Appendix

Lifetime extrapolation of data from the randomised controlled DiGEM trial

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Summary

To estimate the long term cost effectiveness of self monitoring of blood glucose in addition to standardised usual care for non-insulin treated type 2 diabetes, we carried out a secondary analysis of the randomised controlled diabetes glycaemic education and monitoring (DiGEM) trial data predicting the lifetime quality adjusted life expectancy and diabetes complication costs. Main risk factors from the DiGEM study were extrapolated beyond the 12 months trial follow-up using modelling techniques. The extrapolation showed that the initial 12 months effects were only partly offset by incremental lifetime gains in diabetes complication costs and quality adjusted life expectancy that may be achieved from lower risk factor levels achieved by self-monitoring of blood glucose. The long term results support the findings of the within-trial economic evaluation that self monitoring of blood glucose with or without additional instruction in incorporating findings in self care is unlikely to be cost effective in addition to standardised usual care.

Introduction

The within-trial economic evaluation of the DiGEM study was based on a 12 months prospective trial (see bmj.com). Given this time horizon, all relevant costs and effects may not have been captured in the analysis.[1] Therefore, we carried out a secondary analysis predicting the lifetime quality adjusted life expectancy and diabetes complication costs to estimate the longer term cost effectiveness of self monitoring of blood glucose with or without additional instruction in incorporating findings in self care in addition to standardised usual care.

Methods

Costs and effects

We used the United Kingdom Prospective Diabetes (UKPDS) Outcomes Model to extrapolate the longer term effects of changes in haemoglobin A_{1c} and cholesterol levels observed over the 12 months trial follow-up on quality adjusted life expectancy and diabetes treatment costs beyond the trial period. This model, described in detail elsewhere,[2] uses probabilistic discrete time computer simulation based on an integrated system of parametric proportional hazards risk equations to estimate the risk of common complications of diabetes. Treatment costs and utility decrements associated with these complications, obtained from published studies,[3 4] were used to estimate longer term healthcare costs and quality adjusted life years (QALYs) gained with or without the interventions for each group. For the incremental comparisons, we used the difference between 'no intervention' and 'intervention' scenarios for each group to adjust for any baseline variations. According to current guidelines, costs and effects were discounted at a 3.5% annual rate.[5] Long term cost and quality adjusted life expectancy projections were added to within-trial results to estimate the overall lifetime outcomes of the interventions.

Uncertainty

We eliminated Monte Carlo uncertainty by performing 10 000 repeated simulations in the model. To provide a visual representation of the results, bootstrapped costs and health outcomes were mapped onto the cost-effectiveness plane and reported as acceptability curves.[6 7] We also examined the effects of parameter uncertainty and uncertainty

surrounding the original assumption on length of treatment effect on the base case results using sensitivity analyses.

Results

Costs and effects

The extrapolated effects of the interventions and overall lifetime QALYs gained and total costs incurred are given in table I. Compared to no intervention, the mean gain in QALYs beyond the trial period was estimated to be 0.045 per patient in the standardised usual care group, 0.049 per patient in the less intensive self monitoring group and 0.060 per patient in the more intensive self monitoring group. Complications costs were reduced in the beyond trial period by £69, £102 and £97 respectively in the three groups, with no significant difference between groups. The mean estimates of lifetime differences in costs and outcomes between either monitoring group and the control group suggest that both forms of self monitoring are more costly (£59 and £56) and less effective (-0.004 and -0.020 QALYs) than standardised usual care with relatively wide confidence intervals around these point estimates.

Uncertainty

Figure I illustrates the distribution of the joint uncertainty around the difference in costs and effects between the control group and the less and more intensive self monitoring groups plotted on the cost-effectiveness plane.[6] The confidence ellipses show clearly the lack of significant difference between the self monitoring groups and the standardised usual care group either in effects or costs. In the UK, the current cost effectiveness ceiling ratio is approximately £20,000-£30,000 per additional QALY gained.[8] The probability of less intensive self monitoring having a cost effectiveness ratio lower than this does not reach 40% and the probability of more intensive self monitoring being cost effective remains below 15% at this threshold (figure II).

In a sensitivity analysis, we examined the parameter uncertainty introduced by the extrapolation of outcomes. This was undertaken by repeatedly running the model with different sets of bootstrapped parameters,[2] which had the effect of increasing the width of the confidence intervals around the results. These are reported in table II. We also addressed the lack of evidence on treatment effects beyond the one year trial period by

assuming that trial effects could be sustained for five years among compliant patients. This analysis indicated improvement in the cost effectiveness of both self monitoring regimens, but no significant differences between groups were achieved in effects (table II).

