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[Jen Kruger](#), [Alan Brennan](#), [Praveen Thokala](#),
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DP 13/10

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Modelling the potential cost-effectiveness of a targeted follow-up intervention to improve glycaemic response following structured training in flexible intensive insulin therapy

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Abstract

Objective: To use statistical and health economic simulation modelling to estimate the cost-effectiveness of a hypothetical follow-up intervention targeted at people who have undertaken structured training in flexible intensive insulin therapy, based on their initial psychosocial response.

Research Design and Methods: Data from a psychosocial study of 262 people with type 1 diabetes who received structured education in flexible intensive insulin management were used. Multiple linear regression was used to predict HbA1c response following structured education (absolute change in HbA1c from baseline to 12 months) from initial psychosocial response to structured education (change in psychological questionnaire scores from baseline to 3 months). The Sheffield Type 1 Diabetes Policy Model was used to estimate the cost-effectiveness of a follow-up intervention targeted at people not predicted to achieve glycaemic targets from the statistical regression equation.

Results: Initial increases in fear of hypoglycaemia, initial increases in diabetes knowledge, higher baseline body mass index and male gender were found to be predictive of HbA1c outcome after structured education. The simulation modelling suggested that a follow-up intervention targeted based on the regression equations and costing the same as or double a standard five-day structured education program would be cost-effective if it could generate a sustained HbA1c improvement of 0.25-0.5%.

Conclusions: Further research into the design and development of a targeted follow-up intervention would be beneficial as such an intervention may offer a cost-effective method of improving glycaemic outcomes in those patients not achieving glycaemic targets following structured education.

Introduction

Structured education in flexible intensive insulin therapy has been shown to reduce glycosylated haemoglobin (HbA1c) and improve quality of life at six months in people with type 1 diabetes in a randomised controlled trial in the United Kingdom (UK) (1). A psychosocial study published in 2013 found that HbA1c and quality of life benefits were also observed in routine care (2). However, HbA1c response to training in flexible intensive insulin therapy varies between individuals, with some participants experiencing a significant reduction and others, no change over six to 12 months (3). Additional support following structured education may improve glycaemic response in the long term and such a strategy could be an effective addition to the clinical care pathway, especially if the follow-up support was targeted to those participants most in need.

In England and Wales, the organisation responsible for health technology assessment is the National Institute for Health and Clinical Excellence (NICE). The cost-effectiveness of an intervention can be estimated by comparing the outcomes and costs associated with the intervention to the next most effective alternative (4). If these outcomes are estimated as quality-adjusted life years (QALYs) as recommended by NICE (5), the incremental cost-effectiveness ratio, or incremental cost per QALY, can be calculated and compared to alternative uses of health care funding. NICE typically recommends in favour of funding interventions with an incremental cost-effectiveness ratio below a threshold of £20,000 per QALY (5). Structured education in flexible intensive insulin therapy has previously been shown to be cost-effective in the UK (6).

We have hypothesised that it might be possible to predict HbA1c outcomes after people have received training in flexible intensive insulin therapy from their early psychosocial response to the training. A follow-up intervention could then be targeted to provide additional support to those people that are not predicted to experience a certain level of HbA1c improvement. Factors such as expectations of structured education, perceived frequency of hypoglycaemia, baseline HbA1c and body mass index (BMI) have previously been shown to predict HbA1c levels after structured education in type 1 diabetes (7). If a targeted follow-up intervention could improve the longer-term HbA1c response to structured education it could result in lower lifetime incidence of diabetes-related complications and hence cost savings to the healthcare system. In addition to the economic arguments for targeted follow-up support, research has shown that some people have expressed dissatisfaction with the support they receive following structured training in flexible intensive insulin therapy and have emphasised that further individualised support from healthcare professionals may be beneficial (8).

The aim of this study was to use statistical and health economic simulation modelling to estimate the cost-effectiveness of a hypothetical follow-up intervention targeted at people with type 1 diabetes based on their initial psychosocial response to structured education in flexible intensive insulin therapy.

