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Title[1]

Incorporating Psychological Predictors of Treatment Response into Health Economic Simulation Models: A Case Study in Type 1 Diabetes

Running head: Incorporating psychology in health economic models

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Abstract

Background

Health economic modelling has paid limited attention to the effects that patients' psychological characteristics have on the effectiveness of treatments. This case study tests:

1. the feasibility of incorporating psychological prediction models of treatment response within an economic model of type 1 diabetes
2. the potential value of providing treatment to a subgroup of patients
3. the cost-effectiveness of providing treatment to a subgroup of responders defined using five different algorithms.

Methods

Multiple linear regressions were used to investigate relationships between patients' psychological characteristics and treatment effectiveness. Two psychological prediction models were integrated with a patient-level simulation model of type 1 diabetes. Expected Value of Individualized Care analysis was undertaken. Five different algorithms were used to provide treatment to a subgroup of predicted responders. A cost-effectiveness analysis compared using the algorithms to providing treatment to all patients.

Results

The psychological prediction models had low predictive power for treatment effectiveness. Expected Value of Individualized Care results suggested that targeting education at responders could be of value. The cost-effectiveness analysis suggested, for all five algorithms, that providing structured education to a subgroup of predicted responders would not be cost-effective.

Limitations

The psychological prediction models tested did not have sufficient predictive power to make targeting treatment cost-effective. The psychological prediction models are simple linear models of psychological behaviour. Collection of data on additional covariates could potentially increase statistical power.

Conclusions

By collecting data on psychological variables before an intervention, we can construct predictive models of treatment response to interventions. These predictive models can be incorporated into health economic models to investigate more complex service delivery and reimbursement strategies.

Introduction

Health economic modelling has largely ignored the effect that patients' individual psychological, social and behavioural characteristics can have on the effectiveness of a treatment. In their Expected Value of Individualized Care framework, Basu and Meltzer suggest that failing to base treatment decisions on individual characteristics may lead to poorer outcomes than taking a more individualized approach to clinical decision making (1). They recommend collection of data on heterogeneous parameters that are expected to influence treatment outcomes and incorporation of these into economic analyses to estimate the cost-effectiveness of treatments for individual patients (1). Accounting for individually determined differences in treatment response could broaden the possible treatment options that could be evaluated in economic models. For example subgroups defined by psychological characteristics, for which a treatment should or should not be provided, could be identified. This could lead to improvements in overall outcomes and cost-effectiveness.

Patient psychology and behaviour are central to the management of diabetes, particularly treatment of type 1 diabetes (2). Diabetes patients' individual characteristics have a major impact on their self-care health behaviours, for example insulin injection and blood glucose monitoring, which are demanding and complex (3). These health behaviours in turn affect HbA_{1c}, the key clinical measure of glycaemic control. A reduction in HbA_{1c} of 0.5% has previously been reported as a clinically significant improvement for patients with diabetes (4). Published economic models of diabetes such as the Centre for Outcomes Research (CORE) model (5), the United Kingdom Prospective Diabetes Study (UKPDS) model (6) (a model of type 2 diabetes), the Economic Assessment of Glycemic control and Long-term Effects of diabetes (EAGLE) model (7) and others (8-11) do not currently account for psychological factors that may determine self-care behaviours and hence treatment outcomes. The aims of the current study were to: test the feasibility of incorporating psychological prediction models of treatment response within an economic model of a type 1 diabetes structured education programme, conduct an Expected Value of Individualized Care analysis to examine the

potential value of providing treatment to a subgroup of patients, and to investigate the cost-effectiveness of providing treatment to a subgroup of responders defined using five different treatment allocation algorithms.

Methods

Case Description

The Dose Adjustment for Normal Eating (DAFNE) case study presented here provides a real-world example of heterogeneous treatment outcomes and how they can be incorporated within a health economic individual patient-level simulation model. DAFNE is a 5-day structured education programme with a 6-week booster session, aiming to improve patients' self-care behaviours and glycaemic control for adults with type 1 diabetes. DAFNE promotes flexible, intensive insulin therapy with a focus on adjusting insulin doses to match carbohydrate intake in order to allow greater dietary freedom. In 2002 the DAFNE Study Group published the results of a randomized controlled trial that suggested DAFNE improves (i.e. reduces) HbA_{1c} compared with no structured education (12). More recent evidence shows that patients have heterogeneous response to DAFNE in terms of biomedical outcomes. Some patients experience significant HbA_{1c} reductions, whereas others exhibit no change or fail to maintain the original level of HbA_{1c} benefit over the long term (12) [DAFNE Study Group, personal communication 2006] (13). The published cost-effectiveness analysis of the original DAFNE trial did not account for psychological factors and assumed that treatment response to DAFNE was homogeneous (8). This study found that providing DAFNE treatment to all patients dominated providing DAFNE treatment to no patients (i.e. DAFNE produced more quality adjusted life years (QALYs) at a lower cost) (8). Current clinical practice in the UK, as recommended in National Institute for Health and Care Excellence (NICE) guidance is to provide a structured education programme to all adults who have been diagnosed with type 1 diabetes (14).

The cost-effectiveness model

The Sheffield Type 1 Diabetes Policy Model, hereafter the model, was developed as part of the NIHR DAFNE research programme following a detailed review of existing models, structured conceptual modelling and workshops with UK clinical and evidence experts (15). The model is an individual patient-level simulation model which covers all the major diabetic complications (neuropathy, nephropathy, retinopathy, cardiovascular disease, stroke) and acute events (severe hypoglycaemia and diabetic ketoacidosis (DKA)) experienced by a population with type 1 diabetes (16). More detail on the cost-effectiveness model inputs (risk equations, utilities, and costs) and the model process is reported elsewhere (15). In brief, the model simulates individual patients and their annual progression through increasingly severe health states representing the diabetic complications. Patients remain in the model until death. Costs and utilities are attached to the events and health states in the model and are used to estimate costs and QALYs over a lifetime time horizon. The model takes a UK National Health Service (NHS) perspective, with all costs and QALYs discounted at a rate of 3.5% as recommended by NICE (17).

The model has the capacity to model heterogeneous HbA_{1c} treatment response based on individual characteristics. This contrasts with assuming a homogeneous single average HbA_{1c} change for all patients in a treatment cohort as used in many previously published models (7-9). The model uses a regression equation which predicts expected 12 month HbA_{1c} response conditional on each patient's individual characteristics. A random sample from the regression error term is added to each patient's expected 12 month HbA_{1c} response, giving each patient an individual 12 month HbA_{1c} response. This development to the model reflects observations that some patients may experience a large reduction (improvement) in HbA_{1c} after undertaking the DAFNE course, whereas others may experience only a small reduction or even an increase in HbA_{1c}. Another key component of the model is that it also simulates the occurrence of DKA and severe hypoglycaemic events as a function of whether a patient

has received DAFNE or not and their HbA_{1c}, rather than as a fixed probability or a function of HbA_{1c} only.

