NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Icosapent ethyl with statin therapy for reducing the risk of cardiovascular events in people with raised triglycerides [ID3831]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Icosapent ethyl with statin therapy for reducing the risk of cardiovascular events in people with raised triglycerides [ID3831]

Contents:

The following documents are made available to consultees and commentators:

The **final scope** and **final stakeholder list** are available on the NICE website.

1. **Company submission** from Amarin

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submissions** from:
   a. HEART UK – The Cholesterol Charity
   b. Association of British Clinical Diabetologists
   c. NHS England

4. **Evidence Review Group report** prepared by Kleijnen Systematic Reviews

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Post-technical engagement documents

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   a. Response form
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   d. Additional analyses in the secondary prevention (CV1) population
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7. **Technical engagement responses and statements from experts:**
   a. Dr Peter Winocour – clinical expert, nominated by Association of British Clinical Diabetologists
   b. Professor Riyaz Patel – clinical expert, nominated by Cochrane Heart
   c. Jules Payne – patient expert, nominated by HEART UK – The Cholesterol Charity

8. **Technical engagement responses from consultees and commentators:**
   a. British Cardiovascular Society

9. Evidence Review Group critique of responses to technical engagement prepared by Kleijnen Systematic Reviews

a. Amarin
b. Dr Peter Winocour – clinical expert, nominated by Association of British Clinical Diabetologists
c. Professor Riyaz Patel – clinical expert, nominated by Cochrane Heart
d. British Cardiovascular Society

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Icosapent ethyl with statin therapy for reducing the risk of cardiovascular events in adults with elevated triglycerides - ID3831

Document B

Company evidence submission

October 2021

File name	Version	Contains confidential information	Date
ID3831_Icosapent ethyl_Document B_v3.0_[noACiC]_11October21	V3.0	Yes	11/10/2021

Contents

Tables and figures

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

This submission covers the technology's full marketing authorisation for this indication. Further details of the decision problem are presented in Table 1.

Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults on statin therapy with elevated triglycerides who are at high risk of cardiovascular events due to: • established CVD, or • diabetes, and at least 1 other cardiovascular risk factor	Adults on statin therapy with elevated triglycerides who are at high risk of cardiovascular events due to: • established CVD, or • diabetes, and at least 1 other cardiovascular risk factor	In line with the NICE final scope
Intervention	Icosapent ethyl (Vazkepa®) in combination with a statin	Icosapent ethyl (Vazkepa®) in combination with a stable dose of statin	In line with the NICE final scope
Comparator(s)	Established clinical management (including high and low-intensity statins)	Best supportive care, defined as a stable dose of statin therapy	In line with the NICE final scope There are no pharmacological therapies available and routinely used to reduce the risk of cardiovascular events in statin-treated patients with elevated triglycerides, hence the placebo arm of the REDUCE-IT trial is used as the comparator.
Outcomes	The outcome measures to be considered include: • cardiovascular event (including cardiovascular death, nonfatal myocardial	In line with the primary and secondary endpoints in the REDUCE-IT trial, the following outcomes will be captured in the	In line with the NICE final scope

	infarction, nonfatal stroke, coronary revascularisation, and unstable angina) • mortality • hospital admissions • adverse effects of treatment • health-related quality of life.	economic model and the submission: • 5-point major adverse cardiovascular events (MACE) (including cardiovascular death, nonfatal myocardial infarction (including silent myocardial infarction), nonfatal stroke, coronary revascularization, or hospitalisation for unstable angina) • 3-point MACE (including cardiovascular death, nonfatal myocardial infarction, nonfatal stroke) • Composite of cardiovascular death or nonfatal myocardial infarction • Fatal or nonfatal myocardial infarction • Coronary revascularization • Cardiovascular death • Hospitalisation for unstable angina • Fatal or nonfatal stroke • Death from any cause • Health-related quality of life • Adverse events	

		The following analyses of cardiovascular outcomes will be presented: • Time to first event • Difference in total events (first and subsequent events)	
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.	A cost-utility analysis was conducted in Excel. Costs were considered from an NHS and Personal Social Services perspective. Direct health effects for patients were considered.	In line with the NICE final scope
Subgroups to be considered	If the evidence allows the following subgroups will be considered:	The following subgroups were considered:	In line with the NICE final scope

	• adults with established cardiovascular disease (secondary prevention) • adults with diabetes and at least one other cardiovascular risk factor Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	• adults with established cardiovascular disease (secondary prevention) • adults with diabetes and at least one other cardiovascular risk factor	

Abbreviations: CVD – Cardiovascular disease; CVE – Cardiovascular event; MACE – Major adverse cardiovascular events; NHS – National Health Service; NICE – National Institute for Health and Care Excellence.

B.1.2 Description of the technology being appraised

Table 2 presents a brief description of Icosapent ethyl with statin therapy for reducing the risk of cardiovascular events in adults with elevated triglycerides. The Summary of Product Characteristics (SmPC) can be found in Appendix C.

Table 2. Technology being appraised

UK approved name and brand name	Icosapent ethyl (Vazkepa®)
Mechanism of action	Icosapent ethyl is a new active substance composed of highly purified and stable ethyl ester of the omega-3 fatty acid eicosapentaenoic (EPA). The exact mechanisms of action of pure EPA in reducing CV events are not completely understood but appear to modulate multifactorial processes in the whole atherosclerosis pathophysiological pathway by lipid and non-lipid effects.[1] Lipid effects of icosapent ethyl include triglyceride reduction via lipoprotein lipase activity in plasma and reduction of lipogenesis activity in liver.[2] Non-lipid effects of icosapent ethyl are multifactorial: • *Anti-inflammatory and antioxidant* – icosapent ethyl has systemic and localized anti-inflammatory effects.[3] The anti-inflammatory effects of icosapent ethyl may result from displacement of pro-inflammatory arachidonic acid (AA), directing catabolism away from eicosanoids (2-series prostaglandins and thromboxane, and 4-series leukotrienes) to non- or anti-inflammatory mediators. However, the direct clinical meaning of individual findings is not clear. • *Cellular transcription and membrane stabilising effects* – icosapent ethyl regulates genes involved in lipid metabolism and plaque stabilization[4] and alters the membrane function and stabilization.[5] • *Antithrombotic* – icosapent ethyl inhibits platelet aggregation under some ex vivo conditions.[2] • *Atherosclerotic plaque reduction, regression, and stabilisation* – icosapent ethyl with high dose statin therapy has been shown to have a mechanism of action causing double the amount of coronary plaque regression compared to statin therapy alone.[6] Icosapent ethyl has also shown significant decrease of low-attenuation plaque volume in patients with coronary artery disease.[7]
Marketing authorisation/CE mark status	Icosapent ethyl (Vazkepa) received a positive CHMP opinion on 28th January 2021. The date of issue of the marketing authorisation valid throughout the European Union was received on 26th March 2021.

Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Icosapent ethyl is indicated to reduce the risk of cardiovascular events in adult statin-treated patients at high cardiovascular risk with elevated triglycerides (≥ 150 mg/dL [≥ 1.7 mmol/L]) and • established cardiovascular disease, or • diabetes, and at least one other cardiovascular risk factor. Restrictions regarding supply and use: Icosapent ethyl is subject to medical prescription. (SmPC – Appendix C)
Method of administration and dosage	Icosapent ethyl is administered orally. The recommended daily oral dose is 4 capsules taken as two 998 mg capsules twice daily. Icosapent ethyl capsules should be taken with or following a meal and swallowed whole. (SmPC – Appendix C)
Additional tests or investigations	Icosapent ethyl can be prescribed to patients in line with its anticipated marketing authorisation without the need for additional tests or investigations. If medications are taken at the same time as Icosapent ethyl that affect how blood clots, such as an anticoagulant medicine, then blood tests will be required during treatment.
List price and average cost of a course of treatment	The anticipated list price for Icosapent ethyl is £173 per pack of 120 capsules. The annual cost of a course of treatment is £2,106.28 at the anticipated list price.
Patient access scheme (if applicable)	[redacted]

Abbreviations: AA – Arachidonic acid; CE – Cost-effectiveness; CHMP – Committee for Medicinal Products for Human Use; CV – Cardiovascular; CVD – Cardiovascular disease; EPA – Eicosapentaenoic acid; NHS – National Health Service; NHSE – National Health Service England; SmPC – Summary of Product Characteristics; TG – Triglyceride.

B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Disease overview

CVD and risk factors

Cardiovascular disease (CVD) encompasses a heterogenous group of medical conditions often related to progressive atherosclerotic disease in any of the body's major vessels. CVD can be defined by various aetiologies, clinical signs and symptoms including hypertension, coronary heart disease, cerebrovascular disease (stroke), peripheral vascular disease, heart failure, and cardiomyopathies.[8] A main condition underlying most CVD is atherosclerosis, giving rise to atherosclerotic cardiovascular disease (ASCVD).[9] Atherosclerosis is a condition where arteries become clogged with fatty substances called plaques or atheroma. These plaques harden, narrowing arteries, increasing blood pressure as it restricts blood flow and oxygen supply, thus increasing the risk of blood clots in major vessels to the brain or heart.[10]

In the UK, it is estimated that there are 7.6 million people living with CVD which could increase in coming years, due to an ageing and growing population and improved survival rates. CVD is a common cause of death, accounting for more than a quarter (27%) of all deaths in the UK and is the largest cause of premature mortality in deprived areas.[11] In England, it was estimated that 133,297 deaths were reported in 2019.[11]

There is no single direct cause for all CVD events, however there are multiple CV risk factors defined as: biological characteristics, conditions and/or lifestyle modifications that increase an individual's probability of getting or dying from ASCVD in the mid or long term. Modifiable risk factors include: hypertension, dyslipidemia (abnormal levels of lipids in the blood including: high LDL levels, high triglyceride [TG] levels and/or high cholesterol levels), diabetes, physical inactivity, and obesity.[12] Around 80% of people with CVD have at least one other health condition which can contribute further to their morbidity.

Dyslipidemia

Dyslipidemia is characterised by abnormal levels of lipids and lipoproteins in the blood (usually cholesterol and TGs) and is an important risk factor for CVD.[9,13]

Four major types of lipids circulate in plasma: free cholesterol, cholesteryl esters, phospholipids, and TGs.[14,15] Because lipids are not water-soluble, lipoproteins are required to transport them within the circulation which vary in their size, composition, density, and function – predominantly characterised by high-density lipoproteins (HDL) and low-density lipoprotein (LDL) cholesterol.[14–16]

Common forms of dyslipidemia capable of causing CV events include hypercholesterolemia (corresponds to patients with total cholesterol [TC] ≥250 mg/dL without previous CV events, and patients with TC ≥200 mg/dL with a history of CVD or diabetes), and mixed dyslipidemia (corresponds to patients with simultaneous elevation of TC and TG levels ≥200 mg/dL). Hypertriglyceridemia (corresponding to patients with TG ≥200 mg/dL in patients without CV history, and TG ≥150 mg/dL in patients with CV history) is associated with CV events and is now more commonly considered as a risk marker.

Hypertriglyceridemia

Hypertriglyceridemia is a form of dyslipidemia, characterised by high concentrations of TG levels in the blood and is a major contributor for developing atherosclerosis and CVD. Increases in TG levels often occur due to primary causes such as an inherited genetic condition, or secondary causes including a sedentary lifestyle, physical inactivity and medical conditions such as kidney disease, non-alcoholic fatty liver disease, gout, obesity and type 2 diabetes.[17]

Some people with hypertriglyceridemia have normal levels of HDL and LDL cholesterol while others have mixed dyslipidemia, defined as elevations in TG and LDL cholesterol levels that are often accompanied by low levels of HDL cholesterol.[18] An increase in the number of LDL cholesterol particles or interference with LDL metabolic breakdown will lead to elevated TG levels.[19]

Elevated TGs are classified as a level exceeding the normal concentration of 150 mg/dL, with high TG defined as 200 mg/dL to 499 mg/dL.[20] A full lipid profile blood test is typically used to identify hypertriglyceridemia, a fasting sample is no longer required in the UK as per NICE guideline CG181.[21] Hypertriglyceridemia may not be diagnosed until TG levels are severely elevated, as people are typically asymptomatic until TG levels exceed 885.7 mg/dL (10 mmol/L). NICE guideline CG181 recommends that patients with a consistent TG concentration above 885.7 mg/dL should be referred to further specialists for advice on lifestyle modification or medical intervention.

Residual CV risk identified by elevated TG levels

Residual CV risk is defined as the risk of CV events that persists despite treatment for or achievement of targets for CV risk factors. People with increased risk of experiencing CV events are identified by elevated TG levels (≥150 mg/dL) and are at an increased risk of experiencing CV events because of the build-up of fatty deposits in the arteries (atherosclerosis).[22] This can lead to angina, and an increased risk of blood clots, myocardial infarction (MI) and stroke. It can be associated with damage to arteries in organs such as the brain, heart, kidneys and eyes.[18] The risk of events is probably due to the combination of several factors, including lipoprotein unbalance, inflammatory risk and pro-thrombotic status that account for high incidence of new CV events.[23] There is a strong correlation between elevated TGs and residual CV risk, thus facilitating the identification of high-risk patients.[24]

In patients on statin background therapy with controlled LDL-C levels, elevated TG levels have shown to be correlated with elevated residual risk for CV events.[16,25–27] Observational studies have shown that in patients with atherosclerotic diseases with TG ≥150 mg/dL, the hazard ratio (HR) observed was 1.32 for MI and 1.14 for stroke. In patients with TG between 200–499 mg/dL the HR observed was 1.35 for MI, 1.27 for stroke and 1.235 for heart failure (HF).[20,28,29] This shows that patients with elevated TG levels have an increased risk of experiencing a CV event such as MI, stroke and HF. Furthermore, these patients experience increased risk estimates for all-cause mortality compared to patients with normal TG levels.[30] A meta-analysis of 61 studies assessed the correlation between all-cause or CV mortality and TG levels.[31] The collated relative risk of elevated TGs on all-cause mortality was statistically significant for both TG levels 150-200 mg/dL and >200 mg/dL ($p = 0.011$ for both).[31] Similarly,

the collated relative risk of elevated TGs on CV mortality was also statistically significant for both TG levels ($p < 0.02$ for both).[31]

The combination of several risk factors leads to an even greater probability of experiencing CV events, which reduces quality of life.[12]

Major CV events associated with established CVD, such as MI and stroke, have a high rate of morbidity and mortality.[32] In the UK, stroke is the biggest cause of severe disability and it is estimated that there are more than 100,000 strokes each year.[11] Furthermore, there are over 200,000 hospital visits due to MIs in the UK and around 1 million people living in the UK have survived an MI.[11] After experiencing one CV event, there is an increased risk of having one or more CV event of any type, with recurrence rates of 50% and 75% for any CV event or revascularization in patients with a prior MI at 1 year and 3 years, respectively.[16,33] A study of over 380,000 UK AMI survivors estimated the risk of death was 1.5 times higher in patients with recurrent, versus first, MI.[34] A recent retrospective UK database analysis evaluated the incidence of non-fatal major CV events in 69,436 patients with type 2 diabetes and CV risk factors (mean TG level: 159 mg/dL, mean LDL-C level: 119 mg/dl, mean HDL-C level: 46 mg/dl). Patients were matched with up to four individuals in a healthy control cohort (mean TG level: 115 mg/dL). Across all ethnicities, there was a higher incidence of major adverse CV events in the diabetic cohort compared to the healthy control.[35]

Patients in these high-risk groups who have elevated TG levels, despite existing treatment, are at continued high risk of further events despite being at goal for other lipid-related risk factors.

B.1.3.2 Humanistic burden of disease

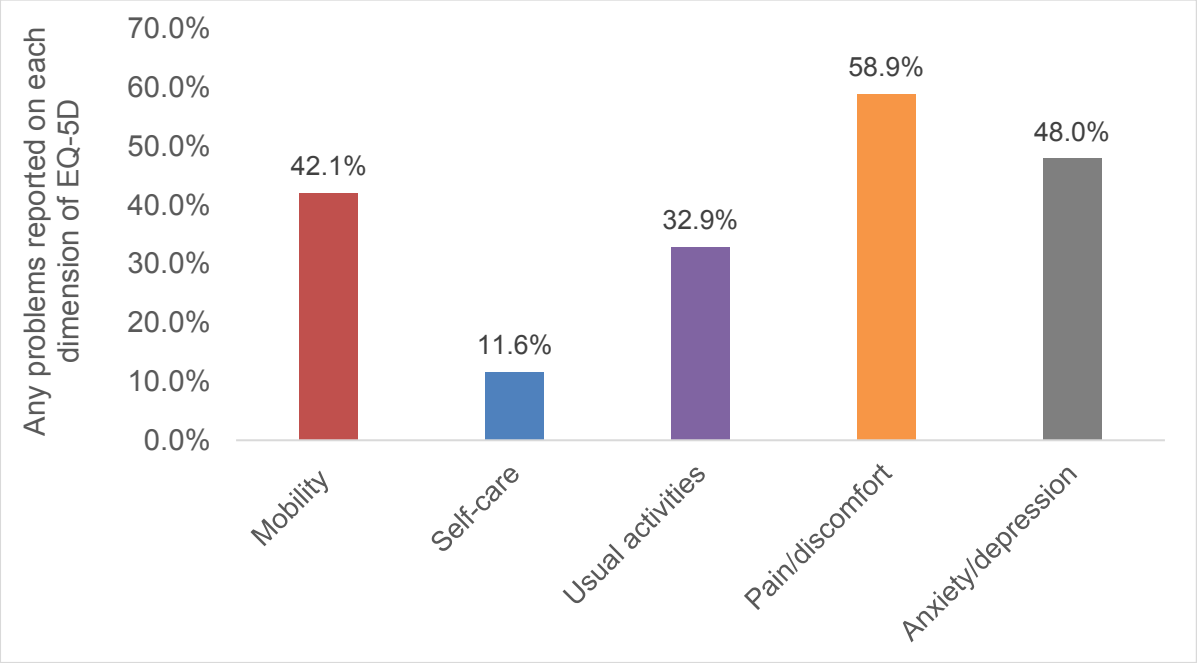
Health-related quality of life burden due to CV events

CV events lead to significant impairments in health-related quality of life (HRQoL) caused by functional impairments and psychosocial limitations further amplified by stress, anxiety and fear, which in themselves can become further CV risk factors.[36] The complex and multifaceted nature of CVD, as well as common CV-related comorbidities/events, can create difficulty when quantifying the impact on HRQoL. Impairments in HRQoL among patients with CVD were analysed in a recent cross-

sectional study derived from data in the EUROASPIRE IV survey.[37] EQ-5D was used to evaluate HRQoL outcomes in over 7,500 patients with chronic heart disease (mean age of 64.1 years). Across 24 European countries, the majority (74.6%) of patients reported problems across all 5 dimensions of the EQ-5D questionnaire.[37] The impact of behavioural risk factors and comorbidities on HRQoL was also considered.

Problems on the five dimensions of the EQ-5D were reported by the majority (74.6%) of patients (Figure 1).[37] Overall, the pain/discomfort dimension of the EQ-5D was rated the highest, followed by anxiety/depression, with the least problems reported for the self-care dimension of the EQ-5D. Furthermore, patients with CVD who also had behavioural risk factors such as obesity, smoking, and a lack of physical activity had lower EQ-5D scores and reported more severe/extreme problems on ≥1 dimension compared to patients without behavioural risk factors. Worse EQ-5D dimension outcomes were also observed in patients who also suffered from comorbid conditions such as diabetes, stroke, HF, or chronic kidney disease compared to those without comorbidities.

Figure 1: Proportion of any problems reported on each dimension of EQ-5D among patients with CVD[37]



It is also important to highlight that the humanistic burden for patients who have residual CV risk, e.g., due to hypertriglyceridemia, will be very large (compared to those without residual CV risk), as experiencing multiple CV events leads to further deterioration in HRQoL, as ratified by UK clinical experts.

Physical and psychological burden of CV events

Living with the consequences of a CV event (such as stroke or MI) can completely transform a patient's daily life as well as impacting their friends and family. Adjusting to life can be tough both physically and psychologically as there is suddenly a change in routine, from cardiac rehabilitation programmes to routine assessments, and hospital assessments to measure health aspects such as blood pressure and ECGs.[38] For patients with residual CV risk, there is increased fear and anxiety in the knowledge that a subsequent CV event may occur. This increase in stress can raise blood pressure which can subsequently increase the likelihood of more CV events occurring.

Recurrent CV events can cause long-term disability and can further complicate the care and management of other conditions. An analysis by the US Health and Retirement Study and Medicare claims reported a significant increase in the frequency of reported functional limitations on daily routine activities by individuals following hospitalisation from CV events (MI or stroke).[39] Furthermore, the European Heart Network report that CV events are responsible for the loss of more than 64 million disability-adjusted life years (DALYs) in Europe and 26 million DALYs in the EU.[40] This accounts for 23% and 19% of all DALYs lost, respectively.

Hospitalisations for major adverse CV events such as stroke, have also been reported to cause cognitive decline in patients. For example, after hospitalisation for stroke, the US Health and Retirement Study and Medicare claims found a fourfold increase in the odds of moderate-to-severe cognitive impairment, even when controlling for pre-hospitalisation cognition.[39]

The physical impact of having a stroke can include spasticity, battling with fatigue, deteriorated fine motor skills and incontinence, which can all have a negative physical and psychological effect on patients.[41] Many stroke survivors also experience overwhelming fatigue both physically and mentally, which can make it more difficult to

carry out daily activities.[42] Ability to carry out daily tasks is also affected by the decline in fine motor skills due to a loss of motor control, proprioception, sensation, and an increase in muscle weakness.[43] For many patients, the sudden short-term effects of not being able to carry out daily tasks can be frustrating, alongside the frequent side effect of incontinence which can be embarrassing and debilitating. Due to a loss of independence, family members can often become carers, facing a physical and psychological burden themselves.

Similarly to having a stroke, the occurrence of a MI can result in symptoms such as tiredness and muscular disorders.[44] A NHS resource for rehabilitation after MI also lists the psychological reactions to a heart attack which include numbness, fear, helplessness, sadness and grief, guilt, shame, anger, and shock.[44] Some of this may stem from the immediate aftermath of the event itself occurring, whilst others may stem from the subsequent longer term consequences, such as an inability to return to work, no longer being allowed to drive, or impact on relationships.[38]

B.1.3.3 Economic burden of CV events in established disease

The economic burden related to residual CV risk is a result of CV complications and event costs. The management and prevention of CV events is likely to reduce the economic burden faced by individuals and society.[45,46]

Economic burden of CV risk in patients with CVD

There are considerable costs to the healthcare system associated with CVD. The total annual healthcare cost of CVD in the UK is estimated at £9 billion each year with the majority of costs generated through hospital admissions and urgent care.[11] The cost to the UK economy when considering premature death, disability and informal costs associated with CVD is estimated to be £19 billion each year.[11]

It has also been reported that the economic burden of ASCVD patients on statin therapy is significantly greater in individuals with high TG levels (200-499 mg/dL) vs normal TG levels (<150 mg/dL).[30] Poorly controlled TGs contribute to the burden of CVD to the NHS. A European study of over 7,000 patients demonstrated that significant numbers of high-risk and very high-CV risk patients (60 – 80% respectively)

were unable to adequately lower their LDL-C levels with statins or other lipid-lowering agents.[47]

Economic burden of CV risk and events in patients with diabetes

Diabetes is a major CV risk factor, with the majority of costs associated with diabetes attributable to vascular complications of the disease, which require inpatient and outpatient care. [48,49]

The estimated annual costs for treating CV complications of diabetes were reported as £27,461,940 for dyslipidemia, £509,656,332 for ischaemic heart disease, £603,069,221 for MI, £308,157,806 for HF, £287,931,944 for stroke and £1,654,855,114 for other CV events.[48]

The prevention of CV events in patients with established CVD or diabetes can significantly reduce the economic burden associated with both diseases since the majority of the costs can be attributed to the occurrence of CV events. Furthermore, it is also important to highlight that the economic burden for patients who have residual CV risk will be very large (compared to those without residual CV risk), as experiencing multiple CV events will lead to further management to treat these events.[50] For example, one study compared the estimated costs after surviving a first or second CV event in patients receiving lipid-modifying therapy prior to the event(s). The incremental costs in the subsequent 30 months (post-CV event/events) were £361 and £1,018 for patients who underwent one or two CV events, respectively. Mean costs for the first event and second event cohorts were: ischemic stroke, £3,512 and £4,572; HF, £2,444 and £3,461; and transient ischemic attack £1,537 and £1,814.[50] This study demonstrates that residual risk causing more than one CV event leads to an increased economic burden for patients.

B.1.3.4 Clinical pathway of care

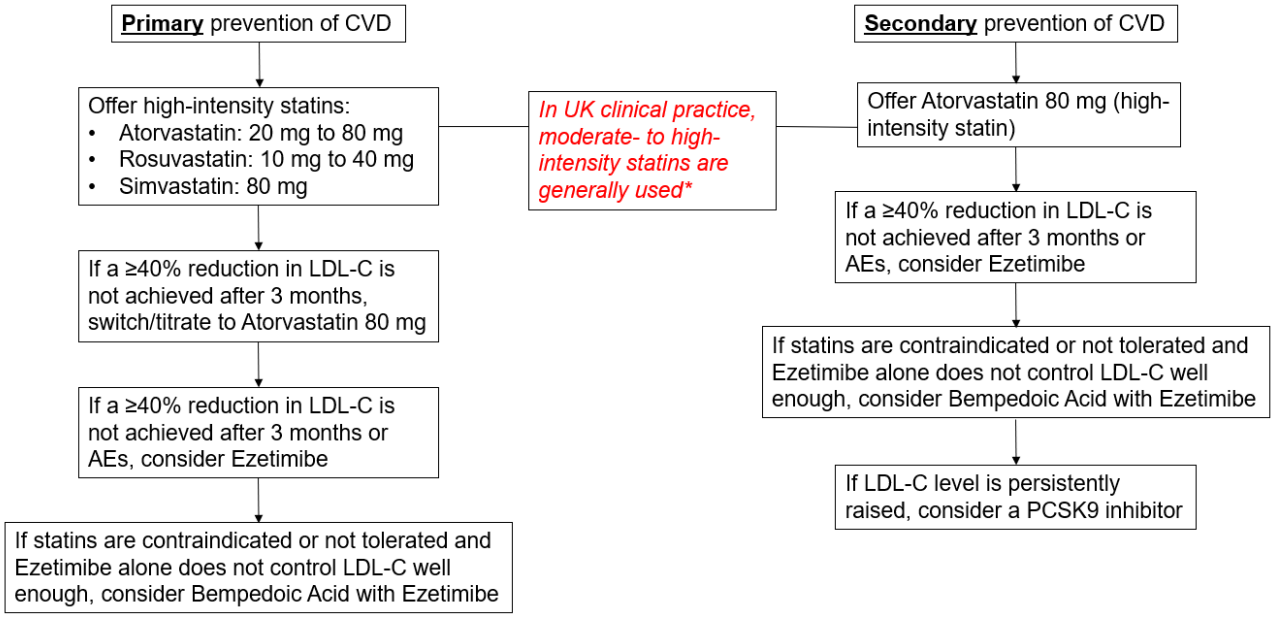
Treatment guidelines

In people at high risk of, or with CVD, NICE clinical guideline CG181 recommends lifestyle modifications including eating a cardioprotective diet, engaging in physical activity and smoking cessation.[21]

When lifestyle modifications are insufficient in reducing modifiable risk factors, statins are recognised by international guidelines as the major therapy for the prevention and reduction of CV events in high-risk patients.[9, 21,51–53] Statins are grouped into different intensity categories according to the percentage reduction in LDL anticipated: low intensity statins if the reduction is 20% to 30%, medium intensity for a reduction between 31% to 40% and high intensity for a reduction above 40%.

Statins are recommended for both primary prevention of CVD (in people with increased risk of CVD in whom lifestyle modification is ineffective or inappropriate) or secondary prevention of CV events in people with CVD (Figure 2). High-intensity statins are recommended for all high-risk patients.[21] However, moderate- to high-intensity statins are used in the vast majority of patients in UK clinical practice, which aligns with the dose intensity of statins used in the REDUCE-IT study.[54] The use of statins has contributed to significant reductions in CV morbidity and mortality in the UK.

Figure 2: Current treatment pathway based on CG181[21], TA385[55], TA694[56], TA393[57] and TA394[58]



*UK clinical experts highlighted that moderate- to high-intensity statins are used in the vast majority of patients in UK clinical practice, which is supported by a European cross-sectional observational study (DA VINCI), and aligns with the dose intensity of statins used in REDUCE-IT.[54]

Abbreviations: AE – Adverse event; CVD – Cardiovascular disease; LDL-C – Low density lipoprotein-cholesterol; PCSK9 – Proprotein convertase subtilisin kexin type 9; UK – United Kingdom.

Despite the proven benefit of statins for patients with established CVD, this population remains at high residual risk of CV events. In addition, those without documented CVD but with established risk factors such as diabetes and comorbid hypertension or hypercholesterolemia are also at elevated risk of major CV events.

Findings from several CV prevention trials have demonstrated significant reductions in CV risk with statin therapy, but persistent CV risk remains in up to 75% of statin-treated patients.[59] This is a medical concern which highlights the need for additional therapeutic interventions. Patients who achieve target LDL-C levels on statins can still be at persistent CV risk due to the ineffective treatment for hypertriglyceridemia.

Anticipated positioning of Icosapent ethyl in the treatment pathway

Icosapent ethyl is anticipated to be offered to patients with high CV risk (defined as either established CVD or diabetes and at least one other CV risk factor), who are on a stable dose of statin therapy with controlled LDL-C levels but elevated TGs.

No treatments are currently recommended in the UK specifically for the prevention of CV events in patients with established CVD or diabetes, with hypertriglyceridemia, who have controlled LDL-C levels and are on a stable dose of statins, presenting a high unmet clinical need. Icosapent ethyl is the first treatment to reduce hepatic TG synthesis and secretion and enhance TG clearance.

The anticipated positioning of Icosapent ethyl in the UK is summarised in Figure 3 and Figure 4.

Figure 3: Anticipated positioning of Icosapent ethyl in patients with diabetes and at least 1 other CV risk factor (primary prevention)

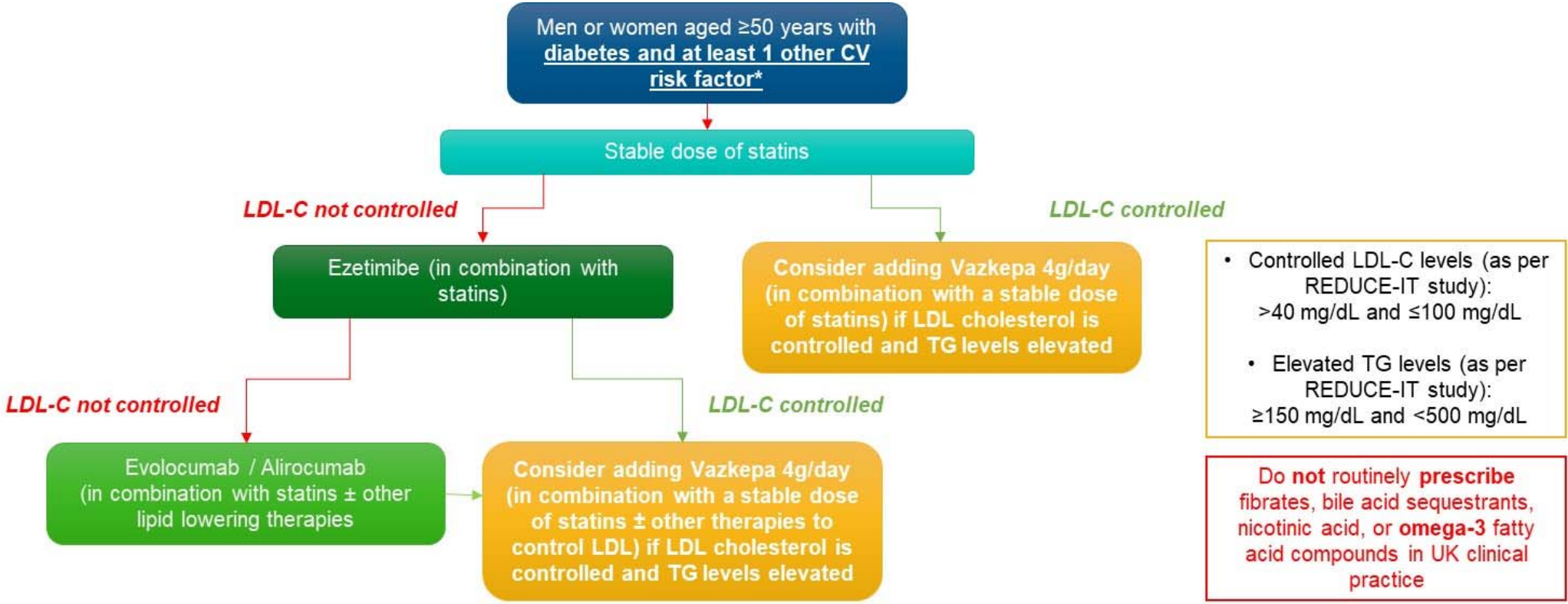


Figure 4: Anticipated positioning of Icosapent ethyl in patients with established CVD (secondary prevention)

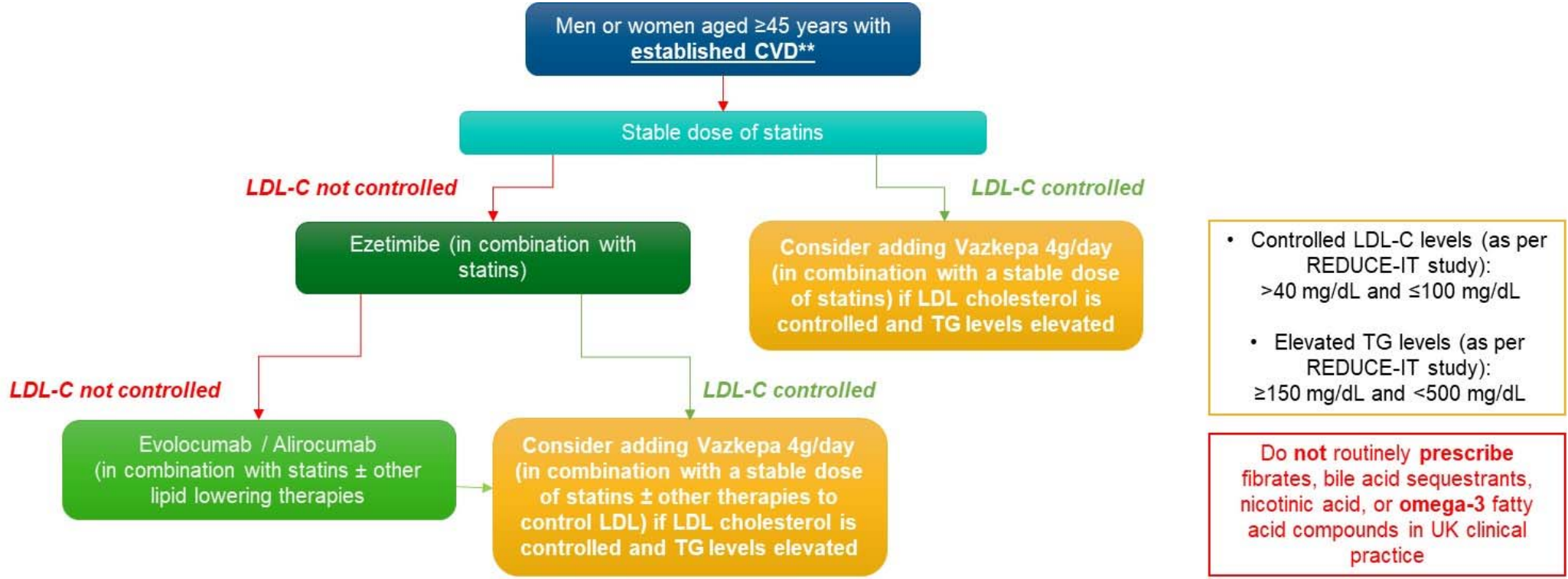


Figure 3:

***** Men or women aged ≥50 years with diabetes and:

One of the following (additional risk factor for CVD):

a) Men >55 years of age and women ≥65 years of age
b) HTN (BP ≥140 mm Hg systolic OR ≥90 mm Hg diastolic) or on antihypertensive medication
c) HDL-C ≤40 mg/dL for men or ≤50 mg/dL for women
d) hsCRP >3.00 mg/L (0.3 mg/dL)
e) Renal dysfunction: CrCl >30 and <60 mL/min
f) Retinopathy, defined as any of the following: non-proliferative retinopathy, pre-proliferative retinopathy, proliferative retinopathy, maculopathy, advanced diabetic eye disease, or a history of photocoagulation
g) Micro- or macroalbuminuria. Microalbuminuria is defined as either a positive micral or other strip test (may be obtained from medical records), an albumin/Cr ratio ≥2.5 mg/mmol, or an albumin excretion rate on timed collection ≥20 mg/min all on ≥2 successive occasions. Macroalbuminuria is defined as Albustix or other dipstick evidence of gross proteinuria, an albumin/Cr ratio ≥25 mg/mmol, or an albumin excretion rate on timed collection ≥200 mg/min all on ≥2 successive occasions.
h) ABI <0.9 without symptoms of intermittent claudication

Figure 4:

****** Men and women aged ≥45 years with ≥1 of the following:

1. Documented CAD (≥1 of the following primary criteria must be satisfied):
    a) Documented multivessel CAD (≥50% stenosis in ≥2 major epicardial coronary arteries, with or without antecedent revascularisation
    b) Documented prior MI
    c) Hospitalisation for high-risk NSTE-ACS (with objective evidence of ischemia: ST-segment deviation or biomarker positivity
2. Documented cerebrovascular or carotid disease (1 of the following primary criteria must be satisfied):
    a) Documented prior ischemic stroke
    b) Symptomatic carotid artery disease with ≥50% carotid arterial stenosis
    c) Asymptomatic carotid artery disease with ≥70% carotid arterial stenosis per angiography or duplex ultrasound
3. Documented PAD (≥1 of the following primary criteria must be satisfied):
    a) ABI <0.9 with symptoms of intermittent claudication
    b) History of aortoiliac or peripheral arterial intervention (catheter-based or surgical)

B.1.4 Equality considerations

We do not expect the assessment of this technology to raise any equality issues.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

See Appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised.

B.2.2 List of relevant clinical effectiveness evidence

The evidence base of icosapent ethyl (Vazkepa, AMR101) for reducing the risk of cardiovascular events in adults on stable statin therapy with elevated triglycerides is provided in REDUCE-IT[60], a phase III, randomised controlled trial that included 8,179 adults (Table 3).

Table 3: Clinical effectiveness evidence for REDUCE-IT

Study	REDUCE-IT, NCT01492361, Bhatt et al. 2019[2,60]
Study design	Phase IIIb, double-blind, randomised (1:1), placebo-controlled, multicentre study, with a treatment and follow-up period of up to a maximum of 6.5 years
Population	Patients on statin with established CVD or at high risk for CVD and elevated TGs. Patients were eligible for inclusion in the study if they met all of the following criteria: TG level of ≥135 mg/dL (1.53 mmol/L), reflecting a 10% allowance due to the variability in TG levels and a target lower end qualifying fasting TG level of ≥150 mg/dL (1.69 mmol/L), and an upper TG level limit of <500 mg/dL (5.64 mmol/L) LDL-C >40 mg/dL (1.04 mmol/L) and ≤100 mg/dL (2.60 mmol/L) and on stable therapy with a statin (with or without ezetimibe) for at least 4 weeks prior to the LDL-C and TG baseline qualifying measurements for randomisation. Either having established CVD (in CV risk category 1) or at high risk for CVD (in CV risk category 2). In summary, the CV risk categories were defined as follows (see Table 4 for full criteria): CV risk category 1 (secondary prevention) – Men and women ≥45 years of age with established CVD CV risk category 2 (primary prevention) – Men and women ≥50 years of age and with the following: Diabetes mellitus (Type 1 or Type 2) requiring treatment with medication

<table>
<tr><td></td><td colspan="5">One or more additional risk factor for CVD
Number of patients recruited receiving:
Icosapent ethyl (n=4,089)
Placebo (n=4,090)</td></tr>
<tr><td>Intervention(s)</td><td colspan="5">Icosapent ethyl four capsules taken as two 1g capsules twice daily; Alternative names: Vazkepa, AMR101</td></tr>
<tr><td>Comparator(s)</td><td colspan="5">Placebo</td></tr>
<tr><td rowspan="2">Indicate if trial supports application for marketing authorisation</td><td>Yes</td><td>X</td><td rowspan="2">Indicate if trial used in the economic model</td><td>Yes</td><td>X</td></tr>
<tr><td>No</td><td></td><td>No</td><td></td></tr>
<tr><td>Rationale for use/non-use in the model</td><td colspan="5">This study investigated icosapent ethyl 4g daily in the population to be treated as per the licenced indication, and includes key outcomes used in the economic model</td></tr>
<tr><td>Reported outcomes specified in the decision problem</td><td colspan="5">Primary endpoint:
• Time from randomisation to the first occurrence of any component of the 5-point major adverse CV events (MACE) composite endpoint:
o CV death
o Nonfatal MI (including silent MI)
o Nonfatal stroke
o Coronary revascularization
o Unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalisation
Key secondary endpoint:
• Time from randomisation to the first occurrence of any component of the 3-point major adverse CV events (MACE) composite endpoint:
o CV death
o Nonfatal MI (including silent MI)
o Nonfatal stroke
Other secondary endpoints:
• Time from randomisation to the first occurrence of any of the following individual or composite endpoints:</td></tr>
</table>

	o **Composite of CV death or nonfatal MI (including silent MI)** o **Fatal or nonfatal MI (including silent MI)** o **Non-elective coronary revascularization represented as the composite of emergent or urgent classifications** o **CV death** o **Unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalisation** o **Fatal or nonfatal stroke** o **Composite of total mortality, nonfatal MI (including silent MI), or nonfatal stroke** o **Total mortality** *Tertiary endpoints:* • **Time from randomisation to the first and all subsequent occurrence of any component of the 5-point major adverse CV events (MACE) *composite* endpoint (this represents the total CV events):** o **CV death** o **Nonfatal MI (including silent MI)** o **Nonfatal stroke** o **Coronary revascularization** o **Unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalisation** *Safety endpoints:* • Adverse events • **Treatment-emergent adverse events** • **Serious treatment-emergent adverse events**

	• **Discontinuation due to treatment-emergent adverse events**
All other reported outcomes	*Tertiary endpoints - where applicable and unless specified otherwise, endpoints represented time from randomisation to the first occurrence of the individual or composite endpoints:* • Primary endpoint in the subset of patients with diabetes mellitus at baseline • Primary endpoint in the subset of patients with metabolic syndrome at baseline • Primary endpoint in the subset of patients with impaired glucose metabolism at baseline (Visit 2 fasting blood glucose [FBG] of 100 to 125 mg/dL) • Key secondary endpoint in the subset of patients with impaired glucose metabolism at baseline (Visit 2 FBG 100 to 125 mg/dL) • Composite of CV death, nonfatal MI (including silent MI), nonfatal stroke, cardiac arrhythmia requiring hospitalisation of ≥24 hours, or cardiac arrest • Composite of CV death, nonfatal MI (including silent MI), non-elective coronary revascularizations (defined as emergent or urgent classifications), or unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalisation • Composite of CV death, nonfatal MI (including silent MI), non-elective coronary revascularizations (defined as emergent or urgent classifications), unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalisation, nonfatal stroke, or peripheral vascular disease (PVD) requiring intervention, such as angioplasty, bypass surgery, or aneurism repair • Composite of CV death, nonfatal MI (including silent MI), non-elective coronary revascularizations (defined as emergent or urgent classifications), unstable angina determined to be

	caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalisation, PVD requiring intervention, or cardiac arrhythmia requiring hospitalisation of ≥24 hours • New congestive heart failure (CHF) • New CHF as the primary cause of hospitalisation • Transient ischemic attack (TIA) • Amputation for PVD • Carotid revascularization • All coronary revascularizations defined as the composite of emergent, urgent, elective, or salvage • Emergent coronary revascularizations • Urgent coronary revascularizations • Elective coronary revascularizations • Salvage coronary revascularizations • Cardiac arrhythmias requiring hospitalisation of ≥24 hours • Cardiac arrest • Ischemic stroke • Hemorrhagic stroke • Fatal or nonfatal stroke in the subset of patients with a history of stroke prior to baseline • New onset diabetes, defined as Type 2 diabetes newly diagnosed during the treatment/follow-up period • New onset hypertension, defined as blood pressure ≥140 mmHg systolic OR ≥90 mmHg diastolic newly diagnosed during the treatment/follow-up period • Fasting TG, total cholesterol (TC), LDL-C, high-density lipoprotein cholesterol (HDL-C), non-HDL-C, very low-density lipoprotein cholesterol (VLDL-C), apolipoprotein B (apo B), high-sensitivity C-reactive protein (hsCRP) (hsCRP and log[hsCRP]), high-sensitivity troponin T

	(hsTnT), and remnant lipoprotein cholesterol (RLP-C) (to be estimated from standard lipid panel, RLP-C = TC – HDL-C – LDL-C [Varbo 2014 applied to fasting lipids]) (based on Intent-to-Treat [ITT] estimands): o Assessment of the relationship between baseline biomarker values and treatment effects within the primary and key secondary endpoints o Assessment of the effect of AMR101 on each marker o Assessment of the relationship between post-baseline biomarker values and treatment effects within the primary and key secondary endpoints by including post-baseline biomarker values (for example, at 4 months, or at 1 year) as a covariate • Change in body weight • Change in waist circumference

Abbreviations: apo B – apolipoprotein B; CHF – Congestive heart failure; CV – Cardiovascular; CVD – Cardiovascular disease; FBG – Fasting blood glucose; HDL-C – High-density lipoprotein cholesterol; hsCRP – high-sensitivity C-reactive protein; hsTnT – high-sensitivity troponin T; ITT – Intent-to-treat; LDL-C – Low-density lipoprotein cholesterol; MACE – major adverse cardiovascular event; MI – Myocardial infarction; PVD – Peripheral vascular disease; RLP-C – Remnant lipoprotein cholesterol; TG – Triglyceride; TIA – Transient ischemic attack; UK – United kingdom; VLDL-C – Very low-density lipoprotein cholesterol.

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1 REDUCE-IT trial methodology[60]

REDUCE-IT[60] was a phase IIIb, multicentre, randomised, double-blind, placebo-controlled study conducted in patients who were ≥45 years of age with established CVD, or who were ≥50 years of age with diabetes in combination with at least one additional risk factor for developing CVD. Recruitment for the study was conducted between November 2011 and August 2016 at 473 sites across 11 countries (US, Australia, Canada, India, South Africa, Netherlands, Ukraine, New Zealand, Russia, Romania and Poland).

In total, 19,212 patients were screened leading to 8,179 patients being randomised in the study (4,089 in the icosapent ethyl group and 4,090 in the placebo group). The screening period consisted of one month of assessment for eligibility, after which patients were randomly assigned according to a computer-generated randomisation scheme to one of two treatment groups at a 1:1 ratio to 4g per day of icosapent ethyl or placebo. The patients, investigators, site staff, sponsor, and contract research organisations (CRO) were blinded to treatment assignments. Additionally, to minimise bias and to avoid potential unblinding, individual results of the post-randomisation efficacy laboratory values (including lipid values) were unavailable to investigators, patients, the sponsor, and the CROs.

Randomisation was stratified by CV risk category, use of ezetimibe, and geographical region (a group of western countries, Eastern European countries, and the Asia–Pacific region). The median follow-up time was 4.9 years and up to a maximum of 6.5 years.

The primary efficacy outcome was the time from randomisation to the first occurrence of any component of the 5-points MACE composite endpoint: CV death, nonfatal MI (including silent MI), nonfatal stroke, coronary revascularization, and unstable angina requiring hospitalisation.

Other outcomes included:

- Key secondary outcome: time from randomisation to the first occurrence of the 3-points MACE composite of: CV death, nonfatal MI (including silent MI), or nonfatal stroke.

- Other secondary outcomes: time from randomisation to the first occurrence of the individual or composite of: CV death or nonfatal MI; fatal or nonfatal MI (including silent MI); non-elective coronary revascularization; CV death; unstable angina requiring hospitalisation; fatal or nonfatal stroke; composite of total mortality, nonfatal MI, or nonfatal stroke; and total mortality.

A summary of the study design and methodology is reported in Table 4.

Table 4: REDUCE-IT study design and methodology

Study	REDUCE-IT, NCT01492361, Bhatt et al. 2019[2,60]
Trial design	Phase IIIb, double-blind, randomised (1:1), placebo-controlled, multicentre study, with a treatment and follow-up period of up to a maximum of 6.5 years
Eligibility criteria	**Inclusion Criteria** Patients were eligible for inclusion in the study if they met the following criteria: • The original protocol stipulated a lower end of qualifying fasting TG level of ≥135 mg/dL (1.53 mmol/L), reflecting a 10% allowance due to the variability in TG levels and a target lower end qualifying fasting TG level of ≥150 mg/dL (1.69 mmol/L), and an upper TG level limit of <500 mg/dL (5.64 mmol/L). Protocol Amendment 1 (16 May 2013) increased the lower end of fasting TG levels from ≥135 mg/dL to ≥200 mg/dL (2.26 mmol/L) to increase enrolment of patients with TG levels at or above 200 mg/dL. • LDL-C >40 mg/dL (1.04 mmol/L) and ≥100 mg/dL (2.60 mmol/L) and on stable therapy with a statin (with or without ezetimibe) for at least 4 weeks prior to the LDL-C and TG baseline qualifying measurements for randomization. – Stable therapy was defined as the same daily dose of the same statin for at least 28 days before the lipid qualification measurements (TG and LDL-C) and, if applicable, the same daily dose of ezetimibe for at least 28 days before the lipid qualification measurements (TG and LDL-C). Patients who had their statin therapy or use of ezetimibe initiated at Visit 1, or had their statin type, statin dose, and/or ezetimibe dose changed at Visit 1, needed to go through a stabilization period of at least 28 days since initiation/change and have their qualifying lipid measurements (TG and LDL-C) after the washout period (at Visit 1.1). – Statins may have been administered with or without ezetimibe. • Either having established CVD (in CV risk category 1) or at high risk for CVD (in CV risk category 2). The CV risk categories were defined as follows: – CV Risk Category 1 (Secondary Prevention Cohort): defined as men and women ≥45 years of age with one or more of the following: o Documented coronary artery disease (CAD); one or more of the following primary criteria must have been satisfied: ▪ Documented multi-vessel CAD (≥50% stenosis in at least two major epicardial coronary arteries, with or without antecedent revascularization). ▪ Documented prior MI.

Study	REDUCE-IT, NCT01492361, Bhatt et al. 2019[2,60]
	▪ Hospitalization for high-risk non-ST-segment elevation acute coronary syndrome, with objective evidence of ischemia: ST-segment deviation or biomarker positivity. o Documented cerebrovascular or carotid disease; one of the following primary criteria must have been satisfied: ▪ Documented prior ischemic stroke. ▪ Symptomatic carotid artery disease with ≥50% carotid arterial stenosis. ▪ Asymptomatic carotid artery disease with ≥70% carotid arterial stenosis per angiography or duplex ultrasound. ▪ History of carotid revascularization (catheter-based or surgical). o Documented peripheral arterial disease; one or more of the following primary criteria must have been satisfied: ▪ Ankle brachial index (ABI) <0.9 with symptoms of intermittent claudication. ▪ History of aorto-iliac or peripheral arterial intervention (catheter-based or surgical). – CV Risk Category 2 (Primary Prevention Cohort): defined as patients with: o Diabetes mellitus (Type 1 or Type 2) requiring treatment with medication. o Men and women ≥50 years of age. o One or more of the following at Visit 1 (additional risk factor for CVD): ▪ Men ≥55 years of age or women ≥65 years of age. ▪ Cigarette smoker or stopped smoking within 3 months before Visit 1. ▪ Hypertension (blood pressure ≥140 mmHg systolic or ≥90 mmHg diastolic) or on antihypertensive medication. ▪ HDL-C ≤40 mg/dL for men or ≤50 mg/dL for women. ▪ hsCRP >3.00 mg/L (0.3 mg/dL). ▪ Renal dysfunction: creatinine clearance (CrCL) >30 and <60 mL/min (>0.50 and <1.00 mL/sec). ▪ Retinopathy, defined as any of the following: non-proliferative retinopathy, pre-proliferative retinopathy, proliferative retinopathy, maculopathy, advanced diabetic eye disease, or a history of photocoagulation. ▪ Micro- or macroalbuminuria ▪ Micral or other strip test (may have been obtained from medical records), an albumin/creatinine ratio ≥2.5 mg/mmol or an

Study	REDUCE-IT, NCT01492361, Bhatt et al. 2019[2,60]
	albumin excretion rate on timed collection ≥20 mg/min all on at least two successive occasions; macroalbuminuria, defined as Albustix or other dipstick evidence of gross proteinuria, an albumin/creatinine ratio ≥25 mg/mmol or an albumin excretion rate on timed collection ≥200 mg/min all on at least two successive occasions. ▪ ABI <0.9 without symptoms of intermittent claudication (patients with ABI <0.9 with symptoms of intermittent claudication were included in CV risk category 1). o Note: Patients with diabetes and CVD, as defined above, were eligible, based on the CVD requirements and were to be included in CV risk category 1. Only patients with diabetes and no documented CVD, as defined above, required at least one additional risk factor as listed, and were to be included in CV risk category 2. • Women were required to meet all 3 of the following criteria: – Not pregnant. – Not breastfeeding. – Not planning on becoming pregnant during the study. • Women of child bearing potential were required to have a negative urine pregnancy test before randomisation. Women were to be considered not of childbearing potential if they met one of the following criteria, as documented by the Investigator: – Had a hysterectomy, tubal ligation or bilateral oophorectomy prior to signing the ICF. – Were post-menopausal, defined as ≥1 year since their last menstrual period or had a follicle-stimulating hormone level in a menopausal range. • Women of childbearing potential were required to agree to use an acceptable method of avoiding pregnancy from Screening to the end of the study, unless their sexual partner(s) was/were surgically sterile or the woman was abstinent. • Understood the study procedures, was willing to adhere to the study schedules, and agreed to participate in the study by giving informed consent prior to screening. • Agreed to follow and maintain a physician recommended diet through the duration of the study. **Exclusion Criteria:** Patients were to be excluded from the study if they met any of the following criteria: • Severe (New York Heart Association class IV) heart failure. • Any life-threatening disease expected to result in death within the next 2 years (other than CVD).

Study	REDUCE-IT, NCT01492361, Bhatt et al. 2019[2,60]
	• Active severe liver disease (evaluated at Visit 1): cirrhosis, active hepatitis, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 × the upper limit of normal (ULN), or biliary obstruction with hyperbilirubinemia (total bilirubin >2 × ULN). • Glycated haemoglobin (HbA1c) >10.0% (or >86 mmol/mol IFCC units) at Screening (Visit 1). If patients failed this criterion at Visit 1, they may have had their antidiabetic therapy optimized and been retested at Visit 1.1. • Poorly controlled hypertension: blood pressure ≥200 systolic mmHg or ≥100 mmHg diastolic (despite antihypertensive therapy). • Planned coronary intervention (such as stent placement or heart bypass) or any non-cardiac major surgical procedure. Patients may have been (re)evaluated for participation in the study (starting with Visit 1.1) after their recovery from the intervention/surgery. • Known familial lipoprotein lipase deficiency (Fredrickson Type 1), apolipoprotein C-II deficiency, or familial dysbetalipoproteinemia (Fredrickson Type 3). • Participation in another clinical study involving an investigational agent within 90 days prior to Screening (Visit 1). Patients were not to participate in any other investigational medication or medical device study while participating in this study. (Participation in a registry or observational study without an additional therapeutic intervention was allowed.) • Intolerance or hypersensitivity to statin therapy. • Known hypersensitivity to any ingredients of the study product or placebo; known hypersensitivity to fish and/or shellfish. • History of acute or chronic pancreatitis. • Malabsorption syndrome and/or chronic diarrhoea (Note: patients who underwent gastric/intestinal bypass surgery were considered to have malabsorption and were not eligible; patients who underwent gastric banding were eligible). • Non-study drug-related, non-statin, lipid-altering medications, supplements or foods. • Other medications (not indicated for lipid alteration) • Known to have acquired immunodeficiency syndrome (AIDS); patients who were HIV-positive without AIDS were allowed. • Requirement for peritoneal dialysis or haemodialysis for renal insufficiency or CrCL <30 mL/min (0.50 mL/sec). • Unexplained creatine kinase concentration >5 × ULN or creatine kinase elevation due to known muscle disease (e.g., polymyositis, mitochondrial dysfunction) at Visit 1. • Any condition or therapy that, in the opinion of the Investigator, might have posed a risk to the patient or made participation in the study not in the patient's best interest. • Drug or alcohol abuse within the previous 6 months, and unable/unwilling to abstain from drug abuse and excessive alcohol consumption during the study or drinking 5 units or more • for men or 4 units or more for women in any one hour.

Study	REDUCE-IT, NCT01492361, Bhatt et al. 2019[2,60]
	• Mental/psychological impairment or any other reason to expect patient difficulty in complying with the requirements of the study or understanding the goal and potential risks of participating in the study.
Settings and location where data were collected	473 participating sites in 11 countries (US, Australia, Canada, India, South Africa, Netherlands, Ukraine, New Zealand, Russia, Romania, Poland)
Trial drugs and concomitant medications	**Trial drugs:** Participants were treated with icosapent four capsules taken as two 1g capsules twice daily, or matched placebo **Permitted concomitant medications:** Stable statin regime, with the statin intensity categories defined as in the American College of Cardiology/American Heart Association cholesterol guidelines and the patient's 10-year CV risk score (which aligns with the regime as indicated in NICE CG181).[61,62]
Outcomes used in the economic model or specified in the scope, including primary outcome	**Primary outcomes:** • **Time from randomisation to the first occurrence of any component of the 5-point MACE *composite*:** o **CV death** o **Nonfatal MI (including silent MI)** o **Nonfatal stroke** o **Coronary revascularization** o **Unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalisation** **Secondary and tertiary outcomes applied in the economic model:** • **Time from randomisation to the first occurrence of any of any of the following *individual or composite* endpoints:** o **Composite of CV death or nonfatal MI (including silent MI)** o **Fatal or nonfatal MI (including silent MI)** o **Non-elective coronary revascularization represented as the composite of emergent or urgent classifications** o **CV death**

Study	REDUCE-IT, NCT01492361, Bhatt et al. 2019[2,60]
	○ **Unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalisation** ○ **Fatal or nonfatal stroke** ○ **Composite of total mortality, nonfatal MI (including silent MI), or nonfatal stroke** ○ **Total mortality** • **Time from randomisation to the first and all subsequent occurrence of any component of the 5-point MACE *composite* endpoint (this represents the total CV events):** ○ **CV death** ○ **Nonfatal MI (including silent MI)** ○ **Nonfatal stroke** ○ **Coronary revascularization** ○ **Unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalisation** **Safety outcomes:** • **Treatment-emergent adverse events** • **Serious treatment-emergent adverse events** • **Discontinuation due to treatment-emergent adverse events**

Abbreviations: ABI – Ankle brachial index; AIDS – Acquired immunodeficiency syndrome; ALT – Alanine aminotransferase; AST – Aspartate aminotransferase; CAD – Coronary artery disease; CrCL – Creatine clearance; CV – Cardiovascular; CVD – Cardiovascular disease; HDL-C – High-density lipoprotein cholesterol; HIV – Human immunodeficiency virus; hsCRP – High-sensitivity C-reactive protein; ICF – Informed Consent Form; IFCC– International federation of clinical chemistry; LDL-C – Low-density lipoprotein cholesterol; MACE – major adverse cardiovascular event; MI – Myocardial infarction; TG – Triglyceride; ULN – Upper limit of normal; US – United states.

B.2.3.2 Baseline characteristics of the REDUCE-IT trial[60]

A total of 8,179 patients were included in the ITT population, with 4,089 and 4,090 patients randomly assigned to receive treatment with icosapent ethyl and placebo, respectively.

The median age of patients was 64 years in both treatment groups, and the majority of patients were recruited from western countries (United States, Canada, the Netherlands, Australia, New Zealand, and South Africa) with 71.1% and 71.0%, in the icosapent ethyl and placebo groups, respectively.

The split between the CV risk stratum was the same across the two treatment groups with 70.7% of patients receiving treatment for secondary prevention of CV events and 29.3% receiving treatment for primary prevention of CV events. The vast majority of patients (>90%) received a moderate to high intensity dose of statins.

Baseline characteristics were considered similar between the intervention and placebo group, denoting a randomisation process that produced an appropriate balance of known or unknown prognostic factors, baseline conditions, medications, or prior treatments.

A summary of demographic and disease-relevant baseline characteristics is reported in Table 5.

Table 5: Baseline characteristics in REDUCE-IT: ITT population[2, 60,63]

	Icosapent ethyl (N = 4,089)	**Placebo (N = 4,090)**
Demographic characteristics		
Age		
Median, yr (IQR)	64.0 (57.0–69.0)	64.0 (57.0–69.0)
≥65 yrs, n (%)	1,857 (45.4)	1,906 (46.6)
Gender		
Sex – Male, n (%)	2,927 (71.6)	2,895 (70.8)
Ethnicity		
Race – White, n (%)	3,691 (90.3)	3,688 (90.2)
Body-mass index		
Median (IQR)	30.8 (27.8–34.5)	30.8 (27.9–34.7)
≥30, n (%)	2,331 (57.0)	2,362 (57.8)
Geographic region, n (%)		
Group of western countries[a]	2,906 (71.1)	2,905 (71.0)
Eastern European countries	1,053 (25.8)	1,053 (25.7)
Asia–Pacific region	130 (3.2)	132 (3.2)
Disease-relevant baseline characteristics		

Cardiovascular risk stratum, n (%)		
Secondary-prevention cohort	2,892 (70.7)	2,893 (70.7)
Primary-prevention cohort	1,197 (29.3)	1,197 (29.3)
Diabetes, n (%)		
Type 1	27 (0.7)	30 (0.7)
Type 2	2,366 (57.9)	2,363 (57.8)
No diabetes	1,695 (41.5)	1,694 (41.4)
Prior atherosclerotic CVD, n (%)	2,816 (68.9)	2,835 (69.3)
Prior non-atherosclerotic CVD (including CHF), n (%)	3,649 (89.2)	3,645 (89.1)
Renal impairment, n (%)	905 (22.1)	911 (22.3)
Hypertension, n (%)	3,541 (86.6)	3,543 (86.6)
Statin intensity, n (%)		
Low	254 (6.2)	267 (6.5)
Medium	2,533 (61.9)	2,575 (63.0)
High	1,290 (31.5)	1,226 (30.0)
Data missing	12 (0.3)	22 (0.5)
Ezetimibe use, n (%)	262 (6.4)	262 (6.4)
TG levels, n/N (%)		
< 150mg/dL	412/4,086 (10.1)	429/4,089 (10.5)
≥ 150mg/dL to < 200mg/dL	1,193/4,086 (29.2)	1,191/4,089 (29.1)
≥ 200mg/dL	2,481/4,086 (60.7)	2,469/4,089 (60.4)
TG levels (mg/dL), median (IQR)	216.5 (176.5–272.0)	216.0 (175.5–274.0)
TG level ≥200 mg/dl and HDL cholesterol level ≤35 mg/dl, n (%)	823 (20.1)	794 (19.4)
Median high-sensitivity CRP level, mg/liter (IQR)	2.2 (1.1–4.5)	2.1 (1.1–4.5)
Median HDL cholesterol level, mg/dl (IQR)	40.0 (34.5–46.0)	40.0 (35.0–46.0)
Median LDL cholesterol level, mg/dl (IQR)	74.0 (61.5–88.0)	76.0 (63.0–89.0)
Median eicosapentaenoic acid level, µg/ml (IQR) —	26.1 (17.1–40.1)	26.1 (17.1–39.9)
Abnormal lipids		
High HDL-c (≥ 1.6mmol/L [60mg/dL])	187 (4.6)	187 (4.6)
Low HDL-c (< 1.0mmol/L [40mg/dL])	1,327 (32.5)	1,259 (30.8)
TGs > 11.3mmol/L (1,000mg/dL)	76 (1.9)	72 (1.8)

[a]*United States, Canada, the Netherlands, Australia, New Zealand, and South Africa*
Abbreviations: CHF – Congestive heart failure; CVD – Cardiovascular disease; HDL-C – High-density lipoprotein cholesterol; ITT–Intent-to-treat; IQR – Inter quartile range; LDL-C – Low-density lipoprotein cholesterol; TG – Triglyceride.

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Details of the numbers of participants eligible to enter the REDUCE-IT trial are provided in Appendix D.

Table 6: REDUCE-IT statistical analysis

Trial number (acronym)	REDUCE-IT, NCT01492361, Bhatt et al. 2019[2, 60,63]
Hypothesis objective	It was hypothesized that the risk of cardiovascular events would be lower with icosapent ethyl therapy than with placebo among patients in whom elevated triglyceride levels served as a marker of residual risk despite statin therapy.
Sample size, power calculation	In this event-driven trial, it was estimated that approximately 1,612 adjudicated primary end-point events would be necessary to provide the trial with 90% power to detect a 15% lower risk of the primary composite end point in the icosapent ethyl group than in the placebo group. It was estimated that a sample size of approximately 7,990 patients would be required to reach this number of end-point events.
Outcome populations	Four populations were defined in the study: • The ITT population was defined as all patients who were randomised. All efficacy analyses, including the primary analysis, were performed on the ITT population. • The modified ITT population was defined as all randomised patients who had study drug dispensed after randomisation. Patients were analysed according to the randomised treatment. • The per-protocol population included all modified ITT patients without any major protocol deviations who had 80% or greater adherence while on treatment. To be included in the per-protocol population, the minimum time on therapy had to be 90 days. • The safety population was defined as all randomised patients and was the same as the ITT population. Patients were analysed for safety according to treatment received.
Statistical analysis	The REDUCE-IT study assessed the primary outcome by counts and Kaplan–Meier estimates of the percentage of patients experiencing each type of event by study completion per treatment arm. HRs and 95% CIs were generated with the use of a Cox proportional hazards model that included trial-group assignment as a covariate, stratified according to CV risk category, geographic region, and use of ezetimibe. The two-sided alpha level for the primary analysis was adjusted to 0.0437 from 0.05 to account for the two interim analyses based on a group sequential design with O'Brien–Fleming boundaries generated using the Lan-DeMets alpha-spending function. Log-rank p-values from the Kaplan–Meier analysis (stratified based on the three randomisation factors) were reported.

	Subgroup analysis was performed using Kaplan–Meier estimates and the log-rank test stratified by stratification factors used at randomisation (except where the subgroup was a stratification factor). The key and other secondary outcomes and tertiary outcomes, as well as the components of the composite outcomes, were analysed using the same methods as the primary outcome analysis. Statistical analyses of secondary outcomes followed a hierarchical sequential approach to control for inflated type I error. Specifically, the key secondary endpoint (the time from randomisation to the first occurrence of the 3-point MACE composite of CV death, nonfatal MI [including silent MI], or nonfatal stroke) was tested only if the primary analysis was statistically significant. Other secondary endpoints were the time from randomisation to the first occurrence of the individual or composite endpoints, as follows (statistically tested in the order listed): • composite of CV death or nonfatal MI (including silent MI) • fatal or nonfatal MI (including silent MI) • nonelective coronary revascularization • CV death • unstable angina requiring emergent hospitalisation • fatal or nonfatal stroke • composite of total mortality, nonfatal MI (including silent MI), or nonfatal stroke • total mortality Testing was done at a significance level of 0.0437 and ceased when a comparison for a secondary endpoint was greater than this threshold. All analyses beyond the primary or the last endpoint meeting statistical significance in this hierarchical order at this alpha level were exploratory, per the analysis plan.
Data management, patient withdrawals	It was planned for approximately 7,990 patients (approximately 3,995 patients per treatment group) to be included in the study. In total, 19,212 patients were screened leading to 8,179 patients participating in the study (4,089 in the icosapent ethyl group and 4,090 in the placebo group). Of the 8,179 patients, 7,314 patients completed the final visit within the 2018 final visit window or died during the study. The remaining patients (865/8,179) discontinued the study early with 9.9% (405/4,089) and 11.2% (460/4,090) in the icosapent ethyl and placebo groups, respectively. Among patients who terminated the study early, the most common reasons overall were: • Withdrawal of consent: 6.9% (281/4,089) and 7.3% (297/4,090) in the icosapent ethyl and placebo groups, respectively. • Incomplete final visit (lost to follow-up): 1.5% (63/4,089) and 2.2% (89/4,090) in the icosapent ethyl and placebo groups, respectively. • Investigator judgment: 0.3% (12/4,089) and 0.3% (12/4,090) in the icosapent ethyl and placebo groups, respectively.
Interim analyses	Two interim analyses were planned for the primary endpoint when adjudication of approximately 60% and 80% of the total target number of primary endpoint events planned (1,612) were reached. The planned interim analyses were based on a group sequential design with O'Brien-Fleming boundaries generated using the Lan-DeMets alpha-spending function. The two Data Monitoring Committee (DMC) interim analysis

	review meetings were performed in September 2016 and August 2017, respectively, at which 59.3% (953 events) and 75.8% (1,218 events) of the final adjudicated primary endpoint events (1,606) had occurred and had been adjudicated. At each interim analysis the sponsor remained blinded to trial results and the DMC had discretion to consider the robustness, consistency, and completeness within the totality of the data beyond the primary endpoint, in support of their recommendation regarding study continuation. Based on the reviews of each interim analysis, the DMC recommended continuation of the study as planned.