Methods

The study consisted of two phases: statistical data analysis to develop predictive equations for HbA1c response to training using patient-level data from a study of participants undertaking the Dose Adjustment for Normal Eating (DAFNE) structured education program, and health

economic simulation modelling to estimate the cost-effectiveness of additional structured support from healthcare professions targeted at individuals not predicted to achieve a specified level of HbA1c response..

Data

DAFNE is a five-day structured training program in flexible intensive insulin therapy for adults with type 1 diabetes mellitus in the UK, based on a German model (9) with a focus on separating basal from mealtime bolus insulin, and carbohydrate counting to increase dietary freedom with bolus insulin adjusted to match flexible food intake. DAFNE is delivered using a structured curriculum to groups of six to eight participants by trained DAFNE educators. DAFNE has been shown to improve HbA1c, quality of life and severe hypoglycaemia (1, 3, 10). The aforementioned psychosocial study (2) collected data on 262 patients who undertook DAFNE training and these data were used to investigate predictors of HbA1c response to DAFNE in the current study. The study was conducted over a 12-month period, with a set of psychosocial questionnaires delivered at baseline and at 3-, 6- and 12-month follow-up. The questionnaires included measures of fear of hypoglycaemia (11), illness perceptions (12, 13), diabetes knowledge (14), general emotional well-being (15) and life satisfaction (16), social support (17, 18), diabetes-specific quality of life (19), diabetes self-care behaviours (20) and diabetes-specific self-efficacy (21), each producing a summary score. Demographic data and biomedical outcomes including HbA1c were also measured in the same participant group at baseline and at 6- and 12-month follow-up.

Statistical Analysis

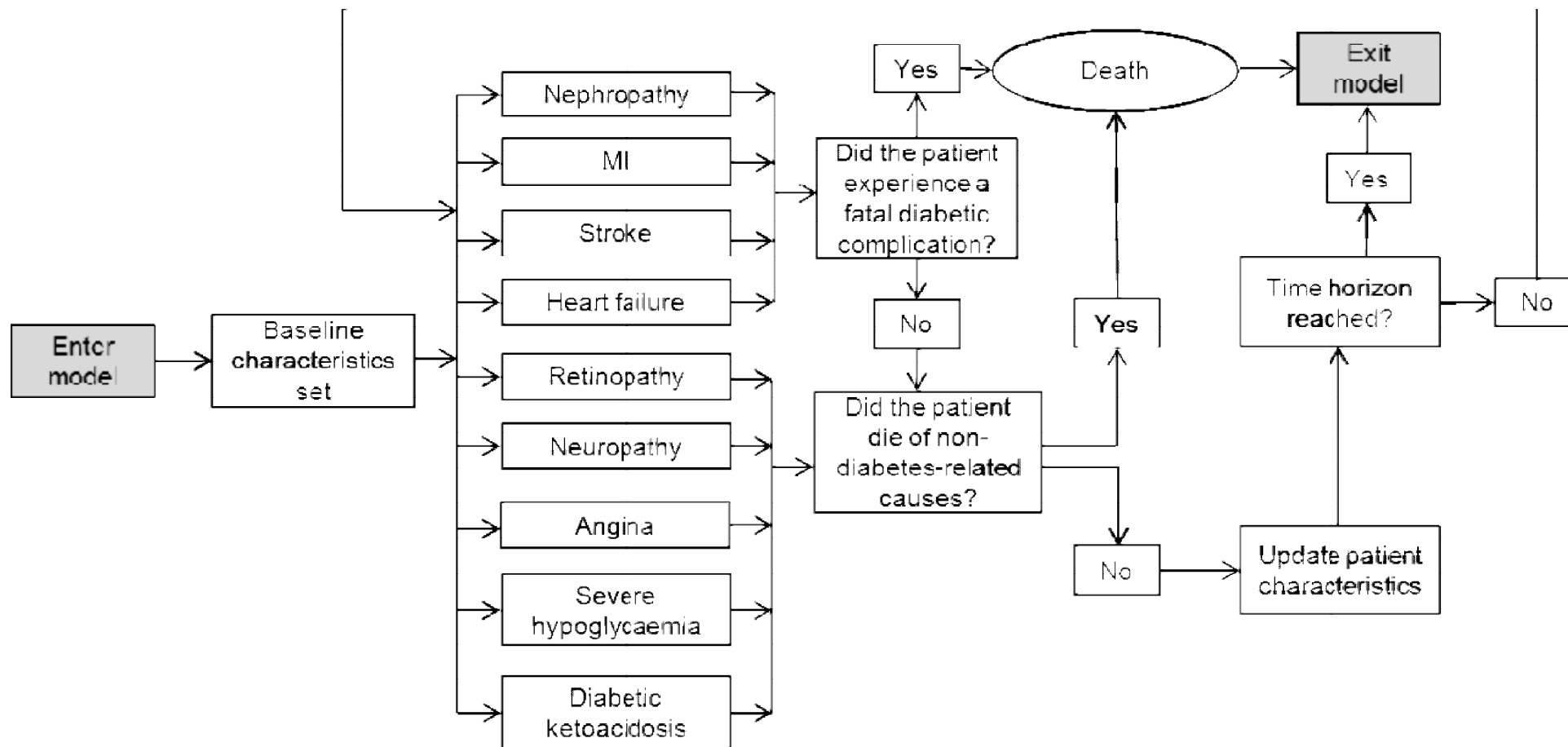
Multiple linear regression was used to estimate predictive models of the change in HbA1c from baseline to 12 months in the DAFNE psychosocial study (2). Linear regression was considered an appropriate analysis method because change in HbA1c was normally distributed and there were no major departures from linearity or homoscedasticity. Predictor variables included baseline to 3-month change in summary scores from each of the psychosocial questionnaires plus biomedical and demographic covariates (age, gender and BMI). Univariate regressions were conducted and those predictor variables that were found to be significant at a $p < 0.10$ level were combined in a multivariate model. Variables were then removed if they were no longer significant at the $p < 0.10$ level in the multivariate model and did not add substantial predictive power to the model. Akaike information criterion, Bayesian information criterion and adjusted R^2 values were compared between models to select the most efficient model for change in HbA1c.