In all analyses using the model, the individual 12-month HbA_{1c} effect was assumed to be maintained for 4 years, after which patients return to their baseline HbA_{1c} level (13). Any patients not receiving DAFNE were assumed to have their 12-month HbA_{1c} effect estimated using a linear regression based upon the 6 month follow up of the patients allocated to the control arm in the original DAFNE trial (12). Follow up data from a later time point in the original DAFNE trial was not available, because all patients in the comparator arm of the trial attended the DAFNE course 6 months after randomization.

Data sources

Two key data sources that form part of the NIHR DAFNE research programme were used in the current study: a psychological dataset and a clinical research database. The NIHR research programme included a psychological questionnaire study to investigate psychological predictors of outcomes after DAFNE (18). Ten psychological questionnaires were administered to 262 patients at baseline and at 3-, 6- and 12-months post-DAFNE. Details of the questionnaires are presented in Table 1. The following clinical and demographic data were also collected from the same participants (n=262):

- HbA_{1c} at baseline, 6- and 12-months post-DAFNE;
- Age;
- Sex;
- Ethnicity;
- Diabetes duration;
- Body mass index (BMI);
- Educational status;

- Employment status;
- Marital status.

In addition, the clinical research database collected clinical and demographic data from 1,069 patients at baseline and 456 patients 12 months post-DAFNE. Variables collected in the research database that were not included in the psychological study were: clinical risk factors (smoking status, blood pressure, cholesterol, triglycerides), treatment regimens (insulin type, insulin dose, pump use, other medication use), presence of diabetic complications, diabetes-related healthcare contacts and inpatient episodes, incidence of severe hypoglycaemia, and hypoglycaemia unawareness. The clinical research database was used to inform the cost-effectiveness model but was not used for the psychological prediction modelling.

The modelled patient cohort was constructed by randomly selecting, with replacement, patients from the psychological study sample to create a cohort of 5,000 simulated patients (19). Patient characteristics were augmented with data from the clinical research database and/or imputation where data were missing from the psychological dataset. The baseline patient characteristics of the modelled cohort are presented in Table 2.

Statistical analysis of psychological dataset

Previous research has not reached a consensus on the appropriate conceptual framework for defining the relationships between psychological factors and clinical outcomes in diabetes. Studies report conflicting evidence about which psychological factors are, and are not, influential on glycaemic control (20-26). In the absence of a consensus, the current study assumed that all baseline psychological factors collected in the NIHR questionnaire study were potential predictors of HbA_{1c} change and that the possible effects of the factors were independent of one another, although

interactions were tested. This assumption supported the use of regression techniques, which are the standard statistical approach to predicting an outcome for given inputs (27).

HbA_{1c} change from baseline to 12 months was selected as the measure of treatment response, with lower 12 month HbA_{1c} values representing a more favourable outcome. Two different definitions of HbA_{1c} change were used as dependent variables to produce two psychological prediction models of treatment response:

Model A: 12-month HbA_{1c} level measured on a continuous scale.

Model B: Absolute change in HbA_{1c} from baseline to 12 months on a continuous scale.

Baseline summary scores from each psychological questionnaire in Table 1 and demographic variables were used as potential predictor variables for all analyses. Ordinary least squares regressions were used to investigate both predictors of treatment response. For both analyses each potential predictor variable was first entered into a univariate model to examine its independent relationship with the HbA_{1c} change outcome. Those variables found to be significant univariate predictors of outcome ($p<0.05$) were then combined in a multivariate model, the interactions between these variables were tested, and variables were dropped that did not remain significant at the $p<0.05$ level in the multivariate model. Baseline HbA_{1c} was included as a predictor variable in Model A where 12-month HbA_{1c} was used as the outcome variable. Baseline HbA_{1c} was not included as a predictor variable in Model B where change in HbA_{1c} was used as the outcome variable, as adjusting for baseline values when analysing change scores has been shown to produce spurious results (28;29). Scatterplots of residuals from both linear models were examined for normality and homoscedasticity. IBM SPSS Statistics 19 was used to conduct the statistical analysis.

Expected Value of Individualized Care

To estimate the maximum value of making patient level rather than population level decisions, an Expected Value of Individualized Care (EVIC) analysis was conducted. This analysis can be used to assess whether it is potentially valuable to implement a treatment allocation algorithm, which will assign patients to receive treatment if they are predicted to respond to it. EVIC is calculated by subtracting the average net monetary benefit (NMB) that would have been gained from making a population level decision from the average NMB that could be gained if the treatment decision was made at the patient level (1). In this case, an EVIC analysis calculates the maximum investment that can be made to perfectly individualize the decision to provide DAFNE treatment (30). Therefore, it indicates whether stratification of DAFNE treatment using a treatment allocation algorithm is potentially worthwhile. To calculate EVIC, a cost-effectiveness analysis comparing DAFNE for all patients to DAFNE for no patients was conducted.

There are two methods for calculating the EVIC; it can be calculated with or without cost internalization. The difference between the two methods is that when deciding between treatments at the individual level, the EVIC with cost internalization assigns each patient their cost-effective treatment option. Whereas the EVIC without cost internalisation assigns each patient their health maximizing treatment option (1). In our implementation here, the EVIC with cost internalization has been used throughout as it is consistent with the UK NHS perspective. As there are two psychological prediction models for the 12-month HbA_{1c} effect of DAFNE, two EVIC analyses were conducted.

Cost-effectiveness analyses

Cost-effectiveness analyses compared using five treatment allocation algorithms to providing DAFNE to all patients, which is current practice in the UK (14). The treatment allocation algorithms compared each patient's predicted change in HbA_{1c} to a defined change in HbA_{1c} cut-off value. Patients with a predicted change in HbA_{1c} below the cut-off value were defined as predicted responders; otherwise the patients were defined as predicted non-responders. All treatment allocation algorithms assign the predicted responders to receive DAFNE and predicted non-responders to not receive DAFNE. The five HbA_{1c} cut off values to be used in the treatment allocation algorithms are -0.5%, -0.4%, -0.3%, -0.2% and -0.1%. It is expected that as the reduction in HbA_{1c} needed to define a patient as a responder is reduced, more patients would be predicted to be a responder. These potential new strategies were selected for evaluation because cost savings might be made by not referring patients for DAFNE training if they were unlikely to experience HbA_{1c} benefit.

Sensitivity analyses

500 probabilistic sensitivity analysis (PSA) runs, each with 5,000 patients, was conducted in all analyses. This ensured that parameter uncertainty taken into account in the expected costs and QALYs. Structural uncertainty was explored by testing how sensitive the cost-effectiveness results were to the use of either model A or model B as psychological prediction models of HbA_{1c} response to DAFNE.