Abbreviations: CI – Confidence interval; CV – Cardiovascular; DMC – Data monitoring committee; HR– Hazard ratio; ITT – Intent-to-treat; MI – Myocardial infarction.

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

A complete quality assessment for the REDUCE-IT trial is provided in Appendix D.

B.2.6 Clinical effectiveness results of the REDUCE-IT trial

B.2.6.1.1 Primary efficacy endpoint: Time from randomisation to the first occurrence of any of the primary composite endpoints

The primary efficacy endpoint in the REDUCE- IT trial[2, 60,63] is a 5-point MACE composite endpoint defined as time from randomisation to the first occurrence of any of the following events:

- CV death
- Nonfatal myocardial infarction (MI) (including silent MI)
- Nonfatal stroke
- Coronary revascularization
- Unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalisation.

Icosapent ethyl demonstrated a statistically significant ($p<0.001$) decline in CV events included in the primary efficacy endpoint during the follow-up period (median 4.9 years) over placebo.

For the ITT population, primary endpoint events occurred in 17.2% of patients in the icosapent ethyl group, compared with 22.0% in the placebo group (hazard ratio [HR]: 0.752; 95% confidence interval [CI], 0.682 to 0.830; $p<0.001$). The absolute

percentage difference between the icosapent ethyl and placebo groups was -4.7% (95% CI, 3.1% to 6.5%). The number of patients needed to be treated with icosapent ethyl to avoid one primary endpoint event was 21 (95% CI, 15 to 33) over a median follow-up of 4.9 years.

The results for patients in the secondary prevention subgroup indicated a significant effect (p=0.1388) on the percentage of patients that experienced the primary endpoint with icosapent ethyl (19.3% versus placebo 25.5%; HR: 0.726; 95% CI, 0.650 to 0.810), similar to that observed in the total population.

In the primary prevention subgroup, the primary outcome occurred in 12.2% of patients who received icosapent ethyl compared with 13.6% of those in the placebo group (HR: 0.876; 95% CI, 0.700 to 1.095). The absolute risk difference between the two groups was 1.4%, which is not considered to be statistically significant. REDUCE-IT was not designed to support conclusions of independent primary endpoint analyses within subgroups. Statistical significance was not expected in the primary prevention subgroup analyses due to this subgroup representing only 29.3% of all patients. Despite contributing 22% only of all first events, the primary prevention cohort hazard ratios and interaction p-values (primary versus secondary prevention) remain consistent with the overall demonstration of benefit in REDUCE-IT.

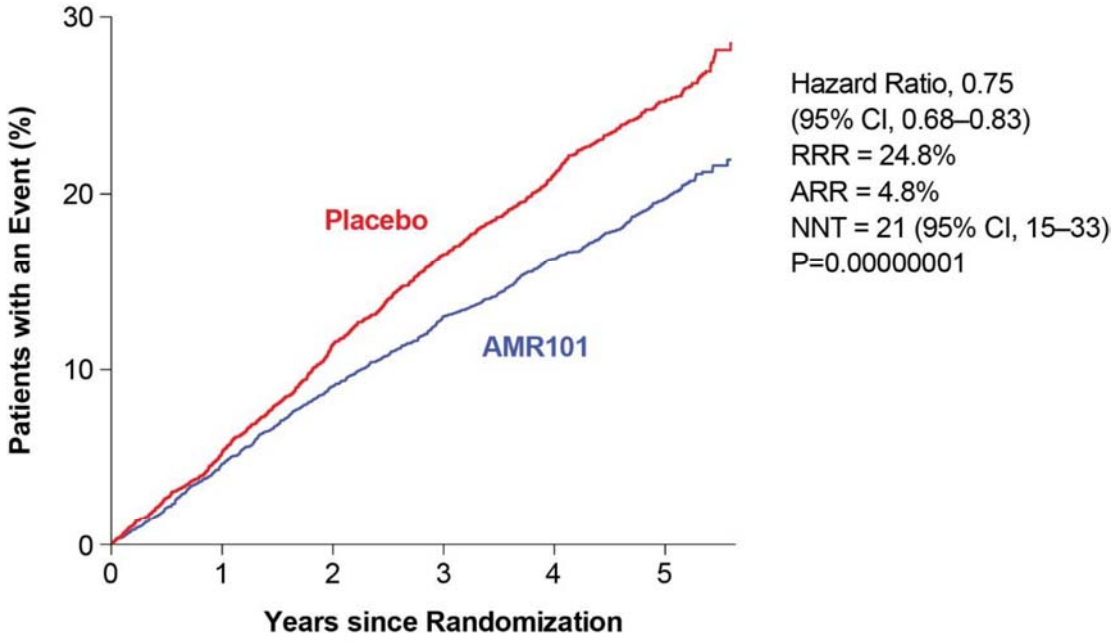
The number of events that occurred for each individual component that contributes to the composite primary endpoint is provided in Table 7 and the associated Kaplan-Meier curve is displayed in Figure 5. A forest plot of the analyses of the primary endpoint by CV risk stratum is presented in Figure 6.

Table 7: Time from randomisation to the first occurrence of any of the 5-point MACE composite outcomes[60]

Outcomes	Icosapent ethyl	Placebo
5-point MACE composite of CV death, nonfatal MI [including silent MI], nonfatal stroke, coronary revascularization, and unstable angina requiring hospitalisation)		
ITT	**N=4,089**	**N=4,090**
n (%)	705 (17.2)	901 (22.0)
HR (95% CI)	0.752 (0.682 to 0.830)	
P-value	0.00000001	
Components contributing to composite outcome, n (%)		
CV death	137 (3.4)	149 (3.6)
Nonfatal MI	205 (5.0)	280 (6.8)
Nonfatal stroke	80 (2.0)	105 (2.6)
Coronary revascularization	189 (4.6)	244 (6.0)
Hospitalisation for unstable angina	94 (2.3)	123 (3.0)
Secondary prevention	[redacted]	[redacted]
n (%)	[redacted]	[redacted]
HR (95% CI)	[redacted]	
Primary prevention	[redacted]	[redacted]
n (%)	[redacted]	[redacted]
HR (95% CI)	[redacted]	

Abbreviations: CI – Confidence interval; CV – Cardiovascular; HR – Hazard ratio; ITT – Intent-to-treat; MACE – Major adverse cardiovascular event; MI – Myocardial infarction.

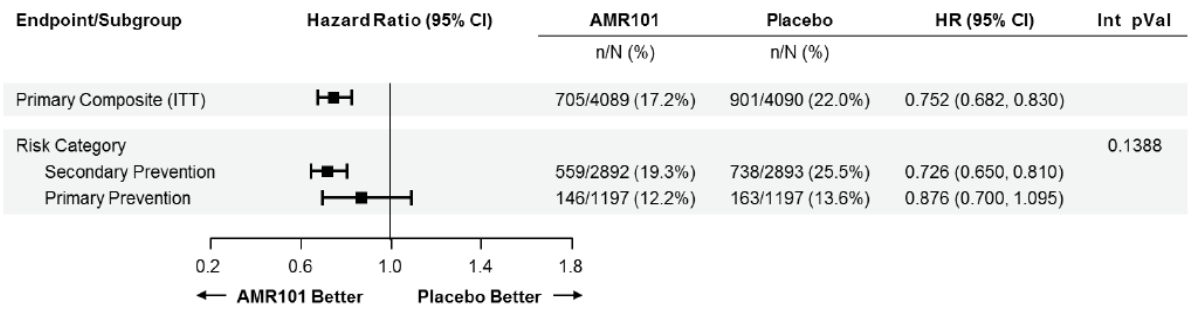
Figure 5: Kaplan–Meier event curves for the primary efficacy 5-point MACE composite endpoint of CV death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina requiring hospitalisation – ITT population[60]



No. at Risk

Placebo	4090	3743	3327	2807	2347	1358
AMR101	4089	3787	3431	2951	2503	1430

Figure 6: Forest plot analysis of the primary endpoint by subgroup 'CV risk stratum'[60]



Sensitivity analyses were conducted to censor patients for death of undetermined cause, study drug discontinuation, study drug discontinuation +30 days, silent MI at the last normal ECG, and silent MI at mid-point between the date of the last normal ECG and the date of the first indicative ECG. Results of these sensitivity analyses were generally consistent with the primary analyses, i.e., there was a significantly lower risk of major adverse CV events with icosapent ethyl than with placebo.

Time-to-event analyses, as done for the primary analysis, were carried out at 1-year and 2-year landmarks for the ITT population.[60] At the 2-year landmark, there was a significantly lower risk of major adverse CV events associated with icosapent ethyl than with placebo (HR: 0.799; 95% CI: 0.693 to 0.920; p=0.0017).[60]

B.2.6.1.2 Key secondary efficacy endpoint: Time from randomisation to the first occurrence of the 3-point MACE composite outcome

Icosapent ethyl demonstrated a statistically significant (p<0.001) decline in CV events included in the composite key secondary endpoint during the follow-up period (median 4.9 years) over placebo.[2, 60,63]

For the ITT population, secondary endpoint events occurred in 11.2% of patients in the icosapent ethyl group, compared with 14.8% in the placebo group (HR, 0.74; 95% CI, 0.65 to 0.83; p<0.001). The absolute percentage difference between the icosapent ethyl and placebo groups was 3.6 (95% CI, 2.1 to 5.0). The number of patients needed to be treated with icosapent ethyl to avoid one secondary endpoint event was 28 (95% CI, 20 to 47). The median follow-up duration for the key secondary endpoint was 4.8 and 4.7 years for the icosapent ethyl and placebo groups, respectively.

The results for patients in the secondary prevention subgroup indicated a non-significant effect (p=0.4107) on the percentage of patients that experienced the secondary endpoint with icosapent ethyl (12.5% versus placebo 16.9%; HR: 0.717; 95% CI, 0.626 to 0.821), similar to that observed in the total population. In the primary prevention subgroup, the secondary outcome occurred in 8.2% of patients who received icosapent ethyl compared with 9.8% of those in the placebo group (HR: 0.814; 95% CI, 0.622 to 1.064).

The number of events that occurred in each individual component that contributes to the key secondary composite endpoint is provided in Table 8, and the associated Kaplan-Meier curve is displayed in Figure 7. A forest plot of the analyses of the secondary endpoint by CV risk stratum is presented in Figure 8.

Table 8: Time from randomisation to the first occurrence of any key secondary endpoint events[60]

Outcomes	Icosapent ethyl	Placebo
3-point MACE composite of CV death, nonfatal MI [including silent MI], and nonfatal stroke		
ITT	**N=4,089**	**N=4,090**
n (%)	459 (11.2)	606 (14.8)
HR (95% CI)	0.735 (0.651 to 0.830)	
P-value	0.0000006	
Components contributing to composite outcome, n (%)		
CV death	149 (3.6)	167 (4.1)
Nonfatal MI	230 (5.6)	325 (7.9)
Nonfatal stroke	80 (2.0)	114 (2.8)
Secondary prevention	**N=2,892**	**N=2,893**
n (%)	361 (12.5)	489 (16.9)
HR (95% CI)	0.717 (0.626 to 0.821)	
Primary prevention	**N=1,197**	**N=1,197**
n (%)	98 (8.2)	117 (9.8)
HR (95% CI)	0.814 (0.622 to 1.064)	

Abbreviations: CI – Confidence interval; CV – Cardiovascular; HR – Hazard ratio; ITT – Intent-to-treat; MACE – Major adverse cardiovascular event; MI – Myocardial infarction.

Figure 7: Kaplan–Meier event curves for the key secondary efficacy 3-point MACE composite endpoint of cardiovascular death, nonfatal MI, and nonfatal stroke - ITT population[60]

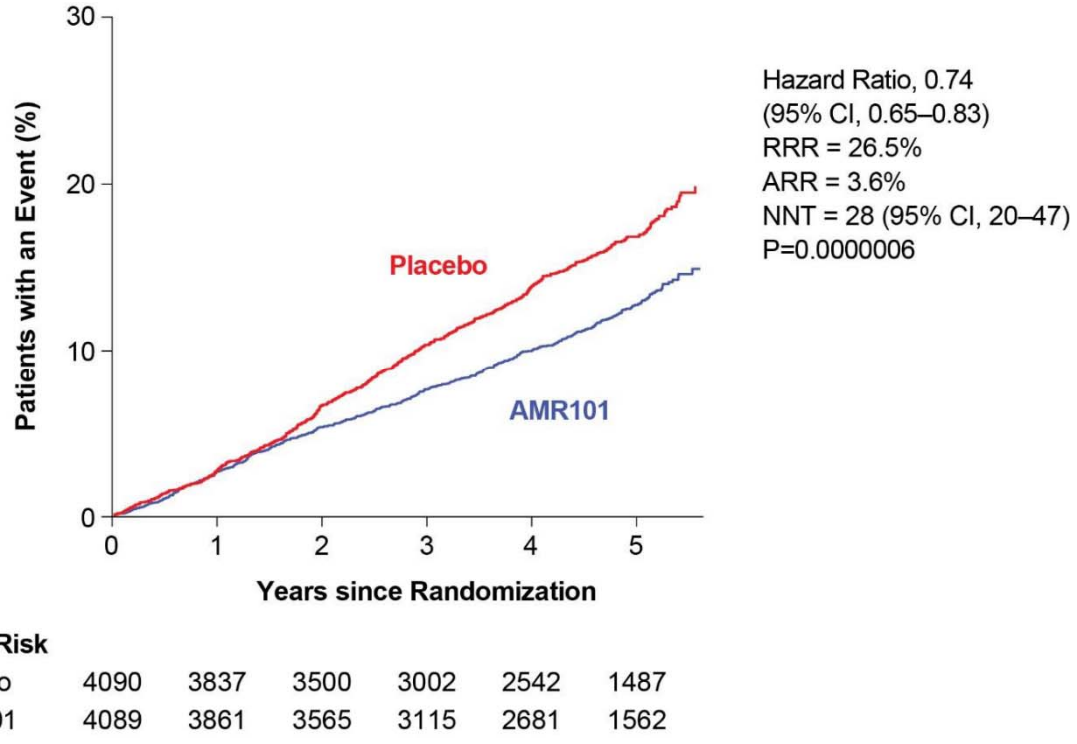
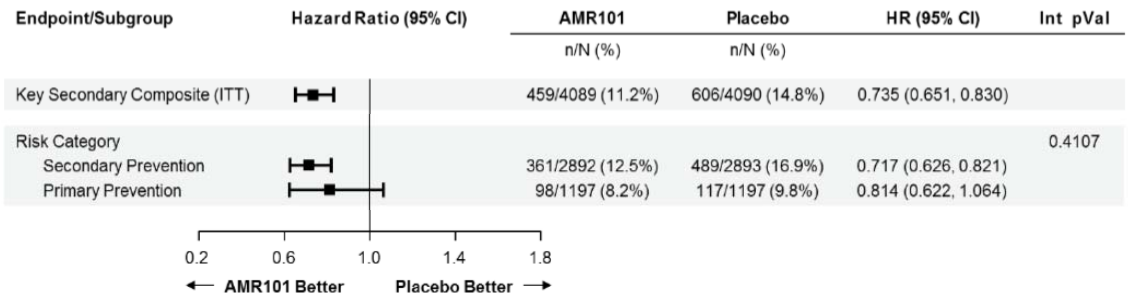


Figure 8: Forest plot analysis of the secondary endpoint by subgroup 'CV risk stratum'[60]



B.2.6.1.3 Other secondary efficacy endpoints

In addition to the primary and key secondary endpoints investigated in the REDUCE-IT trial, other secondary endpoints were recorded over the follow-up period which include:

- Composite of CV death or nonfatal MI
- Fatal or nonfatal MI
- Urgent or emergency revascularization
- CV death (includes adjudicated CV deaths and deaths of undetermined causality)
- Hospitalisation for unstable angina
- Fatal or nonfatal stroke
- Composite of death from any cause, nonfatal MI, or nonfatal stroke
- Death from any cause

Table 9: Time from randomisation to the first occurrence of other secondary endpoint events - ITT population[60,63]

Outcomes	Icosapent ethyl (N=4,089)	Placebo (N=4,090)
CV death or nonfatal MI		
n (%)	392 (9.6)	507 (12.4)
HR (95% CI)	0.753 (0.660 to 0.859)	
P-value	<0.0001	
Fatal or nonfatal MI		
n (%)	250 (6.1)	355 (8.7)
HR (95% CI)	0.688 (0.585 to 0.808)	
P-value	<0.0001	
Fatal MI, n (%)	16 (0.4)	29 (0.7)
HR (95% CI)	0.546 (0.297 to 1.005)	
P-value	0.0484	

Outcomes	Icosapent ethyl (N=4,089)	Placebo (N=4,090)
Nonfatal MI, n (%)	237 (5.8)	332 (8.1)
HR (95% CI)	0.697 (0.590 to 0.823)	
P-value	<0.0001	
Urgent or emergency revascularization		
n (%)	216 (5.3)	321 (7.8)
HR (95% CI)	0.653 (0.550 to 0.776)	
P-value	<0.0001	
CV death		
n (%)	174 (4.3)	213 (5.2)
HR (95% CI)	0.803 (0.657 to 0.981)	
P-value	0.0315	
Hospitalisation for unstable angina		
n (%)	108 (2.6)	157 (3.8)
HR (95% CI)	0.679 (0.531 to 0.868)	
P-value	0.0018	
Fatal or nonfatal stroke		
n (%)	98 (2.4)	134 (3.3)
HR (95% CI)	0.720 (0.555 to 0.934)	
P-value	0.0129	
Fatal stroke, n (%)	14 (0.3)	18 (0.4)
HR (95% CI)	0.767 (0.382 to 1.543)	
P-value	0.4564	
Nonfatal stroke, n (%)	85 (2.1)	118 (2.9)
HR (95% CI)	0.708 (0.536 to 0.936)	
P-value	0.0149	
Death from any cause, nonfatal MI, or nonfatal stroke		
n (%)	549 (13.4)	690 (16.9)
HR (95% CI)	0.772 (0.690 to 0.864)	
P-value	<0.0001	
Death from any cause		
n (%)	274 (6.7)	310 (7.6)
HR (95% CI)	0.870 (0.739 to 1.023)	
P-value	0.0915	

Abbreviations: CI – Confidence interval; CV – Cardiovascular; HR – Hazard ratio; ITT – Intent-to-treat; MI – Myocardial infarction.

A reduction in the rate of CV mortality was observed, with a 4.3% event rate in the icosapent ethyl group versus 5.2% in the placebo group (HR 0.80; 95% CI, 0.65 to 0.98; p=0.0315).

The REDUCE-IT study showed that using icosapent ethyl results in a reduction in nonfatal MI, with an event rate of 5.8% in the icosapent ethyl group versus 8.1% in the placebo group (HR 0.69; 95% CI, 0.59 to 0.83; p<0.001). Also based on this study,

icosapent ethyl reduces the rate of nonfatal strokes (2.1% events in the icosapent ethyl group versus 2.9% in the placebo group; HR 0.70; 95% CI, 0.53 to 0.93; p=0.0149).

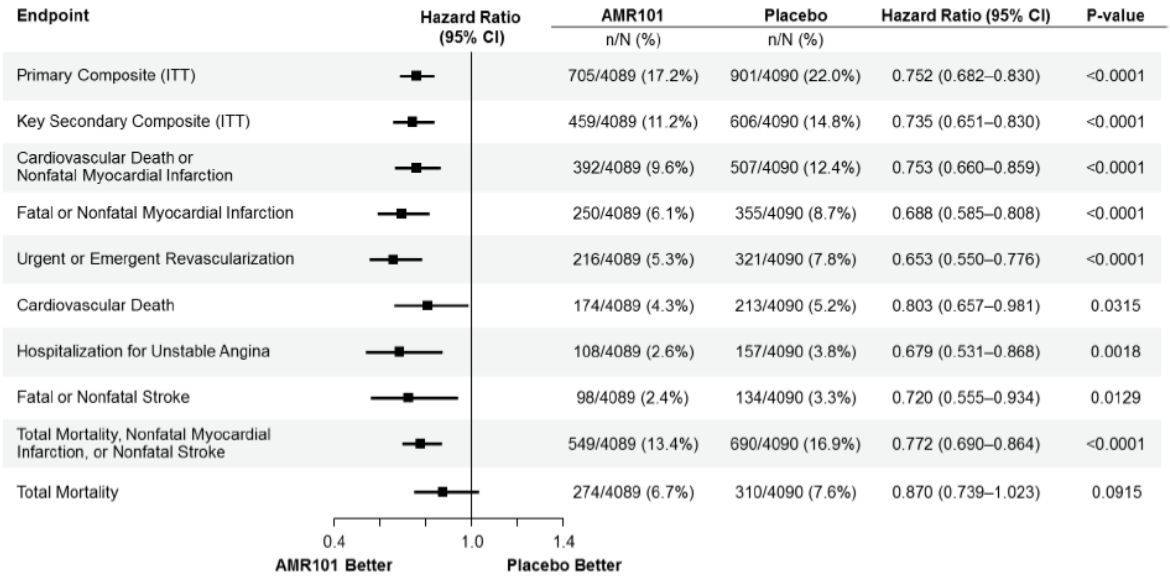
Total coronary revascularizations were reduced with the use of icosapent ethyl (event rate of 9.2%) versus placebo (13.3%) (HR 0.66; 95% CI, 0.58 to 0.75; p<0.001).

Icosapent ethyl was found to reduce the occurrence of hospitalisations due to unstable angina (2.6% versus 3.8% event rate in the icosapent ethyl versus placebo groups, respectively; HR 0.67; 95% CI, 0.53 to 0.86; p=0.0018).

Based on the REDUCE-IT[60] study, icosapent ethyl did not statistically significantly (p=0.0915) reduce overall mortality. The event rates were 6.7% in the icosapent ethyl group versus 7.6% in the placebo group (HR 0.87; 95% CI, 0.74 to 1.02).

Hazard ratios, p-values and the number of patients associated with the relevant secondary outcomes are presented in Table 9 and summarised in Figure 9.

Figure 9: Forest plot of analyses of other secondary endpoint events (ITT population)[1]



B.2.6.1.4 Tertiary efficacy endpoint: Time from randomisation to the first occurrence and all subsequent major CV events in the primary and key secondary composite endpoints[60,64]

The REDUCE-IT study investigated the recurrence of major CV events, which was performed by considering both the first occurrence and all subsequent CV events as defined in the primary and key secondary endpoints.

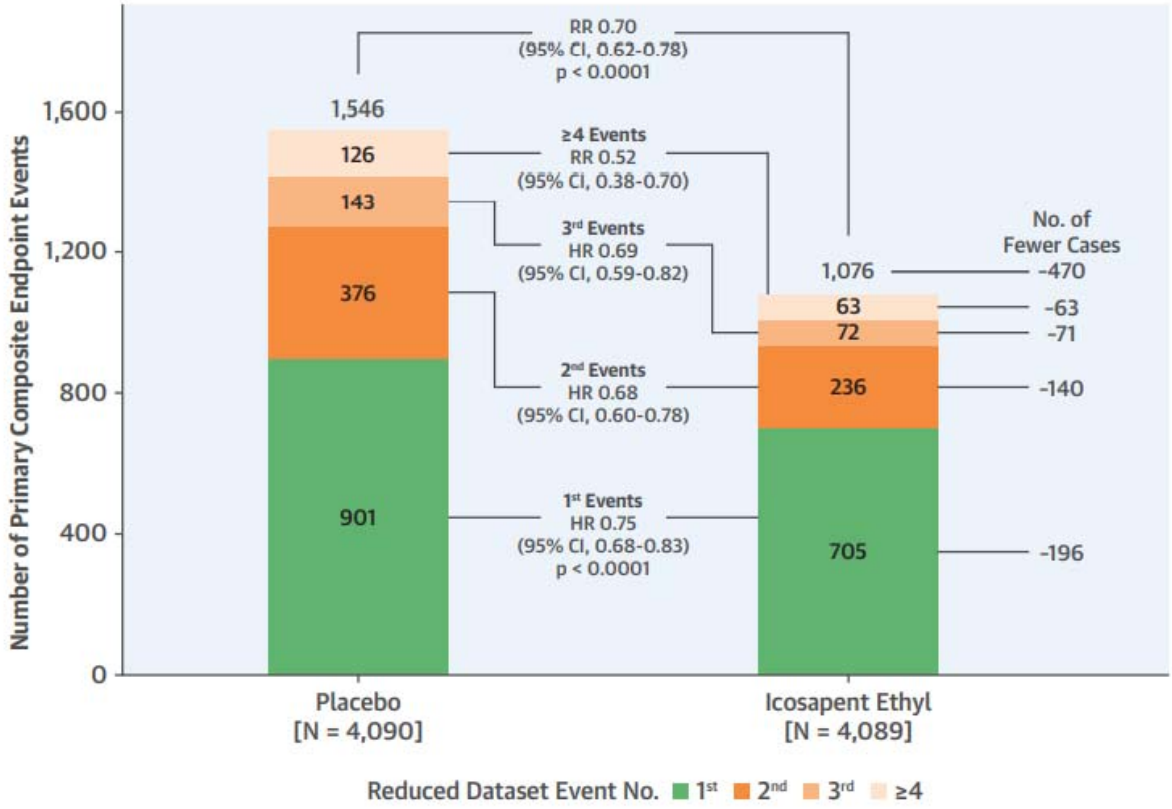
The reduction in the total number of CV events (as per the primary endpoint), was significant in the icosapent ethyl group compared to the placebo group (HR: 0.69; 95% CI 0.61-0.77). The reduction in the first, second, third and fourth occurrence of a primary endpoint event was also statistically significant (Table 10 and Figure 10). A breakdown of the total number of CV events for the secondary and primary prevention subgroups is provided in Table 11 / Figure 11 and Table 12 / Figure 12, respectively, with a larger number of CV events recorded in the placebo group.

Table 10: Total events in the primary endpoint including subsequent events on the same day - ITT population[60]

Event	Icosapent ethyl (N=4,089)	Placebo (N=4,090)	Total (N=8,179)
Primary endpoint events			
n (%)	1,185 (40.7)	1,724 (59.3)	2,909
HR (95% CI)	0.69 (0.61 to 0.77)		
P-value	<0.0001		
≥1 event			
n (%)	705 (43.9)	901 (56.1)	1,606
HR (95% CI)	0.75 (0.68 to 0.83)		
P-value	<0.0001		
≥2 events			
n (%)	299 (39.2)	463 (60.8)	762
HR (95% CI)	0.68 (0.60 to 0.77)		
≥3 events			
n (%)	96 (35.3)	176 (64.7)	272
HR (95% CI)	0.70 (0.59 to 0.83)		
≥4 events			
n (%)	36 (27.9)	93 (72.1)	129
HR (95% CI)	0.49 (0.36 to 0.60)		
Other			
n (%)	49 (35.0)	91 (65.0)	140

Abbreviations: CI – Confidence interval; CV – Cardiovascular; HR – Hazard ratio; ITT – Intent-to-treat.

Figure 10: Graphical representation of the total events in the primary endpoint excluding subsequent events on the same day* - ITT population



* This analysis was undertaken on the reduced dataset where events occurring on the same day were counted as a single event

Table 11: Total events in the primary endpoint including subsequent events on the same day – secondary prevention population[60]

Event, n (%)	Icosapent ethyl (N=2,892)	Placebo (N=2,893)	Total (N=5,785)
Primary endpoint events	[redacted]	[redacted]	[redacted]
1 event	[redacted]	[redacted]	[redacted]
2 events	[redacted]	[redacted]	[redacted]
3 events	[redacted]	[redacted]	[redacted]
≥4 events	[redacted]	[redacted]	[redacted]

Figure 11: Graphical representation of the total events in the primary endpoint including subsequent events on the same day – secondary prevention population[1]

Table 12: Total events in the primary endpoint including subsequent events on the same day – primary prevention population[60]

Event, n (%)	Icosapent ethyl (N=1,197)	Placebo (N=1,197)	Total (N=2,394)
Primary endpoint events			
1 event			
2 events			
3 events			
≥4 events			

Figure 12: Graphical representation of the total events in the primary endpoint including subsequent events on the same day – primary prevention population[60]

The reduction of total key secondary endpoint events was also demonstrated in those who received icosapent ethyl compared to placebo, with a larger number of CV events recorded in the placebo group (Table 13).

Table 13: Total events in the key secondary endpoint including subsequent events on the same day - ITT population[60]

Event, n (%)	Icosapent ethyl (N=4,089)	Placebo (N=4,090)	Total (N=8,179)
Key secondary endpoint events	590 (42.0)	816 (58.0)	1,406
≥1 event	459 (43.1)	606 (56.9)	1,065
≥2 events	96 (37.9)	157 (62.1)	253
≥3 events	20 (35.1)	37 (64.9)	57
≥4 events	6 (42.9)	8 (57.1)	14
Other	9 (52.9)	8 (47.1)	17

Abbreviations: ITT – Intent-to-treat.

B.2.6.1.5 Health-related quality of life

The REDUCE-IT trial did not evaluate the effects of icosapent ethyl on the health-related quality of life of patients.

B.2.7 Subgroup analysis

In the REDUCE-IT[60] trial, data were analysed according to the following pre-specified subgroups for the primary outcome:

- CV risk stratum (secondary-prevention/ primary-prevention). Key results were presented in section B.2.6.
- Baseline characteristics including region, sex and age (<65 years/ ≥65 years)
- Diabetes at baseline (yes/ no)
- Baseline statin intensity (high/ moderate/ low)
- Baseline ezetimibe use
- Baseline triglycerides, estimated GFR and LDL cholesterol
- Baseline triglycerides ≥200 mg/dL and HDL cholesterol ≥35 mg/dL

It is important to note that the outcomes observed in REDUCE-IT are independent of baseline TG and LDL-C levels (i.e., TGs and LDL-C do not act as surrogate markers of efficacy, but as qualitative risk markers of CV risk at baseline). Figure 13 shows the median TG levels over time at each visit in REDUCE-IT and Figure 14 shows the median LDL-C levels over time. These plots demonstrate that TG and LDL-C levels remain approximately constant throughout the study, further supporting the fact that TG and LDL-C levels do not act as surrogate markers of efficacy.

Figure 13: Median triglyceride levels over time (ITT population)

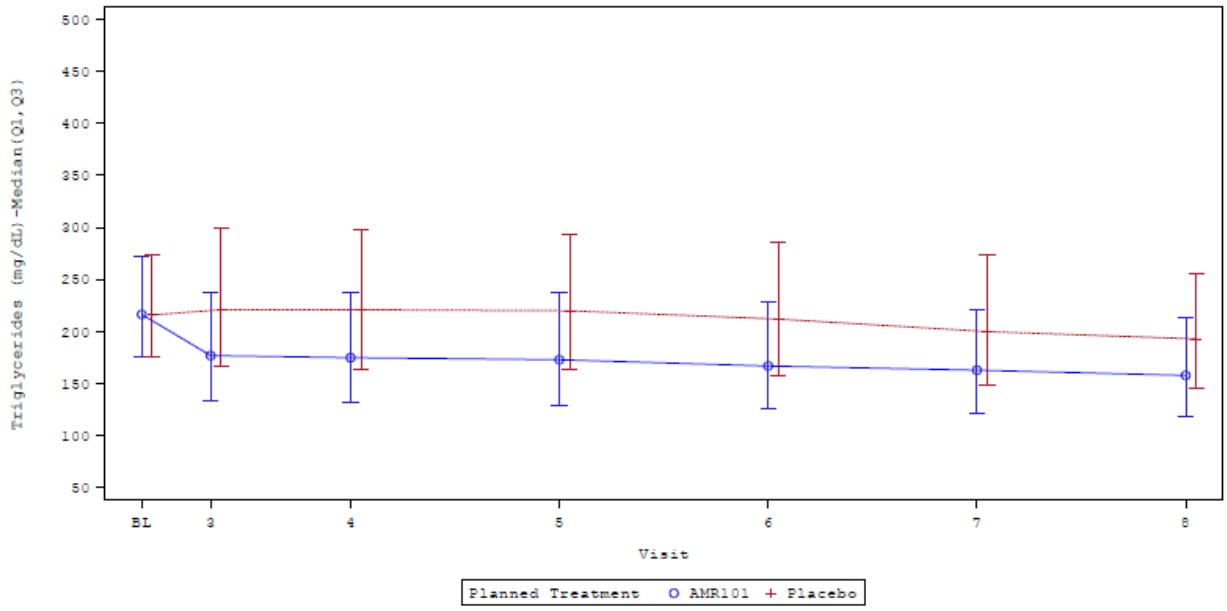
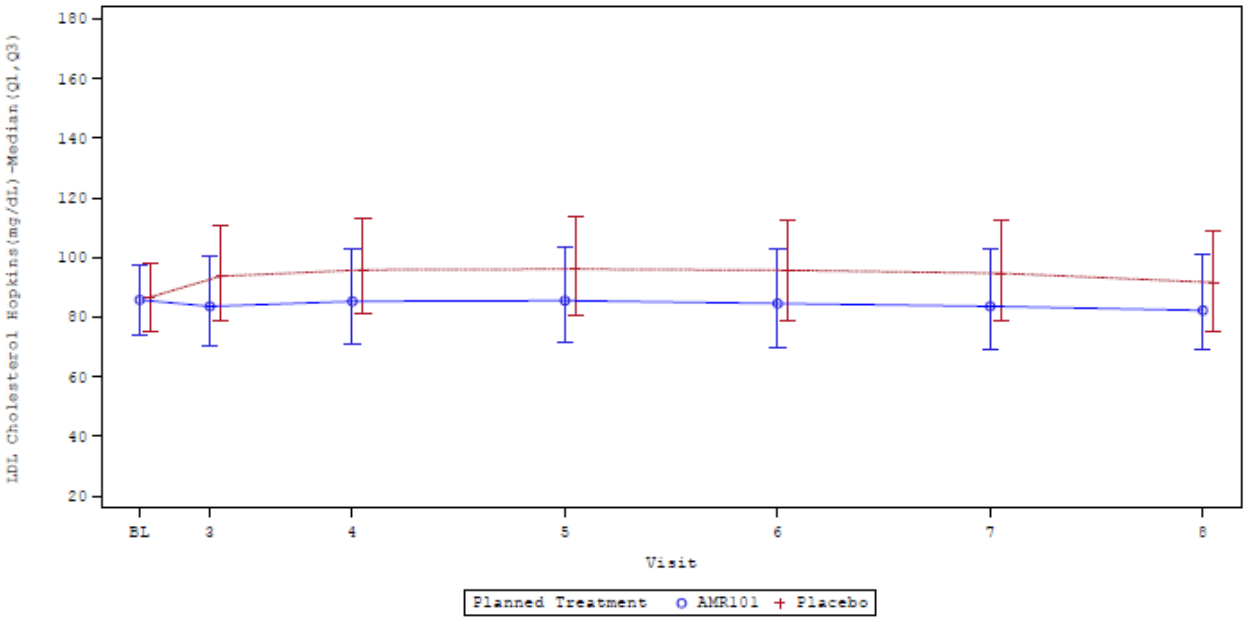


Figure 14: Median LDL-C levels over time (ITT population)



The results of the pre-specified subgroup analyses of the primary efficacy endpoint (a composite endpoint defined as time from randomisation to the first occurrence of CV death, nonfatal MI [including silent MI], nonfatal stroke, coronary revascularization, or unstable angina) in REDUCE-IT were similar to those for the full population: icosapent ethyl reduced the risk of the composite outcome relative to placebo.

Full results of the analysis can be found in Appendix E.

B.2.8 Meta-analysis

A meta-analysis was not conducted, as the only relevant clinical trial identified was REDUCE-IT.

B.2.9 Indirect and mixed treatment comparisons

Given that the phase III trial REDUCE-IT is a randomised clinical trial comparing icosapent ethyl to placebo, (considered as relevant established usual care) and no other relevant randomised clinical trials were identified in the SLR, no indirect or mixed treatment comparison was undertaken.

B.2.10 Adverse reactions in the REDUCE-IT trial

In the REDUCE-IT trial, icosapent ethyl at a dose of 4g/day was safe and well-tolerated in patients at risk of CV events.

Treatment-emergent adverse events (TEAEs) were reported by a similar number of patients in the icosapent ethyl (81.8%) and placebo (81.3%) groups. Serious TEAEs occurred in 1,252 (30.6%) and 1,254 (30.7%) patients in the icosapent ethyl and placebo groups, respectively.

Withdrawal from the study due to TEAEs occurred in 321 patients (7.9%) in the icosapent ethyl group and 335 patients in the placebo group (8.2%). Withdrawals due to serious TEAEs were equal in both treatment arms with 2.2% of patients discontinuing for this reason.

Deaths due to serious TEAEs reported were similar in both treatment groups, with 94 (2.3%) and 102 (2.5%) deaths occurring in the icosapent ethyl and placebo groups, respectively.

When considering individual TEAEs, the most frequently occurring events at an incidence of ≥5% in either treatment group and considered statistically significant between the icosapent ethyl and placebo groups were: diarrhoea (9.0% versus 11.1%, respectively), peripheral edema (6.5% versus 5.0%, respectively), constipation (5.4%

versus 3.6%, respectively), atrial fibrillation (5.3% versus 3.9%, respectively) and anaemia (4.7% versus 5.8%, respectively).

Additionally, a statistically significantly higher incidence of TEAEs associated with bleeding occurred in the icosapent ethyl group than in the placebo group (11.8% versus 9.9%, respectively; p=0.0055).

Table 14: Adverse events – Safety population[60]

	Icosapent ethyl (N = 4,089)	**Placebo (N = 4,090)**
Patients with at least one TEAE, n (%)	3,343 (81.8)	3,326 (81.3)
Serious TEAE	1,252 (30.6)	1,254 (30.7)
TEAE leading to withdrawal of study drug	321 (7.9)	335 (8.2)
Serious TEAE leading to withdrawal of study drug	88 (2.2)	88 (2.2)
Serious TEAE leading to death	94 (2.3)	102 (2.5)
Most frequent TEAE (≥5%)		
Diarrhoea	367 (9.0)	453 (11.1)
Back pain	335 (8.2)	309 (7.6)
Hypertension	320 (7.8)	344 (8.4)
Nasopharyngitis	314 (7.7)	300 (7.3)
Arthralgia	313 (7.7)	310 (7.6)
Upper respiratory tract infection	312 (7.6)	320 (7.8)
Bronchitis	306 (7.5)	300 (7.3)
Chest pain	273 (6.7)	290 (7.1)
Peripheral edema	267 (6.5)	203 (5.0)
Pneumonia	263 (6.4)	277 (6.8)
Influenza	263 (6.4)	271 (6.6)
Dyspnoea	254 (6.2)	240 (5.9)
Urinary tract infection	253 (6.2)	261 (6.4)
Cough	241 (5.9)	241 (5.9)
Osteoarthritis	241 (5.9)	218 (5.3)
Dizziness	235 (5.7)	246 (6.0)
Pain in extremity	235 (5.7)	241 (5.9)
Cataract	235 (5.7)	208 (5.1)
Fatigue	228 (5.6)	196 (4.8)
Constipation	221 (5.4)	149 (3.6)
Atrial fibrillation	215 (5.3)	159 (3.9)

	Icosapent ethyl (N = 4,089)	Placebo (N = 4,090)
Angina pectoris	200 (4.9)	205 (5.0)
Anaemia	191 (4.7)	236 (5.8)

Abbreviations: TEAE – Treatment-emergent adverse events.

Extent of exposure [60,63]

In the REDUCE-IT study, drug exposure was calculated as the number of doses assumed to be taken relative to the documented dosing period from randomisation to the patient's final date in the study.

Overall, 91.9% of patients in the icosapent ethyl group and 91.2% in the placebo group were at least 80% compliant with study drug (i.e., took at least 80% of their prescribed study drug capsules during the study).

Table 15 shows the treatment exposure for the REDUCE-IT study. Approximately 3% of patients in both treatment groups were not adherent with study statin use (i.e., took less than 80% of their prescribed statin during the study), and approximately 0.1% of patients in both groups were not on a stable statin regimen during the study. Less than 4% of patients in each treatment group used fibrates, niacin, bile acid sequestrants, PCSK9 inhibitors, or omega-3 fatty acid compounds after randomisation during the study.

Table 15: Treatment exposure – ITT population[60]

	Icosapent ethyl (N = 4,089)	Placebo (N = 4,090)	Overall (N = 8,179)
Number of capsules per day			
N	3,976	3,980	7,956
Mean (SD)	3.9 (1.12)	4.0 (1.62)	3.9 (1.39)
Overall compliance			
N	3,976	3,980	7,956
Mean % (SD)	98.3 (28.12)	99.2 (40.43)	98.7 (34.83)
Grouped compliance			
< 80%, n (%)	322 (8.1)	350 (8.8)	672 (8.4)
≥ 80%, n (%)	3,654 (91.9)	3,630 (91.2)	7,284 (91.6)

Abbreviations: ITT – Intent-to-treat; SD – Standard deviation.

B.2.11 Ongoing studies

There are no ongoing studies that will provide additional evidence in the next 12 months for the indication being appraised.

B.2.12 Innovation

Icosapent ethyl is a new active substance as per CHMP designation, composed of highly purified ethyl ester of the eicosapentaenoic acid (EPA ≥ 96%) which has been designated a new chemical entity by the Food and Drug Administration (FDA). It will provide an innovative treatment option to reduce the risk of cardiovascular events in adult statin-treated patients with elevated triglycerides, the population assessed in the REDUCE-IT trial. Icosapent ethyl is a new treatment substance in this patient population, as current treatment options for patients with elevated TGs despite statin therapy do not effectively reduce the risk of patients experiencing cardiovascular events.[65] The primary goal for treatment in this specific group of patients is the achievement of a reduced residual risk in CV events, including: CV death, MI, stroke, unstable angina requiring hospitalisation, and the need for urgent revascularization. The REDUCE-IT trial has demonstrated that treatment with icosapent ethyl can result in a reduction in the risk of cardiovascular events, thereby providing a clinical benefit that addresses an area of urgent and high unmet need.

Amarin has reached out to UK clinical experts who confirmed the lack of effective therapies in the population of interest. Therefore, patients in this population currently have no treatments widely available and there is a great unmet need for the introduction of a drug such as icosapent ethyl, which is the only therapy in the European Society of Cardiology (ESC) guidelines for the treatment of patients with hypertriglyceridemia.

B.2.13 Interpretation of clinical effectiveness and safety evidence

The REDUCE-IT[60] study was a large, randomised, double-blind placebo-controlled study in patients at high risk of CV events with hypertriglyceridemia and on stable statin therapy (with the statin intensity aligned with that used in UK clinical practice,

see section B.1.3.4).[54] The baseline median LDL-C levels demonstrate that the statin doses used were optimised to meet controlled LDL-C targets (see Table 5).

The primary and secondary objectives in the REDUCE-IT study are relevant to the decision problem defined in the scope. The trial met its primary objective and demonstrated that icosapent ethyl resulted in a reduction in the composite outcome of CV death, nonfatal MI, nonfatal stroke, coronary revascularization, and hospitalisation for unstable angina versus placebo.

Icosapent ethyl showed consistent and statistically significant treatment effect compared to placebo in the primary and key secondary endpoints. Results were robust with statistical significance demonstrated across several sensitivity and subgroup analyses for these endpoints.

The CV risk profile of the population is high, with 22% of patients in the placebo group and 17.2% of those taking icosapent ethyl (absolute difference of 4.8%) experiencing at least one component of the primary endpoint, which was associated with a 24.8% relative risk reduction ($p<0.001$). Results for the individual components of the composite primary outcome suggested that no one component dominated in driving the treatment effect of icosapent ethyl.

The occurrence of key secondary endpoint events (composite of CV death, nonfatal MI [including silent MI], and nonfatal stroke) was significantly reduced in the icosapent ethyl group, with 11.2% of patients experience at least one component of the key secondary endpoint, compared with 14.8% in the placebo group ($p<0.001$).

Additionally, when considering individual CV events, a statistically significant reduction was demonstrated in the number of CV mortality events ($p<0.05$), nonfatal MI ($p<0.001$), nonfatal stroke ($p<0.05$) and coronary revascularization ($p<0.05$) in participants who received icosapent ethyl when compared to those who received placebo, during the REDUCE-IT follow up period.

The study demonstrated a statistically significant reduction in CV death. A reduction in all-cause mortality was also observed although it was not statically significant. This

is likely attributable to the sample size and the duration of REDUCE-IT, both of which were likely insufficient to evaluate this outcome.

Furthermore, REDUCE-IT investigated the effect of icosapent ethyl on the time from randomisation to the occurrence of any subsequent event included in the primary endpoint (CV death, nonfatal MI, nonfatal stroke, coronary revascularization, and hospitalisation for unstable angina). A significant reduction in the occurrence of a secondary event (patients experiencing multiple or any of the events included in the primary endpoint more than once) was observed in patients who received icosapent ethyl when compared to placebo (HR: 0.68; $p<0.001$) and this reduction was also observed in the third and the fourth occurrence of any event included in the primary endpoint.

Subgroup analyses in REDUCE-IT suggested a potential difference in risk reduction for the composite primary outcome with icosapent ethyl in patients with established CVD or secondary prevention (HR versus placebo 0.726; 95% CI, 0.650 to 0.810) and those at high risk for CVD or primary prevention (HR versus placebo 0.876; 95% CI, 0.700 to 1.095). The results for patients with established CVD were significant ($p=0.1388$), however, the results for patients at high risk for CVD were not. This is due to the fact that the high-risk primary prevention patients contributed fewer first events to each endpoint compared to secondary prevention patients. This is reflective of the study design requiring enrollment of fewer high-risk primary prevention patients (30% of targeted enrollment) than secondary prevention patients, and is consistent with the overall lower event rate in the primary versus secondary prevention subgroup. For example, the primary prevention placebo patients contributed 163 first primary endpoint events, while the secondary prevention placebo patients contributed 738 first primary endpoint events. Despite contributing 22% of all first events, the primary prevention cohort hazard ratios and interaction p-values (primary versus secondary prevention) are consistent with the overall demonstration of benefit in REDUCE-IT. For example, the primary prevention hazard ratios are all below unity for the primary and key secondary endpoints, as well as for each individual component, except hospitalisation for unstable angina, where events were particularly low in the primary prevention cohort.

Within the REDUCE-IT trial, number of TEAEs, serious TEAEs, and withdrawals due to TEAEs were similar between the icosapent ethyl and placebo groups, suggesting that icosapent ethyl is safe and well tolerated.

It is important to highlight that the REDUCE-IT study was not designed to assess the relative contribution of changes in biomarkers (such as TG, LDL-C, non-HDL-C, apo B and hsCRP) on CV outcomes.[60] In other words, these biomarkers do not act as surrogate markers of efficacy.

The REDUCE-IT trial demonstrated that icosapent ethyl (four capsules taken as two 1g capsules twice daily) significantly reduces CV events in high-risk adult statin-treated patients with elevated TGs. Benefits were consistently observed across individual and composite endpoints with icosapent ethyl coming across as safe and well tolerated by the study participants. Within this population, icosapent ethyl presents an important treatment option to further reduce the total burden of CV events, in a high-risk population identified by elevated triglycerides despite treatment with statins, providing a clinical benefit that addresses an area of urgent and high unmet need.

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

An economic systematic literature review (SLR) was conducted on the 8th January 2021 to identify published economic evidence in the management of patients at risk of CV events due to elevated TG.

This SLR sought to identify and summarise the published cost-effectiveness-analyses, healthcare costs and resource use requirements. as well as health-related quality of life (HRQoL) studies. In line with guidance from the Centre for Reviews and Dissemination (CRD),[66] the population, interventions, comparators, outcomes and study type principle were used to define the following review questions:

- Question 1: What cost-effectiveness studies have been conducted in patients at risk of cardiovascular events due to elevated triglycerides?
- Question 2: What are the costs and resource use associated with the management of patients at risk of cardiovascular events due to elevated triglycerides?
- Question 3: What utilities and disutility are associated with patients at risk of cardiovascular events due to elevated triglycerides?

For this economic SLR, a single search strategy, which follow the PICOS (population, interventions, comparators, outcomes and study type), was used to identify cost effectiveness (section B.3.1 Published cost-effectiveness studies), HRQoL (section B.3.4 Measurement and valuation of health effects), and cost and resource use studies (section B.3.5 Cost and healthcare resource use identification, measurement and valuation). Please see Appendix G: Published cost-effectiveness studies for the methods used to identify all relevant studies, and a description and quality assessment of the cost-effectiveness studies identified.

The NICE STA user guide[67] recommends that an overview of each cost-effectiveness study is required only if it is relevant to decision-making in England. Therefore, extraction was only performed for cost-effectiveness studies from a UK perspective (n=2) and a detailed summary is provided in Table 16.

Table 16. Summary list of published cost-effectiveness studies

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
NICE TA393	2016	• Base-case cost-effectiveness analyses for alirocumab, either as an adjunct to statin with ezetimibe or with ezetimibe alone from the perspective of national health service (NHS) and personal social services (PSS) • Markov model that consisted of 12 mutually exclusive health states was used: • 3 initial health states: stable, 0–1 year following an acute coronary syndrome event, 1–2 years following an acute coronary syndrome event • 3 types of events: nonfatal acute coronary syndrome including myocardial infarction and unstable angina requiring hospitalisation, non-fatal ischaemic stroke, and elective revascularisation • 7 post-event health states: post non-fatal acute coronary syndrome (0–1 year, 1–2	• Primary prevention (heterozygous-familial) population (50) • Secondary prevention (heterozygous-familial) population (60) • High risk CVD population (65) • Recurrent events/polyvascular disease population (65)	**Incremental QALYs:** **Primary prevention (heterozygous-familial) population:** • Alirocumab + a statin + ezetimibe vs. a statin + ezetimibe: 1.42 • Alirocumab + a statin vs. ezetimibe + a statin: 0.95 **Secondary prevention (heterozygous-familial) population:** • Alirocumab + a statin + ezetimibe vs. a statin + ezetimibe: 2.33 • Alirocumab + a statin vs. ezetimibe + a statin: 1.70 **High-risk CVD (non-familial) population:** • Alirocumab + a statin vs. a statin: 1.76	**Costs for each health state:** • nonfatal myocardial infarction: £3,337 • unstable angina: £3,313 • acute coronary syndrome: £3,329 • revascularisation: £3,802 • ischaemic stroke: £4,092 • cardiovascular death: £1,174 • non-cardiovascular death: £0 Alirocumab (75 mg or 150 mg single-use prefilled pen; excluding VAT): £168 Alirocumab annual cost of treatment per patient (for 75 mg or 150 mg every 2 weeks): £4,383	**Primary prevention (heterozygous-familial) population:** • Alirocumab + a statin + ezetimibe vs. a statin + ezetimibe: £36,793 • Alirocumab + a statin vs. ezetimibe + a statin: £48,193 **Secondary prevention (heterozygous-familial) population:** • Alirocumab + a statin + ezetimibe vs. a statin + ezetimibe: £16,896 • Alirocumab + a statin vs. ezetimibe + a statin: £20,352 **High-risk CVD (non-familial) population:** • Alirocumab + a statin vs. a statin: £19,751

		years and stable coronary heart disease; that is, more than 2 years after an acute coronary syndrome event), post non-fatal ischaemic stroke (0–1 year, 1–2 years and stable ischaemic stroke; that is, more than 2 years following ischaemic stroke) and stable elective revascularisation • Health states for CV death and non-CV death The cycle length was 1 year and a half cycle correction was applied. An annual discount rate of 3.5% was applied to costs and health effects. The model had a lifetime time horizon.		• Alirocumab + a statin vs. ezetimibe + a statin: 1.29 **High risk CVD (non-familial) people who cannot tolerate statins:** • Alirocumab + ezetimibe vs. ezetimibe: 2.04 • Alirocumab vs. ezetimibe: 1.78 **Recurrent events/polyvascular disease (non-familial) population:** • Alirocumab + a statin vs. a statin: 1.64 • Alirocumab + a statin vs. ezetimibe + a statin: 1.25 **Recurrent events/polyvascular disease (non-familial) population people who cannot tolerate statins:** • Alirocumab + ezetimibe vs. ezetimibe: 2.40 Alirocumab vs. ezetimibe: 2.14		• Alirocumab + a statin vs. ezetimibe + a statin: £24,175 **High risk CVD (non-familial) people who cannot tolerate statins:** • Alirocumab + ezetimibe vs. ezetimibe: £17,256 • Alirocumab vs. ezetimibe: £17,295 **Recurrent events/polyvascular disease (non-familial) population:** • Alirocumab + a statin vs. a statin: £19,447 • Alirocumab + a statin vs. ezetimibe + a statin: £23,078 **Recurrent events/polyvascular disease (non-familial) population people who cannot tolerate statins:** • Alirocumab + ezetimibe vs. ezetimibe: £13,669 Alirocumab vs. ezetimibe: £13,469

NICE TA394	2016	• Cost-effectiveness analysis of evolocumab in reducing CVD for primary hypercholesterolaemia (heterozygous-familial and non-familial) or mixed dyslipidaemia from the perspective of NHS and personal social services • Markov economic model consisting of 24 mutually exclusive states: • 3 acute states (in which the patient could stay for a maximum of 1 year unless the same event occurred in the next cycle): acute coronary syndrome (including myocardial infarction and unstable angina); ischaemic stroke; heart failure • 5 chronic states: no CVD; established CVD (including patients who had a history of stable angina, transient ischaemic attack, carotid stenosis, revascularisation without a history of myocardial infarction, abdominal aortic aneurism, or peripheral vascular disease); 3 post-event states (post-acute coronary	• non-familial hypercholesterolaemia without CVD • non-familial hypercholesterolaemia with CVD • heterozygous-familial hypercholesterolaemia (with or without CVD).		• Patients who started treatment with evolocumab had 1-hour training by a nurse to self-administer the treatment at a cost of £84.00 • Evolocumab costs (140-mg prefilled pen or syringe; excluding VAT; MIMS, March–May 2016): £170.10 Evolocumab annual cost of treatment per patient: 140 mg every 2 weeks: £4,422.60; 420 mg monthly: £6,123.60	**Evolocumab plus statin:** • Non - familial hypercholesterolaemia without CVD: £69,249 • Non-familial hypercholesterolaemia with CVD: £45,439 • Heterozygous-familial hypercholesterolaemia without CVD: £23,536 • Heterozygous-familial hypercholesterolaemia with CVD: £29,910 **Evolocumab:** • Non-familial hypercholesterolaemia without CVD: £38,458 • Non-familial hypercholesterolaemia with CVD: £30,985 • Heterozygous-familial hypercholesterolae

		syndrome, post-ischaemic stroke, post-heart failure) • 13 composite CVD states: (formed of a combination of 2 or 3 acute and post-event states; these were used to remember the history of CV events and model the corresponding outcomes of recurring CV events) • 3 death states: death from coronary heart disease, death from stroke and death from other causes The cycle length in the model was 1 year. Costs and health effects were modelled over a lifetime time horizon and discounted at an annual rate of 3.5%.				mia without CVD: £21,921 • Heterozygous-familial hypercholesterolaemia with CVD: £25,293 **Evolocumab plus ezetimibe:** • Non-familial hypercholesterolaemia without CVD: £41,911 • Non-familial hypercholesterolaemia with CVD: £33,814 • Heterozygous-familial hypercholesterolaemia without CVD: £23,602 • Heterozygous-familial hypercholesterolaemia with CVD: £27,390 **Evolocumab plus ezetimibe plus statin:** • Non-familial hypercholesterolaemia without CVD: £78,459

						• Non-familial hypercholesterolaemia with CVD: £50,257 • Heterozygous-familial hypercholesterolaemia without CVD: £25,583 • Heterozygous-familial hypercholesterolaemia with CVD: £32,698
CV – Cardiovascular; CVD – Cardiovascular disease; GBP – British pound sterling; ICER – Incremental cost-effectiveness ratio; MI – Myocardial infarction; MIMS – Monthly index of medical specialities; NHS – National Health Service; NICE – National Institute for Health and Care Excellence; PSS - Personal social service; QALY – Quality-adjusted life-year; UK – United Kingdom; US – United States; VAT – Value added tax; vs. – versus						

B.3.2 Economic analysis

The economic SLR identified two UK cost-effectiveness studies relevant to decision-making in England to inform the economic analysis of Icosapent ethyl.[57,58] In addition, two non-UK cost-effectiveness models were also identified and deemed relevant to inform the development of the de-novo economic model.[68,69] The perspective of the two non-UK studies includes the Australian healthcare system and US payer perspective and are briefly described in Appendix G.

These four cost-effectiveness studies identified used a Markov model structure with annual cycles to model CV related events. Health states captured patients experiencing no CV events, CV events, post-CV events, CV-related death and all-cause death. Transition probabilities were derived and extrapolated over a lifetime horizon from time-to-event data. NICE TA393 and TA394 are based on the modelling approaches developed for the NICE guidelines on lipid modification and familial hypercholesterolaemia (CG181), and technology appraisals for lipid lowering treatments. In addition, the de-novo model developed for NICE CG181 also used a Markov model structure to assess the cost-effectiveness of statins in the primary and secondary prevention cohorts.[21,57,58] Patients transitioned through the model in annual cycles. The models relied on the standard assumptions of Markov models: that only one event can occur in any cycle (one year), and that there is no memory of which events have happened previously.

To appropriately capture the natural history and risk of CV events in this patient population, a Markov model with daily cycles was used. This allowed for a more accurate representation of the time spent in a post-event state and captured patients experiencing multiple CV events in a short space of time (as some patients in the REDUCE-IT trial experienced a CV event on consecutive days), thus adequately addressing the decision problem. Since the aim of this cost-effectiveness analysis is to model the reduction in risk of CV events, the model methodology used in lipid lowering therapies was deemed generalisable to this decision problem. Although the treatments assessed in previous appraisals target LDL-C instead of TGs, the methods

in which the impact of CV events is modelled is applicable to the target population for Icosapent ethyl.

A *de-novo* model was therefore developed, capturing elements from previous studies however, using post-first event, post-second event and post-third event health states to account for the occurrence of multiple CV events in statin-treated patients with elevated TGs captured in the REDUCE-IT trial.

Patient population

The population considered in the model aligns directly with the ITT cohort from REDUCE-IT, which consists of males and females ≥45 years of age with established CVD (secondary prevention subgroup) or ≥50 years of age with diabetes in combination with one or more additional risk factor for CVD (primary prevention subgroup), with LDL-C levels >40 mg/dL and ≤100 mg/dL and fasting TG levels ≥135 mg/dL and <500 mg/dL, on stable statin therapy for at least four weeks. This aligns with the licenced indication for Icosapent ethyl (section B.1.2 Description of the technology being appraised).[70]

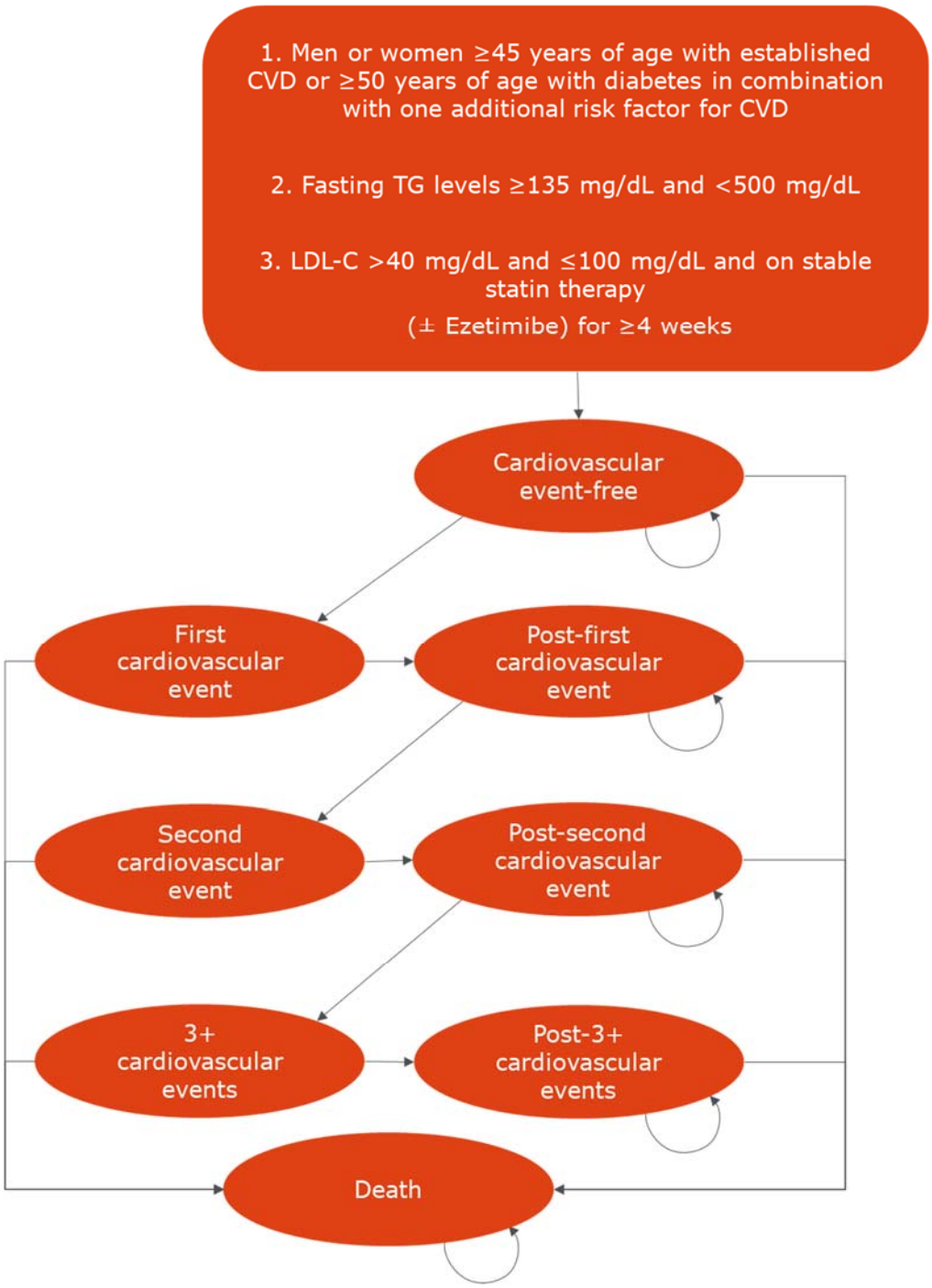
Scenario analyses will be presented for the primary prevention cohort (which constitutes 29% of the modelled population) and the secondary prevention cohort (which constitutes 71% of the modelled population).

Model structure

A *de-novo* probabilistic time-dependent Markov transition model structure with disease-specific health states was deemed most appropriate to capture the long-term risk of major CV events based on methodology presented in previous NICE technology appraisals for lipid lowering therapies and NICE guidelines CG181. The multistate Markov model structure is illustrated in Figure 15 and was used to estimate the cost-effectiveness of Icosapent ethyl in the reduction of CV events in statin-treated patients with elevated TGs who have established CVD, or diabetes, and at least one other CV risk factor compared to placebo. Patients transit through the model through daily cycle lengths in order to appropriately capture the natural history of the patient population and ensure all CV events from the REDUCE-IT trial were captured (section B.3.1

Published cost-effectiveness studies). The CEM was developed in Microsoft® Excel.

Figure 15. Markov model structure



Abbreviations: CVD – cardiovascular disease; LDL-C – Low density lipoprotein cholesterol; mg/dL – milligrams per decilitres; TG – triglycerides.

The Markov state-transition model was used to reflect the natural history of disease and predict the long-term risk of major CV events through eight different health states: cardiovascular event free (CEF), first CV event, post-first CV event, second CV event, post-second CV event, third or more CV events, post-third or more CV events and death (either from fatal CV events [DCV] or death from other causes [DOC]). Each post-event health state used a weighted average of costs and utilities of each CV event including non-fatal MI, non-fatal stroke, unstable angina, and coronary revascularisation (section B.3.5 Cost and healthcare resource use identification, measurement and valuation).

Data from the treatment arms of REDUCE-IT trial was extrapolated using parametric survival methods as per NICE guidelines,[71] and was used to inform the health state transitions from the event free state, to the first, second and third plus event states.

One cohort receives Icosapent ethyl in addition to established clinical management which includes high, moderate or low-intensity statins, whilst the other receives established clinical management only.

Upon treatment initiation, patients enter the model in the event free state, where they are assumed to be at risk of a nonfatal CV event and death, including both CV and non-CV related death. Patients with a nonfatal CV event transit to the post-first CV event health state where they are assumed to be at risk of a subsequent nonfatal CV event and death. After experiencing a second nonfatal event, patients transit to the post-second CV event health state where they are assumed to be at risk of a third or more nonfatal CV event and death. After experiencing the third or more nonfatal event, patients transit to the post-third or more CV events health state where they remain until death. While in the post-third or more CV events health state, patients in the Icosapent ethyl and placebo arm experienced an average of 1.875 and 1.881 CV events, respectively, to reflect what was observed in the REDUCE-IT trial. In all 'alive' health states, patients had a baseline risk of non-CV related death, based on age-specific UK general population mortality rates from the UK Office for National Statistics (ONS), applied to hazard ratios associated with their history of CV events and their

diabetic status. Both death health states are absorbing health states in the model in which patients remain until the time horizon lapses.

A half-cycle correction was applied to reflect the continuous nature of the state transition more accurately. This is based on the assumption that on average, transitions occur half-way through each cycle instead of at the beginning of the cycle, as per the NICE reference case.[72]

The NICE reference case states that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any difference in costs or outcomes between the medicines being compared.[72] As such, a lifetime horizon was adopted. Since patients in the ITT population in the REDUCE-IT trial are aged 64 years old on average, a 36-year time horizon was used to align with the expectation that no patient can live beyond 100 years. The impact of alternative time horizons is explored in scenario analyses.

For each cycle, total costs and QALYs are calculated based on the distribution of patients across the modelled health states and death. These are accumulated over the model time horizon to calculate total costs and QALYs for the two cohorts from which incremental results and the cost per QALY are determined. Costs and outcomes are discounted at 3.5% per annum in line with the NICE reference case.[72] An alternative discount rate of 1.5% is explored in scenario analyses.

The model adopts a UK NHS and PSS perspective on costs, in line with the NICE reference case.[72] The perspective on outcomes considers all direct health effects for patients, in line with the NICE reference case.

Table 17**Error! Reference source not found.** summarises the features of the economic analysis for this appraisal with respect to the NICE reference case.

Table 17. Features of the economic analysis

	Previous appraisals		Current appraisal	
Factor	**TA393**	**TA394**	**Chosen values**	**Justification**
Analytical methods	Markov model cost utility analysis consisting of 12 states	Markov model cost utility analysis consisting of 24 states	Probabilistic time-dependent Markov transition cost-utility analysis consisting of 7 health states and death.	This differs slightly from the approach of other submissions, with this change made to allow for patients to experience multiple events occurring close to each other.
Patient population	Key populations included: • HeFH (both primary and secondary prevention) • Patients at high CV risk due to existing CV disease (secondary prevention –patients with MI, unstable angina, history of revascularisation or other evidence of CHD, ischaemic stroke, peripheral arterial disease (PAD)) • A subgroup of the above patients with existing CV disease at even higher risk, namely patients with	Three subpopulations were modelled including: • non-familial hypercholesterolaemia without CVD • non-familial hypercholesterolaemia with CVD • heterozygous-familial hypercholesterolaemia (with or without CVD).	Adults on a stable dose of statin therapy with elevated TGs who are at high risk of CV events due to: • established CVD, or • diabetes, and at least one other CV risk factor.	This aligns with NICE final scope.

	Previous appraisals		Current appraisal	
	recurrent CV events/ polyvascular disease			
Intervention	Alirocumab in combination with maximal tolerated dose of statins, with or without ezetimibe, or alirocumab on a background of no statins, with or without ezetimibe.	Evolocumab alone or in combination with a statin with or without ezetimibe, or in combination with ezetimibe.	Icosapent ethyl (Vazkepa) in combination with a stable dose of statins with or without ezetimibe	This aligns with NICE final scope.
Comparators	When LDL-C is not adequately controlled with optimised (maximal tolerated dose) statin therapy: • Optimised statin therapy alone (i.e., no additional comparator) • Optimised statin therapy plus ezetimibe When LDL-C is not adequately controlled with optimised statin therapy in combination with ezetimibe: • Optimised statin therapy plus ezetimibe (i.e., no additional comparator)	When optimised statin therapy does not appropriately control LDL-C: • Ezetimibe in combination with a statin When statins are contraindicated or not tolerated: • Ezetimibe	Established clinical management consisting of a stable dose of statins with or without ezetimibe	This aligns with the NICE final scope.

