Sotagliflozin, in combination with insulin, for treating type 1 diabetes [ID1376]

ADDENDUM TO THE ERG REPORT

May 2019

This report was commissioned by the NIHR Systematic Reviews Programme as project number 127657

BMJ Technology Assessment Group

1 INTRODUCTION

The Evidence Review Group (ERG) did not have full working access to the CORE Diabetes Model (CDM) in time to include results for the ERG's preferred base case analysis within the ERG report. This addendum, therefore, provides these results now that the ERG has the required access.

The key changes that the ERG made to the company's base case were:

1. Setting the cohort to the pooled trial population;
2. Applying Hammer *et al.* 2009[1] costs for severe hypoglycaemic events an assuming 50% of patients are hospitalised;
3. Reducing the HbA_{1c} treatment effect to just 1 year;
4. Utilities based on the 2019 ScHARR report (provided by the company at clarification); and,
5. Applying a multiplicative approach to utilities.

The ERG also conducted some scenarios around this base case with the following changes:

1. Using the National Diabetes Audit (NDA)[2] cohort;
2. Using the company's preferred utilities;
3. Assuming the HbA1c treatment effect lasts a further year; and
4. Using the minimum value approach for utilities.

The results of these analyses are given in Section 2 and a discussion of the results is given in Section 3.

2 RESULTS

The results of the ERG base case analysis, as described in Section 1, are given in Section 2.1. The mean results are outlined in Table 1 and a scatterplot, displaying the spread of the samples produced from the 1,000 simulations of the model, is given in Figure 1. The mean results of the scenario analyses described in Section 1, are given in Table 2 to Table 5 in Section 2.2. An assessment of the impact of diabetic ketoacidosis (DKA) on the model results is discussed in Section 2.3, with results of an additional scenario analysis to remove these events given in Table 6.

2.1 ERG's preferred base case

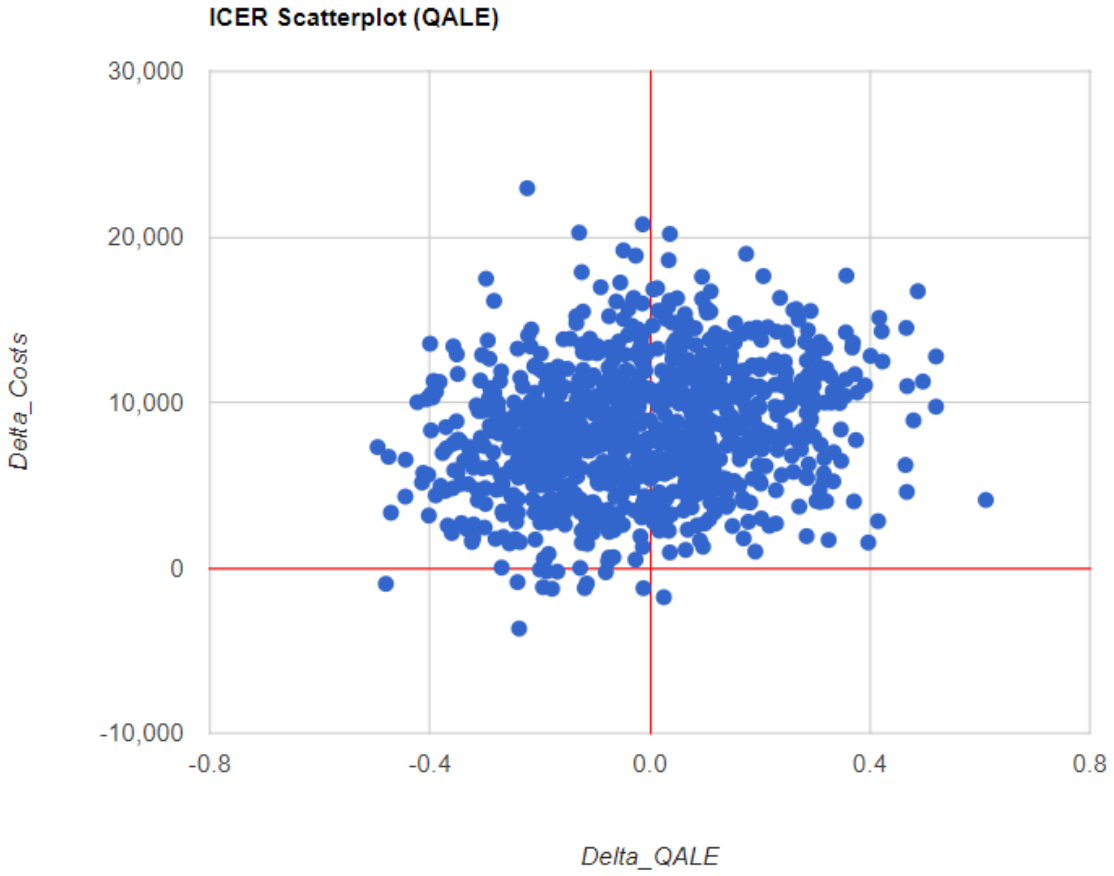
The results of the ERG's changes are presented, incorporating each change cumulatively, in Table 1. An incremental cost effectiveness ratio (ICER) for each individual change compared to the base case is also given.

Table 1. ERG base case ICER (CDM).

	Results per patient	Insulin alone (1)	Sotagliflozin 200 mg in combination with insulin (2)	Incremental value (2-1)
	Company's base case			
	Total costs	£78,731	£78,940	£209
	QALYs	8.695	8.803	0.108
	ICER	-		£1,934
(1)	**Setting the cohort to the pooled trial population (CQ B2)**			
	Total costs	£71,327	£72,277	£950
	QALYs	10.500	10.554	0.055
	ICER (compared with base case)	-		£17,327
	ICER with all changes incorporated (1)	-		£17,327
(2)	**Applying Hammer *et al.* 2009[1] costs for severe hypoglycaemic events an assuming 50% of patients are hospitalised**			
	Total costs	£75,101	£75,433	£332
	QALYs	8.695	8.803	0.108
	ICER (compared with base case)	-		£3,073
	ICER with all changes incorporated (1) + (2)	-		£19,497
(3)	**Reducing the HbA1c treatment effect to just 1 year**			
	Total costs	£78,735	£86,676	£7,942
	QALYs	8.695	8.736	0.041
	ICER (compared with base case)	-		£196,087
	ICER with all changes incorporated (1) + (2) + (3)	-		£1,011,447
(4)	**Utilities based on the 2019 ScHARR report (provided by the company at clarification)**			

	Total costs	£78,731	£78,940	£209
	QALYs	12.346	12.412	0.066
	ICER (compared with base case)	-		£3,148
	ICER with all changes incorporated (1) + (2) + (3) + (4)	-		Sotagliflozin dominated
(5)	**Applying a multiplicative approach to utilities**			
	Total costs	£78,731	£78,940	£209
	QALYs	9.179	9.300	0.121
	ICER (compared with base case)	-		£1,719
	ERG's preferred base case ICER with all changes incorporated (1) + (2) + (3) + (4) + (5)	-		Sotagliflozin dominated
Abbreviation used in the table: CQ, clarification question; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALYs, quality-adjusted life years.				

Figure 1. Scatterplot showing 1,000 simulations of the model for the ERG's preferred base case analysis (CDM).



2.1.1 Comparison of CDM and PRIME results

The company's base case analysis resulted in a much lower ICER in the CDM compared to the equivalent analysis using PRIME, with ICERs of £1,934 and £18,117 per QALY, respectively. The scenario that changed the population to represent the pooled trial with a BMI of greater than or equal to 27kg/m^2, increased the ICER in the CDM to £17,327 per QALY. In PRIME, however, the equivalent change caused a reduction in the ICER to £16,539 per QALY. It's not clear to the ERG exactly why this is the case. Another change that impacts in opposing directions in the two models was the multiplicative application of utilities. In the CDM the ICER reduced to £1,719, whereas in PRIME the ICER increased to £22,359 per QALY. Due to the "black box" nature of the two models, it is difficult to determine exactly why the changes have such dissimilar effects on the results.

The other changes, including the application of the Hammer *et al.* 2009[1] costs for severe hypoglycaemic events while assuming 50% of patients will be hospitalised, and the application of utilities from the ScHARR 2019 report provided by the company at clarification, resulted in similar changes to the ICERs, although the ScHARR utilities caused a slightly greater reduction in QALYs in the CDM than in PRIME.

The ERG notes that comparable analyses could not be performed in CDM and PRIME with regard to the ERG's preferred application of HbA_{1c} treatment effects. The ERG, therefore, cannot fully assess any differential impact that this may have between the two models.

2.2 ERG scenario analyses

Table 2. Scenario 1: Using NDA cohort (CDM).

Treatment	Total costs	Total LYG[a]	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER
Insulin alone	£75,105	29.78	12.78	-	-	-	-
Sotagliflozin 200 mg in combination with insulin	£83,169	29.81	12.81	£8,064	-0.032	0.027	£296,476

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.
a Undiscounted

Table 3. Scenario 2: Using the company's preferred utilities (CDM).