Discussion

In the secondary economic analysis of the DiGEM study, within-trial results were extrapolated over a lifetime using a validated simulation model to account for the long term benefits of the altered risk factors achieved during the trial period. The initial negative effects outweighed any subsequent lifetime gains in QALYs resulting from the lower levels of risk factors in those patients undertaking self monitoring. The extrapolation also suggests that the incremental lifetime savings in diabetes complications do not offset the additional intervention costs. Overall, the results indicate that less intensive or more intensive self monitoring of blood glucose are unlikely to be cost effective in addition to standardised usual care at the observed levels of benefits.

This economic evaluation was designed as an analysis in which the cumulative effect of multiple risk factors could be examined. The rationale for this, stated in the protocol, was that a clinical trial result of no significant differences in individual risk factors could co-exist with significant differences in multivariate risk as a result of the intervention. As reasons for the significantly lower total cholesterol levels found in the two self monitoring groups compared to the control group are unclear, in the beyond trial extrapolation we took into consideration both changes in the haemoglobin A_{1c} and the total cholesterol levels. Had we restricted our analysis of long term benefits only to changes in haemoglobin A_{1c} levels, it is likely that both forms of self monitoring would look even less cost effective.

The original limitations of the within-trial economic evaluation discussed in the main paper are relevant to this secondary analysis (see bmj.com). The interpretation of the longer term cost utility results is further limited due to the uncertainty inherent in any modelling exercise.[9] Although we addressed the uncertainty around the input parameters and the potential impact of continued self monitoring using sensitivity analyses, care

should be taken in interpreting these estimates due to the wide range of additional assumptions needed.

In conclusion, the lifetime cost effectiveness results provide no convincing evidence for routinely recommending self monitoring to patients with non-insulin treated type 2 diabetes.

References

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Appendix tables

Table I Mean (95% confidence interval) quality adjusted life years (QALYs) gained and costs† (£) per patient with non-insulin treated type 2 diabetes receiving standardised usual care, less intensive self monitoring of blood glucose, or more intensive self monitoring of blood glucose

	Standardised usual care group	Less intensive self monitoring group	More intensive self monitoring group	Difference	
	n=152	n=150	n=151	Less intensive group *v* standardised usual care	More intensive group *v* standardised usual care
Trial period					
QALYs gained	0.000 (-0.013 to 0.014)	-0.008 (-0.023 to 0.007)	-0.035 (-0.050 to -0.020)*	-0.008 (-0.029 to 0.012)	-0.036 (-0.056 to -0.015)*
Costs	89 (85 to 93)	181 (173 to 189)	173 (162 to 184)	92 (80 to 103)*	84 (73 to 96)*
Beyond trial extrapolation‡					
QALYs gained	0.045 (0.021 to 0.069)	0.049 (0.027 to 0.071)	0.060 (0.040 to 0.080)	0.004 (-0.027 to 0.035)	0.015 (-0.016 to 0.046)
Costs	-69 (-147 to 9)	-102 (-176 to -28)	-97 (-158 to -37)	-33 (-133 to 67)	-28 (-128 to 72)
Lifetime total					
QALYs gained	0.045 (0.016 to 0.074)	0.041 (0.013 to 0.069)	0.025 (-0.002 to 0.051)	-0.004 (-0.043 to 0.035)	-0.020 (-0.059 to 0.019)
Costs	20 (-58 to 98)	79 (5 to 152)	76 (15 to 137)	59 (-41 to 159)	56 (-44 to 156)

*P<0.05.
†Costs in 2005-6.
‡Compared to no intervention.

Table II Sensitivity analysis: Mean (95% confidence interval) quality adjusted life years (QALYs) gained and costs† (£) per patient with non-insulin treated type 2 diabetes receiving standardised usual care, less intensive self monitoring of blood glucose, or more intensive self monitoring of blood glucose