	Previous appraisals		Current appraisal	
	When statins are contraindicated or not tolerated: • No additional therapy (on background of ezetimibe)			
Perspective	UK NHS/PSS	UK NHS/PSS	UK NHS/PSS	This aligns with NICE reference case which considers all direct health effects for patients
Time horizon	Lifetime	Lifetime	Lifetime (36 years)	A lifetime time horizon is appropriate given the chronic nature of CVD and diabetes. Since the mean age of patients in the ITT population of the REDUCE-IT trial is 64 years old, it is assumed that no patient will live beyond 100 years of age. This aligns with the NICE reference case which states that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any difference in costs or outcomes between the medicines being compared.

	Previous appraisals		Current appraisal	
Cycle length	1 year	1 year	1 day	Deemed the most appropriate to capture all CV events experienced in the REDUCE-IT trial.
Half-cycle correction	Yes	Yes	Yes	The model calculated mid-cycle estimates in each health state by taking the average of patients present at the beginning and end of each cycle.
Discounting	Costs and health outcomes at 3.5% per annum	Costs and health outcomes at 3.5% per annum	Costs and health outcomes at 3.5% per annum	This aligns with the NICE reference case. The impact of alternative discount rates has been tested in sensitivity analyses.
Clinical effectiveness	ODYSSEY trial	LAPLACE-2, GAUSS-2 and RUTHERFORD-2 trials	REDUCE-IT	REDUCE-IT is the only relevant trial.
Treatment waning effect	Extrapolation based on pooled hazard ratios from a meta-analysis of PCSK9 inhibitor trials which were then scaled and expressed per 1mmol/L reduction in LDL-C	Extrapolation based on trial data adjusted by published risk equations and then calibrated using CPRD and HES data	Extrapolation of the treatment effect is based on IPD from REDUCE-IT	Data was extrapolated using parametric curves, in line with the NICE reference case.
Safety	Adverse events not included	Adverse events not included	Adverse events from REDUCE-IT. Only the most frequent (≥5%) TEAEs were included.	NICE reference case prefers RCT data.

	Previous appraisals		Current appraisal	
Source of utilities	ODYSSEY and UK Health Survey for England data	NICE CG181	Baseline: Health state utilities: NICE CG181	Health state utilities informed by NICE CG181 guidance in line with NICE reference cases.
Source of costs	NICE CG181	NICE CG181	Sourced from Danese 2016	This source reflects the costs incurred by patients experiencing CV events corresponding directly with the modelled health states. The reported costs were elicited using UK NHS/PSS perspective aligning with the model's perspective.
Outcomes	• Total costs • Incremental costs • Disaggregated costs • Total QALYs • Incremental QALYs • Disaggregated QALYs • Total LYs • Incremental LYs • Disaggregated LYs • ICERs	• Total costs • Incremental costs • Disaggregated costs • Total QALYs • Incremental QALYs • Disaggregated QALYs • Total LYs • Incremental LYs • Disaggregated LYs • ICERs	• Total costs • Incremental costs • Disaggregated costs • Total QALYs • Incremental QALYs • Disaggregated QALYs • Total LYs • Incremental LYs • Disaggregated LYs • ICERs	Consistent with NICE final scope and the NICE reference case.
Uncertainty	• Univariate sensitivity analysis • Scenario analysis	• Univariate sensitivity analysis • Scenario analysis	• Univariate sensitivity analysis • Scenario analysis	Consistent with NICE reference case.

	Previous appraisals		Current appraisal	
	• Probabilistic sensitivity analysis	• Probabilistic sensitivity analysis	• Probabilistic sensitivity analysis	

CG – Clinical guidelines; CPRD – Clinical practice research datalink; CV – Cardiovascular; CHD – Chronic heart disease; CVD – Cardiovascular disease; HeFH – Heterozygous familial hypercholesterolemia; HES – Hospital episode statistics; ICER – Incremental cost-effectiveness ratio; LDL-C – Low density lipoprotein cholesterol; LY – Life year; NHS – National Health Service; NICE – National Institute for Health and Care Excellence; PAD - Peripheral arterial disease; PSS - Personal social service; QALY – quality-adjusted life-year; TA – Technology appraisal; UK – United Kingdom

Intervention technology and comparators

The cost-effectiveness analysis evaluates Icosapent ethyl (four capsules taken as two 998mg capsules twice daily) in combination with a stable dose of statin therapy (± ezetimibe 10mg) against best supportive care. Since there are no pharmacological therapies available and routinely used to reduce the risk of CV events in statin-treated patients with elevated TGs, the placebo arm of the REDUCE-IT trial is used to inform the clinical efficacy of the best supportive care arm in the model. All patients in both the Icosapent ethyl and placebo cohorts are therefore assumed to be on a stable dose of statin therapy, with or without ezetimibe, and incur the cost of these background therapies in the model.

In line with the current treatment pathway (section B.1 Decision problem, description of the technology and clinical care pathway) based on UK clinical practice and the anticipated positioning of Icosapent ethyl, the vast majority of patients in the primary and secondary prevention cohorts are prescribed a moderate to high intensity dose of statin.[54] The statins used in the economic model are in line with those used in the REDUCE-IT trial, are recommended in NICE CG181 and reflect commonly used statins in UK clinical practice (Table 18).

Table 18. Distribution of statins by intensity in the ITT population in the REDUCE-IT trial and applied in the economic model

Statin intensity	**REDUCE-IT trial**		**Economic model**	
	Statin therapy	Statin distribution	Statin therapy	Statin distribution
Low intensity	Rosuvastatin 10mg Pravastatin 10-20mg Lovastatin 20mg Fluvastatin 20-40mg Pitavastatin 1mg	6.4%	Fluvastatin 20-40mg Pravastatin 10-40mg Simvastatin 10mg	6.4%
Moderate intensity	Atorvastatin 10-20mg Simvastatin 20-40mg Rosuvastatin 5-10mg	62.7%	Atorvastatin 10mg	62.7%

Statin intensity	REDUCE-IT trial		Economic model	
	Pravastatin 40-80mg Lovastatin 40mg Fluvastatin 40mg BID Fluvastatin XL 80mg Pitavastatin 2-4mg			
High intensity	Atorvastatin 40-80mg Rosuvastatin 20-40mg	30.9%	Atorvastatin 20-80mg	30.9%

Abbreviations: mg – milligrams

Within the REDUCE-IT trial, statins were classified by intensity using the American College of Cardiology (ACC) and American Heart Association (AHA) guidelines. The 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults[61] provided guidance on the appropriate intensity of pharmacological treatments to reduce CVD, defining the intensity of statin therapy on the basis of the average expected LDL-C response to a specific statin and dose.

Minor differences exist with regards to the classification of statin intensity by drug dosing between the REDUCE-IT trial and NICE CG181. Under the ACC/AHA guidelines, atorvastatin 20mg would instead be classified as moderate intensity. However, the trial population is deemed to be generalisable to the UK since the vast majority of the population are on moderate to high intensity statins as classified by ACC/AHA guidelines and UK clinical practice.

The proportion of patients using ezetimibe 10mg in REDUCE-IT within the ITT group (a stratification factor in REDUCE-IT) was low, at 6.4%. Concomitant use of ezetimibe is also low in UK clinical practice.[54]

B.3.3 Clinical parameters and variables

B.3.3.1. Key clinical studies

From the clinical evidence presented in section B.2.2 List of relevant clinical effectiveness evidence, the primary endpoint of the REDUCE-IT trial was used to

inform the clinical effectiveness of Icosapent ethyl and therefore provides the evidence base for reducing the risk of CV events among patients in the ITT population with elevated TGs in the economic model.

B.3.3.1.1. Baseline demographics

Characteristics of the population in the economic model align directly with patients included in the REDUCE-IT study as per section B.2.3.2 Baseline characteristics of the REDUCE-IT trial[60]. The median age of patients was 64 years, 28.8% were female and 70.7% of the population were classified as having established CVD. At baseline, the median LDL-C level was 75.0 mg/dL (1.94 mmol/L), the median high-density lipoprotein cholesterol (HDL-C) level was 40.0 mg/dL (1.03 mmol/L), and the median TG level was 216.0 mg/dL (2.44 mmol/L), as presented in Table 19.

Table 19: Baseline characteristics of the ITT population

Model population	Icosapent ethyl (N = 4,089)	Placebo (N = 4,090)	Reference
Median age (IQR)	64 years (57.0-69.0)	64 years (57.0-69.0)	REDUCE-IT
Triglyceride level (mg/dL), median (IQR)	216.5 (176–272)	216.0 (175–274)	REDUCE-IT
Median LDL cholesterol level, mg/dL (IQR)	74.0 (61.5–88.0)	76.0 (63.0–89.0)	REDUCE-IT
Median HDL cholesterol level, mg/dL (IQR)	40.0 (34.5–46.0)	40.0 (35.0–46.0)	REDUCE-IT
Secondary prevention cohort n (%)	2,892 (70.7)	2,893 (70.7)	REDUCE-IT
Primary prevention cohort n (%)	1,197 (29.3)	1,197 (29.3)	REDUCE-IT

Abbreviations: HDL-C – High density lipoprotein cholesterol; IQR – Interquartile range; LDL-C – Low density lipoprotein cholesterol; mg/dL – milligrams per decilitres

B.3.3.2. Clinical Outcomes

To capture all CV events, IPD from the REDUCE-IT trial was used. KM data was used to inform the number of individuals that experience a first event, second event and third or more event in each cycle of the model. Incidence was expressed as the

cumulative incidence of the 5-point MACE, a composite of CV death, nonfatal MI (including silent MI), nonfatal stroke, coronary revascularization, or unstable angina. When considering subsequent events, if multiple events occurred in one calendar day, only the first event that occurred was included in the analysis following methodology in the pre-specified analyses of total ischemic events from Bhatt et al. (2019).

B.3.3.2.1. Extrapolation

In order to extrapolate the clinical data beyond the trial follow-up period, a series of parametric survival models (as published in NICE DSU Technical Support Document 14[71]) were fit to the reconstituted first, second and third event IPD using the Flexsurv for R package for time-to-event data. To account for the range in follow-up data among individuals, data was extrapolated using IPD up until the point that 10% of patients at risk were left in the trial. A wide range of parametric survival models were fitted to the reconstituted data to match the placebo arm. To determine the most appropriate survival functions, model fit was assessed as follows:

- Graphic comparison of the predicted curve from a given parametric function to the Kaplan-Meier curve from the patient data
- Comparison of Akaike information criterion (AIC) statistics and Bayesian information criterion (BIC) statistics
- UK clinical expert opinion

B.3.3.2.1.1 First event

The survival models fit to the first event observed data and the associated long-term extrapolations are presented in Figure 16 and Figure 17 for the Icosapent ethyl arm and Figure 18 and Figure 19 for the placebo arm. All produced a good fit within the trial data. When compared to the West of Scotland Coronary Prevention Study (WOSCOPS) analysing the cumulative CV events over a 20-year follow-up of 3,302 patients receiving pravastatin 40 mg once daily, a total of 414 patients in the pravastatin group died from CV causes, 1,145 died from all causes and a total of 1,398 patients experienced a CV admission.[73] Therefore, when comparing the extrapolated portion with this 20-year external dataset, it can be expected that 55% to 77% of the patients would experience a CV event. Based on the results presented in Table 20 for

Icosapent ethyl and Table 21 for placebo, the most likely scenario chosen is the exponential distribution since it gives the best statistical fit and produces clinically plausible predictions.

Figure 16. Parametric models fitted to the first event: ITT population (Icosapent ethyl)

Figure 17. Long-term extrapolations based on the parametric models fitted to the first event: ITT population (Icosapent ethyl)

Table 20. Parametric distribution fit to the first event using the AIC and BIC (Icosapent ethyl)

Distribution	AIC	BIC	Position	Plausibility based on visual inspection
Exponential	14096.6715	14102.98756	1	Yes
Weibull	14098.6712	14111.30331	2	Yes
Gompertz	14098.15364	14110.78575	2	Yes
Log-logistic	14096.97567	14109.60778	2	Yes
Lognormal	14106.06555	14118.69767	2	Yes
Generalised	14097.83318	14116.78135	6	Yes

Abbreviations: AIC – Akaike information criterion; BIC – Bayesian information criterion.

Figure 18. Parametric models fitted to the first event: ITT population (placebo)

Figure 19. Long-term extrapolations based on the parametric models fitted to the first event: ITT population (placebo)

Table 21. Parametric distribution fit to the first event using the AIC and BIC (placebo)

Distribution	AIC	BIC	Position	Plausibility based on visual inspection
Exponential	17544.86472	17551.18102	1	Yes
Weibull	17544.93864	17557.57124	2	Yes
Gompertz	17546.65148	17559.28408	2	Yes
Log-logistic	17542.80438	17555.43698	2	Yes
Lognormal	17568.1742	17580.8068	2	Yes
Generalised	17545.30549	17564.25439	6	Yes

Abbreviations: AIC – Akaike information criterion; BIC – Bayesian information criterion.

B.3.3.2.1.2 Second event

The survival models fit to the second event observed data and the associated long-term extrapolations are presented in Figure 20 and Figure 21 for Icosapent ethyl and Figure 22 and Figure 23 for placebo. All produced a good fit within the trial data other than generalised gamma for the Icosapent ethyl group that failed to provide a

coefficient output. Based on the results presented in Table 22 and Table 23 the most likely scenario chosen is the exponential since it gives the best statistical fit and produces clinically plausible predictions.[73]

Figure 20. Parametric models fitted to the second event: ITT population (Icosapent ethyl)

Figure 21. Long-term extrapolations based on the parametric models fitted to the second event: ITT population (Icosapent ethyl)

Table 22. Parametric distribution fit to the second event using the AIC and BIC (Icosapent ethyl)

Distribution	AIC	BIC	Position	Plausibility based on visual inspection
Exponential	5219.59696	5225.91301	1	Yes
Weibull	5216.26820	5228.90032	2	Yes
Gompertz	5218.77408	5231.40619	2	Yes
Log-logistic	5216.08251	5228.71463	2	Yes
Lognormal	5214.29565	5226.92776	2	Yes
Generalised gamma	3775.58848	3794.53664	6	Yes

Abbreviations: AIC – Akaike information criterion; BIC – Bayesian information criterion.

Figure 22. Parametric models fitted to the second event: ITT population (placebo)

Figure 23. Long-term extrapolations based on the parametric models fitted to the second event: ITT population (placebo)

Table 23. Parametric distribution fit to the second event using the AIC and BIC (placebo)

Distribution	AIC	BIC	Position	Plausibility based on visual inspection
Exponential	8021.09733	8027.41363	1	Yes
Weibull	8012.82493	8025.45753	2	Yes
Gompertz	8017.06741	8029.70001	2	No
Log-logistic	8012.38626	8025.01886	2	Yes
Lognormal	8018.84069	8031.47329	2	Yes
Generalised gamma	8014.41698	8033.36588	6	Yes

Abbreviations: AIC – Akaike information criterion; BIC – Bayesian information criterion.

B.3.3.2.1.3 Third plus event

The survival models fit to the third plus event observed data and the associated long-term extrapolations are presented in Figure 24 and Figure 25 for Icosapent ethyl and Figure 26 and Figure 27 for placebo. All produced a good fit within the trial data other than the Weibull distribution that failed to provide a coefficient output. Based on the

results presented in Table 24 and Table 25 the most likely scenario chosen is the exponential since it gives the best statistical fit and produces clinically plausible predictions.[73]

Figure 24. Parametric models fitted to the third plus event: ITT population (Icosapent ethyl)

Figure 25. Long-term extrapolations based on the parametric models fitted to the third plus event: ITT population (Icosapent ethyl)

Table 24. Parametric distribution fit to the third plus event using the AIC and BIC (Icosapent ethyl)

Distribution	AIC	BIC	Position	Plausibility based on visual inspection
Exponential	1740.633254	1746.94931	1	Yes
Weibull	NA	NA	-	NA
Gompertz	1736.00986	1748.64197	2	No
Log-logistic	1736.83735	1749.46946	2	Yes
Lognormal	1738.35393	1750.98604	2	Yes
Generalised gamma	1738.71629	1757.66446	5	Yes

Abbreviations: AIC – Akaike information criterion; BIC – Bayesian information criterion; NA – Not applicable.

Figure 26. Parametric models fitted to the third plus event: ITT population (placebo)

Figure 27. Long-term extrapolations based on the parametric models fitted to the third plus event: ITT population (placebo)

Table 25. Parametric distribution fit to the third plus event using the AIC and BIC (placebo)

Distribution	AIC	BIC	Position	Plausibility based on visual inspection
Exponential	3344.58223	3350.89853	1	Yes
Weibull	NA	NA	-	NA
Gompertz	3314.35694	3326.98954	2	No
Log-logistic	3299.53202	3312.16462	2	Yes
Lognormal	3297.54522	3310.17782	2	Yes
Generalised	2596.03068	2614.97958	5	No

Abbreviations: AIC – Akaike information criterion; BIC – Bayesian information criterion; NA – Not applicable.

B.3.3.2.2. Informing the type of event

The distribution of CV death, nonfatal MI, nonfatal stroke, coronary revascularization and unstable angina according to first, second and third plus event are presented in Table 26. The incidence curves inform the number of events occurring in time (time-dependent rates) and the timing of the events, whereas the distribution of primary endpoints informs the probability of a specific type of event. This probability is assumed to be constant over time.

Table 26. Distribution of types of first, second and third plus events

	Icosapent ethyl	Placebo
First event		
CV death	[redacted]	[redacted]
MI	[redacted]	[redacted]
Stroke	[redacted]	[redacted]
Unstable angina	[redacted]	[redacted]
Revascularisation	[redacted]	[redacted]
Total	705	901
Second event		
CV death	[redacted]	[redacted]
MI	[redacted]	[redacted]
Stroke	[redacted]	[redacted]
Unstable angina	[redacted]	[redacted]
Revascularisation	[redacted]	[redacted]
Total	236	376
Third plus event		
CV death	[redacted]	[redacted]
MI	[redacted]	[redacted]
Stroke	[redacted]	[redacted]
Unstable angina	[redacted]	[redacted]
Revascularisation	[redacted]	[redacted]
Total	[redacted]	[redacted]
Patients with third plus CV events	72	143
Number of third plus CV events per person	[redacted]	[redacted]

Abbreviations: CV – Cardiovascular; MI – Myocardial infarction.

B.3.3.2.3. Transitions to the death states

Two forms of mortality are captured within the model; surviving patients can transition to the non-CV related death health state, which captures the baseline risk of non-CV related death, or CV death if a CV related death occurs. Both death health states are the absorbing health states in the model in which patients remain until the time horizon lapses.

To estimate the baseline risk of non-CV related death, the probability of all-cause mortality was estimated for the age-gender matched population demographics in REDUCE-IT from national life tables available from the UK Office for National Statistics (ONS).[74]

To account for prior CV events and diabetes status, an increased risk of mortality compared to the general population is applied based on hazard ratios sourced from the literature (Table 27 and Table 28).

Table 27. Hazard ratios used in the model for secondary prevention

Increased mortality	Value reported in the literature	References
Diabetes	2.3	Emerging Risk Factors Collaboration 2015[75]
MI	1.5	Emerging Risk Factors Collaboration 2015[75]
Stroke	2	Emerging Risk Factors Collaboration 2015[75]
MI + Diabetes	3.5	Emerging Risk Factors Collaboration 2015[75]
Stroke + Diabetes	5.1	Emerging Risk Factors Collaboration 2015[75]
Stroke + MI	2.6	Emerging Risk Factors Collaboration 2015[75]
Stroke + MI + Diabetes	7.9	Emerging Risk Factors Collaboration 2015[75]

Abbreviations: MI – myocardial infarction.

Table 28. Hazard ratios used in the model for primary prevention

Increased mortality	Value reported in the literature	References
Diabetes	1.56	Asia Pacific Cohort Studies Collaboration 2003[76]
First event + diabetes	2.3	Emerging Risk Factors Collaboration 2015[75]
Second event - MI	1.5	Emerging Risk Factors Collaboration 2015[75]
Second event - Stroke	2	Emerging Risk Factors Collaboration 2015[75]
Second event - MI + Diabetes	3.5	Emerging Risk Factors Collaboration 2015[75]
Second event - Stroke + Diabetes	5.1	Emerging Risk Factors Collaboration 2015[75]
Third event - Stroke + MI	2.6	Emerging Risk Factors Collaboration 2015[75]
Third event - Stroke + MI + Diabetes	7.9	Emerging Risk Factors Collaboration 2015[75]

Abbreviations: MI – Myocardial infarction.

The hazard ratios for non-CV mortality in patients with diabetes, who are on treatment for secondary prevention of cardiovascular events were sourced from research by The

Emerging Risk Factors Collaboration (2015), which analysed individual participant data from 18 different countries, recruited in 1960–2007.[75] Compared with the reference group (those without a history of diabetes, stroke, or MI at baseline), the hazard ratios for non-CV mortality were 2.3 (95% CI 2.1–2.6) in patients with a history of diabetes, 2.0 (95% CI 1.9–2.3) in those with stroke, 1.5 (95% CI 1.4–1.7) in those with MI, 3.5 (95% CI 3.0–4.1) in those with both diabetes and MI, 5.1 (95% CI 4.3–6.1) in those with both diabetes and stroke, 2.6 (95% CI 2.2–3.0) in those with both stroke and MI, and 7.9 (95% CI 6.6–9.6) in those with diabetes, stroke, and MI. There were no large differences in the HRs by period of recruitment, and findings were broadly similar to the UK Biobank, which recruited UK participants from 2006–2010, suggesting that the data is still applicable today.

The analysis in the Emerging Risk Factors Collaboration included individuals that had experienced prior CV events, therefore, were not applicable to individuals in our cost-effectiveness model until they had experienced at least one event. Consequently, it was considered appropriate to source alternative hazard ratios for those in the primary prevention cohort that were in the no event state. A main inclusion criteria of the REDUCE-IT trial was that those in the primary prevention group were required to have diabetes, hence, a hazard ratio was sourced to represent their increased risk of non-CV death associated with being diabetic to inform the no event state, then beyond this, event states were informed by the Emerging Risk Factors Collaboration publication.

The hazard ratio for non-CV mortality in patients with diabetes, who are on treatment for primary prevention of CV disease was sourced from a meta-analysis of twenty-four cohort studies from Asia, Australia, and New Zealand by The Asia Pacific Cohort Studies Collaboration (2003).[76] Data from 161,214 participants (4,873 with a history of diabetes at baseline) was analysed to estimate the associations of diabetes with the risks of mortality during follow-up (median 5.4 years). Diabetes was associated with an increased risk of death from any non-CV cause (HR: 1.56; 95% CI 1.38–1.77). There was no clear difference in the hazard ratios for women and men or between Asian and Australasian subgroups, suggesting that these values are applicable to other populations such as the UK.

Individuals in the no event state that did not have diabetes were assumed to have a non-CV mortality risk equivalent to that of the age-adjusted UK norm, and in those that experienced unstable angina or revascularisation it was assumed their non-CV mortality risk would not increase during or after an event, as ratified by UK clinical experts.

Acute and post-event health states within the model were grouped by the number of events a patient has experienced since the beginning of the trial rather than the type of event. Therefore, a weighted average was calculated by multiplying the hazard ratios of each of the four non-fatal events by the distribution of type of event and diabetic status in the Icosapent ethyl and placebo groups. Additionally, the ITT population consists of both secondary prevention and primary prevention individuals therefore the HR for the ITT population had to be further weighted to account for the proportion of individuals in the secondary versus primary prevention group. The weighted hazard ratios for no event, acute and post- first, second and third events are provided in Table 29.

Table 29. Weighted hazard ratios by heath state used in the economic model

	Icosapent ethyl	Placebo
No event	1.544988	1.544988
First event	2.122621	2.123084
Post first event	2.122621	2.123084
Second event	2.265037	2.453237
Post second event	2.265037	2.453237
Third	2.560208	2.597006
Post third	2.560208	2.597006

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality-of-life data from clinical trials

No HRQoL data were collected in the REDUCE-IT study. Hence, HRQoL data was sourced from published literature.

B.3.4.2 Mapping

No HRQoL data were collected in the REDUCE-IT study to map onto a generic outcome measure.

B.3.4.3 Health-related quality-of-life studies

An economic SLR was conducted to identify existing studies investigating HRQoL in the management of adult patients at risk of CV events due to elevated TGs. The HRQoL search was conducted on 8th January 2021 and no date restriction was included. The PICOS principle described in CRD guidance was used to develop the review question below, which guided the search for HRQoL studies.[66] For more details on the search strategies, the inclusion/exclusion criteria, and HRQoL results, please see Appendix G and H, respectively. The review question evaluated in the HRQoL SLR was:

- What utilities and disutilities are associated with patients at risk of cardiovascular events due to elevated triglycerides?

Of the 633 references screened in the initial review that met the selection criteria across all review questions during the title and abstract screening, five met the review question and selection criteria for HRQoL studies and were considered for full text review. Following review of the full texts, four references were kept for extraction, and one reference was excluded due to not reporting any outcomes of interest. Grey literature searching provided four additional references which met the selection criteria for HRQoL studies. Therefore, eight studies met the selection criteria following first and second pass of the HRQoL review and were considered for extraction.

Of the eight studies identified (Table 30), five studies Ara and Brazier 2009, Gao 2019, Jiang 2019, Laires 2015 and Liew 2009 include utilities for individuals with established CVD or at high risk of CVD, two studies were previous NICE TAs in familial hypercholesterolaemia populations and one study was NICE CG181 lipid guidelines.[21, 57,58, 68,77–80]

Two studies, one Korean-based and the other conducted in Portugal reported baseline utilities for both primary and secondary prevention in a CVD population, however, in both studies the definition of secondary prevention differed from that defined in the REDUCE-IT study. In the Portuguese study, the established CVD cohort only considered those that were post-MI or post-unstable angina and the other study defined established CVD as those who had previously experienced a MI or stroke. In

comparison, the REDUCE-IT trial defined established CVD as those that had experienced any prior CVD event, therefore, it is likely the REDUCE-IT study would have captured patients with a lower baseline utility than patients included in these studies.

Of the remaining studies identified, one presents non-CVD population age-adjusted utility estimates in a Chinese population and another only considered post-MI or post-unstable angina when estimating baseline utility for established CVD.

Although the two NICE TAs identified both focus on familial hypercholesterolaemia populations, within the submission it presents multipliers associated with acute and post CVD health states that were then applied to age-adjusted baseline utilities.

TA393 provides the most comprehensive, UK-specific and robust methodology amongst the studies identified in the SLR. Therefore, this publication was used to inform the methodology for the calculation of utilities used in the economic model.

Following a review of all the retrieved publications, NICE CG181 health state multipliers and baseline utilities from Stevanović et al. 2016 and O'Reilly et al. 2011 previously sourced in a global SLR were deemed most appropriate for informing our economic model.

Table 30. Summary of utility values sourced in the SLR

Study	Secondary prevention baseline utility	Primary prevention baseline utility	Acute event utility(+)/ disutility(-)	Post event utility(+)/ disutility(-)
Gao 2019	0.85	-	-	MI: -0.12 Stroke: -0.24
Jiang 2019	-	Male: 0.751 Female:0.728	CHD: -0.439 Stroke: -0.920	AMI: -0.107 Stroke: -0.266
Laires 2015	0.808	1	-	MI: 0.76 Angina:0.77
Liew 2009	0.63	1	-	MI: 0.69 Stroke:0.50 Concurrent MI or stroke: 0.58

Study	Secondary prevention baseline utility	Primary prevention baseline utility	Acute event utility(+)/ disutility(-)	Post event utility(+)/ disutility(-)
NICE TA394	0.88	-	-	Stroke: 0.63
NICE TA393	-	-		Stroke: 0.822 MI:0.765 Unstable Angina: 0.765
NICE guideline CG181	-	-	MI: 0.760 Stroke: 0.628 Coronary revascularisation: 0.808 Unstable angina: 0.770	MI: 0.880 Stroke: 0.628 Coronary revascularisation: 0.880 Unstable angina: 0.880
Ara and Brazier 2009	0.67	0.87	-	-

Abbreviations: AMI – Acute myocardial infarction; CHD – Coronary heart disease; MI – Myocardial infarction

B.3.4.4 Adverse reactions

The impact of serious adverse reactions as reported in the REDUCE-IT trial (section B.2.10 Adverse reactions in the REDUCE-IT trial) were explored to evaluate the consequences on HRQoL for patients experiencing the event. Of the list provided in section B.2.10 Adverse reactions in the REDUCE-IT trial, only the TEAEs with a statistically significant difference between the Icosapent ethyl and placebo groups were considered for inclusion in the economic model: peripheral edema (6.5% versus 5.0%, respectively), constipation (5.4% versus 3.6%, respectively), atrial fibrillation (5.3% versus 3.9%, respectively) and serious bleeding (11.8% versus 9.9%, respectively; p=0.0055).

The effect of AEs on HRQoL was captured in the model through the application of literature sourced utility decrements to the proportion of individuals in the REDUCE-IT trial that experienced peripheral edema, constipation, atrial fibrillation, and serious bleeding in the respective treatment groups.

Utility decrements applied in the economic model along with their sources are presented in Table 31.

Table 31. Summary of adverse event utility decrements

Adverse event disutility	Value	SE	References
Peripheral edema	-0.005	0.0008	Disutility: Sullivan et al. (2016)[81]
Constipation	-0.001	0.0009	Disutility: Christensen et al. (2016)[82]
Atrial fibrillation	-0.032	0.0071	Disutility: Steg et al. (2011)[83]
Serious bleeding	-0.104	0.0260	Disutility: Tengs et al. (2000)[84]

Abbreviations: SE – standard error.

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

Baseline utility

The all-risk stratum baseline utility is intended to represent the population under study, which is formed of 70.7% patients in the secondary prevention cohort and 29.3% patients in the primary prevention cohort. Therefore, a weighted average of the baseline utility values sourced for the primary and secondary prevention subgroups was calculated.

The baseline utility value for the secondary prevention subgroup was informed using Stevanović *et al.* 2016. This study was a multivariate meta-analysis that included 40 studies providing preference-base value in post-acute coronary syndrome, stable angina and coronary heart disease. The average age of patients was 65.35 years which is comparable to the average age of patients in REDUCE-IT. The study is applicable to a UK population as ten of the 40 studies referred to the UK and 53% of the EQ-5D scoring values were based on the UK tariff.

The baseline utility value for the primary prevention subgroup was informed using O'Reilly *et al.* 2011. This study analysed HRQoL data from 1,147 patients with type 2 diabetes and estimated the disutility associated with experiencing a diabetes-related complication. The mean age was 63.7 years which is comparable to the average age of patients in REDUCE-IT. The utility estimates associated with experiencing an event were assumed to be reflective of the primary prevention subgroup reported in the REDUCE-IT study.

Acute CV event utilities and post-event utilities

Table 32 Summary of utility values for cost-effectiveness analysis

State	Multiplier	Utility value: mean (standard error)	Reference in submission (section and page number)	Justification
Baseline utility – secondary prevention	-	0.765	Stevanović et al. 2016	Utility sourced from meta-analysis of 40 studies, of which ten referred to the UK.
Baseline utility – primary prevention	-	0.75	O'Reilly et al. 2011	Utility sourced from analysis of HRQoL data from 1,147 patients with type 2 diabetes.
Acute - nonfatal MI	0.760	0.578 (0.018)	NICE CG181	NICE guideline value
Acute - nonfatal stroke	0.628	0.478 (0.040)	NICE CG181	NICE guideline value
Acute - coronary revascularisation	0.808	0.615 (0.038)	NICE CG181	NICE guideline value
Acute - unstable angina	0.770	0.586 (0.038)	NICE CG181	NICE guideline value
Post - nonfatal MI	0.880	0.669 (0.018)	NICE CG181	NICE guideline value
Post - nonfatal stroke	0.628	0.478 (0.040)	NICE CG181	NICE guideline value
Post - coronary revascularisation	0.880	0.669 (0.038)	NICE CG181	NICE guideline value
Post - unstable angina	0.880	0.669 (0.018)	NICE CG181	NICE guideline value
CV death	0.000	0.000 (0.000)	By definition	-
Death	0.000	0.000 (0.000)	By definition	-
AE disutility - peripheral edema	-	-0.005	Sullivan et al. (2016)[81]	Disutility derived from Sullivan *et al.* (2016)
AE disutility - constipation	-	-0.001	Christensen et al. (2016)[82]	Disutility derived from Christensen et al. (2016)

State	Multiplier	Utility value: mean (standard error)	Reference in submission (section and page number)	Justification
AE disutility - atrial fibrillation	-	-0.032	Steg et al. (2011)[83]	Disutility taken from Steg et al. (2011)
AE disutility - serious bleeding	-	-0.104	Tengs et al. (2000)[84]	Disutility taken from Tengs *et al.* (2000)

Abbreviations: AE – Adverse event; CV – Cardiovascular; CVD – Cardiovascular disease; MI – Myocardial infarction.

First event and post-first event utilities

To calculate the first event acute and post-event health state utilities, multipliers were applied to the baseline utility value, as done in previous NICE appraisals.[57,58] The multiplier utilities were informed by values used by NICE in their lipid modification guidelines CG181.[21] Patients experience an acute disutility for the first 60 days following an event, after which they experience a chronic post-event utility, as ratified by UK clinical experts. The multipliers used are reported in Table 32.

Second and third plus event and post- second and third plus event utilities

Following discussions with UK clinical experts, it was deemed likely that patients with multiple events would have worse utilities than those who would only experience a single event. Hence, to calculate the second event acute and post-event health state utilities, multipliers sourced from lipid modification guidelines CG181[21] were applied to the post-first event utility value. And for the third event acute and post-event health state utilities, multipliers were applied to the post-second event utility value.

Acute and post event health states within the CEM are grouped by the number of events an individual has experienced since the beginning of the trial rather than the type of event. Therefore, a weighted average was calculated by multiplying the utility of each of the four nonfatal events by the distribution of type of event in the Icosapent ethyl and placebo groups.

B.3.5 Cost and healthcare resource use identification, measurement and valuation

B.3.5.1. Resource identification, measurement and valuation studies

An economic SLR was used to identify cost and resource use studies in the management of adult patients at risk of CV events due to elevated TGs. The cost and resource use search was conducted on 8th January 2021 and no date restriction was included. The PICOS principle described in CRD guidance was used to develop the review question below, which guided the search for cost and resource use studies.[66] For more details on the search strategies, the inclusion/exclusion criteria, and cost and resource use results, please see Appendix G and I, respectively. The review question evaluated in the cost and resource use SLR was:

- What are the costs and resource use associated with the management of patients at risk of cardiovascular events due to elevated triglycerides?

Of the 633 references screened in the initial review that met the selection criteria across all review questions during the title and abstract screening, 48 met the review question and selection criteria for cost and resource use studies and were considered for full text review. Following review of the full texts, 33 references were excluded: 19 did not meet the population inclusion criteria, three did not meet the intervention inclusion criteria, 10 references did not report any outcomes of interest, and one reference was of the wrong study type. Grey literature searching provided four additional references which met the selection criteria for cost and resource use studies. Therefore, 19 studies met the selection criteria following first and second pass of the cost and resource use review and were considered for extraction.

Of the 19 identified references, only three provide cost and resource estimates from a UK perspective. A summary of the costs identified in NICE TA393 and NICE TA394 are provided below in Table 33.

Both TA393 and TA394 source costs from NICE CG181 estimated by the clinical guideline development group (GDG). It was noted that, following discussion with the GDG presented in TA393, they were unhappy with the methodology used since most

of the values in the NICE CG181 models were based on assumptions on the resource use of people with CVD, and many aspects of treatment for CVD have changed over the years since those models were developed. Despite looking through more recent literature, the GDG could not find any recent costs for people with CV conditions, so decided it would be preferable to construct their own estimates.

On this basis, the grey literature search was used as a mean to source any additional literature which may be more applicable to the modelled population. One study by Danese *et al.* (2016) was identified. It estimated the economic burden of CV events in patients receiving lipid-modifying therapy in the UK and was used to inform health state costs within the model.

Table 33: Summary of studies identified in the SLR

Study	NICE TA393	NICE TA394
Cost and resource use valuations used in the study	• Cost of alirocumab • Cost of ezetimibe (10 mg) • Cost of atorvastatin (20 mg, 40 mg and 80 mg) • Cost of rosuvastatin (5 mg, 10 mg, 20 mg anf 40 mg) • Annual cost of alirocumab per patient • Cost of urgent revascularisation • Cost of nonfatal MI • Cost of UA • Cost of ACS • Cost of revascularisation • Cost of IS • Cost of CV death • Cost of stroke rehabilitation programme	• Cost of evolocumab • Annual cost of evolocumab per patient

Costs for use in the economic analysis	• Alirocumab (75 mg or 150 mg single-use prefilled pen; excluding VAT):
	  • Pack of one pen: £168
	  • Pack of two pens: £336
	• Alirocumab annual cost of treatment per patient (for 75 mg or 150 mg every 2 weeks): £4,383
	• Ezetimibe annual cost
	• 10mg: £342.97
	• Atorvastatin annual cost 10 mg: £15.51
		Evolocumab costs - (140-mg prefilled pen or syringe; excluding VAT; MIMS, March–May 2016): £170.10
		Evolocumab annual cost of treatment per patient:
		• 140 mg every 2 weeks: £4,422.60
		• 420 mg monthly: £6,123.60

Study	NICE TA393	NICE TA394
	• Atorvastatin annual cost 20 mg: £18.90 • Atorvastatin annual cost 40 mg: £21.77 • Atorvastatin annual cost 80 mg: £34.94 • Rosuvastatin annual cost 5 mg: £235.03 • Rosuvastatin annual cost 10 mg: £235.03 • Rosuvastatin annual cost 20 mg: £339.19 • Rosuvastatin annual cost 40 mg: £386.51 • Cost of nonfatal MI: £3,337.00 • Cost of UA: £3,313.00 • Cost of ACS: £3,329.00 • Cost of revascularisation: £3,802.00 • Cost of IS: £4,092.00 • Cost of CV death: £1,174.00	
Resource use	Based on GDG expert opinion • Hospitalisation • Follow-up care • Medication	NR

Abbreviations ACS – Acute coronary syndrome; CV – Cardiovascular; GDG – Guideline Development Group; IS – Ischemic stroke; MIMS – Monthly Index of Medical Specialities; MI – Myocardial infarction; NICE – National Institute for Clinical Excellence; NR – Not reported; UA – Unstable angina; VAT – Value added tax.

B.3.5.2 Intervention and comparators' costs and resource use

Icosapent ethyl acquisition cost

The list price for Icosapent ethyl is £173 (inclusive of 20% VAT) per pack of 120 capsules. The recommended daily oral dose is 4 capsules taken as two 998 mg capsules twice daily. The annual course of treatment is £2,106.28 at the anticipated list price. To align with daily cycles used in the model, the daily cost is anticipated to be £5.77 (Table 34). Icosapent ethyl is administered orally, therefore, no administration cost or wastage is considered in the cost-effectiveness model.

Table 34. Icosapent ethyl unit drug costs

Drug	Unit size	Cost per pack (£)	Cost per unit (£)	Cost per day (£)	Reference

Icosapent ethyl	120 capsules (998 mg)	£173	£1.44	£5.77	*Amarin*

Concomitant therapies

As discussed in section B.3.2 Economic analysis and in alignment with the licensed indication, the patient population receive a stable dose of statin therapy (+/- ezetimibe 10 mg) as best supportive care in both treatment arms. Table 35 presents the distribution of patients stratified by the intensity of statin therapy based on the REDUCE-IT trial, whereby 93.6% of the trial population were on moderate to high intensity statins.[54] In line with UK clinical practice, patients are prescribed atorvastatin 20-80 mg, classified as a high intensity statin using NICE CG181 and equivalent to moderate and high intensity statin therapy in REDUCE-IT. Commonly prescribed statin regimens in UK clinical practice were included to estimate the cost of statins in the model (Table 36).

Table 35. Statin intensity of concomitant therapies received in the REDUCE-IT trial – ITT population

Statin Intensity	**User**	**Reference**
Low (%)	6.4%	*REDUCE-IT (2019)*
Moderate (%)	62.5%	*REDUCE-IT (2019)*
High (%)	30.8%	*REDUCE-IT (2019)*
Ezetimibe use (%)	6.4%	*REDUCE-IT (2019)*

Table 36. Concomitant drug unit cost and dosage

Drug	**Strength (mg)**	**Dosage Form**	**Unit Price (£)**	**Recommended Dose**	**Statin Intensity (based on REDUCE-IT)**	**Reference**
Ezetimibe (Ezetrol)	10	Tab	0.10	10 mg daily	-	*BNF*
Atorvastatin calcium (Lipitor and generics)	10	Tab	0.03	10 to 80 mg at bedtime	Moderate	*BNF*
	20	Tab	0.04		Moderate	*BNF*
	40	Tab	0.05		High	*BNF*
	80	Tab	0.07		High	*BNF*

Drug	Strength (mg)	Dosage Form	Unit Price (£)	Recommended Dose	Statin Intensity (based on REDUCE-IT)	Reference
Fluvastatin sodium (Lescol and generics)	20	Cap	0.11	20 to 40 mg at bedtime	Low	*BNF*
	40	Cap	0.12		Low	*BNF*
Pravastatin sodium (Pravachol and generics)	10	Tab	0.04	10 to 40 mg at bedtime	Low	*BNF*
	20	Tab	0.04		Low	*BNF*
Simvastatin (Zocor and generics)	10	Tab	0.0300	10 to 80 mg at bedtime	Low	*BNF*

To calculate the total daily cost of concomitant therapies, an average of the daily cost of each statin within the different intensity categories was estimated and weighted by the proportion of patients on low, moderate and high intensity statin therapy as per the REDUCE-IT trial (Table 36). The unit price was based upon the acquisition cost per strength (mg) sourced from the BNF.[85]

Table 37 presents the daily drug costs for each treatment arm. The average daily cost of concomitant therapy alone is £0.05 per patient which is applied to the placebo treatment arm. The daily drug cost of Icosapent ethyl and concomitant therapy is £5.82 per patient.

Table 37. Daily drug costs

	Cost (£)
Placebo + concomitant therapies	£0.05
Icosapent ethyl + concomitant therapies	£5.82

Discontinuation

In the REDUCE-IT study, patients discontinue treatment for multiple reasons (withdrawal of consent, investigator judgment, incomplete follow-up visits and adverse event leading to withdrawal of study). The discontinuation of treatment also reflects the real-world utilisation of a chronic treatment. The discontinuation rate was estimated

by applying a series of parametric survival models that were fit to the IPD of the REDUCE-IT study using the Flexsurv for R package for time-to-discontinuation data. NICE Decision Support Unit (DSU) guidelines were followed in selecting and fitting the following six parametric distributions to the Kaplan Meier data using R: Exponential, Weibull, Gompertz, Log-logistic, Lognormal and Generalised Gamma.[71] The aforementioned parametric survival models were fitted to the reconstituted data for Icosapent ethyl.

Model fit was assessed through the graphical comparison of the predicted curve from a given parametric function to the Kaplan-Meier curve from the patient data, assessment of the clinical validity of the extrapolated portion of the survival curves and comparison of AIC and BIC statistics. Since efficacy data is based on the intention-to-treat analysis, when patients discontinue treatment, only the treatment cost stops, whereas the probability of CV events and death remains the same.

The survival models fit to the discontinuation data for the Icosapent ethyl treatment arm, and the associated long-term extrapolation are presented in Figure 28. All produced a good fit within the trial data. Plausibility of the extrapolation was difficult to assess since no external long-term data on discontinuation of this treatment is available. Therefore, based only on the results presented in Table 38, the most likely scenario is the exponential distribution for the Icosapent ethyl arm.

It is important to note that no discontinuation was applied to the best supportive care arm as this would not be a realistic assumption (i.e., it does not make clinical sense for patients to discontinue a stable dose of statins and receive no treatment).

Figure 28. Long-term extrapolations based on the parametric models fitted to treatment discontinuation – Icosapent ethyl

Table 38. Parametric distribution fit to treatment discontinuation using the AIC and BIC – Icosapent ethyl

Distribution	AIC	BIC	Position	Plausibility based on visual inspection
Exponential	24755.76709	24762.08314	1	Yes
Weibull	24694.76447	24707.39659	2	Yes
Gompertz	24725.4936	24738.12571	2	Yes
Log-logistic	24704.30086	24716.93297	2	Yes
Lognormal	24761.59046	24774.22257	2	Yes
Generalised gamma	24696.09598	24715.04414	6	Yes

Abbreviations: AIC – Akaike information criterion; BIC – Bayesian information criterion.

B.3.5.4 Health-state unit costs and resource use

Acute health state costs

Health care costs associated with CV events were included at the time of first event, second event, third event (initial cycle).

To inform acute health state costs, individual costs were sourced from Danese *et al.* 2016 for the five types of events included in the primary composite endpoint, nonfatal MI, unstable angina and CV death (assuming the cost of CV death is equal to the cost of hospitalisation). This study estimated the economic burden of CV events in patients receiving lipid-modifying therapy in the UK. A retrospective cohort approach was taken, using CPRD data from 2006 to 2012 to identify individuals with their first and second CV-related events. Direct medical costs were estimated from a 2014 cost year in GBP in the acute period after a variety of CV events. Incremental costs were estimated using in person differences to minimise confounding. All healthcare costs retrieved were inflated to 2019 prices using the healthcare component of the consumer price index (CPI).

Coronary artery bypass grafting (CABG) and percutaneous coronary revascularisation are the most frequently used technique for coronary revascularisation. In this model, the proportion of revascularisation was informed by two UK clinical experts who estimated that 80% of revascularisations performed are percutaneous coronary interventions (PCIs) and 20% are CABGs in UK clinical practice (Table 39). The cost of revascularisation was retrieved from NHS reference costs 2018-2019 (Table 40).

Table 39. Approach for revascularisation technique

Health care element	Proportion (%)	Reference
Approach for revascularisation technique		
Percutaneous coronary intervention	80.0%	Assumption validated by UK clinical experts
Coronary artery bypass graft surgery	20.0%	Assumption validated by UK clinical experts

The event health state cost applied are available in Table 41.

Table 40. Acute health care costs sourced to inform acute health state costs

	Cost (£)	SE	Reference
Nonfatal MI			
Acute period	4,678.22	467.82	*Danese et al. 2016*
Nonfatal stroke			

Acute period	3,978.91	397.89	*Danese et al. 2016*
Coronary revascularisation			
Acute period	6,147.04	614.70	*Calculation = (80%*PCI cost)+(20%*CABG cost)*
Percutaneous coronary intervention (PCI)	4,406.97	440.70	*NHS reference costs 2018-2019*
Coronary artery bypass graft surgery (CABG)	13,107.34	1,310.73	*NHS reference costs 2018-2019*
Unstable angina			
Acute period	2,438.43	243.84	*Danese et al. 2016*
Cardiovascular death			
Total	3,719.02	-	
Fatal MI - hospitalisation without procedure	3,719.02	371.90	*Danese et al. 2016*
Fatal stroke - hospitalisation without procedure	3,719.02	371.90	*Danese et al. 2016*

Abbreviations: CABG – Coronary artery bypass graft; MI – Myocardial infarction; NHS – National Health Service; PCI – Percutaneous coronary intervention; SE – Standard error.

As event health states within the model were grouped by the number of events an individual has experienced since the beginning of the trial rather than the type of event, a weighted average was calculated by multiplying the cost of each of the five individual events by the distribution of type of event in the Icosapent ethyl and placebo groups for first, second and third plus event. (Table 41)

Table 41. Weighted average of first, second and third+ event health state costs – ITT population

	Icosapent ethyl	**Placebo**	**Calculation**
First event – Acute	[redacted]	[redacted]	SUMPRODUCT (acute event cost, proportion of type of first event)
Second event - Acute	[redacted]	[redacted]	SUMPRODUCT (acute event cost, proportion of type second event)
Third+ event - Acute	[redacted]	[redacted]	SUMPRODUCT (acute event cost, proportion of type second event)*number of

	Icosapent ethyl	Placebo	Calculation
			events per individuals that have a third event (not including first and second event)

Post-event health state costs

Following the acute cost period, a post event health state cost is applied for the remaining cycles either until patients experience another event and progress to the next event state, or they die.

To inform post health state costs, individual costs were sourced from Danese *et al.* 2016 for the four types of non-fatal events, included in the primary composite endpoint, nonfatal MI, revascularisation, and unstable angina. Direct medical costs were estimated from a 2014 cost year in GBP in the post-event period after a variety of CV events. Incremental costs were estimated using in person differences to minimise confounding. All healthcare costs retrieved were inflated to 2019 prices using the healthcare component of the consumer price index (CPI) and converted into daily costs to account for the daily cycles used in the model (Table 42).

Table 42: Daily long-term health care costs sourced to inform post-event health state costs

Long term care cost	Daily cost (£)	Reference
MI	£2.87	*Danese et al. 2016*
Stroke	£2.86	*Danese et al. 2016*
Revascularisation	£5.19	*Danese et al. 2016*
Unstable angina	£1.12	*Danese et al. 2016*

Abbreviations: MI, Myocardial infarction.

As post event health states within the CEM were grouped by the number of events an individual has experienced since the beginning of the trial rather than the type of event, a weighted average was calculated by multiplying the cost of each of the four nonfatal events by the distribution of type of event in the Icosapent ethyl and placebo groups for first, second and third events (Table 43).

Table 43. Weighted average first, second and third+ post-event health state costs – ITT population

	Icosapent ethyl	Placebo	Calculation
First event – Post	[redacted]	[redacted]	SUMPRODUCT (long-term event cost, proportion of non-fatal first event)
Second event - Post	[redacted]	[redacted]	SUMPRODUCT (long-term event cost, proportion of non-fatal second event)
Third+ event - Post	[redacted]	[redacted]	SUMPRODUCT (long-term event cost, proportion of non-fatal third event)*number of events per individuals that have a third event (not including first and second event)

Follow-up and monitoring costs

Annual medical costs associated with follow-up and monitoring were calculated based on a number of assumptions, as depicted in Table 44 and Table 45. These included the costs of medical appointments as per treatment guidelines and UK clinical expert opinion as well as the costs of laboratory testing, in the first and subsequent years respectively. NICE CG181 states that patients will receive one blood test within 3 months of initiating treatment and then at 12 months as per their annual medicine review. Medical appointments to evaluate the response and adverse events and the initial fasting lipid panel were only considered for the Icosapent ethyl arm. Unit costs for the monitoring and management of patients are presented in Table 46 and daily monitoring and management cost are presented in Table 47.

Table 44: Annual monitoring and management resource use - first year

Annual monitoring and management - first year	Value	Low	High	Reference
Medical visits				
Number of visits for initiation of Icosapent ethyl	1	-	-	*Assumption validated by clinical experts*

Annual monitoring and management - first year	Value	Low	High	Reference
Visit with a general practitioner (%)	90%	0%	100%	*Assumption validated by clinical experts*
Visit with a cardiologist (%)	10%	-	-	
Number of visits - first year	1	1	4	*Assumption validated by clinical experts*
Visit with a general practitioner (%)	90%	0%	100%	*Assumption validated by clinical experts*
Visit with a cardiologist (%)	10%	-	-	
Laboratory tests				
Number tests for initiation of Icosapent ethyl	1	-	-	*Assumption Validated by Clinical Experts)*
Number of tests - first year	1	1	4	*NICE guidance*

Abbreviations: NICE – National Institute for Health and Care Excellence.

Table 45. Annual monitoring and management resource use - subsequent years

Annual monitoring and management - subsequent years	Value	Low	High	Reference
Medical visits				
Number of visits - subsequent years	1	1	4	*Assumption validated by clinical experts*
Visit with a general practitioner (%)	100%	0%	100%	*Assumption validated by clinical experts*
Visit with a cardiologist (%)	0%	-	-	
Laboratory tests				
Number of tests subsequent years	1	1	4	*NICE guidance*

Abbreviations: NICE – National Institute for Health and Care Excellence.

Table 46. Monitoring and management unit costs

Unit cost for medical visits and laboratory tests	Cost (£)	Reference
Main consultation with a cardiologist	150.90	*NHS reference costs 2018-2019 - Consultant led Cardiology (320)*
Follow-up visit with a cardiologist	102.16	*NHS reference costs 2018-2019 - Non-consultant led Cardiology (320)*
Consultation with a GP	39.23	*PSSRU 2020 - GP consultation*
Fasting lipid panel (total cholesterol, triglycerides, HDL-C, LDL-C)	2.00	*NHS reference costs 2018-2019 - Integrated blood services (DAPS03)*

Abbreviations: GP – General Practitioner; HDL-C – High density lipoprotein cholesterol; LDL-C – Low density lipoprotein cholesterol; NHS – National Health Service.

Table 47. Daily calculated monitoring and management costs

Monitoring and management cost	Daily monitoring and management cost (£)
Initial year - Icosapent ethyl	£0.27
Initial year - Placebo	£0.12
Subsequent years - Icosapent ethyl	£0.11
Subsequent years - Placebo	£0.11

B.3.5.4 Adverse reaction unit costs and resource use

The mean cost of adverse events (Table 48) was obtained from NHS reference costs and based on assumptions validated by two UK clinical experts.

Table 48. Costs of adverse events

Adverse events costs	Cost per event (£)	Reference
Peripheral edema	770.28	NHS reference costs 2018/2019 - Average of WH10A-B - Unspecified Edema
Constipation	377.01	NHS reference costs 2018/2019 - VB01Z - Emergency Medicine, any investigation with category 5 treatment
Atrial fibrillation	1,247.91	NHS reference costs 2018/2019 - Average of EB07A-E – Arrhythmia
Serious bleeding	2,814.97	NHS reference costs 2018/2019 - Average of AA23C-G - Haemorrhagic Cerebrovascular Disorders and FD03A-H - Gastrointestinal Bleed

Abbreviations: NHS – National Health Service

Miscellaneous unit costs and resource use

No miscellaneous unit costs and resource use were included in the economic model.

B.3.6 Summary of base-case analysis inputs and assumptions

Summary of base-case analysis inputs

Table 49. Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Cohort size	1000	N/A	B.3.3.1.1. Baseline demographics

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Time horizon	36.00	N/A	Model structure
Total number of cycles	13149.00	N/A	B.3.3.1.1. Baseline demographics
Age	64.00	GAMMA	B.3.3.1.1. Baseline demographics
Percentage male	0.71	BETA (41%-99%)	B.3.3.1.1. Baseline demographics
Discount rate costs	0.04	N/A	Model structure
Discount rate outcomes	0.04	N/A	Model structure
Baseline distribution	N/A	Exponential	B.3.3.2. Clinical outcomes
Icosapent Ethyl transitions	B.3.3.2. Clinical outcomes	Exponential	B.3.3.2. Clinical outcomes
Placebo transitions	B.3.3.2. Clinical outcomes	Exponential	B.3.3.2. Clinical outcomes
Icosapent Ethyl mortality HR: No Event	1.54	GAMMA (1.00-2.20)	B.3.3.2.3. Transitions to the death states
Icosapent Ethyl mortality HR: First event	2.12	GAMMA (1.35-2.97)	B.3.3.2.3. Transitions to the death states
Icosapent Ethyl mortality HR: Post first event	2.12	GAMMA (1.35-2.97)	B.3.3.2.3. Transitions to the death states
Icosapent Ethyl mortality HR: Second event	2.27	GAMMA (1.43-3.16)	B.3.3.2.3. Transitions to the death states
Icosapent Ethyl mortality HR: Post second event	2.27	GAMMA (1.43-3.16)	B.3.3.2.3. Transitions to the death states
Icosapent Ethyl mortality HR: Third event	2.56	GAMMA (1.61-3.55)	B.3.3.2.3. Transitions to the death states
Icosapent Ethyl mortality HR: Post Third event	2.56	GAMMA (1.61-3.55)	B.3.3.2.3. Transitions to the death states
Placebo mortality HR: No Event	1.54	GAMMA (1.00-2.20)	B.3.3.2.3. Transitions to the death states
Placebo mortality HR: First event	2.12	GAMMA (1.35-2.98)	B.3.3.2.3. Transitions to the death states

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Placebo mortality HR: Post first event	2.12	GAMMA (1.35-2.98)	B.3.3.2.3. Transitions to the death states
Placebo mortality HR: Second event	2.45	GAMMA (1.56-3.44)	B.3.3.2.3. Transitions to the death states
Placebo mortality HR: Post second event	2.45	GAMMA (1.56-3.44)	B.3.3.2.3. Transitions to the death states
Placebo mortality HR: Third event	2.60	GAMMA (1.65-3.63)	B.3.3.2.3. Transitions to the death states
Placebo mortality HR: Post Third event	2.60	GAMMA (1.65-3.63)	B.3.3.2.3. Transitions to the death states
Icosapent Ethyl cost per cycle (£)	5.82	GAMMA (3.77-8.31)	B.3.5.2 Intervention and comparators' costs and resource use
Administration cost per cycle with Icosapent Ethyl (£)	0.00	GAMMA	B.3.5.2 Intervention and comparators' costs and resource use
Icosapent Ethyl compliance	[redacted]	BETA (96%-100%)	B.3.5.2 Intervention and comparators' costs and resource use
Placebo cost per cycle (£)	0.05	GAMMA (0.03-0.07)	B.3.5.2 Intervention and comparators' costs and resource use
Administration cost per cycle with Placebo (£)	0.00	GAMMA	B.3.5.2 Intervention and comparators' costs and resource use
Placebo compliance	1.00	BETA	B.3.5.2 Intervention and comparators' costs and resource use
Icosapent Ethyl monitoring costs - First year	0.27	GAMMA (0.18-0.39)	B.3.5.2 Intervention and comparators' costs and resource use
Placebo monitoring costs - First year	0.13	GAMMA (0.08-0.19)	B.3.5.2 Intervention and comparators' costs and resource use
Icosapent Ethyl monitoring costs - Subsequent years	0.11	GAMMA (0.07-0.16)	B.3.5.2 Intervention and comparators' costs and resource use

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Placebo monitoring costs - Subsequent years	0.11	GAMMA (0.07-0.16)	B.3.5.2 Intervention and comparators' costs and resource use
Acute Nonfatal MI health state cost	4678.22	GAMMA (3027.50-6682.39)	B.3.5.4 Health-state unit costs and resource use
Acute Nonfatal stroke health state cost	3978.91	GAMMA (2574.94-5683.49)	B.3.5.4 Health-state unit costs and resource use
Acute UA health state cost	2438.43	GAMMA (1578.02-3483.06)	B.3.5.4 Health-state unit costs and resource use
Acute CR health state cost	6147.04	GAMMA (3978.04-8780.46)	B.3.5.4 Health-state unit costs and resource use
CV Death health state cost	3719.02	GAMMA (2406.76-5312.27)	B.3.5.4 Health-state unit costs and resource use
Long-term Nonfatal MI health state cost	2.87	GAMMA (1.86-4.10)	B.3.5.4 Health-state unit costs and resource use
Long-term Nonfatal stroke health state cost	2.86	GAMMA (1.85-4.08)	B.3.5.4 Health-state unit costs and resource use
Long-term UA health state cost	1.12	GAMMA (0.72-1.60)	B.3.5.4 Health-state unit costs and resource use
Long-term CR health state cost	5.19	GAMMA (3.36-7.42)	B.3.5.4 Health-state unit costs and resource use
Icosapent Ethyl adverse event total cost	0.12	GAMMA (0.08-0.17)	B.3.5.4 Health-state unit costs and resource use
Utility: CV Death	0.00	BETA	B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis
Utility: Post MI	0.67	BETA (0.39-0.91)	B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis
Utility: Post Stroke	0.48	BETA (0.30-0.67)	B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis
Utility: Post UA	0.67	BETA (0.39-0.91)	B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis
Utility: Post CR	0.67	BETA (0.39-0.91)	B.3.4.5 Health-related quality-of-life data used in

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
			the cost-effectiveness analysis
Utility: Acute MI	0.58	BETA (0.35-0.80)	B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis
Utility: Acute Stroke	0.48	BETA (0.30-0.67)	B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis
Utility: Acute UA	0.62	BETA (0.37-0.85)	B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis
Utility: Acute CR	0.59	BETA (0.35-0.81)	B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis
Icosapent Ethyl adverse event total disutility	0.00	BETA	B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis
Placebo adverse event total disutility	0.00	BETA	B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

Abbreviations: CI, confidence interval; CV, Cardiovascular; HR, Hazard ratio; MI, Myocardial infarction; UA, Unstable angina.

Assumptions

Table 50. Assumptions underpinning cost effectiveness model

Variable	Assumed value	Justification
Time horizon	36 years	Patients entering the model have a mean age of 64 years based on clinical trial baseline characteristics. Patients in the cohort are not expected to live beyond 100 years and therefore a 36-year time horizon was deemed appropriate (100-64 = 36).
One year	365.25 days	One year was assumed to be equal to 365.25 days
Half cycle correction applied	NA	A half-cycle correction was applied to both costs and health outcomes in the Markov model to align with conventional modelling standards.

Baseline characteristics of patients	Age (years) = 64 Male (%) = 71.2% Diabetes (%) = 58.5% Statin intensity Low (%) = 6.4% Moderate (%) = 62.5% High (%) = 30.8% Ezetimibe use (%) = 6.4%	The indicated population were enrolled in the REDUCE-IT study, so it is suitable to use the baseline characteristics from REDUCE-IT for both the Icosapent ethyl and placebo cohort.
Wastage assumption	NA	Wastage was not included in the model.
Adverse events	NA	Only adverse events that were significantly different between the Icosapent ethyl and placebo arm of the REDUCE-IT trial were included in the economic model
Extrapolations IPD cut off	2038 days	IPD data used to inform the extrapolations for the event curves included a cut off at the point where less that 10% of randomised patients were at risk. This cut off was implemented to account for large lost to follow-up towards the later timepoints in the trial.
Events per patient in the three plus event state	Icosapent ethyl - [redacted] Placebo - [redacted]	Calculated using the number of third plus events recorded/number of patients that experienced a third event.
All costs associated with an event included at the time of entry to the event state	NA	In line with NICE reference cases.
Acute utility duration	60 days	Consistent with the recommendation of clinical experts consulted.
Clinical and discontinuation extrapolation distributions	Exponential	Best fit as determined by AIC/BIC and also clinical expert opinion
Drug administration cost	£0	Both placebo and Icosapent ethyl are oral drugs, therefore, require no administration cost
Utility - Death	0	By definition

Acute CV event health state disutilities and post-event utilities were applied multiplicatively to baseline utility value	NA	Health state utilities and methodology were informed by NICE CG181 guidance in line with NICE reference cases.
Type of revascularisation	PCI – 80% CABG- 20%	These proportions are consistent with the recommendation of clinical experts consulted.
Patient's management performed by GP	90%	These proportions are consistent with the recommendation of clinical experts consulted.

Abbreviations: AIC - Akaike information criterion; BIC - Bayesian information criterion; CABG - Coronary artery bypass graft; CV - Cardiovascular; IPD - Individual patient data; NA - Not applicable; PCI - Percutaneous coronary intervention; UK - United Kingdom.

B.3.7 Base-case results

Base-case incremental cost-effectiveness analysis results

Base-case incremental cost-effectiveness analysis results are presented in Table 51. Icosapent ethyl was associated with £10,660 incremental costs and 0.364 incremental QALYs, resulting in an ICER of £29,309.

Table 51. Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Placebo	9,951	10.547	7.522	-	-	-	-
Icosapent ethyl	20,611	10.846	7.886	10,660	0.299	0.364	29,309

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

B.3.8 Sensitivity analyses

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was performed to explore the uncertainty around key model inputs. PSA was conducted by varying these inputs simultaneously by assigning distributions and recording the mean model results. A total of 5,000 PSA iterations were run in order to obtain a stable estimate of the mean model results.

The following parameters were kept fixed in the PSA: time horizon, cycle length, age, discount rates for costs and outcomes, transitions across the health states and baseline distribution as well as the cost of treatment with Icosapent ethyl.

Mean incremental results were recorded and illustrated through an incremental cost-effectiveness plane (ICEP). In addition, a cost-effectiveness acceptability curve (CEAC) and cost-effectiveness acceptability frontier (CEAF) were plotted.

The PSA results of Icosapent ethyl versus Placebo are presented in Table 52. The mean PSA results lie close to the deterministic base-case results (Table 51). Patients receiving Icosapent ethyl accrued 7.708 QALYs at a cost of £20,088. Patients receiving Placebo accrued 7.353 QALYs at a cost of £10,195, respectively. This resulted in a mean PSA ICER of £27,875.

The ICEP showing the PSA results is presented in Figure 29 and shows that 100% of the iterations fell in the north-east quadrant where Icosapent ethyl is more costly but more effective. The CEAC and CEAF for the whole cohort are presented in Figure 30 and Figure 31, respectively.

Table 52. PSA results

Technologies	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	Cost per QALY (£)
Placebo	10,195	7.353	-	-	-
Icosapent ethyl	20,088	7.708	9,893	0.355	27,875

Abbreviations: ICER – Incremental cost-effectiveness ratio; PSA – Probabilistic sensitivity analysis; QALYs – Quality-adjusted life years.

