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Abstract:	Objectives Kids in Control OF Food(KICk-OFF) is a 5-day structured education programme for 11-16 year olds with Type-1 diabetes mellitus(T1DM) who are using multiple daily insulin injections. This study evaluates the cost-effectiveness of the KICk-OFF education programme compared to the usual care using data from the KICk-OFF trial. Methods The short-term within-trial analysis covers the two-year post-intervention period. Data on glycated haemoglobin(HbA1c), severe hypoglycaemia and diabetic ketoacidosis(DKA) were collected over a two-year follow-up period. Sub-group analyses have been defined on the basis of baseline HbA1c being below 7.5%(58.5 mmol/mol)(low group), between 7.5% and 9.5%(80.3 mmol/mol)(medium group), and over 9.5%(high group). The long-term cost-effectiveness evaluation has been conducted by using The Sheffield Type-1 Diabetes Policy Model. Results The most favourable within-trial scenario for the KICk-OFF arm led to an ICER of £23,688 (base year 2009) with a cost-effectiveness probability of

	41.3%. Simulating the long-term complications using the full cohort data, the mean ICER for the base case was £28,813 (base year 2011) and the probability of the KICk-OFF intervention being cost-effective at £20,000/QALY threshold was 42.6%, with considerable variation due to treatment effect duration. For the high HbA1c sub-group, the KICk-OFF arm was 'dominant' over the usual care arm in each scenario considered. Conclusions For the whole study population, the cost-effectiveness of KICk-OFF depends on the assumption for treatment effect duration. For the high baseline HbA1c sub-group, KICk-OFF arm was estimated to be dominant over the usual care arm regardless of the assumption on the treatment effect duration.

Cost-effectiveness of structured education in children with type-1 diabetes mellitus

Short title: Cost-effectiveness of education in children with type-1 diabetes mellitus

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Abstract

Objectives

Kids in Control OF Food (KICk-OFF) is a 5-day structured education programme for 11-16 year olds with Type-1 diabetes mellitus (T1DM) who are using multiple daily insulin injections. This study evaluates the cost-effectiveness of the KICk-OFF education programme compared to the usual care using data from the KICk-OFF trial.

Methods

The short-term within-trial analysis covers the two-year post-intervention period. Data on glycated haemoglobin (HbA1c), severe hypoglycaemia and diabetic ketoacidosis (DKA) were collected over a two-year follow-up period. Sub-group analyses have been defined on the basis of baseline HbA1c being below 7.5% (58.5 mmol/mol) (low group), between 7.5% and 9.5% (80.3 mmol/mol) (medium group), and over 9.5% (high group). The long-term cost-effectiveness evaluation has been conducted by using The Sheffield Type 1 Diabetes Policy Model, which is a patient-level simulation model on T1DM. It includes long-term microvascular (retinopathy, neuropathy and nephropathy) and macrovascular (myocardial infarction, stroke, revascularization and angina) diabetes-related complications and acute adverse events (severe hypoglycaemia and diabetic ketoacidosis).

Results

The most favourable within-trial scenario for the KICk-OFF arm led to an ICER of £23,688 (base year 2009) with a cost-effectiveness probability of 41.3%. Simulating the long-term complications using the full cohort data, the mean ICER for the base case was £28,813 (base year 2011) and the probability of the KICk-OFF intervention being cost-effective at £20,000/QALY threshold was 42.6%, with considerable variation due to treatment effect duration. For the high HbA1c sub-group, the KICk-OFF arm was 'dominant' (meaning it provided better health gains at lower costs than usual care) over the usual care arm in each scenario considered.

Conclusions

For the whole study population, the cost-effectiveness of KICk-OFF depends on the assumption for treatment effect duration. For the high baseline HbA1c sub-group, KICk-OFF arm was estimated to be dominant over the usual care arm regardless of the assumption on the treatment effect duration.

Keywords (3 to 5)

Type 1 diabetes mellitus, structured education programme, paediatrics, cost-effectiveness analysis.

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INTRODUCTION

The worldwide type 1 diabetes mellitus (T1DM) prevalence rate is expected to increase by about 50% in 20 years to 55 million by 2030 [1]. Type 1 diabetes usually appears before the age of 40, accounting for around 10 per cent of all people with diabetes [1]. In the UK, recent estimates of T1DM prevalence is one per 700–1,000 children [2], where less than 15% of them meet the recommended glycaemic target [3]. Self-management education programmes for adults with T1DM improve clinical outcomes and are cost-effective [4],[5]. However, literature searches have revealed none have been evaluated in the paediatric population, who would have different individual characteristics and lifetime trajectory regarding the progression of their condition.

Kids in Control OF Food (KICk-OFF) is a 5-day group-based structured education programme for 11-16 year olds with T1DM who are using multiple daily insulin injections. The programme is based on the principles of the Dose Adjustment for Normal Eating (DAFNE) education programme for adults and aims to provide young people with self-management skills to help overcome some of the barriers to effective self-management associated with an intensive insulin regimen [3]. The key modules of the programme include: what is diabetes?; food and diabetes; insulin management; management of hypoglycaemia; sick day rules; diabetes in school and social situations. KICk-OFF course employs interactive and practical learning activities focusing on carbohydrate counting and insulin adjustment in everyday life. The management of hypoglycaemia, ketosis and long-term complications of diabetes are considered with scenario-based teaching. Written material and quizzes support and assess learning. Each course, attended by up to 8 participants, was taught by three KICk–OFF research educators [6]. Parents received a one-day course.

The KICk-OFF trial was a cluster-randomised controlled trial which recruited 480 patients across 31 paediatric diabetes centres in the UK with a 2-year post-intervention follow-up period [3]. Centres were randomised to either KiCK-OFF(intervention) or usual care. Usual care is centre-specific education delivered without a clear structure [3].

This paper evaluates the cost-effectiveness of the KICk-OFF education programme compared to usual care. We undertake two analyses. First, the within-trial analysis examines the cost-effectiveness of the intervention over the trial period only (24 months). This provides limited insights, as the potential effects of better blood glucose control and other effects accrue to participants over the long-term. The second analysis estimates the longer-term (lifetime) diabetes-related complications in both arms and thus estimates of the long-term cost-effectiveness using an adapted version of the previously published Sheffield Type 1 Diabetes Policy Model [7].

METHODS

31 KICk-OFF courses were delivered between October 2009 and August 2010. Data on the primary health outcome of the trial, the patients' glycated haemoglobin (HbA1c), were collected at both the 12 and 24-month follow-up intervals. Incidence of severe hypoglycaemia and incidence of diabetic ketoacidosis (DKA) were also collected. As many centres routinely teach carbohydrate counting, albeit via less intensive methods than KICk-OFF, the randomisation was stratified by the education level being low, medium and high (corresponding to 0-

4.5 hours, 5-6.5 hours and over 7 hours of education per participant per annum) prior to KICk-OFF education. Sub-group analyses have been defined on the basis of baseline HbA1c being below 7.5% (58.5 mmol/mol) (low group), between 7.5% and 9.5% (80.3 mmol/mol) (medium group), and over 9.5% (high group). The outcomes of the model were lifetime costs and Quality-Adjusted Life Years (QALYs) discounted at 3.5% in line with the recommendations by NICE [8]. The economic analyses were evaluated from the perspective of the UK National Health Service (NHS).