Treatment	Total costs	Total LYG[a]	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER
Insulin alone	£67,653	30.63	11.13	-	-	-	-
Sotagliflozin 200 mg in combination with insulin	£76,048	30.56	11.14	£8,395	-0.074	0.006	£1,311,720

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.
a Undiscounted

Table 4. Scenario 3: HbA_{1c} treatment effect extended to 3 years (CDM).

Treatment	Total costs	Total LYG[a]	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER
Insulin alone	£67,653	30.63	12.98	-	-	-	-
Sotagliflozin 200 mg in combination with insulin	£75,878	30.58	12.98	£8,224	-0.053	-0.005	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.
a Undiscounted

Table 5. Scenario 4: Minimum value approach for utilities (CDM).

Treatment	Total costs	Total LYG[a]	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER
Insulin alone	£67,653	30.63	12.40	-	-	-	-
Sotagliflozin 200 mg in combination with insulin	£76.048	30.56	12.38	£8,395	-0.074	-0.015	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.
a Undiscounted

2.3 Impact of diabetic ketoacidosis (DKA) events

Within the pooled subpopulation with a body mass index (BMI) ≥ 27 kg/m^2, 2.6%, 3.5% and 0.3% of patients receiving sotagliflozin 200 mg, sotagliflozin 400mg and insulin alone had at least one episode of DKA during 52 weeks of treatment. Based on these results, the DKA event rates per 100 patient years applied in the CDM were 3.2 for sotagliflozin 200 mg and 0.4 for insulin alone.

DKA events can have an important impact on costs, utilities as well as the risk of mortality. In the company's base case analysis and the ERG's preferred base case analysis, the cost to treat a DKA event (£1,556) was estimated from NHS Reference Costs 2016-17, the disutility (-0.0091) was estimated from Peasgood *et al.* 2016 and the risk of mortality (0.05% per year) was estimated from Wolowacz *et al.* 2015.[2-4]

To explore the impact of DKA events in the model, the ERG ran an analysis excluding DKA events. The impact of this was large and switched the incremental quality-adjusted life years (QALYs) from negative to positive in favour of sotagliflozin. As a result, sotagliflozin was no longer dominated by insulin. However, the ICER is still above the standard upper willingness-to-pay threshold of £30,000 per QALY used by NICE. The results of this analysis are given in Table 6.

Table 6. ERG base case ICER with and without DKA events (CDM).

Results per patient	Insulin alone (1)	Sotagliflozin 200 mg in combination with insulin (2)	Incremental value (2-1)
ERG's preferred base case			
Total costs	£67,653	£76,048	£8,395
QALYs	12.981	12.965	-0.016
ICER	-		Sotagliflozin dominated
ERG's preferred base case excluding DKA events			
Total costs	£67,464	£76,669	£9,204
QALYs	12.977	13.051	0.054
ICER	-		£171,401
Abbreviation used in the table: DKA, diabetic ketoacidosis; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALYs, quality-adjusted life years.			

3 TECHNICAL TEAM PREFERRED ANALYSIS

The NICE technical team for this appraisal specified their preferred base case analysis to be largely in line with the ERG's preferred analysis but with a change to the application of treatment discontinuation. The change applied the treatment discontinuation rates observed in the pooled inTandem trials for the first year followed by treatment discontinuation for all patients after 2 years. This is in contrast to the ERG's assumption that treatment is continued for 5 years for all patients, as clinical expert opinion sought by the ERG suggested that treatment may continue even after the treatment effect returns to the baseline values.

To apply appropriate costs with treatment discontinuation incorporated, the ERG reduced the cost of sotagliflozin by the proportion who discontinued in the first year. After this time, treatment costs in the sotagliflozin group were set equal to the insulin-only group. The proportion who discontinued was based on discontinuation due to treatment-emergent adverse events (TEAEs), as data on overall discontinuation was not available. The proportion who discontinued due to TEAEs in the sotagliflozin group of the pooled inTandem trial population used for the treatment effectiveness, was 4.3%. The results of this analysis are given in Table 7.

The ERG also conducted a scenario to test the sensitivity of the rates of DKA for the NICE preferred base case analysis by removing all DKA events from each treatment group. The results of this are provided in Table 8.

Table 7. NICE technical team preferred base case.

Treatment	Total costs	Total LYG[a]	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER
Insulin alone	£67,653	30.63	12.98	-	-	-	-
Sotagliflozin 200 mg in combination with insulin	£68,085	30.56	12.97	£431	-0.047	-0.016	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.
a Undiscounted

Table 8. NICE technical team preferred base case without DKA events.

Treatment	Total costs	Total LYG[a]	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER
Insulin alone	£67,464	30.67	13.00	-	-	-	-
Sotagliflozin 200 mg in combination with insulin	£68,647	30.80	13.05	£1,182	0.056	0.054	£22,017

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.
a Undiscounted

4 DISCUSSION

The results of the ERG's preferred base case are very different to the company's preferred base case. The ERG's results show that sotagliflozin is dominated by insulin alone, in contrast to the company's ICER of £1,934 per quality-adjusted life-year QALY, which was well below the standard upper willingness-to-pay threshold of £30,000 per QALY used by NICE.

The reason for such contrasting results is that the overall QALY gain, even in the company's base case analysis, is not large, with an increase of 0.108. Although the ERG considers that this value is likely to be overestimated because of the potentially implausible extrapolations of treatment effects beyond the trial period, this is still a relatively modest benefit. This value represents the margin, in terms of QALYs, between the company's apparently cost-effective ICER of £1,934 per QALY and an infinite ICER, thus, demonstrating how sensitive the model results are to any changes that may reduce this QALY gain.

The ERG's preferred base case ICER, however, removes this benefit entirely and shows that insulin alone generates a greater QALY yield. The incremental value for sotagliflozin compared to insulin alone in the ERG's preferred base case was -0.016. The reason for this is that sotagliflozin has both positive and negative treatment effects that can impact on the QALYs gained. The key parameter driving the positive benefits for sotagliflozin is the improvement, at least in the short term, of HbA_{1c} levels. However, sotagliflozin treatment increases the risk of ketoacidosis, which can be fatal. Given the relatively modest difference in treatment effects with sotagliflozin or insulin, subtle differences in assumptions can flip the QALY difference to be either positive or negative.

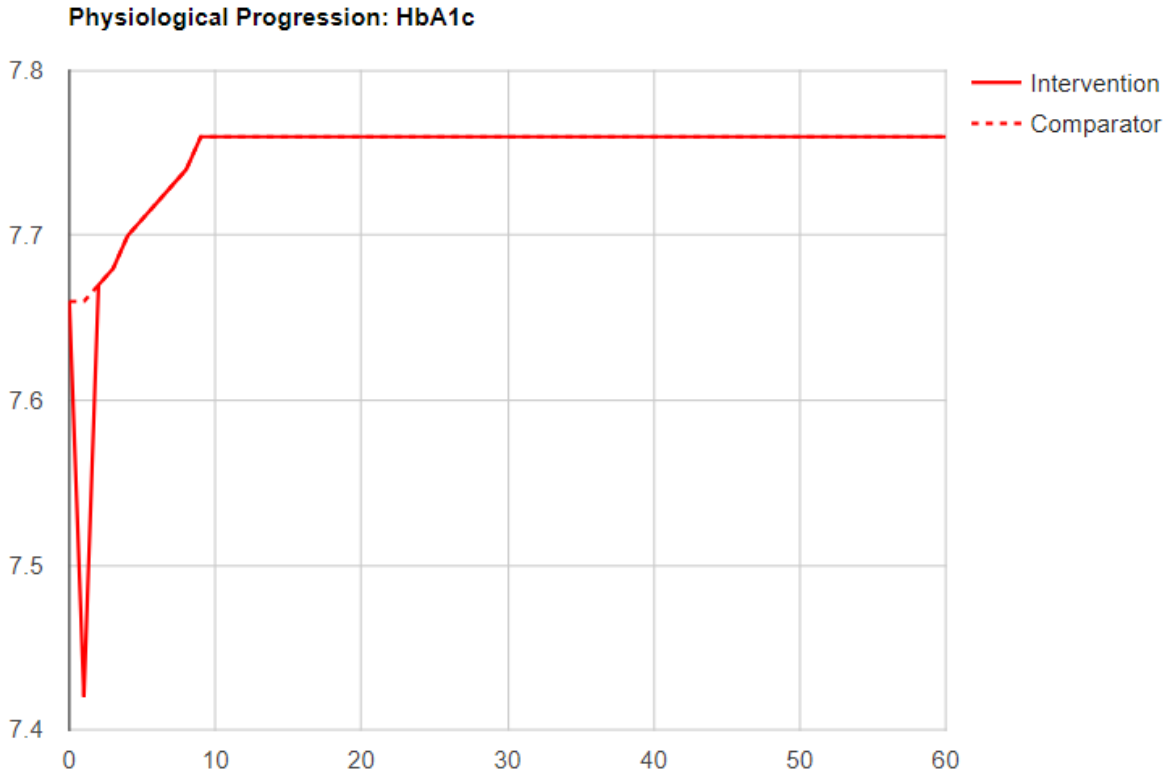
The ERG considers the company to have potentially overestimated the benefits in terms of HbA_{1c}, as the trial data appear to show a trend back towards the insulin alone group. If the observed trend continues beyond the trial period (1-year), then the treatment will be lost by approximately the end of the second year. The ERG, therefore, chose to reduce the duration of effect for HbA_{1c} in its preferred base case to return to the insulin alone group by the end of the second year. The ERG notes that the model has annual cycles and, therefore, it does not capture the initial decreasing and then increasing effect within the first and second years, respectively. It only takes the values at baseline, year 1 and year 2, from which point on the difference in treatment effect is kept constant at zero. This limitation may, therefore, not fully capture the treatment effect accurately. Other physiological parameters did not show a clear trend over the trial period, therefore, the ERG assumed that these effects were maintained for the duration of treatment as the company did in their preferred analysis (Appendix A).