Figure 29. Incremental cost-effectiveness plane

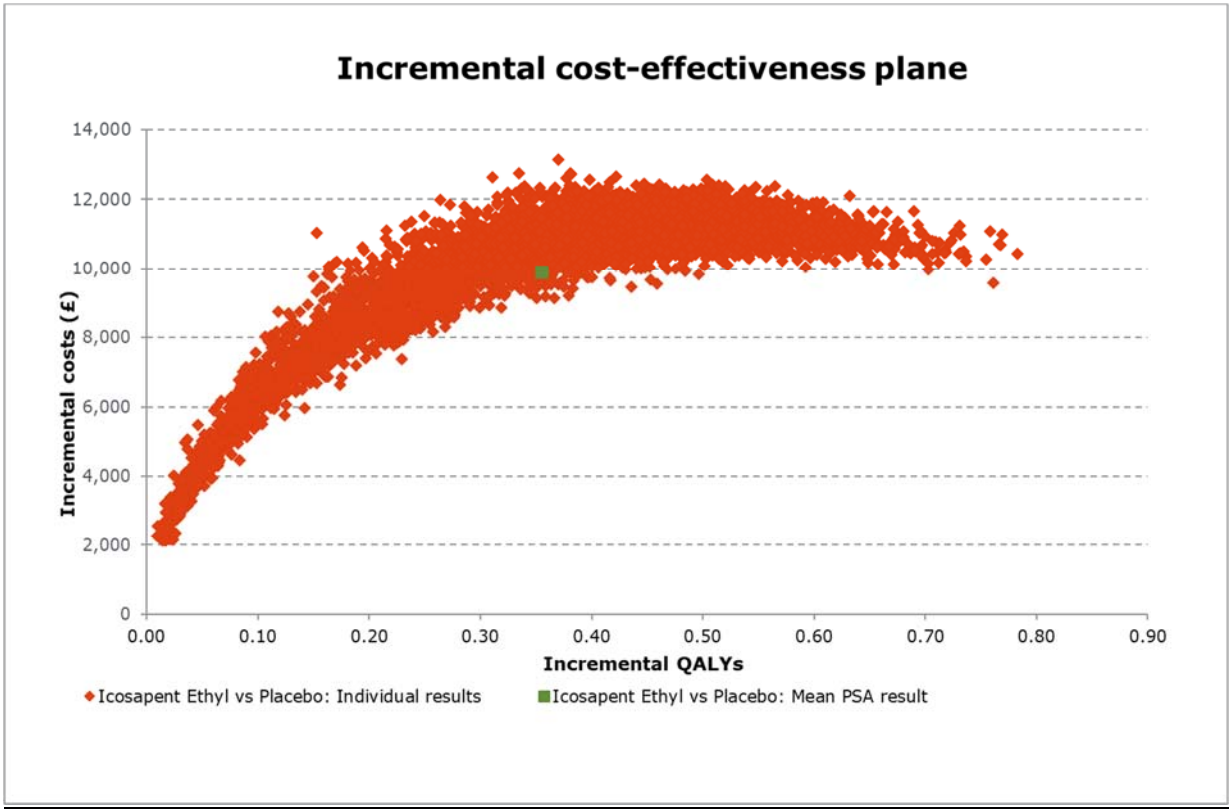


Figure 30. Cost-effectiveness acceptability curve

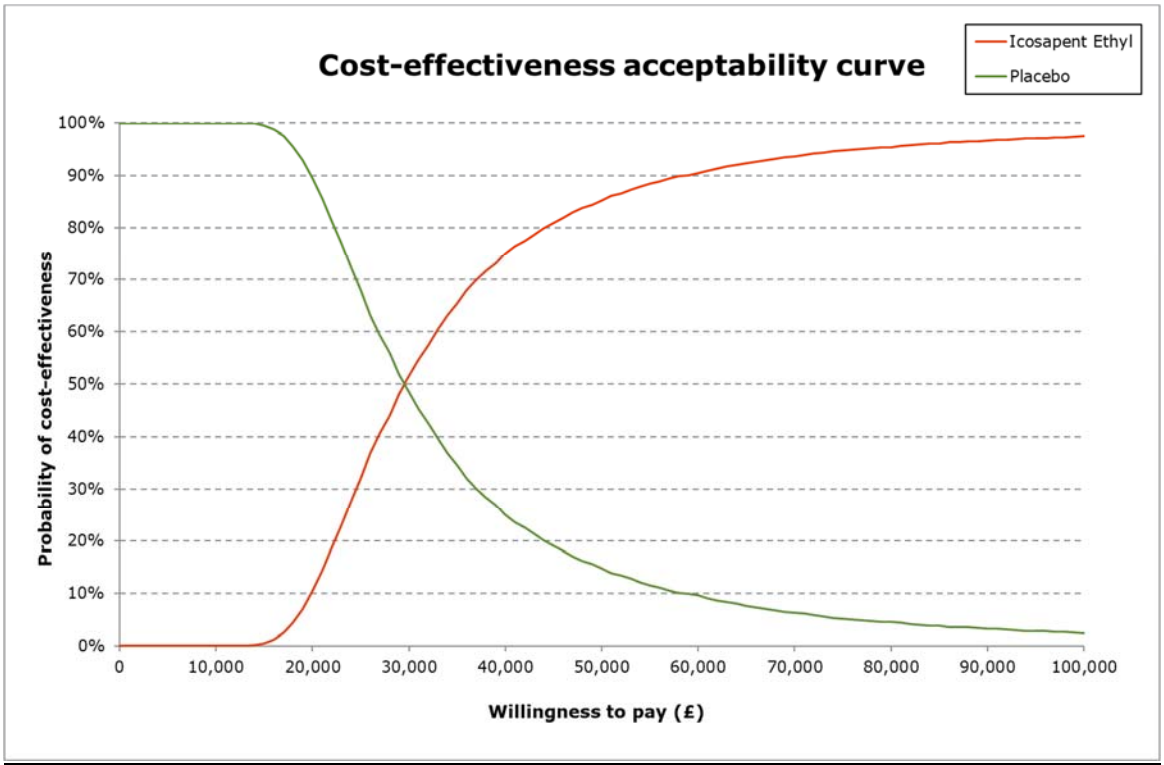
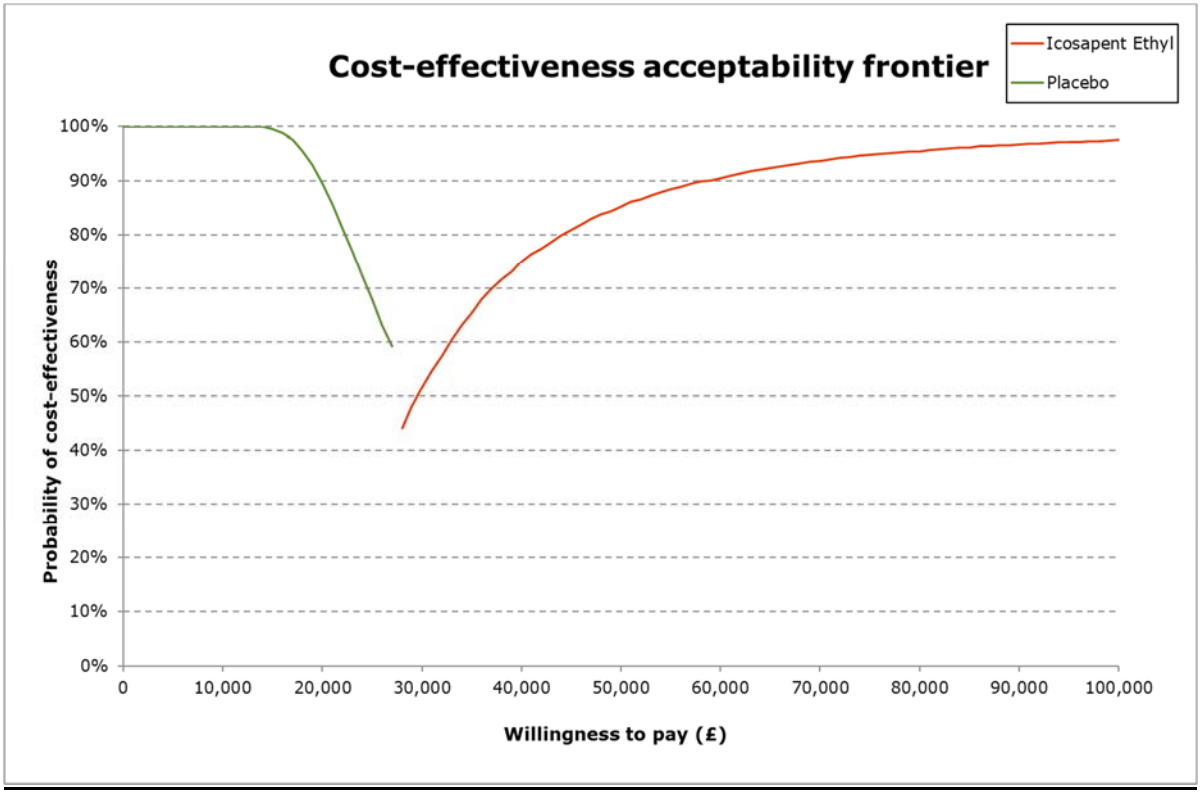


Figure 31. Cost-effectiveness acceptability frontier



Deterministic sensitivity analysis

One-way sensitivity analysis (OWSA) was performed to assess the impact of individual parameters on the model results. OWSA considered upper and lower CIs sourced from literature in the first instance or calculated from the pre-specified probabilistic distributions assigned to each parameter as an alternative. Where the standard error was unavailable to calculate upper and lower CIs, this was assumed to be 10% of the mean value. A tornado diagram is presented in

Figure 32 for Icosapent ethyl versus Placebo to illustrate the level of uncertainty around the ICER. The top 20 most sensitive parameters are presented and the associated results in tabular format for all relevant variables are presented in Table 53.

The OWSA results demonstrated the model was most sensitive to the cost of Icosapent ethyl per cycle.

Figure 32. Tornado diagram of Icosapent ethyl versus placebo

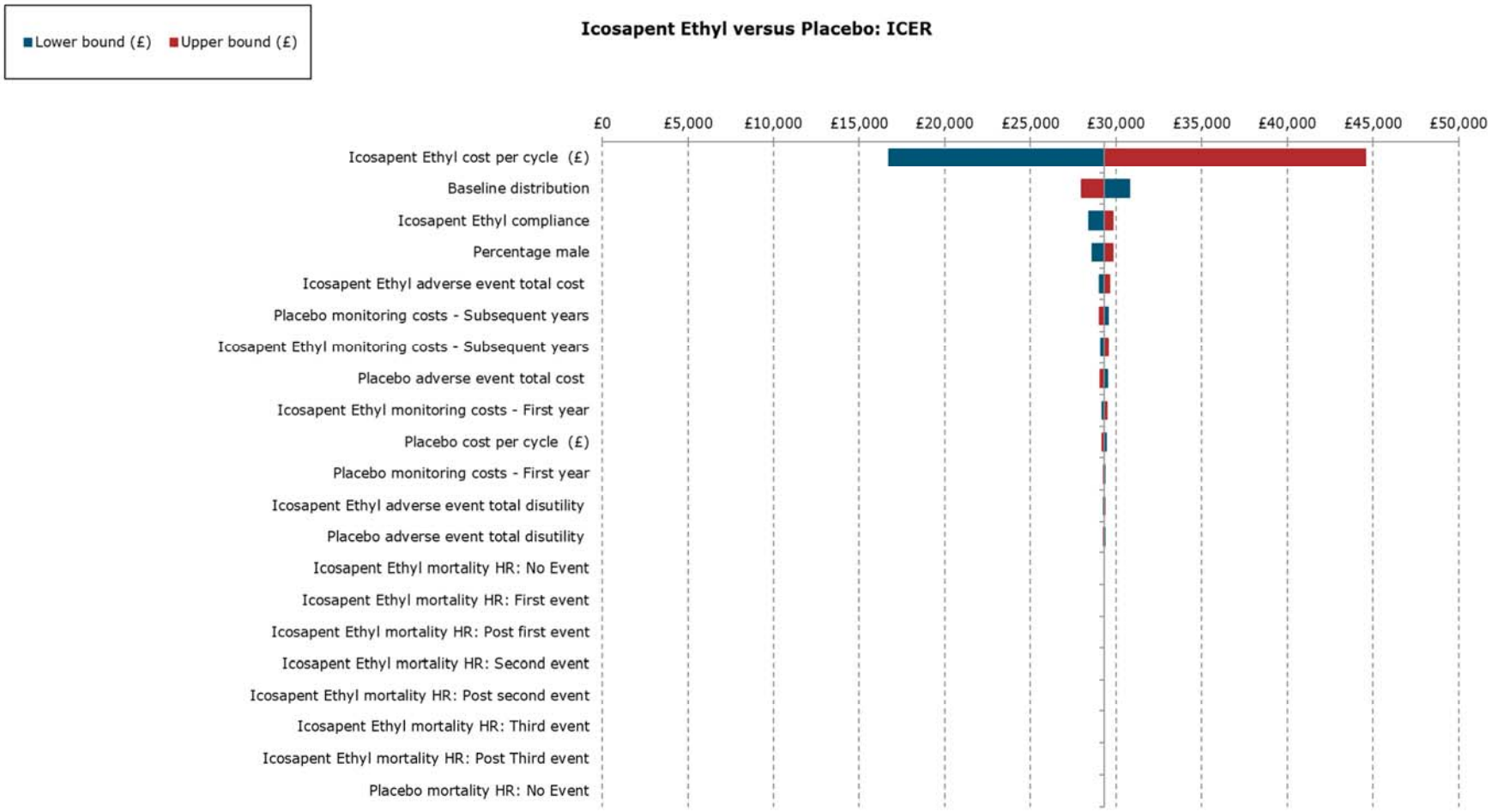


Table 53. OWSA results for Icosapent ethyl versus Placebo

Parameter	Lower bound (£) ICER	Upper bound (£) ICER	Difference (£) ICER
Icosapent ethyl cost per cycle (£)	£16,745	£44,562	£27,817
Baseline distribution	£30,771	£27,968	£2,803
Icosapent ethyl compliance	£28,425	£29,805	£1,380
Percentage male	£28,594	£29,817	£1,223
Icosapent ethyl adverse event total cost	£29,053	£29,619	£566
Placebo monitoring costs - Subsequent years	£29,525	£29,047	£478
Icosapent ethyl monitoring costs - Subsequent years	£29,109	£29,551	£442
Placebo adverse event total cost	£29,492	£29,087	£405
Icosapent ethyl monitoring costs - First year	£29,191	£29,452	£261
Placebo cost per cycle (£)	£29,415	£29,179	£236
Placebo monitoring costs - First year	£29,332	£29,281	£51
Icosapent ethyl adverse event total disutility	£29,308	£29,309	£1
Placebo adverse event total disutility	£29,309	£29,308	£1
Icosapent ethyl mortality HR: No Event	£29,309	£29,309	£0
Icosapent ethyl mortality HR: First event	£29,309	£29,309	£0
Icosapent ethyl mortality HR: Post first event	£29,309	£29,309	£0
Icosapent ethyl mortality HR: Second event	£29,309	£29,309	£0
Icosapent ethyl mortality HR: Post second event	£29,309	£29,309	£0
Icosapent ethyl mortality HR: Third event	£29,309	£29,309	£0
Icosapent ethyl mortality HR: Post Third event	£29,309	£29,309	£0
Placebo mortality HR: No Event	£29,309	£29,309	£0

Abbreviations: HR – Hazard ratio; ICER – Incremental cost-effectiveness ratio.

Scenario analysis

Various scenario analyses were conducted to explore the uncertainty around structural assumptions on the cost and QALY outcomes modelled. (Table 54 and Table 55)

Scenario analysis varying discount rate

A scenario analysis was conducted varying the discount rate, to explore the impact of applying a greater or lesser weight to future costs and benefits. The discount rates explored were: 0% and 5%, relative to a 3.5% discount rate at baseline for both costs and benefits. (Table 54)

Table 54. Scenario analysis varying the discount rate

Discount rate	Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
0%	Placebo	13,995	14.000	9.883	-	-	-	-
	Icosapent ethyl	26,677	14.510	10.468	12,682	0.510	0.586	21,658
3.5% (base case)	Placebo	9,951	10.547	7.522	-	-	-	-
	Icosapent ethyl	20,611	10.846	7.886	10,660	0.299	0.364	29,309
5%	Placebo	8,745	9.483	6.790	-	-	-	-
	Icosapent ethyl	18,725	9.726	7.093	9,980	0.243	0.303	32,990

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; QALYs – Quality-adjusted life years

Scenario analysis varying duration of acute utility application

A scenario analysis was conducted varying the duration of acute utility application, to explore the impact of changing the assumption made with respect to the number of days an individual experiences an acute utility following a CV event. The acute utility durations explored were: 30 and 60 days, relative to the 60-day assumption made in the base case. (Table 55)

Table 55. Scenario analysis varying duration of acute utility application

Acute utility	Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
30 days	Placebo	9,951	10.547	7.524	-	-	-	-
	Icosapent ethyl	20,611	10.846	7.887	10,660	0.299	0.363	29,336
60 days (base case)	Placebo	9,951	10.547	7.522	-	-	-	-
	Icosapent ethyl	20,611	10.846	7.886	10,660	0.299	0.364	29,309
90 days	Placebo	9,951	10.547	7.520	-	-	-	-
	Icosapent ethyl	20,611	10.846	7.884	10,660	0.299	0.364	29,282

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; QALYs – Quality-adjusted life years.

Summary of sensitivity analyses results

The results of sensitivity analyses showed that Icosapent ethyl is cost-effective at a threshold of £30,000/ QALY. The ICER was most sensitive to variation in the cost of Icosapent ethyl however, the OWSA demonstrated that the ICER was in a similar range to the base-case, varying between £27,968 to £30,771, for the other sensitive parameters.

Mean PSA results estimating the incremental costs and QALYs were close to the base-case results demonstrating the robustness of the model. All of the iterations (100%) did fall in the quadrant where Icosapent ethyl is more costly but more effective compared to placebo.

B.3.9 Subgroup analysis

Scenario analysis for different subpopulations

A scenario analysis was conducted for the primary and secondary prevention subgroups to test the sensitivity of model results (Table 56).

Table 56. Scenario analysis varying population

Population	Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Secondary prevention	Placebo	11,371	10.322	7.336	-	-	-	-
	Icosapent ethyl	21,853	10.707	7.791	10,481	0.384	0.456	22,999
Primary prevention	Placebo	6,131	11.119	8.003	-	-	-	-
	Icosapent ethyl	17,628	11.190	8.116	11,497	0.071	0.113	101,828

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; QALYs – Quality-adjusted life years.

The large ICER for the primary prevention cohort is due to the fact that the high-risk primary prevention patients contributed fewer first events to each endpoint compared to secondary prevention patients. This is reflective of the study design requiring enrolment of fewer high-risk primary prevention patients (30% of targeted enrolment) than secondary prevention patients, and is consistent with the overall lower event rate in the primary versus secondary prevention subgroup, leading to larger uncertainty in the cost-effectiveness results within this subgroup.

B.3.10 Validation

Validation of cost-effectiveness analysis

The model has undergone thorough internal and external validation. It was developed internally by a health economist and quality checked by multiple internal health economists. Two UK clinical experts were involved in informing the key model assumptions. All feedback and external ratification went into the final model and this written submission.

B.3.11 Interpretation and conclusions of economic evidence

Over a 36-year time horizon, the ITT population receiving Icosapent ethyl accrued 7.522 QALYs at a cost of £20,611, whilst patients receiving placebo accrued 7.886 QALYs at a cost of £9,951. The resulting ICER in the base case was £29,309 per QALY, which is below the NICE threshold of £30,000 per QALY. Similar ICERs below £30,000 per QALY were found for the secondary prevention cohort.

Probabilistic results were similar to the deterministic ICERs. OWSA found that results were most sensitive to the treatment cost of Icosapent ethyl, baseline distribution and Icosapent ethyl compliance. Scenario analyses were all found to be well below a cost-effectiveness threshold of £30,000 per QALY. As such Icosapent ethyl may be considered a cost-effective use of NHS resources.

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B.5 Appendices

- ID3831_Icosapent ethyl_Appendix C_SmPC
- ID3831_Icosapent ethyl_Appendix D_Clinical SLR
- ID3831_Icosapent ethyl_Appendix E_Subgroup analyses
- ID3831_Icosapent ethyl_Appendix F_Adverse reactions
- ID3831_Icosapent ethyl_Appendix G_Cost effectiveness studies
- ID3831_Icosapent ethyl_Appendix H_HRQoL studies
- ID3831_Icosapent ethyl_Appendix I_Cost and resource studies
- ID3831_Icosapent ethyl_Appendix J_Clinical outcomes and disaggregated results

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Icosapent ethyl with statin therapy for reducing the risk of cardiovascular events in adults with elevated triglycerides [ID3831]

Clarification questions

August 2021

File name	Version	Contains confidential information	Date
ID3831 icosapent ethyl ERG Clarification letter to PM_comments_v1.0_20Aug21_[redacted]	1.0	Yes	20/08/21

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Literature searches

A1. Priority question. Regarding appendix D: Identification, selection and synthesis of clinical evidence, Table 1. The Evidence Review Group (ERG) is currently unable to fully critique these searches due to the lack of hits per line for each strategy.

Please provide full search strategies in their original format including hits per line.

Company response

Please find below the original search strategies that were conducted on the Ovid platform for both Medline and Embase databases. The number of hits per line are presented in Table 1 - Table 3. Table 3 presents the search strategy that was executed in PubMed.

Table 1. Search strategies performed in Medline for the clinical SLR

#	Query (MEDLINE)	Results from 9th Dec 2020
1	exp Hydroxymethylglutaryl CoA Reductase Inhibitors/	42,741
2	(statin or statins).tw.	41,199
3	(HMGCoA adj reductase).tw.	268

4	1 or 2 or 3	59,531
5	exp Cardiovascular Diseases/	2,512,832
6	cardiovascular.tw.	472,274
7	heart disease$.tw.	173,414
8	exp Hypertriglyceridemia/	7,268
9	Triglycerides/ or Dyslipidemias/	88,673
10	Hypertriglycerid$.tw.	14,806
11	5 or 6 or 7 or 8 or 9 or 10	2,836,091
12	diabetes mellitus/	123,453
13	exp diabetes mellitus, type 2/	144,586
14	12 or 13	263,830
15	11 or 14	3,015,444
16	4 and 15	35,362
17	Eicosapentaenoic Acid/	6,563
18	(icosapent ethyl or Vascepa or triglyceride* lowering drug*).mp.	246
19	fenofibrate/ or hypolipidemic agents/	16,678
20	(fenofibric acid* or fenofibrate* or tricor or triglide or antara or trilipix or lipofen or fibricor or fenoglide or lipanthyl or apteor or fenolip or lipcor or lipsin or docfenofi or fenofibra*t or fenogal or liperial or lipidil or lipohexal or fenofix or febrira or lipirex or fenobeta or durafenat or elipsia or xafenor or liparison or secalip or cencaran or fegenor or fenathol or fenocor or fenox or genothyl or livesan or panlipal or substichol or lipsin or fulcro or tilene or nolipax or lipofene or fenolibs or fulcrosupra or funogeal or fenardin or grofibrat or catalip or fenose or lipivim or lipofib or lipantil).ab,ti,kw.	3,746
21	Bezafibrates/	0
22	17 or 18 or 19 or 20 or 21	24,416
23	Stroke/ or Myocardial Infarction/	274,747
24	Coronary Disease/ or Coronary Artery Disease/ or Coronary Artery Bypass/ or Myocardial Revascularization/	234,798
25	Angina, Unstable/	9,192
26	Myocardial Ischemia/	39,830
27	(major adverse cardiac event* or MACE or MACEs).ab,ti.	12,298
28	(cardiovascular death or cardiovascular mortality).ab,ti.	20,779
29	23 or 24 or 25 or 26 or 27 or 28	529,130
30	16 and 22 and 29	1,090
31	Randomized controlled trial.pt.	539,556
32	Controlled clinical trial.pt.	94,320
33	Randomized.ab.	529,280
34	Placebo.ab.	220,248
35	Drug therapy.fs.	2,357,130
36	Randomly.ab.	363,058
37	Trial.ab.	562,602
38	Groups.ab.	2,229,449

39	31 or 32 or 33 or 34 or 35 or 36 or 37 or 38	5,081,025
40	exp animals/ not humans.sh.	4,870,600
41	39 not 40	4,418,305
42	30 and 41	877
43	limit 42 to English language	745

Table 2. Search strategies performed in Embase for the clinical SLR

#	Query (Embase)	Results from 9th Dec 2020
1	exp hydroxymethylglutaryl coenzyme A reductase inhibitor/	166,100
2	(statin or statins).tw.	67,960
3	HMG CoA*.tw.	11,347
4	or/1-3	179,014
5	exp cardiovascular disease/	4,313,560
6	(cardio* or cardia* or heart*).tw.	2,453,277
7	exp hypertriglyceridemia/	28,562
8	triglycerid*.tw.	168,287
9	Dyslipidemia/ or hypertriglycerid?emia*.tw.	96,245
10	or/5-9	5,252,437
11	4 and 10	121,836
12	Diabetes mellitus/	586,537
13	Non insulin dependent diabetes mellitus/	280,041
14	12 or 13	824,167
15	10 or 14	5,641,156
16	4 and 15	125,610
17	icosapentaenoic acid ethyl ester/	832
18	(icosapent ethyl or vascepa).mp.	352
19	antilipemic agent/ or fenofibrate/ or bezafibrate/	42,318
20	(fenofibric acid* or fenofibrate* or tricor or triglide or antara or trilipix or lipofen or fibricor or fenoglide or lipanthyl or apteor or fenolip or lipcor or lipsin or docfenofi or fenofibra*t or fenogal or liperial or lipidil or lipohexal or fenofix or febrira or lipirex or fenobeta or durafenat or elipsia or xafenor or liparison or secalip or cencaran or fegenor or fenathol or fenocor or fenox or genothyl or livesan or panlipal or substichol or lipsin or fulcro or tilene or nolipax or lipofene or fenolibs or fulcrosupra or funogeal or fenardin or grofibrat or catalip or fenose or lipivim or lipofib or lipantil).ab,ti,kw.	5,474
21	fenofibrate plus simvastatin/ or fenofibrate plus pravastatin/	54
22	17 or 18 or 19 or 20 or 21	43,664
23	cerebrovascular accident/	228,585
24	heart infarction/	278,471
25	coronary artery disease/	202,739
26	(unstable angina or myocardial infarction or MI).ab,ti.	325,745

27	major adverse cardiac event/	9,324
28	(MACE* or cardiovascular death or cardiovascular mortality).ab,ti.	65,616
29	23 or 24 or 25 or 26 or 27 or 28	812,753
30	16 and 22 and 29	4,502
31	Crossover procedure/	67,721
32	Double blind procedure/	186,289
33	Single blind procedure/	43,338
34	Randomized controlled trial/	669,763
35	Crossover$.ti,ab,ot.	81,091
36	Cross over$.ti,ab,ot.	34,478
37	Placebo$.ti,ab,ot.	329,387
38	(doubl$ adj blind$).ti,ab,ot.	222,077
39	Allocat$.ti,ab,ot.	170,348
40	Random$.ti,ab,ot.	1,691,542
41	Trial$.ti.	441,375
42	31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41	2,199,040
43	30 and 42	1,000
44	limit 43 to English language	902

Table 3. Search strategies performed in PubMed for the clinical SLR

#	Query (PubMed)	Results from 9th Dec 2020
1	(((((((((Hydroxymethylglutaryl CoA Reductase Inhibitors) OR (statin)) OR (statins)) OR (HMGCoA)) OR (HMGCoA reductase)) AND (((((Hydroxymethylglutaryl CoA Reductase Inhibitors) OR (statin)) OR (statins)) OR (HMGCoA)) OR (HMGCoA reductase))) AND ((cardiovascular disease) OR (hypertriglyceridemia))) AND (((((((eicosapentaenoic acid) OR (icosapent ethyl)) OR (vascepa)) OR (triglyceride lowering agent)) OR (triglyceride lowering drug)) OR (fenofibrate))) AND (((((((((stroke) OR (myocardial infarction)) OR (coronary disease)) OR (coronary revascularization)) OR (unstable angina)) OR (major adverse cardiac event)) OR (MACE)) OR (cardiovascular death)) OR (cardiovascular mortality))) AND ((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti] NOT (animals(8) NOT humans (8)))) Filters: Publication date from 2019/01/01 to 2020/12/09	20

A2. Priority question. In Table 1 (Appendix G: Economic systematic literature review) the first strategy reports a search of Medline via Embase.

Please confirm that by this you are referring to a search of Embase and the Medline content within it, rather than a multifile search of the separate Embase and Medline databases at the same time.

Company response

We can confirm that this refers to the economic SLR, where a search of Embase and the Medline content within it was conducted, and not a multifile search of the separate databases at the same time.

A3. Please provide the date range for both the Medline and Embase searches in the clinical effectiveness section.

Company response

No date restriction was applied for the searches in both Medline and Embase. Therefore, the searches spanned from databases' inception to the date of search (i.e., 9th December 2020).

A4. Please confirm the host for the Medline, Embase searches. Section D1.1.2. states that this was via Embase.com but the syntax appears to be that of Ovid.

Company response

This is a transcription error; we confirm that the host for Medline and Embase searches as part of the clinical systematic literature review was the Ovid platform and not the Embase.com platform.

A5. Please explain the inclusion of terms for fenofibrate, hypolipidemic agents, and bezafibrates as these appear to be outside the scope.

Company response

The clinical systematic literature review was conducted for several markets, not just for the UK alone. For the UK clinical setting, therapies such as fenofibrates, hypolipidemic agents, and bezafibrates are not applicable, and so are not considered

appropriate. Any publications associated with these were therefore excluded when assessing just the UK market for the NICE submission.

A6. In the Embase strategy, there appears to be error in line 15. The facets for cardiovascular disease and diabetes appear to have combined using AND rather than OR as in the Medline search:

5	exp cardiovascular disease/
6	(cardio* or cardia* or heart*).tw.
7	exp hypertriglyceridemia/
8	triglycerid*.tw.
9	Dyslipidemia/ or hypertriglycerid?emia*.tw.
10	Or/ 5-9
11	4 and 10
12	Diabetes mellitus/
13	Non insulin dependent diabetes mellitus/
14	12 or 13
15	10 and 14
16	4 and 15

Please correct and rerun this search to ensure that no relevant references have been missed.

Company response

Thank you for highlighting this transcription error. After double checking the search strategies that were executed in Medline as of 9th December 2020, line 15 was "10 **or** 14" and not "10 and 14". Please see the Table 2 presented above for more details. Therefore, the search did not need to be rerun.

A7. Regarding the Cochrane Central Register of Controlled Trials (CENTRAL) search, please:

a. Provide the full original strategy as run including host, date searched and hits per line.

b. Explain the rationale behind only searching CENTRAL for the years 2019-2020.

Company response

a. The host for the search executed in CENTRAL was the Cochrane Library: https://www.cochranelibrary.com/central.

The CENTRAL database was only used to supplement the original search strategies that were executed in the two electronic bibliographical databases (Medline and Embase). Two additional limits were added to the search strategy:

- Publication year from 2019 to 2020
- Trials only

Therefore, as indicated in the submitted report, the following keywords were combined with the additional limits applied:

1. Icosapent ethyl (All text) (45 trials)
2. Hypertriglyceridemia (Title Abstract Keyword) (293 trials)
3. Cardiovascular disease (Title Abstract Keyword) (7,306 trials)
4. 1 AND 2 AND 3 (21 trials)

With this strategy, there were 21 trials of potential interest that were additionally reviewed as part of the pragmatic searches.

b. The rationale for only searching CENTRAL for the years 2019-2020 was to capture all recent randomised clinical trials of potential interest that would not have been captured by the search strategies developed in Medline and Embase. We expected recent publications to not have been indexed and/or published yet in Medline or Embase. Therefore, we decided to search for clinical trials presented on the CENTRAL platform for the two years preceding the date of the search.

A8. Please provide more information, and justify, if any additional searches were run to identify papers on adverse events.

Company response

No additional searches were run to identify papers on adverse events. However, in addition to Medline, Embase and the CENTRAL database, additional searches were performed by hand searching the reference lists of the retrieved publications. Also, the reference list of published systematic literature reviews or network meta-analyses that were identified throughout the search were reviewed manually to ensure comprehensiveness of the search.

A9. Please confirm the database host and date span searched for the Embase strategy in the cost effectiveness section.

Company response

The database host searched for the Embase strategy in the cost-effectiveness section was: https://www.embase.com/#advancedSearch/default

The date span included all publications up to and including 8th January 2021.

A10. The ERG has some concerns regarding some limitations of searches reported in section G1.3 of the company submission (CS).

a. There appears to be a disparity between the population as described in the scope in Table 5 “Adult patients with dyslipidaemia and at risk of cardiovascular events” and the search facet for population in the Embase search (Table 1) which appears to be looking for dyslipidemia in CVD : ('cardiovascular diseases' OR 'cardiovascular disease' OR 'heart disease'/de OR 'cvd' OR 'coronary adj2 disease') AND (('elevated':ti,ab OR 'high':ti,ab OR 'increased':ti,ab) AND (triglyceride*:ti,ab OR 'tg':ti,ab) OR 'hypertriglycerid?emia*':ti,ab OR 'dyslipidemia':ti,ab) This combination excludes “adults on statin therapy with elevated triglycerides who are at high risk of cardiovascular events due to diabetes, and at least 1 other cardiovascular risk factor” as described in the National Institute for Health and Care Excellence (NICE) final scope reported in the clinical effectiveness section.

b. This facet for dyslipidemia AND CVD is further limited by the addition of an interventions facet, resulting in the following search structure:

(CVD/heart disease AND elevated triglyceride/ hypertriglycerid?emia/dyslipidemia) AND (Statins or icosapent ethyl) AND (Economics OR HRQoL OR Resource Use filter)

This combining of the population facet with Statins is also continued in some of the additional searches such as the EQ-5D (EuroQol-5 dimensions) website and ScHARRHUD (although these searches search for either cardiovascular disease (CVD) or dyslipidemia). Using ScHARRHUD as an example where the company submission (CS) found 0 hits, a simple search for CVD or Dyslipidemia returns 18 hits.

Search from	Search strategy	Search results
CS	*('cvd' or 'cardiovascular disease' or 'dyslipidaemia' or 'hypertriglyceridemia' or 'elevated triglyceride') and ('statin' or 'omega-3 fatty acid' or 'cholesteryl ester transfer protein inhibitor' or 'pcsk9' or 'icosapent ethyl')*	0
ERG	(cvd or cardiovascular disease or dyslipidaemia or hypertriglyceridemia or elevated triglyceride)	18

The ERG is concerned that the restrictiveness of these searches may have adversely affected the recall of results.

Please rerun the affected searches, provide the relevant information on these searches and ensure that no relevant references have been missed.

Company response

a. The population was kept broad in the inclusion/exclusion criteria tables to make sure that enough references were retrieved in the systematic literature review across the review questions. It was a concern that more restrictive wording, (e.g., similar to that suggested by the ERG: 'adults on statin therapy with elevated triglycerides who are at high risk of cardiovascular events due to diabetes, and at least 1 other cardiovascular risk factor') would have retrieved very little evidence due to the specificity of the inclusion/exclusion criteria. The two searches are aligned, however a

broader population was included in the inclusion/exclusion criteria to capture as much evidence as possible in the initial database searching stage with a narrower, more specific population being captured in the search terms themselves (as well as the grey literature, see answer part b).

b. For the grey literature (targeted) searching, during the initial search, a broader population was considered, as is presented by the ERG here, however, due to the vast amount of hits that return for just 'cardiovascular disease' alone, it was decided to combine the disease search term with the interventions to restrict the returned hits whilst retaining all literature containing the specified population of interest. Restricting this search strategy allowed a focus to capture only relevant information from websites that was not picked up by database searching.

Necessary and relevant actions were taken to ensure that no relevant literature was missed. This included searching of the NICE website and relevant HTA appraisals, as well as searching: the CEA-registry, RePEc website, EQ-5D website, ScHARRHUD, ISPOR conference proceedings, ESC Congress conferences, and the ICER website. Furthermore, following the database searching and the grey literature search, it was noted that there were no applicable UK cost and resource use specific papers applicable to this submission, therefore EMBASE was searched again but using specific search terms focusing on UK-based costs.

Section B: Clarification on effectiveness data

Decision problem and treatment pathway

B1. Priority question. The population specified in Table 1 of the CS (The decision problem) aligns with the NICE scope, however, on page 27 of the CS, the company stated:

"Vazkepa is anticipated to be offered to patients with high* cardiovascular (*CV) risk (defined as either established CVD or diabetes and at least one other CV risk factor), who are on a stable dose of statin therapy with controlled* low density lipoprotein-cholesterol *(LDL-C) levels but elevated* triglycerides *(TGs)."

Moreover, based on Figures 3 and 4, Vazkepa will be offered to adults ≥50 years of age (diabetes with another CV risk factor) or ≥45 years of age (established CVD).

a. **Please provide the sources of information for the age cut-off, i.e. ≥50 years of age (diabetes with another CV risk factor) or ≥45 years of age (established CVD) and comment if the Figures 3 and 4 reflect the current United Kingdom (UK) clinical practice.**

b. **Please consider revising the decision problem and include the information on the narrower population (i.e. adults ≥50 years of age [diabetes with another CV risk factor] or ≥45 years of age [established CVD]) and additional restrictions (i.e. controlled LDL-C levels).**

c. **Please comment on the likely consequences of including a narrower population than specified in the decision problem (Table 1 of the CS).**

Company response

General comments: We acknowledge the discrepancies surrounding the population between the decision problem and other areas of the CS. By specifying the inclusion criteria (such as the age) of the REDUCE-IT study to better describe the population eligible to icosapent ethyl, we introduced confusing wording.

We would therefore like to correct the wording in the above quoted statement to align with the population described in the decision problem, which is based on the full licensed indication of icosapent ethyl: '*adults on statin therapy with elevated triglycerides who are at high risk of cardiovascular events due to either established CVD, or diabetes and at least one other cardiovascular risk factor.*'

The corrected figures 3 and 4 in the CS are presented here as Figure 1 and Figure 2. They are aligned with the decision problem and with the expected future clinical practice in the UK, as per the input received from two UK clinical experts (see question C17. c).

Figure 1. Anticipated positioning of icosapent ethyl in patients with diabetes and at least 1 other CV risk factor (high risk primary prevention) – this is the updated Figure 3 in the CS.

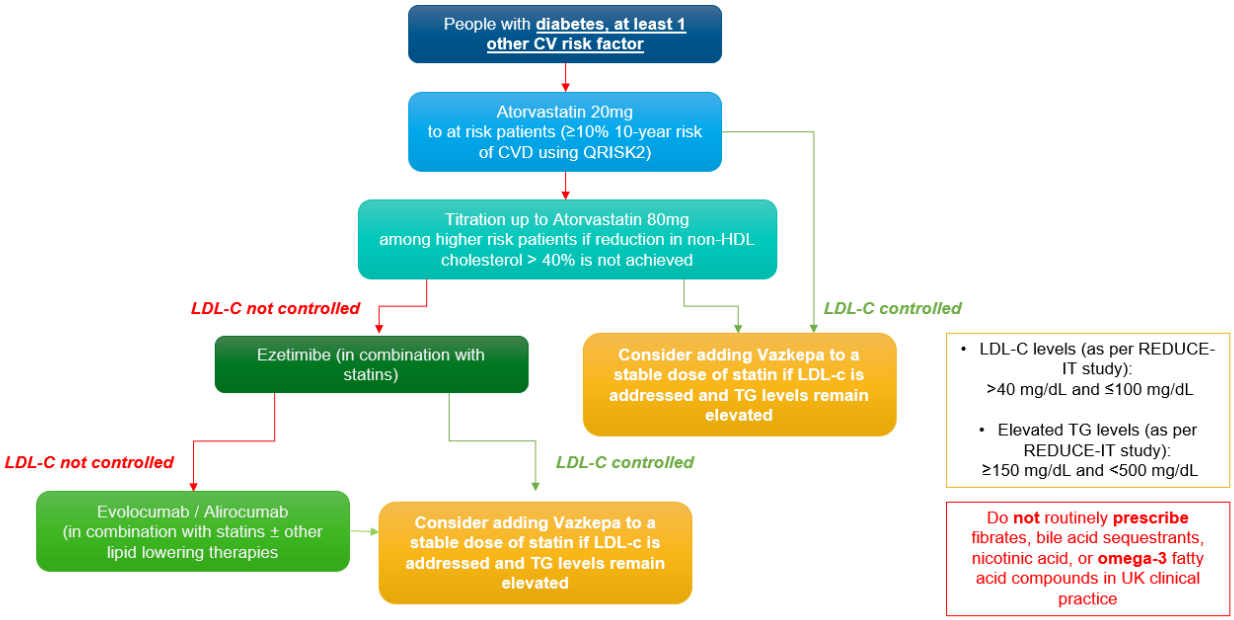
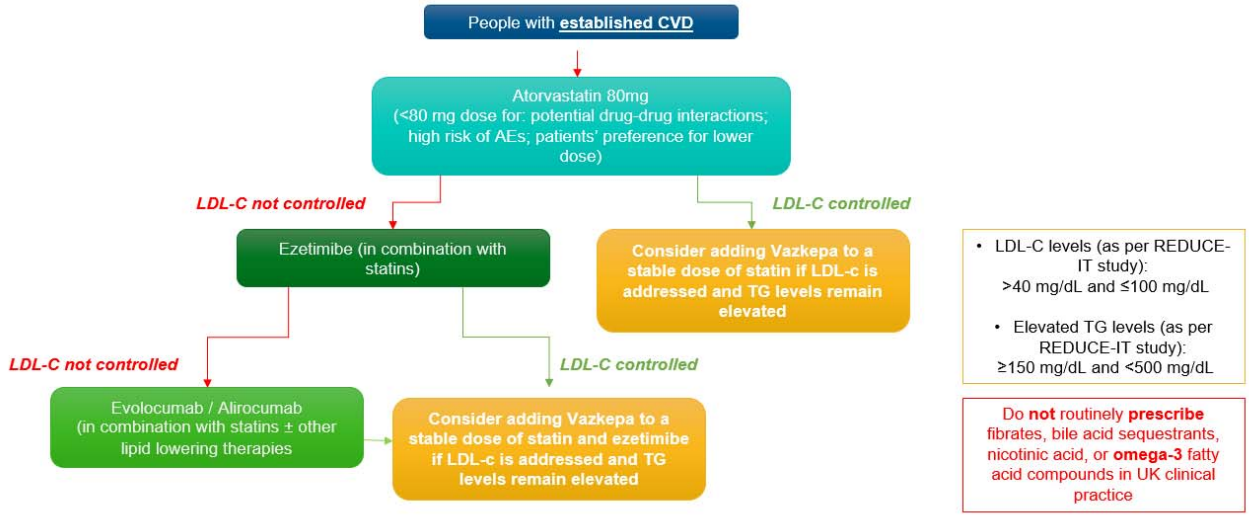


Figure 2. Anticipated positioning of icosapent ethyl in patients with established CVD (secondary prevention) - this is the updated Figure 4 in the CS.



B2. Priority question. The NICE scope defines the intervention as '*icosapent ethyl in combination with a statin*' whereas the decision problem and treatment pathway (page 28 and Figures 3 and 4 of the CS) are more specific, referring to

icosapent ethyl being used in combination with a stable dose of statin. The REDUCE-IT trial (Table 4 of the CS) defines stable statin therapy as '….*the same daily dose of the same statin for at least 28 days before the lipid qualification measurements (TG and LDL-C).*'

a. **Please define "the stable dose of statin" and how this relates to NICE clinical guideline (CG) 181.**

b. **Considering the aforementioned definition, please comment if the decision problem aligns with the NICE scope in Table 1. If the information does not align, please justify.**

Company response

a. Patients included in the REDUCE-IT trial were required to be on stable statin therapy (with or without ezetimibe) for at least 28 days prior to the LDL-C and TG qualifying measurements. Stable statin therapy was defined as the same daily dose of the same statin for at least 28 days before lipid qualification. This is a standard design requirement employed across clinical studies that include lipid qualification, as 28 days of statin therapy allows for essentially all statin-induced lipid-lowering efficacy to be reached, while also minimising the window between qualifying to randomisation visits for patients and investigative sites.

NICE clinical guidelines technically differ in that they mirror more common clinical practice and the timing of return patient visits to their clinicians; three months allows for fuller attainment of the potential impact from multiple medication or lifestyle modifications. It is common for study inclusion criteria and clinical practice to differ slightly, but these differences do not substantially impact the overarching goal of allowing sufficient time to adequately measure the impact of a newly initiated or modified statin therapy.

Furthermore, for both patients with established cardiovascular disease or at high risk for cardiovascular events due to diabetes and other risk factors, the NICE guidelines recommend statin therapy as a first line option, and further recommend refinement of statin therapy intensity based on a patient's statin response and underlying risk. These recommendations are well-aligned with the REDUCE-IT lipid inclusion requirements being based on stable statin therapy.

b. We consider the definition of the statin dosing to be aligned with the NICE scope and the decision problem mentioning adults on statins.

B3. Priority question. Comparator details appear to differ between the NICE scope and the decision problem: '*Established clinical management (including high and low-intensity statins)*' and '*Best supportive care, defined as a stable dose of statin therapy*', respectively.

Please clarify whether these two definitions are referring to the same comparator regimen.

Company response

We can confirm that the two definitions above are referring to the same comparator regimen. This is because patients receiving a 'stable dose of statin therapy' would receive statins at a high-, moderate- or low-dose intensity depending on their needs.

B4. Priority question. Some discrepancies in the outcomes were identified between the scope and the decision problem in Table 1 of the CS:

a. **The scope lists '*unstable angina*' (among the cardiovascular event outcomes) and '*hospital admissions*' as separate outcomes but the decision problem mentions '*Hospitalisation for unstable angina*' (and no other hospital admissions). Please confirm which outcomes were used for the systematic literature review (SLR).**

b. **Please clarify whether outcomes (1) '*Fatal or nonfatal myocardial infarction*' and (2) '*Fatal or nonfatal stroke*' are a composite outcome or two separate outcomes. For both, please explain which outcomes were used for the SLR.**

Company response

The systematic literature review considered 'unstable angina' and 'hospital admissions' as separate outcomes, in order to identify as many relevant publications as possible without being too restrictive. This was to ensure no important publications were missed. However, 'hospitalisation for unstable angina' was considered as part of

the decision problem as this outcome was collected in the REDUCE-IT trial, and consequently was considered in refinement of the identified literature and the submission and economic models to inform the evidence base for icosapent ethyl.

The outcome 'Fatal or nonfatal myocardial infarction (including silent myocardial infarction)' is a composite outcome. Similarly, the outcome 'Fatal or nonfatal stroke' is a composite outcome, separate from the composite myocardial infarction outcome. As before, the systematic literature review considered the general terms 'myocardial infarction' and 'stroke' in order to identify as many relevant publications as possible without being too restrictive. This was to ensure no important publications were missed. However as described above for unstable angina, the outcomes 'Fatal or nonfatal myocardial infarction (including silent myocardial infarction)' and 'Fatal or nonfatal stroke' were considered as part of the decision problem as they were outcomes collected in the REDUCE-IT trial, and consequently were considered in refinement of the identified literature and in the submission and economic models to inform the evidence base for icosapent ethyl.

B5. Section B.1.3.4 of the CS (page 26) states that *"moderate- to high-intensity statins are used in the vast majority of patients in UK clinical practice, which aligns with the dose intensity of statins used in the REDUCE-IT study."*

a. Please provide the actual numbers of patients receiving low, moderate and high-intensity statins within the UK.

b. Please compare the information from the point above to the patient numbers in the REDUCE-IT trial.

Company response

a. The actual number of patients receiving low-, moderate- and high-intensity statins within the UK can be taken from the DA VINCI study, which is an 18 country, cross-sectional, observational study of patients prescribed lipid lowering therapies for primary or secondary prevention in primary or secondary care across Europe. The leading author of this study (who was also used to validate model assumptions as part of the submission – see question C17.c) highlighted that the estimates for the number of patients receiving statins from the DA VINCI study are reflective of those observed in current UK clinical

practice. The table below summarises the number of patients receiving low-, moderate- or high-intensity statins within the UK as per the DA VINCI study:

Statin intensity	Percentage of patients receiving the statin intensity (overall population of DA VINCI)
Low-intensity statin	4%
Moderate-intensity statin	55%
High-intensity statin	32%

b. In the REDUCE-IT trial, the statin intensity categories were defined as in the American College of Cardiology/American Heart Association cholesterol guidelines and the patient's 10-year CV risk score (which aligns with the regime as recommended in NICE CG181 and reflects commonly used statins in UK clinical practice). As such, the estimates for the percentage of patients receiving each of the statin intensities in REDUCE-IT were very similar to those from the DA VINCI study (see B5. a), and therefore can be considered comparable (i.e., the percentages of patients receiving each statin intensity from REDUCE-IT aligns with and reflects those observed in UK clinical practice):

Statin intensity	Percentage of patients receiving the statin intensity (overall population of REDUCE-IT)
Low-intensity statin	6.4%
Moderate-intensity statin	62.7%
High-intensity statin	30.9%

Systematic literature review

B6. Priority question. Figure 1 and Table 4 of appendix D list two eligible studies; REDUCE-IT and JELIS. However, JELIS is not covered by the CS. Based on the included reference from the Appendix D, JELIS compares eicosapentaenoic acid (EPA) with statins or statin alone (controls). The summary of product characteristics (SmPC) for Vazkepa states that *"icosapent ethyl is a stable ethyl ester of the omega-3 fatty acid, EPA"*.

Please explain why the trial was included in the eligible studies and why it was excluded from the CS. If needed, please provide all relevant results for JELIS.

Company response

The Japan EPA Lipid Intervention Study (JELIS) is a prospective, randomised, open-label, blinded endpoint evaluation (PROBE design) study. It is the only CV outcome study beyond REDUCE-IT identified by the literature search that administered an EPA-only therapy (not icosapent ethyl/Vazkepa) in statin-treated patients and therefore is relevant for inclusion in the literature search findings. The JELIS study reported a 19% relative risk reduction in major coronary events with EPA therapy versus control (Yokoyama 2007), however, both the population included in the trial and the dose of EPA used in the trial are different to those included in the licensed indication of icosapent ethyl.

JELIS enrolled 18,645 Japanese patients with statin-naïve hypercholesterolemia and without any TG inclusion requirement, who were randomised to low-intensity statin regimens with or without ethyl EPA. As such, the population included is different to the licensed population for icosapent ethyl, which was based on a global study that restricted enrolment to patients already on statin therapy with persistently elevated TGs. In addition, JELIS patients were randomly assigned to receive either 1.8 g/day ethyl EPA with statin (EPA group; n=9326) or statin only (controls; n=9319). Therefore, the dose received by patients in the JELIS trial is different to the licensed dose for icosapent ethyl (two 998 mg capsules twice daily).

Therefore, while JELIS is relevant for reporting within the literature search results, the study design is substantively different enough from the indicated population for

Icosapent ethyl, that JELIS was not included in the modelling efforts (see also the response to question B8).

B7. Section D.1.1.4 of the CS provides some information regarding the inclusion and exclusion criteria for SLR.

a. Please provide the inclusion and exclusion criteria in the table with separate information for each part of the PICO (population, intervention, comparator(s), outcome(s)).

b. Please justify the reasons for any exclusion criteria listed (e.g. cross-over trials and conference proceedings, limit to English language, comparison between "*Vazkepa and current treatment options to a statin*").

c. The criteria for the population of interest included the ranges for TGs and LDL-C levels. Please justify why the ranges were included and comment if they are used in the UK clinical practice, e.g. by providing supporting evidence.

d. Inclusion criteria stated that *"studies comparing Vazkepa as a monotherapy or combination therapy"*.

   1) Please specify the intervention and comment if the intervention aligns with the NICE scope and the decision problem.

   2) Please comment on why the company searched for Vazkepa used as a monotherapy when the scope and the marketing authorisation suggests that icosapent ethyl should only be used in conjunction with a statin (therefore monotherapy does not seem appropriate).

   3) Please include more information about what medications were allowed in "combination therapy".

e. Please provide information about the comparator of interest and comment if the comparator aligns with the NICE scope and the decision problem.

f. Please clarify if any observational studies were considered and if not, please justify.

Company response

a. Please find below Table 4 presenting the inclusion and exclusion criteria along with the PICO framework for the present systematic literature review.

Table 4. Eligibility criteria used in the search strategy for the clinical SLR

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Adult men and women with established CVD, or with DM and at least one other CVD risk factor, who had fasting LDL cholesterol ranging from >40 mg/dL and ≤100 mg/dL and triglyceride level of 135 to 499 mg/dL (1.52 to 5.63 mmol/L) despite stable statin therapy for at least 4 weeks.	-
Intervention	Comparative studies involving Icosapent ethyl (received as an adjunctive therapy to statin)	- Studies comparing Icosapent ethyl (in monotherapy – i.e., not as an adjunctive therapy to statin) to a statin
Comparators	None or standard of care	-
Outcomes	- Studies reporting at least one of the following efficacy outcomes: cardiovascular death, non-fatal stroke, non-fatal MI, coronary	- Clinical trials only reporting laboratory outcomes such as change in the level of triglycerides or

Clinical effectiveness	Inclusion criteria	Exclusion criteria
	revascularization, unstable angina (considered separately or as a composite outcome – i.e., MACE-5). - Studies comparing adverse events of interest (i.e., peripheral oedema, AF, anaemia, serious bleeding, constipation, myalgia, rhabdomyolysis) between the two groups of treatments (intervention group versus comparator)	cholesterol (without any clinical endpoints)
Study design	Phase 3 clinical trials	- Clinical trials with a cross-over design - Protocol of clinical trials, without results reported - Ongoing trials, without available results - Format of publication: conference proceedings
Language restriction	Publications written in English	Publications written in any other language

b. The following exclusion criteria were considered for the following reasons:

- *Cross-over trials:* Cross-over trials were considered as an inappropriate study design in the current clinical context since the clinical outcomes of interest were neither temporary nor reversible. More specifically, because of the risk of carrying over the effect of the first intervention period to the subsequent period and the irreversible nature of the clinical outcomes of interest (i.e., major adverse cardiac events), a cross-over trial design was considered inappropriate.

- *Conference proceedings:* Conference proceedings were excluded due to the limited information presented in this brief format. Therefore, summarising and/or appraising the methods used as well as the risk of bias of studies reported in abstracts was considered inappropriate.

- *English language:* The systematic review was limited to publications written in English due to the limited linguistic capacity of the reviewers who performed the search.

- *Icosapent ethyl and current treatment options to a statin:* The objective of this exclusion criteria was to exclude clinical trials comparing icosapent ethyl (in monotherapy) to a statin. Therefore, we suggest re-wording the exclusion criteria as “clinical trials comparing icosapent ethyl (in monotherapy) to a statin” (as presented in Table 4). The justification of this criterion was that we were interested in the population of patients currently receiving a statin. Therefore, clinical trials aiming to compare the intervention of interest (i.e., icosapent ethyl) to a statin were considered out of scope.

- *Clinical trials only reporting laboratory outcomes:* The objective of this criterion was to include only clinical outcomes, and to consider studies reporting laboratory outcomes to be outside the scope. The rationale for this decision was that we did not want to base our assessment of efficacy on intermediate measures, which may not have proven clinical significance. The lack of connection between biomarker changes and clinical outcomes with icosapent ethyl therapy has been supported by REDUCE-IT analyses.

- *Protocol of clinical trials without results reported/ongoing trials without available results:* The objective of these two exclusion criteria was to limit the scope of

the review to publications presenting results. However, the published protocols of clinical trials of potential interest (when available) could be reviewed to complement and/or confirm information, in particular information related to the methods.

c. The NICE guidelines do not state a target for triglyceride levels, though they suggest that specialist advice should be sought if triglyceride concentrations remain above 10 mmol/L. Diabetes UK states that treatment for high triglyceride levels should consider other cholesterol levels and whether triglyceride levels are consistently too high. Diabetes UK advises fasting triglyceride levels should be below 1.7 mmol/L, and HEART UK experts state that non-fasting triglyceride level should be below 2.3 mmol/L. Given the lack of relevant treatment guidance in the UK, other guidelines might be referenced by clinicians. The 2019 ESC/EAS guidelines without defining a goal stated that triglyceride levels <1.7 mmol/L (<150 mg/dL) indicates lower risk and higher levels indicate a need to look for other risk factors. The ranges for TGs and LDL-C levels were specified as a criterion for the population to better reflect the label population described in the European Medicines Agency (EMA) summary of product characteristics (SmPC) and to mimic the population that was studied in the REDUCE-IT trial. These criteria were pre-defined in the systematic literature review protocol that was developed before conducting the search.

d. 1) The intervention of interest was icosapent ethyl, used as an adjunctive treatment to statin(s), which aligns with the NICE scope and decision problem.

   2) Thank you for highlighting this. The use of icosapent ethyl in monotherapy was not considered being under the scope of the systematic literature review since our population of interest was that of patients receiving a background therapy of statin. Icosapent ethyl was searched as an individual term to ensure that any possibly relevant papers containing this therapy would be picked up in the search (without

being too restrictive), but monotherapy studies were not included in the final search results.

3) The initial systematic literature review aimed to include studies comparing, as a monotherapy or combination therapy, at least one of the following interventions: Icosapent ethyl and any comparator of interest (i.e., fenofibrates and bezafibrates were considered as comparators of interest outside the UK). In the UK context, the comparator of interest was standard of care, therefore any study implicating icosapent ethyl in combination with statin therapy was considered of interest.

e. The comparator considered in the clinical systematic literature review aligns with the NICE scope and decision problem, since it searched for all current treatment options within the given disease area in which patients take statins. There was no specific singular comparator of interest within the UK clinical setting, therefore the comparator of interest was the current standard of care, and so the clinical systematic literature review aimed to search all current treatment options within the disease area and specific population.

f. Since the objective of the clinical systematic literature review was to identify randomised controlled trials, no observational studies were considered. In addition, if the results could have been quantitatively summarised through a meta-analysis or used to develop indirect comparisons, we considered that mixing the results from observational and interventional studies would have been inadequate due to the high level of heterogeneity between these two types of design (e.g., different methods and risk of bias in terms of internal and external validity).

B8. Appendix D of the CS did not include information on the process of risk of bias assessment.

Please provide this information and provide reference to the NICE Single Technology Appraisal (STA) user guide used.

Company response

This was provided in section D1.3 of Appendix D but has also been provided again in the table below, summarising the methodological quality/risk assessment for both the REDUCE-IT and JELIS trials (N=2 studies applicable to the UK from the clinical systematic literature review). The table follows the format as per the guidelines set out in the NICE STA user guide.

Study Acronym/ I.D.	REDUCE-IT NCT01492361 (Bhatt et al., 2019)	JELIS NCT00231738 (Yokoyama et al., 2007)
Was randomisation carried out appropriately?	**Yes** 1:1 randomisation with three stratification factors (CV risk category, geographic region and baseline use of ezetimibe) was performed before treatment allocation.	**Yes** Randomisation was managed using the statistical coordination center at the Toyama Medical and Pharmaceutical University. Permuted-block randomization with a block size of four was used.
Was the concealment of treatment allocation adequate?	**Yes** This was a double-blind trial. No further details provided on the methods used to conceal the allocation sequence.	**No** This was an open label trial.
Were the groups similar at the outset of study in terms of prognostic factors?	**Yes** All baseline characteristics were well balanced between the active and placebo groups.	**Yes** All baseline characteristics were well balanced between the active and placebo groups.
Were the care providers, participants and outcome assessors blind to treatment allocation?	**Yes**, REDUCE-IT was a double-blind trial.	**No** This was an open label trial.
Were there any unexpected imbalance in drop-outs between groups?	**No** Dropouts' rates were similar between the active and control groups. Proportions of patients who discontinued the study early, as well as the reasons for early discontinuation were reported.	**No** Dropouts' rates were similar between the active and control groups. Reasons for early discontinuation were reported for each group.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	**Unclear** Selective outcome reporting was not examined by the authors. Therefore, there is no sufficient details in the publication to conclude on this methodological aspect.	**Unclear** Selective outcome reporting was not examined by the authors. Therefore, there is no sufficient details in the publication to conclude on this methodological aspect.
Did the analysis include an intention-to-treat analysis? If so was this appropriate and were appropriate methods used to account for missing data?	**Yes** All analyses were performed according to the intention-to-treat principle, which is considered appropriate to avoid overestimating treatment effect. Proportions of patients who completed the study were high and well described.	**Yes** All analyses were performed according to the intention-to-treat principle, which is considered appropriate to avoid overestimating treatment effect. Proportions of patients who completed the study were high and well described.

B9. Table 5 of the appendix D (Excluded studies) includes at least one duplicate reference (Bhatt et al. 2019).

a. Please check the table for any other duplicates and list the remaining references alphabetically according to first author surname.

b. Please list the excluded references for REDUCE-IT and JELIS as linked references for the included studies even if they did not contribute data to the SLR.

Company response

a. The updated table of excluded studies is below (removing duplicates and reordered alphabetically).

Citation	Reason for exclusion
Athyros VG, Papageorgiou AA, Athyrou VV, Demitriadis DS, Kontopoulos AG. Atorvastatin and micronized fenofibrate alone and in combination in type 2 diabetes with combined hyperlipidemia. Diabetes Care. 2002 Jul;25(7):1198-202. doi: 10.2337/diacare.25.7.1198. PMID: 12087019.	Outcomes
Bays HE, Jones PH, Mohiuddin SM, Kelly MT, Sun H, Setze CM, Buttler SM, Sleep DJ, Stolzenbach JC. Long-term safety and efficacy of fenofibric acid in combination with statin therapy for the treatment of patients with mixed dyslipidemia. J Clin Lipidol. 2008 Dec;2(6):426-35. doi: 10.1016/j.jacl.2008.10.001. Epub 2008 Nov 12. PMID: 21291776.	Intervention
Cortellaro M, Cofrancesco E, Boschetti C, Cortellaro F, Mancini M, Mariani M, Paoletti R. Effects of fluvastatin and bezafibrate combination on plasma fibrinogen, t-plasminogen activator inhibitor and C reactive protein levels in coronary artery disease patients with mixed hyperlipidaemia (FACT study). Fluvastatin Alone and in Combination Treatment. Thromb Haemost. 2000 Apr;83(4):549-53. PMID: 10780315.	Outcomes
Derosa G, Cicero AE, Bertone G, Piccinni MN, Ciccarelli L, Roggeri DE. Comparison of fluvastatin + fenofibrate combination therapy and fluvastatin monotherapy in the treatment of combined hyperlipidemia, type 2 diabetes mellitus, and coronary heart disease: a 12-month, randomized, double-blind, controlled trial. Clin Ther. 2004 Oct;26(10):1599-607. doi: 10.1016/j.clinthera.2004.10.008. PMID: 15598476.	Outcomes
Elam Marshall B, Lovato Laura C, Ginsberg Henry N, & null null. (2015). Abstract 15997: The Effect of Combined Statin/Fibrate Therapy on Cardiovascular Disease is Influenced by Sex and Dyslipidemia: ACCORDION-Lipid Long-Term Follow-up. Circulation, 132(suppl_3), A15997–A15997. https://doi.org/10.1161/circ.132.suppl_3.15997	Study type
Elam MB, Ginsberg HN, Lovato LC, Corson M, Largay J, Leiter LA, Lopez C, O'Connor PJ, Sweeney ME, Weiss D, Friedewald WT, Buse JB, Gerstein HC, Probstfield J, Grimm R, Ismail-Beigi F, Goff DC Jr, Fleg JL, Rosenberg Y, Byington RP; ACCORDION Study Investigators. Association of Fenofibrate Therapy With Long-term Cardiovascular Risk in Statin-Treated Patients With Type 2 Diabetes. JAMA Cardiol. 2017 Apr 1;2(4):370-380. doi: 10.1001/jamacardio.2016.4828. Erratum in: JAMA Cardiol. 2017 Apr 1;2(4):461. PMID: 28030716; PMCID: PMC5470410.	Study type
Ellen RL, McPherson R. Long-term efficacy and safety of fenofibrate and a statin in the treatment of combined hyperlipidemia. Am J Cardiol. 1998 Feb 26;81(4A):60B-65B. doi: 10.1016/s0002-9149(98)00040-x. PMID: 9526816.	Outcomes
Farnier M, Ducobu J, Bryniarski L. Efficacy and safety of adding fenofibrate 160 mg in high-risk patients with mixed hyperlipidemia not controlled by pravastatin 40 mg monotherapy. Am J Cardiol. 2010 Sep 15;106(6):787-92. doi: 10.1016/j.amjcard.2010.05.005. Epub 2010 Aug 2. PMID: 20816118.	Outcomes
Ferrières J, Bataille V, Puymirat E, Schiele F, Simon T, Danchin N; FAST-MI investigators. Applicability of the REDUCE-IT trial to the FAST-MI registry. Are the results of randomized trials relevant in routine clinical practice? Clin Cardiol. 2020 Nov;43(11):1260-1265. doi: 10.1002/clc.23437. Epub 2020 Jul 28. PMID: 32720384; PMCID: PMC7661650.	Study type
Gerstein HC, Miller ME, Ismail-Beigi F, Largay J, McDonald C, Lochnan HA, Booth GL; ACCORD Study Group. Effects of intensive glycaemic control on ischaemic heart disease: analysis of data from the randomised, controlled ACCORD trial. Lancet. 2014	Intervention

Nov 29;384(9958):1936-41. doi: 10.1016/S0140-6736(14)60611-5. Epub 2014 Jul 31. PMID: 25088437; PMCID: PMC4397008.	
Ginsberg HN, Bonds DE, Lovato LC, Crouse JR, Elam MB, Linz PE, O'connor PJ, Leiter LA, Weiss D, Lipkin E, Fleg JL; ACCORD Study Group. Evolution of the lipid trial protocol of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Am J Cardiol. 2007 Jun 18;99(12A):56i-67i. doi: 10.1016/j.amjcard.2007.03.024. Epub 2007 Apr 12. PMID: 17599426.	Study type
Ginsberg HN, Elam MB, Lovato LC, Crouse JR 3rd, Leiter LA, Linz P, Friedewald WT, Buse JB, Gerstein HC, Probstfield J, Grimm RH, Ismail-Beigi F, Bigger JT, Goff DC Jr, Cushman WC, Simons-Morton DG, Byington RP, ACCORD Study Group: Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med. 2010 Apr 29;362(17):1563-74. doi: 10.1056/NEJMoa1001282. Epub 2010 Mar 14. Erratum in: N Engl J Med. 2010 May 6;362(18):1748. PMID: 20228404; PMCID: PMC2879499.	Comparator
Habib, G., Paillard, F., Charpentier, G., Angellier, J.-F., Roux, T., Portal, J.-J., & Maigret, P. (2000). A multicenter, open-label, randomized study comparing the efficacy of atorvastatin versus usual care in reducing refractory hypercholesterolemia in high-risk patients to target levels. Current Therapeutic Research, 61(4), 175–190. https://doi.org/10.1016/S0011-393X(00)89032-3	Outcomes
Ihm, S.-H., Chung, W.-B., Lee, J.-M., Hwang, B.-H., Yoo, K.-D., Her, S.-H., Song, W.-H., Chae, I.-H., Park, T.-H., Kim, J.-H., Jeon, D. W., Cho, B.-R., Kang, S.-H., Park, S.-D., Lee, J.-B., Woo, J.-T., Lee, B.-W., Han, K.-A., Won, K.-H., … Seung, K.-B. (2020). Efficacy and Tolerability of Pitavastatin Versus Pitavastatin/Fenofibrate in High-risk Korean Patients with Mixed Dyslipidemia: A Multicenter, Randomized, Double-blinded, Parallel, Therapeutic Confirmatory Clinical Trial. Clinical Therapeutics, 42(10), 2021-2035.e3. https://doi.org/10.1016/j.clinthera.2020.08.002	Outcomes
Klempfner R, Goldenberg I, Fisman EZ, Matetzky S, Amit U, Shemesh J, Tenenbaum A. Comparison of statin alone versus bezafibrate and statin combination in patients with diabetes mellitus and acute coronary syndrome. Am J Cardiol. 2014 Jan 1;113(1):12-6. doi: 10.1016/j.amjcard.2013.08.033. Epub 2013 Oct 2. PMID: 24157192.	Study type
Koh KK, Quon MJ, Han SH, Chung WJ, Ahn JY, Seo YH, Choi IS, Shin EK. Additive beneficial effects of fenofibrate combined with atorvastatin in the treatment of combined hyperlipidemia. J Am Coll Cardiol. 2005 May 17;45(10):1649-53. doi: 10.1016/j.jacc.2005.02.052. PMID: 15893182.	Outcomes
Kontopoulos AG, Athyros VG, Papageorgiou AA, Hatzikonstandinou HA, Mayroudi MC, Boudoulas H. Effects of simvastatin and ciprofibrate alone and in combination on lipid profile, plasma fibrinogen and low density lipoprotein particle structure and distribution in patients with familial combined hyperlipidaemia and coronary artery disease. Coron Artery Dis. 1996 Nov;7(11):843-50. doi: 10.1097/00019501-199611000-00009. PMID: 8993943.	Intervention
Kwon TG, Jang AY, Kim SW, Hong YJ, Bae JH, Lee SY, Kim SH, Han SH. Design and rationale of a randomized control trial testing the effectiveness of combined therapy with STAtin plus FENOfibrate and statin alone in non-diabetic, combined dyslipidemia patients with non-intervened intermediate coronary artery disease - STAFENO study. Trials. 2020 Apr 22;21(1):353. doi: 10.1186/s13063-020-04291-5. PMID: 32321551; PMCID: PMC7178941.	Study type
Leitersdorf E, Muratti EN, Eliav O, Meiner V, Eisenberg S, Dann EJ, Sehayek E, Peters TK, Stein Y. Efficacy and safety of a combination fluvastatin-bezafibrate treatment for familial hypercholesterolemia: comparative analysis with a fluvastatin-cholestyramine	Outcomes

combination. Am J Med. 1994 May;96(5):401-7. doi: 10.1016/0002-9343(94)90165-1. PMID: 8192170.	
Margolis KL, O'Connor PJ, Morgan TM, Buse JB, Cohen RM, Cushman WC, Cutler JA, Evans GW, Gerstein HC, Grimm RH Jr, Lipkin EW, Narayan KM, Riddle MC Jr, Sood A, Goff DC Jr. Outcomes of combined cardiovascular risk factor management strategies in type 2 diabetes: the ACCORD randomized trial. Diabetes Care. 2014 Jun;37(6):1721-8. doi: 10.2337/dc13-2334. Epub 2014 Mar 4. PMID: 24595629; PMCID: PMC4030092.	Intervention
Miyoshi T, Kohno K, Asonuma H, Sakuragi S, Nakahama M, Kawai Y, Uesugi T, Oka T, Munemasa M, Takahashi N, Mukohara N, Habara S, Koyama Y, Nakamura K, Ito H; PEACH Investigators. Effect of Intensive and Standard Pitavastatin Treatment With or Without Eicosapentaenoic Acid on Progression of Coronary Artery Calcification Over 12 Months - Prospective Multicenter Study. Circ J. 2018 Jan 25;82(2):532-540. doi: 10.1253/circj.CJ-17-0419. Epub 2017 Sep 1. PMID: 28867681.	Comparator
Niki T, Wakatsuki T, Yamaguchi K, Taketani Y, Oeduka H, Kusunose K, Ise T, Iwase T, Yamada H, Soeki T, Sata M. Effects of the Addition of Eicosapentaenoic Acid to Strong Statin Therapy on Inflammatory Cytokines and Coronary Plaque Components Assessed by Integrated Backscatter Intravascular Ultrasound. Circ J. 2016;80(2):450-60. doi: 10.1253/circj.CJ-15-0813. Epub 2015 Dec 11. PMID: 26667367.	Outcomes
Olsson AG, Pedersen T, Bergdahl B. Trials of lipid-lowering therapy in secondary prevention of coronary heart disease. Curr Opin Lipidol. 1995 Dec;6(6):369-73. doi: 10.1097/00041433-199512000-00007. PMID: 8750250.	Study type
Pauciullo P, Borgnino C, Paoletti R, Mariani M, Mancini M. Efficacy and safety of a combination of fluvastatin and bezafibrate in patients with mixed hyperlipidaemia (FACT study). Atherosclerosis. 2000 Jun;150(2):429-36. doi: 10.1016/s0021-9150(00)00379-8. PMID: 10856536.	Outcomes
Peterson Benjamin, Bhatt Deepak, Steg Philippe, Miller Michael, Brinton Eliot, Ketchum Steven, Juliano Rebecca, Jiao Lixia, Doyle Ralph, Granowitz Craig, Pinto Duane, Giugliano Robert, Budoff Matthew, Tardif Jean-Claude, Verma Subodh, & Ballantyne Christie. (2020). TCT CONNECT-3 Treatment With Icosapent Ethyl to Reduce Ischemic Events in Patients With Prior Percutaneous Coronary Intervention: Insights From REDUCE-IT PCI. Journal of the American College of Cardiology, 76(17 Supplement S), B1–B2. https://doi.org/10.1016/j.jacc.2020.09.018	Study type
Sano K, Nakamura T, Hirano M, Kitta Y, Kobayashi T, Fujioka D, Saito Y, Yano T, Watanabe K, Watanabe Y, Mishina H, Obata JE, Kawabata K, Kugiyama K. Comparative study of bezafibrate and pravastatin in patients with coronary artery disease and high levels of remnant lipoprotein. Circ J. 2010 Aug;74(8):1644-50. doi: 10.1253/circj.cj-10-0079. Epub 2010 Jun 22. PMID: 20574136.	Comparator
Shah HD, Parikh KH, Chag MC, Shah UG, Baxi HA, Chandarana AH, Naik AM, Shah JN, Iyer S, Shah KJ, Goyal RK. Beneficial effects of the addition of fenofibrate to statin therapy in patients with acute coronary syndrome after percutaneous coronary interventions. Exp Clin Cardiol. 2007 Summer;12(2):91-6. PMID: 18650989; PMCID: PMC2359602.	Outcomes
Watanabe T, Miyamoto T, Miyasita T, Shishido T, Arimoto T, Takahashi H, Nishiyama S, Hirono O, Matsui M, Sugawara S, Ikeno E, Miyawaki H, Akira F, Kubota I. Combination therapy of eicosapentaenoic acid and pitavastatin for coronary plaque regression evaluated by integrated backscatter intravascular ultrasonography (CHERRY study)-	Study type

rationale and design. J Cardiol. 2014 Sep;64(3):236-9. doi: 10.1016/j.jjcc.2013.12.008. Epub 2014 Feb 3. PMID: 24503140.	
Webb et al. 2009. Predicted cardiovascular event reductions with the co-administration of fenofibric acid and low- or moderate-dose statin therapy in special populations with mixed dyslipidemia	Study type
Yang LP, Keating GM. Fenofibric acid: in combination therapy in the treatment of mixed dyslipidemia. Am J Cardiovasc Drugs. 2009;9(6):401-9. doi: 10.2165/11203920-000000000-00000. PMID: 19929038.	Study type
Zhu L, Hayen A, Bell KJL. Legacy effect of fibrate add-on therapy in diabetic patients with dyslipidemia: a secondary analysis of the ACCORDION study. Cardiovasc Diabetol. 2020 Mar 5;19(1):28. doi: 10.1186/s12933-020-01002-x. PMID: 32138746; PMCID: PMC7059389.	Study type

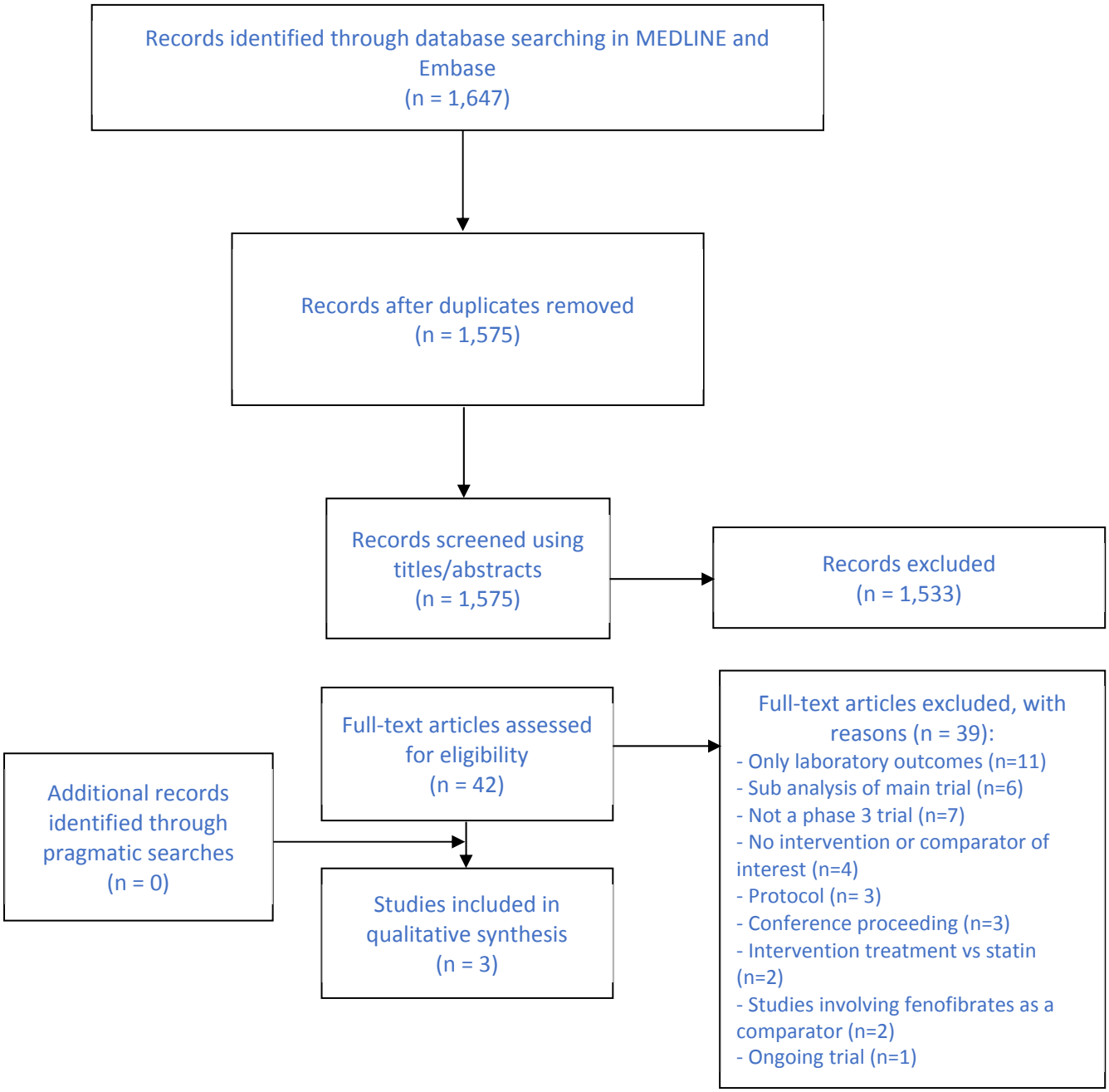
b. The below table shows the included studies from the systematic literature review (N=2; REDUCE-IT and JELIS trials, UK-applicable) as well as all other REDUCE-IT and JELIS trial publications that were assessed as part of the systematic literature review but excluded at the second pass stage with reasons.

