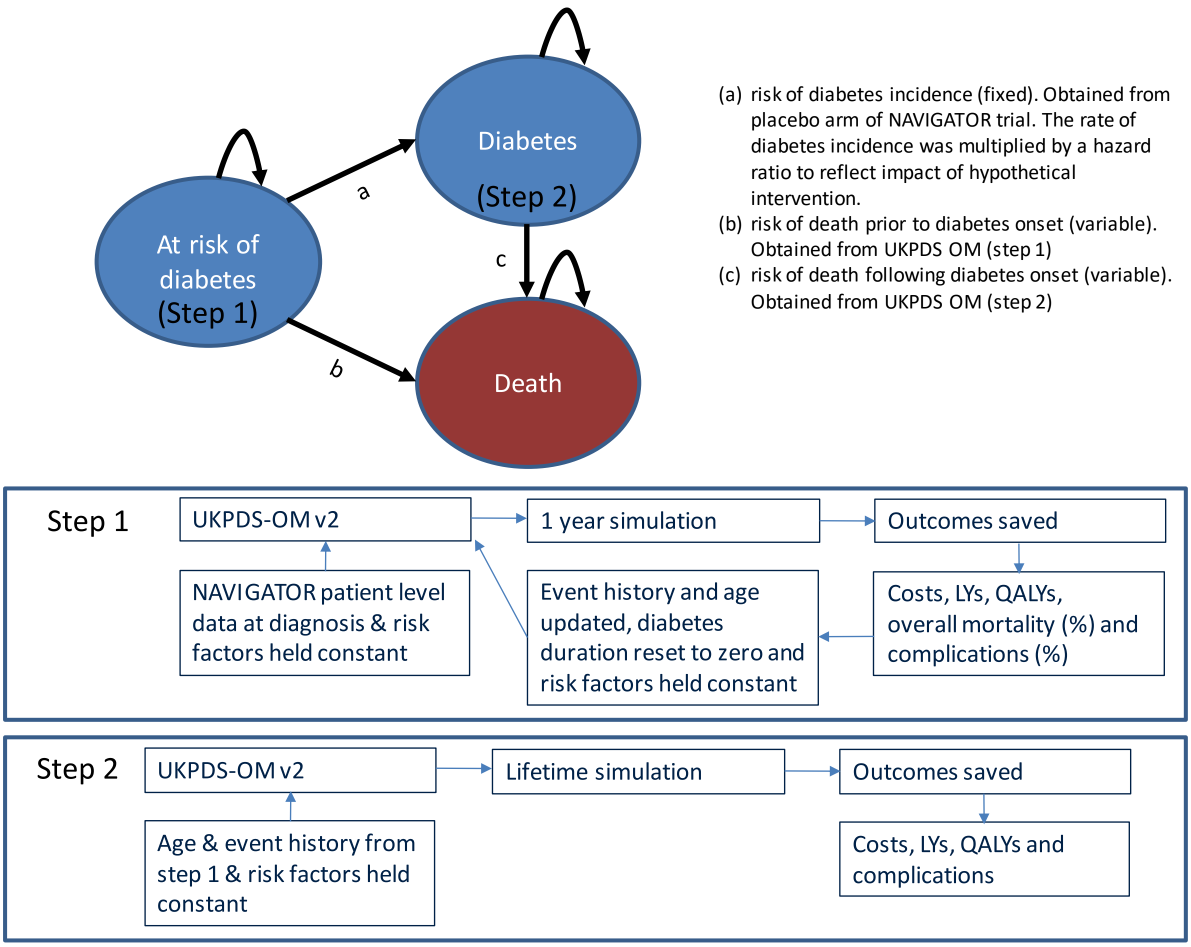
Online appendix

Figure A.1. Modelling framework to estimate



Step 1 was used to estimate outcomes (costs, life years and QALYs) and mortality prior to diabetes onset for each year and each individual in the ‘at risk of diabetes’ health state. Individual-level mortality rate estimated in Step 1 was used to determine the transition to ‘death’ state from ‘at risk of diabetes’ state. Step 2 was used following progression to diabetes health state to produce costs, life years and QALYs from diabetes onset to end of simulation.