Within-Trial Analyses

The mean KICk-OFF intervention cost itself was reported based on professional diaries of the educators and expenses reported by all the participating centres (Table S1 in supplementary information). The costing of the intervention was undertaken based on the costs associated with educator time, venue, educator accommodation, parent day expenses, educator travel, participant travel to venue, website, course food, equipment and materials, educator food, activity/exercise sessions and the education of the educators. Over 80% of the intervention cost was attributable to the educator time (Table S1). The average increase in the unstructured education time before (2010) and after (2012) KICk-OFF education was very similar in both arms (0.2 and 0.5-hour increase per centre per annum, on average). Therefore, the cost of the KICk-OFF intervention is considered as an additional cost to the existing education cost (i.e. the cost of usual care is considered as zero).

Relevant patient costs for the within-trial analyses were based on individual-level data collected during the two-year follow-up after the completion of the trial. The within-trial resource use was collected from participants using designated questionnaires and covered insulin use, hospital admissions, and NHS contacts. Unit costs reported in Table S1 were multiplied with the resource use data collected in the trial to calculate the total costs.

A health utility is a continuum where values of zero and one are assigned to health conditions judged equivalent to death and optimal health, respectively [9]. The Health Utilities Index Mark 2 (HUI-2) [10] and The Child Health Utility 9D (CHU9D) [11] were used as the measures of health outcome within the KICk-OFF trial. There are currently three generic paediatric preference based measures available (HUI-2, AQoL-6D, CHU9D) and one in development (EQ-5D-Y) [12]. HUI-2 is a Canadian measure that is extensively validated with UK preference weights available and used as the primary outcome measure in this study. The AQoL-6D was developed in Australia with no UK preference weights and has a relatively limited number of applications [13]. The CHU9D was developed in Sheffield and is currently in use in over 30 studies nationally and internationally. Currently, EQ-5D-Y does not have preference weights and given that the EuroQol Group do not recommend the use of the adult weights [12], a QALY value cannot be calculated based on this measure. A recent study trialled the use of the EQ-5D-Y and CHU9D, although for a younger cohort, and favoured the use of the CHU9D [14]. Therefore, HUI-2 is listed as the primary and CHU9D is listed as the secondary outcome measures for the KICk-OFF trial.

Statistical Analysis

The statistical analysis needs to accounts for dependence between individuals and their clusters in order to avoid any potential bias in the results [15]. In addition, the within-trial utility and cost values observed at the end of the follow-up period should be adjusted for the baseline utility and cost values [16],[17]. Consequently, two linear models where baseline utility and baseline cost were used as covariates were fitted, using generalised estimating equations to control for clustering.

Preliminary analysis showed the utility and cost data had considerable number of missing observations - 23% (91/396) of the individuals had complete utility and 36% (144/396) had complete cost data at baseline and all follow-up time points, which is reduced further to 10% (40/396) when considering individuals who have complete data on both utilities and costs. A multiple imputation was employed to address this problem [18]. This exercise not only avoids information loss, but also reduces any potential bias due to missing data on the initial randomisation.

Imputed values were estimated by using the chained predictive mean matching method, as this method is suitable for predicting variables that are bounded, continuous and have a non-normal distribution, such as the left-skewed EQ-5D data [18]. Using the multiple imputation method, the sample size increased to 389, of which 322 individuals had both cost and utility data. The linear model with baseline utility as a covariate, using generalised estimating equations to control for clustering, was applied to this dataset. All analyses are performed using STATA release 12.0 [19].

Long-term Modelling

An incremental model-based analysis was performed to evaluate the long-term cost-effectiveness of the KICk-OFF arm in comparison to the usual care arm over a lifetime horizon. A detailed description of The Sheffield Type 1 Diabetes Policy Model (henceforth, the Model) is provided elsewhere [7]. In summary, the Model is a patient-level simulation, where each diabetes-related complication is represented using Markov sub-models. The incidence of adverse diabetic events and long-term diabetes-related complications were predicted using individual characteristics and biomedical information, with HbA1c being the principal predictor of future events. Microvascular complications (nephropathy, neuropathy, retinopathy, macular oedema), cardiovascular complications (myocardial infarction, stroke, heart failure, angina) and adverse events (severe hypoglycaemia and diabetic ketoacidosis) were modelled. As there is no information on existing complications and given the young age group, it is assumed that patients do not have any existing complications at the baseline. The use of individual level Monte Carlo simulation technique for patient progression to a more severe health state allows the development of multiple complications for a single individual in each annual cycle.

The initial effects of KICk-OFF on HbA1c levels, and hypoglycaemia and DKA event numbers are taken from the within trial statistical analyses and applied to 5000 simulated patients within the model. For the base case, the effect of the structured education programme on individual HbA1c was assumed to last for four years in line with evidence published on the sustained effects of previous structured education programmes in T1DM adults [20]. The same assumption was made for the effect of the programme on the hypoglycaemia and DKA risks. After this time, we have assumed that the HbA1c, hypoglycaemia and DKA progression reverts back to the baseline levels. For each of the long-term complications and adverse events, simulated a utility decrement

is used in the Model as shown in Table S3. We also incorporate the annual cost (reference [7] - Table 5) of each particular complication, which includes hospital admission and NHS contact costs, together with the insulin use observed within-trial (base year 2011).

The model outcomes were evaluated using the incremental cost-effectiveness ratio (ICER), which divides the cost difference of the intervention arm versus the control arm by the corresponding QALY difference, and can be thought of as the cost per QALY gained by due to the KICk-OFF programme. Results are also presented using net monetary benefit which is the difference between the expected QALYs multiplied by the willingness-to-pay threshold and expected costs [8].

Sensitivity Analysis for the Long-term Modelling

500 probabilistic sensitivity analysis (PSA) runs were undertaken in line with the internal capacity of the Simul8 software programme. The uncertainty around both the within-trial analysis and the long-term modelling analysis were represented by cost-effectiveness planes (CEPs) and the resulting cost-effectiveness acceptability curves (CEACs), which illustrate the probability that a particular intervention is cost-effective over a range of possible values for the maximum willingness-to-pay for a unit improvement in QALYs [21].

The maintenance period for the HbA1c, as well as hypoglycaemia and DKA benefits, were modelled for four years based on the literature on the T1DM education programme designed for an adult population [20]. Given the lack of relevant literature on the maintenance period of these benefits for a paediatric cohort, sensitivity analyses have been undertaken based on the two extremes: one-year effect, going back to the baseline level at year 2, in line with the post-intervention follow-up period, and lifetime maintenance period.

RESULTS

Patient characteristics

The mean age for the cohort was 13.1 years with an average time since diagnosis of 5 years. 45% of the participants were male (Tables S1). For the KICk-OFF arm, the mean HbA1c was 9.28 % (77.9 mmol/mol) at baseline, 9.30% (78.1 mmol/mol) at 12-months and 9.18% (76.8 mmol/mol) at 24-months. For the usual care arm, the mean HbA1c value was 9.12% (76.2 mmol/mol) at baseline, 9.17% (76.7 mmol/mol) at 12-months and 9.26% (77.7mmol/mol) at 24-months (Table 1). Non-parametric test on identifying HbA1c levels over time (baseline and ordered data collection points) indicated that the only statistically significant trend observed in HbA1c levels is by the group whose HbA1c levels were higher than 9.5% at baseline (*nptrend* command in STATA [19]). Patient characteristics, such as systolic blood pressure(116.2 mmHg), low density lipoprotein (LDL) cholesterol (2.7 mmol/l), high density lipoprotein (HDL) cholesterol(1.5 mmol/l), total cholesterol(4.4 mmol/l), and triglyceride(1.2 mmol/l) were not collected, and therefore, were based on the characteristics of the under 20-year old population in the DAFNE trial.