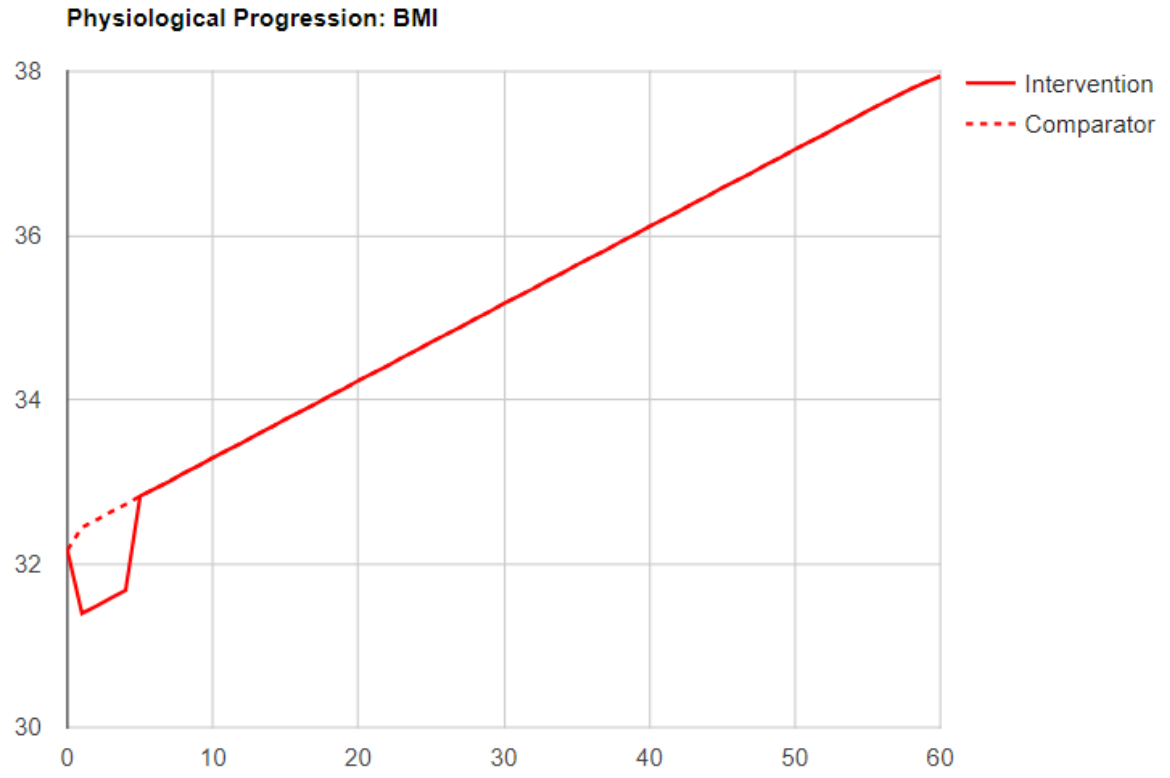
The ERG notes a limitation in the results of its preferred base case analysis being that the body mass index (BMI) disutility based on the ScHARR 2019 report could not be implemented within the time frame as it required manual input for each BMI value between 25 and 50 in increments of 0.1. However,

as the disutility per unit change in BMI (-0.0052) compared to the company's value (-0.0028) was not greatly different, and the impact is only applied in the first 5 years, the ERG considers this unlikely to have an important impact on the results.