Relative effectiveness of hypothetical intervention

We estimated the median time to diabetes using the formula: ln(2)/rate. For example, the median time in the placebo arm of the NAVIGATOR trial was 8.6 years (80.4 per 1000 person years). We then added 1, 3, 5, 7 and 9 years to the median time and converted it back to a rate. Hence, the new rate of diabetes incidence if the intervention delayed onset by one year was 72.0 per 1000 person years (median time to diabetes 9.6 years).

The hazard ratio was estimated by dividing the new rate of diabetes incidence following intervention by the rate in the placebo arm. Using the example above, for an intervention delaying the onset of diabetes by 1 year the hazard ratio was estimated to be 0.90 (72.0/80.4). Hence, the hazard ratios for interventions delaying the onset of diabetes by 3, 5, 7 and 9 years were 0.74 (59.6/80.4), 0.63 (50.9/80.4), 0.55 (44.4/80.4) and 0.49 (39.3/80.4), respectively.

The estimated hazard ratios were then applied to the rate of diabetes incidence to simulate the impact of the hypothetical interventions. It is worth noting that the hazard ratios were estimated in a scenario that excluded death as a competing risk. Therefore, once death was allowed as a competing risk in the modelling framework the delay in the median time to diabetes onset was larger than 1, 3, 5, 7 and 9 years respectively.

Propagating uncertainty

We reduced Monte-Carlo simulation error for predicted outcomes when using UKPDS-OM2 by averaging 5,000 simulations per patient. We propagated parameter uncertainty through the model into the different outcomes by performing 300 random draws of the sets of fully correlated coefficients from all risk event equations.

Risk factor trajectories

In the base case, we held risk factors constant from baseline. In sensitivity analysis, we explored the impact of these assumptions by changing the trajectories of HbA1c, BMI, LDL, HDL and systolic blood pressure (SBP) over time based on their values at start of simulation. To achieve this, we used unpublished risk factor equations based on UKPDS longitudinal data. These assume the risk factors to be independent of each other and make future predictions of their values based on age, log of year, sex, risk factor value at baseline, previous year value of risk factor and ethnicity, where applicable. The equations are currently being submitted to a peer-reviewed journal.

Table A.1: NAVIGATOR and UKPDS-OM2 population characteristics

Characteristics	NAVIGATOR	UKPDS-OM2
Patients	3058	5102
Median follow up post diagnosis of diabetes (years)	6.5	17.6
Age at diagnosis (years)	66 (6.9)	52 (9)
% men	52	59
% white	83	82
% Asian Indian	N/A	10
% Afro-Caribbean/Black	2	8
% Oriental	7	N/A
% Other	8	0
HBA1c (%)	6.1 (0.6)	6.5 (1.4)
SBP (mmHG)	136 (16)	135 (21)
Total cholesterol (mmol/l)	5.2 (1.1)	N/A
LDL (mmol/l)	4.0 (1.1)	3.5 (1.0)
HDL (mmol/l)	1.3 (0.3)	1.1 (0.3)
Smokers (%)*	11.2	31
BMI (kg/m2)	31.5 (5.7)	27.7 (5.3)
Previous history (%)		
Atrial fibrillation	4	1
PVD	1	8
MI	15	0
IHD	29	0
Stroke	3	0
Amputation	0	0
Renal failure	1	0
Heart failure	1	0

N/A: not available
HbA1c First year of baseline n=4675; SBP First year of baseline n=4916; LDL First year of baseline n=4541; HDL first year of baseline n=4579; Smokers n=5,062.

Table A.2: Relative risk for different types of macro and micro-vascular events from a change in duration of diabetes relative to a recently diagnosed patient, holding everything else constant*

Duration of diabetes (year)	Ischaemic heart disease	Myocardial infarction (Men)	Myocardial infarction (Women)	Heart failure	Stroke	Amputation	Blindness in one eye	Renal failure	Ulcer
1	1.42	1.00	1.59	1.86	1.76	3.19	1.00	1.00	1.00
2	1.64	1.00	1.94	2.42	2.24	5.50	1.00	1.00	1.00
3	1.80	1.00	2.20	2.88	2.62	7.87	1.00	1.00	1.00
4	1.93	1.00	2.42	3.28	2.95	10.29	1.00	1.00	1.00
5	2.04	1.00	2.61	3.64	3.24	12.75	1.00	1.00	1.00
6	2.13	1.00	2.78	3.96	3.50	15.23	1.00	1.00	1.00
7	2.22	1.00	2.93	4.27	3.74	17.75	1.00	1.00	1.00
8	2.30	1.00	3.07	4.55	3.97	20.28	1.00	1.00	1.00
9	2.37	1.00	3.20	4.82	4.18	22.84	1.00	1.00	1.00

* estimated using the UKPDS-OM2 equations based on the UKPDS data(14). We predicted the absolute risk of each event at years 1,..,9 and divided it by the predicted risk of a newly diagnosed patient.