Within-Trial Cost-Effectiveness Results

Table 2 reports the within-trial cost-effectiveness analysis undertaken by using both the complete case data only and with imputed data on HUI2 patient-reported outcome measures completed by children. Two other measures (HUI2 completed by parents and CHU9D) are reported in Tables S4 and S5, respectively. The costing analysis based on the within-trial data showed that the mean cluster-adjusted cost per individual during the 24-months trial period was £7,165 for the KICk-OFF arm and £4,787 for usual care arm (Table 2). When the cost data were analysed for individuals with complete utility data only, the cost of each arm reduced, suggesting that the cost per individual for those individuals with a missing utility data was higher on average than the overall mean. Once the missing utility data had been imputed, the mean cost value for each arm approached back to the level of 'complete cost cases'. A regression-based adjustment, which controls for the baseline value and the treatment arm, applied on the cost values [17]. This approach resulted in costs differences that were similar to the simple adjusted differences when complete case data were used, whereas they were significantly different when imputed data was used (Table 2). One explanation is the higher cost values observed using the imputed data compared to the complete case data, combined with the fact that, unlike the simple-adjusted difference where baseline values are subtracted from the two-year values, the regression-based approach accounts for the 'regression to the mean' problem [16],[22].

Based on the complete case data on HUI2 Children, the mean per patient two-year QALY value at baseline was considerably higher (0.0578) for the usual care arm (Table 2), which supports the importance of adjusting utility values for baseline value [16]. Using the simple adjustment and regression-based approach to adjust for baseline values, the utility differences between the two arms were favouring the usual care arm. The differences between the simple-adjusted and regression-based adjusted incremental QALY values was smaller when the imputed data were used, due to higher sample size reducing the uncertainty around the mean estimates, together with the inherent reduction of variability in imputed data.

Out of the twelve sets of analyses presented in Tables 2, S4 and S5, nine resulted in the KICk-OFF arm being 'dominated' by the usual care arm, and two analyses resulted in a mean ICER that would not be evaluated as cost-effective at the £20,000/QALY threshold in the UK. The only ICER that might potentially be cost-effective was based on complete case CHU9D data with simple adjustment (£23,688) (Table S5), which had a cost-effectiveness probability of 41.3% at £20,000 per QALY.

Long-term Modelling Results

The descriptive statistics for the parameters used in the long-term model and the utility decrements are reported in Supplementary Information (Tables S1-S3).

The mean number of estimated lifetime events for the full trial cohort and high baseline HbA1c trial cohort (>9.5% or 80.3mmol/mol) are reported in Table 3 and Table 4, respectively. The 'treatment effect duration' refers to the sustained impact of the changes observed in the HbA1c level, and hypoglycaemia and DKA event numbers after the KICk-OFF course. In addition to the base case of '4-year treatment effect' [20], 1-year and lifetime treatment effect durations are also reported.

The base case discounted lifetime costs per patient for the usual care arm and KICk-OFF arms were £101,279 and £102,404, respectively, giving a difference of £1,135[95% CI £-2,734, £3,970] (Table 3). These represent the sum of discounted lifetime costs for insulin, interventions, long-term complications and adverse events. The total cost for both arms reduced when treatment duration assumed to be 1-year only, increasing the incremental cost to £1,845 [95% CI -£984, £4,185]. The total cost for both arms increased when treatment duration assumed to be lifetime, resulting in an incremental cost of -£2,437[95% CI -£14,546, £6,152]. For the high baseline HbA1c group, which are expected to experience a higher number of complication-related events in the long-term, the costs per patient for both arms were higher. The lifetime costs per high baseline HbA1c patient for the usual care and KICk-OFF arms were £150,569 and £146,146, respectively, giving a difference of -£4,423[95% CI £-13,321, £238] in the base case. The incremental cost value increased to -£774[95% CI £-5,422, £2,157] in the 1-year treatment effect duration scenario, and reduced to -£18,400[95% CI £-46,818, -£4,829] in the lifetime treatment effect scenario (Table 4).

The discounted long-term QALYs for the usual care and KICk-OFF arms are estimated at 17.9646 and 18.0039, respectively, leading to a difference of 0.0394 [95% CI -0.0845, 0.2013], which corresponds to 14.39 days per person in perfect health. 1-year treatment duration assumption led to an incremental QALY difference of 0.0106 [95% CI -0.0843, 0.1115]. The total QALYs for both arms reduced when treatment duration assumed to be lifetime, resulting in an incremental QALY of 0.2178[95% CI -0.2012, 0.7029]. For the high baseline HbA1c group, which are expected to experience a higher number of complication-related events in the long-term, the QALYs per patient for both arms were lower. The incremental QALY value for the base case was 0.2012 [95% CI -0.0238, 0.4716], which reduced to 0.0703 [95% CI -0.0652, 0.2151] with 1-year treatment effect duration and increased to 0.7510 [95% CI 0.1967, 1.6083] with lifetime treatment effect duration assumptions.

In the base case, assuming a 4-year treatment effect duration, the incremental cost-effectiveness ratio (ICER) is £28,813 with a cost-effectiveness probability of 42.6% using a £20,000/QALY threshold, 1-year assumption resulted in a cost-ineffective ICER of £174,471 (15.8%) and a lifetime assumption led to an outcome where KICk-OFF arm was dominant with a cost-effectiveness probability of 79.8%. For the high baseline HbA1c group, however, the KICk-OFF arm was dominant in all three scenarios, with cost-effectiveness probabilities of 79.6%, 96.4% and 100% for 1-year, 4-year and lifetime treatment effect durations, respectively.

The cost effectiveness planes (CEPs) and the cost effectiveness acceptability curves (CEACs) are provided in Supplementary Information document, Figures S1 and S2, respectively. These figures highlight the parameter uncertainty in the ICER estimates.

DISCUSSION

This paper evaluates the cost-effectiveness of KICk-OFF T1DM structured education programme over the usual care arm, which is centre-specific education delivered without a clear structure. After adjusting for baseline, at each time point the mean HbA1c level for the whole intervention group was not significantly different from that of controls. The within-trial analysis, which is limited due to the short follow-up period it covers and the limited number of complication-related events a cohort of this age group would experience, has showed more favourable results for the usual care arm. The most favourable within-trial scenario for the KICk-OFF arm was observed when the CHU9D instrument was used to capture the QALYs. The results changed considerably when two extremes were considered for the treatment effect duration, with 1-year duration leading to a cost-

ineffective outcome and a lifetime duration resulting in a cost-saving outcome for the KICk-OFF arm. This demonstrates that the short-term QALY gains identified within the trial, which were favouring the usual care arm, are overturned by the longer-term health effects generated by the greater HbA1c improvement observed for the KICk-OFF arm compare to usual care arm. The uncertainty of the results has been illustrated with the cost-effectiveness planes which indicated that uncertainty increases in parallel with the length of the treatment duration assumption. Although the base case results for the overall group show that the KICk-OFF programme may be considered as 'not cost-effective' at £20,000/QALY threshold and 'cost-effective' at £30,000/QALY threshold, there is considerable evidence that the programme would lead to cost-effective outcomes for the high baseline HbA1c group irrespective of the treatment effect duration assumed.

In addition to patient-level modelling and fully accounting for parameter uncertainty, which allowed to capture individual heterogeneity and illustrated the robustness of the results, the strengths of the study include using data from a UK-based, multi-centre RCT of a structured education programme. However, the study also has a number of limitations. First, the effectiveness of the KICk-OFF education programme was only represented by the change in HbA1c levels, hypoglycaemia and DKA risks. The effect of baseline HbA1c level, and the duration of the changes in HbA1c levels were explored in sensitivity analyses, but there is also the potential to incorporate KICk-OFF's effect directly on other indicators such as weight or physical activity [5]. In addition, although it is the best evidence available, the Model used published data from non-UK settings to define risk of long-term complications, some of which are from studies published several years ago [5]. Finally, the issue of missing observations, especially in the utilities data used for the within-trial analyses, is addressed by a recognised imputation method selected as part of the sensitivity analysis. Further research should investigate the impact of alternative imputation methods on the cost-effectiveness analyses. Alternative data sources that have been used to populate the disutility parameters for comorbidities in long-term cost-effectiveness model introduces heterogeneity into the analyses; however, there is not a single source that reports all disutility parameters of interest.

