculation and represents the number of patients assumed to be currently treated with the baseline product.

$P_t =$ £2,250 per patient per year for a two year course of treatment (treatment cost = £4,500 per patient).

H = 15 years, the time horizon for the NPV calculations

$r = 0.15$, the discount rate.

Based on the above assumptions, the expected revenue calculations for the 5 – year trial illustrated in section 4 above is shown in Table A4.4 below.

5.3 Calculation of expected NPV

Finally, the expected net present value of a trial of given design and sample size, NPV_n, is given by:

$$NPV_n = PTR_n - PTC_n$$

which in this case equals £68,392,368 - £10,528,233 = £57,864,135. This value was used to plot, in Figure 4, the expected NPV for a trial of 5 years duration with total sample size of 1500 and the percentage of patients without metastatic bone disease as the primary endpoint. Similar calculations were repeated across a large range of sample sizes and designs to produce Figure 4.

Table A4.4

Year	t^2	M_t	$E_n \Pr_t(A \mid \mathrm{J})$	$E_n \Pr_t(A \mid \mathrm{J}).M_t$	Number Treated[1]	TR_t	PTR_t
8	7	15000	0.5783	8675	8675	£19,518,098	£ 7,337,576
9	8	15000	0.5783	8675	17350	£39,036,196	£12,761,002
10	9	15000	0.5783	8675	17350	£39,036,196	£11,096,523
11	10	15000	0.5783	8675	17350	£39,036,196	£ 9,649,151
12	11	15000	0.5783	8675	17350	£39,036,196	£ 8,390,566
13	12	15000	0.5783	8675	17350	£39,036,196	£ 7,296,144
14	13	15000	0.5783	8675	17350	£39,036,196	£ 6,344,473
15	14	15000	0.5783	8675	17350	£39,036,196	£ 5,516,933
						Total $PTR_{n=1500}$	**£68,392,368**

1. Each patient is assumed to receive treatment for 2 years at an annual cost of £2,250.
2. Year 8 (t = 7) is assumed to be spent acquiring marketing authorisation hence no revenue is received.