Table A.3: Quality of life mean estimates and costs† used in the simulation exercise. US costs expressed in $2017 prices and UK costs expressed in £2017 prices

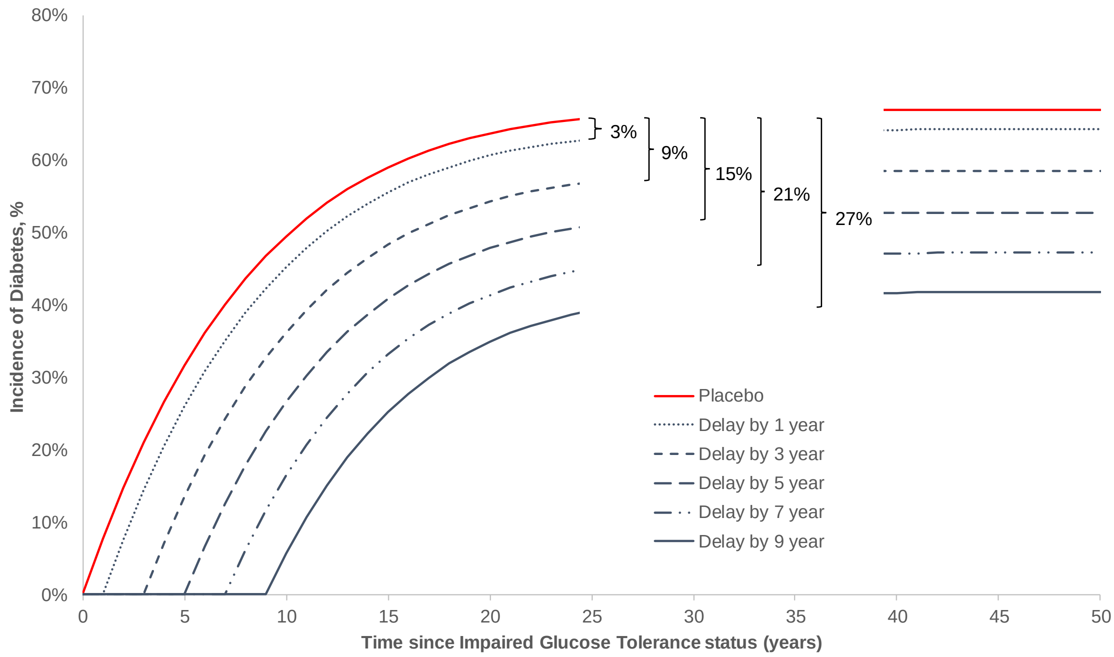
	US		UK	
Category	**Mean estimate**	**Source**	**Mean estimate**	**Source**
Quality of life decrement				
Initial utility	0.807	Alva 2014(16)	0.807	Alva 2014(16)
IHD	0.000	Alva 2014(16)	0.000	Alva 2014(16)
MI	-0.065	Alva 2014(16)	-0.065	Alva 2014(16)
Heart failure	-0.101	Alva 2014(16)	-0.101	Alva 2014(16)
Stroke	-0.165	Alva 2014(16)	-0.165	Alva 2014(16)
Amputation	-0.172	Alva 2014(16)	-0.172	Alva 2014(16)
Blindness	0.000	Alva 2014(16)	0.000	Alva 2014(16)
Renal failure	-0.330	Lung 2011 (18)	-0.330	Lung 2011 (18)
Ulcer	-0.210	Lung 2011 (18)	-0.210	Lung 2011 (18)
Costs				
IGT management costs‡	$6,762	Khan 2017 and ADA 2018	£636-£2,149*	DPP(22) and Alva 2015(17)
Diabetes management costs‡	$9,158	ADA 2018 (21)	£827-£2,792*	Alva 2015(17)
In the year of non-fatal event§				
IHD	$24,617	Ward 2014 (15)	£10,276-£18,785*	Alva 2015(17)
MI	$64,912	Ward 2014 (15)	£7,265-£13,102*	Alva 2015(17)
Heart failure	$27,322	Ward 2014 (15)	£3,807-£6,332*	Alva 2015(17)
Stroke	$48,437	Ward 2014 (15)	£7,092-£11,931*	Alva 2015(17)
Amputation	$10,397	Ward 2014 (15)	£12,310-£18,918*	Alva 2015(17)
Blindness	$3,291	Ward 2014 (15)	£2,858-£5,661*	Alva 2015(17)
Renal failure	$82,472	Ward 2014 (15)	£20,578	NHS Blood and Transplant 2009 (20)
Ulcer	$2,469	Ward 2014 (15)	£7,076	Kerr 2014 (19)
In the year of fatal event				
IHD	$24,617	Ward 2014 (15)	£4,453-£6,421*	Alva 2015(17)
MI	$64,912	Ward 2014 (15)	£2,211-£8,004*	Alva 2015(17)
Stroke	$48,437	Ward 2014 (15)	£4,964-£7,674*	Alva 2015(17)
In subsequent years§				
IHD	$2,189	Ward 2014 (15)	£1,526-£4,770*	Alva 2015(17)
MI	$2,189	Ward 2014 (15)	£1,498-£4,575*	Alva 2015(17)
Heart failure	$2,189	Ward 2014 (15)	£2,075-£5,539*	Alva 2015(17)
Stroke	$17,872	Ward 2014 (15)	£1,567-£4,755*	Alva 2015(17)
Amputation	0	Ward 2014 (15)	£3,031-£6,550*	Alva 2015(17)
Blindness	$3,291	Ward 2014 (15)	£1,037-£3,000*	Alva 2015(17)
Renal failure	$82,472	Ward 2014 (15)	£20,578	NHS Blood and Transplant 2009 (20)
Ulcer	$2,469	Ward 2014 (15)	£1,072	Kerr 2014 (19)