The generalizability of the results of this study is limited to cohorts with similar characteristics, such as having a cohort of children (aged 11-16 years) and using the UK-based costs to analyse the resource use. However, with small refinements, the Sheffield Type 1 Diabetes Policy Model could be used to analyse the effects of additional interventions. For example, the Model will be used to analyse trials for adolescents (aged 16-21) called Working with Insulin, Carbs, Ketones and Exercise to manage Diabetes (WICKED) [23].

CONCLUSION

In conclusion, the results of this study suggest that, for the whole study population, the cost-effectiveness of the KICk-OFF structured education programmes depends on the assumption on the treatment effect duration , which had mean baseline HbA1c of 9.20% (77.0 mmol/mol) and mean 24-month follow-up HbA1c of 9.22% (77.3 mmol/mol).For the high baseline HbA1c sub-group, which was defined as having an HbA1clevel over 9.5% (80.3 mmol/mol) at the baseline, resulting in a mean baseline HbA1c value of 11.04% and a 24-month follow-up value of 10.55%, KICk-OFF arm was estimated to be cost-effective (in fact dominant i.e. providing better health gains at lower costs than usual care) regardless of the assumption on the treatment effect duration.

Conflict of Interest: This paper presents independent research commissioned by the Diabetes UK, grant number 07/0003555. The views expressed in this publication are those of the authors. None of the authors have any further financial arrangement to disclose.

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Table 1 - Blood glucose (HbA1c level %) outcomes of the KICk-OFF trial

Overall cohort	KICk-OFF mean (SD) [N]	Usual care mean (SD) [N]	Difference mean (95% CI)[p-value]
Baseline	9.28 (1.71) [202]	9.12 (1.57) [189]	0.16 (-0.16 to 0.49) [0.32]
6-months follow-up	9.31 (1.72) [199]	9.14 (1.60) [171]	0.17 (-0.17 to 0.51) [0.33]
12-months follow-up	9.30 (1.68) [196]	9.17 (1.68) [174]	0.13 (-0.22 to 0.47) [0.47]
24-months follow-up	9.18 (1.85) [186]	9.26 (1.80) [175]	-0.08 (-0.46 to 0.29) [0.65]
test for trend over time (p-value)	0.501	0.860	
Baseline HbA1c level over 9.5%			
Baseline	11.15 (1.33) [72]	10.89 (1.12) [65]	0.27 (-0.15 to 0.69) [0.21]
6-months follow-up	10.93 (1.46) [71]	10.50 (1.45) [60]	0.43 (-0.08 to 0.94) [0.09]
12-months follow-up	10.54 (1.61) [69]	10.39 (1.80) [61]	0.15 (-0.44 to 0.74) [0.62]
24-months follow-up	10.34 (2.13) [65]	10.79 (1.86) [59]	-0.45 (-1.17 to 0.26) [0.21]
test for trend over time (p-value)	0.000	0.502	
Baseline HbA1c level 9.5%and under			
Baseline	8.24 (0.72) [130]	8.19 (0.77) [124]	0.05 (-0.13 to 0.24) [0.56]
6-months follow-up	8.41 (1.08) [128]	8.40 (1.13) [111]	0.01 (-0.27 to 0.29) [0.96]
12-months follow-up	8.63 (1.29) [127]	8.52 (1.18) [113]	0.11 (-0.21 to 0.42) [0.50]
24-months follow-up	8.55 (1.31) [121]	8.49 (1.17) [116]	0.07 (-0.25 to 0.38) [0.68]
test for trend over time (p-value)	0.073	0.236	

Table 2 - Within-trial per patient cost and QALYs (based on HUI2 Children measure) over 2-year trial period

Complete Case	KICk-OFF mean (SD) [n=23]	Usual care mean (SD) [n=17]	Difference mean (95% CI)[p-value]	Simple Adjusted Difference mean (95% CI)[p-value]	Regression-based adjustment mean (95% CI) [p-value]
Complete Case - Costs*					
Costs at year 2	£ 5,795 (1,765)	£ 4,456 (2,086)	£ 1,340 (105 to 2,574) [0.03]		
Costs at baseline	£ 4,002 (1,926)	£ 4,062 (2,977)	- £ 60 (-1,630 to 1,510) [0.94]	£ 1,400 (-38 to 2,838) [0.06]	£ 1,605 (543 to 2,594) [0.01]
Complete Case - QALYs*					
QALYs at year 2	1.7671 (0.2150)	1.8384 (0.1119)	-0.0713 (-0.1873 to 0.0445) [0.22]		
QALYs at baseline	1.7701 (0.2756)	1.8279 (0.1568)	-0.0578 (-0.2087 to 0.0930) [0.44]	-0.0136 (-0.1264 to 0.0992) [0.81]	-0.0403 (-0.1184 to -0.0398) [0.20]
Mean ICER (CE%)**				DOMINATED (8.7%)	DOMINATED (0.6%)
Imputed Cases - Costs*	[n=175]	[n=147]			
Costs at year 2	£ 7,215 (4,689)	£ 4,684 (2,736)	£ 2,530 (1,703 to 3,357) [0.00]		
Costs at baseline	£ 5,854 (6,724)	£ 4,538 (4,359)	£ 1,317 (47 to 2,586) [0.04]	£ 1,215 (9 to 2,419) [0.05]	£ 2,169 (1,480 to 2,854) [0.00]
Imputed Cases - QALYs*					
QALYs at year 2	1.7434 (0.1716)	1.7706 (0.1602)	-0.0272 (-0.0639 to 0.0093) [0.14]		
QALYs at baseline	1.7616 (0.2159)	1.7586 (0.2011)	0.0029 (-0.0431 to 0.0489) [0.90]	-0.0302 (-0.0594 to -0.0010) [0.04]	-0.0299 (-0.0539 to 0.0059) [0.01]
Mean ICER (CE%)**				DOMINATED (0.5%)	DOMINATED (0%)

*Base year for costs and QALYs is 2009. **(CE%) stands for cost-effectiveness probability.

Table 3 - Full Cohort Long-Term Model Outcomes and Economic Evaluation of KICk-OFF vs. usual care treatment arms (for 5,000 simulated individuals over their lifetime)