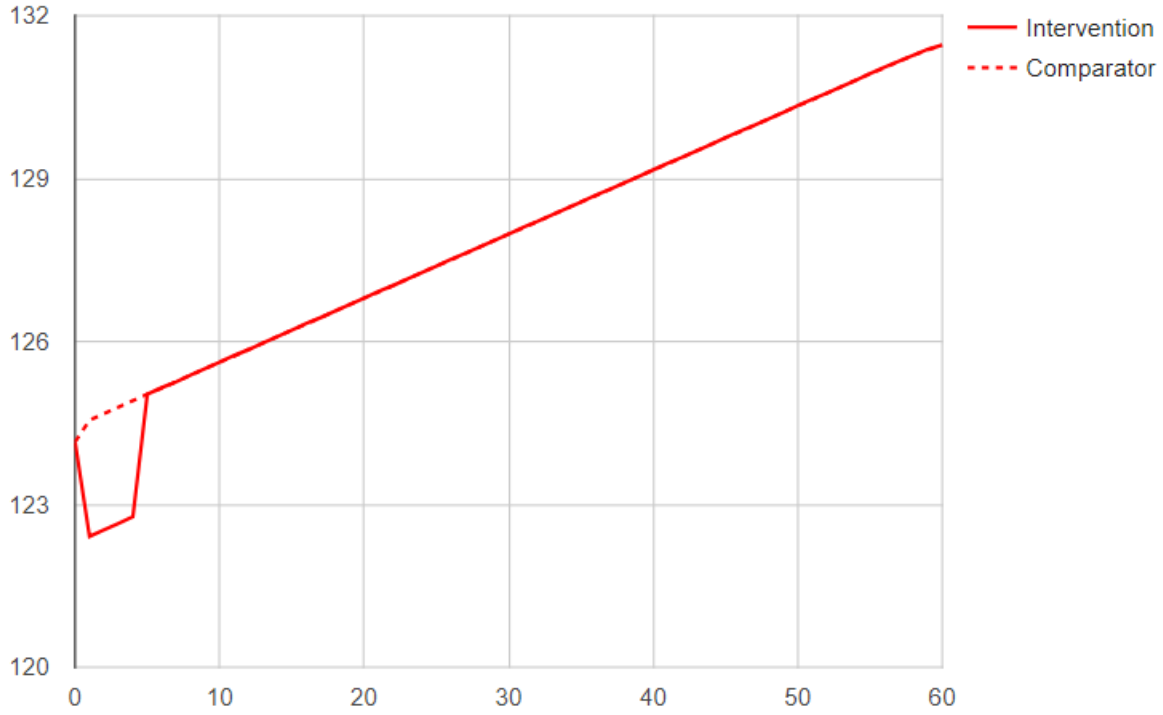
APPENDICES

A. Progression graphs for physiological parameters in ERG's base case analysis

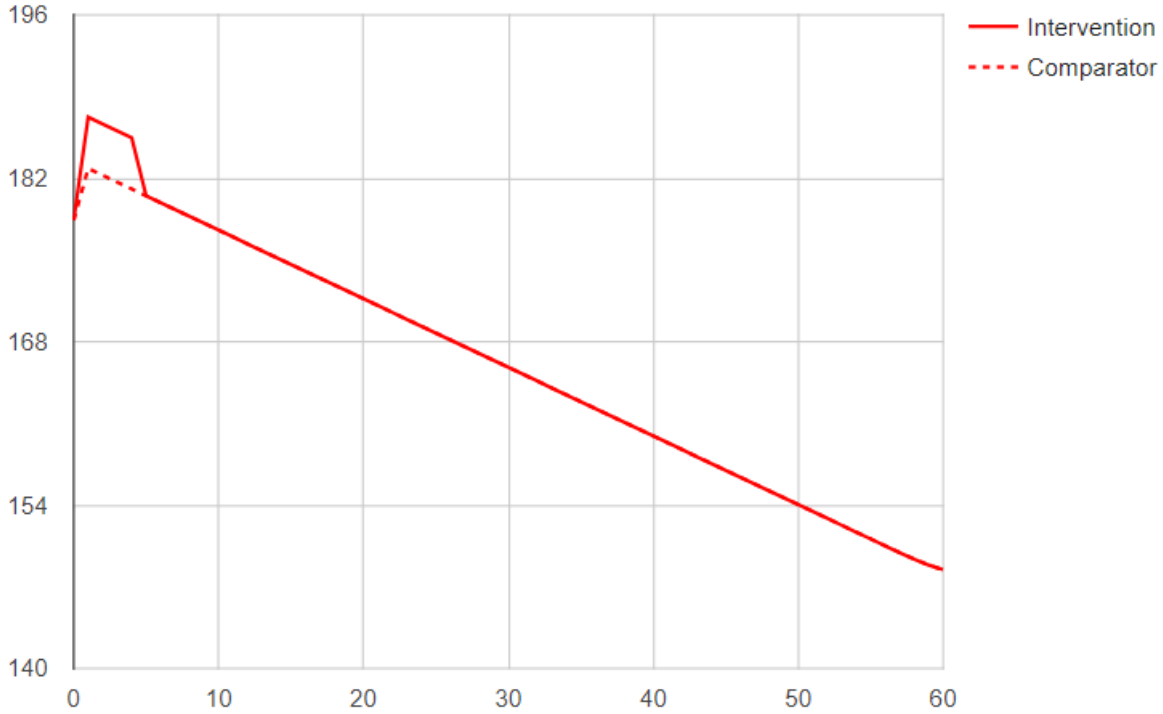




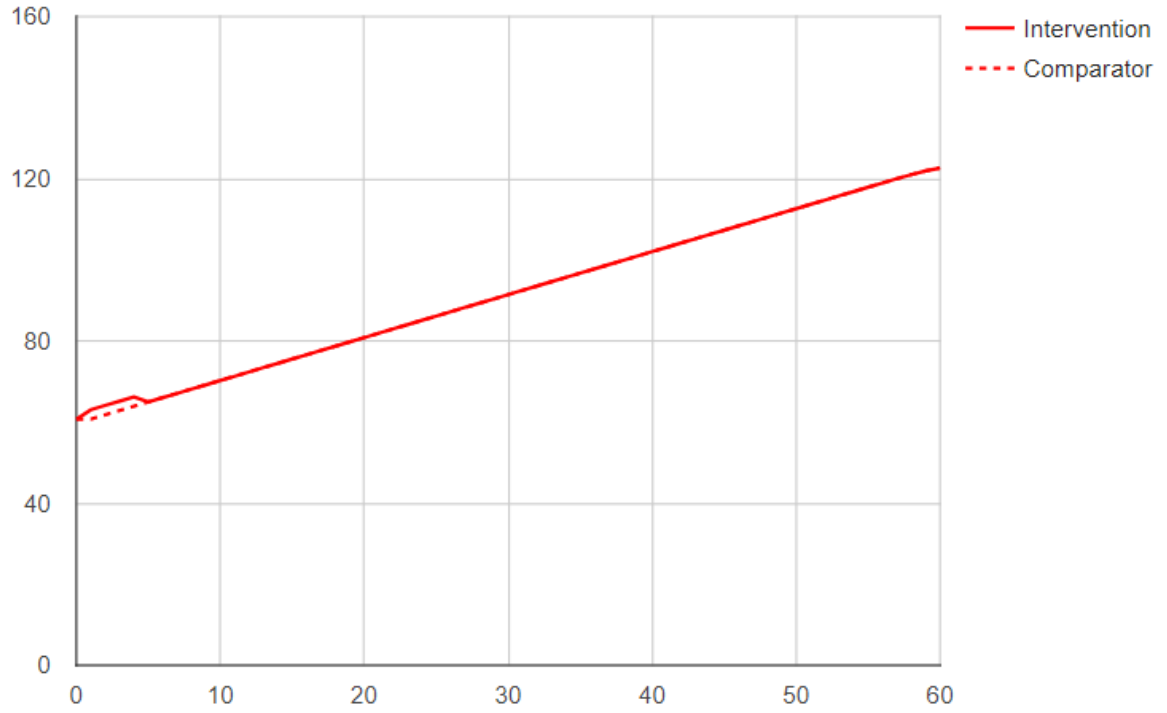
Physiological Progression: SBP



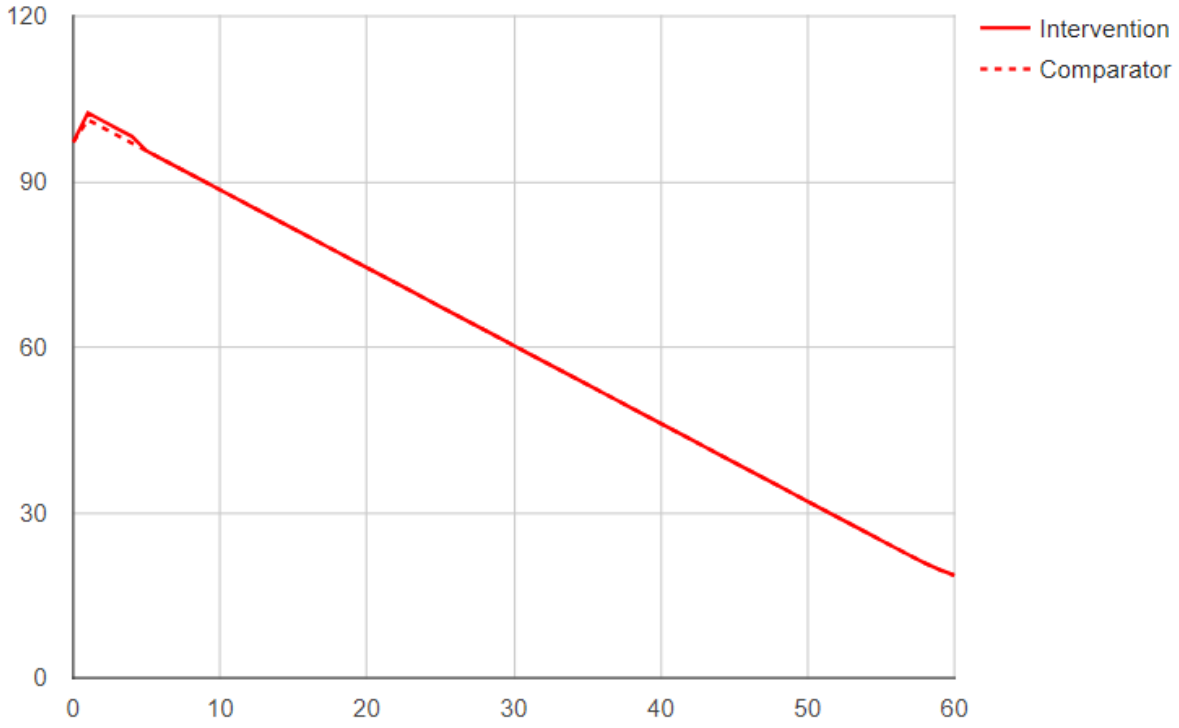
Physiological Progression: Total Cholesterol