†US costs include medications, outpatient consultations, emergency department visits and inpatient stays(15). UK costs include non-inpatient contacts (e.g. general practitioner, nurse, hospital eye clinic, etc.) and inpatient stay(17). ‡ US diabetes management costs obtained from ADA 2018 excluding costs of complications. UK diabetes management costs obtained from UKPDS and concern costs in the absence of complications(17). IGT costs estimated by applying ratio of IGT and diabetes costs per individual from Khan 2007(23) for the US setting (0.74) and DPP(22) for the UK setting (0.77).
§ In the US analysis, IGT/diabetes management costs ($6,762/$9,158) were added to costs of non-fatal events in the year of the event and in subsequent years. In the UK analysis, management costs were already included in the costs of complications and no further costs were added to them.
* Costs varied by sex and age group (up to 50, 51-60, 61-70, 71-80, 81+).

Figure A.2: Simulated incremental complication costs and incremental quality-adjusted life years (QALYs) gained of postponing versus no postponing for different annual postponement in US and UK setting*

* Excluding costs of intervention and assuming rate of diabetes progression of 80.4 per 1000 person years.

Figure A.3. Simulating impact of delaying onset of diabetes in at risk population*



*Simulated cumulative incidence of diabetes among individuals with IGT using the observed rate from NAVIGATOR (placebo arm in Nateglinide comparison, 80.4 per 1000 person years) allowing for death as a competing risk. The relative effectiveness of each hypothetical intervention was modelled by shifting the onset of diabetes delay by 1, 3, 5, 7 and 9 years for all individuals.

Table A.4.Outcomes of population at risk of diabetes progression (80.4 per 1000 person years) with relative effectiveness of each hypothetical intervention modelled by shifting the onset of diabetes by 1, 3, 5, 7 and 9 years for all individuals.