Results

Psychological prediction model results

The two psychological prediction models produced differing results as shown in Table 3. Psychological prediction model A suggested that baseline HbA_{1c} and fear of hypoglycaemia were

predictive of 12-month HbA_{1c}. The adjusted R^2 suggested that this model explained 53.4% of the variance in 12-month HbA_{1c}. Patients with higher baseline HbA_{1c} and higher baseline fear of hypoglycaemia were predicted to have higher 12-month HbA_{1c}. This appears in line with expectations because patients afraid of hypoglycaemia may be reluctant to apply the DAFNE principles which aim to reduce HbA_{1c} due to concerns that adjusting their insulin dosage may lead to hypoglycaemia. The model correctly categorized 87.3% of non-responders but only 31.9% of responders.

Psychological prediction model B suggested that BMI, sex, and baseline fear of hypoglycaemia were predictive of change in HbA_{1c} from baseline to 12 months. The fear of hypoglycaemia results corresponded with those of prediction model A. The results also suggested that male patients and patients with higher BMI were more likely to experience an improvement in HbA_{1c}. The adjusted R^2 suggested that this prediction model explained 5.4% of the variance in change in HbA_{1c}. The model correctly categorized 90% of non-responders but only 16.5% of responders.

A comparison of the sensitivity and specificity of each psychological prediction model is presented in Table 4. Both models were better at predicting non-responders than responders. Figure 1 presents a further comparison of the models' predictive power. For each model, the observed change in HbA_{1c} from baseline to 12 months is plotted against the expected change. This figure confirms that both models were better at predicting non-responders than responders.

EVIC results

Figure 2i shows the cost-effectiveness plane for the comparison of DAFNE for all versus DAFNE for none using both prediction models. In this figure, three things are shown. Each PSA run (the 500 mid-grey squares) shows the incremental cost and incremental QALYs for one sample of the parameter values averaged over all 5,000 simulated patients. Likewise each patient (the light grey dots) shows

the incremental cost and incremental QALYs for each patient averaged over all 500 PSA runs. Finally, the mean (the dark triangle) shows the expected incremental costs and incremental QALYs for DAFNE versus no DAFNE averaged over all 5,000 simulated patients and all 500 PSA runs.

The first thing to note that is the position of the mean shows that, for both prediction models the policy of offering DAFNE to all patients compared to the policy of not offering DAFNE to all patients generated on average more QALYs (model A: 0.0898, model B: 0.0519) for lower costs (model A: -£2,358, model B: -£1,578), suggesting that offering DAFNE to all patients dominated offering DAFNE to no patients.

The second key point is that the PSA results suggest that this conclusion is relatively certain. Figure 2ii presents the cost-effectiveness acceptability curve for providing DAFNE to all patients and the expected value of perfect information (EVPI) per patient. At a cost-effectiveness threshold of £20,000 per QALY, DAFNE has a greater than 90% probability of being cost-effective for the whole population (model A: 98.6%, model B: 92.0%). The EVPI per patient was £6.18 and £63.48 for prediction models A and B respectively. This indicates the decision to provide DAFNE to all patients (when compared against DAFNE for none) is likely to be insensitive to plausible parameter variation.

However, it is the third key issue, that of individual level heterogeneity that is the real focus of EVIC analysis. DAFNE was more costly for a minority of patients (model A: 29.1%, model B: 32.1%) and was more effective for a majority of patients (model A: 64.2%, model B: 59.2%). More importantly, based on a cost-effectiveness threshold of £20,000 per QALY, DAFNE is cost-effective for the majority of patients (model A: 72.8%, model B: 67.4%). This can be seen in Figure 2i, in that around 70% of the simulated patients (light grey dot) are to the right of and below the cost-effectiveness threshold line. An EVIC calculation is essentially a though experiment which goes through the following steps:- first, imagine that we had some way of pre-identifying the precise future outcome for each individual, and second, imagine instead of giving the treatment to all people we would give it

to those who would 'benefit' from it (in our analysis that would be those who turn out to be right and below the cost-effectiveness line), then third, what would be the overall resulting costs, QALYs and NMB of such a perfectly accurate individualized care strategy compared with our baseline adoption decision of giving DAFNE to all patients.

When applying this process to our case study, the resulting EVIC per patient was a net monetary benefit of £1,016 and £1,568 for prediction models A and B respectively at a cost-effectiveness threshold of £20,000 per QALY. This is equivalent to a net QALY gain per person of 0.0508 or 0.0708 respectively. In the context of an intervention where the estimated mean QALY difference between a DAFNE for all strategy and a DAFNE for none strategy are 0.0898 (model A) and 0.0519 (model B) it can be seen that these EVIC values can be considered substantial. Figure 2iii presents the individual cost-effectiveness acceptability curve and the EVIC per patient at a range of different threshold values. This supports the testing of treatment allocation algorithms for patients considered eligible to receive DAFNE.

Cost-effectiveness results

The cost-effectiveness analysis suggested that the new policy of using the treatment allocation algorithm would not be cost-effective and indeed would be dominated by current practice of offering DAFNE to all patients. Detailed results from the cost-effectiveness analysis for giving DAFNE only to predicted responders as defined using the HbA_{1c} cut-off value of -0.5% are presented in Table 5. We present the detailed results for this cut-off value, because it has previously been reported as a clinically significant change in HbA_{1c} for diabetes patients (4). For both psychological prediction models the new policy generated fewer QALYs (model A: -0.05, model B: -0.03) for higher costs (model A: +£1,226, model B: +£1,024). The parameter uncertainty is demonstrated by the cost-effectiveness planes presented in Figure 3. The mean effect and the majority of PSA runs lie in the

North-West quadrant of the cost-effectiveness plane for both prediction models. This indicates that DAFNE for all dominates using this treatment allocation algorithm, for this HbA_{1c} cut-off value.

The results of the other HbA1c cut-off values used to define a patient as a responder or non-responder in the treatment allocation algorithm are presented in Table 6. In all but one treatment allocation algorithm, the new policy of using the treatment allocation algorithm was dominated, generating fewer QALYs and higher costs than current practice of DAFNE for all. In the scenario where prediction model B was used with a HbA_{1c} cut-off value of 0.1%, the treatment allocation algorithm was not dominated. Despite generating more QALYs it had substantially higher costs and with an ICER of approximately £71,000 per QALY gained, would still not be considered to be cost-effective against the upper range of the usual maximum acceptable ICER used by NICE of £30,000 per QALY (17). This suggests that, even if the HbA_{1c} response subgroups are defined differently, the allocation of DAFNE to predicted responders on the basis of model A or model B is very unlikely to be cost-effective compared to current practice of giving DAFNE to all.