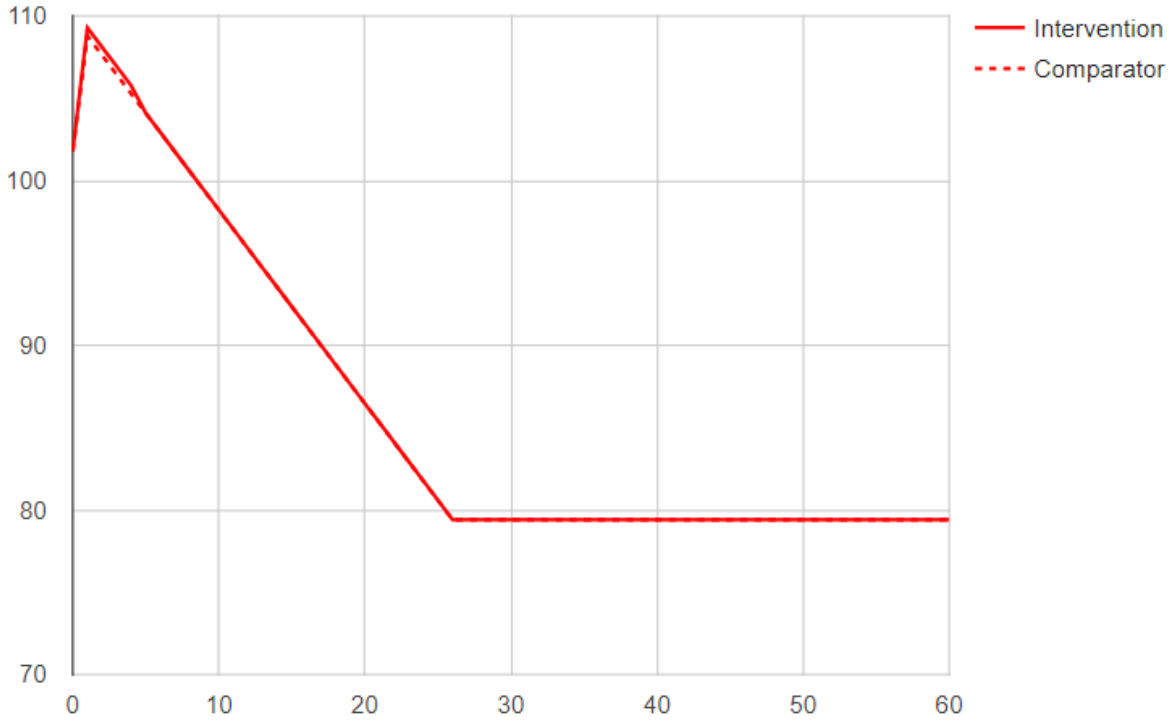
Physiological Progression: HDL



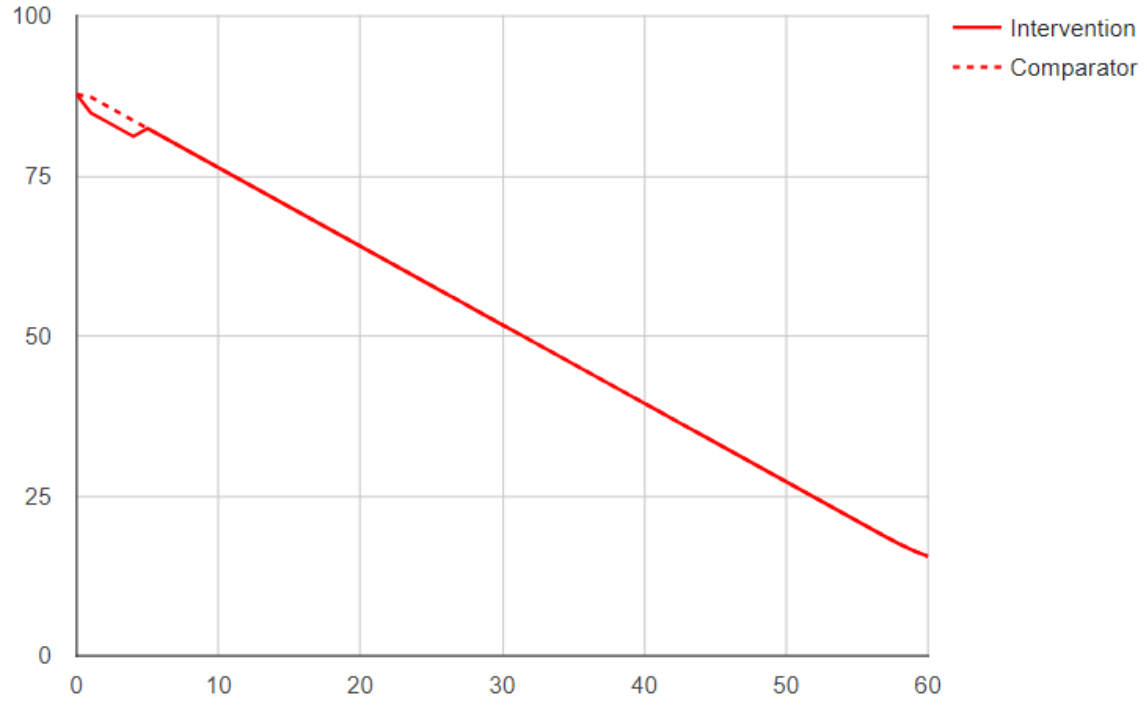
Physiological Progression: LDL

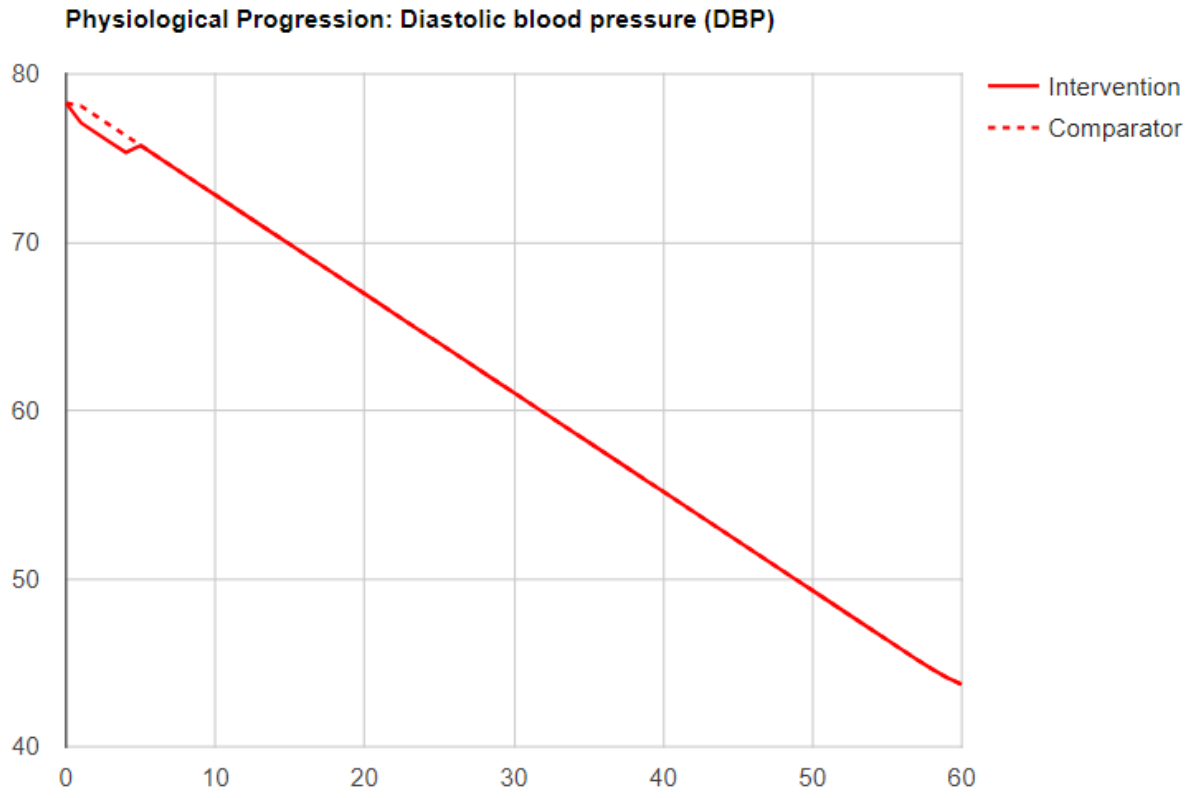


Physiological Progression: Triglyceride

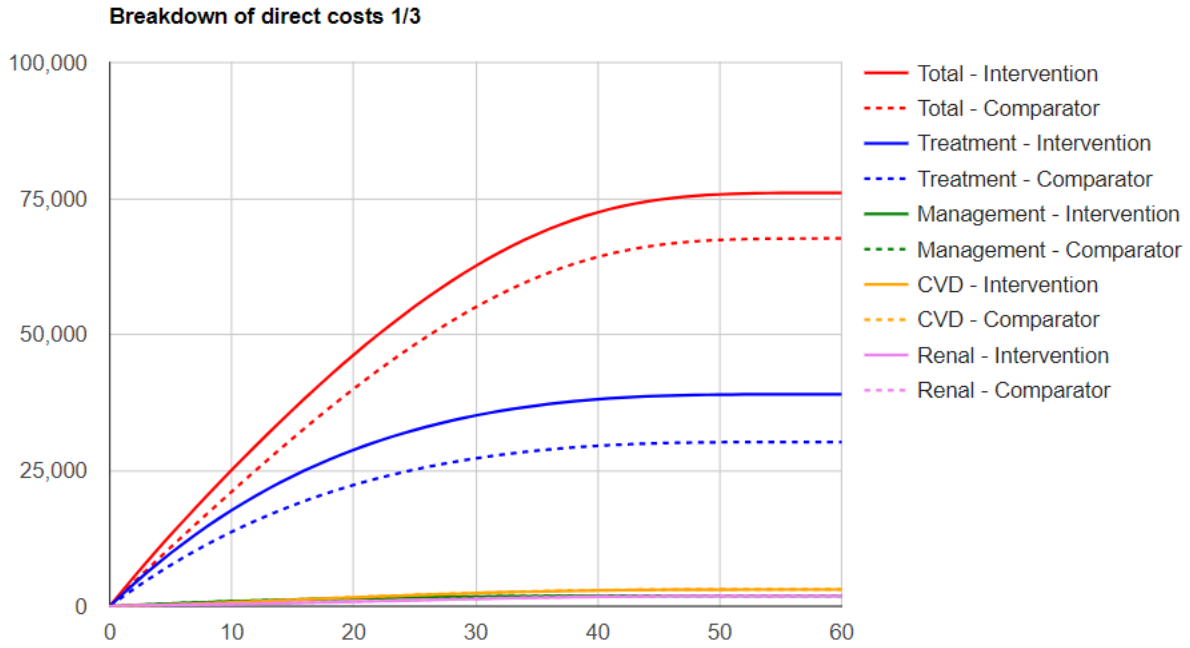


Physiological Progression: Estimated glomerular filtration rate (eGFR)