Health Economic Simulation Modelling

The Sheffield Type 1 Diabetes Policy Model, a patient-level simulation model of type 1 diabetes, was used to conduct the economic evaluation (22). The model simulates individuals with type 1 diabetes and uses their characteristics, including HbA1c, to predict the incidence of long-term diabetes-related complications and short-term adverse events. The simulated events include microvascular complications (nephropathy, neuropathy, retinopathy and macular oedema), macrovascular complications (myocardial infarction, stroke, heart failure and angina) and adverse events (severe hypoglycaemia and diabetic ketoacidosis). The risks of developing these events are based on clinical and epidemiological literature (23-29).

Figure 1 presents an overview of the structure of the model. The model uses annual time cycles, and during each year probabilities are compared against random numbers to determine whether each patient progresses to a more severe health state for each complication. Individuals exit the model if they experience a fatal diabetes-related complication, if they die of non-diabetic causes, or if the specified model time horizon is reached. Further details of the structure, data sources and processes of the Sheffield Type 1 Diabetes Policy Model have been reported elsewhere (22).

Figure 1: The Sheffield Type 1 Diabetes Policy Model



The model was used to simulate the lifetime costs and QALYs for 50,000 individuals under two treatment conditions: an intervention group (“targeted follow-up”) in which people predicted from their 3-month change in psychosocial characteristics not to experience at least a 0.5% reduction in HbA1c by 12 months were assumed to receive a hypothetical follow-up intervention that incurred costs and generated a HbA1c reduction versus a control group in which no-one received targeted follow-up after structured training (“current practice”). All costs are reported in 2011-12 £GBP. “What If?” scenario analyses were run to explore the cost-effectiveness of an intervention which achieves an improvement in HbA1c of 0.25%, 0.5% and 1% at an additional cost the same as (£359 per person (30)) or double (£718 per person) the cost of the DAFNE structured education program. This covers a scenario where follow-up would be delivered in a group setting and the potentially more expensive option of individual follow-up support. The cost and HbA1c benefit of targeted follow-up was assumed to be the same for all participants that received the follow-up intervention.