Discussion

This study used data on psychological variables collected before, during and after an educational intervention for self-management of type 1 diabetes to produce estimates of predicted response in terms of the glucose control measure HbA_{1c} at 12-months follow-up. We found that sex, fear of hypoglycaemia, baseline HbA_{1c} and BMI are predictive of response within two different psychological prediction models. The two prediction models are poor at correctly predicting responders but strong at correctly predicting non-responders. The predictive models have then been used to derive a potential strategy for targeting the educational intervention just at those predicted to achieve response. A cost-effectiveness model has been adapted to analyse this targeted strategy. In this this case study the treatment allocation algorithms for targeting structured education were not cost-effective, as the prediction models did not have sufficient predictive powered to detect patients

who responded to DAFNE. However, in other cases targeting treatment based on patients' psychological characteristics may be cost-effective.

The methods used to produce the psychological prediction models, which are used to predict response to DAFNE, have four important limitations. First, a priori hypotheses were not specified about the relationship between psychological variables and HbA_{1c}. It has been suggested that conducting this type of post-hoc analysis is less likely to offer a reliable explanation of individual differences in treatment response (31;32). Nevertheless the predictive factors found within the study have good face validity and the psychological rationale for each appears plausible. Second, the data that were collected in the psychological study and therefore used in the statistical modelling were based on a conceptual model of the psychology of diabetes self-management proposed by the DAFNE psychology team rather than on a published theory of health behaviour (although the conceptual model was informed by social cognition models and other published evidence e.g.(33-35)). The psychological prediction models tested had moderate predictive power of HbA_{1c} response to DAFNE, and this may have been limited because some of the predictors of DAFNE response were not collected or are not observable. Other variables such as personality factors (25;36) or attitudes towards the DAFNE course (37) could have provided additional predictive power to the regression models. Combining more detailed information from future psychological questionnaire data collected from DAFNE graduates with published qualitative findings (e.g.(38-40)) would allow the psychological prediction models to be refined. A third limitation is the sample size of the psychological study, which may not have been large enough to detect some relationships between the collected psychological variables and HbA_{1c} response outcomes. Finally, the statistical analysis used simple linear regression to explore relationships. More advanced techniques such as latent class modelling or mixture modelling could potentially offer alternative analysis methodologies and may unearth predictive relationships between variables that were not identified by the current study. More advanced statistical modelling techniques could also have allowed the prediction of other outcomes of DAFNE such as change in the risk of severe hypoglycaemia alongside prediction of HbA_{1c} change.

An issue with the psychological prediction models is the somewhat different results produced by both models. Discussion in the psychological literature suggests that covariance adjusted models (i.e. Model A) are generally preferred to change score models (i.e. Model B) although some have claimed otherwise (41). Based on this literature and on the greater predictive power demonstrated by Model A, we would suggest this model is to be preferred to Model B.

If a psychological prediction model is potentially cost-effective, then it is important to account for the cost of eliciting information used to predict treatment benefits or costs (1). A limitation of the current study is that we assumed that predictor variable data is collected at zero cost in the cost-effectiveness analysis. Background variables such as gender and BMI are likely to be routinely collected and therefore easily available. However, questionnaire variables such as fear of hypoglycaemia and thoughts about diabetes seriousness would need additional data collection which is not part of routine care. Normally, the cost of data collection would be estimated using either estimates of staff time and unit costs or a threshold analysis to identify the maximum cost of data collection at which the intervention is cost-effective. However, in the current study, the new intervention was found to be dominated by current practice even under the assumption that the additional data collection is cost free, therefore additional estimates of data collection cost were unnecessary.

Another limitation of the current study is that only patient heterogeneity in treatment response was considered. Patient heterogeneity in other factors, such as baseline risk and treatment costs, was not considered. However, if information was available on these aspects of patient heterogeneity it would be possible to incorporate these factors of patient heterogeneity into health economic models using similar methodologies to those used in the case study to incorporate patient heterogeneity in treatment response.

It is important to acknowledge that ethical issues could be raised, if a patient's psychological characteristics determined whether or not they received treatment. The analyses undertaken in economic analysis only consider the cost and health consequences of providing a treatment. Ethical input should be sought if treatment allocation algorithms, based upon patient's psychological characteristics, were to be adopted based upon the results of an economic model.

The results of this study suggest that a new policy of offering DAFNE only to those patients who are predicted by psychological prediction models to respond would not be cost-effective compared to current practice of offering DAFNE to everyone, because of the poor prediction of responders and the relatively low cost of DAFNE. No recommendations for changes to current practice are therefore indicated.

Further research could investigate collecting data directly, representing patients' behavioural response to an intervention (which may be a more accurate predictor of HbA_{1c} response than the cognitive psychological variables collected here) and incorporating patients' behavioural response into a health economic simulation model. However, as the behaviours promoted by DAFNE are highly complex it would be a challenge to link a prediction model of self-care behaviour to long term outcomes within the model. This task would be considerably eased if there was a strong relationship between the measure of self-care behaviours collected in the psychological questionnaire study (42) and HbA_{1c} change, which was not the case in the current study. A DAFNE-specific measure of self-care behaviours is currently under development and may prove to have a stronger relationship with HbA_{1c} outcomes, in which case further work could explore this method of predicting individual treatment response and incorporate it in cost-effectiveness modelling. Other variables that could provide additional predictive power to prediction models of treatment response could also be collected in future research.

The results of this study demonstrate that improvements can be made to the way we model the cost-effectiveness of interventions in disease areas where patients' psychological and behavioural characteristics are important. As Sculpher (32) posited, "appropriately reflecting subgroups and heterogeneity in decisions has the potential to increase population health gains". Modelling patients' psychological characteristics alongside their clinical characteristics has allowed heterogeneity in response to DAFNE to be reflected and linked back to underlying psychological factors that affect patients' propensity to benefit from the intervention. The implications of this methodology are that policy questions that could not be addressed using purely clinically-driven cost-effectiveness models can now be explored. The method opens up the opportunity to ask 'what types of patients will do well after DAFNE?', 'for what types of patients is DAFNE more cost-effective?', and 'what additional support needs to be provided for the potential non-responders?'. The subgroups here are psychologically rather than clinically defined, and we may be able to improve the clinical- and cost-effectiveness of DAFNE by 'treating' psychological characteristics such as fear of hypoglycaemia prior to patients' attendance at the DAFNE course. Potentially there will be cost and health consequences from 'treating' psychological characteristics. Where there is appropriate data, treating the psychological characteristics should be analysed as a separate treatment option using the methods appropriate to the perspective taken in the analysis.

Based on the experience of conducting this study we have made eleven recommendations for researchers wishing to conduct further research using psychological data to inform cost-effectiveness models. These recommendations are presented in Table 7 and cover data collection strategies, project planning, data analysis methods and suggestions for integrating the results of psychological data analysis with a cost-effectiveness model. Whilst our study and these recommendation focussed on variability of individual response in the context of psychological factors, the recommendations made in Table 7 may still be useful when incorporating psychological data analysis on other aspects of patient heterogeneity, such as heterogeneous baseline risk of events, or heterogeneous costs, into a cost-effectiveness model.