Outcomes (over 50 years)	**No delay**	**1 year delay**	**3 year delay**	**5 year delay**	**7 year delay**	**9 year delay**
Cumulative incidence of diabetes,%	67.0	64.2	58.5	52.8	47.2	41.7
Hazard ratio vs no delay	-	0.93	0.79	0.68	0.58	0.49
US setting*						
Life years	11.90 (11.65-12.13)	11.94 (11.72-12.15)	12.01 (11.82-12.18)	12.06 (11.91-12.20)	12.11 (11.99-12.22)	12.15 (12.06-12.24)
QALYs	9.51 (9.32-9.68)	9.55 (9.38-9.71)	9.61 (9.47-9.74)	9.66 (9.55-9.77)	9.71 (9.62-9.79)	9.75 (9.67-9.82)
Costs (excluding intervention)	$161,457 (156792-166367)	$159,629 (155250-164380)	$155,972 (152056-160414)	$152,838 (149144-157007)	$150,169 (146453-154398)	$147,918 (144201-152244)
Δ Life years vs no delay	-	0.04 (0.02 to 0.06)	0.11 (0.05 to 0.15)	0.16 (0.07 to 0.25)	0.21 (0.10 to 0.32)	0.25 (0.12 to 0.38)
Δ QALY vs no delay	-	0.04 (0.02 to 0.06)	0.10 (0.05 to 0.15)	0.16 (0.09 to 0.23)	0.21 (0.12 to 0.30)	0.25 (0.15 to 0.36)
Δ Costs vs no delay (excluding intervention)	-	-$1,828 (-2423 to -1262)	-$5,485 (-7075 to -3987)	-$8,620 (-10994 to -6443)	-$11,288 (-14272 to -8569)	-$13,539 (-16993 to -10361)
Max annual cost of intervention to be cost-effective at $100,000/QALY	-	$864 (764-964)	$2,004 (1733-2275)	$2,797 (2389-3206)	$3,370 (2848-3892)	$3,795 (3176-4413)
UK setting*	**No delay**	**1 year delay**	**3 year delay**	**5 year delay**	**7 year delay**	**9 year delay**
Life years	11.43 (11.19-11.64)	11.47 (11.25-11.66)	11.53 (11.35-11.68)	11.58 (11.43-11.70)	11.62 (11.51-11.72)	11.65 (11.56-11.73)
QALYs	9.13 (8.94-9.30)	9.17 (9.00-9.32)	9.23 (9.10-9.35)	9.28 (9.17-9.37)	9.32 (9.23-9.40)	9.35 (9.28-9.42)
Costs (excluding intervention)	£38,321 (37208-39470)	£38,078 (37057-39146)	£37,549 (36638-38471)	£37,088 (36344-37922)	£36,689 (36034-37426)	£36,348 (35746-37040)
Δ Life years vs no delay		0.04 (0.02 to 0.06)	0.10 (0.04 to 0.16)	0.15 (0.06 to 0.25)	0.20 (0.08 to 0.31)	0.23 (0.09 to 0.36)
Δ QALY vs no delay		0.04 (0.02 to 0.06)	0.10 (0.05 to 0.15)	0.15 (0.08 to 0.22)	0.19 (0.10 to 0.28)	0.22 (0.12 to 0.33)
Δ Costs vs no delay (excluding intervention)		-£242 (-385 to -107)	-£772 (-1166 to -395)	-£1,233 (-1817 to -659)	-£1,631 (-2361 to -899)	-£1,973 (-2813 to -1141)
Max annual cost of intervention to be cost-effective at £20,000/QALY	-	£478 (384-573)	£982 (762-1202)	£1,262 (963-1560)	£1,433 (1082-1784)	£1,533 (1143-1922)

*discounted at 3%; **discounted at 3.5%

Table A.5: Maximum annual cost of intervention in the US and UK for intervention to be cost-effective relative to no delay by varying the rate of progression to diabetes with relative effectiveness of each hypothetical intervention modelled by shifting the onset of diabetes by 1, 3, 5, 7 and 9 years for all individuals.

Annual rate of progression (per 1000 person years)	1 year delay	3 year delay	5 year delay	7 year delay	9 year delay
US setting*					
45.5	$490	$1,208	$1,749	$2,162	$2,480
80.4 (base case)	$864	$2,004	$2,797	$3,370	$3,795
114.3	$1,225	$2,684	$3,632	$4,286	$4,756
288	$3,049	$5,225	$6,306	$6,951	$7,380
693	$7,050	$8,378	$8,899	$9,183	$9,381
UK setting**					
45.5	£248	£561	£764	£901	£989
80.4 (base case)	£478	£982	£1262	£1433	£1533
114.3	£704	£1332	£1643	£1821	£1918
288	£1689	£2429	£2694	£2825	£2882
693	£3091	£3362	£3459	£3506	£3512