	1-year treatment effect duration			4-year treatment effect duration			Lifetime treatment effect duration		
Clinical results (over lifetime horizon)	KICk-OFF	Usual Care	Inc*	KICk-OFF	Usual Care	Inc*	KICk-OFF	Usual Care	Inc*
Microalbuminuria	4,085	4,087	-2	4,097	4,103	-6	4,030	4,120	-90
Macroalbuminuria	3,487	3,489	-2	3,505	3,513	-8	3,466	3,608	-143
End-stage renal disease	3,264	3,267	-3	3,284	3,293	-10	3,262	3,401	-139
Death attributable to end-stage renal disease	2,212	2,215	-3	2,228	2,239	-11	2,228	2,335	-107
Background retinopathy	2,882	2,891	-10	2,943	2,971	-27	2,963	3,114	-150
Proliferative retinopathy	1,368	1,371	-4	1,402	1,422	-20	1,481	1,593	-112
Macular oedema	1,131	1,137	-6	1,154	1,163	-9	1,121	1,150	-29
Blindness	154	155	-1	159	162	-3	162	172	-10
Clinical neuropathy	2,910	2,912	-2	2,932	2,943	-12	2,903	3,026	-123
Amputation	985	986	-1	995	1,001	-6	977	1,009	-32
Non-fatal myocardial infarction	1,445	1,442	3	1,439	1,430	9	1,408	1,378	30
Fatal myocardial infarction	1,417	1,414	3	1,410	1,405	5	1,381	1,349	32
Non-fatal Stroke	290	290	-1	290	290	1	284	277	7
Fatal stroke	83	83	1	82	82	0	81	79	2
Non-fatal heart failure	618	617	1	615	613	1	604	589	14
Fatal heart failure	37	37	0	36	37	0	36	35	1
Angina	1,571	1,569	2	1,567	1,556	11	1,531	1,500	32
Severe hypoglycaemia	8,926	8,672	254	9,643	9,088	555	29,168	21,624	7544
Diabetic ketoacidosis	5,703	5,472	231	6,630	6,611	18	23,941	27,436	-3495
Number of patient years	235,266	235,115	151	234,570	233,983	587	234,000	229,586	4414
Life years per patient	47.05	47.02	0.03	46.91	46.80	0.12	46.80	45.92	0.88
Cost-effectiveness results									
Intervention cost	£1,690	£0	£1,690	£1,690	£0	£1,690	£1,690	£0	£1,690
Discounted lifetime insulin costs	£24,667	£24,340	£327	£24,620	£24,263	£357	£24,558	£23,998	£560
Discounted lifetime cost of long-term complications	£73,920	£74,161	-£240	£74,868	£75,807	-£939	£76,040	£80,435	-£4,395
Discounted lifetime cost of adverse events	£997	£929	£68	£1,236	£1,210	£26	£3,453	£3,745	-£292
Combined total average discounted lifetime cost	£101,274	£99,429	£1,845	£102,414	£101,279	£1,135	£105,742	£108,179	-£2,437
Mean discounted QALYs lived if no complications	18.6554	18.6463	0.0090	18.6200	18.5871	0.0329	18.5733	18.3843	0.1890
Discounted QALYs lost due to long-term complications	-0.5925	-0.5948	0.0023	-0.6015	-0.6082	0.0067	-0.5988	-0.6233	0.0244
Discounted QALYs lost due to adverse events	-0.0117	-0.0109	-0.0008	-0.0146	-0.0143	-0.0002	-0.0410	-0.0454	0.0044
Combined total average discounted lifetime QALYs	18.0512	18.0406	0.0106	18.0039	17.9646	0.0394	17.9335	17.7157	0.2178
ICER (unadjusted)			£174,471			£28,813			DOMINANT
ICER (jackknife)			£166,073			£28,580			DOMINANT
Net Monetary Benefit at threshold of £20,000 per QALY			-£1,633			-£347			£6,793
Probability KICk-OFF arm is cost-effective at £20,000/QALY			15.8%			42.6%			79.8%

*"Inc" refers to "incremental".

Table 4 - High* Baseline Hba1c Cohort Long-Term Model Outcomes and Economic Evaluation of KICk-OFF vs. usual care treatment arms (for 5,000 simulated individuals over their lifetime)

	1-year treatment effect duration			4-year treatment effect duration			Lifetime treatment effect duration		
Clinical results (over lifetime horizon)	KICk-OFF	Usual Care	Inc*	KICk-OFF	Usual Care	Inc*	KICk-OFF	Usual Care	Inc*
Microalbuminuria	4751	4754	-3	4750	4761	-11	4401	4608	-207
Macroalbuminuria	4666	4671	-5	4667	4681	-15	4071	4408	-337
End-stage renal disease	4470	4478	-8	4471	4493	-22	3880	4231	-351
Death attributable to end-stage renal disease	3178	3188	-10	3176	3208	-31	2734	3018	-283
Background retinopathy	4548	4578	-30	4561	4611	-49	3901	4256	-351
Proliferative retinopathy	2719	2764	-44	2760	2880	-120	2218	2669	-451
Macular oedema	1462	1456	6	1442	1393	49	1339	1280	58
Blindness	276	281	-5	277	288	-11	234	263	-29
Clinical neuropathy	3996	4008	-12	4004	4039	-35	3502	3852	-79
Amputation	1277	1283	-6	1275	1289	-15	1147	1226	-355
Non-fatal myocardial infarction	1125	1120	5	1129	1110	19	1240	1172	68
Fatal myocardial infarction	1061	1054	7	1062	1044	19	1191	1111	80
Non-fatal Stroke	222	220	1	223	218	5	247	232	15
Fatal stroke	62	63	0	63	62	1	70	65	4
Non-fatal heart failure	473	470	3	474	466	8	526	492	*34*
Fatal heart failure	28	28	0	28	28	1	32	30	2
Angina	1210	1205	5	1212	1193	20	1358	1264	94
Severe hypoglycaemia	2742	2532	211	3308	2744	564	16996	8280	8716
Diabetic ketoacidosis	11928	12734	-806	12402	17514	-5112	21586	99712	*-78126*
Number of patient years	191342	190516	825	191641	189299	2342	208805	195157	13648
Life years per patient	38.27	38.10	0.17	38.33	37.86	0.47	41.76	39.03	2.73
Cost-effectiveness results									
Intervention cost	£1,690	£0	£1,690	£1,690	£0	£1,690	£1,690	£0	£1,690
Discounted lifetime insulin costs	£20,701	£21,702	-£1,001	£20,732	£21,603	-£871	£22,865	£21,882	£983
Discounted lifetime cost of long-term complications	£122,514	£123,788	-£1,274	£121,772	£125,819	-£4,046	£106,298	£119,614	-£13,316
Discounted lifetime cost of adverse events	£1,827	£2,016	-£189	£1,951	£3,147	-£1,196	£5,066	£12,823	-£7,757
Combined total average discounted lifetime cost	£146,732	£147,506	-£774	£146,146	£150,569	-£4,423	£135,919	£154,319	-£18,400
Mean discounted QALYs lived if no complications	16.6301	16.5731	0.0569	16.6551	16.4974	0.1576	17.2887	16.7098	0.5789
Discounted QALYs lost due to long-term complications	-0.8829	-0.8938	0.0109	-0.8774	-0.9058	0.0284	-0.7918	-0.8651	0.0733
Discounted QALYs lost due to adverse events	-0.0228	-0.0253	0.0024	-0.0243	-0.0395	0.0152	-0.0631	-0.1619	0.0988
Combined total average discounted lifetime QALYs	15.7244	15.6541	0.0703	15.7534	15.5521	0.2012	16.4339	15.6829	0.7510
ICER (unadjusted)			DOMINANT			DOMINANT			DOMINANT
ICER (jackknife)			DOMINANT			DOMINANT			DOMINANT
Net Monetary Benefit at threshold of £20,000 per QALY			£2,179			£8,448			£33,420
Probability KICk-OFF arm is cost-effective at £20,000/QALY			79.6%			96.4%			100.00%

*'High Baseline HbA1c' is defined as an HbA1c over 9.5% (80.3mmol/mol). **"Inc" refers to "incremental".