We conclude that none of the 5 treatment allocation algorithms for allocating DANFE to predicted responders appear to be cost-effective compared with DAFNE for all patients. The framework that we have developed to incorporate psychological predictors of treatment response into a cost-effectiveness model can be generalized for use in other case studies where psychological or other predictors of individual response are available. The prior use of EVIC analysis can be useful to identify case studies where, the use of treatment allocation algorithms might be cost-effective. Patients experience heterogeneous responses to healthcare interventions and it is an oversimplification to assume that this heterogeneity is not, at least in part, due to differences in patients' psychological characteristics. Accounting for these differences within a cost-effectiveness model is both feasible and relatively simple if the appropriate data are collected alongside clinical outcomes. We hope that our experience and our recommendations will aid researchers wishing to incorporate psychological predictors of treatment response into their own cost-effectiveness models.

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Questionnaire	Psychological construct measured	Example question	Reference
Personal Models of Diabetes: seriousness subscale	Thoughts (beliefs) about diabetes seriousness	How serious is your diabetes?	(43;44)
Personal Models of Diabetes: treatment effectiveness subscale	Thoughts (beliefs) about diabetes treatment effectiveness	How important is controlling your blood sugar levels for avoiding complications from your diabetes?	(43;44)
Revised Self-Care Inventory	Diabetes self-care behaviours	How often do you check blood glucose with monitor?	(42)
Confidence in Diabetes Scale	Diabetes-specific self-efficacy	How sure are you that you can perform the prescribed number of daily insulin injections?	(45)
Hypoglycaemia Fear Survey: worry subscale	Fear of hypoglycaemia	How often do you worry about no one being around to help you during a hypoglycaemic reaction?	(46)
WHO-5	Overall well being	Over the last 2 weeks how often have you felt cheerful and in good spirits?	(47)
Life Satisfaction	Overall life satisfaction	Thinking about your own life and personal circumstances, how satisfied are you with your life as a whole?	(48)
Social Support Questionnaire:	Level of social support received	Whom can you really count on to distract you from	(49;50)

number of people offering social support		your worries when you feel under stress?	
Social Support Questionnaire: satisfaction with support rating	Satisfaction with social support received	How satisfied are you with the support you receive to distract you from your worries when you feel under stress?	(49;50)
Michigan Knowledge Questionnaire	Diabetes knowledge	What effect does unsweetened fruit juice have on blood glucose?	(51)

Table 1: Questionnaire measures collected in the psychological DAFNE study at baseline, 3-, 6-, and 12-months

Patient characteristic	Value	Source of information
Number of modelled patients	10,000	
Part A: continuous variables	mean (SD)	
Age (years)	40 (14)	Psychological dataset
Diabetes duration (years)	18 (13)	Psychological dataset
Systolic blood pressure (mmHg)	131 (16)	Clinical research database
Low-density lipoprotein (mmol/l)	1.22 (0.75)	Clinical research database
High-density lipoprotein (mmol/l)	1.60 (0.47)	Clinical research database
Triglycerides (mmol/l)	2.45 (0.77)	Clinical research database
BMI	26.10 (4.26)	Psychological dataset
Baseline HbA_{1c}	8.54 (1.52)	Psychological dataset
Baseline fear of hypoglycaemia (46)	30.73 (10.79)	Psychological dataset
Baseline diabetes knowledge (51)	20.16 (2.00)	Psychological dataset
Baseline thoughts about diabetes seriousness (43, 44)	8.97 (2.48)	Psychological dataset
Part B: categorical variables	%	
Gender	50% male, 50% female	Psychological dataset
Smoking status	17% current, 60% former, 23% non	Clinical research database
Ethnicity	100% ‘other’	Assumption
Physical activity level	100% medium physical activity	Assumption
Initial neuropathy status	94% No neuropathy 4% Clinically confirmed neuropathy 2% Diabetic foot syndrome	Clinical research database
Initial retinopathy status	74% No retinopathy 19% Background retinopathy	Clinical research database

	7% Proliferative retinopathy	
Initial myocardial infarction status	99% No history of MI 1% First MI	Clinical research database
Initial stroke status	99% No history of stroke 1% First stroke	Clinical research database
Initial heart failure status	100% No history of HF	Clinical research database

Table 2: Baseline characteristics of the modelled patient cohort

Predictor variable	Coefficient	Standard error	P value
Prediction model A (adjusted R^2 = 0.534)			
12month HbA_{1c} = 1.365 + (0.752*baseline HbA_{1c}) + (0.018*baseline fear of hypoglycaemia)			
Constant	1.365	0.432	0.002
Baseline HbA_{1c}	0.752	0.047	<0.001
Baseline fear of hypoglycaemia	0.018	0.006	0.004
Prediction model B (adjusted R^2 = 0.054)			
ΔHbA_{1c} = 0.652 + (0.014*baseline fear of hypoglycaemia) – (0.043*BMI) – (0.309*Gender)			
Constant	0.652	0.492	0.187
Baseline fear of hypoglycaemia	0.014	0.007	0.045
BMI	-0.043	0.017	0.012
Gender (male = 1, female = 0)	-0.309	0.150	0.041
No DAFNE Prediction Model			
ΔHbA_{1c} = 1.145 + (0.615*No DAFNE)+(0.818* baseline HbA_{1c})			
Constant	1.145	0.897	0.202
No DAFNE (DAFNE=0, No DAFNE =1)	0.615	0.200	0.002
Baseline HbA_{1c}	0.818	0.095	<0.001

Table 3: Psychological prediction model results

Prediction model A: Sensitivity = 0.319 / Specificity = 0.873		
Predicted	Observed	
	Responder	Non-responder
Responder	29 (12.0%)	19 (7.9%)
Non-responder	62 (25.7%)	131 (54.4%)
Prediction model B: Sensitivity = 0.165 / Specificity = 0.900		
Predicted	Observed	
	Responder	Non-responder
Responder	14 (6.2%)	14 (6.2%)
Non-responder	71 (31.6%)	126 (56.0%)

Table 4: Sensitivity and specificity of the two statistical prediction models

	Control: DAFNE for all	Intervention: DAFNE only for predicted responders	Difference (intervention – control)
Prediction Model A			
Total discounted QALYs	14.16	14.11	-0.05
Total discounted costs	£59,805	£61,031	£1,226
ICER			Dominated
Mean percentage of patients receiving DAFNE	100%	22.3%	
Net Monetary Benefit at £20,000 per QALY	£223,405	£221,208	-£2196
Probability that the intervention is cost-effective at £20,000 per QALY	90.2%	9.8%	
Prediction Model B			
Total discounted QALYs	14.12	14.09	-0.03
Total discounted costs	£60,586	£61,627	£1,042
ICER			Dominated
Mean percentage of patients receiving DAFNE	100%	15.8%	
Net Monetary Benefit at £20,000 per QALY	£221,866	£220,259	-£1,607
Probability that the intervention is cost-effective at £20,000 per QALY	84.0%	16.0%	