Trial	Citation
REDUCE-IT	Included: - Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, Doyle RT Jr, Juliano RA, Jiao L, Granowitz C, Tardif JC, Ballantyne CM; REDUCE-IT Investigators. Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia. N Engl J Med. 2019 Jan 3;380(1):11-22. doi: 10.1056/NEJMoa1812792. Epub 2018 Nov 10. PMID: 30415628. - * Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, Doyle RT Jr, Juliano RA, Jiao L, Granowitz C, Tardif JC, Gregson J, Pocock SJ, Ballantyne CM; REDUCE-IT Investigators. Effects of Icosapent Ethyl on Total Ischemic Events: From REDUCE-IT. J Am Coll Cardiol. 2019 Jun 11;73(22):2791-2802. doi: 10.1016/j.jacc.2019.02.032. Epub 2019 Mar 18. PMID: 30898607 Excluded: - Bhatt DL, Miller M, Brinton EA, Jacobson TA, Steg PG, Ketchum SB, Doyle RT Jr, Juliano RA, Jiao L, Granowitz C, Tardif JC, Olshansky B, Chung MK, Gibson CM, Giugliano RP, Budoff MJ, Ballantyne CM; REDUCE-IT Investigators. REDUCE-IT USA: Results From the 3146 Patients Randomized in the United States. Circulation. 2020 Feb 4;141(5):367-375. doi: 10.1161/CIRCULATIONAHA.119.044440. Epub 2019 Nov 11. PMID: 31707829; PMCID: PMC7004453. *(Exclusion reason: study type)* - Bhatt, D. L., Brinton, E. A., Miller, M., Steg, P. G., Jacobson, T. A., Ketchum, S. B., Doyle, R. T., Juliano, R. A., Jiao, L., Granowitz, C., Ganda, O., Welty, F. K., Busch, R. S., Goldberg, A. C., Herrington, D. M., Budoff, M., Tardif, J.-C., & Ballantyne, C. M. (2020). 4-LB: Substantial Cardiovascular Benefit from Icosapent Ethyl in Patients with Diabetes: REDUCE-IT DIABETES. Diabetes, 69(Supplement 1). https://doi.org/10.2337/db20-4-LB *(Exclusion reason: study type)*
JELIS	Included: - Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito Y, Ishikawa Y, Oikawa S, Sasaki J, Hishida H, Itakura H, Kita T, Kitabatake A, Nakaya N, Sakata T, Shimada K, Shirato K; Japan EPA lipid intervention study (JELIS) Investigators. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. Lancet. 2007 Mar 31;369(9567):1090-8. doi: 10.1016/S0140-6736(07)60527-3. Erratum in: Lancet. 2007 Jul 21;370(9583):220. PMID: 17398308. Excluded: - Matsuzaki M, Yokoyama M, Saito Y, Origasa H, Ishikawa Y, Oikawa S, Sasaki J, Hishida H, Itakura H, Kita T, Kitabatake A, Nakaya N, Sakata T, Shimada K, Shirato K, Matsuzawa Y; JELIS Investigators. Incremental effects of eicosapentaenoic acid on cardiovascular events in statin-treated patients with coronary artery disease. Circ J. 2009 Jul;73(7):1283-90. doi: 10.1253/circj.cj-08-1197. Epub 2009 May 8. PMID: 19423946. *(Exclusion reason: study type)* - Oikawa S, Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito Y, Ishikawa Y, Sasaki J, Hishida H, Itakura H, Kita T, Kitabatake A, Nakaya N, Sakata T, Shimada K, Shirato K; JELIS Investigators, Japan. Suppressive effect of EPA on the incidence of coronary events in hypercholesterolemia with impaired glucose metabolism: Sub-analysis of the Japan EPA Lipid Intervention Study (JELIS). Atherosclerosis. 2009 Oct;206(2):535-9. doi: 10.1016/j.atherosclerosis.2009.03.029. Epub 2009 Apr 5. PMID: 19447387. *(Exclusion reason: study type)* - Saito Y, Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Ishikawa Y, Oikawa S, Sasaki J, Hishida H, Itakura H, Kita T, Kitabatake A, Nakaya N, Sakata T, Shimada K, Shirato K; JELIS Investigators, Japan. Effects of EPA on coronary artery disease in hypercholesterolemic patients with multiple risk factors: sub-analysis of primary prevention cases from the Japan EPA Lipid Intervention Study (JELIS). Atherosclerosis. 2008 Sep;200(1):135-40. doi:

	10.1016/j.atherosclerosis.2008.06.003. Epub 2008 Jun 19. Erratum in: Atherosclerosis. 2009 May;204(1):233. PMID: 18667204. *(Exclusion reason: study type)* - Tanaka K, Ishikawa Y, Yokoyama M, Origasa H, Matsuzaki M, Saito Y, Matsuzawa Y, Sasaki J, Oikawa S, Hishida H, Itakura H, Kita T, Kitabatake A, Nakaya N, Sakata T, Shimada K, Shirato K; JELIS Investigators, Japan. Reduction in the recurrence of stroke by eicosapentaenoic acid for hypercholesterolemic patients: subanalysis of the JELIS trial. Stroke. 2008 Jul;39(7):2052-8. doi: 10.1161/STROKEAHA.107.509455. Epub 2008 May 1. Erratum in: Stroke. 2008 Sep;39(9): e149. PMID: 18451347. *(Exclusion reason: study type)* - Yokoyama M, Origasa H; JELIS Investigators. Effects of eicosapentaenoic acid on cardiovascular events in Japanese patients with hypercholesterolemia: rationale, design, and baseline characteristics of the Japan EPA Lipid Intervention Study (JELIS). Am Heart J. 2003 Oct;146(4):613-20. doi: 10.1016/S0002-8703(03)00367-3. PMID: 14564313. *(Exclusion reason: study type)*

*Please note, this reference by Bhatt et al 2019 was wrongly excluded by the agency that ran the clinical SLR. In the CS, it was not excluded as it provided relevant information to the decision problem; this publication was included, an updated version of the clinical SLR PRISMA diagram (UK-applicable) is shown below to reflect this in Figure 3.

Figure 3. Updated PRISMA diagram for UK-applicable clinical SLR



B10. Please comment on this trial registry entry (https://clinicaltrials.gov/ct2/show/NCT02926027). Was it identified during the searches? If so, were relevant information extracted?

Company response

The EVAPORATE study (https://clinicaltrials.gov/ct2/show/NCT02926027) was an investigator-initiated/sponsored study funded by Amarin Pharma, Inc. As an investigator-initiated study, the company did not conduct the study, nor determine the

analysis plan, endpoint adjudication, or study measures. The primary study objective was to determine whether IPE would reduce plaque progression over 9 to 18 months compared to placebo in statin-treated patients. EVAPORATE was an imaging study that did not report cardiovascular outcome events, as defined in the NICE scope and decision problem, and therefore EVAPORATE was not included in the search results.

Eligible trials

B11. Priority question. The REDUCE-IT trial did not include any patients from the UK. Therefore:

a. **Please comment how applicable the trial is to the UK clinical setting, especially given the differences in both the primary and secondary efficacy composite endpoint results of the REDUCE-IT by region, age, sex, ethnicity and baseline triglycerides. For any differences between the proportion of patients in each subgroup in the REDUCE-IT and the UK clinical population, please state whether these differences are likely to impact on the cost-effectiveness estimate, and the likely direction.**

b. **Please comment on whether the clinical population in the UK are likely to have the same proportion of patients in primary and secondary prevention, as defined in the REDUCE-IT category. If not, please comment on any potential differences and how these will impact on the cost-effectiveness analysis.**

c. **Please also state the proportion of patients in the UK receiving ezetimibe, and, whether this aligns with the REDUCE-IT study. If not, please indicate whether this is likely to be a source of bias in the cost-effectiveness analysis.**

d. **Please comment if the placebo arm is representative of the current UK clinical practice.**

Company response

a. A total of 473 sites in 11 countries and three geographic regions enrolled and/or followed patients, including European countries. The contributing countries with

the highest enrollment included the United States (38.5% [3146/8179]); the Netherlands (20.5% [1678/8179]); and Ukraine (10.2% [836/8179]). The remaining participating countries (Australia, Canada, New Zealand, South Africa, Poland, Romania, Russian Federation, and India) each individually enrolled <10% of the overall patient population.

Randomisation was stratified by cardiovascular risk category, use of ezetimibe (yes/no), and by geographical region. Overall, most patients were male (71.2% [5822/8179]) and white (90.2% [7379/8179]). The mean age of patients was 63.4 years (range 44 to 92 years), with 46.0% (3763/8179) of patients aged > 65 years. At baseline, the median LDL cholesterol level was 75.0 mg per deciliter (1.94 mmol per liter) and the median triglyceride level was 216.0 mg per deciliter (2.44 mmol per liter). The treatment groups were well balanced across demographic and baseline characteristics.

Numerous prespecified subgroups were tested within the primary and key secondary endpoints, and there were no notable differences detected in efficacy by region, sex, ethnicity, or baseline triglyceride level (as denoted by interaction p-values and substantially overlapping 95% confidence intervals), nor in other prespecified baseline subgroup analyses such as those by cardiovascular risk stratum, ezetimibe use, diabetes, estimated glomerular filtration rate, statin intensity, or low-density lipoprotein cholesterol. The subgroup analyses by age suggest that patients above and below 65 years likely both derive benefit, but that benefit may be greater in the younger cohort. Nonetheless, this difference is not expected to differ by region (e.g., within the UK versus other regions), particularly when considering the lack of regional impact on the overall study results; the interaction p-value for the regional subgroup analysis for the primary endpoint was 0.30, and for the key secondary endpoint it was 0.54. Overall, the subgroup analyses of the primary and key secondary endpoints in REDUCE-IT suggest highly consistent efficacy across subgroups.

Available literature for high cardiovascular risk patients in the UK suggests generally similar proportions of patients as observed in REDUCE-IT, with any differences not being likely to impact the cost-effectiveness estimate or

direction in any substantive manner (*Steen DL, Khan I, Ansell D, Ray k et al. Retrospective examination of lipid-lowering treatment patterns in a real world high-risk cohort in the UK in 2014: comparison with the National Institute for Health and Care Excellence (NICE) 2014 lipid modification guidelines. BMJ Open 2017;7:e013255. doi:10.1136/bmjopen-2016- 013255; Danese MD, Gleeson M, Kutikova L, et al. Management of lipid-lowering therapy in patients with cardiovascular events in the UK: a retrospective cohort study. BMJ Open 2017;7:e013851. doi:10.1136/ bmjopen-2016-013851*). When considering the UK, patients that might be eligible for icosapent ethyl based on the indication of patients with established cardiovascular disease or at high risk for cardiovascular events due to the presence of diabetes and other risk factors, and considering the generally consistent benefit observed across subgroup analyses of the primary and key secondary endpoints in REDUCE-IT, no substantive impact on the cost-effectiveness estimate or direction are expected.

b. REDUCE-IT was designed such that the established cardiovascular disease (secondary prevention) cohort was to contribute approximately 70% of randomised patients, as there was a higher cardiovascular event rate expected in this cohort, while the diabetes plus risk factors (high risk primary prevention) cohort was to contribute approximately 30% of patients. As is common in cardiovascular outcome studies, these proportions were established to assess the effect of icosapent ethyl through a continuum of patients at high risk for cardiovascular events, while also supporting timely study conduct and readout.

   We were unable to identify references providing exact UK populations that correlate with the REDUCE-IT population, but insights can be drawn from the available literature. The number of patients in the UK with established cardiovascular disease can be sourced from Ray *et. al*., which estimated there were 3.3 million individuals with ASCVD in 2014, and the majority of these patients (80% = 2.6 million) were on statin therapy. Estimating the number of statin-treated patients in the UK at high-risk for cardiovascular events based on the presence of diabetes and other risk factors requires evaluation of data across differing studies. In 2020, the total number of patients living in the UK

with a diagnosis of diabetes was 3.9 million, and it is estimated that 35% have concomitant ASCVD (Lautsch *et al.* 2019). This would equate to approximately 65% of patients in the UK with diabetes (regardless of statin use) not having a prior cardiovascular event, or approximately 2.6 million patients. We assumed that 70% will have at least one risk factor (Steen *et al*. described the most common risk factor as being hypertension and present in 62 to 77% of their cohort): 2.6 million x 70% : 1.9 million.

Of patients with type II diabetes without a prior cardiovascular event and with at least one additional risk factor, approximately 62% (Steen *et al*.) were treated with statin per NICE guidance (*tps://www.nice.org.uk/guidance/ng185/chapter/Recommendations#drug-therapy-for-secondary-prevention*), which would equate to approximately 1.2 million patients in the UK who have diabetes without a prior cardiovascular event, with at least one additional risk factor and are also on statins.

Therefore, according to these references, approximately 3.9 million statin-treated patients in the UK might potentially fall within the icosapent ethyl indication, before the evaluation of their triglyceride levels: 2.7 million with established cardiovascular disease (~67%) and 1.2 million with diabetes and other risk factors, but without a prior cardiovascular event (~33%). These proportions of patients in the UK that might correspond to the Icosapent ethyl label are not meaningfully different from the proportion of patient populations enrolled in REDUCE-IT. These relative proportions are not expected to substantively change when the elevated TGs criteria is applied.

c. In the REDUCE-IT trial, 6.4% of patients received ezetimibe in addition to a statin, which is in close agreement with published data reporting ezetimibe use in statin-treated patients in the UK between 4 and 9% *(LLT use in UK* + Ray *et al.* 2020*)*.

d. In REDUCE-IT, patients were to remain on statin therapy and were treated based on the standard of care by their individual clinicians to manage risk factors such as diabetes and hypertension. The high proportion of REDUCE-IT patients taking antihypertensive ([redacted]), antithrombotic ([redacted]), ACE inhibitors

or ARBs ([redacted]), ACE Inhibitors ([redacted]), and antidiabetic ([redacted]) medications, are indicative of appropriate baseline treatment within this at-risk patient population, and are representative of the current UK clinical practice per the REDUCE-IT trial and NICE guidelines. (*tps://www.nice.org.uk/guidance/ng185/chapter/Recommendations#drug-therapy-for-secondary-prevention*).

B12. Please report all outcomes (primary, secondary, tertiary) of REDUCE-IT (the composite endpoint and a breakdown of all outcomes in the composite endpoint) separately for the two subgroups (primary and secondary prevention).

Company response

[redacted]

B13. Table 3 of document B of the CS (the REDUCE-IT trial details) mentions the following primary endpoint: "*Unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalisation*". Emergent hospitalisation is also mentioned at the top of page 37 of document B.

Please confirm if you mean '*emergent'* or '*emergency'* hospitalisation as definitions may affect the economic analysis. Please provide the relevant definitions.

Company response

We can confirm that the correct term is 'emergent' as currently used in the company submission.

As per the REDUCE-IT study protocol, an 'emergent hospitalisation' is defined as hospitalisation that is performed immediately because of the acute nature of the medical condition (e.g., acute limb ischemia, acute aortic dissection), and the increased morbidity or mortality associated with a temporal delay in treatment. An 'urgent/emergency hospitalisation' is one that is not emergent but required to be performed on a timely basis (≤ 24 hours) (e.g., a patient who has been stabilised

following initial treatment of acute limb ischemia, and there is clinical consensus that a definitive hospitalisation should occur within the next 24 hours).

B14. In section B.2.6.1.1 (the last paragraph on the page 49 of the CS) and in section E.1.1, the company states that "*the results for patients in the secondary prevention subgroup indicated a significant effect (p=0.1388) on the percentage of patients that experienced the primary endpoint with icosapent ethyl (19.3% versus placebo 25.5%; HR: 0.726; 95% CI, 0.650 to 0.810), similar to that observed in the total population*".

a. Please provide the actual P value for this comparison as it appears to be incorrect.

b. Please provide the actual P value for primary-prevention cohort.

Company response

a. The actual P value is p<0.0001

b. For the high-risk primary prevention cohort, the percentage of patients that experienced the primary endpoint with icosapent ethyl was 12.2% versus 13.6% for placebo (HR: 0.876; 95% CI, 0.700 to 1.095; p=0.2443).

The results for patients with established CVD were significant (p<0.0001), however, the results for patients at high risk for CVD were not, as this cohort contributed fewer first events to each endpoint compared to the secondary prevention cohort. This is reflective of the study design that was designed to detect a statistical difference in the full projected 1,612 primary endpoint events, and that required enrolment of fewer high-risk primary prevention patients (approximately 30% targeted enrolment indirectly based on the secondary prevention target of at least 70%; 29% randomised) than secondary prevention patients (71%), and is consistent with the overall lower event rate in the primary versus secondary prevention subgroup. For example, the primary prevention placebo patients contributed 163 first primary endpoint events, while the secondary prevention placebo patients contributed 738 first primary endpoint events. Despite contributing 22% of all first events, the primary prevention cohort hazard ratios and interaction p-values (primary versus secondary prevention) were consistent with the overall demonstration of benefit in REDUCE-IT. For example, the primary

prevention hazard ratios are all below unity for the primary and key secondary endpoints, as well as for each individual component, except hospitalisation for unstable angina, where events were particularly low in the primary prevention cohort.

B15. Please provide efficacy results stratified by relevant characteristics, e.g. geographic region. Please justify the inclusion of South Africa in the group of "Western countries" and provide results with and without results from South Africa.

Company response

Of the prespecified regional categories including Westernized, Eastern European, and Asian-Pacific, the medical practices in South Africa most aligned with the Westernized group. Nonetheless, as demonstrated below, removal of the South African cohort from the Westernized subgroup does not substantively alter study findings or conclusions in the overall population (Figure 4), or in the secondary (Figure 5) or primary (Figure 6) prevention cohorts.

Figure 4. Forest plot of primary and key secondary composite endpoints by Westernised region with and without South Africa ITT population

Figure 5. Forest plot of primary and key secondary composite endpoints by Westernised region with and without South Africa ITT population + secondary population

Figure 6. Forest plot of primary and key secondary composite endpoints by Westernised region with and without South Africa ITT population + primary population

Section C: Clarification on cost-effectiveness data

Base case correction

Following comments from the ERG, we can confirm there were a small number of minor errors in our original CEM.

- Correction in Markov trace due to negative and FALSE values
- Correction of the disutility applied for constipation
- Removal of half-cycle correction

Any corrections to the original model used to inform the CS are provided in a change log in version 5.0 of the CEM, the updated base case results are provided below.

Population	Technologies	Total Costs (£)	Total LYG	Total QALYs	Incremental Costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
ITT	Placebo	9,961	10.553	7.526	-	-	-	-
	Icosapent ethyl	20,619	10.851	7.890	10,658	0.299	0.364	29,317
CV1	Placebo	11,382	10.328	7.340	-	-	-	-
	Icosapent ethyl	21,861	10.712	7.795	10,479	0.384	0.456	23,004
CV2	Placebo	6,137	11.125	8.007	-	-	-	-
	Icosapent ethyl	17,635	11.195	8.120	11,498	0.071	0.113	101,645

Model structure

C1. Priority question. Based on the Markov trace calculations, it becomes apparent that a partitioned survival approach (rather than a state transition approach) is used. The proportions of the cohort that are post 1st, post 2nd and post 3rd event at successive points in time are not estimated by using transition probabilities and health state occupancy in previous cycles. Instead, these proportions are directly based upon parametric survival models, i.e. the proportion post 2nd event is independent on the proportion of patients that are post 1st event. This structural independence between the endpoints that is assumed in a partitioned survival approach is potentially problematic (according to NICE Decision Support Unit (DSU) technical support document (TSD) 19).

a. **Please clarify that a partitioned survival approach is adopted in the economic model to estimate the proportions of the cohort that are post 1st, post 2nd and post 3rd event.**

b. **Please justify the use of a partitioned survival approach given the issues highlighted in NICE DSU TSD 19.**

c. **According to NICE DSU TSD 19, the lack of a link between clinical endpoints assuming structural independence between modelled endpoints (e.g. proportion of patients with 2nd event is estimated independent on the proportion of patients with 1st event) also limits the**

degree to which the biological and clinical plausibility of extrapolations generated by the partitioned survival approach can be subject to scrutiny and sensitivity analyses. Please justify the plausibility of the extrapolations made in the economic model.

d. **NICE DSU TSD 19 recommends the use of state transition models alongside partitioned survival models to verify the plausibility of extrapolations and explore key clinical uncertainties in the extrapolation period. Please use state transition modelling to assist in verifying the plausibility of the partitioned survival model extrapolations and to address uncertainties in the extrapolation period (NICE DSU TSD 19, recommendation 11).**

e. **Please clarify if and how logical inconsistencies are handled in the economic model (e.g. higher proportion post second than post first events).**

Company response

We can confirm a partition survival methodology was adopted in the economic model, and any reference to a 'state transition approach' was an oversight within the write up of the company submission. As stated by the ERG, the economic model uses individual patient data (IPD) from the REDUCE-IT study to inform the proportion of individuals at any given time that have experienced a 1st, 2nd, or 3rd event.

Although partition survival (PS) models are commonly used in oncology, as discussed in NICE DSU 19, there are many benefits to applying a PS approach. We believe these benefits can be optimised beyond an oncology setting. When designing the methodology for our model, the main objectives were to reflect what would truly be seen in clinical practice while being intuitively appealing, easy to communicate and easy to construct.

After considering previous appraisals and the CADTH's submission for icosapent ethyl, we concluded that they all failed to model one key aspect, multiple subsequent events, which we believed to be pivotal in demonstrating the full value of icosapent ethyl in terms of the impact of reducing CV events on QoL and costs.

A PS approach is generally considered appropriate in situations where time-to-event endpoints are modelled and where individuals are solely able to progress in a specific order through states for example, unable to skip or return to a previous state. Both of these key assumptions are reflective of what is observed in the REDUCE-IT trial with the primary endpoint being the time to the first occurrence of a composite endpoint including stroke, MI, revascularisation, hospitalisation or CV death, and individuals being unable to experience a second event until they have experienced a first event.

When constructing the model, limitations of our approach were considered. For example, to control for death, we moved patients that experienced death to a death state, then redistributed for surviving patients. Furthermore, over the trial period, it would not be possible for an individual to experience a second event prior to a first event; therefore, there would be no issues surrounding a crossover of the first event and second event endpoints reported during the trial period. Beyond the trial period, extrapolations were used for the 1st, 2nd and 3rd event curves. Any curves that crossed over the previous event curve were disregarded and considered clinically implausible.

We acknowledge issues regarding the assumption that outcomes are independent with a PS approach, however, do not believe a state transition model to be appropriate for modelling a true representation of what is observed in clinical practice. In state transition models, one transition per state is considered over the whole-time horizon and does not account for the number of events that occur in patients changing over time, hence, we will not be providing the requested scenario.

C2. Priority question. The modelling approach deviates substantially from other economic models developed for similar decision problems. This includes NICE technology appraisal (TA) 393, NICE TA394, NICE TA420 as well as the company submission to the Canadian Agency for Drugs and Technologies in Health (CADTH) for icosapent ethyl to prevent cardiovascular events in statin-treated patients. Differences include 1) the cycle length (1 year in NICE TA393, NICE TA394 and the CADTH submission, 3 months in NICE TA394; one day in this CS); 2) the inclusion of tunnel states for minimally 1 year post non-fatal cardiovascular event (included in NICE TA393, NICE TA394 and NICE TA420, one day event state included in this CS) to account for differences in input parameters directly post non-fatal cardiovascular events (e.g. temporary

increased mortality, decreased quality of life, increased costs) and; 3) explicit modelling of non-fatal cardiovascular events such as acute coronary syndrome/myocardial infract and stroke (in NICE TA393, NICE TA394 and NICE TA420; implicit in this CS).

a. **Please justify the deviations from other economic models developed for similar decision problems (including the company's CADTH submission) elaborating on the aforementioned aspects as well as other differences.**

b. **Please perform scenario analyses (and provide an update version of the economic model) incorporating abovementioned issues 1, 2 and 3 (question C2) ensuring a model structure that is more consistent with previous NICE TAs as well as common modelling practices in this disease area.**

Company response

As stated in our response to C1, the aim when considering the methodology for the model was to reflect the occurrence of CV events in clinical practice as much as possible as well as minimise the number of assumptions that needed to be made.

When reviewing the icosapent ethyl CADTH submission and the data from the REDUCE-IT trial, it became apparent that by only including the first event a patient experiences, it was only capturing [redacted] of events experienced by individuals in the REDUCE-IT trial. We then reviewed previous NICE appraisals which evaluated outcomes related to CV events and found a maximum of two events were considered in all of these appraisals.

We assessed the feasibility of constructing a model with multiple subsequent events, using a similar methodology to previous appraisals, and identified a number of issues summarised below:

Cycle length

Firstly, a one year or three-month cycle length would only allow for a single event to take place during this time period, therefore, all events would not be able to be included. Secondly, an assumption of the type of event which should be included

would have to be made. For example, in a model with a one-year cycle, where an individual experiences both an unstable angina hospitalisation at one month post randomisation and then a stroke at eight months, an assumption would have to be made as to which event should be included in this cycle.

Therefore, it was determined that to take into account all the CV events occurring in the REDUCE-IT trial, and not having to make assumptions on which events to retain in a specific cycle, a daily cycle was the most appropriate cycle length.

Length of tunnel states

Similar issues to those identified for the cycle length were discussed when considering the length of tunnel states. During the acute period of events, individuals would be unable to experience a secondary event, therefore, the decision was made to apply all costs associated with an event on the specific day the event occurs including rehab costs etc. and apply a utility for the acute period for the next 60 days post event, as recommended by two UK clinical experts that were consulted (see question C17). Patients were then able to quickly progress to the post-event state where they were able to experience a subsequent event the next calendar day.

Explicit modelling of nonfatal cardiovascular events

Modelling explicit non-fatal cardiovascular events was considered and determined unfeasible to achieve our aim of modelling multiple subsequent events; this approach would have required significant numbers of health states and data analysis on small groups of patients, for example, a health state for Stroke-MI-Stroke and any other combinations of events that could have occurred. Hence, grouping by the number of events experienced was seen as the most pragmatic approach.

Due to the issues presented, we do not believe the scenario requested would be plausible, robust or representative of what is expected to be seen in clinical practice, therefore, would not be appropriate for decision making.

C3. Priority question. The company adopted daily cycles to capture *"patients experiencing multiple CV events in a short space of time"* as well as a half cycle correction. However, according to CS Figure 5, less than 30% of patients had an

event in the first 5 years since randomisation. Based on this (as well as the data presented in for instance CS Table 7), a monthly or potentially 3 months cycle time would likely be appropriate and less computationally expensive.

a. **Please support the statement *"patients experiencing multiple CV events in a short space of time"* with data from the REDUCE-IT trial.**

Company response

As shown in Table 5, large proportions of patients are experiencing multiple events whether a yearly, 3-month or monthly cycle is used.

Table 5. Multiple Events (of Primary Composite Endpoint) Within Cycle - ITT Population

Number of Subjects (%) with Multiple Events	AMR101 n/N (%)	Placebo n/N (%)	Overall n/N (%)
Using Monthly Cycle	[redacted]	[redacted]	[redacted]
Using 3-Month Cycle	[redacted]	[redacted]	[redacted]
Using Yearly Cycle	[redacted]	[redacted]	[redacted]

N: Total number of subjects with multiple events regardless of cycle. Monthly cycle: 30 days; 3-month cycle: 90 days; Yearly cycle: 365 days.

b. **Please support the statement *"as some patients in the REDUCE-IT trial experienced a CV event on consecutive days"* with data, including how often this occurs.**

c. **Please justify the daily cycle time, given the rate of events observed in the intention-to-treat (ITT) population of REDUCE-IT (as illustrated in for instance in CS Figure 5 and CS Table 7).**

Company response

Several costly events such as strokes, MI and revascularization are missed when a monthly cycle is used, as shown in Table 6. Therefore, a daily cycle has been used in order to ensure such events are accounted for.

Table 6. Missed Events (of Primary Composite Endpoint) Using Monthly Cycle

Number of Missed Events	Icosapent ethyl	Placebo	Overall
Using Monthly Cycle	[redacted]	[redacted]	[redacted]
Any MI	[redacted]	[redacted]	[redacted]
Any Stroke	[redacted]	[redacted]	[redacted]
CV Death including Undetermined Death	[redacted]	[redacted]	[redacted]
Coronary Revascularization	[redacted]	[redacted]	[redacted]
Unstable Angina	[redacted]	[redacted]	[redacted]

Missed events are events that are not counted as first event per subject within monthly cycle. For multiple events on the same day event type assignment follows this severity order: CV Death > MI > Stroke > Revasc > UA.

d. Please justify the half cycle correction given the daily cycle time used in the economic model.

Company response

The half cycle correction was included in the economic model to align with NICE DSU recommendations, though it has minimal impact on the ICER as shown in Table 7. Hence, we have removed this assumption from our base case.

Table 7. Impact of mid-cycle correction on ICER (ITT population)

	ICER (£)
With mid-cycle correction	£29,314
Without mid-cycle correction	£29,317

C4. The model structure includes tunnel states for the 'day' that patients experience a (1st, 2nd or 3rd) cardiovascular event. These 'event' states seem redundant and inconsistent with common modelling practices (post 1st, 2nd and 3rd cardiovascular event health states with event related disutilities and costs for minimally one year after a nonfatal cardiovascular event).

Please justify the use and necessity of these tunnel states for the 'day' that patients experience a (1st, 2nd or 3rd) cardiovascular event.

Company res***ponse***

Several costly events ([redacted] in the icosapent ethyl arm and [redacted] in the placebo arm) such as stroke, MI and revascularisation are missed when a monthly cycle is used, as shown in Table 6. Therefore, a daily cycle has been used in order to ensure such events and costs are accounted for. A daily tunnel state allows subsequent events to occur the day after an event, and prevents costly events from being missed.

Population

C5. Priority question. The CS distinguishes between two subgroups: primary prevention and secondary prevention. The ERG asked for the outcomes separately for each subgroup in question B11.

a. **Please clarify exactly which model inputs are different for the subgroup analyses, and fully justify the subgroup specific estimates for these input parameters.**

Company response

The inputs that are updated to reflect the population when the subgroup is changed are baseline characteristics (age and gender), clinical inputs and the distribution of the types of CV events experienced, as reported in the REDUCE-IT trial. The changes to these inputs impact the hazard ratios informing non-CV related mortality, average costs and utilities associated with icosapent ethyl and the placebo / BSC arms as well as the ICER.

b. **Please provide the probabilistic results of the base case and sensitivity and scenario analyses in the CS per subgroup (primary and secondary prevention).**

Company response

Provided below are the probabilistic results of the base case, sensitivity and scenario analyses for the CV1 and CV2 subgroups to align with those provided for the ITT in the company submission. Due to time constraints, only 1,000 iterations have been run per cohort.

Table 8. PSA results

Population	Technologies	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	Cost per QALY (£)
CV1	Placebo	11,712	7.195	-	-	-
	Icosapent ethyl	21,393	7.643	9,681	0.447	21,650
CV2	Placebo	6,256	7.806	-	-	-
	Icosapent ethyl	17,042	7.909	10,786	0.103	104,740

Table 9. OWSA results for Icosapent ethyl versus Placebo – CV1

Parameter	Lower bound (£) ICER	Upper bound (£) ICER	Difference (£) ICER
Icosapent Ethyl cost per cycle (£)	£12,660	£35,562	£22,902
Baseline distribution	£24,340	£21,790	£2,549
Icosapent Ethyl compliance	£22,276	£23,412	£1,136
Percentage male	£22,356	£23,346	£990
Icosapent Ethyl adverse event total cost	£22,794	£23,260	£466
Placebo monitoring costs - Subsequent years	£23,181	£22,789	£392
Icosapent Ethyl monitoring costs - Subsequent years	£22,841	£23,202	£361
Placebo adverse event total cost	£23,153	£22,823	£329
Icosapent Ethyl monitoring costs - First year	£22,905	£23,124	£220
Placebo cost per cycle (£)	£23,093	£22,896	£198
Placebo monitoring costs - First year	£23,021	£22,983	£38
Icosapent Ethyl adverse event total disutility	£23,004	£23,004	£1
Placebo adverse event total disutility	£23,004	£23,004	£0

Icosapent Ethyl mortality HR: No Event	£23,004	£23,004	£0
Icosapent Ethyl mortality HR: First event	£23,004	£23,004	£0
Icosapent Ethyl mortality HR: Post first event	£23,004	£23,004	£0
Icosapent Ethyl mortality HR: Second event	£23,004	£23,004	£0
Placebo mortality HR: Post second event	£23,004	£23,004	£0
Placebo mortality HR: Third event	£23,004	£23,004	£0
Placebo mortality HR: Post Third event	£23,004	£23,004	£0
Administration cost per cycle with Icosapent Ethyl (£)	£23,004	£23,004	£0
Administration cost per cycle with Placebo (£)	£23,004	£23,004	£0
Placebo compliance	£23,004	£23,004	£0
Acute Nonfatal MI health state cost	£23,004	£23,004	£0
Acute Nonfatal stroke health state cost	£23,004	£23,004	£0
Acute UA health state cost	£23,004	£23,004	£0
Acute CR health state cost	£23,004	£23,004	£0
CV Death health state cost	£23,004	£23,004	£0
Long-term Nonfatal MI health state cost	£23,004	£23,004	£0
Long-term Nonfatal stroke health state cost	£23,004	£23,004	£0
Long-term UA health state cost	£23,004	£23,004	£0
Long-term CR health state cost	£23,004	£23,004	£0
Utility: No Event	£23,004	£23,004	£0
Utility: CV Death	£23,004	£23,004	£0

Utility: Post MI	£23,004	£23,004	£0
Utility: Post Stroke	£23,004	£23,004	£0
Utility: Post UA	£23,004	£23,004	£0
Utility: Post CR	£23,004	£23,004	£0
Utility: Acute MI	£23,004	£23,004	£0
Utility: Acute Stroke	£23,004	£23,004	£0
Utility: Acute UA	£23,004	£23,004	£0
Utility: Acute CR	£23,004	£23,004	£0

Table 10. OWSA results for Icosapent ethyl versus Placebo - CV2

Parameter	Lower bound (£) ICER	Upper bound (£) ICER	Difference (£) ICER
Icosapent Ethyl cost per cycle (£)	£63,948	£147,413	£83,465
Baseline distribution	£112,949	£92,731	£20,218
Icosapent Ethyl compliance	£98,993	£103,133	£4,140
Percentage male	£100,176	£103,077	£2,901
Icosapent Ethyl adverse event total cost	£100,877	£102,577	£1,700
Placebo monitoring costs - Subsequent years	£102,301	£100,849	£1,451
Icosapent Ethyl monitoring costs - Subsequent years	£101,039	£102,381	£1,342
Placebo adverse event total cost	£102,215	£100,953	£1,263
Icosapent Ethyl monitoring costs - First year	£101,310	£102,053	£743
Placebo cost per cycle (£)	£101,955	£101,269	£686
Placebo monitoring costs - First year	£101,737	£101,533	£204
Icosapent Ethyl adverse event total disutility	£101,640	£101,651	£11
Placebo adverse event total disutility	£101,649	£101,641	£8

Icosapent Ethyl mortality HR: No Event	£101,645	£101,645	£0
Icosapent Ethyl mortality HR: First event	£101,645	£101,645	£0
Icosapent Ethyl mortality HR: Post first event	£101,645	£101,645	£0
Icosapent Ethyl mortality HR: Second event	£101,645	£101,645	£0
Icosapent Ethyl mortality HR: Post second event	£101,645	£101,645	£0
Icosapent Ethyl mortality HR: Third event	£101,645	£101,645	£0
Icosapent Ethyl mortality HR: Post Third event	£101,645	£101,645	£0
Placebo mortality HR: No Event	£101,645	£101,645	£0
Placebo mortality HR: First event	£101,645	£101,645	£0
Placebo mortality HR: Post first event	£101,645	£101,645	£0
Placebo mortality HR: Second event	£101,645	£101,645	£0
Placebo mortality HR: Post second event	£101,645	£101,645	£0
Placebo mortality HR: Third event	£101,645	£101,645	£0
Placebo mortality HR: Post Third event	£101,645	£101,645	£0
Administration cost per cycle with Icosapent Ethyl (£)	£101,645	£101,645	£0
Administration cost per cycle with Placebo (£)	£101,645	£101,645	£0
Placebo compliance	£101,645	£101,645	£0
Acute Nonfatal MI health state cost	£101,645	£101,645	£0
Acute Nonfatal stroke health state cost	£101,645	£101,645	£0

Acute UA health state cost	£101,645	£101,645	£0
Acute CR health state cost	£101,645	£101,645	£0
CV Death health state cost	£101,645	£101,645	£0
Long-term Nonfatal MI health state cost	£101,645	£101,645	£0
Long-term Nonfatal stroke health state cost	£101,645	£101,645	£0
Long-term UA health state cost	£101,645	£101,645	£0
Long-term CR health state cost	£101,645	£101,645	£0
Utility: No Event	£101,645	£101,645	£0
Utility: CV Death	£101,645	£101,645	£0
Utility: Post MI	£101,645	£101,645	£0
Utility: Post Stroke	£101,645	£101,645	£0
Utility: Post UA	£101,645	£101,645	£0
Utility: Post CR	£101,645	£101,645	£0
Utility: Acute MI	£101,645	£101,645	£0
Utility: Acute Stroke	£101,645	£101,645	£0
Utility: Acute UA	£101,645	£101,645	£0
Utility: Acute CR	£101,645	£101,645	£0

Table 11. Scenario analysis varying the discount rate - CV1

Discount rate	Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
0%	Placebo	15,888	13.655	9.590	-	-	-	-
	Icosapent ethyl	28,397	14.297	10.313	12,510	0.642	0.724	17,283
3.5% (base case)	Placebo	11,382	10.328	7.340	-	-	-	-
	Icosapent ethyl	21,861	10.712	7.795	10,479	0.384	0.456	23,004
5%	Placebo	10,032	9.301	6.639	-	-	-	-
	Icosapent ethyl	19,833	9.615	7.020	9,801	0.314	0.381	25,733

Table 12. Scenario analysis varying the discount rate - CV2

Discount rate	Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
0%	Placebo	8,815	14.965	10.700	-	-	-	-
	Icosapent ethyl	22,574	15.100	10.892	13,759	0.135	0.192	71,694
3.5% (base case)	Placebo	6,137	11.125	8.007	-	-	-	-
	Icosapent ethyl	17,635	11.195	8.120	11,498	0.071	0.113	101,645
5%	Placebo	5,352	9.957	7.185	-	-	-	-
	Icosapent ethyl	16,094	10.012	7.277	10,742	0.055	0.092	116,579

Table 13. Scenario analysis varying duration of acute utility application – CV1

Acute utility	Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
30 days	Placebo	11,382	10.328	7.342	-	-	-	-
	Icosapent ethyl	21,861	10.712	7.797	10,479	0.384	0.455	23,024
60 days (base case)	Placebo	11,382	10.328	7.340	-	-	-	-
	Icosapent ethyl	21,861	10.712	7.795	10,479	0.384	0.456	23,004
90 days	Placebo	11,382	10.328	7.337	-	-	-	-
	Icosapent ethyl	21,861	10.712	7.793	10,479	0.384	0.456	22,983

Table 14. Scenario analysis varying duration of acute utility application – CV2

Acute utility	Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
30 days	Placebo	6,137	11.125	8.008	-	-	-	-
	Icosapent ethyl	17,635	11.195	8.121	11,498	0.071	0.113	101,762
60 days (base case)	Placebo	6,137	11.125	8.007	-	-	-	-
	Icosapent ethyl	17,635	11.195	8.120	11,498	0.071	0.113	101,645
90 days	Placebo	6,137	11.125	8.006	-	-	-	-
	Icosapent ethyl	17,635	11.195	8.119	11,498	0.071	0.113	101,529

c. **Please provide a model file that allows for the probabilistic subgroup analyses mentioned above.**

Company response

As requested, separate versions of the cost-effectiveness model containing the PSA for the CV1 and CV2 subgroups have now been provided.

- CV1 File name: Icosapent Ethyl cost-effectiveness model_v5.0_PSA_OWSA CV1
- CV2 File name: Icosapent Ethyl cost-effectiveness model_v5.0_PSA_OWSA CV2

C6. The population in the CS consists of the full licensed indication (adults on statin therapy with elevated triglycerides who are at high risk of cardiovascular events due to: established CVD, or diabetes and at least 1 other cardiovascular risk factor), which according to the company reflects the ITT population in REDUCE-IT (please see question B1).

Please fully justify that the population in the submission (REDUCE-IT and the economic model) reflects the licensed population (also with regard to age and blood levels)

Company response

The REDUCE-IT trial is the only trial upon which the licensed indication of icosapent ethyl is based. As stated above in question B1, the lack of an age inclusion is not expected to have a substantive impact on the population eligible for icosapent ethyl. The decision problem reflects the licensed indication based on the REDUCE-IT trial.

Effectiveness

C7. Priority question. To model health state occupancy, mainly parametric survival models were used in the CS. In section 3.3.2.1.1 of the CS, it is mentioned that *"it can be expected that 55% to 77% of the patients would experience a CV event"*. Furthermore, it is stated that *"the most likely scenario chosen is the exponential distribution since it gives the best statistical fit and produces clinically plausible predictions"*. However, from Figure 17 in the CS, it is unclear which predictions are corresponding to the exponential

distribution (e.g. the orange line appears to be missing/overlapping with another line). Furthermore, it is unclear how the (long-term) clinical plausibility of the survival curve was assessed, exactly which data were used, and some assumptions require some additional elaboration.

a. **In the CS, it is mentioned that *"to account for the range in follow-up data among individuals, data was extrapolated using IPD* [individual participant data] *up until the point that 10% of patients at risk were left in the trial"*. Please elaborate on this assumption and explain how this was implemented.**

Company response

Towards the end of the follow-up period, the number of individuals still considered at risk decreased significantly. By year six, only [redacted] and [redacted] individuals had follow-up data in the icosapent ethyl and placebo groups, respectively. To account for the large number of individuals without follow-up, it was decided that any observations which took place after the point that only 10% of individuals were remaining at risk, were to be removed from the KM data set to be used for the 1st, 2nd and 3rd event extrapolations. The aim of this assumption was to create the most robust extrapolations as they can be sensitive to the final portion of the curve.

b. **In the CS, it is mentioned that *"in order to extrapolate the clinical data beyond the trial follow-up period, a series of parametric survival models were fit to the reconstituted first, second and third event IPD using the Flexsurv for R package for time-to-event data"*. Please explain what exactly is meant with reconstituted data, elaborate on this assumption, and explain how this was used to estimate the survival models.**

Company response

The term reconstituted is used to refer to the PLD following the removal of the events which occurred during the period where less than 10% of patients were at risk.

c. **It is unclear to the ERG which data were used to estimate the parametric survival models for the second and third event. For example, to estimate time to second event, were all ITT patients considered and time until**

second event was estimated or were only those patients with a first event included in the model? Please explain which data were used for the estimation of each of the survival models for the two event types. In addition, please elaborate on the implications of the included data.

Company response

We can confirm all patients that were considered for the 1st event curve were included and considered for the extrapolations of the 2nd and 3rd event curves. Patients were ***not*** only included in the curve if they had experienced a 1st event. For example, if at 10 years the curve states 80% of individuals are free of a 2nd event, this is of the total ITT population, ***not*** 80% of those that experience a first event.

d. **Related to the question above, please provide numbers of patients at risk included for the full duration of follow-up for all figures in which the parametric survival models are displayed (e.g. Figures 16 to 27).**

Company response

Please find the number at risk provided below for the ITT population curves:

Month	Icosapent ethyl	Placebo
0 months	[redacted]	[redacted]
3 months	[redacted]	[redacted]
6 months	[redacted]	[redacted]
9 months	[redacted]	[redacted]
12 months	[redacted]	[redacted]
15 months	[redacted]	[redacted]
18 months	[redacted]	[redacted]
21 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]
27 months	[redacted]	[redacted]
30 months	[redacted]	[redacted]
33 months	[redacted]	[redacted]
36 months	[redacted]	[redacted]
39 months	[redacted]	[redacted]
42 months	[redacted]	[redacted]
45 months	[redacted]	[redacted]
48 months	[redacted]	[redacted]

Month	Icosapent ethyl	Placebo
51 months	[redacted]	[redacted]
54 months	[redacted]	[redacted]
57 months	[redacted]	[redacted]
60 months	[redacted]	[redacted]
63 months	[redacted]	[redacted]
66 months	[redacted]	[redacted]
69 months	[redacted]	[redacted]
72 months	[redacted]	[redacted]
75 months	[redacted]	[redacted]

e. **In the CS it is mentioned that *"it can be expected that 55% to 77% of the patients would experience a CV event"*. However, the West of Scotland Coronary Prevention Study (WOSCOPS) that is being referred to states that *"the average follow-up period was 4.9 years"*. Please explain how the estimates mentioned in the CS were derived from that study or, if applicable, provide the correct reference. Moreover, please provide detailed information on how the range of 55%-77% was determined. Based on the information provided in the CS, 55% patients would experience a CV event (i.e. (414 + 1,398)/3,302 = 0,55). It is unclear how the upper limit of 77% was derived.**

Company response

According to the WOSCOPS study, out of the 3,302 patients receiving pravastatin 40 mg once daily, a total of 414 patients died from cardiovascular cause, 1,145 died from all causes and a total of 1,398 patients experienced a cardiovascular admission. The 55% estimates the number of patients with a cardiovascular event and was derived as follows: (414 + 1,398)/3,302. However, for the model, it is also relevant to confirm the number of patients still in the event free state, and therefore we must include patients who died from all causes (cardiovascular and other), hence the 77%, is derived as follows: (1,145 + 1,398)/3,302.

f. **Please provide a table with the predictions of the proportions of patients that is event-free after 20 years for each of the parametric survival curves for both icosapent and placebo and compare this to the estimates derived from the WOSCOPS (or another study if WOSCOPS is not applicable).**

Moreover, from Figure 17 in the CS, it is unclear which predictions are corresponding to the exponential distribution (e.g. the orange line appears to be missing/overlapping with another line). Please clarify.

Company response

Provided below in Table 15 are the predictions of the proportions of patients that are event-free after 20 years for each of the parametric survival curves. It can be seen from Table 15 that the exponential distribution's results lie between the other various types of distributions, ruling out any potential bias in selection.

Table 15. Predictions of the proportions of patients event free after 20 years

Distribution	% of patients event free after 20 years: Icosapent ethyl	% of patients event free after 20 years: Placebo
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]
Gamma	[redacted]	[redacted]

The estimated proportions of event-free patients were presented to relevant UK clinical experts who in turn validated these results (see C7.g. for the rationale behind why WOSCOPS is not applicable to compare against).

A graph showing only the exponential distribution for the proportion of patients free of a first event in both the icosapent ethyl and placebo arms is shown below (Figure 7) for clarity, taken directly from the cost-effectiveness model.

Figure 7: Exponential distribution of the proportion of patients free of a first event

g. **From Figure 19 in the CS, it appears as if the exponential model results in an estimated proportion of 10% of the patient being event-free after 20 years. This seems to deviate from the estimates in WOSCOPS. Please justify the use of the exponential distribution, especially considering the goodness of fit statistics are relatively similar between models. Please provide additional validation of the extrapolated outcomes of the parametric survival models to motivate the choice of each survival model.**

Company response

The quoted figure of 10% of patients estimated as being event-free after 20 years is incorrect. We would like to redraw your attention back to Figure 19 in the CS, where 20 years can be seen at day 7,305, which results in an [redacted] of patients estimated at being event-free at this time. This value of 10% may have been interpreted by looking at the end of the extrapolation graph, where this 10% reflects those patients event-free at >36 years.

The estimated proportions of event-free patients were presented to relevant UK clinical experts who in turn validated these results.

The WOSCOPS study is not an appropriate study for comparison. The WOSCOPS study uses the term 'event' for a death, and does not therefore accurately capture the subsequent CV events of the population as is done in this CS. Furthermore, the population is not appropriate for comparison in this study as it looks at patients 45-64 years of age, whereas this CS looks at patients ≥64 years of age, and so mortality will

not be comparable between these two populations. Another limitation of the WOSCOPS publication is that it studies primary prevention only, the case presented in the CS presents a mixed cohort of primary and secondary prevention patients, meaning that the CS proposed population would be at a higher risk of CV events and/or death compared to those patients in WOSCOPS, making it an inappropriate comparison.

h. **In sections B3.3.2.1.2 and B3.3.2.1.3 of the CS the survival curves for the second and third event are presented. It is stated that *"the most likely scenario chosen is the exponential since it gives the best statistical fit and produces clinically plausible predictions"*. Please provide the clinical evidence that was used to determine the clinical plausibility of the survival curves. Please provide additional validation of the extrapolated outcomes of the parametric survival models to motivate the choice of each survival model.**

Company response

There is no long-term data (20-years and onwards) on second and third subsequent events. However, two UK clinical experts agreed that the ratios of patients experiencing second and third subsequent events in the extrapolation is what they would expect to see in UK clinical practice. These clinical experts agreed on the plausibility of the survival curves, noting two distributions resulted in outliers (Weibull and Gompertz) leaving the other distributions (lognormal, log-logistic and exponential) to be evaluated for suitability, and the distribution chosen in this case (exponential curve) has the best statistical fit, in line with what would be expected in UK clinical practice.

i. **The chosen parametric survival models in the CS base-case have not been subject to scenario analyses. Please add sensitivity analyses exploring alternative survival models to estimate time to event probabilities.**

Company response

Scenario analyses for all the distributions considered for the time-to-event curves are presented in the tables below:

Table 16. Scenario analyses for all distributions (Event 1) – ITT

Parametric survival model	Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Exponential	Placebo	9,961	10.553	7.526	-	-	-	-
	Icosapent ethyl	20,619	10.851	7.890	10,658	0.299	0.364	29,317
Weibull	Placebo	10,078	10.521	7.495	-	-	-	-
	Icosapent ethyl	20,618	10.852	7.890	10,539	0.331	0.395	26,713
Gompertz	Placebo	10,079	10.518	7.493	-	-	-	-
	Icosapent ethyl	20,449	10.919	7.951	10,370	0.401	0.458	22,637
Log-logistic	Placebo	9,696	10.634	7.602	-	-	-	-
	Icosapent ethyl	20,379	10.946	7.977	10,683	0.312	0.375	28,478
Lognormal	Placebo	9,258	10.748	7.714	-	-	-	-
	Icosapent ethyl	20,038	11.064	8.090	10,780	0.316	0.376	28,701
Generalised gamma	Placebo	9,856	10.584	7.556	-	-	-	-
	Icosapent ethyl	20,357	10.950	7.982	10,501	0.366	0.426	24,657

Table 17. Scenario analyses for all distributions (Event 2) – ITT

Parametric survival model	Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Exponential	Placebo	9,961	10.553	7.526	-	-	-	-
	Icosapent ethyl	20,619	10.851	7.890	10,658	0.299	0.364	29,317
Weibull	Placebo	10,174	10.507	7.478	-	-	-	-
	Icosapent ethyl	20,764	10.825	7.860	10,590	0.318	0.383	27,660
Gompertz	Placebo	10,470	10.449	7.415	-	-	-	-
	Icosapent ethyl	21,019	10.778	7.811	10,549	0.329	0.396	26,644
Log-logistic	Placebo	10,061	10.533	7.504	-	-	-	-
	Icosapent ethyl	20,708	10.836	7.872	10,647	0.303	0.368	28,899
Lognormal	Placebo	9,814	10.585	7.559	-	-	-	-
	Icosapent ethyl	20,538	10.868	7.906	10,724	0.282	0.347	30,888
	Placebo	-	-	-	-	-	-	-

Generalised gamma	Icosapent ethyl	-	-	-	-	-	-	-

Table 18. Scenario analyses for all distributions (Event 3) – ITT

Parametric survival model	Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Exponential	Placebo	9,961	10.553	7.526	-	-	-	-
	Icosapent ethyl	20,619	10.851	7.890	10,658	0.299	0.364	29,317
Weibull	Placebo	-	-	-	-	-	-	-
	Icosapent ethyl	-	-	-	-	-	-	-
Gompertz	Placebo	11,333	10.452	7.424	-	-	-	-
	Icosapent ethyl	21,484	10.757	7.801	10,151	0.305	0.377	26,947
Log-logistic	Placebo	11,148	10.453	7.432	-	-	-	-
	Icosapent ethyl	20,853	10.824	7.865	9,704	0.371	0.432	22,442
Lognormal	Placebo	10,543	10.503	7.480	-	-	-	-
	Icosapent ethyl	20,656	10.848	7.886	10,113	0.344	0.406	24,892
Generalised gamma	Placebo	-	-	-	-	-	-	-
	Icosapent ethyl	-	-	-	-	-	-	-

Table 19. Scenario analyses for all distributions (Event 1) – CV1

Parametric survival model	Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Exponential	Placebo	11,382	10.328	7.340	-	-	-	-
	Icosapent ethyl	21,861	10.712	7.795	10,479	0.384	0.456	23,004
Weibull	Placebo	11,463	10.308	7.320	-	-	-	-
	Icosapent ethyl	21,834	10.721	7.804	10,371	0.413	0.484	21,409
Gompertz	Placebo	11,389	10.326	7.338	-	-	-	-
	Icosapent ethyl	21,623	10.801	7.878	10,233	0.474	0.541	18,918
Log-logistic	Placebo	11,037	10.425	7.432	-	-	-	-
	Icosapent ethyl	21,567	10.820	7.897	10,530	0.395	0.466	22,620
	Placebo	10,608	10.531	7.538	-	-	-	-

Lognormal	Icosapent ethyl	21,226	10.931	8.006	10,618	0.400	0.468	22,669
Generalised gamma	Placebo	11,255	10.363	7.373	-	-	-	-
	Icosapent ethyl	21,565	10.816	7.895	10,310	0.454	0.522	19,743

Table 20. Scenario analyses for all distributions (Event 2) – CV1

Parametric survival model	Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Exponential	Placebo	11,382	10.328	7.340	-	-	-	-
	Icosapent ethyl	21,861	10.712	7.795	10,479	0.384	0.456	23,004
Weibull	Placebo	11,608	10.280	7.288	-	-	-	-
	Icosapent ethyl	22,018	10.685	7.765	10,410	0.405	0.477	21,824
Gompertz	Placebo	11,897	10.225	7.226	-	-	-	-
	Icosapent ethyl	22,338	10.630	7.706	10,441	0.406	0.479	21,785
Log-logistic	Placebo	11,459	10.314	7.323	-	-	-	-
	Icosapent ethyl	21,945	10.699	7.780	10,486	0.385	0.457	22,957
Lognormal	Placebo	11,188	10.371	7.384	-	-	-	-
	Icosapent ethyl	21,753	10.732	7.817	10,565	0.361	0.433	24,402
Generalised gamma	Placebo	-	-	-	-	-	-	-
	Icosapent ethyl	-	-	-	-	-	-	-

Table 21. Scenario analyses for all distributions (Event 3) – CV1

Parametric survival model	Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Exponential	Placebo	11,382	10.328	7.340	-	-	-	-
	Icosapent ethyl	21,861	10.712	7.795	10,479	0.384	0.456	23,004
Weibull	Placebo	-	-	-	-	-	-	-
	Icosapent ethyl	-	-	-	-	-	-	-
Gompertz	Placebo	13,107	10.215	7.221	-	-	-	-
	Icosapent ethyl	22,946	10.608	7.693	9,839	0.393	0.472	20,853
Log-logistic	Placebo	12,810	10.219	7.235	-	-	-	-

	Icosapent ethyl	22,213	10.675	7.760	9,404	0.455	0.525	17,911
Lognormal	Placebo	12,035	10.279	7.292	-	-	-	-
	Icosapent ethyl	21,933	10.705	7.788	9,898	0.426	0.497	19,933
Generalised gamma	Placebo	-	-	-	-	-	-	-
	Icosapent ethyl	-	-	-	-	-	-	-

Table 22. Scenario analyses for all distributions (Event 1) – CV2

Parametric survival model	Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Exponential	Placebo	6,137	11.125	8.007	-	-	-	-
	Icosapent ethyl	17,635	11.195	8.120	11,498	0.071	0.113	101,645
Weibull	Placebo	-	-	-	-	-	-	-
	Icosapent ethyl	-	-	-	-	-	-	-
Gompertz	Placebo	7,526	10.630	7.558	-	-	-	-
	Icosapent ethyl	18,056	10.985	7.939	10,530	0.355	0.380	27,701
Log-logistic	Placebo	6,308	11.077	7.960	-	-	-	-
	Icosapent ethyl	17,631	11.207	8.129	11,323	0.130	0.169	67,169
Lognormal	Placebo	5,831	11.236	8.109	-	-	-	-
	Icosapent ethyl	17,279	11.359	8.264	11,447	0.123	0.156	73,413
Generalised gamma	Placebo	6,555	10.982	7.876	-	-	-	-
	Icosapent ethyl	17,661	11.189	8.113	11,106	0.207	0.238	46,709

Table 23. Scenario analyses for all distributions (Event 2) – CV2

Parametric survival model	Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Exponential	Placebo	6,137	11.125	8.007	-	-	-	-
	Icosapent ethyl	17,635	11.195	8.120	11,498	0.071	0.113	101,645
Weibull	Placebo	-	-	-	-	-	-	-
	Icosapent ethyl	-	-	-	-	-	-	-
Gompertz	Placebo	6,829	10.967	7.841	-	-	-	-

	Icosapent ethyl	17,973	11.117	8.039	11,144	0.150	0.198	56,229
Log-logistic	Placebo	6,431	11.054	7.935	-	-	-	-
	Icosapent ethyl	17,766	11.165	8.088	11,335	0.111	0.153	74,182
Lognormal	Placebo	6,221	11.104	7.986	-	-	-	-
	Icosapent ethyl	17,645	11.194	8.118	11,424	0.090	0.132	86,256
Generalised gamma	Placebo	-	-	-	-	-	-	-
	Icosapent ethyl	-	-	-	-	-	-	-

Table 24. Scenario analyses for all distributions (Event 3) – CV2

Parametric survival model	Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Exponential	Placebo	6,137	11.125	8.007	-	-	-	-
	Icosapent ethyl	17,635	11.195	8.120	11,498	0.071	0.113	101,645
Weibull	Placebo	-	-	-	-	-	-	-
	Icosapent ethyl	-	-	-	-	-	-	-
Gompertz	Placebo	6,473	11.070	7.960	-	-	-	-
	Icosapent ethyl	17,697	11.181	8.109	11,224	0.111	0.149	75,534
Log-logistic	Placebo	6,490	11.059	7.953	-	-	-	-
	Icosapent ethyl	17,663	11.190	8.115	11,174	0.130	0.162	68,894
Lognormal	Placebo	6,478	11.061	7.955	-	-	-	-
	Icosapent ethyl	17,619	11.199	8.123	11,141	0.138	0.168	66,279
Generalised gamma	Placebo	-	-	-	-	-	-	-
	Icosapent ethyl	-	-	-	-	-	-	-

j. All survival models were stratified for icosapent and placebo separately, i.e. separately for both treatment arms. Please justify the use of stratified models.

Company response

Although survival models were considered separately, the distributions chosen were consistent across both treatment arms for all curves. If the AIC and BIC best fit had differed between treatment arms, we would have likely chosen a consistent distribution, however, due to the nature of the results, we did not consider this issue.

C8. Priority question. In the CS base-case no treatment waning was assumed, which means that the time to the next event was assumed to be different for the two comparators during the whole duration of the time horizon, i.e. for each event treatment-specific survival curves were estimated resulting in a treatment benefit of icosapent for all events.

a. **Please justify the assumption of no treatment waning, i.e. that there is a lifetime difference in treatment response based on the initial treatment, also supporting this with further evidence, e.g. expert opinion.**

b. **Please provide results for scenarios assuming treatment waning for icosapent. This should be three scenarios in which treatment waning is assumed 1) after the first, 2) second, and 3) third event.**

Company response

There is no evidence to suggest treatment waning is applicable for icosapent ethyl. Throughout the REDUCE-IT study period, efficacy did not decrease over time, therefore there is no evidence to suggest this assumption would be observed in clinical practice.

Additionally, the scenario requested of waning on the efficacy of first, second and third event should be interpreted with caution. This is due to the need to make assumptions surrounding the time-period over which the waning effect should be implemented.

Provided in Table 25 to Table 27 are scenarios for no waning (base case) and waning over 10- and 20-years post trial completion after first, second and third events. The scenario is implemented to assume efficacy of the event curve post trial period will decrease at constant rate until equal to placebo at the chosen time period. For example, if after the first event 10-years is selected, icosapent ethyl will take full extrapolated efficacy for all curves until the end of the trial period, following this it will take a weighted average of icosapent ethyl and placebo curves, with the proportion

informed by placebo increasing at 1/(365.25*10) per cycle until equal to placebo at 10-years post trial period.