		Standardised usual care group n=152	Less intensive self monitoring group n=150	More intensive self monitoring group n=151	Difference	
					Less intensive group *v* standardised usual care	More intensive group *v* standardised usual care
Trial period						
Parameter uncertainty	QALYs	0.000 (-0.013 to 0.014)	-0.008 (-0.023 to 0.007)	-0.035 (-0.050 to -0.020)*	-0.008 (-0.029 to 0.012)	-0.036 (-0.056 to -0.015)*
	Costs	89 (85 to 93)	181 (173 to 189)	173 (162 to 184)	92 (80 to 103)*	84 (73 to 96)*
Deaths excluded	QALYs	0.002 (-0.010 to 0.015)	-0.006 (-0.021 to 0.009)	-0.030 (-0.044 to -0.016)*	-0.008 (-0.028 to 0.011)	-0.032 (-0.052 to -0.013)*
	Costs	89 (85 to 93)	183 (175 to 190)	174 (163 to 185)	94 (85 to 102)*	85 (73 to 97)*
Trial effects maintained for 5 years	QALYs	0.000 (-0.013 to 0.014)	-0.008 (-0.023 to 0.007)	-0.035 (-0.050 to -0.020)	-0.008 (-0.029 to 0.012)	-0.036 (-0.056 to -0.015)*
	Costs	89 (85 to 93)	181 (173 to 189)	173 (162 to 184)*	92 (80 to 103)*	84 (73 to 96)*
Beyond trial extrapolation‡						
Parameter uncertainty	QALYs	0.045 (-0.910 to 1.000)	0.049 (-0.867 to 0.966)	0.060 (-0.958 to 1.078)	0.004 (-1.319 to 1.327)	0.015 (-1.380 to 1.410)
	Costs	-69 (-5533 to 5394)	-102 (-5632 to 5428)	-97 (-5760 to 5566)	-33 (-7807 to 7741)	-28 (-7897 to 7841)
Deaths excluded	QALYs	0.045 (0.021 to 0.070)*	0.050 (0.028 to 0.073)*	0.062 (0.041 to 0.082)*	0.005 (-0.027 to 0.037)	0.016 (-0.015 to 0.048)
	Costs	-69 (-148 to 9)	-104 (-179 to -29)*	-100 (-162 to -38)*	-34 (-136 to 67)	-30 (-132 to 71)
Trial effects maintained for 5 years	QALYs	0.117 (0.082 to 0.152)	0.148 (0.113 to 0.184)	0.144 (0.116 to 0.173)	0.031 (-0.015 to 0.078)	0.027 (-0.019 to 0.074)
	Costs	229 (137 to 322)	572 (472 to 672)	538 (455 to 621)	343 (213 to 472)*	309 (180 to 438)*
Lifetime total						
Parameter uncertainty	QALYs	0.045 (-0.910 to 1.000)	0.041 (-0.875 to 0.957)	0.025 (-0.993 to 1.042)	-0.004 (-1.327 to 1.319)	-0.020 (-1.416 to 1.375)
	Costs	20 (-5444 to 5483)	79 (-5451 to 5609)	76 (-5587 to 5739)	59 (-7715 to 7833)	56 (-7813 to 7925)
Deaths excluded	QALYs	0.048 (0.019 to 0.076)	0.044 (0.016 to 0.073)	0.032 (0.006 to 0.058)	-0.003 (-0.042 to 0.035)	-0.016 (-0.055 to 0.023)
	Costs	20 (-59 to 98)	79 (4 to 154)	74 (12 to 137)	59 (-43 to 161)	55 (-47 to 156)
Trial effects maintained for 5 years	QALYs	0.117 (0.079 to 0.155)	0.140 (0.101 to 0.179)	0.109 (0.075 to 0.143)	0.023 (-0.029 to 0.075)	-0.008 (-0.060 to 0.044)
	Costs	318 (225 to 412)	753 (650 to 856)	711 (622 to 801)	434 (300 to 569)*	393 (259 to 527)*

*P<0.05.
†Costs in 2005-6.
‡Compared to no intervention.