The 50,000 simulated individuals were representative of the participants in the DAFNE psychosocial study (2). Costs and QALYs were estimated over a lifetime horizon from an NHS perspective and discounted at a rate of 3.5% as recommended by NICE (5).

Results

Statistical Analysis

The regression model suggested that 3-month improvement in fear of hypoglycaemia, 3-month improvement in diabetes knowledge, higher BMI and male gender were predictive of

12-month improvement in HbA1c following training in flexible intensive insulin therapy.

Table 1 presents the results of the regression model. Using a liberal alpha level of $p < 0.10$ the results suggested that males, people with higher BMI, people with a larger increase in fear of hypoglycaemia and people with a larger increase in diabetes knowledge after undertaking training in flexible intensive insulin therapy would be more likely to experience a reduction in HbA1c over the first 12 months after undertaking structured education. The regression model explained just 6.4% of the variance in 12-month change in HbA1c, indicating very low predictive power.

Table 1: Multiple linear regression model of change in HbA1c from baseline to 12 months on 3-month change predictors

Predictor variable	Coefficient	Standard error	P-value
Constant	0.657	0.462	0.157
3-month change in fear of hypoglycaemia (continuous)	-0.017	0.010	0.086
3-month change in diabetes knowledge (continuous)	-0.063	0.038	0.097
Body mass index (continuous)	-0.028	0.017	0.105
Gender (male = 1; female = 0)	-0.334	0.157	0.035
Adjusted $R^2 = 0.064$			

The predictive equation from the regression model was:

$$Y_1 = Y_0 + 0.657 - 0.017x_1 - 0.063x_2 - 0.028x_3 - 0.334x_4 \quad (\text{Eq. 1})$$

Where Y_1 = 12-month HbA1c

Y_0 = Baseline HbA1c (continuous)

x_1 = 3-month fear of hypoglycaemia – baseline fear of hypoglycaemia (continuous)

x_2 = 3-month diabetes knowledge – baseline diabetes knowledge (continuous)

x_3 = BMI (continuous)

x_4 = Gender (male = 1; female = 0).

Health Economic Simulation Modelling

The modelling suggested that most participants undertaking structured training (85%) would require targeted follow-up based on their 12-month HbA1c value predicted from their BMI, gender, 3-month change in fear of hypoglycaemia and 3-month change in diabetes knowledge using the regression model outlined above. 15% of people were predicted to achieve glycaemic targets of a 0.5% improvement following structured education and therefore were assumed not to require additional support. These predictions were based on the criterion that people would receive targeted additional support if they were predicted to have less than 0.5% (5mmol/mol) HbA1c improvement at 12 months.