Table 25. Scenarios assuming treatment waning for Icosapent ethyl - ITT

	Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
No waning (base case)								
ITT	Placebo	9,961	10.553	7.526	-	-	-	-
	Icosapent ethyl	20,619	10.851	7.890	10,658	0.299	0.364	29,317
Applied to first, second and third event curves								
10-year post trial period	Placebo	9,961	10.553	7.526	-	-	-	-
	Icosapent ethyl	21,876	10.634	7.663	11,915	0.081	0.137	87,240
20-year post trial period	Placebo	9,961	10.553	7.526	-	-	-	-
	Icosapent ethyl	21,396	10.700	7.740	11,435	0.147	0.214	53,407
Applied to second and third event curves								
10-year post trial period	Placebo	9,961	10.553	7.526	-	-	-	-
	Icosapent ethyl	21,413	10.745	7.778	11,452	0.192	0.252	45,509
20-year post trial period	Placebo	9,961	10.553	7.526	-	-	-	-
	Icosapent ethyl	21,130	10.775	7.814	11,169	0.223	0.288	38,727
Applied to third event curve only								
10-year post trial period	Placebo	9,961	10.553	7.526	-	-	-	-
	Icosapent ethyl	21,063	10.800	7.843	11,102	0.248	0.317	35,072
20-year post trial period	Placebo	9,961	10.553	7.526	-	-	-	-
	Icosapent ethyl	20,907	10.815	7.858	10,946	0.262	0.332	33,020

Table 26. Scenarios assuming treatment waning for Icosapent ethyl - CV1

	Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
No waning (base case)								
	Placebo	11,382	10.328	7.340	-	-	-	-
	Icosapent ethyl	21,861	10.712	7.795	10,479	0.384	0.456	23,004
Applied to first, second and third event curves								
10-year post trial period	Placebo	11,382	10.328	7.340	-	-	-	-
	Icosapent ethyl	23,386	10.458	7.527	12,004	0.130	0.188	63,920
20-year post trial period	Placebo	11,382	10.328	7.340	-	-	-	-
	Icosapent ethyl	22,796	10.538	7.621	11,414	0.209	0.282	40,490
Applied to second and third event curves								
10-year post trial period	Placebo	11,382	10.328	7.340	-	-	-	-
	Icosapent ethyl	22,878	10.579	7.655	11,496	0.251	0.315	36,492
20-year post trial period	Placebo	11,382	10.328	7.340	-	-	-	-
	Icosapent ethyl	22,509	10.618	7.702	11,127	0.290	0.362	30,702
Applied to third event curve only								
10-year post trial period	Placebo	11,382	10.328	7.340	-	-	-	-
	Icosapent ethyl	22,424	10.653	7.740	11,042	0.325	0.400	27,594
20-year post trial period	Placebo	11,382	10.328	7.340	-	-	-	-
	Icosapent ethyl	22,223	10.670	7.758	10,841	0.342	0.418	25,928

Table 27. Scenarios assuming treatment waning for Icosapent ethyl - CV2

	Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
No waning (base case)								
CV2	Placebo	6,137	11.125	8.007	-	-	-	-

	Icosapent ethyl	17,635	11.195	8.120	11,498	0.071	0.113	101,645
Applied to first, second and third event curves								
10-year post trial period	Placebo	6,137	11.125	8.007	-	-	-	-
	Icosapent ethyl	18,018	11.122	8.047	11,881	- 0.003	0.040	300,727
20-year post trial period	Placebo	6,137	11.125	8.007	-	-	-	-
	Icosapent ethyl	17,875	11.141	8.069	11,738	0.016	0.062	189,314
Applied to second and third event curves								
10-year post trial period	Placebo	6,137	11.125	8.007	-	-	-	-
	Icosapent ethyl	17,793	11.169	8.097	11,656	0.045	0.090	130,222
20-year post trial period	Placebo	6,137	11.125	8.007	-	-	-	-
	Icosapent ethyl	17,741	11.176	8.103	11,604	0.052	0.096	120,373
Applied to third event curve only								
10-year post trial period	Placebo	6,137	11.125	8.007	-	-	-	-
	Icosapent ethyl	17,766	11.165	8.095	11,629	0.040	0.088	131,725
20-year post trial period	Placebo	6,137	11.125	8.007	-	-	-	-
	Icosapent ethyl	17,724	11.174	8.103	11,587	0.049	0.096	120,940

C9. Priority question. It is mentioned in the CS that two forms of mortality are captured within the model; surviving patients can transition to the non-CV related death health state, which captures the baseline risk of non-CV related death, or CV death if a CV related death occurs. In Table 29 of the CS the weighted hazard ratios for mortality by heath state used in the economic model are presented. This constitutes the baseline risk of non-CV related death. For all health states, icosapent is associated with lower hazard ratios.

a. **Please justify and elaborate on the use of treatment-dependent hazard ratios for the baseline risk of non-CV related death, especially considering CV related death has already been captured in the CV death state, and the clinical plausibility of the mortality advantage of icosapent.**

Company response

Treatment-dependent non-CV related hazard ratios were implemented in the model to reflect the increased risk associated with non-CV death in each of the health states,

compared to the mortality risk associated with that of the general population norm. This assumption was informed by a study by The Emerging Risk Factors Collaboration, which reports that the all-cause mortality rate of patients with no prior CV event was 6.8 per 1000 person-years, in comparison to the all-cause mortality rates of patients with a history of diabetes, stroke, and MI being 15.6, 16.1 and 16.8 per 1000 person-years, respectively.

To calculate the baseline risk of non-CV related death, a hazard ratio for each treatment arm was applied to the all-cause mortality rate. The hazard ratios were calculated using a weighted average of the hazard ratios for each event based on the proportion of events that occurred in each group. The treatment-dependent hazard ratios are appropriate for this model as they are informed using the distribution of events in each treatment arm.

Although we believe hazard ratios included for non-CV related mortality due to the type of event experienced would be plausible, we have explored an additional scenario in which hazard ratios are treatment-independent and equivalent to those of the UK population norm, to demonstrate this assumption has minimal impact on the model results.

Table 28. Scenario analysis varying non-CV mortality - ITT

Non-CV mortality	Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Base case	Placebo	9,961	10.553	7.526	-	-	-	-
	Icosapent ethyl	20,619	10.851	7.890	10,658	0.299	0.364	29,317
Non-CV mortality equal to the general population norm	Placebo	12,579	12.473	8.790	-	-	-	-
	Icosapent ethyl	23,463	12.653	9.126	10,884	0.180	0.336	32,377

Table 29. Scenario analysis varying non-CV mortality – CV1

Non-CV mortality	Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Base case	Placebo	11,382	10.328	7.340	-	-	-	-

	Icosapent ethyl	21,861	10.712	7.795	10,479	0.384	0.456	23,004
Non-CV mortality equal to the general population norm	Placebo	14,424	12.278	8.604	-	-	-	-
	Icosapent ethyl	25,045	12.526	9.034	10,621	0.248	0.429	24,735

Table 30. Scenario analysis varying non-CV mortality – CV2

Non-CV mortality	Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Base case	Placebo	6,137	11.125	8.007	-	-	-	-
	Icosapent ethyl	17,635	11.195	8.120	11,498	0.071	0.113	101,645
Non-CV mortality equal to the general population norm	Placebo	7,666	12.986	9.282	-	-	-	-
	Icosapent ethyl	19,699	12.972	9.358	12,033	-0.014	0.076	159,004

b. Please provide a scenario in which non-CV related death is assumed to be treatment-independent.

Company response

A scenario is provided below with non-CV related mortality for the placebo arm equal to the icosapent ethyl treatment arm.

Table 31. Scenario analysis varying non-CV mortality - ITT

Non-CV related mortality	Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Base case	Placebo	9,961	10.553	7.526	-	-	-	-
	Icosapent ethyl	20,619	10.851	7.890	10,658	0.299	0.364	29,317
Placebo non-CV mortality equal to icosapent ethyl	Placebo	10,017	10.593	7.553	-	-	-	-
	Icosapent ethyl	20,619	10.851	7.890	10,602	0.258	0.337	31,462

Table 32. Scenario analysis varying non-CV mortality – CV1

Non-CV related mortality	Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Base case	Placebo	11,382	10.328	7.340	-	-	-	-
	Icosapent ethyl	21,861	10.712	7.795	10,479	0.384	0.456	23,004
Placebo non-CV mortality equal to icosapent ethyl	Placebo	11,468	10.383	7.375	-	-	-	-
	Icosapent ethyl	21,861	10.712	7.795	10,394	0.329	0.420	24,742

Table 33. Scenario analysis varying non-CV mortality – CV2

Non-CV related mortality	Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Base case	Placebo	6,137	11.125	8.007	-	-	-	-
	Icosapent ethyl	17,635	11.195	8.120	11,498	0.071	0.113	101,645
Placebo non-CV mortality equal to icosapent ethyl	Placebo	6,159	11.151	8.025	-	-	-	-
	Icosapent ethyl	17,635	11.195	8.120	11,475	0.044	0.095	121,182

c. **Mortality is assumed to be relatively constant over time and is only updated after each event, e.g. not time or age-dependent. It is unclear to the ERG why mortality non-CV related death has not been modelled using parametric survival models. Please justify the exclusion of parametric survival models for mortality.**

Company response

The non-CV related mortality currently applied in our base case is adjusted for age, as the hazard ratio is applied to the UK general population. By applying the hazard ratio to the UK population norm, this allows for the increase in risk associated as individuals age.

The only data that would be available to inform survival curves would be PLD from the REDUCE-IT trial. Clinical trials generally have better all-cause mortality than real-

world data due to strict inclusion and exclusion criteria (e.g. excluding those with additional risks), therefore, we believe modelling mortality with data from the REDUCE-IT trial would not be representative of non-CV death in UK clinical practice.

For these reasons, hazard ratios were sourced from the Emerging Risk Factors Collaboration 2015, which analysed individual participant data from 18 different countries, recruited in 1960–2007. There were no large differences in the hazard ratios by period of recruitment, and findings were broadly similar to the UK Biobank, which recruited UK participants from 2006–2010, suggesting that the data is still applicable today.

d. **Please fit six parametric distributions to the Kaplan Meier mortality data as dependent outcome, i.e. Exponential, Weibull, Gompertz, Log-logistic, Lognormal and Generalised Gamma.**

Company response

Please find below Kaplan Meier survival curves for non-CV related mortality from the REDUCE-IT trial for five of the six requested distributions. The Weibull distribution for both treatment groups failed to provide a coefficient output.

Figure 8. Parametric models fit to non-CV related mortality data (Icosapent ethyl)

Figure 9. Parametric models fit to non-CV related mortality data (Placebo)

Table 34. Parametric models fit to non-CV related mortality data using the AIC and BIC (Icosapent ethyl)

Distribution	AIC	BIC	Position	Plausibility based on visual inspection
Exponential	2416.55726	2422.873316	1	Yes
Weibull	NA	NA	NA	NA
Gompertz	2399.723458	2412.355569	2	No
Log-logistic	2401.621737	2414.253849	2	Yes
Lognormal	2404.913634	2417.545746	2	Yes
Generalised gamma	1617.202603	1636.15077	5	No

Table 35. Parametric models fit to non-CV related mortality data using the AIC and BIC (Placebo)

Distribution	AIC	BIC	Position	Plausibility based on visual inspection
Exponential	2347.715557	2354.031857	1	Yes
Weibull	NA	NA	NA	NA
Gompertz	2344.138294	2356.770894	2	No
Log-logistic	2342.022522	2354.655122	2	Yes
Lognormal	2342.764574	2355.397175	2	Yes
Generalised gamma	2343.976229	2362.92513	5	Yes

e. Please add a scenario in the model in which mortality is estimated using parametric survival curves.

Company response

The CV-related mortality curves are unplausible, with 4/5 curves extrapolated only providing an estimate of less than [redacted] of individual experiencing non-CV related death by the age of 100, and cumulative mortality over the trial period being less than what is expected to be seen in the UK general population for a 64-year-old (see also the limitations of this approach as mentioned in C9.c.). We have provided a scenario which uses these curve estimates for all distributions combined with UK general population mortality.

Table 36. Scenario analyses varying parametric survival curves - ITT

Survival curves to inform non-CV related mortality	Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Exponential	Placebo	11,774	11.826	8.354	-	-	-	-
	Icosapent ethyl	22,368	11.987	8.661	10,594	0.161	0.307	34,511
Log-logistic	Placebo	11,514	11.641	8.233	-	-	-	-

	Icosapent ethyl	21,852	11.649	8.431	10,338	0.009	0.198	52,319
Lognormal	Placebo	11,742	11.802	8.339	-	-	-	-
	Icosapent ethyl	22,222	11.890	8.595	10,480	0.088	0.256	40,906
Weibull	Placebo	-	-	-	-	-	-	-
	Icosapent ethyl	-	-	-	-	-	-	-
Gompertz	Placebo	-	-	-	-	-	-	-
	Icosapent ethyl	-	-	-	-	-	-	-
Generalised gamma	Placebo	-	-	-	-	-	-	-
	Icosapent ethyl	-	-	-	-	-	-	-

Table 37. Scenario analyses varying parametric survival curves – CV1

Survival curves to inform non-CV related mortality	Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Exponential	Placebo	13,445	11.595	8.149	-	-	-	-
	Icosapent ethyl	23,657	11.761	8.501	10,212	0.167	0.352	28,991
Log-logistic	Placebo	13,104	11.382	8.013	-	-	-	-
	Icosapent ethyl	23,136	11.457	8.295	10,032	0.075	0.282	35,585
Lognormal	Placebo	13,376	11.551	8.121	-	-	-	-
	Icosapent ethyl	23,540	11.691	8.454	10,163	0.141	0.333	30,529
Weibull	Placebo	-	-	-	-	-	-	-
	Icosapent ethyl	-	-	-	-	-	-	-
Gompertz	Placebo	12,017	10.732	7.601	-	-	-	-
	Icosapent ethyl	20,885	10.142	7.404	8,868	-0.590	-0.197	Dominated
Generalised gamma	Placebo	13,365	11.544	8.116	-	-	-	-
	Icosapent ethyl	17,530	8.295	6.098	4,165	-3.249	-2.019	Dominated

Table 38. Scenario analyses varying parametric survival curves – CV2

Survival curves to inform non-CV related mortality	Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Exponential	Placebo	7,253	12.428	8.894	-	-	-	-
	Icosapent ethyl	19,177	12.552	9.062	11,924	0.124	0.168	71,107
Log-logistic	Placebo	7,141	12.296	8.804	-	-	-	-
	Icosapent ethyl	18,377	11.826	8.558	11,235	-0.471	-0.247	Dominated
Lognormal	Placebo	7,264	12.441	8.903	-	-	-	-
	Icosapent ethyl	18,842	12.247	8.850	11,578	-0.194	-0.053	Dominated
Weibull	Placebo	-	-	-	-	-	-	-
	Icosapent ethyl	-	-	-	-	-	-	-
Gompertz	Placebo	6,365	11.420	8.211	-	-	-	-
	Icosapent ethyl	16,023	9.740	7.098	9,658	-1.680	-1.113	Dominated
Generalised gamma	Placebo	7,107	12.258	8.779	-	-	-	-
	Icosapent ethyl	18,171	11.636	8.427	11,063	-0.622	-0.351	Dominated

C10. Priority question. The model is based on a 5-point major adverse cardiovascular event (MACE) composite endpoint defined as time from randomisation to the occurrence of any of the following events: CV death, nonfatal myocardial infarction (MI; including silent MI), nonfatal stroke, coronary revascularization, unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalisation. The ERG has various questions related to the use of this composite outcome:

a. **As reported in CS Table 26, the distribution of types of first, second and third plus events is different per treatment, i.e. icosapent vs. placebo. Furthermore, the type of event does not seem to be associated with time, e.g. aging of the cohort. Please justify the use of treatment-dependent and time-independent distributions of the types first, second, and third**

events. In addition, elaborate on the clinical plausibility of these assumptions.

b. **Please include a scenario in which the distributions of the types of first, second, and third events are assumed to be treatment-independent.**

Company response

Provided below is a scenario with distributions of the types of first, second, and third events in the placebo treatment arm are assumed to be equal to the icosapent ethyl treatment arm.

Table 39. Scenario in which the distributions of the types of first, second, and third events are assumed to be treatment independent

	Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
ITT	Placebo	9,866	10.496	7.496	-	-	-	-
	Icosapent ethyl	20,619	10.851	7.890	10,753	0.356	0.394	27,311
CV1	Placebo	11,375	10.292	7.319	-	-	-	-
	Icosapent ethyl	21,861	10.712	7.795	10,487	0.420	0.476	22,010
CV2	Placebo	5,939	11.057	7.986	-	-	-	-
	Icosapent ethyl	17,635	11.195	8.120	11,695	0.138	0.134	87,334

c. **Please include a scenario in which the distributions of the types of first, second, and third events are assumed to be time-dependent.**

Company response

This scenario is not plausible with the data from the trial.

d. **Both CS Tables 7 and 26 present the distribution of types of first, second and third plus events as different per treatment. However, the distributions do not seem to match. Please explain why the proportions between Tables 7 and 26 do not match.**

Company response

The number of events that occurred for each individual component that contributes to the composite primary endpoint is provided in Table 7 in the CS. The distribution of CV death, nonfatal MI, nonfatal stroke, coronary revascularization and unstable angina according to first, second and third plus event are presented in Table 26 in the CS. The first event distribution aligns with the ITT results.

e. **In CS Table 7, unstable angina is referred to as *"unstable angina requiring hospitalization"*, whereas in CS Table 26 it is described as *"unstable angina"*. Please elaborate on which definition was used in the model.**

Company response

We confirm that the inputs used in the model are those for unstable angina requiring hospitalisation, and this discrepancy was solely due to a simplification of wording within the model.

Adverse events

C11. The individual treatment-emergent adverse events *(*TEAE*s)* with an incidence of ≥5% in either treatment arm and statistically significantly different were included in the model. However, the cost-effectiveness model only includes four while two other adverse events, diarrhoea and anaemia, that fulfilled the criteria (as mentioned in *CS* A.6.5) were left out.

a. Please provide an explanation why the adverse events diarrhoea and anaemia were not included.

Company response

We can confirm diarrhoea and anaemia were not considered in the model because only adverse events that were statistically significantly in favour of placebo were taken into account. The incidence of anaemia was 4.7% versus 5.8%, and the incidence of diarrhoea was 9.0% versus 11.1%, for the icosapent ethyl and placebo groups, respectively.

b. The disutility for peripheral oedema of 0.01 used in the model is different to the disutility described in the reference of Sullivan (https://doi.org/10.1016/j.jval.2016.05.018) (0.03) although the last one is the

disutility for peripheral oedema in individuals with diabetes. Please check this and provide more information which disutility you exactly derived from the article by Sullivan et al.

Company response

The disutility value of 0.005 used in the model was calculated using the unadjusted mapped EQ-5D score for individuals without diabetes and with peripheral edema from Sullivan *et al.* (utility value = 0.736). The disutility was calculated by subtracting the utility value 0.736 from 1, and was adjusted to only last seven days.

c. The disutility for constipation in CS B 3.4.4. Table 31 is 0.001 while the reference of Christensen (https://doi.org/10.1016/j.sjpain.2015.12.007) seems to indicate a larger impact on quality of life as a result of constipation (difference between currently constipated or not is 0.07), suggesting a larger disutility than 0.001. Please explain how the 0.001 was derived. In addition, the model does not use 0.001 but 0.000. Please check this and make sure it is consistent with the CS report.

Company response

The disutility value of 0.001 was calculated using the difference between patients that were currently constipated or not (utility value = 0.074) from Christensen *et al.* and adjusted to only last seven days as it was assumed the adverse events would not last longer than a week. To confirm, there was an error in the model and it has been corrected to use 0.001 as the disutility value for constipation in the updated CEM provided.

d. The disutility for serious bleeding is taken from Tengs et al. (ref: https://doi.org/10.1097/00005650-200006000-00004). However, it is unclear whether the disutility is based on the same preference-based measure as the other (dis)utilities in the model (the EQ-5D). Please check this. If that is not the case, then use the disutility for serious bleeding based on the EQ-5D.

Company response

To confirm, the disutility for serious bleeding taken from Tengs *at al.* is not based on the EQ-5D however, we were not able to source a more appropriate disutility value for

serious bleeding from the literature, therefore the value from Tengs *et al.* will still be used in the model.

Quality of life

C12. Section B.3.4.5 of the CS describes that baseline utilities were derived from Stevanovic (https://doi.org/10.1371/journal.pone.0152030) and O'Reilly (https://doi.org/10.1007/s11136-010-9828-9) for primary and secondary prevention and the multipliers for the acute/post acute health states from CG181.

a. Please provide a justification for using the utility multipliers from CG181 as input for the acute and post-acute health states in the model.

Company response

The utility multipliers from CG181 were obtained from a study by Ward *et al.* that modelled the cost-effectiveness of statin treatment versus placebo in both the primary and secondary prevention of CVD, and a study by The National Collaborating Centre for Primary Care (NCCPC) that modelled the cost-effectiveness of high intensity statin treatment against medium intensity statin treatment in the secondary prevention of CVD. The values were considered appropriate by NICE in the latest lipid guidance, and they appropriately reflect the target population of icosapent ethyl.

b. Please provide sensitivity analyses with utility values from ODYSSEY (TA 393) to examine the impact on the incremental cost-effectiveness ratio (ICER).

Company response

A scenario applying utilities sourced form ODYSSEY (TA 393) is provided in the Table 40.

Table 40. Sensitivity analysis applying utilities sourced from ODYSSEY (TA393)

Population	Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
ITT	Placebo	9,961	10.553	7.831	-	-	-	-
	Icosapent ethyl	20,619	10.851	8.116	0.299	0.285	37,460	37,460
CV1	Placebo	11,382	10.328	7.692	-	-	-	-

	Icosapent ethyl	21,861	10.712	8.049	10,479	0.384	0.358	29,294
CV2	Placebo	6,137	11.125	8.187	-	-	-	-
	Icosapent ethyl	17,635	11.195	8.276	11,498	0.071	0.089	129,009

c. In the model, the references for the baseline utilities for primary and secondary prevention are the articles by Ara and Brazier while Stevanovic and O'Reilly are not mentioned. Please explain which baseline utilities were exactly used and from which source.

Company response

We confirm the baseline utilities used within the model were those described on page 108 (Section B.3.4.5) of the company submission, based on the studies by Stevanović *et al*. and O'Reilly *et al*. The reference provided in the CEM was an oversight and has been updated in the latest version of the CEM.

C13. In the CS it is mentioned that *"patients experience an acute disutility for the first 60 days following an event, after which they experience a chronic post-event utility, as ratified by UK clinical experts"*.

a. Please explain step-by-step how this 60-day disutility was included in the model. Please include references to the corresponding sheets/cells in the model.

b. Given the way the 60-day acute disutilities are implemented in the CS base-case, please provide information on how it is prevented that (dis)utilities are overestimated when a patient would get a fatal event within the first 60-days after the CV event.

c. Given the way the 60-day acute disutilities are implemented in the CS base-case, please justify that the full 60 days are indeed incorporated for each event when applicable (i.e. when the full 60 days are applicable and a shorter duration when a shorter duration is applicable).

Company response

The live health state distributions (clinical input sheet B132:BI15133) have been used to calculate the proportion of total events that have occurred in the previous 60 days. It calculates this by using a total of the event proportions that have occurred from cycle 0 – current cycle then dividing by the total proportion of events that have occurred in the previous 60 days.

Due to being unable to track individual patients, this proportion is an estimate for the cohort. When calculating, it works out the proportion of patients that have experienced an event in the last 60 days regardless of if they have died or had a nonfatal event. This proportion is then applied to all patients in the cohort of interest after CV mortality and non-CV mortality are applied to the cohort; therefore, it is used to estimate the proportion of surviving patients in the specific cohort that have had an event in the last 60 days.

Costs and resource use

C14. Priority question. The analysis considers time to treatment discontinuation of icosapent ethyl, and the distribution to model this was chosen based on goodness of fit statistics.

a. **Please confirm that after discontinuation of icosapent ethyl patients use statins alone.**

Company response

Patients who discontinue icosapent ethyl receive standard of care aligned with their current treatment regimen. In regard to prespecified medications, this will be statin alone for the majority of individuals. A small proportion of patients will receive ezetimibe in addition to their statin regimen. All patients continue to receive standard of care for other risk factors (e.g., hypertension, diabetes) as determined by their regular clinicians.

b. **Please justify that the chosen distribution is plausible to model the extrapolation of time to treatment discontinuation beyond the time horizon of REDUCE-IT.**

Company response

In the absence of clinical practice experience with icosapent ethyl, the distribution for the TTD curves were chosen based on best fit curve using the AIC and BIC and visual inspection.

c. **Please perform scenario analyses with all distributions that were fitted to model time to treatment discontinuation (Exponential, Weibull, Gompertz, Log-logistic, Lognormal and Generalised Gamma), and provide a model file that enables these analyses.**

Company response

Scenario analyses for all distributions considered for the treatment discontinuation curve are presented in Table 41 to Table 43.

Table 41: Scenario analyses with all distributions considered for the treatment discontinuation curve - ITT

Parametric survival model	Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Exponential	Placebo	9,961	10.553	7.526	-	-	-	-
	Icosapent ethyl	20,619	10.851	7.890	10,658	0.299	0.364	29,317
Weibull	Placebo	9,961	10.553	7.526	-	-	-	-
	Icosapent ethyl	21,268	10.851	7.890	11,307	0.299	0.364	31,102
Gompertz	Placebo	9,961	10.553	7.526	-	-	-	-
	Icosapent ethyl	22,017	10.851	7.890	12,056	0.299	0.364	33,163
Log-logistic	Placebo	9,961	10.553	7.526	-	-	-	-
	Icosapent ethyl	21,810	10.851	7.890	11,849	0.299	0.364	32,594
Lognormal	Placebo	9,961	10.553	7.526	-	-	-	-
	Icosapent ethyl	22,250	10.851	7.890	12,289	0.299	0.364	33,805
Generalised gamma	Placebo	9,961	10.553	7.526	-	-	-	-
	Icosapent ethyl	21,014	10.851	7.890	11,053	0.299	0.364	30,404

Table 42: Scenario analyses with all distributions considered for the treatment discontinuation curve – CV1

Parametric survival model	Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Exponential	Placebo	11,382	10.328	7.340	-	-	-	-
	Icosapent ethyl	21,861	10.712	7.795	10,479	0.384	0.456	23,004
Weibull	Placebo	11,382	10.328	7.340	-	-	-	-
	Icosapent ethyl	22,515	10.712	7.795	11,133	0.384	0.456	24,439
Gompertz	Placebo	11,382	10.328	7.340	-	-	-	-
	Icosapent ethyl	23,260	10.712	7.795	11,878	0.384	0.456	26,074
Log-logistic	Placebo	11,382	10.328	7.340	-	-	-	-
	Icosapent ethyl	23,005	10.712	7.795	11,623	0.384	0.456	25,514
Lognormal	Placebo	11,382	10.328	7.340	-	-	-	-
	Icosapent ethyl	23,422	10.712	7.795	12,040	0.384	0.456	26,430
Generalised gamma	Placebo	11,382	10.328	7.340	-	-	-	-
	Icosapent ethyl	22,072	10.712	7.795	10,690	0.384	0.456	23,466

Table 43: Scenario analyses with all distributions considered for the treatment discontinuation curve – CV2

Parametric survival model	Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Exponential	Placebo	6,137	11.125	8.007	-	-	-	-
	Icosapent ethyl	17,635	11.195	8.120	11,498	0.071	0.113	101,645
Weibull	Placebo	6,137	11.125	8.007	-	-	-	-
	Icosapent ethyl	18,268	11.195	8.120	12,131	0.071	0.113	107,244
Gompertz	Placebo	6,137	11.125	8.007	-	-	-	-

	Icosapent ethyl	19,081	11.195	8.120	12,944	0.071	0.113	114,433
Log-logistic	Placebo	6,137	11.125	8.007	-	-	-	-
	Icosapent ethyl	18,915	11.195	8.120	12,779	0.071	0.113	112,968
Lognormal	Placebo	6,137	11.125	8.007	-	-	-	-
	Icosapent ethyl	19,375	11.195	8.120	13,239	0.071	0.113	117,034
Generalised gamma	Placebo	6,137	11.125	8.007	-	-	-	-
	Icosapent ethyl	17,962	11.195	8.120	11,825	0.071	0.113	104,537

C15. Priority question. The choice of source for estimates for acute health state costs (Table 40 of the CS), post-event health state costs (Table 42 of the CS) and follow up and monitoring costs (Tables 44 and 47 of the CS) deviates from previous TAs (TA393 and TA394) which use CG181 as a source.

a. **Please justify the choice of Danese et al. 2016 as source instead of using CG181. Why does the company think the costs of specific events will differ for patients receiving lipid modifying treatment compared to those not receiving that therapy? If there is no theoretical or empirical reason for events costs to differ then a broader evidence search would be justified.**

Company response

Danese *et al*. 2016 was used as a reference source for costs because the estimates within this paper were calculated using real-world data for the UK, and incremental costs were estimated using within-person differences to minimise confounding. All patients received lipid-modifying therapy, maximising the relevance for this population. Danese *et al*. 2016 enabled us to retrieve all the cost inputs for this model from a single source, whereas CG181 did not include costs for coronary revascularization. The costs from Danese *et al*. 2016 were also used in the CADTH submission as they were considered to be the most recent and relevant costs, whereas CG181 used inflated costs from older papers (2005-2008).

b. **Please explain how exactly the post event costs (CS Table 40) were imputed from the results reported in Danese et al. 2016 (most notably Table 2).**

Company response

The costs provided in Table 2 (Column 8) of Danese *et al*. 2016 were inflated to 2019 using the CPI, then divided by 365.25 to determine an average daily cost.

c. **Please explain and justify for each acute event, for which period post-event costs are considered in the model, and how it is prevented that these costs are overestimated if another acute event (including a fatal event) takes place within this period.**

Company response

We acknowledge this could be a limitation of our analysis however, we would expect the majority of acute costs to be incurred immediately when an event occurs due to hospitalisation and treatment for a non-fatal event.

d. **Please provide a comparison of the estimates of these costs in the CS (which are based on Danese et al. 2016 or expert opinion) with estimates from CG181.**

Company response

In cases where data from CG181 was not available, data from the base case dataset have been applied. The average costs are shown in Table 44.

Table 44. Average costs - ITT

Cost type	Danese *et al.* 2016 (Base case)		CG181	
	Icosapent Ethyl	Placebo	Icosapent Ethyl	Placebo
First event				
Acute period	[redacted]	[redacted]	[redacted]	[redacted]
Post event	[redacted]	[redacted]	[redacted]	[redacted]
Second event				
Acute period	[redacted]	[redacted]	[redacted]	[redacted]
Post event	[redacted]	[redacted]	[redacted]	[redacted]
3+ event				
Acute period	[redacted]	[redacted]	[redacted]	[redacted]
Post event	[redacted]	[redacted]	[redacted]	[redacted]

e. **Please perform scenario analyses with CG181 as source for acute health state costs and post-event health state costs.**

Company response

Table 45. Scenario analyses using CG181 as a source for acute health state and post-event state costs

Population	Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
ITT	Placebo	10,738	10.553	7.526	-	-	-	-
	Icosapent ethyl	21,244	10.851	7.890	10,506	0.299	0.364	28,899
CV1	Placebo	12,101	10.328	7.340	-	-	-	-
	Icosapent ethyl	22,447	10.712	7.795	10,346	0.384	0.456	22,711
CV2	Placebo	7,139	11.125	8.007	-	-	-	-
	Icosapent ethyl	18,370	11.195	8.120	11,232	0.071	0.113	99,291

f. **Please perform scenario analysis with Ryder et al. (PharmacoEconomics 2019 37, 895–919) as source for acute health state costs and post-event health state costs. This publication includes other UK based cost estimates for CVE, i.e.**

   i. **Luengo-Fernandez R, Yiin GS, Gray AM, Rothwell PM. Population-based study of acute- and long-term care costs after stroke in patients with AF. Int J Stroke. 2013;8(5):308–14.**

   ii. **Walker S, Asaria M, Manca A, Palmer S, Gale CP, Shah AD, et al. Long-term healthcare use and costs in patients with stable coronary artery disease: a population-based cohort using linked health records (CALIBER). Eur Heart J Qual Care Clin Outcomes. 2016;2(2):125–40**

   iii. **Gray AM, Murphy J, Altman DG, Benedetto U, Campbell H, Flather M, et al. One-year costs of bilateral or single internal mammary grafts in the arterial revascularisation trial. Heart (British Cardiac Society). 2017;103(21):1719–26.**

Company response

Scenario analysis using Ryder *et al*. is presented in Table 46. In cases where data from Ryder *et al*. was not available, data from the base case dataset has been used instead.

Table 46. Scenario analyses using Ryder *et al*. as a source for acute health state and post-event state costs

Population	Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
ITT	Placebo	14,811	10.553	7.526	-	-	-	-
	Icosapent ethyl	24,588	10.851	7.890	9,777	0.299	0.364	26,894
CV1	Placebo	16,615	10.328	7.340	-	-	-	-
	Icosapent ethyl	26,200	10.712	7.795	9,585	0.384	0.456	21,040
CV2	Placebo	10,062	11.125	8.007	-	-	-	-
	Icosapent ethyl	20,639	11.195	8.120	10,578	0.071	0.113	93,510

Scenario and sensitivity analyses

C16. Please perform the following scenario and sensitivity analyses (deterministic and probabilistic analysis).

a. Scenario analyses with a time horizon of 5 and 10 years.

Company response

Table 47. Scenario analyses varying time horizon

Population	Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
5 years								
ITT	Placebo	2,954	4.283	3.197	-	-	-	-
	Icosapent ethyl	9,600	4.307	3.238	6,646	0.024	0.041	161,412
CV1	Placebo	3,502	4.260	3.189	-	-	-	-
	Icosapent ethyl	9,980	4.294	3.245	6,478	0.034	0.056	116,530
CV2	Placebo	1,690	4.335	3.209	-	-	-	-

	Icosapent ethyl	8,734	4.336	3.219	7,044	0.001	0.010	741,278
10 years								
ITT	Placebo	5,791	7.278	5.332	-	-	-	-
	Icosapent ethyl	15,153	7.358	5.459	9,363	0.080	0.128	73,222
CV1	Placebo	6,788	7.204	5.275	-	-	-	-
	Icosapent ethyl	15,935	7.316	5.445	9,147	0.112	0.169	54,049
CV2	Placebo	3,371	7.451	5.457	-	-	-	-
	Icosapent ethyl	13,346	7.458	5.488	9,975	0.007	0.031	317,940

b. If the search (see question A10) results in additional papers, please justify why these are considered to be relevant or not. If the search results in additional relevant papers, please use the information in these papers in additional sensitivity and scenario analyses.

Company response

No additional papers have been included.

c. All sensitivity and scenario analyses in the CS and the analyses requested in this clarification letter for the primary prevention subgroup and secondary prevention subgroup separately.

Company response

CS scenarios for the CV1 and CV2 subgroup have been provided in question C.5 and any requested in this clarification letter have been presented alongside the ITT scenario results.

Validation and transparency

C17. Priority question. B.3.10 of the CS states that the *"model has undergone thorough internal and external validation"*. Further (reporting of) validation of the economic model would be desirable.

a. Please use the AdViSHE tool (https://doi.org/10.1007/s40273-015-0327-2) to assess the validity of the economic model.

b. **Please report on the face validity assessment of the:**
    i. **model structure,**
    ii. **model assumptions,**
    iii. **model inputs,**
    iv. **intermediate outcomes and**
    v. **final outcomes.**

c. **The company refers to (clinical) expert opinion to support assumptions and choices made for the economic model. Please clarify**
    i. **what expert(s) was/were used to derive the expert opinion?**
    ii. **why this expert(s) would qualify as expert for this specific aspect?**
    iii. **what were the expert response(s)?**
    iv. **whether an advisory board meeting was held and what the output of this meeting was (i.e. meeting summary/notes)?**

d. **Please conduct a cross validation with other economic models focusing on a related decision problem. This includes NICE TA393, NICE TA394, NICE TA420 as well as the CS to the CADTH for icosapent ethyl to prevent cardiovascular events in statin-treated patients. Please consider the:**
    i. **model structure,**
    ii. **model assumptions,**
    iii. **model inputs,**
    iv. **intermediate outcomes and**
    v. **final outcomes.**

e. **Please assess the external validity of model inputs, intermediate outcomes as well as final outcomes using**
    i. **evidence used to develop the economic model**
    ii. **evidence not used to develop the economic model**

Company response

An additional quality assessment of the model has been completed by an internal health economist outside of the immediate project team. The model structure diagram was presented to UK clinical experts who believed it reflected the disease progression

well, however, they did not have the technical knowledge to comment on the implementation of the formulas in the model. All model assumptions and inputs were also ratified by these UK clinical experts. As icosapent ethyl is the first treatment for the targeted indication, the model outcomes could not be validated or compared to existing data in the literature. However, please find an overview of the QC conducted in the file called “CEM QC_Final version_18Aug21”. This QC involved checking the face validity of the model as well as pressure testing input parameters to check the validity of the model results. Furthermore, all input parameters and formulas have been quality checked by an internal health economist outside of the immediate project team.

The model assumptions and inputs were validated by two UK clinical experts. The experts used to derive the expert opinion to support assumptions and decisions made with regard to the economic model were: ***Professor Kausik Ray*** and ***Professor Chris Packard***. They both qualify as experts for this specific aspect due to their expertise within this disease area:

Professor Kausik Ray: currently a Professor of Public Heath in the Department of Public Health and Primary Care at Imperial College London as well as Honorary Consultant Cardiologist at the Imperial College NHS Trust. Research interests have focused on the prevention of cardiovascular disease with a special interest in lipids and diabetes. His work has influenced American Heart Association/American College of Cardiology and European Society of Cardiology guidelines, and his work on statins and diabetes risk in particular led to a global label change for statins by the FDA and EMEA. He is a Fellow of the American College of Cardiology, the European Society of Cardiology, the American Heart Association and the Royal College of Physicians. He is also a member of the British Cardiovascular Society and European Atherosclerosis Society. He has been the national lead investigator and has served on the steering and executive committees for several major medical trials.

Professor Chris Packard: currently an Honorary Senior Research Fellow at the Institute of Cardiovascular and Medical Sciences at the University of Glasgow. Over his career he has focussed on two aspects of atherosclerosis research, lipoprotein metabolism and how it is affected by diets and drugs, and large-scale clinical trials of lipid lowering agents. More recently his interest has widened to include investigations

of emerging risk factors for coronary heart disease and the consequences for social deprivation for health. As study director and one of the main investigators of the West of Scotland Coronary Prevention Study (WOSCOPS) and the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER), Professor Packard helped establish the evidence base for statin use in coronary heart disease prevention.

An advisory board meeting was not held. Instead, 1:1 interviews were conducted with both clinical experts with interview summary/notes taken for each interview and responses combined. The expert responses have been added as an attachment to these clarification questions. See file called "Validation of assumptions in the UK cost-effectiveness model_v1.0_05_July_2021 – responses".

After considering previous NICE appraisals (Table 48**Table *48*. A brief summary of similar appraisalsTable *48*.**) and the CADTH submission for icosapent ethyl, we concluded that they all failed to model one key aspect, multiple subsequent events, as they all considered a cycle length of one year. Our shorter cycle length is pivotal in demonstrating the true value of icosapent ethyl in terms of the impact of reducing CV events and associated costs. Treatment waning was not considered, and assumptions were different for each appraisal.

Table 48. A brief summary of similar appraisals

	TA393	**TA394**	**TA420**
Model structure	Markov, 1 year cycle	Markov, 1 year cycle Composite states - no data to inform them, and several arbitrary assumptions made about the costs and health effects in these states	n/a
Model assumptions	The relationship between LDL-C	Treatment would last indefinitely,	Maximum treatment length of 3 years

	concentration and CVD was the same for patients with or without a history of CVD		
Model inputs	ODYSSEY trials	Lack of long-term data, the rate ratio from Benn *et al.* (2012) highly overestimated the risk of CVD among people with heterozygous-familial hypercholesterolaemia, and cast doubt about the validity of the estimated cost-effectiveness of evolocumab for this population.	Use of secondary outcomes (from PEGASUS-TIMI 54) as inputs were deemed acceptable due to the large population. Risk was based on the ITT population, so likely to be conservative.

As mentioned before, icosapent ethyl is the first treatment for the targeted indication, therefore the model outcomes could not be validated or compared to existing data in the literature. However, a comprehensive quality assessment of the model was conducted, and model assumptions and inputs were validated by UK clinical experts.

C18. Technical validation was conducted in a manner which is not sufficiently transparent for the ERG (detailed descriptions with results of the tests are missing in CS section B.3.9.1). Moreover, the Markov traces contain negative values, and the "Check" columns contain "FALSE" values (e.g. cell AH14009 in both Markov trace worksheets), these issues both indicate a lack of technical (or internal) validity.

a. Please elaborate (and potentially provide a corrected version of the economic model with a change log) regarding the abovementioned issues that potentially threaten the technical (or internal) validity of the economic model.

b. Please use the TECH-VER checklist (https://doi.org/10.1007/s40273-019-00844-y) to assess the technical verification of the economic model and report the results.

Company response

Negatives and FALSE values in the traces were being caused by the constant CV death rate which did not have a restriction included to stop including new CV death patients once all individuals in the cohort had died. We have included the cells edited to correct this in a change log within the latest version of the CEM.

Due to time constraints, an additional quality assessment using an internal checklist has been completed by an internal health economist not involved in the development of the original CEM. Please find an overview of this QC in the file called "CEM QC_Final version_18Aug21" .

Any changes implemented to correct errors identified by the ERG or internal QC have been provided in the CEM model.

c. In addition to the issues mentioned above, there are inconsistencies between the CS and the economic model. For instance, in the CS it is stated that *"where the standard error was unavailable to calculate upper and lower CIs, this was assumed to be 10% of the mean value"*. However, in the economic model 20% is used. Similarly, the description on the "Introduction" worksheet is inconsistent with the CS. Please cross check the CS and economic model for inconsistency, clarify these inconsistencies and potentially provide a corrected version of the economic model with a change log.

Company response

This was an oversight in the write up, the correct value is 20%.

d. Whenever possible empirical estimates should be used to inform the standard errors for use in sensitivity analyses (instead of using X% of the mean). For

instance, for CS Table 40 empirically estimated standard errors should be used for the estimates retrieved from Danese 2016(https://doi.org/10.1136/bmjopen-2016-011805).

Company response

This has now been updated in the model parameters sheet of the CEM.

C19. Figure 29 of the CS seems to indicate that there is a curvilinear relationship between the incremental costs and incremental effects.

a. Please provide the economic model, including the probabilistic results that were used to construct CS Figures 29 to 31.

Company response

The updated results have now been provided for in the economic models submitted.

b. Please clarify what causes the curvilinear relationship between the incremental costs and effects and elaborate on the plausibility.

Company response

There is no reason to believe the PSA is incorrect, as the model been through a full QC (see file called “CEM QC_Final version_18Aug21”).

C20. The use of the daily cycle time with half cycle correction as well as the tunnel states for the ‘day’ that patients experience a (1st, 2nd or 3rd) cardiovascular event (see also questions in the model structure section C1-C4) make the model more complex, less transparent and “computationally expensive”

Please elaborate whether the trade-off between the daily cycle, half cycle correction, the tunnel states for the ‘day’ that patients experience an event and model complexity, transparency as well as computational burden justifies including these model features.

Company response

Several costly events such as strokes and MI are missed when a monthly cycle is used, as shown in Table 6, therefore a daily cycle has been used in order to ensure such events are accounted for. The half cycle correction was included in the economic model to align with NICE DSU recommendations, though it has minimal impact on the

ICER as shown in Table 7. During the acute period of events, individuals would be unable to experience a secondary event, therefore the decision was made to apply all costs associated with an event on the specific day the event occurs including rehab costs etc. and apply utilities for the acute period for the next 60 days post event, as recommended by two UK clinical experts that were consulted. Patients were then able to quickly progress to the post-event state where they were able to experience a subsequent event the next calendar day. Without these features, the model would not truly be reflective of what happens in real-world UK clinical practice.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Icosapent ethyl with statin therapy for reducing the risk of cardiovascular events in adults with elevated triglycerides [ID3831]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]
2. Name of organisation	HEART UK- The Cholesterol Charity
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	HEART UK is the Nation's Cholesterol Charity providing support to individuals with raised cholesterol, atherosclerosis and other lipid conditions. We provide high quality literature, a Cholesterol Helpline run by cardiac nurses and dietitians, an extensive website, a range of educational videos, the Ultimate Cholesterol Lowering Plan© and a range of electronic communication tools aimed at increasing the awareness of cholesterol. HEART UK also supports the health care professionals who work and care for patients (and their families) with raised and unhealthy patterns of high cholesterol and other dyslipidaemias. HEART UK hosts a world class annual scientific conference and other networking events for clinicians, researchers, GP's, nurses and dietitians. The charity maintains a health professional membership scheme, provides resources and training to health care professionals.
4b. Has the organisation received any funding from the	£0 from the manufacturer of Icosapent ethyl £25,200 from each of Daiichi-Sankyo, Amgen, Bayer and Novatis for membership of the CVD Collaborative

manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	£25,000 from each of Novatis, Boehringer Ingelheim, Sanofi, Daiichi-Sankyo for the Primary Care Education Programme £60,000 for a cholesterol awareness and testing campaign £10,800 from Novatis for an LP(a) audit £6,994 from Bayer for adaptation of 24 recipes
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	We have a Cholesterol Helpline with direct contact via telephone and email. The helpline supports people with information to make informed choices. Additionally we have an extensive website that receives over 4million views a year and extensive engagement on social media.

Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	NHS Health Checks, which includes a cholesterol test, are important cornerstone of CVD prevention and can be the first indication of a need for treatment. However, NHS Health Checks are delivered inconsistently across the country with very poor uptake in many places. Diet and lifestyle advice and medication to treat high cholesterol following an NHS Health Check, where a patient has raised LDL-C also varies enormously across the country. In 2020 97% of NHS Health Checks were cancelled. Access to cholesterol testing is variable and we regularly hear reports of people being denied access to a test, including people where a family history indicates familial hypercholesterolaemia.
8. Is there an unmet need for patients with this condition?	Cardiovascular disease (CVD) is the underlying cause of 26% of all deaths in the UK, which includes heart attacks, strokes and dementia. This equates to approximately 160,000 deaths each year or an average of 435 people each day. At least, 42,000 of these deaths occur prematurely and, in many cases, can be prevented. Over half the adult population in England have raised cholesterol yet accessing cholesterol test to measure cholesterol levels is a serious barrier and adherence to medication, usually statins is very poor and reportedly 75% of patients stop taking lipid lowering therapies after years.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Many patients are reluctant to express doubts and concerns about medicines and frequently will stop taking medicine without exploring all additional alternatives. For example, 75% of people started on a statin discontinuing treatment within 2 years and will be at an increased risk of major CV events. Those at high CVD risk who report a potential intolerance to recommended high intensity statin treatment may be offered a lower dose statin, an alternative statin or be advised to stop taking statins for 4 – 6 weeks before ezetimibe. This pathway may not always be completed by many patients because it is time consuming and doesn't demonstrate any positive benefit for the patient and will account for some of the variations in prescribing and patients discontinuing treatment.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	1. Those living in England's most deprived areas are almost 4 times as likely to die prematurely from CVD than those in the least deprived areas. 2. Having a poor diet and being overweight or obese increases the risk of developing CVD. Between 1993 and 2000, there was a sharp increase in obesity, though the rate of increase has since slowed. According to NHS Digital's Health Survey for England, in 2019 36% of adults were overweight and 28% were obese. People living in the most deprived areas had the highest prevalence of obesity and very high waist circumference. 3. Compared with the general population, people with severe mental illness are much more likely to develop and die from preventable physical health conditions, like CVD. This increased risk is largely caused by modifiable lifestyle factors, many of which people with severe mental illness may find more difficult manage than the general population. 4. People with learning disabilities are at increased risk of developing CVD from both genetic factors and lifestyle factors such as poor diet and inactivity.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues	
13. Are there any other issues that you would like the committee to consider?	There are already too many barriers to prevent patients from accessing effective treatments that they are willing to take for the rest of their lives, starting from a point of poor awareness of the importance of managing healthy cholesterol, getting a test, taking action and onwards to treatment options. This medication offers a solution to the long term treatment of patients, which will lead to a reduction in the number of heart attacks, strokes and other consequences of poorly managed and high cholesterol by introducing an additional option.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- Long term adherence to lipid lowering therapies is very poor
- Access to long term treatment remains very poor
- CVD is worsening
- There are already too many barriers to effective treatments that are accepted by the patient. No more should be introduced.
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Icosapent ethyl with statin therapy for reducing the risk of cardiovascular events in adults with elevated triglycerides [ID3831]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**ABCD**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ **Yes** a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**ABCD (Association of British Clinical Diabetologists) – specialist body and charitable trust**
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	**No**

If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Correct dyslipidaemia and reduce CVD
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	NNT < 30 to prevent 1 primary outcome

x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Statisn –Fibrates-PSKI
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	No
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please	Yes but no UK guidance based on REDUCE-IT

state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	Enhance DM and non DM CVD prevention in addition to statins
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	As part of CVD prevention strategy
• How does healthcare resource use differ between the technology and current care?	No effective alternative and OTC fish oils contain both DHA and EPA with less effect
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist lipid and DM-CVD clinics and primary care
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Enhanced on basis of residual unmet need
• Do you expect the technology to increase length of life more than current care?	Yes
• Do you expect the technology to increase health-related quality of life more than current care?	Yes
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	DM = non DM benefit
The use of the technology	

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	No important challenges to introduction
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Lipid measurement as per standard care
15. Do you consider that the use of the technology will result in any substantial health-	No

related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	yes
• Is the technology a 'step-change' in the management of the condition?	Yes - In as much as not currently available and additional clear benefit
• Does the use of the technology address any particular unmet need of the patient population?	Residual dyslipid after statins and in those with CVD

17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Bleeding risk
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	All CVD outcomes including revascularisation
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	

• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. How do data on real-world experience compare with the trial data?	None yet
Equality	
21a. Are there any potential equality issues that should be taken into account when considering this treatment?	No

21b. Consider whether these issues are different from issues with current care and why.	

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.

- Significant unmet clinical need and residual dyslipidaemia common after statin Rx for CVD esp in diabetes
- Current therapies contain birth DHA and EPA fatty acids which diminish the benefit
- There is robust clinical evidence from REDUCE-IT trial of benefit
-
-

Thank you for your time.

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NHS England Submission

Icosapent ethyl for treatment of hypertriglyceridemia

1. Hypertriglyceridemia (defined as >1.69mmol/L) is a common metabolic disorder in adults and plays a causal role in contributing to Atherosclerotic Cardiovascular Disease (ASCVD) risk. While there is incontrovertible evidence that high-intensity statins reduce the risk for ASCVD events in the primary and secondary care settings a substantial amount of residual risk remains despite significant reduction in low-density lipoprotein cholesterol (LDL-C). Medications available to treat elevated triglycerides to address the goal of reducing residual risk and ASCVD events (including niacin, fibrates, and omega-3 fatty acids) have failed to show benefit in statin treated patients.

2. The REDUCE-IT trial explored the effect of high-dose, purified omega-3 fatty acids for triglyceride lowering on the prevention of ASCVD. In the trial of individuals at high ASCVD risk, administration of 4g/day of Icosapent ethyl (an ethyl ester of eicosapentaenoic acid [EPA]) compared to mineral oil placebo for 4.9 years resulted in a 25% lower risk of ASCVD events in statin treated patients.

3. NHSE note publication of the trial results generated considerable debate, as the findings were very different from previous studies of omega-3 fatty acids. The magnitude of the benefit, similar to that seen with some statins, was much greater than predicted based on change in triglyceride levels. In addition, the mineral oil comparator raised levels of atherogenic lipoproteins and C-reactive protein at 1 year.

4. The authors of the REDUCE-IT trial acknowledge the ASCVD benefits are not explained by the degree of change in triglycerides or atherogenic and inflammatory biomarkers and postulate the majority of the cardiovascular benefit is driven by pleiotropic effects of EPA; based on the finding that on-treatment levels of EPA correlated with outcome benefit. The authors also acknowledged the deleterious effects of mineral oil on lipid traits and C-reactive protein could increase the estimated risk of ASCVD.

5. Recently, the results of the STRENGTH trial have been published. In this population with established ASCVD or at high risk for ASCVD, administration of 4g/day eicosapentaenoic acid (EPA-75%) and docosahexaenoic acid (DHA-25%) compared to corn oil for 3.5 years had no beneficial effect on risk for ASCVD. In both REDUCE-IT and STRENGH the active interventions produced almost identical reductions in triglyceride levels. The plasma levels of EPA were 45% higher in REDUCE-IT but a post hoc analysis of STRENGTH that looked at event rates according to tertiles of achieved EPA and DHA (with the top tertile having higher plasma levels of EPA than REDUCE-IT) found no evidence that EPA was beneficial or DHA was harmful.

6. Given these divergent findings, Danish investigators tested the hypothesis that the contrasting results on prevention of ASCVD in REDUCE-IT and STRENGTH trials could be explained by differences in the effect of active and comparator oils on lipid traits and C-reactive protein. The analysis used individual patient data from the Copenhagen General Population Study (CGPS) to mimic designs for the trials. The authors concluded different effects of comparator oils could partly explain the contrasting results. The deleterious effect of mineral oil in REDUCE-IT increased predicted ASCVD risk by 7%. However, 13% of the additional risk reduction in REDUCE-IT remained unexplained.

7. NHSE conclude that 2 trials in similar populations have shown markedly contrasting effects of high-dose purified omega-3 fatty acids for triglyceride lowering for prevention of ASCVD ranging from no benefit to a 25% reduction in ASCVD events. The reasons for these divergent findings remain uncertain but NHSE regard the clinical data to have high clinical relevance as both studies showed an increased incidence of bleeding and atrial fibrillation with omega-3 fatty acid administration.

8. NHSE has some concerns about the generalisability of REDUCE-IT in relation to the contemporary management of high-risk patients for prevention of ASCVD outcomes in the NHS. In contrast to LDL-C reduction, lowering triglycerides is not accepted by regulators as a valid surrogate for future CV event reduction; a message further emphasised by the lack of association between lowering of triglycerides and event reduction in REDUCE-IT. The therapeutic target for treatment of lipoprotein abnormalities must be primarily directed at lowering LDL-C. NHSE note the small percentage of patients (6.4%) received Ezetimibe and even smaller (<4% but unknown percentage) received proprotein convertase subtilisin kexin type 9 (PCSK-9) inhibitors; both NICE approved interventions. Further, inclisiran is NICE approved for high-risk populations similar to those included in the REDUCE-IT trial. People are eligible for the Inclisiran if the LDL-C is >2.6 mmol/L despite maximum tolerated statin, with or without ezetimibe. The benefit of Icosapent for patients eligible for these treatments is unknown. NHSE note ezetimibe and PCSK-9 inhibitors will further reduce triglyceride levels (5-10% for each drug) beyond the statin effect. Therefore, a percentage of patients on combination therapy compared with statin monotherapy, could have a triglyceride levels below the threshold for prescribing Icosapent.

9. NHSE also questions the generalisability of the trial findings in relation to current practice for management of Type2 diabetes mellitus (including those with established ASCVD and those at high-risk primary prevention). NHSE note the median BMI in REDUCE–IT was 31Kg/M2 and the mean HbA1c was 7% (53 mmol/mol). NHSE note:

    1. Before pharmacological therapy for hypertriglyceridemia is considered, patients are advised to lose weight (if appropriate), increase exercise, receive dietary advice and potential secondary causes for hypertriglyceridemia are addressed and treated. All of these interventions can decrease triglyceride levels.

2. Poor blood glucose control is associated with hypertriglyceridemia and glucose control should be optimised for each patient depending on individual circumstances.

3. Updated NICE guidance, recommends earlier use of SGLT2 inhibitors for patients with diabetes at high risk for ASCVD events, independently of glucose control. The cardiovascular risk protection benefit associated with SGLT2 inhibitor administration would not have been fully appreciated during the enrolment period for the REDUCE-IT trial. NHSE is uncertain how many patients in REDUCE-IT were receiving SGLT2 inhibitors or if Icosapent adds additional benefits for patients receiving these drugs. Similar questions arise for patients receiving GLP-1 agonists. In addition to ASCVD protection, weight loss (especially with GLP-1 agonists) and the glucose lowering effects would also reduce triglyceride levels possibly below the threshold for prescribing Icosapent.

10. NHSE note the concerns expressed by the ERG in relation to the company modelling for this appraisal. NHSE note treatment effectiveness is based on the REDUCE-IT trial comparison of the intervention oil Vs the comparator oil. Given the deleterious effect of the mineral oil comparator on lipid and inflammatory biomarkers, NHSE considers the treatment effect is likely overestimated. At the very least, NHSE would expect the company to provide a scenario where the magnitude of the treatment effect is reduced by 7% to account for the estimated increased risk for ASCVD events associated with mineral oil use in the comparator arm of the study.

11. NHSE note HRQoL data was not collected in the REDUCE-IT trial. NHSE are concerned current therapeutic advances in the management of hyperlipidaemia and Type 2 diabetes mellitus for protection of ASCVD are not fully represented in the REDUCE-IT trial population. In the NHS today, many patients in REDUCE-IT would likely be receiving these interventions would have a lower risk for future CV events compared with the situation 5-10 years ago. The benefits of Icosapent for patients receiving these interventions is uncertain but would likely be diminished as patients on optimised therapy have a lower risk for future ASCVD events.

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Erasmus School of Health Policy & Management

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Icosapent ethyl for the treatment of hypertriglyceridaemia [ID3831]

Produced by Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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Any de-personalised data are highlighted in pink throughout the report.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Nigel Armstrong acted as project lead, health economist and systematic reviewer on this assessment, critiqued the clinical effectiveness and cost effectiveness methods and evidence and contributed to the writing of the report. Sabine Grimm acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Bram Ramaekers, Ben Wijnen and Brigitte Essers acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Robert Wolf, Susan O'Meara and Edyta Ryczek acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Caro Noake critiqued the search methods in the submission and contributed to the writing of the report. Manuela Joore acted as health economist on this assessment, critiqued the company's economic evaluation, contributed to the writing of the report and provided general guidance. Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report, and supervised the project.

Abbreviations

ABI	Ankle-brachial index
AE	Adverse events
AIDS	Acquired immunodeficiency syndrome
AIC	Akaike information criterion
ALT	Alanine aminotransferase
Apo B	apolipoprotein B
ASCVD	atherosclerotic CVD
AST	Aspartate aminotransferase
BCS	Best case scenario
BI	Budget impact
BIC	Bayesian information criterion
BMI	Body mass index
BNF	British National Formulary
BSC	Best supportive care
CAD	Coronary artery disease
CADTH	Canadian Agency for Drugs and Technologies in Health
CE	Cost effectiveness
CEA	Cost effectiveness analysis
CEAC	Cost effectiveness acceptability curve
CENTRAL	Cochrane Central Register of Controlled Trials
CG	Clinical Guideline
CHF	Congestive heart failure
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CNS	Central nervous system
CrCL	Creatine clearance
CRD	Centre for Reviews and Dissemination
CRP	C-reactive protein
CS	Company's submission
CSR	Clinical study report
CT	Computerised tomography
CTR	Clinical trial results
CV	Cardiovascular
CVD	Cardiovascular disease
DM	Diabetes mellitus
DMC	Data monitoring committee
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EMA	European Medicines Agency
EPA	Eicosapentaenoic acid
eMIT	Electronic market information tool
EORTC	European Organisation for Research and Treatment of Cancer
EPA	Eicosapentaenoic acid
EPAR	European Public Assessment Report
EQ-5D	European Quality of Life-5 Dimensions
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
EUR	Erasmus University Rotterdam
FAS	Full analysis set
FAD	Final appraisal document
FBG	Fasting blood glucose
FDA	Food and Drug Administration
FE	Fixing errors

FV	Fixing validations
GHS	Global health status
HbA1c	Glycated haemoglobin
HDL-C	High-density lipoprotein cholesterol
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRQoL	Health-related quality of life
hsCRP	high-sensitivity C-reactive protein
hsTnT	high-sensitivity troponin T
HSUV	Health state utility value
HTA	Health technology assessment
IC	Indirect comparison
ICD	International Statistical Classification of Diseases and Related Health Problems
ICER	Incremental cost effectiveness ratio
ICF	Informed consent form
IDFS	Invasive disease-free survival
IFCC	International federation of clinical chemistry
ITC	Indirect treatment comparison
ITT	Intention to treat
IV	Intravenous
JELIS	Japan EPA Lipid Intervention Study
KSR	Kleijnen Systematic Reviews
LDL-C	Low-density lipoprotein cholesterol
LVEF	Left ventricular ejection fraction
LYs	Life years
LYG	Life years gained
MACE	Major adverse cardiovascular event
MAIC	Match-adjusted indirect comparison
MeSH	Medical subject headings
MHRA	Medicines and Healthcare Products Regulatory Agency
MI	Myocardial infarction
MJ	Matters of judgement
MOS SF-36	Medical Outcomes Study Short Form Survey
MTA	Multiple technology appraisal
MTC	Mixed treatment comparison
NA	Not applicable
NCCN	National Comprehensive Cancer Network
NCRI	National Cancer Research Institute
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NLM	National Library of Medicine
NMA	Network meta-analysis
NR	Not reported
NYHA	New York Heart Association
ONS	Office for National Statistics
OS	Overall survival
partSA	Partitioned survival analysis
PAS	Patient access scheme
pCR	Pathological complete response
PFS	Progression-free survival
PH	Proportional hazards
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred reporting items for systematic reviews and meta-analyses

PRO	Patient reported outcome
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PVD	Peripheral vascular disease
Q3W	Every three weeks
QALY	Quality adjusted life year
QLQ-C30	Quality of Life Questionnaire
QoL	Quality of life
RCT	Randomised controlled trial
REDUCE-IT	Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial
RLP-C	Remnant lipoprotein cholesterol
RR	Relative risk; Risk ratio
SAE	Serious adverse events
SC	Subcutaneous
ScHARR	School of Health and Related Research
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
SoC	Standard of care
STA	Single technology appraisal
STEEP	Standardised definitions for efficacy endpoints
TA	Technology assessment
TC	Total cholesterol
TEAE	Treatment emergent adverse events
TG	Triglyceride
TIA	Transient ischemic attack
tpCR	Total pathological complete response
TSD	Technical Support Document
TTO	Time trade-off
TTOT	Time-to-off treatment
UK	United Kingdom
ULN	Upper limit of normal
UMC	University Medical Centre
USA	United States of America
VLDL-C	Very low-density lipoprotein cholesterol
WHO	World Health Organization
WOSCOPS	West of Scotland Coronary Prevention Study
WTP	Willingness-to-pay

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1. EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the evidence review group (ERG) as being potentially important for decision making. If possible, it also includes the ERG's preferred assumptions and the resulting incremental cost effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 presents the key model outcomes. Section 1.3 discusses the decision problem, Section 1.4 issues relate to the clinical effectiveness, and Section 1.5 issues related to the cost effectiveness. Other key issues are discussed in Section 1.6 while a summary in presented in Section 1.7.

Background information on the condition, technology and evidence and information on key as well as non-key issues are in the main ERG report, see Sections 2 (background), 3 (decision problem), 4 (clinical effectiveness) and 5 (cost effectiveness) for more details.

All issues identified represent the ERG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the ERG's key issues

Table 1.1: Summary of key issues

ID1457	Summary of issue	Report sections
1	Population of main clinical effectiveness evidence, REDUCE-IT trial, narrower than scope and decision problem	2.1, 3.2, 4.2
2	The period to determine a stable dose of statin in REDUCE-IT is likely to be less than in clinical practice	2.2
3	Composite outcomes (MACE) instead of disaggregated outcomes e.g. CV death used as primary outcome and used in the model	2.4, 3.2.5, 4.2.2
4	Unclear generalisability of the results to patients in the UK NHS setting	3.2.3
5	Model structure – partitioned survival analysis (partSA)	4.2.2
6	Use of reconstituted data	4.2.6
7	Limited evidence available for (long-term) validation of survival curves	4.2.6
8	Use of stratified parametric models, methodological guidance not followed	4.2.6
9	Long-term extrapolation, assumption of no treatment waning	4.2.6
10	Use of treatment-dependent non-CV related death hazard ratios	4.2.6
11	Health-related quality of life sensitive to choice of utility source	4.2.8
12	Event costs not adjusted for time since previous event	4.2.9
13	The distribution to extrapolate time to discontinuation	4.2.9
14	Inconsistent use of sources and calculation of event costs	4.2.9
15	Incomplete model validation and face validity check	5.3

The key differences between the company's preferred assumptions and the ERG's preferred assumptions are around the appropriateness of the chosen model structure approach and methods used for long-term extrapolation of treatment effectiveness and discontinuation.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Reduced risk of cardiovascular events.

Overall, the technology is modelled to affect costs by:

- Additional costs of icosapent ethyl,
- Reduced risk of cardiovascular events.

The modelling assumptions that have the greatest effect on the ICER are:

- Long-term treatment effectiveness (survival analysis and waning assumptions)
- Model choice for time to treatment discontinuation (TTD)
- Non-CV-related death hazard ratios
- Choice of utility values

1.3 The decision problem: summary of the ERG's key issues

The decision problem addressed in the company submission (CS) is broadly in line with the final scope issued by NICE. However, there are some potential discrepancies in population and concomitant treatments.

Table 1.2: Key issue 1 - Population of main clinical effectiveness evidence, REDUCE-IT trial, narrower than scope and decision problem

Report section	Section 2.1, 3.2, 4.2
Description of issue and why the ERG has identified it as important	The population within the decision scope is in line with the NICE final scope. The Summary of Medicinal Product Characteristics for icosapent ethyl includes more specific information about elevated triglyceride i.e. defining this as ≥ 150 mg/dL (≥ 1.7 mmol/L). Moreover, the evidence base for this CS includes only one trial i.e. REDUCE-IT. The trial inclusion criteria (section 3.2.3) restrict the eligibility to: - age ≥ 50 or ≥ 45 years of age for primary and secondary prevention cohort, respectively; - controlled LDL-C levels (> 40 mg/dL and ≤ 100 mg/dL); - elevated TG levels (≥ 135 mg/dL and < 500 mg/dL). Subgroup analysis indicates that age might have a substantial effect on outcome.
What alternative approach has the ERG suggested?	Restrict the population in the decision problem based on the eligibility criteria for REDUCE-IT or provide evidence as to the effect of lying outside the REDUCE-IT inclusion criteria, particularly for age.

Report section	Section 2.1, 3.2, 4.2
What is the expected effect on the cost effectiveness estimates?	The cost effectiveness estimates may differ due to inclusion of less restrictive population eligible for icosapent ethyl.
What additional evidence or analyses might help to resolve this key issue?	Current evidence is restricted to population included in the REDUCE-IT trial. Further evidence might be needed to include all adults as per the NICE final scope.

Table 1.3: Key issue 2 - The period to determine a stable dose of statin in REDUCE-IT is likely to be less than in clinical practice

Report section	Section 2.2
Description of issue and why the ERG has identified it as important	The NICE final scope and SmPC mention icosapent ethyl as being used in combination with a statin and the CS (decision problem consideration) specified this further by saying that the intervention should be used with a 'stable dose' of statin (but does not define 'stable dose'). The REDUCE-IT trial defines a 'stable dose' as the same daily dose of the same statin (and if applicable the same daily dose of ezetimibe) for at least 28 days before the lipid qualification measurements. It is likely that the period required to establish a stable dose of statin therapy in current UK clinical practice is up to three months because of factors such as the time intervals between clinic visits. In their response to the clarification letter, the company confirmed that they had used the REDUCE-IT trial definition of a 'stable dose of statin' in their submission. They also asserted that the 28-day period to determine a stable dose in a research context (i.e., the REDUCE-IT trial) was consistent with the value of up to three months that might be used in clinical practice. However, no evidence was presented to support this statement.
What alternative approach has the ERG suggested?	The ERG suggests providing additional evidence to determine to what extent the definition used in the REDUCE-IT trial matches with current clinical practice in the UK and the potential impact of any discrepancy.
What is the expected effect on the cost effectiveness estimates?	Unknown
What additional evidence or analyses might help to resolve this key issue?	The ERG suggests providing additional evidence to determine to what extent the definition used in the REDUCE-IT trial matches with current clinical practice in the UK and the potential impact of any discrepancy.

Table 1.4: Key issue 3 - Composite outcomes (MACE) instead of disaggregated outcomes e.g. CV death used as primary outcome and used in the model

Report section	Section 2.4, 3.2.5, 4.2.2
Description of issue and why the ERG has identified it as important	The NICE final scope listed a series of single outcomes whereas composite outcomes (e.g., 5-point MACE) were specified within the decision problem consideration. The individual constituents of the 5-point MACE are: CV death; nonfatal MI; nonfatal stroke; coronary revascularisation; and hospitalisation for unstable angina. The 5-point MACE was the primary efficacy endpoint in the REDUCE-IT trial and individual participant data for this outcome were used for estimation of time to event outcomes for the economic model. The ERG notes that the hazard ratios for CV death, 0.803 (0.657 to 0.981) and death from any cause 0.870 (0.739 to 1.023) are larger (lower treatment effect) than that for 5-point MACE (0.752 [0.682 to 0.830]) (see Sections 2.4 and 3.2.5). It is possible that using the 5-point MACE masks the treatment effect in relation to individual outcomes such CV death.
What alternative approach has the ERG suggested?	The ERG suggests exploring the impact of using single outcomes versus the composite outcome on cost effectiveness estimation.
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	The ERG suggests exploring the impact of using single outcomes versus the composite outcome on cost effectiveness estimation.

1.4 The clinical effectiveness evidence: summary of the ERG's key issues

Table 1.5: Key issue 4 - Unclear generalisability of the results to patients in the UK NHS setting

Report section	Section 3.2.3
Description of issue and why the ERG has identified it as important	The only eligible trial for this submission, the REDUCE-IT, did not include patients from the UK and it is not clear if the patients included in the trial are representative of the UK NHS setting. In the response to the clarification letter, the company provided more details and included the reference to the UK-based cohort study of high-risk patients by Steen et al. (2016). However, as the patient characteristics in the REDUCE-IT trial are combined for the primary and secondary cohort, the full comparison between the studies cannot be made. Some differences are highlighted in the ERG comment in section 3.2.3.
What alternative approach has the ERG suggested?	ERG recommends an explicit comparison ideally in a table for each population, the whole population and for each subgroup, between REDUCE-IT and any source that aligns with UK clinical practice.
What is the expected effect on the cost effectiveness estimates?	The cost effectiveness estimates could be not applicable to the UK NHS setting in situations where patients characteristics substantially differ between the REDUCE-IT trial and patients in the UK.

Report section	Section 3.2.3
What additional evidence or analyses might help to resolve this key issue?	ERG recommends an explicit comparison ideally in a table for each population, the whole population and for each subgroup, between REDUCE-IT and any source that aligns with UK clinical practice.

1.5 The cost effectiveness evidence: summary of the ERG's key issues

A full summary of the cost effectiveness evidence review conclusions can be found in Section 6.4 of this report. The company's cost effectiveness results are presented in Section 5, the ERG's summary and detailed critique in Section 4, and the ERG's amendments to the company's model and results are presented in Section 6. The key issues in the cost effectiveness evidence are discussed in the issue tables below.