Table 5: Economic evaluation of DAFNE to be provided only for predicted responders (response defined as 0.5% reduction in HbA_{1c}) versus DAFNE for all

	Control: DAFNE for all	**Intervention: DAFNE only for predicted responders** Definition of a predicted responder			
		Δ HbA_{1c} $\leq$-0.4%	Δ HbA_{1c} $\leq$-0.3%	Δ HbA_{1c} $\leq$-0.2%	Δ HbA_{1c} $\leq$-0.1%
Prediction Model A					
Total discounted QALYs	14.16	14.13	14.13	14.14	14.14
Total discounted costs	£59,805	£60,825	£60,641	£60,465	£60,250
ICER	N/A	Dominated	Dominated	Dominated	Dominated
Mean percentage of patients receiving DAFNE	100%	29.6%	37.6%	46.4%	55.7%
Net Monetary Benefit at £20,000 per QALY	£223,405	£221,689	£221,982	£222,301	£222,629
Prediction Model B					
Total discounted QALYs	14.12	14.10	14.11	14.12	14.12
Total discounted costs	£60,586	£61,358	£61,086	£60,858	£60,749
ICER	N/A	Dominated	Dominated	Dominated	£71,222
Mean percentage of patients receiving DAFNE	100%	25.9%	37.1%	48.7%	60.3%
Net Monetary Benefit at £20,000 per QALY	£221,866	£220,719	£221,146	£221,579	£221,749

Table 6: Economic Evaluation Sensitivity Analyses – using different thresholds for the reduction in HbA_{1c} used to define the predicted responders

	Recommendation
1	If a pre-existing patient-level simulation model exists, conduct an EVIC analysis to explore the potential value in individualising care.
2	If there is potential value in individualising care, seek advice from multi-disciplinary experts working in the disease area including psychology researchers and clinicians
3	Form a priori hypotheses regarding the relationships between psychological variables and treatment effectiveness
4	Base hypotheses and analyses on psychological theories of health behaviour or on published evidence regarding the relationships between psychological variables and treatment effectiveness
5	Plan analysis of psychological data prior to data collection, at the conceptual modelling stage for the new or revized health economic model to ensure all important variables for your analysis are collected
6	Ensure sample size for the collection of psychological data is large enough to detect the hypothesized relationships by conducting sample size calculations
7	Collect psychological data from the same patients for whom the clinical effectiveness data is collected, at the same time points as the clinical effectiveness data
8	Test and validate any prediction models of treatment effectiveness against observed treatment response rates
9	Develop a new or revized economic model to integrate psychological data
10	Undertake health economic analyses of alternative options for stratifying the treatment based upon the prediction models
11	Account for the cost of collecting psychological predictor variables when comparing a potential treatment allocation algorithm to current care

Table 7: Eleven recommendations for collecting and analysing psychological data alongside primary research in order to inform cost-effectiveness models

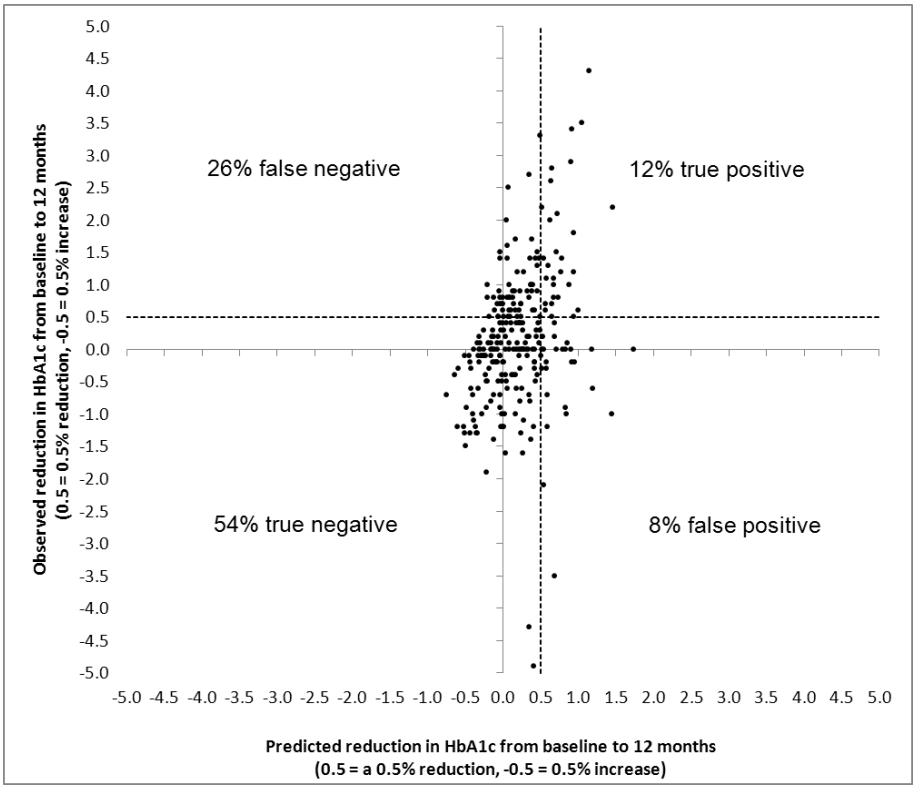
Figure 1: Comparing validity of two prediction models - rates of true positives, true negatives, false positives and true negatives.

Dashed lines represent the threshold for a patient being classed as a responder (i.e. experiencing an HbA_{1c} reduction of 0.5% or more). Percentages refer to the percentage of patients falling into each quadrant as defined by the responder thresholds.