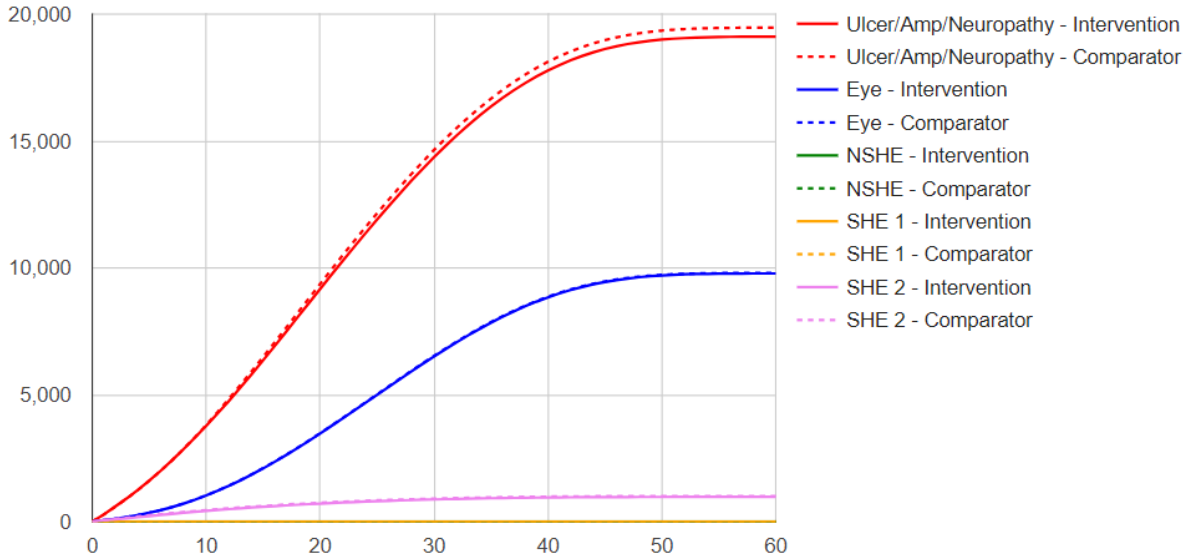




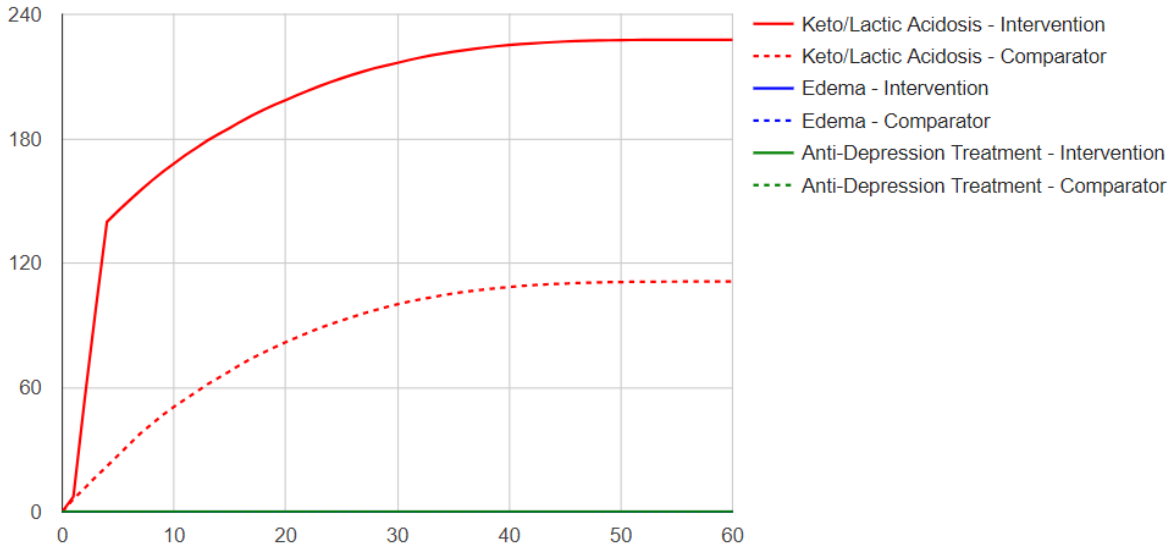
B. *Breakdown of costs and event incidences graphs for the ERG's preferred base case analysis*