Cost-effectiveness of structured education in children with type-1 diabetes mellitus

Short title: Cost-effectiveness of educating diabetic children

Supplementary Information

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Table S1 - Unit Costs		
Intervention Cost	**Unit cost***	**Source**
KICk-OFF intervention cost per participant	£1,690	KICk-OFF trial data, calculated based on the educator time, venue, educator accommodation, parent day, educator travel, participant travel to course, website, course food, equipment & materials, educator food and activity exercise sessions
Breakdown of the intervention cost per participant		
Educator Time (3 educators)	£1,367	81% of the intervention cost (KICk-OFF trial), based on 41 average teaching week hours for 12 teaching weeks, 12 average non-teaching week hours spent for delivery of the course for 24 non-teaching weeks, 9 average hours for parents day for 9 parents day weeks, using a weighted average of the hourly wage for Band 6 (£44) and Band 7 (£52) nurses [1]
Venue hire	£70	4% of the intervention cost (KICk-OFF trial)
Educator Accommodation	£68	4% of the intervention cost (KICk-OFF trial)
Parent day expenses	£61	4% of the intervention cost (KICk-OFF trial)
Educator Travel	£33	2% of the intervention cost (KICk-OFF trial)
Participant travel to course	£21	1% of the intervention cost (KICk-OFF trial)
Website	£18	1% of the intervention cost (KICk-OFF trial)
Course food	£16	1% of the intervention cost (KICk-OFF trial)
Equipment & materials	£12	1% of the intervention cost (KICk-OFF trial)
Educator Food	£11	1% of the intervention cost (KICk-OFF trial)
Activity/exercise sessions	£8	>1% of the intervention cost (KICk-OFF trial)
Education of the educators	£5	>1% of the intervention cost (KICk-OFF trial)
NHS contact cost		
Consultant led face-to-face/clinic contact	£136.2	[2] NSRC1 National Schedule of Reference Costs Year : 2010-11 NHS Trusts Consultant Led: weighted average of"Follow up Attendance Non-Admitted Face to Face" (307: Diabetic Medicine) and "First Attendance Non-Admitted Face to Face" (307: Diabetic Medicine)
Non-consultant led face-to-face/clinic contact	£97.92	[2] NSRC1 National Schedule of Reference Costs Year: 2010-11 NHS Trusts Non-Consultant Led: weighted average of "Follow up Attendance Non-Admitted Face to Face" (307: Diabetic Medicine) and "First Attendance Non-Admitted Face to Face" (307: Diabetic Medicine)
Non-consultant led non-face-to-face/clinic contact	£41.08	[2] NSRC1 National Schedule of Reference Costs Year : 2010-11 NHS Trusts Non-Consultant Led: weighted average of"Follow up Attendance Non-Admitted Non Face to Face" (307: Diabetic Medicine) and "First Attendance Non-Admitted Non Face to Face" (307: Diabetic Medicine)
Accident and Emergency Services: Walk in Centres: Not Leading to Admission	£45.21	[2] NSRC1 National Schedule of Reference Costs Year:2010-11 NHS VB09Z: Trusts Category 1 investigation with category 1-2 treatment (National Average Unit Cost)
Insulin cost		
Insulin unit	£0.02	[3]
Daily needle cost	£0.08	[3], personal communication with healthcare professionals, assuming the use of a quick acting needle for a day and a background insulin needle for three days
Daily blood testing strip cost	£1.32	[3], based on mean number of strips per day: 4.4 (KICk-OFF trial)
Daily lancet cost	£0.23	[3], personal communication with healthcare professionals, assuming one lancet for each injection, 5 injections a day
Annual cost of insulin pen	£8.04	[3], original DAFNE trial, personal communication from manufacturers
Admission Costs		
Admission cost for first day	£385	[2] NSRC1 National Schedule of Reference Costs Year : 2010-11- Non-Elective Inpatient (Short Stay) – KB01B National Average Unit Cost
Admission cost for each additional day	£226	[2] NSRC1 National Schedule of Reference Costs Year : 2010-11- Non-Elective Inpatient (Long Stay) Excess Bed Day -KB01B National Average Unit Cost
Paramedic cost per case	£178	[4]

*Base year for unit costs is 2011.

-All event costs associated with the long-term complications are reported elsewhere [5], [6].

-If any cost data was left blank, and that individual has reported at least one other cost, the cost that was left blank is assumed as zero.

Table S2 - Individual Characteristics Used as Inputs for the Long-Term Model and Costs Observed in KICk-OFF trial

Baseline characteristics	KICk-OFF mean (SD) [N=204]	Usual care mean (SD) [N=193]
Age (years)	13.0 (1.5)	13.2 (1.6)
Time since diagnosis (years)	4.8 (3.1)	5.2 (3.6)
Sex (proportion male)	47%	43%
Costs for Complete Cases	**KICk-OFF [mean (SD) [n=88]]**	**Usual care [mean (SD) [n=55]]**
Intervention cost	£ 1,690 (269)	0
Overnight admission cost	£ 1,065 (3,413)	£ 387 (1,792)
Insulin cost	£ 2,317 (668)	£ 2,287 (515)
NHS contact cost	£ 2,093 (2,002)	£ 2,113 (1,846)
Total Cost	£ 7,165 (4,530)	£ 4,787 (3,102)

Table S3. Utility parameters and decrements used in the long-term cost-effectiveness analysis

Health state or event	Utility	S.E	Beta distribution		Source(s)
			Alpha	Beta	
Baseline utility values					
Male with Type 1 diabetes and no complications	0.888	0.006	2452.36	309.3067	[7]
Complications /covariates	**Disutility Decrement**	**S.E.**	**Gamma Distribution**		**Source(s)**
			Alpha	**Beta**	
Female Type 1 & no complications	-0.030	0.008	14.06	0.002133	[7]
Nephropathy					
Microalbuminuria	0				Assumption
Macroalbuminuria	-0.017	0.01	2.89	0.005882	[8] Table 2
End-stage renal	-0.078	0.026	9.00	0.008667	[8] Table 2 (Type II)
Neuropathy					
Clinical neuropathy	-0.055	0.01	30.25	0.001818	[8]
Clinically confirmed neuropathy	-0.055	0.01	30.25	0.001818	[8]
Diabetic Foot Syndrome	-0.076	0.016	22.56	0.003368	[8] Table 2 (sores)
PAD with amputation	-0.172	0.045	14.61	0.011773	[9] (table IV)
Retinopathy					
Background retinopathy	-0.0368	0.009	16.90	0.002189	[7]
Proliferative retinopathy	-0.0531	0.018	8.35	0.006231	[7]
Blindness	-0.208	0.013	256.00	0.000813	[8]
Cardivascular					
MI (First year)	-0.065	0.03	4.69	0.013846	[9] (Table IV)
MI (Subsequent years)	-0.057	0.03	3.61	0.015789	[9] (Table IV)
HF	-0.101	0.032	9.96	0.010139	[9] (Table IV)
Stroke	-0.165	0.035	22.22	0.007424	[9] (Table IV)
Angina	-0.090	0.018	24.01	0.003749	[10] (IHD Table 4**)**
Hypoglycaemia episode unable to treat yourself	-0.0012	0.001	1.44	0.000833	[7]
DKA	-0.0165	0.005	10.89	0.001515	[7]

Tables S4 and S5 show the within-trial analyses on HUI2 Parent and CHU9D instruments, using both completed cases and imputed cases. It is important to clarify that the imputation has been used only as part of the within-trial analyses (especially where individual patient utilities data were missing) and imputation is not included in the long-term cost-effectiveness modelling of the KICk-OFF intervention which is the key analysis from a NICE decision making perspective. That said, justification of imputation methods is an important issue.

In the multiple imputation literature, data are "missing completely at random" (MCAR) if the probability of a particular value being missing is completely independent of both the observed data and the unobserved data. In other words, the complete cases are a random sample. If the data are MCAR, then both complete cases analysis and multiple imputation give unbiased estimates. If the probability of a particular value being missing depends only on the observed data, then the data is "missing at random" (MAR) and the complete cases are not a random sample. With MAR data, complete cases analysis gives biased results but multiple imputation does not. If one believes data are MAR rather than MCAR, then you should consider using multiple imputation.