*discounted at 3% and using $100,000 per QALY threshold; **discounted at 3.5% and using £20,000 per QALY threshold

Table A.6.Outcomes of US and UK population at risk of diabetes (80.4 per 1000 person years) conditional on effectiveness of hypothetical intervention and assuming IGT management costs to be the same as diabetes management costs ($9,158 and £827-£2,792 per year)

Outcomes (over 50 years)	No delay	1 year delay	3 year delay	5 year delay	7 year delay	9 year delay
Cumulative incidence of diabetes,%	67.0	63.8	58.2	53.4	49.3	45.7
Hazard ratio vs no delay	-	0.92	0.79	0.69	0.61	0.55
US setting*						
Life years	11.90	11.92	11.97	12.00	12.03	12.05
	(11.67-12.13)	(11.70-12.14)	(11.77-12.17)	(11.82-12.18)	(11.86-12.20)	(11.89-12.21)
QALYs	9.51	9.53	9.57	9.60	9.63	9.65
	(9.33-9.69)	(9.36-9.71)	(9.42-9.73)	(9.46-9.75)	(9.50-9.77)	(9.53-9.78)
Costs (excluding intervention)	$176,734	$176,298	$175,562	$174,966	$174,475	$174,062
	(172008-181632)	(171699-180942)	(171237-179815)	(170823-179155)	(170483-178626)	(170109-178180)
Δ Life years vs no delay	-	0.03	0.07	0.10	0.13	0.15
		(0.01 to 0.04)	(0.04 to 0.10)	(0.05 to 0.15)	(0.07 to 0.19)	(0.08 to 0.22)
Δ QALY vs no delay	-	0.02	0.07	0.10	0.13	0.15
		(0.01 to 0.03)	(0.04 to 0.09)	(0.06 to 0.13)	(0.08 to 0.17)	(0.09 to 0.20)
Δ Costs vs no delay		-$436	-$1,172	-$1,768	-$2,260	-$2,672
		(-720 to -184)	(-1937 to -494)	(-2924 to -744)	(-3739 to -950)	(-4423 to -1123)
Max annual cost of intervention to		$427	$1,045	$1,469	$1,778	$2,013
be cost-effective at $100,000/QALY		(350-503)	(854-1236)	(1197-1741)	(1445-2111)	(1632-2393)
UK setting*						
Life years	11.43	11.45	11.49	11.52	11.54	11.56
	(11.21-11.63)	(11.25-11.64)	(11.30-11.67)	(11.35-11.68)	(11.38-11.69)	(11.41-11.70)
QALYs	9.13	9.15	9.19	9.22	9.24	9.26
	(8.97-9.29)	(9.00-9.31)	(9.05-9.33)	(9.09-9.35)	(9.12-9.37)	(9.15-9.38)
Costs (excluding intervention)	£40,223	£40,139	£39,998	£39,884	£39,790	£39,711
	(39089-41366)	(39054-41236)	(38986-41014)	(38934-40830)	(38891-40676)	(38856-40562)
Δ Life years vs no delay	-	0.02	0.06	0.09	0.11	0.13
		(0.01 to 0.03)	(0.04 to 0.09)	(0.05 to 0.13)	(0.07 to 0.17)	(0.08 to 0.20)
Δ QALY vs no delay	-	0.02	0.06	0.09	0.11	0.13
		(0.01 to 0.03)	(0.04 to 0.08)	(0.06 to 0.12)	(0.08 to 0.16)	(0.09 to 0.18)
Δ Costs vs no delay	-	-£84	-£225	-£339	-£433	-£512
(excluding intervention)		(-148 to -21)	(-403 to -55)	(-611 to -83)	(-781 to -105)	(-924 to -124)
Max annual cost of intervention to	-	£182	£446	£627	£758	£858
be cost-effective at £20,000/QALY		(151-214)	(367-525)	(513-740)	(619-897)	(698-1017)

*discounted at 3%; **discounted at 3.5%

Table A.7: Maximum annual cost of intervention in the US and UK for intervention to be cost-effective relative to no delay by varying the rate of progression to diabetes and assuming IGT management costs to be the same as diabetes management costs ($9,158 and £827-£2,792 per year)