Table 1.6: Key issue 5 - Model structure – partSA

Report section	**Section 4.2.2**
Description of issue and why the ERG has identified it as important	Uncertainty about modelling approach and structural assumptions. The partSA approach does not account for interdependency between endpoints (i.e. time to subsequent event is independent of time to first event). This may cause bias in model outcomes that could not be quantified. Furthermore, there is uncertainty over whether a one-day cycle is indeed appropriate.
What alternative approach has the ERG suggested?	Ideally use an individual patient level simulation. Consider exploring a model structure with weekly cycle length, or whichever deemed clinically most appropriate (based on the duration of the acute phase as the minimum cycle length), to capture clinically distinct events, potentially using a hierarchy of events to account for events that occur in consecutive days or close together.
What is the expected effect on the cost effectiveness estimates?	Largely unknown, potentially favourable to icosapent ethyl based on costs being likely more over-estimated in the comparator arm than in the treatment arm.
What additional evidence or analyses might help to resolve this key issue?	Consider verifying outcomes of partSA approach by providing results of a state transition model, or ideally an individual patient level model.

Table 1.7: Key issue 6 - Use of reconstituted data

Report section	**Section 4.2.6**
Description of issue and why the ERG has identified it as important	Use of "reconstituted data" in which observations which took place after the point that only 10% of individuals were remaining at risk were removed from the dataset. In the CS base-case, the company used a "reconstituted" dataset in which any observations which took place after the point that only 10% of individuals were remaining at risk, were to be removed from the KM data set to be used for the 1st, 2nd and 3rd event extrapolations. The ERG does not agree with this assumption as removing data is likely to increase uncertainty related to the extrapolations and hence making them less robust.

What alternative approach has the ERG suggested?	Re-estimate parametric survival curves using the complete KM data.
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	As mentioned above, re-estimate parametric survival curves using the complete KM data.

Table 1.8: Key issue 7 - Limited evidence available for (long-term) validation of survival curves

Report section	**Section 4.2.6**
Description of issue and why the ERG has identified it as important	The long-term predictions for the first event based on the parametric survival curves were validated against the WOSCOPS study, however, the company stated that "the WOSCOPS study is not an appropriate study for comparison". To this extent, the company consulted two UK clinical experts. Although the ERG acknowledges the lack of available long-term follow data for validation purposes, the ERG would like to emphasise that the long-term extrapolations based on the survival curves are subject to uncertainty.
What alternative approach has the ERG suggested?	Exploring alternative survival models to estimate time to event probabilities.
What is the expected effect on the cost effectiveness estimates?	The type of distribution did not seem to have a large impact on the ICER.
What additional evidence or analyses might help to resolve this key issue?	Long-term observational data.

Table 1.9: Key issue 8 - Use of stratified parametric models, methodological guidance not followed

Report section	**Section 4.2.6**
Description of issue and why the ERG has identified it as important	All survival models were stratified for icosapent and placebo separately, i.e. separately for both treatment arms. However, the use of stratified models was not further justified in the CS (e.g. by looking at cumulative hazards and/or scaled Schoenfeld residuals; see NICE DSU TSD 14)
What alternative approach has the ERG suggested?	Follow NICE DSU TSD14.
What is the expected effect on the cost effectiveness estimates?	Impact on the ICER is unknown.

What additional evidence or analyses might help to resolve this key issue?	Additional information following the model selection process algorithm as mentioned in NICE DSU TSD 14.

Table 1.10: Key issue 9 - Long-term extrapolation, no treatment waning assumed

Report section	**Section 4.2.6**
Description of issue and why the ERG has identified it as important	In the CS base-case no treatment waning was assumed, which means that the time to the next event was assumed to be different for the two comparators during the whole duration of the time horizon. The follow-up of the REDUCE-IT study is notably shorter than the time horizon in the economic model. Hence, it is unclear to the ERG whether the benefits of icosapent could be assumed to last over the full-time horizon and whether those benefits were also applicable post first, second, or third CV event.
What alternative approach has the ERG suggested?	Examine the impact of treatment waning. Upon request, the company did provide scenario analyses for waning of treatment effect over 10- and 20-years post trial completion after first, second and third events. Perhaps experts could be consulted on this.
What is the expected effect on the cost effectiveness estimates?	The impact of treatment waning on the ICER is dependent on assumptions regarding the timing of waning. In the scenarios explored by the company, the ICER varied between £87,240 per QALY gained when assuming treatment waning after the first, second and third event and both treatments have similar hazard ratios at 10 years and £33,020 per QALY gained when assuming treatment waning after the third event only and both treatments have similar hazard ratios at 20 years.
What additional evidence or analyses might help to resolve this key issue?	Long-term observational data.

Table 1.11: Key issue 10 - Use of treatment-dependent non-CV related death hazard ratios

Report section	**Section 4.2.6**
Description of issue and why the ERG has identified it as important	In the CS, two forms of mortality were captured within the model; surviving patients could transition to the non-CV related death health state, which captured the baseline risk of non-CV related death, or CV death if a CV related death occurred. It is unclear to the ERG why non-CV death should be considered to be treatment-dependent given that CV related death has already been captured in the CV death state.
What alternative approach has the ERG suggested?	Treatment-independent non-CV related death hazard ratios.
What is the expected effect on the cost effectiveness estimates?	Upon request, the company provided an additional scenario in which hazard ratios are treatment-independent and equivalent to those of the UK population norm, which increased the ICER from £29,317 per QALY gained to £32,377 per QALY gained.
What additional evidence or analyses	The scenario implemented by the company assumed hazard ratios equivalent to those of the UK population norm, which the company refers to in the CS not to be representative to the REDUCE-IT study

might help to resolve this key issue?	population. Hence, the ERG chose to assume the mean of the weighted hazard ratios for non-CV death by health state and apply these hazard ratios to both treatments.

Table 1.12: Key issue 11 - Health-related quality of life sensitive to choice of utility source

Report section	**Section 4.2.8**
Description of issue and why the ERG has identified it as important	The company's sensitivity analysis shows that model outcomes are sensitive to choice of health state utility values.
What alternative approach has the ERG suggested?	Provide justification for the choice of utility values.
What is the expected effect on the cost effectiveness estimates?	Alternative utility values from Ara et al (used in TA393) increased the ICERs.
What additional evidence or analyses might help to resolve this key issue?	Provide justification for the choice of utility values.

Table 1.13: Key issue 12 - Event costs not adjusted for time since previous event

Report section	**Section 4.2.9**
Description of issue and why the ERG has identified it as important	Full event and post-event costs are estimated for all patients including those who experience the event shortly after the previous one. This leads to over-estimation of event costs.
What alternative approach has the ERG suggested?	A model structure that appropriately takes into account the duration of acute and post-event costs. The current model structure with a one-day tunnel state for the acute event, and patients residing in the post-event state until another event takes place is not capable of doing that. The ERG suggests a microsimulation or a model with post-event tunnel states up to 6 months post event, as has been adopted in previous models in the field that incorporated two subsequent events (and CV death as a possible third event). Alternatively, consider including post-event costs in a similar way as post-event 60-day disutilities.
What is the expected effect on the cost effectiveness estimates?	An overestimation of the cost-consequences of events will lower the ICER as the number of events is lower for icosapent ethyl than for the comparator.
What additional evidence or analyses might help to resolve this key issue?	An adapted model structure as described above. To explore the magnitude of the bias, event costs could be calculated in a similar fashion to event utilities (which accrue 60 days post-event).

Table 1.14: Key issue 13 - The distribution to extrapolate time to discontinuation

Report section	**Section 4.2.9**
Description of issue and why the ERG has identified it as important	The distribution to model time to discontinuation is selected based on goodness of fit, in absence of long-term data of the use of icosapent ethyl in clinical practice. The goodness of fit statistics are however quite similar for five distributions, while the extrapolations based on these distributions do differ in the long-term.

Report section	Section 4.2.9
What alternative approach has the ERG suggested?	This is an area of uncertainty for which the impact is shown in scenario analyses. Potentially consult experts on long-term number of patients on treatment
What is the expected effect on the cost effectiveness estimates?	The scenario analyses showed that the choice for one of the distributions with second best fit could increase the ICER to £33,805 in the ITT population, and ICERs of £26,430 and £117,034 for the secondary and primary prevention population, respectively.
What additional evidence or analyses might help to resolve this key issue?	Data on long-term use of icosapent ethyl in clinical practice will help to resolve this issue.

Table 1.15: Key issue 14 – Inconsistent use of sources and calculation of event costs

Report section	Section 4.2.9
Description of issue and why the ERG has identified it as important	It was unclear why the company did not use Danese 2016 for all event costs. The ERG could not verify all costs as estimated by the company.
What alternative approach has the ERG suggested?	The ERG has performed their own cost calculations.
What is the expected effect on the cost effectiveness estimates?	The ICER increased with the ERG's amendments.
What additional evidence or analyses might help to resolve this key issue?	Updated model with re-calculated costs.

Table 1.16: Key issue 15: Incomplete model validation and face validity check

Report section	Section 5.3
Description of issue and why the ERG has identified it as important	Validity assessment not conducted and/or described appropriately by the company.
What alternative approach has the ERG suggested?	Appropriately conducting and describing validity assessments.
What is the expected effect on the cost effectiveness estimates?	Unclear
What additional evidence or analyses might help to resolve this key issue?	Providing complete responses to clarification questions C17, C18 and C19 considering validation and transparency (including addressing the ERG concerns described in section 5.2 of the ERG report).

1.6 Other key issues: summary of the ERG's view

None.

1.7 Summary of the ERG's view

Table 1.17: Summary of ERG's preferred assumptions and base-case ICER (deterministic, whole population)

Scenario	Incremental cost	Incremental QALYs	ICER
Company base-case	£10,658	0.364	£29,317
ERG_1 adjustment to cost inputs	£12,030	0.364	£33,092
ERG_2 treatment-dependent non-CV related HRs	£10,606	0.340	£31,225
ERG_3 Log-logistic for TTD	£11,849	0.364	£32,594
ERG_4 Treatment waning up to 10 years post-trial	£11,915	0.137	£87,240
ERG base-case (ERG_1-4)	£13,663	0.111	£122,598

Table 1.18: Summary of ERG's scenario analysis results (deterministic, whole population)

Scenario	Incremental cost	Incremental QALYs	ICER
Treatment waning up to 20 years post- trial	£13,498	0.190	£71,169
Exponential TTD conditional on ERG base-case	£12,546	0.111	£112,577

2. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

Table 2.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Population	Adults on statin therapy with elevated triglycerides (TGs) who are at high risk of cardiovascular events due to: established cardiovascular disease, or; diabetes, and at least 1 other cardiovascular risk factor.	Adults on statin therapy with elevated TGs who are at high risk of cardiovascular events due to: established cardiovascular disease, or; diabetes, and at least 1 other cardiovascular risk factor.	In line with the NICE Final Scope	The population described within the decision problem is in line with the NICE final scope. The NICE final scope and the decision problem are broadly in line with the indication described in the SmPC for icosapent ethyl. However, the SmPC includes more specific, information about elevated TGs, defining this as ≥ 150 mg/dL (≥ 1.7 mmol/L).* The REDUCE-IT trial recruited a narrower population than those described in the NICE Final Scope, decision problem or SmPC: Primary prevention – age ≥ 50 years with diabetes and at least 1 other CV risk factor, on stable dose of statins with controlled LDL-C (> 40 mg/dL and ≤ 100 mg/dL) and elevated TG levels (≥ 135 mg/dL and < 500 mg/dL for

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
				first 60% of participants recruited, then ≥ 200 mg/dL following a protocol change) Secondary prevention - age ≥ 45 years with established CVD, on stable dose of statins with controlled LDL-C and elevated TG (levels for both as for primary prevention).$ The company's product positioning information originally used the same criteria as the REDUCE-IT trial to define eligible primary and secondary prevention populations.~ However, the company updated the product positioning information in their response to the clarification letter and removed the eligibility criteria regarding patients' age.^
Intervention	Icosapent ethyl in combination with a statin	Icosapent ethyl (Vazkepa®) in combination with a stable dose of statin	In line with the NICE final scope	Definition of 'stable dose of statin' not explained in the CS (a definition is provided for the REDUCE-IT trial i.e., stable dose of statin for at least 4 weeks with well-controlled LDL-C)$

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
				In their response to the clarification letter, the company stated that they had used a definition of 'stable dose of statin' that was in line with that of the REDUCE-IT trial.^
Comparator(s)	Established clinical management (including high and low-intensity statins)	Best supportive care, defined as a stable dose of statin therapy	In line with the NICE final scope. There are no pharmacological therapies available and routinely used to reduce the risk of cardiovascular events in statin-treated patients with elevated triglycerides, hence the placebo arm of the REDUCE-IT trial is used as the comparator.	In their response to the clarification letter, the company confirmed that the two comparator definitions (i.e., those in the NICE final scope and decision problem consideration) refer to the same regimen, with patients receiving statins at a high-moderate- or low-dose intensity depending on their needs.^ The ERG is satisfied with this clarification and notes that participants in the placebo arm of REDUCE-IT received statins, sometimes combined with ezetimibe.
Outcomes	The outcome measures to be considered include: cardiovascular events (including cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, coronary revascularisation and unstable angina)	In line with the primary and secondary endpoints in the REDUCE-IT trial, the following outcomes will be captured in the economic model and the submission: 5-point major adverse cardiovascular events (MACE)	In line with the NICE final scope	The decision problem describes a series of composite outcomes relating to adverse cardiovascular events whereas the NICE final scope specifies single outcomes under a heading 'Cardiovascular events'.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
	mortality hospital admissions adverse effects of treatment health-related quality of life.	(including cardiovascular death, nonfatal myocardial infarction [including silent myocardial infarction], nonfatal stroke, coronary revascularization or hospitalisation for unstable angina) 3-point MACE (including cardiovascular death, nonfatal myocardial infarction or nonfatal stroke) Composite of cardiovascular death or nonfatal myocardial infarction Fatal or nonfatal myocardial infarction Coronary revascularization Cardiovascular death Hospitalisation for unstable angina Fatal or nonfatal stroke Death from any cause Health-related quality of life Adverse events The following analyses of cardiovascular outcomes will be presented: Time to first event		The decision problem mentions 'Hospitalisation for unstable angina' as an outcome whilst 'unstable angina' and 'hospital admissions' are separate outcomes in the NICE final scope. In their response to the clarification letter, the company explained that 'unstable angina' and 'hospital admissions' were viewed as separate outcomes for the SLR. The composite outcome of 'hospitalisation for unstable angina' was considered as part of the decision problem because it was reported in the REDUCE-IT trial.^ Furthermore, the company clarified that the general terms 'myocardial infarction' and 'stroke' were considered for the SLR whereas the outcomes of 'fatal or nonfatal myocardial infarction' and 'fatal or nonfatal stroke' in the decision problem are both composite outcomes and were reported as such in the REDUCE-IT trial.^

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
		Difference in total events (first and subsequent events)		
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.	A cost-utility analysis was conducted in Excel. Costs were considered from an NHS and Personal Social Services perspective. Direct health effects for patients were considered.	In line with the NICE final scope	Mostly in line with NICE scope, with the exceptions of estimation of health effects (methodological guidance not followed) and health-related quality of life (not all estimates based on EQ-5D).
Subgroups to be considered	If the evidence allows the following subgroups will be considered: • adults with established cardiovascular disease (secondary prevention)	The following subgroups were considered: • adults with established cardiovascular disease (secondary prevention)	In line with the NICE final scope	In line with the NICE final scope.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
	• adults with diabetes and at least one other cardiovascular risk factor. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	• adults with diabetes and at least one other cardiovascular risk factor.		
Special considerations including issues related to equity or equality	None mentioned	None mentioned	N/A	

Based on Table 1 of the CS[1]

*from Appendix C of CS[2]; $ from Bhatt et al 2019[3]; ~ from Figures 3 & 4 of Document B[1]; ^ from company's response to Clarification Letter[4]

CS = company submission; CV = cardiovascular; CVD = cardiovascular disease; ERG = Evidence Review Group; LDL-C = low-density lipoprotein cholesterol; MACE = major adverse cardiovascular events; mg/dL = milligrams per decilitre; mmol/L = millimoles per litre; N/A = not applicable; NHS = National Health Service; NICE = National Institute of Health and Care Excellence; REDUCE-IT = Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial; SLR = systematic literature review; SmPC = summary of product characteristics; TG(s) = triglycerides(s).

2.1 Population

The population described within the decision problem is:

"Adults on statin therapy with elevated triglycerides who are at high risk of cardiovascular events due to:

- *established cardiovascular disease, or;*
- *diabetes, and at least 1 other cardiovascular risk factor."*[1]

This is in line with the NICE final scope.[5] The summary of product characteristics (SmPC) for icosapent ethyl is more specific in terms of defining 'elevated triglycerides': *"adult statin-treated patients at high cardiovascular risk with elevated triglycerides (≥ 150 mg/dL [≥ 1.7 mmol/L])"*.[2] In relation to this indication, Vazkepa® received a positive opinion from the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) on 28 January 2021 and the issue of the marketing authorisation valid throughout the European Union was received on 26 March 2021 (Table 2 in Document B).[1]

The sole source of clinical effectiveness evidence, the REDUCE-IT trial,[3] stratified the recruited participants in relation to primary and secondary prevention of cardiovascular events (this reflects subgroups mentioned within the NICE final scope and the decision problem consideration).[5] Within each REDUCE-IT strata, the population was narrower than those described in the NICE final scope, the decision problem consideration or the SmPC because of age restrictions (participants had to be aged at least 50 years for primary prevention and at least 45 years for secondary prevention). The definition of elevated triglyceride levels in REDUCE-IT (common to both population strata) differed to the SmPC because of allowing for variation in obtained values and the protocol for this changed during the trial: ≥ 135 mg/dL and < 500 mg/dL for first 60% of participants recruited, then ≥ 200 mg/dL. In addition, the REDUCE-IT trial stipulated that low-density triglyceride (LDL-C) levels be controlled for all participants (> 40 mg/dL and ≤ 100 mg/dL) (see Table 3 in Document B).[1, 3]

The company's positioning statements for primary and secondary prevention of cardiovascular events reflect the REDUCE-IT trial's criteria for age, co-morbidity and TG and LDL-C thresholds (p27 and Figures 3 and 4 in Document B).[1]

ERG comment: A narrower population to the NICE scope and decision problem was recruited to the main source of evidence, REDUCE-IT, because of age restriction which differed between primary prevention and secondary prevention population strata. It is not clear to what extent the REDUCE-IT population excludes people who might be seen in clinical practice in the United Kingdom (UK) (i.e., younger than 50 years and 45 years for primary and secondary prevention respectively). Also, Figures 5 and 6 of Appendix E indicate that the hazard ratio (HR) for the primary and secondary endpoints does vary depending on whether less than 65 years old or not, which might suggest wider age-related implications.[6] Therefore, it is unclear to what extent this exclusion impacts cost effectiveness estimates. The clarification letter included a correction to Figures 3 and 4 that rejected the age restrictions.[4] However, given that this restriction did apply to the REDUCE-IT trial, the discrepancy therefore remains an area of substantial uncertainty and thus a key issue.

2.2 Intervention

The NICE final scope and SmPC describe the intervention (icosapent ethyl) as being used in combination with a statin.[2, 5] The CS is more specific, mentioning *"Icosapent ethyl (Vazkepa®) in combination with a stable dose of statin"* within the consideration of the decision problem (Table 1,

Document B) and the product placement information (Figures 3 and 4 of Document B) however does not define a stable dose further.[1] A definition is provided in the REDUCE-IT trial:

"Patients were required to be on stable statin therapy for ≥4 weeks with well-controlled LDL-C to investigate the potential benefit of icosapent ethyl 4 g/day beyond the current standard of care."[3]

This information is paraphrased in Table 4 of Document B where it is described as *"….the same daily dose of the same statin for at least 28 days before the lipid qualification measurements (TG and LDL-C) and, if applicable the same daily dose of ezetimibe for at least 28 days before the lipid qualification measurements (TG and LDL-C)"*.[1]

ERG comment: It is not clear whether the REDUCE-IT definition of a stable dose of statin therapy matches with current clinical practice in the UK. In addition, it is not clear what definition of a stable dose of statin was used in the CS and whether differences in definition could impact on the clinical- and cost effectiveness estimates for icosapent ethyl. The clarification response stated that the 28 day value of period to determine stable in the REDUCE-IT trial was consistent with the value of up to three months that might be used in clinical practice: "*It is common for study inclusion criteria and clinical practice to differ slightly, but these differences do not substantially impact the overarching goal of allowing sufficient time to adequately measure the impact of a newly initiated or modified statin therapy*."[4] However, no evidence was presented to support this assertion and therefore this remains a key issue.

2.3 Comparators

The company claims that the comparator definition in the CS is in line with that in the NICE final scope however, the descriptions are not exactly the same. The NICE final scope stated *"Established clinical management (including high and low-intensity statins)"* as the comparator whilst the decision problem consideration described *"Best supportive care, defined as a stable dose of statin therapy"* (Table 1 in Document B).[1, 5] The CS outlined that no pharmacological therapies are currently available to reduce the risk of cardiovascular events in statin-treated patients with elevated triglycerides and from this argued the appropriateness of using the placebo arm of the REDUCE-IT trial as the comparator (these patients received statins and 6.4% in both treatment arms also received ezetimibe).[3] The proportion of patients in REDUCE-IT taking each of low, medium and high intensity statins at baseline was reported in the CS.[1]

ERG comment: The clarification response reported that the comparator definition in the decision problem is the same as that in the NICE final scope.[4] It also reported the proportion of patients in UK clinical practice (represented by the DA VINCI study) taking each intensity level of statin as compared to REDUCE-IT (see Table 2.2 below).

Table 2.2: Statin intensity distribution

Statin intensity	Percentage of patients receiving the statin intensity (overall population of REDUCE-IT)	Percentage of patients receiving the statin intensity (overall population of DA VINCI)
Low-intensity statin	6.4%	4%
Moderate-intensity statin	62.7%	55%
High-intensity statin	30.9%	32%
Source: Table 18 in the CS (REDUCE-IT) and company response to clarification letter (DA VINCI).[1, 4]		

Appendix E shows in a subgroup analysis that, whilst there is some similarity in effectiveness between high and moderate intensity (both with 95% CI that does not cross 1), that in the low intensity subgroup is more uncertain (95% CI does cross 1) (HR: 0.664, 0.633 and 1.200 respectively), notwithstanding the much smaller sample size. This has not been identified as a key issue because subgroup analysis by statin intensity was not mentioned in the scope.[5]

2.4 Outcomes

The NICE final scope lists several single (i.e., stand-alone) outcomes whereas the decision problem lists only a set of composite outcomes e.g. 5-point major adverse cardiovascular event (MACE) (Table 1 in Document B).[1, 5] Whilst there is some overlap between the two lists (i.e., the decision problem includes some single outcomes that also feature in the NICE final scope) there are some outcomes that may not be common (e.g., fatal or nonfatal myocardial infarction; and fatal or nonfatal stroke appear as part of the decision problem discussion). In addition, the NICE final scope lists hospital admissions (reason unspecified) and unstable angina as separate outcomes, but these are combined within the decision problem (*"Hospitalisation for unstable angina"*). The REDUCE-IT trial did not evaluate the effects of icosapent ethyl on the health-related quality of life (HRQoL) of patients. The outcomes listed for the decision problem are largely in line with those reported in the REDUCE-IT trial.

ERG comment: It is possible that adopting composite outcomes belies important differences in comparative effectiveness in terms of the single outcomes. However, the ERG could be to a large extent reassured that this is probably not a major problem given the similarity in distribution of type of event in 5-point MACE shown in Table 26 of the CS.[1, 5] Nevertheless, the HRs for each of the serious events of CV death, 0.803 (0.657 to 0.981) and death from any cause 0.870 (0.739 to 1.023) are higher than that for 5-point MACE (0.752 (0.682 to 0.830)) (see Section 3.2.5). The uncertainty of modelling using events disaggregated as opposed to composite might have an effect on cost effectiveness and, as such, warrants being a key issue.

2.5 Other relevant factors

In the CS, the company stated that no equality issues were expected with this submission (Section B1.4).[1] No other relevant factors were mentioned.

3. CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The company performed a systematic review to evaluate the evidence on clinical effectiveness (efficacy and safety) of icosapent ethyl in addition to stable statin therapy compared with stable statin therapy alone for adults with elevated triglycerides.

3.1.1 Searches

Appendix D of the CS provided details of the systematic literature searches used to identify clinical efficacy and safety evidence. Database searches were conducted in December 2020. A summary of the resources searched are provided in Table 3.1.

Table 3.1: Resources searched for clinical efficacy and safety. December 2020.

Search strategy element	Resource	Host/source	Date range	Date searched
Databases	Embase	Ovid	Inception-2020/12/09	9.12.20
	MEDLINE & MEDLINE In-Process	Ovid	Inception-2020/12/09	9.12.20
	PubMed	NLM	2019-2020	9.12.20
	CENTRAL	Wiley	2019-2020	9.12.20
Additional searches	Additional publications were identified by hand searching reference lists of the retrieved publications, SLRs and network meta-analyses			

CENTRAL = Cochrane Central Register of Controlled Trials; NLM = National Library of Medicine; SLR = systematic literature review.

ERG comment:

- In their response to clarification the company provided full copies of the search strategies which included the date range searched and hits per line. They also confirmed that the host for the MEDLINE/Embase searches was Ovid and that CENTRAL was searched via the Wiley interface.
- A top up search of PubMed from 2019-2020/12/09 was conducted in order to identify any additional publications that may have been missed by the main MEDLINE/Embase searches due to the delay between the date of online publication and the date of indexation in bibliographic databases. The hand searching of reference lists of retrieved publications was also reported.
- Searches reported using the Cochrane sensitivity-maximising RCT study design filter.
- After assessing the search numbers received at clarification, the ERG noted that the search results for both the PubMed (n=20) and CENTRAL (n=21) searches appear to be missing from the PRISMA diagram (Appendix D, Figure 1). There is an entry for pragmatic searches (n=0), but it is unclear if this is referring to these searches.
- The ERG queried an error in line 15 of the Embase strategy. The facets for cardiovascular disease and diabetes appeared to have been mis-combined using AND rather than OR as had been reported in the MEDLINE search. The company reported that this had been a transcription

error and a corrected copy of the full search strategy was provided in their clarification response.

- The ERG queried why the CENTRAL search had been limited to the last two years. The company responded that the search was intended:

  "…to capture all recent randomised clinical trials of potential interest that would not have been captured by the search strategies developed in Medline and Embase. We expected recent publications to not have been indexed and/or published yet in Medline or Embase. Therefore, we decided to search for clinical trials presented on the CENTRAL platform for the two years preceding the date of the search."[4]

  The ERG noted that the full strategy, confirmed at clarification contained only the following free text terms:

1.	Icosapent ethyl (All text)	(45 trials)
2.	Hypertriglyceridemia (Title Abstract Keyword)	(293 trials)
3.	Cardiovascular disease (Title Abstract Keyword)	(7,306 trials)
4.	**1 AND 2 AND 3**	**(21 trials)**

  The ERG is concerned that as this was the only additional search, other than the MEDLINE/Embase searches, the combination of limited search terms, no subject headings and two-year date limit was unnecessarily restrictive.

- The ERG queried whether any separate adverse event (AE) searches were performed. The company responded that no additional searches had been run other than those stated in the clinical effectiveness searches (Appendix D), they also reported that additional hand searching of the reference lists of retrieved publications and published systematic literature reviews and network meta-analyses was undertaken in order to ensure the comprehensiveness of the searches used to identify studies reporting safety data. Guidance by the Centre for Reviews and Dissemination (CRD)[7] recommends that if searches have been limited by a study design filter additional searches should be undertaken to ensure that adverse events that are long-term, rare or unanticipated are not missed. Whilst reference checking may have mitigated against some loss of recall, the ERG considered that it was possible that some relevant evidence may not have been identified as a consequence of the RCT limits used.
- The ERG queried the inclusion of terms for fenofibrate, hypolipidemic agents, and bezafibrates in the clinical effectiveness searches, as these appear to be outside the scope of this review. The company clarified that the searches reported for the clinical systematic literature review were intended to inform submissions for several markets, not just the UK and that therapies not appropriate for the UK were excluded from the NICE submission.
- Searches contained limited use of free text synonyms. There were no free text terms included for individual statins such as Atorvastatin, Lovastatin, Meglutol, Pravastatin, Rosuvastatin Calcium or Simvastatin. Additional terms for icosapent ethyl, including amr 101 or epadel or lax 101 or miraxion or mnd 21 or eicosapentaenoic acid ethyl ester were also missing. However, this is unlikely to have adversely affected the recall of results due to the use of Emtree/MeSH subject heading in the MEDLINE and Embase searches, but best practice is to ensure a full use of both free text and Subject headings.
- The ERG was concerned that limiting the MEDLINE and Embase searches to English language only may have introduced potential language bias. Current best practice states that *"Whenever possible review authors should attempt to identify and assess for eligibility all possibly relevant reports of trials irrespective of language of publication"*.[8]

- The ERG queried the structure of the clinical effectiveness searches: (statins AND (Cardio OR diabetes)) AND (Eicosapentaenoic Acid OR Vascepa OR fenofibrate etc) AND (Cardiac events) AND (limits: RCTs/No Animals/English only). The ERG felt this approach was overly restrictive. Unfortunately, the ERG was unable to undertake independent clinical effectiveness searches and review the results within the Single Technology Appraisal (STA) timeline, as this would be outside of the ERG remit, so are unable to say what impact these limitations may have had on the overall recall of results. However, combined with the other limitations listed above, the ERG is concerned that some relevant papers may have been missed.

3.1.2 Inclusion criteria

As stated above, the company performed a systematic review to evaluate the evidence on clinical effectiveness (efficacy and safety) of icosapent ethyl in addition to stable statin therapy compared with stable statin therapy alone for adults with elevated triglycerides. The study eligibility criteria are presented in Table 3.2. Patients were included in the trial if they fulfilled the eligibility criteria related to:

- fasting TG levels (lower level of ≥135 mg/dL [1.53 mmol/L] and an upper level limit of <500 mg/dL [5.64 mmol/L]). Protocol amendment increased the lower level to ≥200 mg/dL (2.26 mmol/L) to increase enrolment of patients with TG levels at or above 200 mg/dL.
- LDL-C levels (>40 mg/dL [1.04 mmol/L] and ≤100 mg/dL [2.60 mmol/L]) and on stable therapy with a statin (with or without ezetimibe) for at least 4 weeks before baseline measurements
- Established CVD (secondary prevention cohort; patients ≥45 years of age) or at high risk for CVD (primary prevention cohort; included diabetes and at least 1 other CV factor; patients ≥50 years of age).

Definition of stable therapy was as follows: *"the same daily dose of the same statin for at least 28 days before the lipid qualification measurements (TG and LDL-C) and, if applicable, the same daily dose of ezetimibe for at least 28 days before the lipid qualification measurements (TG and LDL-C)."*[1]

Table 3.2: Study eligibility criteria

	Inclusion criteria	Exclusion criteria
Population	Studies including the following as a population or subpopulation: Adult men and women with established CVD or with DM and other CVD risk factors who had fasting TG levels ranging from 135 to 499 mg/dL (1.52 to 5.63 mmol/L) and LDL-C levels ranging from >40 mg/dL to ≤100 mg/dL despite stable statin therapy for at least 4 weeks.	None.
Interventions	Icosapent ethyl (Vazkepa®; received as an adjunctive therapy to statin)	None specified.
Comparators	None or standard of care	Clinical trials comparing icosapent ethyl in monotherapy to a statin

	Inclusion criteria	Exclusion criteria
Outcomes	Studies reporting at least one of the following efficacy outcomes: • cardiovascular death • non-fatal stroke • non-fatal MI • coronary revascularisation • unstable angina (considered separately or as a composite outcome i.e., MACE-5) Studies reporting the following AEs: • peripheral oedema • atrial fibrillation • anaemia • serious bleeding • constipation • myalgia • rhabdomyolysis	Studies only reporting laboratory outcomes such as change in the level of TGs or cholesterol (without any clinical endpoints)
Study design	Phase 3 clinical trials	Cross-over trials Protocols of clinical trials with no results reported Ongoing trials, without available results
Language restrictions	Restricted to English language only	Reports in languages other than English
Publication format restrictions	Not specified	Conference proceedings
Source: based on Section D1.1.4 in Appendix D of the CS[9] AE = adverse event; CS = company submission; CVD = cardiovascular disease; dL = decilitre; DM = diabetes mellitus; LDL-C = low-density lipoprotein cholesterol; MACE-5 = 5- point major adverse cardiovascular events; mg = milligram; MI = myocardial infarction; NICE = National Institute for Health and Clinical Excellence; TG = triglyceride		

ERG comment: In the clarification letter, the company was asked to provide more details regarding the eligibility criteria for the systematic literature review (SLR) and Table 3.2 was updated accordingly.[4] The criteria for SLR aligned with eligibility criteria for REDUCE-IT trial. However, the ERG has some comments:

- Considering exclusion of conference proceedings, the company stated: *"Conference proceedings were excluded due to the limited information presented in this brief format. Therefore, summarising and/or appraising the methods used as well as the risk of bias of studies reported in abstracts was considered inappropriate."* As the conference proceedings were excluded, it is not clear how many eligible abstracts exist in the literature. The ERG agrees that conference abstracts include limited information, however, some reports might not be yet available as full publications and conference abstract could provide relevant data.
- Based on the response to the clarification letter, observational studies were not considered in the SLR as the company's objective was to identify only randomised controlled trials (RCTs).

Furthermore, the company stated *"(...) if the results* [of RCTs and observational studies] *could have been quantitatively summarised through a meta-analysis or used to develop indirect comparisons, we considered that mixing the results from observational and interventional studies would have been inadequate due to the high level of heterogeneity between these two types of design (...)"*.[4] The ERG is not fully supportive of this approach considering that only a single RCT was identified as relevant for this submission. Since the company did not include observational studies in their SLR, it is unclear how many papers relevant to this topic may have been missed. The safety of icosapent ethyl was considered part of the NICE Final Scope, and due to the exclusion of observational study designs from the SLR, some relevant material might have been missed.

However, the ERG considers that neither of these issues is likely to be a source of substantial uncertainty in clinical effectiveness.

3.1.3 Critique of data extraction

The data extraction was carried out by two reviewers using a predefined extraction form. Any discrepancies were resolved by consensus between reviewers. The company stated that *"Data was extracted in a format which aligns with Cochrane methodology and NICE reporting requirements."*[1]

ERG comment: The ERG agrees that the process of data extraction reflects best practice in systematic reviewing. The extraction form was not included as part of submission and therefore the ERG is not able to comment on the quality and level of details included in the form.

3.1.4 Quality assessment

Although tabulated details of the methodological quality assessment of the REDUCE-IT and JELIS trials were presented as part of Appendix D,[9] details of the process of quality assessment were lacking within the CS.[1]

ERG comment: The company was asked in the clarification letter to provide more details regarding the process of risk of bias assessment and include a supporting reference. The response did not provide details of the process of risk of bias assessment therefore, the ERG is not able to comment on the appropriateness of the company's methods. The company stated that *"The table follows the format as per the guidelines set out in the NICE STA user guide."* without providing a supporting reference.

3.1.5 Evidence synthesis

The results of the eligible trial i.e. REDUCE-IT were provided for primary, secondary and tertiary outcomes. HRQoL was reported separately. No pooling of data was necessary for this assessment.

3.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

The CS identified one eligible trial i.e. REDUCE-IT relevant to this submission.[1] A summary of the study is provided in the Table 3.3 below.

Table 3.3: Overview of the clinical evidence for icosapent ethyl

Study	REDUCE-IT, NCT01492361, Bhatt et al. 2019[10, 11]				
Study design	Phase IIIb, double-blind, randomised (1:1), placebo-controlled, multicentre study, with a treatment and follow-up period of up to a maximum of 6.5 years				
Population	Patients on statin with established CVD or at high risk for CVD and elevated TGs. Patients were eligible for inclusion in the study if they met all of the following criteria: TG level of ≥135 mg/dL (1.53 mmol/L), reflecting a 10% allowance due to the variability in TG levels and a target lower end qualifying fasting TG level of ≥150 mg/dL (1.69 mmol/L), and an upper TG level limit of <500 mg/dL (5.64 mmol/L) LDL-C >40 mg/dL (1.04 mmol/L) and ≤100 mg/dL (2.60 mmol/L) and on stable therapy with a statin (with or without ezetimibe) for at least 4 weeks prior to the LDL-C and TG baseline qualifying measurements for randomisation. Either having established CVD (in CV risk category 1) or at high risk for CVD (in CV risk category 2). In summary, the CV risk categories were defined as follows:* CV risk category 1 (secondary prevention) – Men and women ≥45 years of age with established CVD CV risk category 2 (primary prevention) – Men and women ≥50 years of age and with the following: Diabetes mellitus (Type 1 or Type 2) requiring treatment with medication One or more additional risk factor for CVD Number of patients recruited receiving: Icosapent ethyl (n=4,089) Placebo (n=4,090)				
Intervention(s)	Icosapent ethyl four capsules taken as two 1g capsules twice daily; Alternative names: Vazkepa, AMR101				
Comparator(s)	Placebo				
Indicate if trial supports application for marketing authorisation	Yes	X	Indicate if trial used in the economic model	Yes	X
	No			No	
Rationale for use/non-use in the model	This study investigated icosapent ethyl 4g daily in the population to be treated as per the licenced indication, and includes key outcomes used in the economic model				

Reported outcomes specified in the decision problem	*Primary endpoint:* Time from randomisation to the first occurrence of any component of the 5-point major adverse CV events (MACE) *composite* endpoint: CV death Nonfatal MI (including silent MI) Nonfatal stroke Coronary revascularization Unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalisation *Key secondary endpoint:* Time from randomisation to the first occurrence of any component of the 3-point major adverse CV events (MACE) *composite* endpoint: CV death Nonfatal MI (including silent MI) Nonfatal stroke *Other secondary endpoints:* Time from randomisation to the first occurrence of any of the following *individual or composite* endpoints: Composite of CV death or nonfatal MI (including silent MI) Fatal or nonfatal MI (including silent MI) Non-elective coronary revascularization represented as the composite of emergent or urgent classifications CV death Unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalisation Fatal or nonfatal stroke Composite of total mortality, nonfatal MI (including silent MI), or nonfatal stroke Total mortality *Tertiary endpoints:* Time from randomisation to the first and all subsequent occurrence of any component of the 5-point major adverse CV events (MACE) *composite* endpoint (this represents the total CV events): CV death Nonfatal MI (including silent MI)

	Nonfatal stroke Coronary revascularization Unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalisation *Safety endpoints:* Adverse events Treatment-emergent adverse events Serious treatment-emergent adverse events Discontinuation due to treatment-emergent adverse events
All other reported outcomes	*Tertiary endpoints - where applicable and unless specified otherwise, endpoints represented time from randomisation to the first occurrence of the individual or composite endpoints:* Primary endpoint in the subset of patients with diabetes mellitus at baseline Primary endpoint in the subset of patients with metabolic syndrome at baseline Primary endpoint in the subset of patients with impaired glucose metabolism at baseline (Visit 2 fasting blood glucose [FBG] of 100 to 125 mg/dL) Key secondary endpoint in the subset of patients with impaired glucose metabolism at baseline (Visit 2 FBG 100 to 125 mg/dL) Composite of CV death, nonfatal MI (including silent MI), nonfatal stroke, cardiac arrhythmia requiring hospitalisation of ≥24 hours, or cardiac arrest Composite of CV death, nonfatal MI (including silent MI), non-elective coronary revascularizations (defined as emergent or urgent classifications), or unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalisation Composite of CV death, nonfatal MI (including silent MI), non-elective coronary revascularizations (defined as emergent or urgent classifications), unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalisation, nonfatal stroke, or peripheral vascular disease (PVD) requiring intervention, such as angioplasty, bypass surgery, or aneurism repair Composite of CV death, nonfatal MI (including silent MI), non-elective coronary revascularizations (defined as emergent or urgent classifications), unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalisation, PVD requiring intervention, or cardiac arrhythmia requiring hospitalisation of ≥24 hours New congestive heart failure (CHF) New CHF as the primary cause of hospitalisation Transient ischemic attack (TIA) Amputation for PVD

	Carotid revascularization All coronary revascularizations defined as the composite of emergent, urgent, elective, or salvage Emergent coronary revascularizations Urgent coronary revascularizations Elective coronary revascularizations Salvage coronary revascularizations Cardiac arrhythmias requiring hospitalisation of ≥24 hours Cardiac arrest Ischemic stroke Haemorrhagic stroke Fatal or nonfatal stroke in the subset of patients with a history of stroke prior to baseline New onset diabetes, defined as Type 2 diabetes newly diagnosed during the treatment/follow-up period New onset hypertension, defined as blood pressure ≥140 mmHg systolic OR ≥90 mmHg diastolic newly diagnosed during the treatment/follow-up period Fasting TG, total cholesterol (TC), LDL-C, high-density lipoprotein cholesterol (HDL-C), non-HDL-C, very low-density lipoprotein cholesterol (VLDL-C), apolipoprotein B (apo B), high-sensitivity C-reactive protein (hsCRP) (hsCRP and log[hsCRP]), high-sensitivity troponin T (hsTnT), and remnant lipoprotein cholesterol (RLP-C) (to be estimated from standard lipid panel, RLP-C = TC – HDL-C – LDL-C [Varbo 2014 applied to fasting lipids]) (based on Intent-to-Treat [ITT] estimands): Assessment of the relationship between baseline biomarker values and treatment effects within the primary and key secondary endpoints Assessment of the effect of AMR101 on each marker Assessment of the relationship between post-baseline biomarker values and treatment effects within the primary and key secondary endpoints by including post-baseline biomarker values (for example, at 4 months, or at 1 year) as a covariate Change in body weight Change in waist circumference

Based on the Table 3 of the CS.[1]
*Table 3 in the CS shows further details of criteria for the two CV risk categories.[1]

Abbreviations: apo B = apolipoprotein B; CHF = Congestive heart failure; CV = Cardiovascular; CVD = Cardiovascular disease; FBG = Fasting blood glucose; HDL-C = High-density lipoprotein cholesterol; hsCRP = high-sensitivity C-reactive protein; hsTnT = high-sensitivity troponin T; ITT = Intent-to-treat; LDL-C = Low-density lipoprotein cholesterol; MACE = major adverse cardiovascular event; MI = Myocardial infarction; PVD = Peripheral vascular disease; REDUCE-IT = Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial; RLP-C = Remnant lipoprotein cholesterol; TC = total cholesterol; TG = Triglyceride; TIA = Transient ischemic attack; UK = United kingdom; VLDL-C = Very low-density lipoprotein cholesterol.

ERG comment: The company identified two trials from the systematic literature review (SLR) i.e., REDUCE-IT and JELIS, but only the former was covered by the CS.[1] The ERG asked the company to justify the inclusion of JELIS in the results of SLR. In their response to the clarification letter, the company stated that whilst JELIS is *"relevant for reporting within the literature search results, the study design is substantively different enough from the indicated population for Icosapent ethyl, that JELIS was not included in the modelling efforts (...)"*.[4] The inclusion criteria for the SLR (Table 3.2 in section 3.1.2) specified the intervention as "Icosapent ethyl (Vazkepa®; received as an adjunctive therapy to statin)" whereas JELIS included an eicosapentaenoic acid (EPA)-based therapy (not icosapent ethyl/Vazkepa®). Therefore, JELIS is not relevant for inclusion in the submission. The ERG agrees that the study does not fit the criteria stated within the NICE final scope.[5]

3.2.1 Details of included trials

The CS identified one phase IIIb, multicentre, randomised, double-blind, placebo-controlled trial in patients who were ≥45 years of age with established CVD, or who were ≥50 years of age with diabetes in combination with at least one additional risk factor for developing CVD eligible for icosapent ethyl (REDUCE-IT). The evidence supporting the effectiveness of icosapent ethyl is derived from this trial. Details of trial design and methodology are presented in Table 3.4.

Recruitment for the study was conducted between November 2011 and August 2016 with amendment of the eligibility criteria on 16 of May 2013 to increase enrolment of patients with TG levels at or above 200 mg/dL (increase of the lower end of fasting TG levels from ≥135 mg/dL to ≥200 mg/dL). None of the patients were recruited in the UK.

Table 3.4: Summary of REDUCE-IT study design and methodology

Study	REDUCE-IT, NCT01492361, Bhatt et al. 2019[10, 11]
Trial design	Phase IIIb, double-blind, randomised (1:1), placebo-controlled, multicentre study, with a treatment and follow-up period of up to a maximum of 6.5 years
Eligibility criteria	Inclusion Criteria Patients were eligible for inclusion in the study if they met the following criteria: The original protocol stipulated a lower end of qualifying fasting TG level of ≥135 mg/dL (1.53 mmol/L), reflecting a 10% allowance due to the variability in TG levels and a target lower end qualifying fasting TG level of ≥150 mg/dL (1.69 mmol/L), and an upper TG level limit of <500 mg/dL (5.64 mmol/L). Protocol Amendment 1 (16 May 2013) increased the lower end of fasting TG levels from ≥135 mg/dL to ≥200 mg/dL (2.26 mmol/L) to increase enrolment of patients with TG levels at or above 200 mg/dL. LDL-C >40 mg/dL (1.04 mmol/L) and ≤100 mg/dL (2.60 mmol/L) and on stable therapy with a statin (with or without ezetimibe) for at least 4 weeks prior to the LDL-C and TG baseline qualifying measurements for randomization. Stable therapy was defined as the same daily dose of the same statin for at least 28 days before the lipid qualification measurements (TG and LDL-C) and, if applicable, the same daily dose of ezetimibe for at least 28 days before the lipid qualification measurements (TG and LDL-C). Patients who had their statin therapy or use of ezetimibe initiated at Visit 1, or had their statin type, statin dose, and/or ezetimibe dose changed at Visit 1, needed to go through a stabilization period of at least 28 days since initiation/change and have their qualifying lipid measurements (TG and LDL-C) after the washout period (at Visit 1.1). Statins may have been administered with or without ezetimibe. Either having established CVD (in CV risk category 1) or at high risk for CVD (in CV risk category 2). The CV risk categories were defined as follows: CV Risk Category 1 (Secondary Prevention Cohort): defined as men and women ≥45 years of age with one or more of the following: Documented coronary artery disease (CAD); one or more of the following primary criteria must have been satisfied: Documented multi-vessel CAD (≥50% stenosis in at least two major epicardial coronary arteries, with or without antecedent revascularization). Documented prior MI. Hospitalization for high-risk non-ST-segment elevation acute coronary syndrome, with objective evidence of ischemia: ST-segment deviation or biomarker positivity. Documented cerebrovascular or carotid disease; one of the following primary criteria must have been satisfied: Documented prior ischemic stroke. Symptomatic carotid artery disease with ≥50% carotid arterial stenosis. Asymptomatic carotid artery disease with ≥70% carotid arterial stenosis per angiography or duplex ultrasound.

Study	REDUCE-IT, NCT01492361, Bhatt et al. 2019[10, 11]
	History of carotid revascularization (catheter-based or surgical). Documented peripheral arterial disease; one or more of the following primary criteria must have been satisfied: Ankle brachial index (ABI) <0.9 with symptoms of intermittent claudication. History of aorto-iliac or peripheral arterial intervention (catheter-based or surgical). CV Risk Category 2 (Primary Prevention Cohort): defined as patients with: Diabetes mellitus (Type 1 or Type 2) requiring treatment with medication. Men and women ≥50 years of age. One or more of the following at Visit 1 (additional risk factor for CVD): Men ≥55 years of age or women ≥65 years of age. Cigarette smoker or stopped smoking within 3 months before Visit 1. Hypertension (blood pressure ≥140 mmHg systolic or ≥90 mmHg diastolic) or on antihypertensive medication. HDL-C ≤40 mg/dL for men or ≤50 mg/dL for women. hsCRP >3.00 mg/L (0.3 mg/dL). Renal dysfunction: creatinine clearance (CrCL) >30 and <60 mL/min (>0.50 and <1.00 mL/sec). Retinopathy, defined as any of the following: non-proliferative retinopathy, pre-proliferative retinopathy, proliferative retinopathy, maculopathy, advanced diabetic eye disease, or a history of photocoagulation. Micro- or macroalbuminuria Micral or other strip test (may have been obtained from medical records), an albumin/creatinine ratio ≥2.5 mg/mmol or an albumin excretion rate on timed collection ≥20 mg/min all on at least two successive occasions; macroalbuminuria, defined as Albustix or other dipstick evidence of gross proteinuria, an albumin/creatinine ratio ≥25 mg/mmol or an albumin excretion rate on timed collection ≥200 mg/min all on at least two successive occasions. ABI <0.9 without symptoms of intermittent claudication (patients with ABI <0.9 with symptoms of intermittent claudication were included in CV risk category 1). Note: Patients with diabetes and CVD, as defined above, were eligible, based on the CVD requirements and were to be included in CV risk category 1. Only patients with diabetes and no documented CVD, as defined above, required at least one additional risk factor as listed, and were to be included in CV risk category 2. Women were required to meet all 3 of the following criteria: Not pregnant. Not breastfeeding. Not planning on becoming pregnant during the study.

Study	REDUCE-IT, NCT01492361, Bhatt et al. 2019[10, 11]
	Women of child bearing potential were required to have a negative urine pregnancy test before randomisation. Women were to be considered not of childbearing potential if they met one of the following criteria, as documented by the Investigator: Had a hysterectomy, tubal ligation or bilateral oophorectomy prior to signing the ICF. Were post-menopausal, defined as ≥1 year since their last menstrual period or had a follicle-stimulating hormone level in a menopausal range. Women of childbearing potential were required to agree to use an acceptable method of avoiding pregnancy from screening to the end of the study, unless their sexual partner(s) was/were surgically sterile or the woman was abstinent. Understood the study procedures, was willing to adhere to the study schedules, and agreed to participate in the study by giving informed consent prior to screening. Agreed to follow and maintain a physician recommended diet through the duration of the study. Exclusion Criteria: Patients were to be excluded from the study if they met any of the following criteria: Severe (New York Heart Association class IV) heart failure. Any life-threatening disease expected to result in death within the next 2 years (other than CVD). Active severe liver disease (evaluated at Visit 1): cirrhosis, active hepatitis, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 × the upper limit of normal (ULN), or biliary obstruction with hyperbilirubinemia (total bilirubin >2 × ULN). Glycated haemoglobin (HbA1c) >10.0% (or >86 mmol/mol IFCC units) at screening (Visit 1). If patients failed this criterion at Visit 1, they may have had their antidiabetic therapy optimized and been retested at Visit 1.1. Poorly controlled hypertension: blood pressure ≥200 systolic mmHg or ≥100 mmHg diastolic (despite antihypertensive therapy). Planned coronary intervention (such as stent placement or heart bypass) or any non-cardiac major surgical procedure. Patients may have been (re)evaluated for participation in the study (starting with Visit 1.1) after their recovery from the intervention/surgery. Known familial lipoprotein lipase deficiency (Fredrickson Type 1), apolipoprotein C-II deficiency, or familial dysbetalipoproteinemia (Fredrickson Type 3). Participation in another clinical study involving an investigational agent within 90 days prior to screening (Visit 1). Patients were not to participate in any other investigational medication or medical device study while participating in this study. Participation in a registry or observational study without an additional therapeutic intervention was allowed. Intolerance or hypersensitivity to statin therapy. Known hypersensitivity to any ingredients of the study product or placebo; known hypersensitivity to fish and/or shellfish. History of acute or chronic pancreatitis.

Study	REDUCE-IT, NCT01492361, Bhatt et al. 2019[10, 11]
	Malabsorption syndrome and/or chronic diarrhoea (Note: patients who underwent gastric/intestinal bypass surgery were considered to have malabsorption and were not eligible; patients who underwent gastric banding were eligible). Non-study drug-related, non-statin, lipid-altering medications, supplements or foods. Other medications (not indicated for lipid alteration) Known to have acquired immunodeficiency syndrome (AIDS); patients who were HIV-positive without AIDS were allowed. Requirement for peritoneal dialysis or haemodialysis for renal insufficiency or CrCL <30 mL/min (0.50 mL/sec). Unexplained creatine kinase concentration >5 × ULN or creatine kinase elevation due to known muscle disease (e.g., polymyositis, mitochondrial dysfunction) at Visit 1. Any condition or therapy that, in the opinion of the Investigator, might have posed a risk to the patient or made participation in the study not in the patient's best interest. Drug or alcohol abuse within the previous 6 months, and unable/unwilling to abstain from drug abuse and excessive alcohol consumption during the study or drinking 5 units or more for men or 4 units or more for women in any one hour. Mental/psychological impairment or any other reason to expect patient difficulty in complying with the requirements of the study or understanding the goal and potential risks of participating in the study.
Settings and location where data were collected	473 participating sites in 11 countries (US, Australia, Canada, India, South Africa, Netherlands, Ukraine, New Zealand, Russia, Romania, Poland)
Trial drugs and concomitant medications	Trial drugs: Participants were treated with icosapent four capsules taken as two 1g capsules twice daily, or matched placebo Permitted concomitant medications: Stable statin regime, with the statin intensity categories defined as in the American College of Cardiology/American Heart Association cholesterol guidelines and the patient's 10-year CV risk score (which aligns with the regime as indicated in NICE CG181).[12, 13]
Outcomes used in the economic model or specified in the scope, including primary outcome	Primary outcomes: Time from randomisation to the first occurrence of any component of the 5-point MACE *composite*: CV death Nonfatal MI (including silent MI) Nonfatal stroke Coronary revascularization Unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalisation

Study	REDUCE-IT, NCT01492361, Bhatt et al. 2019[10, 11]
	Secondary and tertiary outcomes applied in the economic model: Time from randomisation to the first occurrence of any of any of the following *individual or composite* endpoints: Composite of CV death or nonfatal MI (including silent MI) Fatal or nonfatal MI (including silent MI) Non-elective coronary revascularization represented as the composite of emergent or urgent classifications CV death Unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalisation Fatal or nonfatal stroke Composite of total mortality, nonfatal MI (including silent MI), or nonfatal stroke Total mortality Time from randomisation to the first and all subsequent occurrence of any component of the 5-point MACE *composite* endpoint (this represents the total CV events): CV death Nonfatal MI (including silent MI) Nonfatal stroke Coronary revascularization Unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalisation Safety outcomes: Treatment-emergent adverse events Serious treatment-emergent adverse events Discontinuation due to treatment-emergent adverse events

Based on Table 4 of the CS.[1]

Abbreviations: ABI = Ankle brachial index; AIDS = Acquired immunodeficiency syndrome; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; CAD = Coronary artery disease; CG = clinical guideline; CrCL = Creatine clearance; CS = company submission; CV = Cardiovascular; CVD = Cardiovascular disease; HbA1c = glycated haemoglobin; HDL-C = High-density lipoprotein cholesterol; HIV = Human immunodeficiency virus; hsCRP = High-sensitivity C-reactive protein; ICF = Informed Consent Form; IFCC = International federation of clinical chemistry; LDL-C = Low-density lipoprotein cholesterol; MACE = major adverse cardiovascular event; MI = Myocardial infarction; NICE = National Institute for Health and Care Excellence; REDUCE-IT = Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial; TG = Triglyceride; ULN = Upper limit of normal; US = United states.

3.2.2 Statistical analysis of included trials

The statistical analysis as performed in the REDUCE-IT trial is summarised in Table 3.5.

The intention to treat (ITT) population, defined as all patients who were randomised, was used for all efficacy analyses, including the primary analysis. Patients were analysed for efficacy according to the randomised treatment. The safety population was defined as all randomised patients (same as the ITT population) and patients were analysed for safety according to treatment received. The study included 8,179 participants (4,089 in the icosapent ethyl group and 4,090 in the placebo group) and 7,314 patients completed the final visit within the 2018 final visit window or died during the study. The most common reason for the termination of participation in the study was withdrawal of consent (6.9% and 7.3% for the icosapent ethyl and placebo groups respectively), followed by incomplete final visit (lost to follow-up; 1.5% and 2.2%, respectively), investigator judgment (0.3% and 0.3%, respectively) and other (1.2% and 1.5%, respectively).[1]

Table 3.5: Statistical analysis in REDUCE-IT trial

Trial number (acronym)	REDUCE-IT, NCT01492361, Bhatt et al. 2019[10, 11, 14]
Hypothesis objective	It was hypothesized that the risk of cardiovascular events would be lower with icosapent ethyl therapy than with placebo among patients in whom elevated triglyceride levels served as a marker of residual risk despite statin therapy.
Sample size, power calculation	In this event-driven trial, it was estimated that approximately 1,612 adjudicated primary end-point events would be necessary to provide the trial with 90% power to detect a 15% lower risk of the primary composite end point in the icosapent ethyl group than in the placebo group. It was estimated that a sample size of approximately 7,990 patients would be required to reach this number of end-point events.
Outcome populations	Four populations were defined in the study: The ITT population was defined as all patients who were randomised. All efficacy analyses, including the primary analysis, were performed on the ITT population. The modified ITT population was defined as all randomised patients who had the study drug dispensed after randomisation. Patients were analysed according to the randomised treatment. The per-protocol population included all modified ITT patients without any major protocol deviations who had 80% or greater adherence while on treatment. To be included in the per-protocol population, the minimum time on therapy had to be 90 days. The safety population was defined as all randomised patients and was the same as the ITT population. Patients were analysed for safety according to treatment received.

Statistical analysis	The REDUCE-IT study assessed the primary outcome by counts and Kaplan–Meier estimates of the percentage of patients experiencing each type of event by study completion per treatment arm. HRs and 95% CIs were generated with the use of a Cox proportional hazards model that included trial-group assignment as a covariate, stratified according to CV risk category, geographic region, and use of ezetimibe. The two-sided alpha level for the primary analysis was adjusted to 0.0437 from 0.05 to account for the two interim analyses based on a group sequential design with O'Brien–Fleming boundaries generated using the Lan-DeMets alpha-spending function. Log-rank p-values from the Kaplan–Meier analysis (stratified based on the three randomisation factors) were reported. Subgroup analysis was performed using Kaplan–Meier estimates and the log-rank test stratified by stratification factors used at randomisation (except where the subgroup was a stratification factor). The key and other secondary outcomes and tertiary outcomes, as well as the components of the composite outcomes, were analysed using the same methods as the primary outcome analysis. Statistical analyses of secondary outcomes followed a hierarchical sequential approach to control for inflated type I error. Specifically, the key secondary endpoint (the time from randomisation to the first occurrence of the 3-point MACE composite of CV death, nonfatal MI [including silent MI], or nonfatal stroke) was tested only if the primary analysis was statistically significant. Other secondary endpoints were the time from randomisation to the first occurrence of the individual or composite endpoints, as follows (statistically tested in the order listed): composite of CV death or nonfatal MI (including silent MI) fatal or nonfatal MI (including silent MI) nonelective coronary revascularization CV death unstable angina requiring emergent hospitalisation fatal or nonfatal stroke composite of total mortality, nonfatal MI (including silent MI), or nonfatal stroke total mortality Testing was done at a significance level of 0.0437 and ceased when a comparison for a secondary endpoint was greater than this threshold. All analyses beyond the primary or the last endpoint meeting statistical significance in this hierarchical order at this alpha level were exploratory, per the analysis plan.
Data management, patient withdrawals	It was planned for approximately 7,990 patients (approximately 3,995 patients per treatment group) to be included in the study. In total, 19,212 patients were screened leading to 8,179 patients participating in the study (4,089 in the icosapent ethyl group and 4,090 in the placebo group). Of the 8,179 patients, 7,314 patients completed the final visit within the 2018 final visit window or died during the study. The remaining patients (865/8,179) discontinued the study early with 9.9% (405/4,089) and 11.2% (460/4,090) in

	the icosapent ethyl and placebo groups, respectively. Among patients who terminated the study early, the most common reasons overall were: Withdrawal of consent: 6.9% (281/4,089) and 7.3% (297/4,090) in the icosapent ethyl and placebo groups, respectively. Incomplete final visit (lost to follow-up): 1.5% (63/4,089) and 2.2% (89/4,090) in the icosapent ethyl and placebo groups, respectively. Investigator judgment: 0.3% (12/4,089) and 0.3% (12/4,090) in the icosapent ethyl and placebo groups, respectively.
Interim analyses	Two interim analyses were planned for the primary endpoint when adjudication of approximately 60% and 80% of the total target number of primary endpoint events planned (1,612) were reached. The planned interim analyses were based on a group sequential design with O'Brien-Fleming boundaries generated using the Lan-DeMets alpha-spending function. The two Data Monitoring Committee (DMC) interim analysis review meetings were performed in September 2016 and August 2017, at which 59.3% (953 events) and 75.8% (1,218 events) of the final adjudicated primary endpoint events (1,606) had occurred respectively, and had been adjudicated. At each interim analysis the sponsor remained blinded to trial results and the DMC had discretion to consider the robustness, consistency, and completeness within the totality of the data beyond the primary endpoint, in support of their recommendation regarding study continuation. Based on the reviews of each interim analysis, the DMC recommended continuation of the study as planned.

Based on Table 6 of the CS.[1]

Abbreviations: CI = Confidence interval; CS = company submission; CV = Cardiovascular; DMC = Data monitoring committee; HR = Hazard ratio; ITT = Intent-to-treat; MACE = major adverse cardiovascular event; MI = Myocardial infarction; REDUCE-IT = Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial.

3.2.3 Trial participants characteristics

The baseline characteristics of patients within the ITT population of the REDUCE-IT trial are presented in Table 3.6.

Table 3.6: Baseline characterises of patients in the ITT population of the REDUCE-IT trial

	Icosapent ethyl (N = 4,089)	**Placebo (N = 4,090)**
Demographic characteristics		
Age		
Median, yr (IQR)	64.0 (57.0–69.0)	64.0 (57.0–69.0)
≥65 yrs, n (%)	1,857 (45.4)	1,906 (46.6)
Gender		
Sex – Male, n (%)	2,927 (71.6)	2,895 (70.8)
Ethnicity		
Race – White, n (%)	3,691 (90.3)	3,688 (90.2)
Body-mass index		
Median (IQR)	30.8 (27.8–34.5)	30.8 (27.9–34.7)
≥30, n (%)	2,331 (57.0)	2,362 (57.8)
Geographic region, n (%)		
Group of western countries[a]	2,906 (71.1)	2,905 (71.0)
Eastern European countries	1,053 (25.8)	1,053 (25.7)
Asia–Pacific region	130 (3.2)	132 (3.2)
Disease-relevant baseline characteristics		
Cardiovascular risk stratum, n (%)		
Secondary-prevention cohort	2,892 (70.7)	2,893 (70.7)
Primary-prevention cohort	1,197 (29.3)	1,197 (29.3)
Diabetes, n (%)		
Type 1	27 (0.7)	30 (0.7)
Type 2	2,366 (57.9)	2,363 (57.8)
No diabetes	1,695 (41.5)	1,694 (41.4)
Prior atherosclerotic CVD, n (%)	2,816 (68.9)	2,835 (69.3)
Prior non-atherosclerotic CVD (including CHF), n (%)	3,649 (89.2)	3,645 (89.1)
Renal impairment, n (%)	905 (22.1)	911 (22.3)
Hypertension, n (%)	3,541 (86.6)	3,543 (86.6)
Statin intensity, n (%)		
Low	254 (6.2)	267 (6.5)
Medium	2,533 (61.9)	2,575 (63.0)
High	1,290 (31.5)	1,226 (30.0)
Data missing	12 (0.3)	22 (0.5)
Ezetimibe use, n (%)	262 (6.4)	262 (6.4)

	Icosapent ethyl (N = 4,089)	Placebo (N = 4,090)
TG levels, n/N (%)		
< 150mg/dL	412/4,086 (10.1)	429/4,089 (10.5)
≥ 150mg/dL to < 200mg/dL	1,193/4,086 (29.2)	1,191/4,089 (29.1)
≥ 200mg/dL	2,481/4,086 (60.7)	2,469/4,089 (60.4)
TG levels (mg/dL), median (IQR)	216.5 (176.5–272.0)	216.0 (175.5–274.0)
TG level ≥200 mg/dl and HDL-C level ≤35 mg/dl, n (%)	823 (20.1)	794 (19.4)
Median high-sensitivity CRP level, mg/litre (IQR)	2.2 (1.1–4.5)	2.1 (1.1–4.5)
Median HDL-C level, mg/dl (IQR)	40.0 (34.5–46.0)	40.0 (35.0–46.0)
Median LDL-C level, mg/dl (IQR)	74.0 (61.5–88.0)	76.0 (63.0–89.0)
Median eicosapentaenoic acid level, µg/ml (IQR) —	26.1 (17.1–40.1)	26.1 (17.1–39.9)
Abnormal lipids		
High HDL-C (≥ 1.6mmol/L [60mg/dL])	187 (4.6)	187 (4.6)
Low HDL-C (< 1.0mmol/L [40mg/dL])	1,327 (32.5)	1,259 (30.8)
TGs > 11.3mmol/L (1,000mg/dL)	76 (1.9)	72 (1.8)

Based on Table 5 of the CS.[1]
[a]*United States, Canada, the Netherlands, Australia, New Zealand, and South Africa*
Abbreviations: CHF = Congestive heart failure; CRP = C-reactive protein; CS = company submission; CVD = Cardiovascular disease; HDL-C = High-density lipoprotein cholesterol; IQR = Inter quartile range; ITT = Intent-to-treat; LDL-C = Low-density lipoprotein cholesterol; n = number; REDUCE-IT = Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial; TG = Triglyceride; yr = year.

ERG comment: The patients' baseline characteristics were balanced between treatment arms. The ERG therefore has no concerns regarding the risk of bias in the REDUCE-IT trial.

However, it is unclear if the patient population is generalisable to the UK clinical setting. As the REDUCE-IT trial did not include any patients from the UK, the company was asked to provide more details and compare the population in the trial to eligible patients in the UK.

In response to the clarification letter,[4] the company provided the reference to the paper by Steen et al. (2016)[15] which is a retrospective study of lipid-lowering treatment patterns in a high-risk cohort in the UK in 2014. However, it is not possible to make an informative comparison between the participants from Steen et al. (2016)[15] with the treatment arms from the REDUCE-IT trial.[1] Steen et al. (2016)[15] present the results for participants with prior atherosclerotic CVD (ASCVD) and those without CVD (with and without diabetes) separately whereas the baseline characteristics of participants in the two prevention cohorts from the REDUCE-IT trial are only provided for the whole population (Table 3.6).[1]

In comparison with the overall population from Steen et al. (2016)[15] the REDUCE-IT trial included a higher proportion of males, younger participants and people with a higher BMI on average.[1] The REDUCE-IT trial included 71.6% and 70.8% males in the icosapent ethyl and placebo arms respectively[1] whereas Steen et al (2016) included 60.7% and 50.3% in the ASCVD and non-ASCVD

cohorts, respectively.[15] The mean (standard deviation [SD]) age of participants in the REDUCE-IT trial was 63.4 (8.37) and 63.4 (8.43) years for icosapent ethyl and placebo respectively (as per the clinical study report)[10] whilst in Steen et al (2016) the values were 72.6 and 69.7 years in the ASCVD and non-ASCVD cohorts respectively (SD values not provided).[15] The mean (SD) BMI values for the REDUCE-IT trial were 31.5 (5.41) and 31.7 (5.47) for the icosapent ethyl and placebo arms respectively[1] and in Steen et al (2016) the mean values were 28.3 and 30.1 in the ASCVD and non-ASCVD cohorts respectively (SD values not provided).[15]

Explicit comparison between overall or subgroup populations of the REDUCE-IT trial and sources aligned with UK clinical practice is lacking. The ERG identifies this as a Key Issue.

3.2.4 Quality assessment of the included RCT

Details of the process and tool used for the risk of bias assessment is reported in section 3.1.4. The results of the risk of bias assessment are provided in Table 3.7.

Table 3.7: The risk of bias assessment of the REDUCE-IT trial

Study Acronym/ I.D.	REDUCE-IT NCT01492361 (Bhatt et al., 2019)
Was randomisation carried out appropriately?	Yes 1:1 randomisation with three stratification factors (CV risk category, geographic region and baseline use of ezetimibe) was performed before treatment allocation.
Was the concealment of treatment allocation adequate?	Unclear No further details provided on the methods used to conceal the allocation sequence.
Were the groups similar at the outset of study in terms of prognostic factors?	Yes All baseline characteristics were well balanced between the active and placebo groups.
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes, REDUCE-IT was a double-blind trial.
Were there any unexpected imbalance in drop-outs between groups?	No Dropouts' rates were similar between the active and control groups. Proportions of patients who discontinued the study early, as well as the reasons for early discontinuation were reported.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Unclear Selective outcome reporting was not examined by the authors. Therefore, there is no sufficient details in the publication to conclude on this methodological aspect.
Did the analysis include an intention-to-treat analysis? If so was this appropriate and were appropriate methods used to account for missing data?	Yes All analyses were performed according to the intention-to-treat principle, which is considered appropriate to avoid overestimating treatment effect. Proportions of patients who completed the study were high and well described.
Based on Table 6 of the Appendix D of the CS[1]	

CS = company submission; CV = cardiovascular; REDUCE-IT = Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial.

ERG comment: the ERG have no concerns regarding risk of bias of the included REDUCE-IT trial.