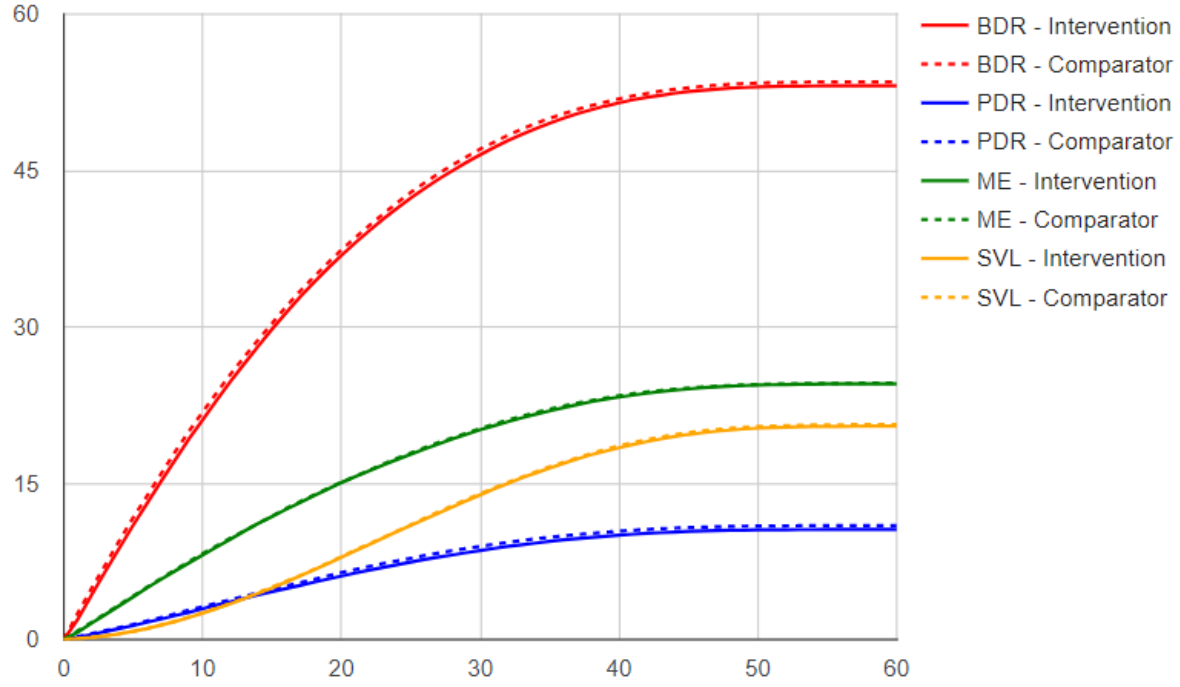
Breakdown of direct costs 2/3



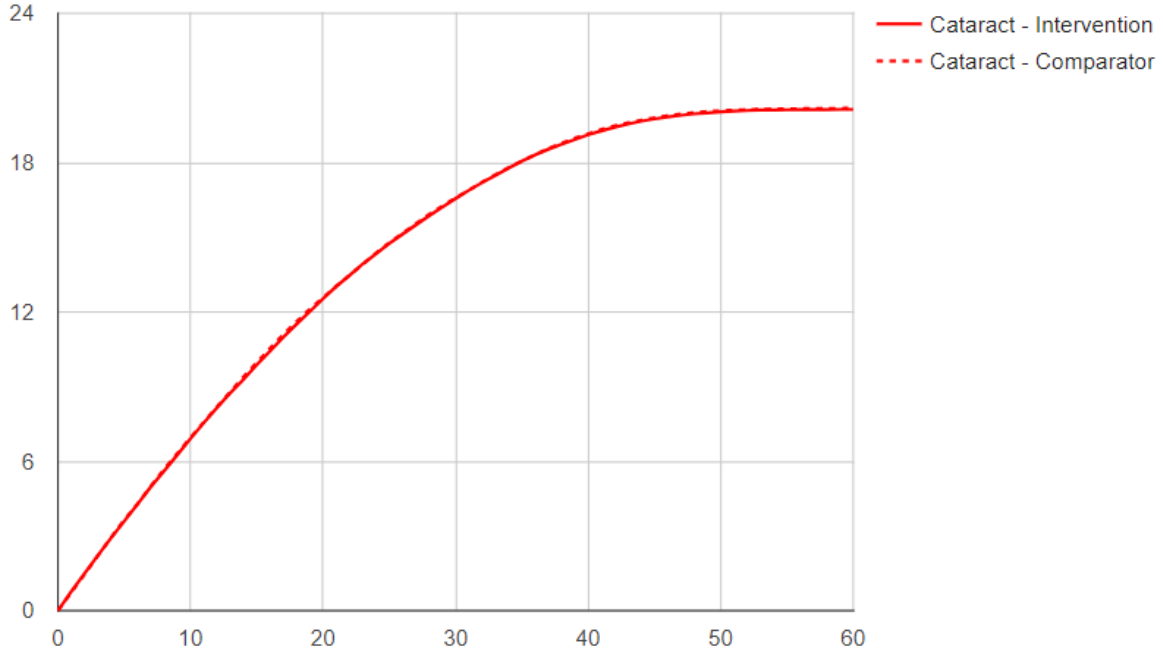
Breakdown of direct costs 3/3



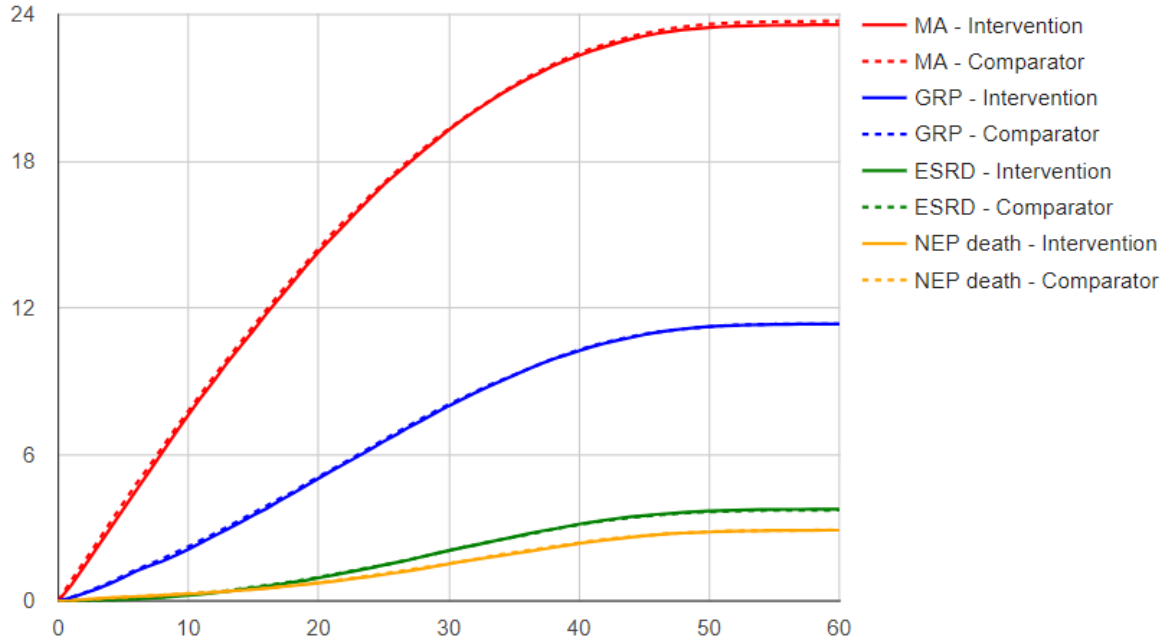
Cumulative Incidence Eye Disease 1/2



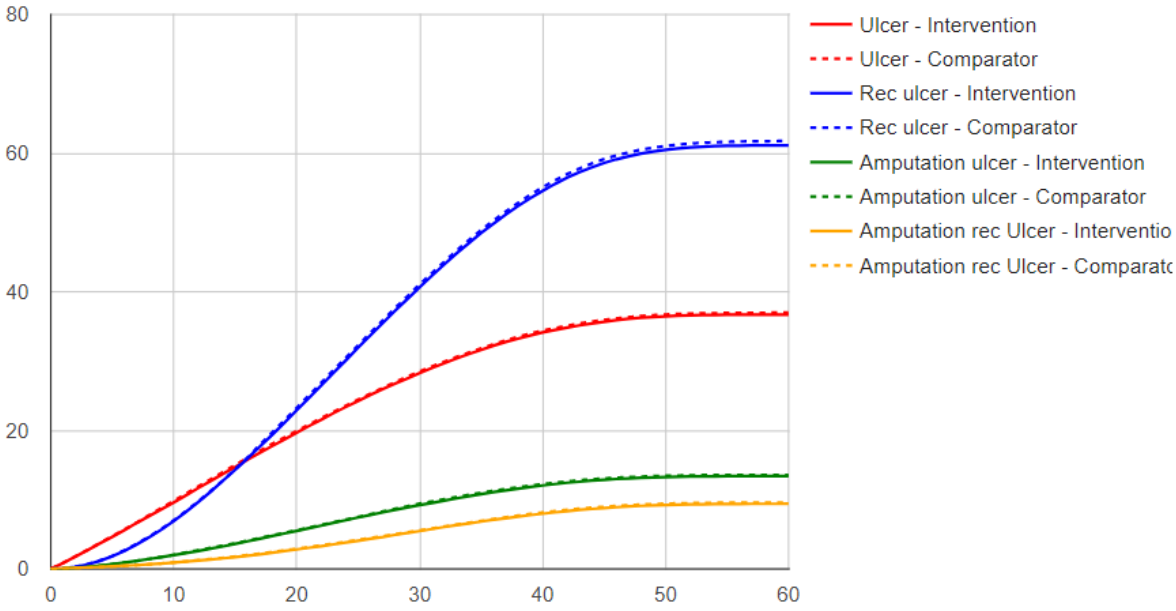
Cumulative Incidence Eye Disease 2/2



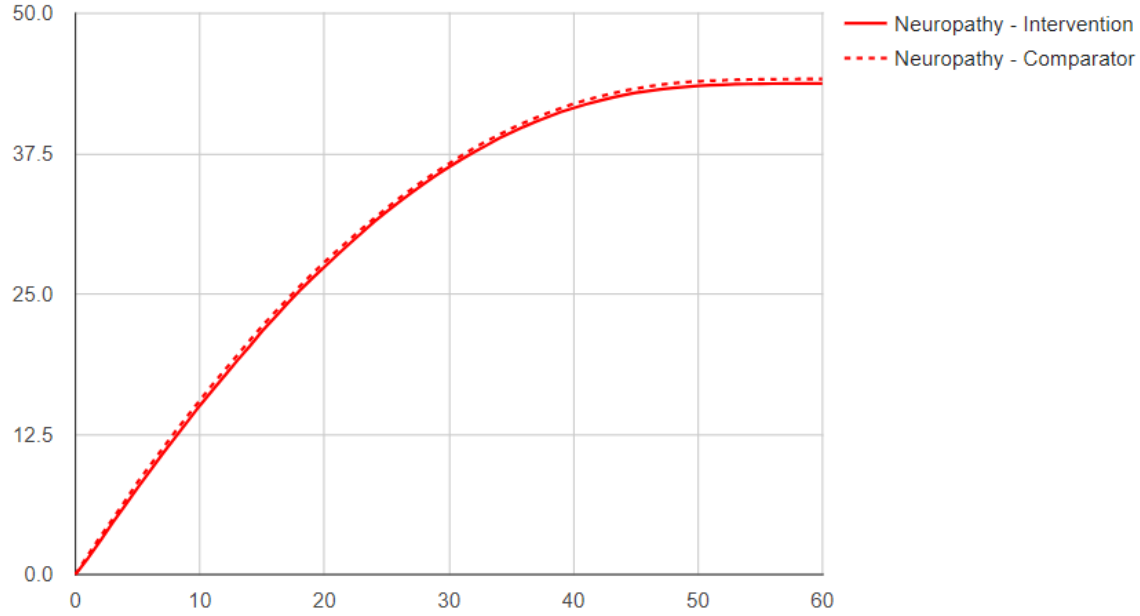
Cumulative Incidence Renal Disease



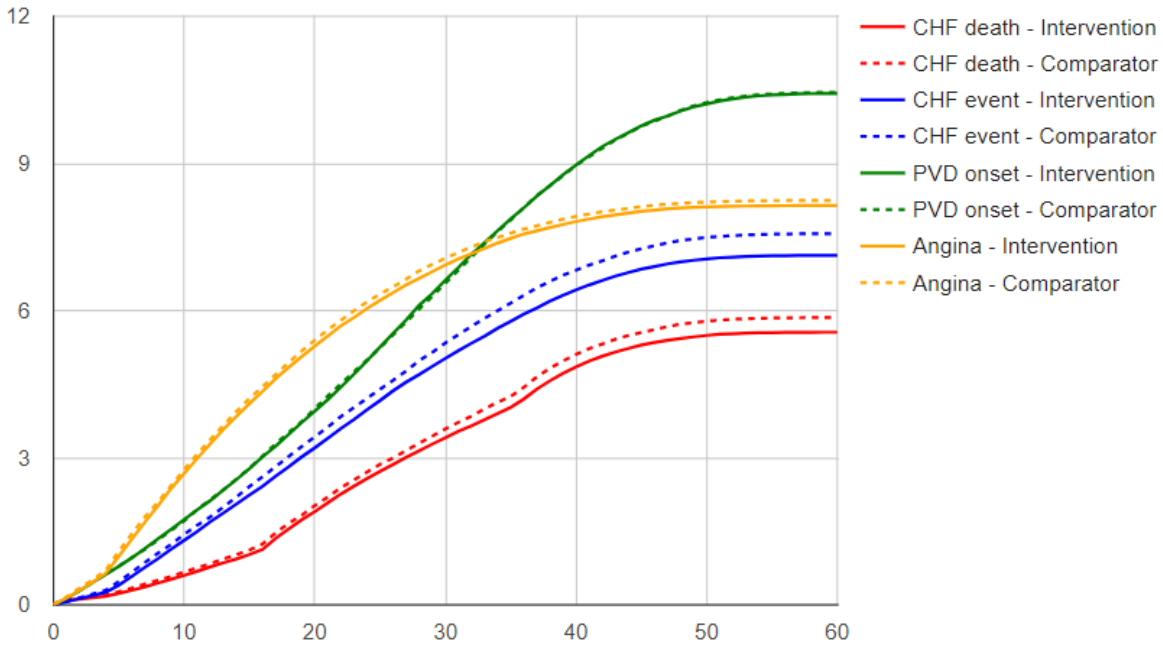
Cumulative Incidence Ulcer 1/2



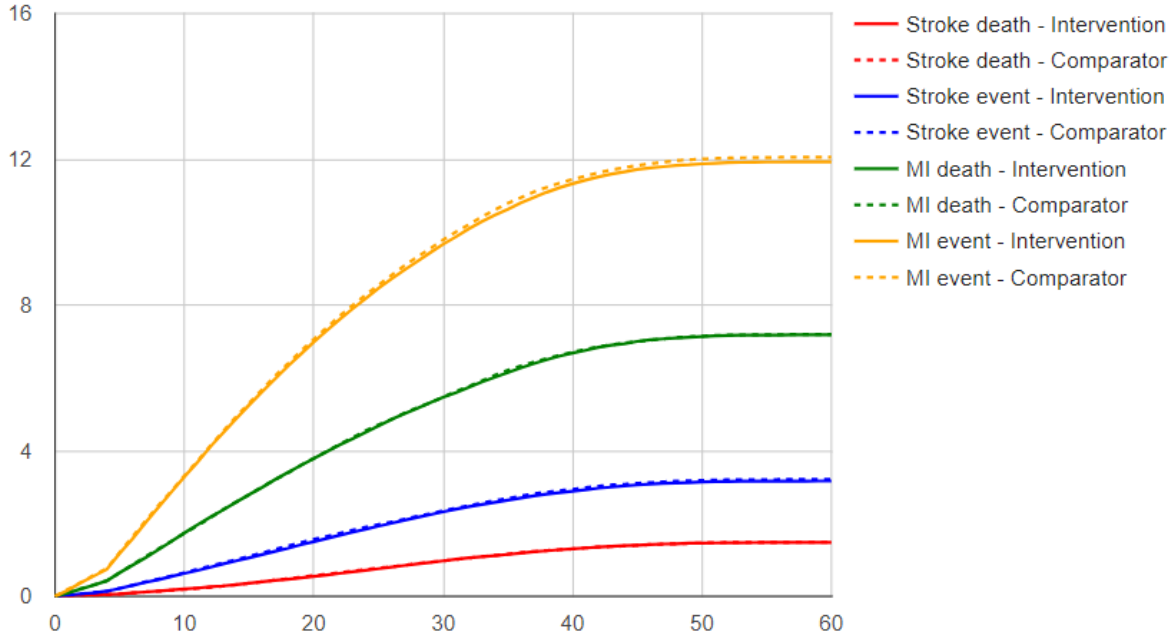
Cumulative Incidence Ulcer 2/2



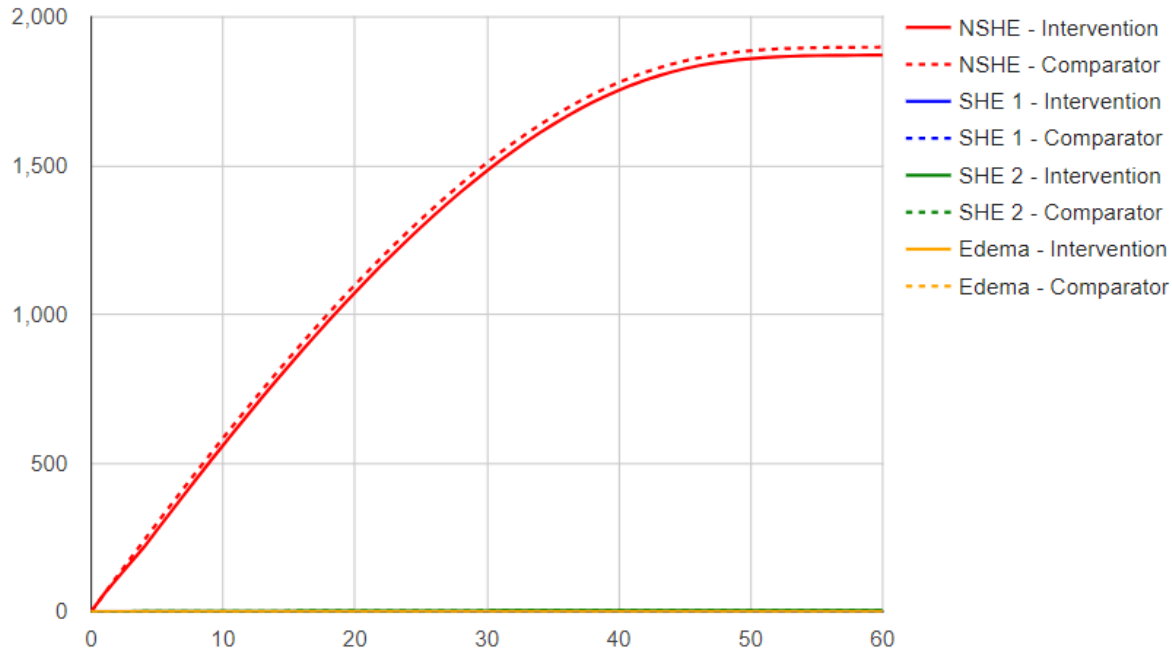
Cumulative Incidence CVD 1/2