We have undertaken statistical analyses that indicate that the data are not MCAR. This means that MAR should be utilised.

The next question is whether missingness is related to unobserved data in some way. Because we have a considerable amount of data on baseline characteristics and on changes in clinical parameters, we have already tested for these factors. We considered whether there were any other unobserved factors that might affect missingness. We did not identify any in this process. Our statisticians did not identify any formal statistical methods to test for this latter question.

Table S4 - Within-trial per patient cost and QALYs with HUI2 Parent measure over 2-year trial period					
Complete Case	**KICk-OFF mean (SD) [n=25]**	**Usual care mean (SD) [n=18]**	**Difference mean (95% CI)[p-value]**	**Simple Adjusted Difference mean (95% CI)[p-value]**	**Regression-based adjustment mean (95% CI) [p-value]**
Complete Case - Costs*					
Costs at year 2	£ 5,836 (1,770)	£ 4,410 (2,247)	£ 1,426 (188 to 2,663) [0.03]		
Costs at baseline	£ 3,758 (1,869)	£ 4,008 (2,888)	-£ 250 (-1,714 to 1,215) [0.73]	£ 1,675 (298 to 3,052) [0.02]	£ 1,649 (624 to 2,665) [0.00]
Complete Case - QALYs*					
QALYs at year 2	1.7940 (0.1859)	1.7819 (0.1501)	0.0121 (-0.0952 to 0.1195) [0.82]		
QALYs at baseline	1.7475 (0.2694)	1.7352 (0.2140)	0.0123 (-0.1425 to 0.1670) [0.87]	-0.0002 (-0.1043 to 0.1040) [1.00]	0.0106 (-0.0543 to 0.0755) [0.85]
Mean ICER (CE%)**				DOMINATED (10.9%)	155,556 (5.4%)
Imputed Cases - Costs*	**[n=176]**	**[n=147]**			
Costs at year 2	£ 7,197 (4,681)	£ 4,684 (2,736)	£ 2,513 (1,688 to 3,337) [0.00]		
Costs at baseline	£ 5,861 (6,701)	£ 4,538 (4,359)	£ 1,323 (58 to 2,588) [0.04]	£ 1,190 (-11 to 2,390) [0.05]	£ 2,159 (1,464 to 2,860) [0.00]
Imputed Cases - QALYs*					
QALYs at year 2	1.7434 (0.1750)	1.7385 (0.1715)	0.0049 (-0.0332 to 0.0430) [0.80]		
QALYs at baseline	1.7409 (0.2144)	1.7345 (0.2140)	0.0063 (-0.0407 to 0.0534) [0.60]	-0.0014 (-0.0336 to 0.0307) [0.46]	-0.0018 (-0.0277 to 0.0252) [0.99]
Mean ICER (CE%)**				DOMINATED (4.3%)	DOMINATED (0%)

*Base year for costs is 2009. **(CE%) stands for cost-effectiveness probability.

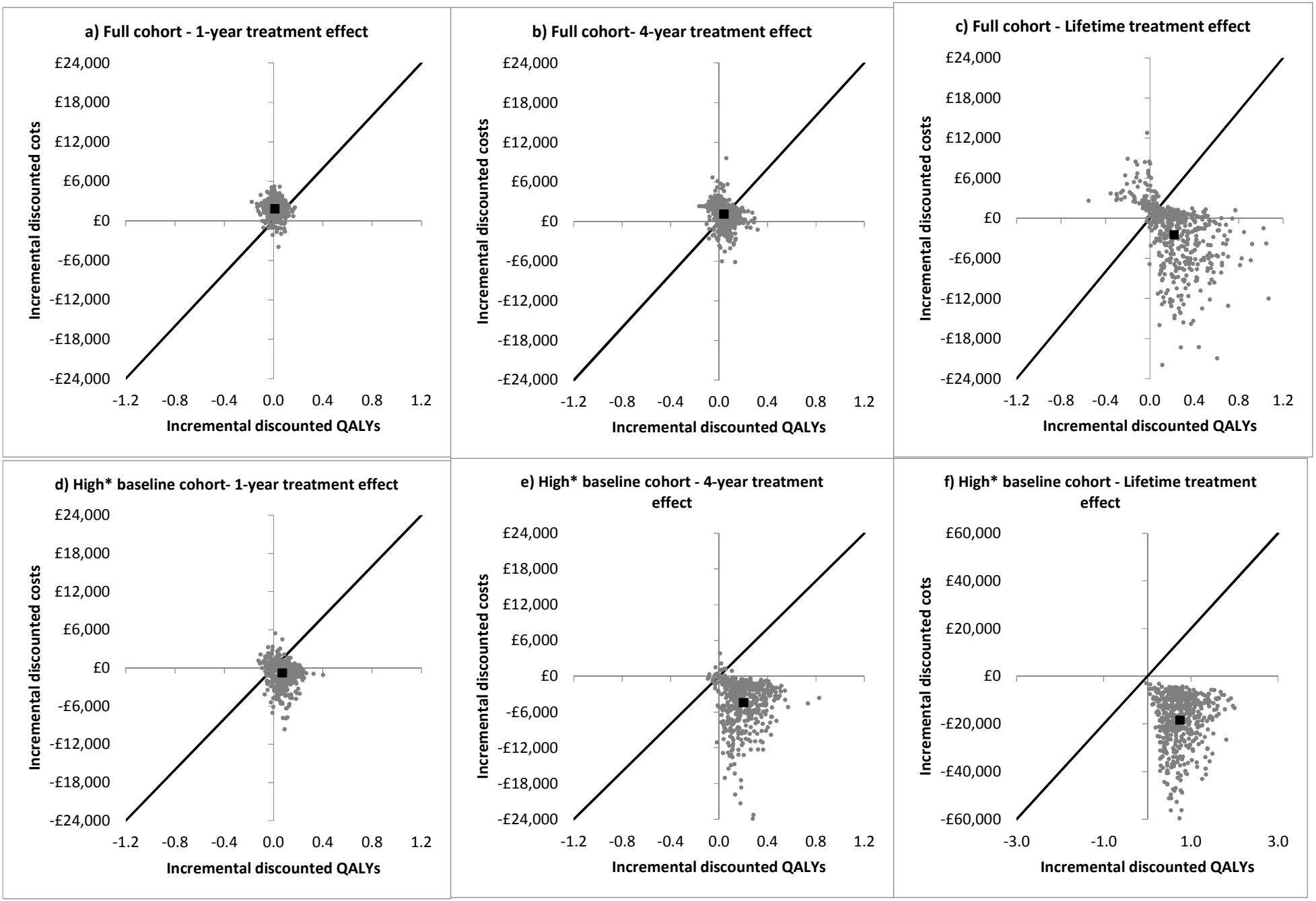
Table S5 - Within-trial per patient cost and QALYs with CHU9D measure over 2-year trial period					
Complete Case	**KICk-OFF mean (SD) [n=25]**	**Usual care mean (SD) [n=18]**	**Difference mean (95% CI)[p-value]**	**Simple Adjusted Difference mean (95% CI)[p-value]**	**Regression-based adjustment mean (95% CI) [p-value]**
Complete Case - Costs*					
Costs at year 2	£ 5,955 (1,923)	£ 4,642 (2,216)	£ 1,313 (34 to 2,593) [0.04]		
Costs at baseline	£ 3,913 (1,898)	£ 3,936 (2,901)	-£ 23 (-1,500 to 1,454) [0.98]	£ 1,336 (-145 to 2,817) [0.08]	£ 1,571 (446 to 2,696) [0.01]
Complete Case - QALYs*					
QALYs at year 2	1.7814 (0.1221)	1.8484 (0.0784)	-0.0670 (-0.1333 to -0.0007) [0.05]		
QALYs at baseline	1.7253 (0.2195)	1.8487 (0.0919)	-0.1233 (-0.2345 to -0.0122) [0.03]	0.0564 (-0.0225 to 0.0135) [0.16]	-0.0142 (-0.0596 to 0.0286) [0.40]
Mean ICER (CE%)**				£23,688 (41.3%)	DOMINATED (0.5%)
Imputed Cases - Costs*	**[n=175]**	**[n=146]**			
Costs at year 2	£ 7,199 (4,695)	£ 4,690 (2,745)	£ 2,509 (1,680 to 3,338) [0.00]		
Costs at baseline	£ 5,830 (6,723)	£ 4,545 (4,372)	£ 1,285 (11 to 2,558) [0.05]	£ 1,224 (15 to 2,433) [0.05]	£ 2,182 (1,523 to 2,878) [0.00]
Imputed Cases - QALYs*					
QALYs at year 2	1.7904 (0.1251)	1.8016 (0.1039)	-0.0112 (-0.0368 to 0.0143) [0.39]		
QALYs at baseline	1.7718 (0.1811)	1.7885 (0.1616)	-0.0166 (-0.0547 to 0.0213) [0.69]	0.0055 (-0.0181 to 0.0291) [0.65]	-0.0033 (-0.0190 to 0.0117) [0.76]
Mean ICER (CE%)**				£225,545 (3.8%)	DOMINATED (0%)