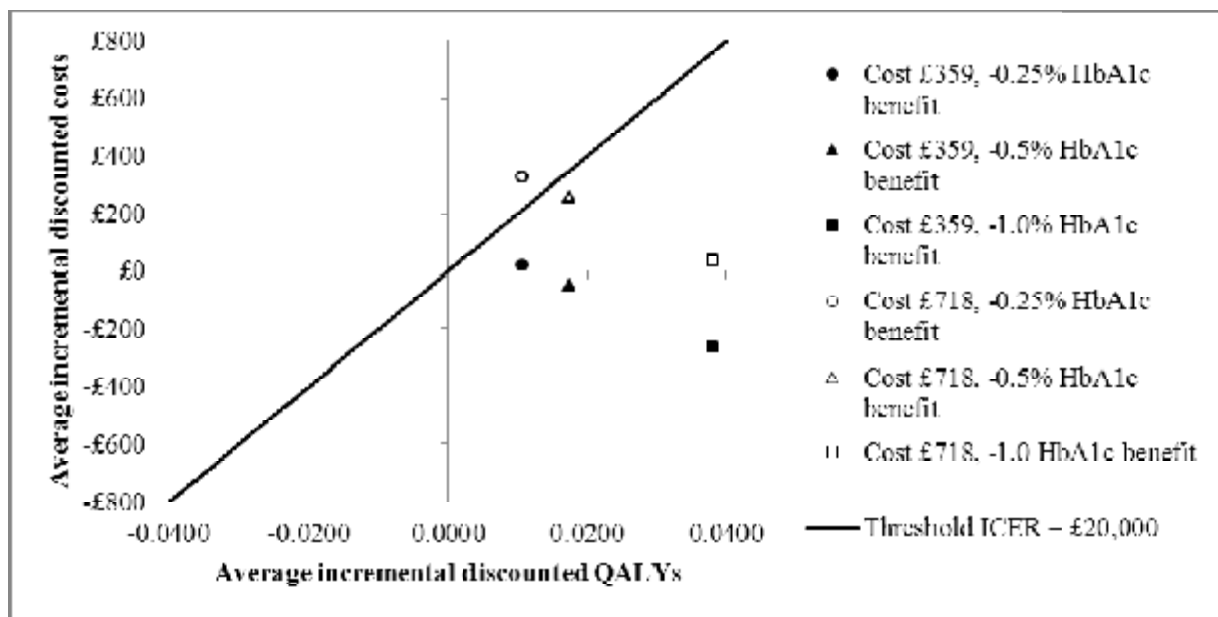
The results of the simulation modelling are presented in Table 2 and Figure 2. The simulation modelling suggested that targeted support costing the same as a five-day structured education program teaching flexible intensive insulin therapy (£359) could dominate current practice (i.e. generate more QALYs for lower costs) over a lifetime horizon if it generated a 12-month HbA1c reduction of 0.5% or more. If a targeted follow-up intervention costing £359 generated a 12-month HbA1c reduction of just 0.25%, it was estimated that it would generate more QALYs for higher costs over a lifetime horizon. The

incremental cost-effectiveness ratio under these assumptions was £1,605 per QALY which is still well below the NICE threshold of £20,000 per QALY and therefore under these assumptions a targeted follow-up intervention would still be considered cost-effective.

Table 2: Economic evaluation of a targeted follow-up intervention versus current practice

	Mean discounted cost	Mean discounted QALY	Incremental discounted cost	Incremental discounted QALY	ICER
Current practice	£47,632	10.5841	-	-	-
Targeted follow-up cost £359 and generated -0.25% HbA1c reduction	£47,650	10.5947	£17	0.0106	£1,605
Targeted follow-up cost £359 and generated -0.5% HbA1c reduction	£47,582	10.6014	-£51	0.0173	Dominant
Targeted follow-up cost £359 and generated -1.0% HbA1c reduction	£47,365	10.6221	-£268	0.0380	Dominant
Targeted follow-up cost £718 and generated -0.25% HbA1c reduction	£47,956	10.5947	£323	0.0106	£30,411
Targeted follow-up cost £718 and generated -0.5% HbA1c reduction	£47,888	10.6014	£256	0.0173	£14,734
Targeted follow-up cost £718 and generated -1.0% HbA1c reduction	£47,671	10.6221	£38	0.0380	£1,004

Figure 2: The cost-effectiveness of targeted follow-up versus current practice on the cost-effectiveness plane



These results were sensitive to the assumed cost of the targeted follow-up intervention. If the targeted follow-up intervention was assumed to cost double that of a five-day structured education program on flexible intensive insulin therapy (£718), the intervention was estimated to be cost-effective (i.e. generating more QALYs for higher costs with an incremental cost-effectiveness ratio below £20,000 per QALY), based on the assumption that it would lead to a 12-month HbA1c reduction of 0.5% or more. If a targeted follow-up intervention costing £718 was assumed to generate a 12-month HbA1c reduction of just 0.25%, it was estimated to generate more QALYs for higher costs but with an incremental cost-effectiveness ratio of £30,411. As this is above the NICE threshold of £20,000 per QALY the targeted follow-up intervention would not be considered cost-effective under these assumptions.