Annual rate of progression (per 1000 person years)	1 year delay	3 year delay	5 year delay	7 year delay	9 year delay
US setting*					
45.5	$168	$447	$667	$846	$993
80.4 (base case)	$427	$1,045	$1,469	$1,778	$2,013
114.3	$716	$1,637	$2,202	$2,583	$2,855
288	$2,204	$3,938	$4,660	$5,050	$5,292
693	$4,945	$6,468	$6,855	$7,026	$7,119
UK setting**					
45.5	£71	£189	£282	£358	£420
80.4 (base case)	£182	£446	£627	£758	£858
114.3	£307	£702	£944	£1,107	£1,223
288	£961	£1,714	£2,026	£2,194	£2,297
693	£2,165	£2,835	£3,003	£3,076	£3,114

*discounted at 3% and using $100,000 per QALY threshold; **discounted at 3.5% and using £20,000 per QALY threshold

Figure A.4. Average risk factor trajectories held constant (blue line) and predicted annually from baseline onwards regardless of diabetes onset using UKPDS-based equations (orange line) during first 20 years of simulation

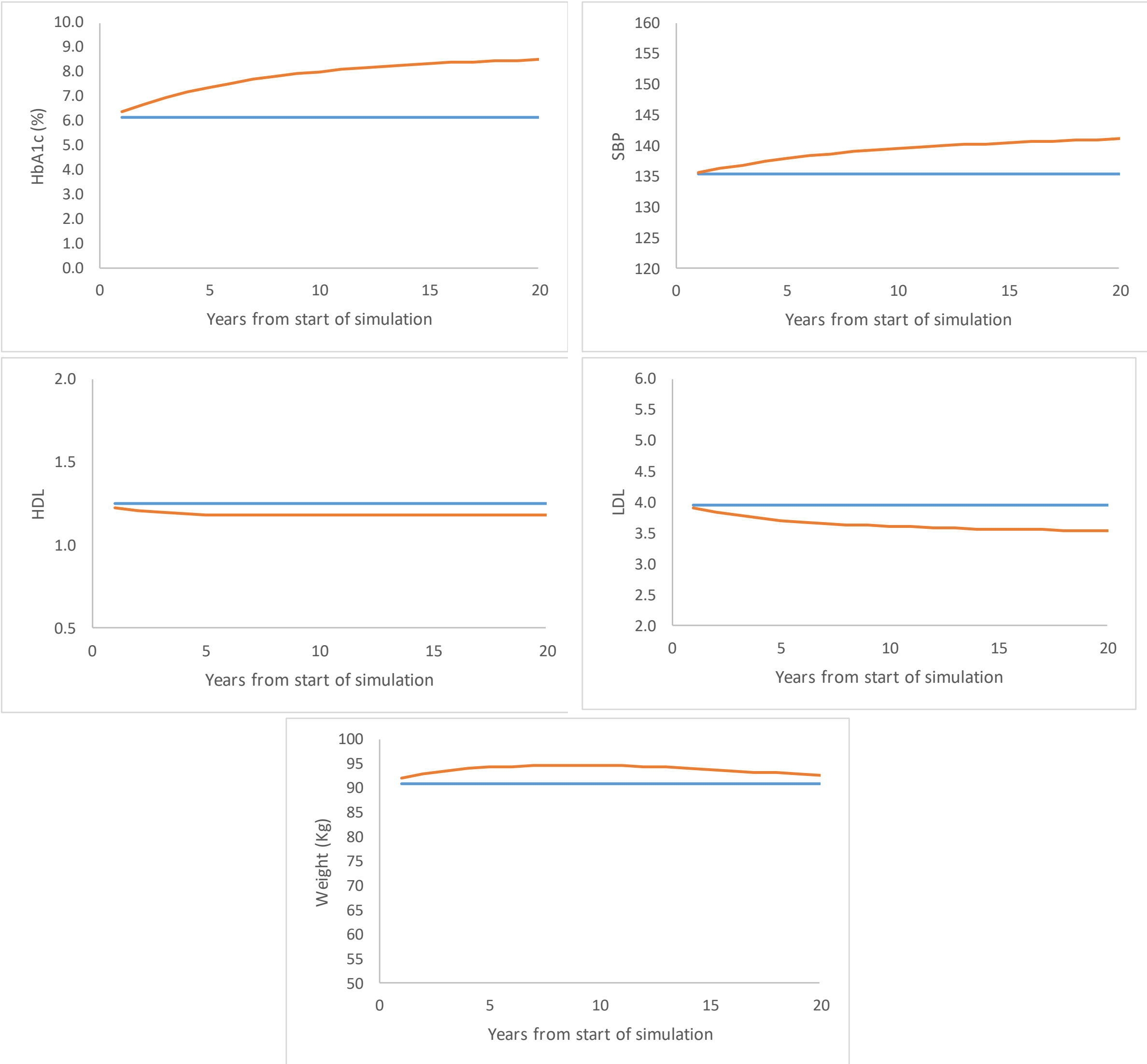


Table A.8: Maximum annual cost of intervention in the US for intervention to be cost-effective relative to no delay by varying the rate of progression to diabetes and allowing risk factors to change over time (scenario 1 and 2)*

Annual rate of progression (per 1000 person years)	1 year delay	3 year delay	5 year delay	7 year delay	9 year delay
Base case: risk factors held constant					
45.5	$225	$596	$891	$1,129	$1,327
80.4 (base case)	$567	$1,389	$1,954	$2,367	$2,680
114.3	$947	$2,170	$2,921	$3,428	$3,792
288	$2,857	$5,144	$6,110	$6,636	$6,964
693	$6,144	$8,238	$8,818	$9,085	$9,235
Scenario 1: risk factors were predicted annually from baseline onwards regardless of diabetes onset					
45.5	$239	$633	$946	$1,200	$1,410
80.4 (base case)	$599	$1,468	$2,068	$2,506	$2,839
114.3	$995	$2,285	$3,081	$3,620	$4,007
288	$2,946	$5,342	$6,370	$6,936	$7,293
693	$6,201	$8,426	$9,085	$9,399	$9,582