*Base year for costs is 2009. **(CE%) stands for cost-effectiveness probability.

The cost effectiveness planes (CEPs) provided in Figure S1 highlight the parameter uncertainty in the ICER estimates. The limited uncertainty observed in the 1-year treatment effect duration (Figure S1a) has gradually increased with the 4-year (Figure S1b) and lifetime (Figure S1c) duration assumptions. The same pattern emerged for the CEPs on the high baseline HbA1c group, with most of the PSA samples being located in the south-east quadrant where the KICk-OFF intervention is dominant under the 4-year (Figure S1e) and lifetime (Figure S1f) treatment effect duration assumptions.

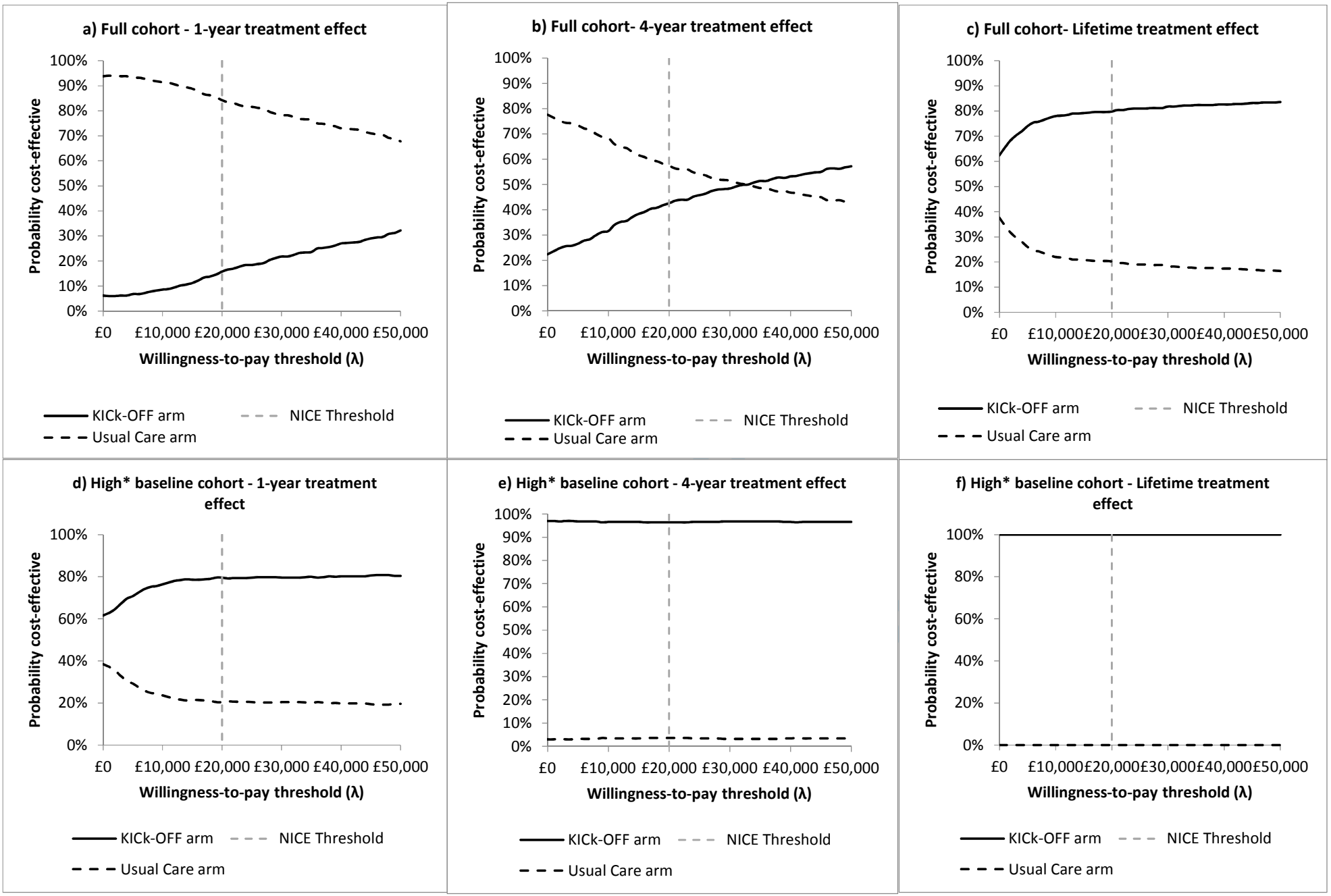
The cost effectiveness acceptability curves (CEACs) provided in Figure S2 report the cost-effectiveness probability of each arm over a range of willingness-to-pay thresholds up to £50,000/QALY. Reflecting the uncertainty illustrated in Figure S1, Figure S2a shows a higher cost-effectiveness probability for the usual care arm throughout using the 1-year treatment effect duration. Two lines for the treatment arms intersect Figure S2b around £32,000/QALY threshold, meaning the cost-effectiveness probability of the KICk-OFF arm exceeds that of usual care arm at a higher threshold level using on the 4-year duratio. Figure S2c allocates a higher cost-effectiveness probability for the KICk-OFF arm throughout the willingness-to-pay thresholds considered. For the high baseline HbA1c group, the line representing KICk-OFF arm was drawn higher than that of the usual care arm, indicating a higher cost-effectiveness probability at 1-year (Figure S2d), 4-year (Figure S2e) and lifetime (Figure S2f) treatment duration assumptions.

Figure S1. Cost Effectiveness Planes (CEPs) using Full Cohort and High* Baseline Sample at assumptions on the length of alternative treatment benefit periods



*'High Baseline HbA1c' is defined as an HbA1c over 9.5% (80.3mmol/mol).

Figure S2. Cost Effectiveness Acceptability Curves (CEACs) using Full Cohort and High* Baseline Sample at assumptions on the length of alternative treatment benefit periods



*'High Baseline HbA1c' is defined as an HbA1c over 9.5% (80.3mmol/mol).

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