Most of the differences in costs between the targeted follow-up intervention and the current practice control were due to reduced incidence and progression of nephropathy and retinopathy. The differences in QALYs between targeted follow-up and current practice were largely due to extended life expectancy as well as reduced incidence and progression of nephropathy, neuropathy and retinopathy.

Discussion

This economic evaluation used a patient-level simulation model of type 1 diabetes to evaluate the potential cost-effectiveness of providing structured follow-up intervention to adults who are predicted not to achieve a glycaemic target of a 0.5% HbA1c improvement following structured education on flexible intensive insulin therapy. The results of the analysis suggested that increases in fear of hypoglycaemia and diabetes knowledge are predictive of HbA1c response to structured education. The health economic simulation modelling indicated that targeted support costing the same or double the cost of a five-day UK structured education program could be cost-effective if a 0.25% or 0.5% HbA1c reduction could be realised respectively. These levels are similar to the 0.5% (6 months) and 0.3% (12 months) reductions observed following initial structured education in routine care (2).

The results of this health economic simulation modelling exercise are dependent on assumptions about the effectiveness of the hypothetical targeted follow-up intervention and therefore their applicability to clinical practice is limited. The likelihood that a targeted follow-up intervention could generate adequate HbA1c benefit (i.e. a reduction of 0.5% or more) is uncertain, and this uncertainty was not captured in the current analysis. A German study found that a teaching and treatment program, for patients with type 1 diabetes that

failed to achieve therapeutic goals despite their participation in standard training programs, did not generate a statistically significant change in HbA1c at 18 months, although a reduction in the incidence of severe hypoglycaemia was observed (31).

People with type 1 diabetes have requested more ongoing support following structured training in flexible intensive insulin therapy in the UK; particularly individual level follow-up support from healthcare professionals (8). Coupled with the evidence from the present study that additional follow-up support may be cost-effective, this emphasises the need for further research into the most effective ways of supporting people with type 1 diabetes following structured training.

This study has several limitations that should be considered when interpreting these results. First, the hypothetical nature of the assumptions regarding the cost and treatment effect of the targeted follow-up intervention means there is no immediate applicability of the findings to clinical practice. Second, the statistical analysis generally had poor predictive power for HbA1c response after structured education. Most people receiving structured education were predicted from the regression model not to achieve the HbA1c target of a 0.5% improvement and therefore were assumed to require targeted follow-up. If response to standard structured education programs could be predicted more reliably then targeting could be more efficient and the cost-effectiveness of the intervention could be improved. Additional variables that have been shown to be predictive of HbA1c response after structured education but were not collected in the psychosocial study (2) such as expectations about the course (7) or measures of diabetes-specific self-care behaviours taught during structured education could be included in future studies aiming to predict HbA1c outcomes. Third, the model did not fully account for uncertainty in model inputs by conducting probabilistic sensitivity analyses. Finally, the

analysis did not account for variability in response to targeted follow-up, assuming instead that follow-up generated the same level of HbA1c improvement for all individuals.

The methods employed in this study could be further expanded to inform the design, development and pilot evaluation of a targeted follow-up intervention following structured education in flexible intensive insulin therapy. For example, the Sheffield Type 1 Diabetes Policy Model could be used to estimate which area of benefit of a follow-up intervention (HbA1c, incidence of severe hypoglycaemia or quality of life) it would be most worth investing in.

This study has demonstrated the potential cost-effectiveness of a targeted follow-up intervention following structured training in flexible intensive insulin therapy for adults with type 1 diabetes. The economic case for funding structured follow-up support could be further strengthened if outcomes following structured training could be predicted with greater power. Further research into the design and development of a targeted follow-up intervention is indicated as such an intervention may improve glycaemic outcomes in those patients not achieving glycaemic targets following structured education.

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J.K. conducted the statistical and economic analysis and drafted the paper. J.K. and A.B. conceived of and designed the study. P.T. and H.B. and S.H. contributed to the development of the Sheffield Type 1 Diabetes Policy Model. D.C., M.C. and R.B. collected data in the DAFNE psychosocial study and commented on the statistical analysis. All authors critically revised the paper for important intellectual content.

No conflicts of interest are declared.

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