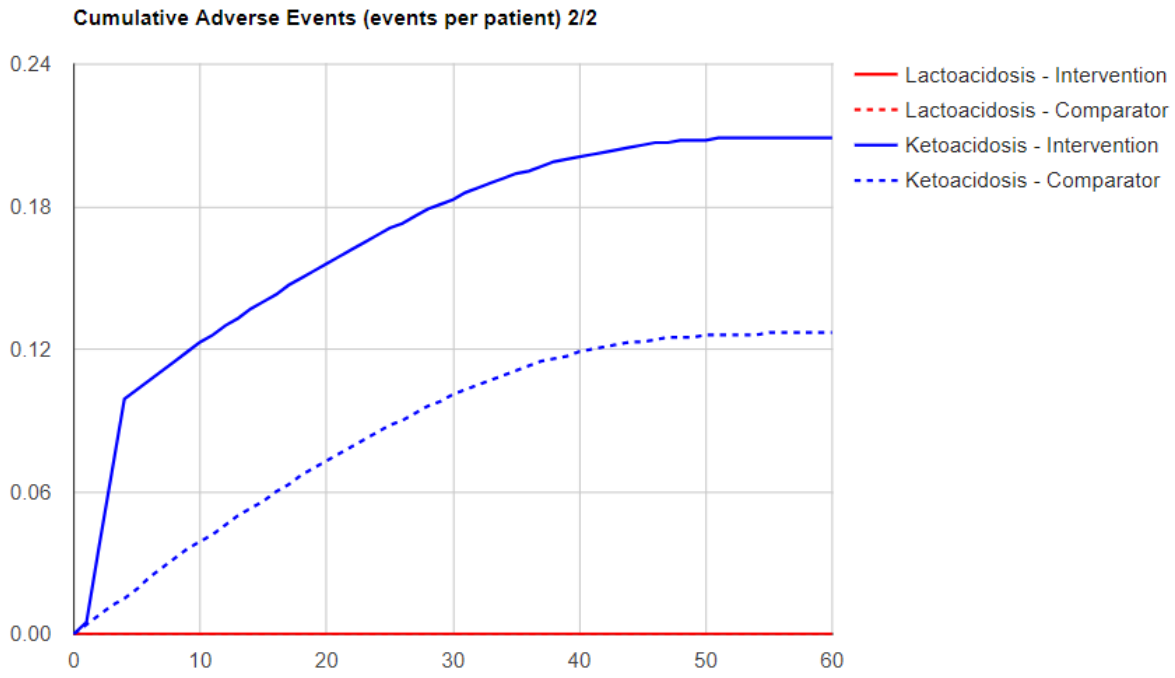


Cumulative Incidence CVD 2/2



Cumulative Adverse Events (events per patient) 1/2





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3. Peasgood T, Brennan A, Mansell P, Elliott J, Basarir H, Kruger J. The Impact of Diabetes-Related Complications on Preference-Based Measures of Health-Related Quality of Life in Adults with Type I Diabetes. *Med Decis Making* 2016; **36**: 1020-33.

4. Wolowacz S, Pearson I, Shannon P, Chubb B, Gundgaard J, Davies M, et al. Development and validation of a cost-utility model for Type 1 diabetes mellitus. *Diabet Med* 2015; **32**: 1023-35.