Appendix figures

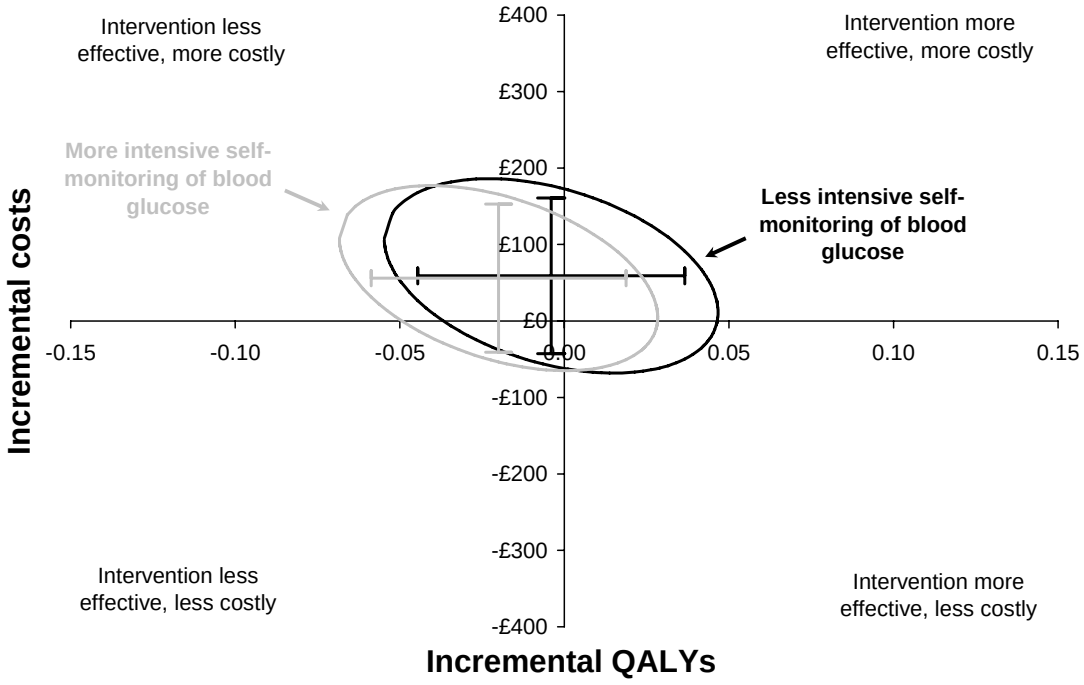

Figure I Cost utility analysis of self monitoring compared with standardised usual care on the cost-effectiveness plane

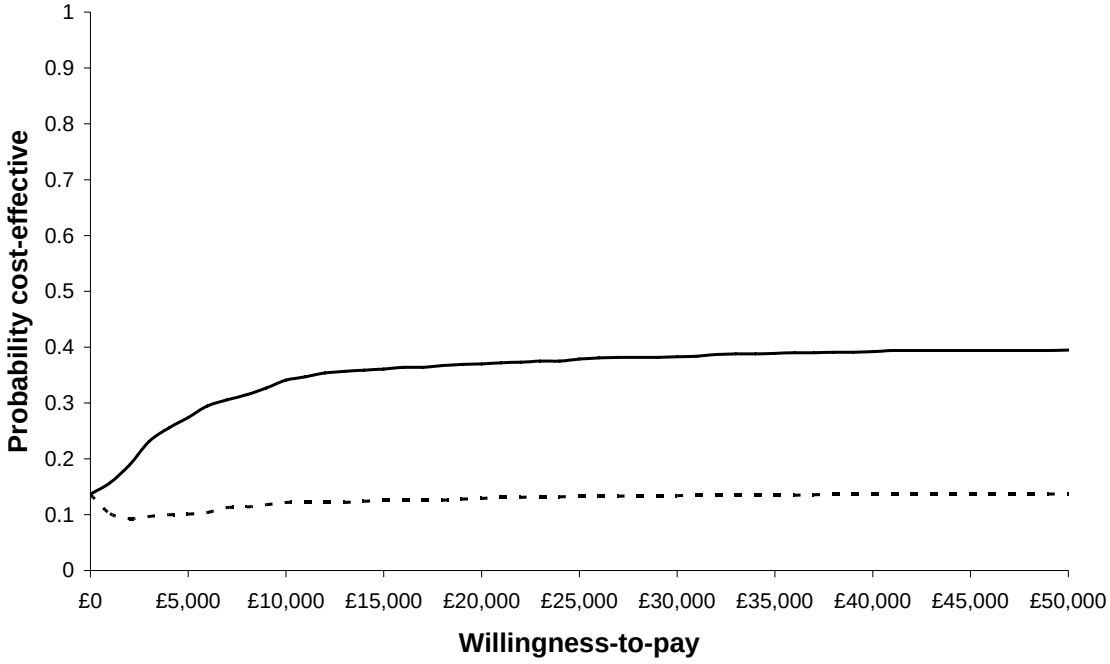

Figure II Cost-effectiveness acceptability curves: probability that self monitoring is cost effective compared with standardised usual care as a function of decision makers' maximum willingness-to-pay for an additional quality adjusted life year (____ less intensive self monitoring, _ _ _ more intensive self monitoring)