Figure 2: Would individualized care be potentially valuable in principle? - Cost-effectiveness of providing DAFNE for all versus DAFNE for none presented on (i) the cost-effectiveness plane, (ii) CEACs and EVPI plots, (iii) iCEACs and EVIC plots

Figure 3: Would individualized care using currently available prediction models be cost-effective in practice? - The cost-effectiveness of providing DAFNE only to predicted responders, as defined by a predicted fall in HbA_{1c} of 0.5% in the 12 months following DAFNE treatment, versus DAFNE for all presented on the cost-effectiveness plane

1a) Prediction model A



1b) Prediction model B

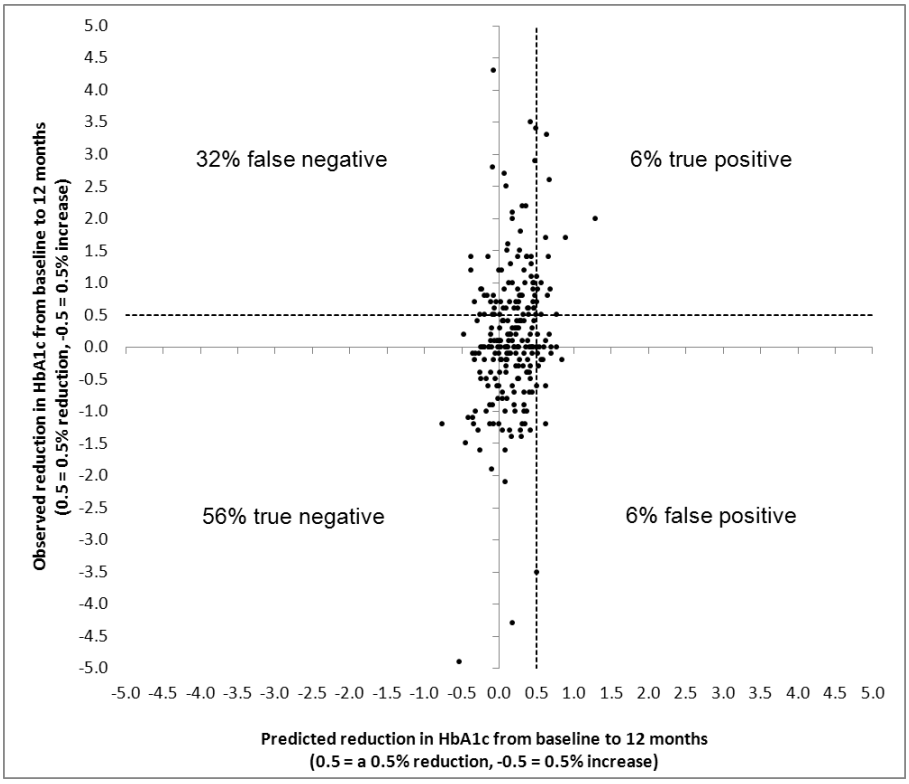
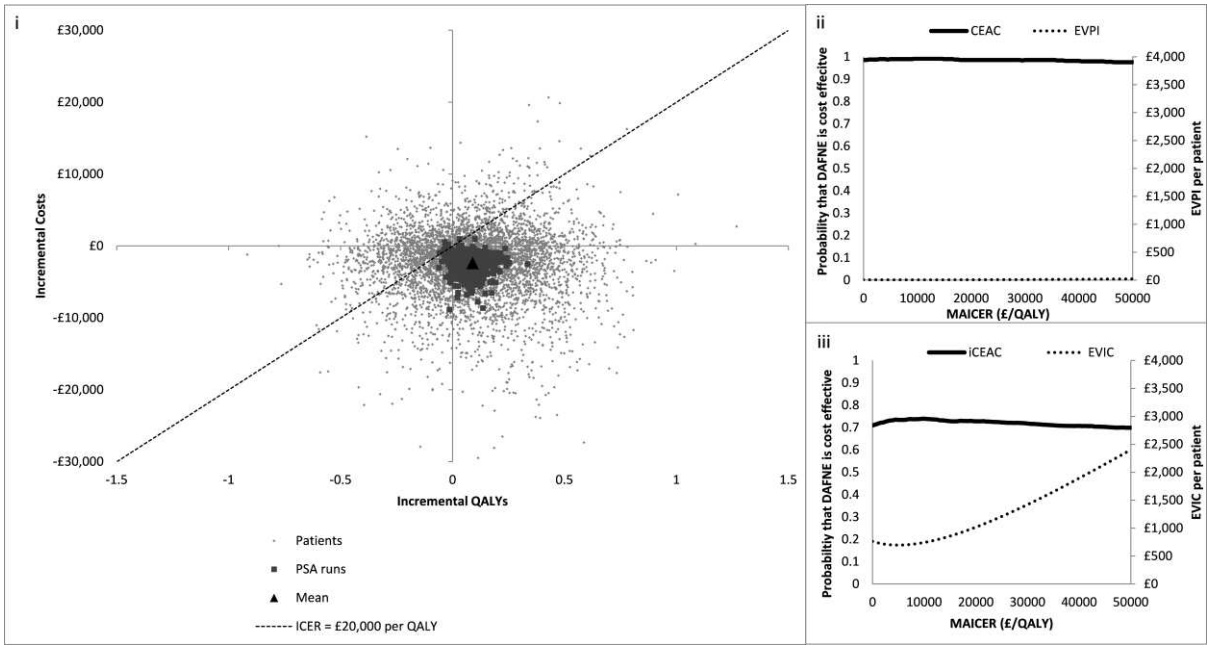