Scenario 2: risk factors were held constant up to diabetes onset and then predicted annually from that point onwards					
45.5	$245	$651	$972	$1,232	$1,447
80.4 (base case)	$619	$1,515	$2,132	$2,582	$2,923
114.3	$1,033	$2,367	$3,187	$3,740	$4,137
288	$3,115	$5,611	$6,665	$7,239	$7,597
693	$6,664	$8,962	$9,602	$9,896	$10,062

*discounted at 3% and using $100,000 per QALY threshold

Table A.9: Maximum annual cost of intervention in the US for intervention to be cost-effective relative to no delay using $50,000 and $200,000 per QALY threshold and varying the rate of progression to diabetes (mean and 95%CI)

Annual rate of progression (per 1000 person years)	1 year delay	3 year delay	5 year delay	7 year delay	9 year delay
Using $50,000 per QALY*					
45.5	$154 (134-173)	$408 (355-461)	$610 (530-689)	$773 (672-875)	$909 (789-1029)
80.4 (base case)	$386 (342-430)	$946 (835-1056)	$1,332 (1173-1490)	$1,613 (1419-1808)	$1,828 (1605-2051)
114.3	$642 (575-709)	$1,473 (1313-1632)	$1,985 (1764-2205)	$2,331 (2067-2595)	$2,580 (2283-2877)
288	$1,913 (1766-2060)	$3,460 (3166-3755)	$4,119 (3745-4493)	$4,480 (4055-4905)	$4,707 (4246-5168)
693	$3,992 (3766-4218)	$5,450 (5073-5826)	$5,871 (5419-6324)	$6,069 (5569-6570)	$6,184 (5649-6718)
Using $200,000 per QALY*					
45.5	$367 (266-468)	$973 (702-1244)	$1,453 (1044-1861)	$1,841 (1320-2362)	$2,163 (1547-2778)
80.4 (base case)	$930 (703-1156)	$2,276 (1708-2843)	$3,200 (2387-4013)	$3,873 (2874-4872)	$4,383 (3239-5527)
114.3	$1,557 (1214-1899)	$3,564 (2747-4380)	$4,794 (3664-5925)	$5,623 (4268-6977)	$6,216 (4693-7739)
288	$4,743 (3998-5488)	$8,513 (7014-10012)	$10,091 (8185-11998)	$10,946 (8777-13116)	$11,478 (9123-13832)
693	$10,448 (9321-11575)	$13,813 (11914-15712)	$14,712 (12421-17003)	$15,115 (12573-17657)	$15,338 (12620-18057)

*discounted at 3%