Figure 1

2a) Prediction Model A



2b) Prediction Model B

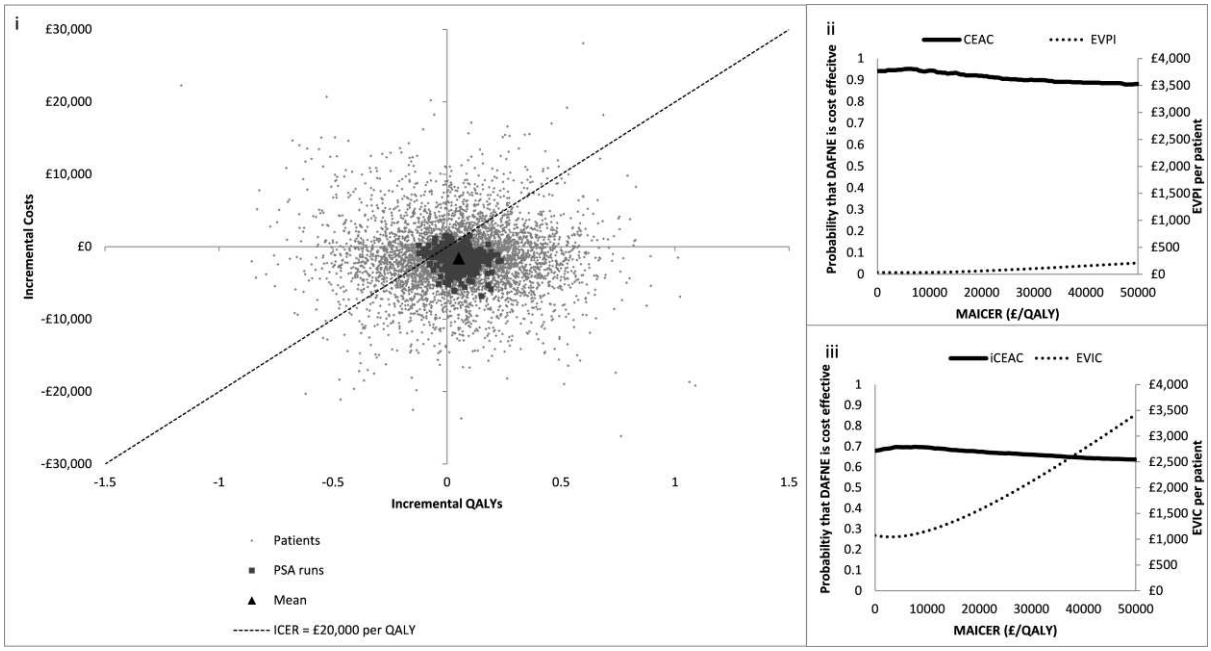
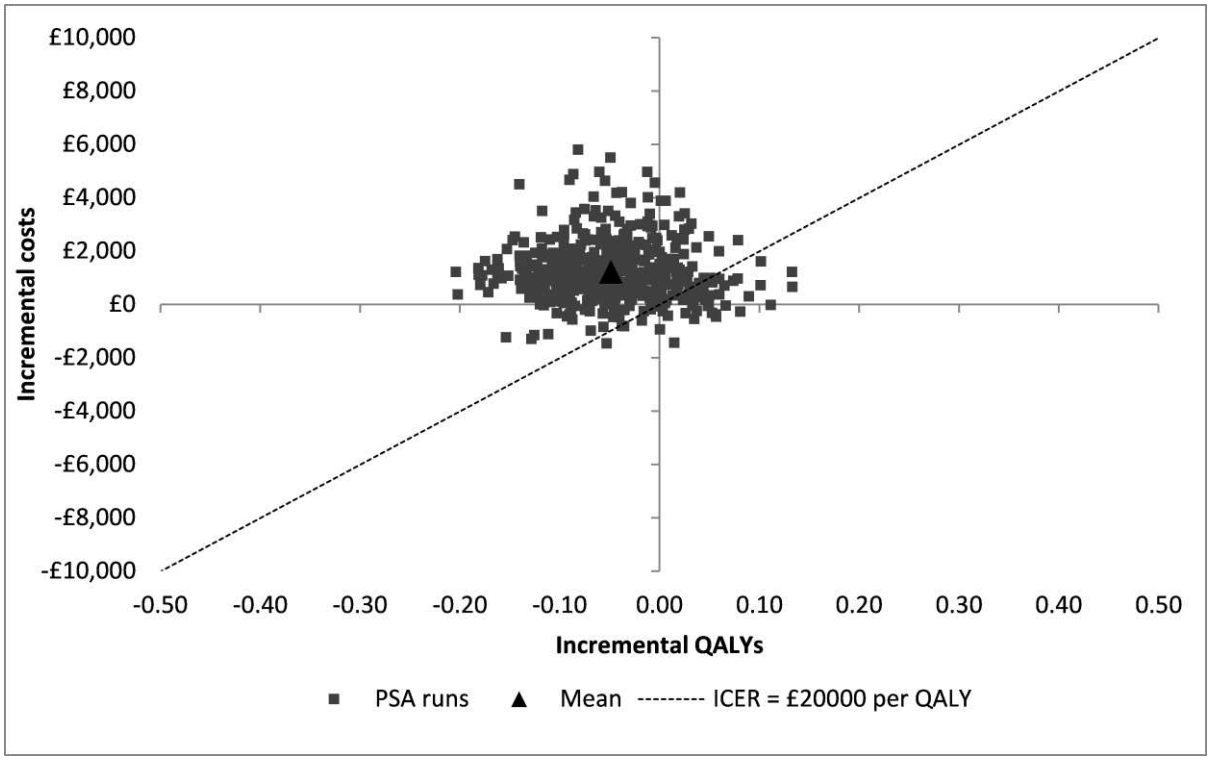


Figure 2

3a) Prediction model A



3b) Prediction model B

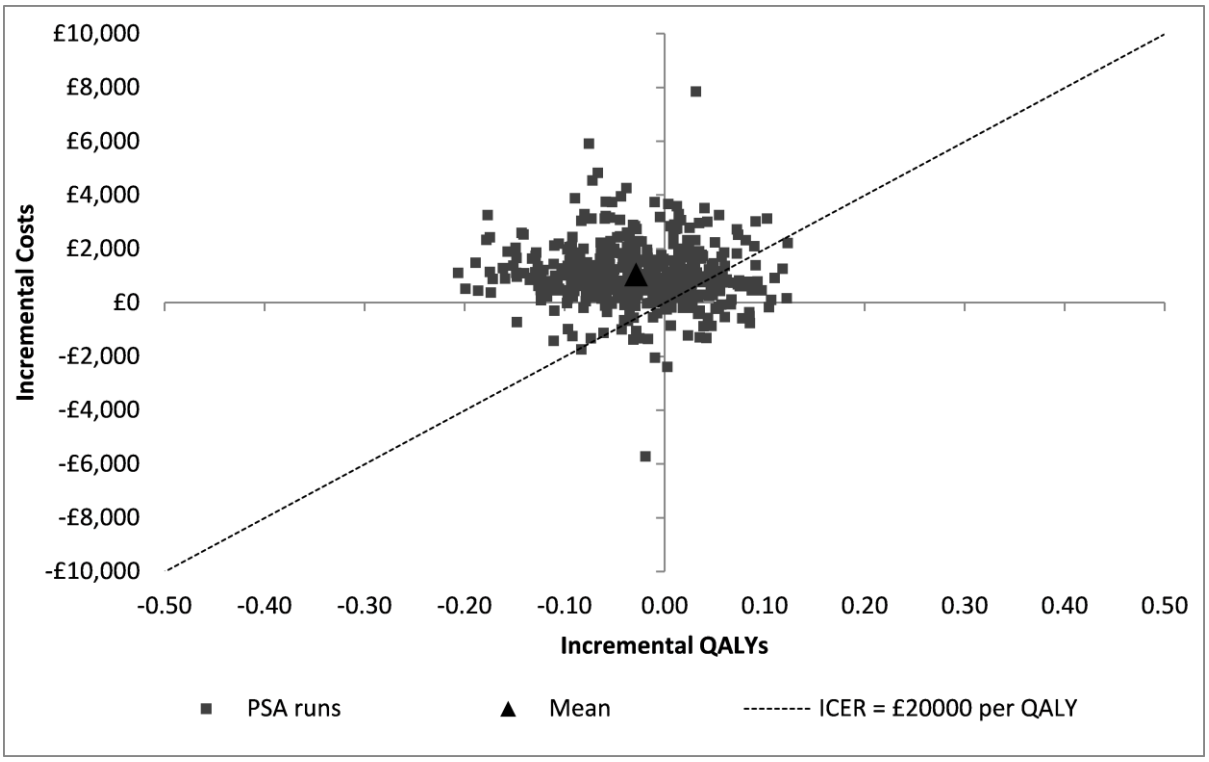


Figure 3