3.2.5 Efficacy results

The primary efficacy endpoint in the REDUCE- IT trial is a 5-point MACE composite endpoint defined as time from randomisation to the first occurrence of any of the following events:

- CV death
- Nonfatal myocardial infarction (MI) (including silent MI)
- Nonfatal stroke
- Coronary revascularization
- Unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalisation.

The results are shown in Table 3.8.

Table 3.8: Time from randomisation to the first occurrence of any of the 5-point MACE

Outcomes	Icosapent ethyl	Placebo
5-point MACE composite of CV death, nonfatal MI (including silent MI), nonfatal stroke, coronary revascularisation and unstable angina requiring hospitalisation		
ITT	N=4,089	N=4,090
n (%)	705 (17.2)	901 (22.0)
HR (95% CI)	0.752 (0.682 to 0.830)	
P-value	0.00000001	
Components contributing to composite outcome, n (%)		
CV death	137 (3.4)	149 (3.6)
Nonfatal MI	205 (5.0)	280 (6.8)
Nonfatal stroke	80 (2.0)	105 (2.6)
Coronary revascularization	189 (4.6)	244 (6.0)
Hospitalisation for unstable angina	94 (2.3)	123 (3.0)
Secondary prevention	[redacted]	[redacted]
n (%)	[redacted]	[redacted]
HR (95% CI)	[redacted]	
Primary prevention	[redacted]	[redacted]
n (%)	[redacted]	[redacted]
HR (95% CI)	[redacted]	

Source: Table 7, CS[1]
CI – Confidence interval; CS = company submission; CV – Cardiovascular; HR – Hazard ratio; ITT – Intent-to-treat; MACE – Major adverse cardiovascular event; MI – Myocardial infarction; n = number.

Results by risk subgroup were also reported and are reproduced in Table 3.9.

Table 3.9: Time from randomisation to the first occurrence of any of the 5-point MACE, by risk subgroup

	Icosapent ethyl	Placebo
Secondary prevention		
N	[redacted]	[redacted]
n (%)	[redacted]	[redacted]
HR (95% CI)	[redacted]	
[redacted]		
N	[redacted]	[redacted]
n (%)	[redacted]	[redacted]
HR (95% CI)	[redacted]	
P-value	[redacted]	

Source: Table 7, CS[1]
CI – Confidence interval; CS = company submission; HR – Hazard ratio; MACE – Major adverse cardiovascular event; n = number.

Results were also presented for the time to 3-point MACE composite outcome (HR 0.735, 95% CI 0.651 to 0.830) and for a set of disaggregated outcomes (Table 3.10).

Table 3.10: Time from randomisation to the first occurrence of other secondary endpoint events - ITT population

Outcomes	Icosapent ethyl (N=4,089)	Placebo (N=4,090)
CV death or nonfatal MI		
n (%)	392 (9.6)	507 (12.4)
HR (95% CI)	0.753 (0.660 to 0.859)	
P-value	<0.0001	
Fatal or nonfatal MI		
n (%)	250 (6.1)	355 (8.7)
HR (95% CI)	0.688 (0.585 to 0.808)	
P-value	<0.0001	
Fatal MI, n (%)	16 (0.4)	29 (0.7)
HR (95% CI)	0.546 (0.297 to 1.005)	
P-value	0.0484	
Nonfatal MI, n (%)	237 (5.8)	332 (8.1)
HR (95% CI)	0.697 (0.590 to 0.823)	
P-value	<0.0001	
Urgent or emergency revascularization		
n (%)	216 (5.3)	321 (7.8)
HR (95% CI)	0.653 (0.550 to 0.776)	
P-value	<0.0001	
CV death		

Outcomes	Icosapent ethyl (N=4,089)	Placebo (N=4,090)
n (%)	174 (4.3)	213 (5.2)
HR (95% CI)	0.803 (0.657 to 0.981)	
P-value	0.0315	
Hospitalisation for unstable angina		
n (%)	108 (2.6)	157 (3.8)
HR (95% CI)	0.679 (0.531 to 0.868)	
P-value	0.0018	
Fatal or nonfatal stroke		
n (%)	98 (2.4)	134 (3.3)
HR (95% CI)	0.720 (0.555 to 0.934)	
P-value	0.0129	
Fatal stroke, n (%)	14 (0.3)	18 (0.4)
HR (95% CI)	0.767 (0.382 to 1.543)	
P-value	0.4564	
Nonfatal stroke, n (%)	85 (2.1)	118 (2.9)
HR (95% CI)	0.708 (0.536 to 0.936)	
P-value	0.0149	
Death from any cause, nonfatal MI, or nonfatal stroke		
n (%)	549 (13.4)	690 (16.9)
HR (95% CI)	0.772 (0.690 to 0.864)	
P-value	<0.0001	
Death from any cause		
n (%)	274 (6.7)	310 (7.6)
HR (95% CI)	0.870 (0.739 to 1.023)	
P-value	0.0915	

Source: Table 9, CS[1]
CI – Confidence interval; CS = company submission; CV – Cardiovascular; HR – Hazard ratio; ITT – Intent-to-treat; MI – Myocardial infarction; n = number.

The results for subsequent events are shown in Table 3.11.

Table 3.11: Total events in the primary endpoint including subsequent events on the same day - ITT population

Event	Icosapent ethyl (N=4,089)	Placebo (N=4,090)	Total (N=8,179)
Primary endpoint events			
n (%)	1,185 (40.7)	1,724 (59.3)	2,909
HR (95% CI)	0.69 (0.61 to 0.77)		
P-value	<0.0001		
≥1 event			

Event	Icosapent ethyl (N=4,089)	Placebo (N=4,090)	Total (N=8,179)
n (%)	705 (43.9)	901 (56.1)	1,606
HR (95% CI)	0.75 (0.68 to 0.83)		
P-value	<0.0001		
≥2 events			
n (%)	299 (39.2)	463 (60.8)	762
HR (95% CI)	0.68 (0.60 to 0.77)		
≥3 events			
n (%)	96 (35.3)	176 (64.7)	272
HR (95% CI)	0.70 (0.59 to 0.83)		
≥4 events			
n (%)	36 (27.9)	93 (72.1)	129
HR (95% CI)	0.49 (0.36 to 0.60)		
Other			
n (%)	49 (35.0)	91 (65.0)	140

Source: Table 10, CS[1]
CI – Confidence interval; CS = company submission; CV – Cardiovascular; HR – Hazard ratio; ITT – Intent-to-treat; n = number.

ERG comment: The results show that icosapent ethyl is generally effective in reducing the rates of all events, including MACE and subsequent events. It also appears to be more effective in the secondary prevention subgroup. As already mentioned in Section 2.4, there also appears to be less of an effect on CV and any cause death.

3.2.6 Safety results

All data on treatment-emergent adverse events (TEAEs) were derived from the safety population of the REDUCE-IT trial.[1] A TEAE was defined as *"an event that first occurs or worsens in severity on or after the date of dispensing study drug and within 30 days after the completion or withdrawal from study"*.[11] The REDUCE-IT trial safety population was defined as all randomised patients, analysed according to treatment received.[1] Table 3.12 (below) summarises the data on different categories of TEAEs and suggests that a similar majority of participants receiving icosapent ethyl or placebo experienced at least one TEAE (around 81%). Furthermore, similar proportions of participants across treatment groups experienced the other categories of TEAE (serious TEAE, TEAE leading to withdrawal of study drug, serious TEAE leading to withdrawal of study drug and serious TEAE leading to death) (Table 3.12).

Table 3.13 (below) summarises the proportion of participants experiencing specific types of TEAEs in the icosapent ethyl and placebo treatment arms. Proportions were similar between treatment groups for most types of TEAEs, the exceptions being: diarrhoea and anaemia (more frequent among those receiving placebo); and peripheral oedema, constipation and atrial fibrillation (more common for icosapent ethyl).

One of the journal publications for the REDUCE-IT trial provided further information on gastrointestinal TEAEs (summarised in Table 3.14 below). This suggested that gastrointestinal disorders overall occurred more frequently among participants receiving placebo.[11]

The same paper provided tabulation of serious bleeding TEAEs by category and specific type. The proportions of participants experiencing any given category or specific type of TEAE were all below 3% for both treatment arms.[11] Of note, the proportions of participants with bleeding-related disorders overall as reported in the paper appears discrepant with data reported in the CS (summarised in Table 3.15 below).[1, 11] All per-group proportions for specific types of bleeding TEAEs reported in the paper were below 1% and those data are not reproduced here. No between group differences were apparent for any category or any specific type of bleeding TEAE.[11]

Table 3.12: Summary of TEAE categories reported in the REDUCE-IT trial safety population

Category of TEAE	Icosapent ethyl (N = 4,089), n (%)	Placebo (N = 4,090), n (%)	P-value for between-group difference*
Patients with at least one TEAE	3,343 (81.8)	3,326 (81.3)	0.63
Serious TEAE	1,252 (30.6)	1,254 (30.7)	0.98
TEAE leading to withdrawal of study drug**	321 (7.9)	335 (8.2)	0.60
Serious TEAE leading to withdrawal of study drug**	88 (2.2)	88 (2.2)	1.00
Serious TEAE leading to death***	94 (2.3)	102 (2.5)	0.61

Based on Table 14 of the CS[1]
*Fisher's Exact test; from Supplementary Table 5 of Bhatt et al (2019b)[11]
**Withdrawal of study drug excludes patients who were off drug in study for 30 days or more and restarted study drug.[11]
***The most common TEAEs leading to death by system organ class were: neoplasms (1.1%); infections and infestations (0.4%); respiratory, thoracic and mediastinal disorders (0.2%); cardiac disorders (0.2%); and vascular disorders (0.1%). One serious TEAE leading to death by system organ class was statistically significantly different between treatment groups, namely cardiac disorders, occurring in 3 (0.1%) of patients receiving icosapent ethyl and 15 (0.4%) receiving placebo (p = 0.008).[11]
CS = company submission; REDUCE-IT = Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial; TEAE – treatment-emergent adverse event

Table 3.13: Summary of the most frequently reported TEAEs (≥5% in either treatment arm) in the REDUCE-IT safety population

Type of TEAE	Icosapent ethyl (N = 4,089), n (%)	Placebo (N = 4,090), n (%)	P-value for between-group difference*
Diarrhoea	367 (9.0)	453 (11.1)	0.002
Back pain	335 (8.2)	309 (7.6)	0.29
Hypertension	320 (7.8)	344 (8.4)	0.35
Nasopharyngitis	314 (7.7)	300 (7.3)	0.56
Arthralgia	313 (7.7)	310 (7.6)	0.90
Upper respiratory tract infection	312 (7.6)	320 (7.8)	0.77
Bronchitis	306 (7.5)	300 (7.3)	0.80
Chest pain	273 (6.7)	290 (7.1)	0.48

Type of TEAE	Icosapent ethyl (N = 4,089), n (%)	Placebo (N = 4,090), n (%)	P-value for between-group difference*
Peripheral oedema	267 (6.5)	203 (5.0)	0.002
Pneumonia	263 (6.4)	277 (6.8)	0.56
Influenza	263 (6.4)	271 (6.6)	0.75
Dyspnoea	254 (6.2)	240 (5.9)	0.52
Urinary tract infection	253 (6.2)	261 (6.4)	0.75
Cough	241 (5.9)	241 (5.9)	1.00
Osteoarthritis	241 (5.9)	218 (5.3)	0.27
Dizziness	235 (5.7)	246 (6.0)	0.64
Pain in extremity	235 (5.7)	241 (5.9)	0.81
Cataract	235 (5.7)	208 (5.1)	0.22
Fatigue	228 (5.6)	196 (4.8)	0.11
Constipation	221 (5.4)	149 (3.6)	<0.001
Atrial fibrillation	215 (5.3)	159 (3.9)	0.003
Angina pectoris	200 (4.9)	205 (5.0)	0.84
Anaemia	191 (4.7)	236 (5.8)	0.03

Based on Table 14 of the CS[1]
*Fisher's Exact test; from Supplementary Table 6 of Bhatt et al (2019b)[11]
CS = company submission; REDUCE-IT = Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial; TEAE – treatment-emergent adverse event

Table 3.14: Summary of gastrointestinal TEAEs (≥3% in either treatment arm) in the REDUCE-IT safety population

Type of gastrointestinal TEAE	Icosapent ethyl (N = 4,089), n (%)	Placebo (N = 4,090), n (%)	P-value for between-group difference
Gastrointestinal disorders overall	1,350 (33.0)	1,437 (35.1)	0.04
Diarrhoea*	367 (9.0)	453 (11.1)	0.002
Constipation*	221 (5.4)	149 (3.6)	<0.001
Nausea	190 (4.6)	197 (4.8)	0.75
Gastroesophageal reflux disease	124 (3.0)	118 (2.9)	0.70

Based on supplementary Table 7 of Bhatt et al (2019b)[11]
*The same data appear in Table 3.12
REDUCE-IT = Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial; TEAE – treatment-emergent adverse event

Table 3.15: Summary of serious bleeding TEAE categories reported in the REDUCE-IT trial safety population

Category of serious bleeding TEAE	Icosapent ethyl (N = 4,089), n (%)	Placebo (N = 4,090), n (%)	P-value for between-group difference
Reported in the CS[1]			
TEAEs associated with bleeding	482* (11.8)	404* (9.9)	0.0055
Reported in Bhatt et al (2019b)[11]			
Patients with serious bleeding-related disorders overall	111 (2.7)*	85 (2.1)*	0.06
Gastrointestinal bleeding	62 (1.5)	47 (1.1)	0.15
Central nervous system bleeding	14 (0.3)	10 (0.2)	0.42
Other bleeding	41 (1.0)	30 (0.7)	0.19

Based on Section B.2.10 of the CS[1] and Supplementary Table 8 of Bhatt et al (2019b)[11]
*From CSR.[10]
CS = company submission; CSR = clinical study report; REDUCE-IT = Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial; TEAE – treatment-emergent adverse event

ERG comment: The data on TEAEs were derived from a single source, namely the REDUCE-IT trial.[1, 16] The ERG considers that the most obvious safety concern was the significantly higher rate of serious bleeding. This and three others (peripheral oedema, constipation and atrial fibrillation) were selected for inclusion in the economic model, on the basis of incidence ≥5% in at least one study arm and statistically significant between-group difference in the proportion of participants experiencing the events (Section B.3.4.4 of CS).[1]

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

As mentioned in the Appendix D, "No indirect or mixed treatment comparisons were undertaken."[1]

3.4 Critique of the indirect comparison and/or multiple treatment comparison

Not applicable.

3.5 Additional work on clinical effectiveness undertaken by the ERG

No additional work on clinical effectiveness was undertaken by the ERG.

3.6 Conclusions of the clinical effectiveness section

The company performed a systematic review to evaluate the evidence on clinical effectiveness (efficacy and safety) of icosapent ethyl in addition to stable statin therapy compared with stable statin therapy alone for adults with elevated triglycerides. The ERG considers that it was conducted well enough to not provide any substantial uncertainty in clinical effectiveness. The clinical effectiveness evidence is derived from the REDUCE-IT trial. This is a phase IIIb, multicentre, randomised, double-blind, placebo-controlled trial in patients who were ≥45 years of age with established CVD, or who were ≥50 years of age with diabetes in combination with at least one additional risk factor for developing CVD eligible for icosapent ethyl.

Patients' baseline characteristics were well distributed between treatment arms. The ERG therefore has no concerns regarding the risk of bias in the REDUCE-IT trial. However, it is unclear if the patient population is generalisable to the UK clinical setting as the REDUCE-IT trial did not include any patients from the UK. In response to the clarification letter,[4] the company provided the reference to the paper by Steen et al. (2016)[15] which is a retrospective study of lipid-lowering treatment patterns in a high-risk cohort in the UK in 2014. However, it is not possible to make an informative comparison between the participants from Steen et al. (2016)[15] and REDUCE-IT because the characteristics for Steen et al. were presented by subgroup (primary vs. secondary prevention) whereas those for REDUCE-IT were presented for the whole population. The lack of explicit comparison between REDUCE-IT and sources aligned with UK clinical practice for the overall population or for each subgroup leads the ERG to identify this as a Key Issue.

The results show that icosapent ethyl is generally effective in reducing the rates of all events, including the primary efficacy endpoint, which is a 5-point MACE composite endpoint defined as time from randomisation to the first occurrence of any of the following events:

- CV death
- Nonfatal myocardial infarction (MI) (including silent MI)
- Nonfatal stroke
- Coronary revascularisation
- Unstable angina

It also appears to be more effective in the secondary prevention subgroup. As already mentioned in Section 2.4, there also appears to be less of an effect on CV and any cause death. The ERG considers that the most obvious safety concern with icosapent ethyl from REDUCE-IT was the significantly higher rate of serious bleeding.

4. COST EFFECTIVENESS

4.1 ERG comment on company's review of cost effectiveness evidence

This section pertains mainly to the review of cost effectiveness analysis studies. However, the search section (4.1.1) also contains summaries and critiques of other searches related to cost effectiveness presented in the company submission. Therefore, the following section includes searches for the cost effectiveness analysis review, measurement and evaluation of health effects as well as for cost and healthcare resource identification, measurement and valuation.

4.1.1 Searches performed for cost effectiveness section

One set of systematic literature searches was performed to identify cost effectiveness analyses, HRQoL and healthcare cost and resource use studies (CS Appendix G)

Appendix G of the CS reported the literature searches used to identify cost effectiveness studies and costs and healthcare costs and resource use studies. Searches were conducted in January 2021. A summary of the resources searched are provided in Table 4.1. The following paragraphs contain summaries and critiques of all searches related to cost effectiveness presented in the company submission.

Table 4.1: Resources searched for cost effectiveness studies, HRQoL and healthcare cost and resource use studies, January 2021

Search strategy element	Resource	Host/source	Date range	Date searched
Databases	Embase	Embase.com	Inception-2021/01/8	8.1.21
	MEDLINE	Medline content via Embase.com		
	CEA Registry	Interface/URL: http://healtheconomics.tuftsmedicalcenter.org/cear2n/search /search.aspx	1976 - 2019	9.2.21
	ScHARRHUD	https://www.scharrhud.org/index.php?recordsN1&m=search	2008-2017	9.2.21
	EQ-5D Publications Database	https://euroqol.org/	All	9.2.21
	WHO ICTRP	https://www.who.int/clinical-trials-registry-platform	Not available*	
Conference proceedings	ISPOR	https://www.ispor.org/heor-resources/presentations-database/search	2018-2021	9.2.21
	ESC Congress conference proceedings	https://esc365.escardio.org/?_ga=2.143277117.949075749.1613040738-1887725694.1611741182	2018-2021	9.2.21

Search strategy element	Resource	Host/source	Date range	Date searched
websites	NICE	https://www.nice.org.uk/	1990 - 2021	9.2.21
	RePEc website	https://econpapers.repec.org/scripts/search.pf	2019 - 2021	9.2.21
	ICER	https://icer.org/	All	9.2.21
* This was unavailable to access/search due to heavy traffic generated by the COVID-19 outbreak				
CEA Registry = Cost Effectiveness Analysis Registry; EQ-5D = EuroQol-5 Dimension; ESC = European Society of Cardiology; HRQoL = health-related quality of life; ICER = Institute for Clinical and Economic Review; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; NICE = National Institute for Health and Care Excellence; RePEc = Research Papers in Economics; ScHARRHUD = School of Health and Related Research Health Utilities Database; WHO ICTRP= World Health Organisation International Clinical Trials Registry Platform.				

ERG comment:

- A good range of resources were searched for the economic SLR and searches were clearly structured and documented.
- The company conducted a single search of Embase.com on the understanding that it now contains all MEDLINE and MEDLINE In-Process content. Whilst the ERG accepts this single approach as being adequate, the ERG considers it preferable to conduct a separate companion MEDLINE search in order to fully utilise the power of database specific study design filters developed to make the most of an individual database's subject headings. However, given the searches of additional grey literature resources reported by company, it is unlikely that this omission would have impacted on the overall recall of results.
- The economics searches were structured to look for:

(CVD/heart disease AND elevated triglyceride/ hypertriglycerid?emia/dyslipidemia)
AND
(Statins or icosapent ethyl)
AND
(Economics OR HRQoL OR Resource Use filter)

The ERG was concerned that this approach may have been overly restrictive and queried its use at clarification. The company responded *"during the initial search, a broader population was considered, as is presented by the ERG here, however, due to the vast amount of hits that return for just 'cardiovascular disease' alone, it was decided to combine the disease search term with the interventions to restrict the returned hits whilst retaining all literature containing the specified population of interest."* They went on to state that: *"there were no applicable UK cost and resource use specific papers applicable to this submission, therefore EMBASE was searched again but using specific search terms focusing on UK-based costs."*[4] Details of this additional Embase search were not provided therefore the ERG cannot comment on its effect on the overall recall of results. However, the ERG remains concerned that the combination terms for cardiovascular disease, dyslipidaemia and statins was overly restrictive. Whilst the ERG acknowledges that a pragmatic approach was needed due to the size of the literature for cardiovascular disease alone, a safer option in this instance may have been to limit by date rather than by introducing other search facets. This is of particular relevance to the HRQoL searches where best practice does not recommend the use of an interventions facet when looking for Utilities data. *"Firstly, the 'Intervention' and 'Comparison' elements in PICO are*

not usually relevant to HSUVs reviews, where the aim is often to identify HSUV data for particular health states that are not necessarily attached to an intervention".[17]

- Whilst the additional grey literature searches were broader in that they searched for (CVD OR dyslipidaemia), in some searches these terms were still combined with a facet for (statins OR icosapent ethyl). In their request for clarification the ERG included the example of the search reported for the School of Health and Related Research Health Utilities Database (ScHARRHUD) where the strategy employed by the CS found 0 hits, a simple search for CVD or dyslipidaemia by the ERG returned 18 hits. The ERG remains concerned that some relevant papers may have been missed and believes that a broader approach to the search strategy design would have been beneficial.

Search from	Search strategy	Search results
CS	('cvd' or 'cardiovascular disease' or 'dyslipidaemia' or 'hypertriglyceridemia' or 'elevated triglyceride') and ('statin' or 'omega-3 fatty acid' or 'cholesteryl ester transfer protein inhibitor' or 'pcsk9' or 'icosapent ethyl')	0
ERG	(cvd or cardiovascular disease or dyslipidaemia or hypertriglyceridemia or elevated triglyceride)	18

4.1.2 Inclusion/exclusion criteria

Inclusion and exclusion criteria for the review on cost effectiveness studies, utilities and costs and resource use are presented in Table 4.2.

Table 4.2: Inclusion/exclusion criteria for the economic review

	Inclusion criteria	Exclusion criteria
Patient population	Adult patients with dyslipidaemia and at risk of cardiovascular events	Studies that dot not include patients of interest to the SLR. Studies with a mixed population that do not present outcomes separately for patients of interest and patients not of interest
Intervention/comparator	Statins, any other fibrate, omega-3 fatty acid, cholesteryl, ester transfer protein inhibitor, PCSK9 inhibitor or ezetimibe	No intervention/comparators of interest
Outcomes(s) 1 **(Published economic evaluations)**	-Cost per QALY gained -Cost per life year gained	None
Outcomes(s) 2 **(Utility studies)**	-Utility values produced using generic, preference-based measures of patient utility,	Proxy questionnaire responses

	Inclusion criteria	Exclusion criteria
	disease specific measures or vignettes -Instrument responses should be elicited from patients -Valuations of utilities should be based on general population preferences	
Outcomes(s) 3 (Cost/resource use studies)	-Any outcomes quantifying the costs and resource use requirements of cardiovascular events -Any outcomes quantifying the costs and resource use associated with disease or treatment related adverse events -Costs should be reported as incurred by the NHS in the UK	No reported outcomes of interest
Study design 1 (Cost effectiveness analysis studies)	Economic evaluations: Cost effectiveness analysis Cost utility analysis Cost minimisation analysis Economic evaluations alongside clinical trials Cost benefit analysis	Cost burden Cost study Burden of disease study Resource use study Comment articles Individual case study reports
Study design 2 (Utility studies)	Quality of life studies Economic evaluations reporting patient utility values	None
Study design 3 (Cost/resource use studies)	Cost and/or resource use studies Economic evaluation	None
Source: Appendix G & H Table 3,4,5[18, 19] CS = company submission; NHS = National Health Service; QALY = quality adjusted life year; SLR – systematic literature review; UK = United Kingdom		

ERG comment: In the clarification response the company stated that the population was kept broad in the inclusion/exclusion criteria tables to make sure that enough references were retrieved in the systematic literature review across the review questions.[4] The two searches are aligned but a broader population was included in the inclusion/exclusion criteria to capture as much evidence as possible in the initial database searching stage with a narrower, more specific population being captured in the search terms themselves. The rationale for excluding cost effectiveness studies after full text reviewing is considered appropriate given the defined inclusion and exclusion criteria.

4.1.3 Conclusions of the cost effectiveness review

The CS provided an overview of the cost effectiveness, quality of life and resource use/costs studies. For the cost effectiveness, the SLR resulted in 633 references of which 12 met the selection criteria. Ten studies (Table 8 Appendix G CS) present study results from a non-UK perspective. Two cost

effectiveness studies (Table 6 of Appendix G CS) were relevant for extraction because of the UK perspective as recommended by the NICE STA user guide. These are NICE Technology Appraisal (TA) 393 and NICE TA 394.[20, 21] TA 393 assessed the cost effectiveness of alirocumab either as an adjunct to statin with ezetimibe or with ezetimibe alone from the perspective of the NHS and Personal Social Services (PSS) while NICE TA 394 assessed the cost effectiveness of evolocumab in reducing CVD for primary hypercholesterolaemia or mixed dyslipidaemia from the NHS and PPS perspective.

4.2 Summary and critique of company's submitted economic evaluation by the ERG

4.2.1 NICE reference case checklist

Table 4.3: NICE reference case checklist

Element of health technology assessment	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	In line with reference case
Perspective on costs	NHS and PSS	In line with reference case
Type of economic evaluation	Cost utility analysis with fully incremental analysis	In line with reference case
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	In line with reference case
Synthesis of evidence on health effects	Based on systematic review	Partly in line with reference case. Mainly based on the REDUCE-IT pivotal trial. Estimation of parametric survival models not in line with recommendations from NICE DSU technical support document 14.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Partly in line with reference case; not all health effects are based on the EQ-5D
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	In line with reference case
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Partly in line with reference case. Not all health effects are based on the EQ-5D
Equity considerations	An additional QALY has the same weight regardless of the	In line with reference case

Element of health technology assessment	Reference case	ERG comment on company's submission
	other characteristics of the individuals receiving the health benefit	
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	In line with reference case
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	In line with reference case

DSU = Decision Support Unit; EQ-5D = EuroQol-5 Dimension; NHS = National Health Service; NICE = National Institute for Health and Clinical Excellence; PPS = personal social services; QALY = quality adjusted life year; REDUCE-IT = Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial; UK = United Kingdom.

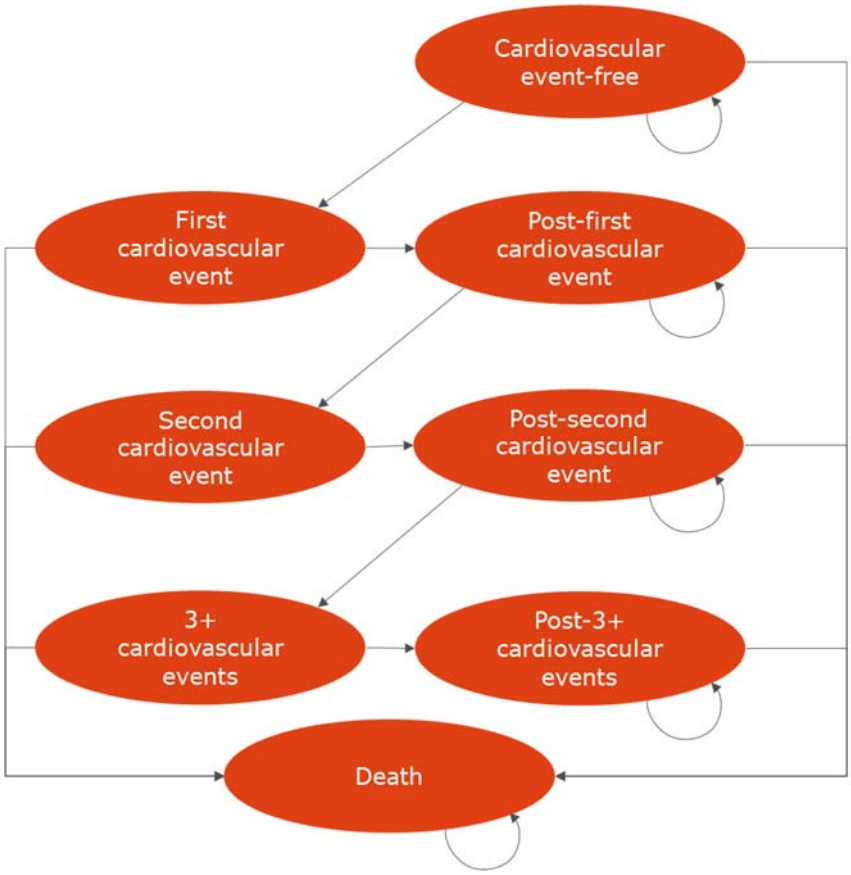
4.2.2 Model structure

The company developed a *de novo* health state cohort model, with one day cycle time, programmed in Microsoft® Excel. The model structure consisted of eight health states based on the occurrence of cardiovascular events and death. Specifically, the following health states were included (see also Figure 4.1):

- Cardiovascular event-free (starting health state)
- First cardiovascular event (one day tunnel state)
- Post first cardiovascular event
- Second cardiovascular event (one day tunnel state)
- Post second cardiovascular event
- Third cardiovascular event (one day tunnel state)
- Post third or more cardiovascular event
- Death (any cause, absorbing health state)

The REDUCE-IT trial (ITT population) was used to estimate parametric survival models to inform the health state occupancy of the alive health states. These parametric survival models were estimated using composite endpoints and subsequently the patients that experienced an event were subdivided between the event types (i.e., CV death, MI, stroke, unstable angina and revascularisation; see CS Table 26).

Figure 4.1: Model structure



Source: Based on CS Figure 15

ERG comment: The main concerns of the ERG relate to: a) the appropriateness of the partitioned survival approach; and b) deviations from other economic models developed for similar decision problems.

a) Appropriateness of the partitioned survival approach

In their response to clarification question C1, the company confirmed that a partitioned survival (partSA) model approach was used to estimate the proportions of the cohort that are post first, post second and post third event. Furthermore, NICE DSU Technical Support Document (TSD) 19 recommends the use of state transition modelling to assist in verifying the plausibility of partitioned survival model extrapolations and to address uncertainties in the extrapolation period (NICE DSU TSD 19, recommendation 11) as an important limitation of a partSA model is the assumption of structural independence between endpoints.[22] For this particular problem this means that the probability of having a second, or third, event would be independent of the time at which the first event happened. In other words, time to second and third event would be estimated from baseline. Although the company acknowledged this issue (response to clarification question 1),[4] an additional state transition model that would verify results of the partSA model was not provided. The company's justification for not providing this verification and/or abandon a state transition approach is not compelling. Therefore, the impact of the limitations related to the partitioned survival model (highlighted in NICE DSU TSD 19), such as the extrapolations of different time to event curves while assuming structural independence between these endpoints, is unclear.

b) Deviations from other economic models developed for similar decision problems (including the company's submission for the Canadian Agency for Drugs and Technologies in Health [CADTH])

The modelling approach deviates substantially from other economic models developed for similar decision problems. This includes NICE TA393, NICE TA394, NICE TA420 as well as the company submission to CADTH for icosapent ethyl to prevent cardiovascular events in statin-treated patients. Differences include 1) the model structure, including non-explicit modelling of non-fatal cardiovascular events such as acute coronary syndrome/myocardial infarction and stroke (in NICE TA393, NICE TA394 and NICE TA420; implicit in this CS); 2) the cycle length (one year in NICE TA393, NICE TA394 and the CADTH submission, three months in NICE TA394; one day in this CS) and;3) the inclusion of tunnel states for minimally one year post non-fatal cardiovascular events (included in NICE TA393, NICE TA394 and NICE TA420, one day event state included in this CS) to account for differences in input parameters directly post non-fatal cardiovascular events (e.g., temporary increased mortality risk, decreased quality of life, increased costs).[20, 21, 23]

1. Model structure, including not explicit modelling non-fatal cardiovascular events such as acute coronary syndrome/myocardial infarction and stroke

The company justified their model choice stating that previous appraisals and the CADTH submission for icosapent ethyl all failed to model the multiple subsequent events (they included the first or the first and second event), which have an impact on HRQoL and costs. In order to capture multiple subsequent events the company had to change the model structure adopted in previous appraisals. The company stated in response to clarification question C2 that a model that only included the first event would only capture [redacted] of events experienced by individuals in the REDUCE-IT trial.[4] However, unfortunately it remained unclear how many events would be missed by incorporating first and second events and therefore it continues to be unclear to the ERG whether it was necessary to incorporate the third event as well. More importantly, in other appraisals (e.g. NICE TA420) subsequent events were not excluded but modelled implicitly assuming that the impact (on probabilities, HRQoL and costs) of subsequent event does not differ (i.e. the impact of the second and third event is identical) which might not be unreasonable.[23]

Additionally, the company's approach deviates from previous appraisals as it does not explicitly model non-fatal cardiovascular events such as acute coronary syndrome/myocardial infarction and stroke (considered unfeasible as stated by the company in clarification response C2).[4] In contrast, the events were estimated using composite endpoints and subsequently the patients that experienced an event were subdivided between the event types (i.e. CV death, MI, stroke, unstable angina and revascularisation; see CS Table 26).[1] This subdivision was assumed to be constant over time (in contrast with previous appraisals). Unfortunately, the impact of this simplifying assumption is not explored by the company and thus unclear.

The impact of the limitations related to the partitioned survival model (highlighted in NICE DSU TSD 19), such as the extrapolations of different time to event curves while assuming structural independence between these endpoints, is unclear.

2. Daily cycle length

The company assumed that during the acute phases of the model structure (i.e. the tunnel states) patients were not able to experience subsequent events (i.e. there is no arrow between the different tunnel states). Consequently, the company justified their daily cycle length stating that with longer cycle lengths multiple events might be missed (as a result of the abovementioned assumption). It was unclear how long the acute period lasts (it was described as six months long in Danese 2016),[24] but a one-day cycle length may be shorter than appropriate and allowing patients to experience

subsequent events during the acute phase might have been a more appropriate alternative to the one-day cycle. Especially, given that (despite individuals might experience multiple events in a short period as illustrated in clarification response Table 5), on a cohort level less than 30% of patients had an event in the first five years since randomisation according to CS Figure 5.[1, 4] Therefore, the necessity of a daily cycle is questionable in a cohort model.

In addition, a short cycle length may also make a model more error-prone when the time horizon is relatively long (here a 36-year time horizon was adopted) because it becomes more difficult to de-bug and validate: in this case, errors were made towards the later cycles in the model proving this point. These errors were resolved by the company in response to the clarification letter.[4] Furthermore, a short cycle length adds to the computational expense of the model. In this case, the probabilistic sensitivity analysis (PSA) is extremely slow (28 hours for 5,000 simulations), which is probably caused by very large sheets (Clinical Inputs sheet has over 45,000 rows).

3. One-day tunnel states

Event states were tunnel states of one cycle length, i.e. events were modelled to last one day only. Costs were applied to this one day. Utilities were applied for 60 days post event. The ERG was not fully convinced that the one-day tunnel states were necessary, as patients could have moved to the post-event states directly. The ERG considered that utilities were applied to the 60 days post event anyway, and costs could have been applied in the post event state, too. Subsequent transition probabilities were not dependent on when patients transitioned to prior events. The company did not respond to this concern. The ERG considers that the company's approach is not wrong but may be unnecessarily complicated.

The ERG's main concern, however, was that by applying event and post event state costs to the one-day tunnel state, costs are over-estimated in patients that move to the next event faster than the period costs apply (e.g., rehabilitation period). For instance, costs may be over-estimated if patients experienced the next event before finishing rehabilitation but the model would incur the full cost of rehabilitation. This may result in over-estimation of costs in the treatment arm with greater number of events, i.e., likely the comparator arm. The magnitude of this potential over-estimate depends on the number of such occurrences and is unclear.

4. Conclusions regarding deviations from other economic models developed for similar decision problems

Deviations from other economic models developed for similar decision problems are acceptable when the model improves substantially as a result – but in this case the ERG is not convinced that the one-day cycle length and inclusion of one-day tunnel states were appropriate (as argued above). Moreover, not explicitly modelling of non-fatal cardiovascular events such as acute coronary syndrome/myocardial infarction and stroke might bias the results with unclear direction and magnitude. Given the chosen cohort modelling approach, there is clearly a trade-off here between model complexity and appropriately capturing the CV events. The ERG continues to doubt that the deviations made by the company strikes the correct balance and an approach as adopted in for instance NICE TA420 might have been preferred (this individual patient-level model potentially also provides the flexibility required to explicitly model up to three events as preferred by the company).[23]

4.2.3 Population

The population considered in the model aligns with the licenced indication and the ITT cohort from REDUCE-IT: males and females ≥45 years of age with established CVD (secondary prevention subgroup) or ≥50 years of age with diabetes in combination with one or more additional risk factor for CVD (primary prevention subgroup), with LDL-C levels >40 mg/dL and ≤100 mg/dL and fasting TG levels ≥135 mg/dL and <500 mg/dL, on stable statin therapy for at least four weeks.[25] This is a subpopulation from the population listed in the final scope.[5] Subgroup analyses are presented for the primary prevention cohort (which constitutes 29% of the modelled population) and the secondary prevention cohort (which constitutes 71% of the modelled population).

The key baseline patient characteristics in the economic model are based on the ITT cohort from REDUCE-IT and listed in Table 4.4 below.

Table 4.4: Key baseline patient characteristics used in the economic model

Model population*	**Icosapent Ethyl N=4,089**	**Placebo N=4,090**
Median age (IQR)	64 years (57.0-69.0)	64 years (57.0-69.0)
Triglyceride level (mg/dL), median (IQR)	216.5 (176–272)	216.0 (175–274)
Median LDL-C level, mg/dL (IQR)	74.0 (61.5–88.0)	76.0 (63.0–89.0)
Median HDL-C level, mg/dL (IQR)	40.0 (34.5–46.0)	40.0 (35.0–46.0)
Secondary prevention cohort n (%)	2,892 (70.7)	2,893 (70.7)
Primary prevention cohort n (%)	1,197 (29.3)	1,197 (29.3)

*Source: REDUCE-IT, Table 19 CS[1]
Abbreviations: HDL-C – High density lipoprotein cholesterol; IQR – Interquartile range; LDL-C – Low density lipoprotein cholesterol; mg/dL – milligrams per decilitres; n = number.

ERG comment: The main concerns of the ERG relate to: a) REDUCE-IT ITT population generalisability; b) the modelled population appearing to be a subpopulation from the final NICE scope; and c) lack of transparency regarding the modelling of the subgroups.

a) As highlighted above, the lack of explicit comparison between REDUCE-IT and sources aligned with UK clinical practice for the overall population or for each subgroup mean that the generalisability to UK clinical practice is not fully demonstrated (Section 3.2.3).

b) A narrower population to the NICE scope and decision problem was recruited to the main source of evidence, REDUCE-IT, because of age restrictions, which differed between primary prevention and secondary prevention population strata (see Section 2.1). This also raises the question over whether the cost effectiveness model results are generalisable to the population in the NICE scope.

c) The ERG asked which model inputs are different for the subgroup analyses. The company clarified that the inputs that are subgroup specific are baseline characteristics (age and gender), clinical inputs and the distribution of the types of CV events experienced, as reported in the REDUCE-IT trial. The changes to these inputs impact the HRs informing non-CV related mortality, average costs and utilities associated with icosapent ethyl and the placebo/best supportive care (BSC) groups.

4.2.4 Interventions and comparators

The intervention considered in the CS was icosapent ethyl (four capsules taken as two 998mg capsules twice daily) in combination with a stable dose of statin therapy with or without ezetimibe 10mg. The comparator considered was BSC. The company used the placebo arm of the REDUCE-IT trial (placebo with a stable dose of statin therapy with or without ezetimibe 10mg) to inform the comparator, as currently no other pharmacological therapies are available and routinely used to reduce the risk of CV events in statin-treated patients with elevated TGs. For use in the model, to estimate costs, the distribution of statins by intensity in the ITT population of REDUCE-IT was adapted to better reflect NICE CG181 and commonly used statins in the UK, see Table 4.5 and section 4.2.9.[26] Ezetimibe 10mg was used by 6.4% in the ITT population in REDUCE-IT, was considered similar to the UK situation. No stopping rule was considered.

Table 4.5: Distribution of statin intensity in REDUCE-IT and the economic model

Statin intensity	REDUCE-IT trial		Economic model	
	Statin therapy	Statin distribution	Statin therapy	Statin distribution
Low	Rosuvastatin 10mg Pravastatin 10-20mg Lovastatin 20mg Fluvastatin 20-40mg Pitavastatin 1mg	6.4%	Fluvastatin 20-40mg Pravastatin 10-40mg Simvastatin 10mg	6.4%
Moderate	Atorvastatin 10-20mg Simvastatin 20-40mg Rosuvastatin 5-10mg Pravastatin 40-80mg Lovastatin 40mg Fluvastatin 40mg BID Fluvastatin XL 80mg Pitavastatin 2-4mg	62.7%	Atorvastatin 10mg	62.7%
High	Atorvastatin 40-80mg Rosuvastatin 20-40mg	30.9%	Atorvastatin 20-80mg	30.9%

Source: Table 18 CS[1]
Abbreviation: mg – milligram; REDUCE-IT = Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial.

ERG comment: The main concern of the ERG relates to the definition of a stable dose of statins.

The REDUCE-IT definition of a stable dose of statin therapy (the same daily dose of the same statin for at least 28 days before lipid qualification) does not match with current clinical practice in the UK according to NICE guidance (three months instead of 28 days).[26] In addition, it is not clear what definition of a stable dose of statin was used in the CS and whether differences in definition could impact on the clinical and cost effectiveness estimates for icosapent ethyl (see Section 2.2).

4.2.5 Perspective, time horizon and discounting

The analysis is performed from the NHS and PSS perspective. Discount rates of 3.5% are applied to both costs and benefits. The model cycle length is one day with a 36-year time horizon to align with the expectation that no patient can live beyond 100 years horizon.

ERG comment: In the CS, the company states a 36-year time horizon was used. This was considered to represent a lifetime time horizon. The approach is in concordance with the NICE reference case.

4.2.6 Treatment effectiveness and extrapolation

The main source of evidence on treatment effectiveness used for the intervention and comparator is the REDUCE-IT trial for the comparison of icosapent and placebo (see Section 3.2.5 for more detail). Patient baseline characteristics used in the model were age, sex, presence of diabetes, statin intensity, type of prevention (i.e. primary/secondary), and ezetimibe use, derived from the REDUCE-IT ITT population in the company's base-case analysis (see Table 19 and Table 35 of the CS).[1]

The company used survival analysis to inform the number of individuals that experience a first event, second event and third or more event in each cycle of the model and to extrapolate beyond the trial follow-up period. Incidence was expressed as the cumulative incidence of the 5-point MACE, a composite of CV death, nonfatal MI (including silent MI), nonfatal stroke, coronary revascularisation, or unstable angina. Survival analysis on TTD data from REDUCE-IT were used to estimate treatment discontinuation for icosapent.

In the CS, it was stated that a series of parametric survival models were fitted to the reconstituted first, second and third event individual patient data (IPD) using the Flexsurv for R package for time-to-event data.[1] Six parametric distributions were selected and fitted to the Kaplan Meier (KM) data. Furthermore, the company accounted for the range in follow-up data among individuals using IPD up until the point that 10% of patients at risk were left in the trial. Finally, to determine the most appropriate survival functions, model fit was assessed as follows:

- Graphic comparison of the predicted curve from a given parametric function to the Kaplan-Meier curve from the patient data,
- Comparison of Akaike information criterion (AIC) statistics and Bayesian information criterion (BIC) statistics,
- UK clinical expert opinion.

First event

The company selected independent exponential models to estimate the time to first event. According to the company, the proportional hazards assumption could be supported. The exponential model had the best statistical fit and was considered to provide plausible predictions by clinical experts. The company did not consider the hazard pattern and whether this was in line with clinical expectations (increasing or constant hazards). Predictions of the survival curves were compared to 20-year follow-up data from the West of Scotland Coronary Prevention Study (WOSCOPS).[27] The company stated that, when comparing the extrapolated portion with this 20-year external dataset, it can be expected that 55% to 77% of the patients would experience a CV event.[1]

Second event

To estimate time to second event, all patients that were considered for the first event curve were included and considered for the extrapolations of the second event curve. The company selected independent exponential models to estimate the time to second event as it was considered to provide

the best statistical fit and produced clinically plausible predictions. According to the company, all models produced a good fit within the trial data other than generalised gamma for the icosapent group that failed to provide a coefficient output.[1]

Third plus event

To estimate time to third event, all patients that were considered for the first event curve were included and considered for the extrapolations of the third event curve. The company selected independent exponential models to estimate the time to third plus event as it was considered to provide the best statistical fit and produced clinically plausible predictions.[1]

Time to treatment discontinuation

The discontinuation rate was estimated by applying a series of parametric survival models that were fit to the IPD of the ITT data of the REDUCE-IT study.[1] The company stated that, since efficacy data were based on the ITT analysis, when patients discontinue treatment only the treatment cost stops whereas the probability of CV events and death remains the same. No discontinuation was applied to the best supportive care arm as this was considered not be a realistic assumption. According to the company, plausibility of the extrapolation was difficult to assess since no external long-term data on discontinuation of this treatment was available. Therefore, based only on the goodness of fit statistics presented in Table 38 of the CS,[1] the company chose the exponential distribution to be the best performing model.

Informing the type of event

The distribution of CV death, nonfatal MI, nonfatal stroke, coronary revascularization and unstable angina according to first, second and third plus event were taken from the REDUCE-IT trial and are presented in Table 4.6.

Table 4.6: Distribution of types of first, second and third plus events

		Icosapent	Placebo
First event			
	CV death	[redacted]	[redacted]
	MI	[redacted]	[redacted]
	Stroke	[redacted]	[redacted]
	Unstable angina	[redacted]	[redacted]
	Revascularisation	[redacted]	[redacted]
	Total	[redacted]	[redacted]
Second event			
	CV death	[redacted]	[redacted]
	MI	[redacted]	[redacted]
	Stroke	[redacted]	[redacted]
	Unstable angina	[redacted]	[redacted]
	Revascularisation	[redacted]	[redacted]
	Total	[redacted]	[redacted]
Third plus event			

		Icosapent	Placebo
	CV death	[redacted]	[redacted]
	MI	[redacted]	[redacted]
	Stroke	[redacted]	[redacted]
	Unstable angina	[redacted]	[redacted]
	Revascularisation	[redacted]	[redacted]
	Total	[redacted]	[redacted]
	Patients with third plus CV events	[redacted]	[redacted]
	Number of third plus CV events per person	[redacted]	[redacted]

Source: CS Table 26 [1]

CV = cardiovascular; MI = myocardial infarction.

Transitions to the death states

Two forms of mortality were captured within the model; surviving patients could transition to the non-CV related death health state, which captures the baseline risk of non-CV related death, or CV death if a CV related fatal event occurs. To estimate the baseline risk of non-CV related death, the probability of all-cause mortality was estimated for the age-gender matched population demographics in REDUCE-IT from national life tables available from the UK Office for National Statistics (ONS).[28] Next, to account for prior CV events (i.e. stroke and MI) and diabetes status, an increased risk of mortality compared to the general population was applied based on hazard ratios sourced from the literature.

The hazard ratios for non-CV related mortality in patients with diabetes, who are on treatment for secondary prevention of cardiovascular events were sourced from research by The Emerging Risk Factors Collaboration (2015).[29] The hazard ratio for non-CV related mortality in patients with diabetes, who are on treatment for primary prevention of CV disease was sourced from a meta-analysis of 24 cohort studies from Asia, Australia, and New Zealand by The Asia Pacific Cohort Studies Collaboration (2003).[30]

A weighted average was calculated by multiplying the hazard ratios of prior CV events (i.e. stroke and MI) and diabetes status by the distribution of type of event and diabetic status in the icosapent and placebo groups. Additionally, the ITT population consisted of both secondary prevention and primary prevention individuals therefore the HR for the ITT population had to be further weighted to account for the proportion of individuals in the secondary versus primary prevention group. The weighted hazard ratios for no event, acute and post- first, second and third events are provided in Table 4.7.

Table 4.7: Weighted hazard ratios for death by health state used in the economic model

	Icosapent	Placebo
No event	1.544988	1.544988
First event	2.122621	2.123084
Post first event	2.122621	2.123084
Second event	2.265037	2.453237
Post second event	2.265037	2.453237
Third	2.560208	2.597006
Post third	2.560208	2.597006

	Icosapent	Placebo
Source: CS Table 29 [1]		

ERG comment: The main concerns of the ERG relate to: a) the use of "reconstituted data" in which observations which took place after the point that only 10% of individuals were remaining at risk were removed from the dataset; b) limited evidence available for (long-term) validation of survival curves; c) use of stratified parametric survival models for icosapent ethyl and placebo separately; d) in the CS base-case no treatment waning was assumed; e) use of treatment-dependent non-CV related hazard ratios; f) unclear to the ERG why non-CV related death has not been modelled using parametric survival models; and g) use of treatment-dependent and time-independent distributions of the types first, second, and third events.

a) Use of "reconstituted data" in which observations which took place after the point that only 10% of individuals were remaining at risk were removed from the dataset

   In the CS base-case, the company used a "reconstituted" dataset in which any observations which took place after the point that only 10% of individuals were remaining at risk, were to be removed from the KM data set to be used for the first, second and third event extrapolations. In response to clarification question C7, the company argued that "*The aim of this assumption was to create the most robust extrapolations as they can be sensitive to the final portion of the curve*".[4] The ERG notes that the company's practice goes against NICE DSU guidance [31] that states: *"Unless a very clear rationale is offered, all data should be included in the survival analysis."* Removing data is likely to increase uncertainty related to the extrapolations, hence making them less robust. Given that the parametric survival curves based on the actual KM data were not incorporated in the model by the company, the ERG was unable to resolve this issue.

b) Limited evidence available for (long-term) validation of survival curves

   In sections B3.3.2.1.1, B3.3.2.1.2 and B3.3.2.1.3 of the CS the survival curves for the first, second and third event were presented. For all three events, it was stated that "*the most likely scenario chosen is the exponential since it gives the best statistical fit and produces clinically plausible predictions"*[1]. The long-term predictions for the first event based on the parametric survival curves were validated against the WOSCOPS study.[27] However, in response to clarification question C7g, the company stated that *"the WOSCOPS study is not an appropriate study for comparison*".[4] Moreover, regarding the second and third events, the company stated that *"there is no long-term data (20-years and onwards) on second and third subsequent events"*.[1] To this extent, the company consulted two UK clinical experts which both agreed *"that the ratios of patients experiencing second and third subsequent events in the extrapolation is what they would expect to see in UK clinical practice"*.[1] Furthermore, the company has presented a ranking of the goodness-of-fit statistics for the various parametric survival models for each event (per arm) but the ranking appears to be incorrect. For example, in CS Table 23 where the parametric distribution fit to the second event is presented, the exponential distribution is ranked first however both the Weibull and log-logistic distributions have lower AIC and BIC. A similar issue is presented in CS Table 25 regarding the parametric distribution fit to the third plus event. Although the ERG acknowledges the lack of available long-term follow data for validation purposes, the ERG would like to emphasise that the long-term extrapolations based on the survival curves are subject to uncertainty. In response to clarification question C7i the company did provide scenario analyses exploring alternative survival models to estimate time to event probabilities.[4] The type of distribution did not have a large impact on the ICER.

c) Use of stratified parametric survival models for icosapent ethyl and placebo separately

All survival models were stratified for icosapent ethyl and placebo separately, i.e. separately for both treatment arms. However, the use of stratified models was not further justified in the CS (e.g. by looking at cumulative hazards and/or scaled Schoenfeld residuals; see NICE DSU TSD 14 [31]). In response to clarification question C7j, the company stated that *"if the AIC and BIC best fit had differed between treatment arms, we would have likely chosen a consistent distribution"*.[4] Hence, model selection/development is not in line with the model selection process algorithm as mentioned in NICE DSU TSD 14.[31] The ERG could not explore the appropriateness and impact of using stratified models.

d) In the CS base-case no treatment waning was assumed

In the CS base-case no treatment waning was assumed, which means that the time to the next event was assumed to be different for the two comparators during the whole duration of the time horizon, i.e. for each event treatment-specific survival curves were estimated resulting in a treatment benefit of icosapent for all events. It is unclear to the ERG whether this assumption holds true in clinical practice as there is limited evidence provided on treatment waning by the company. In response to clarification question C8, the company states that *"there is no evidence to suggest treatment waning is applicable for icosapent ethyl. Throughout the REDUCE-IT study period, efficacy did not decrease over time, therefore there is no evidence to suggest this assumption would be observed in clinical practice"* [4]. This quote from the company is potentially flawed as absence of evidence for treatment waning is not evidence of absence of treatment waning beyond the observed data period. Moreover, it is unclear what the company referred to by stating that efficacy did not decrease over time: time to event curves are estimated separately for the icosapent ethyl and placebo arms and no hazard ratios are therefore available to investigate the relative efficacy over time. Furthermore, the icosapent ethyl time-to-event curves take into account that patients have discontinued. This does not mean, however, that these curves also accurately reflect further discontinuation that will occur beyond the end of trial follow-up. The follow-up of the REDUCE-IT study is notably shorter than the time horizon in the economic model. Hence, it is unclear to the ERG whether the benefits of icosapent could be assumed to last over the full-time horizon and whether those benefits were also applicable post first, second, or third CV event, especially taking into account that many more patients will have discontinued treatment with icosapent ethyl. In the CADTH submission,[14] icosapent ethyl was assumed to only be used for the first five years, at which point all patients would discontinue treatment. However, this was appraised to underestimate both the treatment impact and the costs associated with icosapent ethyl. In NICE TA420,[23] which looked at alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia, the committee concluded that *"the positive recommendation should only be for the length of time for which evidence had been presented, specifically 3 years"*. Upon request, the company did provide scenario analyses for waning of treatment effect over 10- and 20-years post trial completion after first, second and third events (see response to clarification question C8).[4] In these scenarios, the event curve post trial period is assumed to decrease at a constant rate until equal to placebo at the chosen time period. For example, if after the first event 10-years is selected, icosapent ethyl will take full extrapolated efficacy for all curves until the end of the trial period, following this it will take a weighted average of icosapent ethyl and placebo curves, with the proportion informed by placebo increasing at 1/(365.25*10) per cycle until equal to placebo at 10-years post trial period. The ERG prefers the use of the treatment waning scenario in the base-case, as this takes account of an increasing number of patients discontinuing treatment with icosapent ethyl after the trial ended. However, it has to be acknowledged that the choice of treatment waning duration and rate is arbitrary.

e) Use of treatment-dependent non-CV related hazard ratios

In the CS, two forms of mortality were captured within the model; surviving patients could transition to the non-CV related death health state, which captured the baseline risk of non-CV related death, or CV death if a CV related death occurred. In Table 4.5 the weighted hazard ratios for mortality by health state used in the economic model are presented. This constitutes the baseline risk of non-CV related death. For all health states, icosapent ethyl is associated with lower hazard ratios. It was unclear to the ERG why non-CV death should be considered to be treatment-dependent given that CV related death has already been captured in the CV death state. Hence, the ERG is unclear about the clinical plausibility of the mortality advantage of icosapent ethyl. Upon request, the company provided an additional scenario in which hazard ratios are treatment-independent and equivalent to those of the UK population norm (in response to CQ9), which increased the ICER from £29,317 per QALY gained to £32,377 per QALY gained.[4] However, this scenario assumes hazard ratios equivalent to those of the UK population norm, which the company refers to in the CS not to be representative to the REDUCE-IT study population. Hence, the ERG chose to assume the mean of the weighted hazard ratios for non-CV death by health state and applied these hazard ratios to both treatments. This resulted in the hazard ratios presented in Table 4.8.

Table 4.8: Mean weighted hazard ratios for non-CV related mortality by event status used in the ERG base-case model

	Hazard ratio (treatment independent)
No event	1.544988
First event	2.122852
Post first event	2.122852
Second event	2.359137
Post second event	2.359137
Third	2.578607
Post third	2.578607

Source: CS Table 29 & CS model [1]

CV = cardiovascular; ERG Evidence Review Group

f) It is unclear to the ERG why mortality has not been modelled using alternative parametric survival models (instead of assuming a constant transition probability, i.e. exponential distribution).

Given that the model closely resembles a PartSA model, it is unclear to the ERG why CV and non-CV related mortality has not been modelled using parametric survival models. In response to clarification question C9d, the company provided an additional scenario in which parametric survival models were fitted to the KM data of non-CV related deaths, but it argued that the extrapolated results did not seem to be clinically plausible.[4] It should be noted that based on Tables 34 and 35 the loglogistic and lognormal seem to be good (if not better) alternatives to the exponential (better statistical fit and potentially clinically plausible).[1] In their response, the company did not elaborate on using parametric survival models for CV related mortality. The ERG considers that using full survival analysis and considering alternatives to the exponential may be appropriate for CV and non-CV related mortality.

g) Use of treatment-dependent and time-independent distributions of the types first, second, and third events.

The model is based on a 5-point MACE composite endpoint defined as time from randomisation to the occurrence of any of the following events: CV death; nonfatal MI (including silent MI); nonfatal stroke; coronary revascularisation; and unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalisation. As reported in CS Table 26, the distribution of types of first, second and third plus events is different per treatment, i.e., icosapent vs. placebo.[1] Furthermore, the type of event does not seem to be associated with time (e.g. time since randomisation). In response to clarification question C10,[4] the company did not elaborate on the clinical plausibility of these assumptions but did provide scenario analyses in which distributions of the types of first, second, and third events in the placebo treatment arm were assumed to be equal to the icosapent ethyl treatment arm. This resulted in a slightly lower ICER: from £29,317 per QALY gained in the base-case to £27,311 per QALY gained. Given the lack of a clinical validation for the use of either treatment-dependent or treatment-independent distributions of CV events, the ERG used treatment-dependent distributions in its base-case to be in line with the clinical trial evidence.

4.2.7 Adverse events

The following four individual treatment adverse events: peripheral oedema, constipation, serious bleeding and atrial fibrillation were included in the cost effectiveness model based on the criteria of an incidence ≥5% and statistically significantly difference between intervention and comparator.

ERG comment: The company submission mentions six treatment emergent adverse events (incidence ≥5% and statistically significantly different) while the cost effectiveness model only includes four. The ERG missed the rationale for leaving diarrhoea and anaemia out of the model. The company response stated that they did not include these two because they only considered adverse events in the CE model that were statistically significantly in favour of placebo.[4] The ERG considers this explanation sufficient.

4.2.8 Health-related quality of life

The utility values were estimated for the following health states as shown in Table 4.8

Health-related quality of life data identified in the review

According to the CS, the SLR identified eight studies, five studies including utilities for individuals with established CVD or at high risk of CVD, two studies were previous NICE TAs in familial hypercholesterolaemia and one was NICE CG181 (Table 30 in CS).[1, 26] Out of all studies, the company considered NICE TA393 to be the most informative for the methodology regarding the calculation of utilities in the model.[20] However, the company used NICE CG181[26] health state multipliers as input and baseline utilities from Stevanovic[32] and O'Reilly[33] (which were not identified in the SLR but in a previous global SLR).

Health state utility values

A summary of all utility values used in the cost effectiveness analysis is provided in Table 4.9.

Table 4.9: Health state utility values

Health state	Multiplier	Utility value	Reference	Justification
Baseline utility-secondary prevention	-	0.765	Stevanovic et al.[32]	Meta analysis of 40 studies of which ten referred to UK
Baseline utility-primary prevention	-	0.75	O'Reilly et al.[33]	Utility sourced from HRQoL data from 1147 patients with type 2 diabetes
Acute-nonfatal MI	0.760	0.578 (0.018)	NICE CG 181[26]	NICE guideline value
Acute-nonfatal stroke	0.628	0.478 (0.040)		NICE guideline value
Acute-coronary revascularisation	0.808	0.615 (0.038)		NICE guideline value
Acute-unstable angina	0.770	0.586 (0.038)		NICE guideline value
Post-nonfatal MI	0.880	0.669 (0.018)		NICE guideline value
Post-nonfatal stroke	0.628	0.478 (0.040)		NICE guideline value
Post-coronary revascularisation	0.880	0.669 (0.038)		NICE guideline value
Post-unstable angina	0.880	0.669 (0.018)		NICE guideline value
CV death	0.000	0.000 (0.000)	By definition	
Death	0.000	0.000 (0.000)	By definition	
AE disutility-peripheral oedema	-	-0.005	Sullivan et al.(2016)[34]	
AE disutility-constipation	-	-0.001	Christensen et al.(2016)[35]	
AE disutility-atrial fibrillation	-	-0.032	Steg et al. (2011)[36]	
AE disutility-serious bleeding	-	-0.104	Tengs et al.(2000)[37]	

Source: CS Table 32[1]

AE = adverse event; CG = clinical guideline; CS = company submission; CV = cardiovascular; HRQoL = health-related quality of life; MI = myocardial infarction; NICE = National Institute for Health and Care Excellence; UK = United Kingdom.

Disutility values

The disutility values of the four individual treatment adverse events included in the CE model are based on the references mentioned in Table 4.9.

ERG comment: The main concerns of the ERG relate to: a) sensitivity of the model to the choice of utility values; and b) a lack of transparency regarding the disutilities used in the analyses.

a. There appeared to be an inconsistency between the references used for baseline utilities in the CE model and those mentioned in the CS (Stevanovic[32] and O'Reilly[33]). The ERG asked to clarify which studies were used as input. The company explained in response to the clarification questions that the baseline utilities were indeed based on Stevanovic[32] and O'Reilly[33] which was corrected in the updated CE model. The company considered baseline utilities by Stevanovic and O'Reilly appropriate because they reflected the target population of icosapent ethyl. The ERG also asked for a sensitivity analysis using the utility values from the NICE TA393[20] to examine the impact on the incremental cost effectiveness ratio (ICER). The company provided a sensitivity analysis in the clarification response applying the utilities from NICE TA393 (see Table 40 of the clarification letter response[4]). The ERG noticed that using the utilities from NICE TA393 increased the ICERs for all groups.[20]
b. 1) It was unclear which disutility for peripheral oedema and constipation exactly was derived from Sullivan et al and Christensen et al.[34, 35] In their response, the company explained that the disutility of 0.005 for peripheral oedema[34] was calculated using the unadjusted EQ-5D score for individuals without diabetes and with peripheral oedema (0.736) by subtracting this utility value from 1 and adjusting it to last only seven days.[34] The disutility of 0.001 for constipation[35] was calculated using the difference between currently constipated or not (0.074) and again adjusted to only last seven days as it was assumed that adverse events would not last longer than a week. A rationale behind the duration of seven days for the adverse events is lacking. It is also unclear whether the same duration is used for the calculation of all four adverse events. 2) The disutility for constipation used in the model (0.000) was different to the one mentioned in the CS (0.001). This turned out to be an error and was corrected in the updated CE model. 3). The disutility for serious bleeding was not based on the EQ-5D. It was derived from Tengs et al.[37] In their response, the company stated they were not able to source a more appropriate disutility value for serious bleeding.[4]

4.2.9 Resources and costs

The cost categories included in the model were drug costs, acute health state costs, post-event health state costs, follow-up and monitoring costs and costs of adverse events. Unit prices were based on NHS reference prices, British National Formulary (BNF), and the Personal Social Services Research Unit (PSSRU).

Resource use and costs data identified in the review

The company conducted a SLR with the following review question: What are the costs and resource use associated with the management of patients at risk of cardiovascular events due to elevated triglycerides? This resulted in the identification of three studies (Appendix I CS) that provided cost and resource estimates from a UK perspective.[20, 21, 24] The study by Danese et al., 2016 estimated the economic burden of CV events in patients receiving lipid-modifying therapy in the UK and was used to inform health state costs within the model.[24]

Drug costs (without PAS)

The list price for icosapent ethyl is £173 (inclusive of 20% VAT) per pack of 120 capsules. The recommended daily oral dose is four capsules taken as two 998mg capsules twice daily. The annual course of treatment is £2,106.28 at the anticipated list price. To align with daily cycles used in the model, the daily cost is anticipated to be £5.77. No administration cost or wastage was considered in the model. Compliance with icosapent ethyl treatment obtained from the REDUCE-IT trial was included in the model (98.3%, Table 15 of the CS).[1]

In alignment with the licensed indication, the patient populations receive a stable dose of statin therapy (with or without ezetimibe 10mg) as best supportive care in both the intervention and the comparator. In REDUCE-IT 6.4% of patients were on low intensity statins, 62.5% on moderate intensity statins and 30.8% on high intensity statins. Ezetimibe was used by 6.4% of the patients in REDUCE-IT. To calculate the total daily cost of commonly prescribed statins in the UK, an average of the daily cost of each statin within the different intensity categories was estimated and weighted by the proportion of patients on low, moderate and high intensity statin therapy as per the REDUCE-IT trial. The unit price was based upon the acquisition cost per strength (mg) sourced from the BNF[38] (See Table 36 CS).[1] This resulted in an average daily cost of statins of £0.05.

Discontinuation of icosapent ethyl was based on REDUCE-IT. Survival models were fitted to the discontinuation data of the icosapent ethyl arm. All distributions were deemed plausible based on visual inspection and statistical fit was determined (Table 38 CS).[1] The exponential distribution showed the best goodness of fit and was used in the base case analysis (Figure 4.2)

Figure 4.2: Long-term extrapolation of treatment discontinuation of icosapent ethyl based on REDUCE-IT

Source: Based on Figure 28 of the CS[1]

Acute health state costs and post-event health state costs

Acute health state costs were included at the time of first, second and third event, for the five types of events included in the primary composite endpoint in REDUCE-IT (CV death, nonfatal MI (including silent MI), nonfatal stroke, coronary revascularisation, and unstable angina requiring hospitalisation). These costs were sourced from Danese 2016.[24] Regarding the technique used for coronary

revascularisation, the proportion of patients receiving percutaneous coronary interventions (80%) and CABGs (20%) was based on expert opinion. Post-event health state costs were applied after each event, until the patient experiences another event or dies. The costs of the four non-fatal events in the model were also based on Danese 2016, inflated to 2019 and recalculated to daily costs (Table 4.10).[24]

Table 4.10: Acute and post-event health state costs per event

Health state	Costs	SE	Source
Acute health state event costs			
Nonfatal MI	£4,678.22	£467.82	Danese et al. 2016[24]
Nonfatal stroke	£3,978.91	£397.89	Danese et al. 2016[24]
Coronary revascularisation	£6,147.04	£614.70	80% PCI and 20% CABG
PCI	£4,406.97	£440.70	NHS reference costs 2018-2019[39]
CABG	£13,107.34	£1,310.73	NHS reference costs 2018-2019[39]
Unstable angina	£2,438.43	£243.84	Danese et al. 2016[24]
Cardiovascular death	£3,719.02		Assumed equal to hospitalisation
Fatal MI/stroke	£3,719.02		Hospitalisation without procedure
Post-event health state daily costs			
MI	£2.87		Danese et al. 2016[24]
Stroke	£2.86		
Revascularisation	£5.19		
Unstable angina	£1.12		

Sources: Table 40 and Table 42 of the CS[1]
CABG = coronary artery bypass graft; CS = company submission; MI = myocardial infarction; NHS = National Health Service; PCI = percutaneous coronary intervention; SE = standard error.

Subsequently, as event health states within the model were grouped by the number of events an individual has experienced since the beginning of the trial rather than the type of event, a weighted average was calculated by multiplying the cost of each of the individual events by the distribution of type of event in the icosapent ethyl and placebo groups for first, second and third plus event (Table 4.11).

Table 4.11: Acute and post-event health state costs as used in the model

Health state	Icosapent ethyl	Comparator
Acute health state event costs		
First event	[redacted]	[redacted]
Second event	[redacted]	[redacted]
Third event	[redacted]	[redacted]
Post-event health state daily costs		
First event	[redacted]	[redacted]
Second event	[redacted]	[redacted]
Third event	[redacted]	[redacted]

Sources: Table 41 and Table 43 of the CS[1]

Monitoring and follow up and costs

The resource use associated with monitoring were based on assumptions / expert opinion and considered the costs of a medical appointment (90% general practitioner and 10% cardiologist) and laboratory

testing in the first year of treatment. For icosapent ethyl an additional medical appointment at treatment initiation and the initial fasting lipid panel were considered. For subsequent years one medical appointment with the general practitioner with laboratory testing was considered for both icosapent ethyl and the comparator. This resulted in daily monitoring and follow up costs in the first year of £0.27 for icosapent ethyl and £0.12 for the comparator. Daily follow up costs in subsequent years amounted to £0.11 for both icosapent ethyl and the comparator (Tables 44-47 CS[1]).

Adverse event costs

In the model the costs of the adverse events peripheral oedema (£770.28), constipation (£377.01), atrial fibrillation (£1,247.91) and serious bleeding (£2,814.97) were considered. These costs were based on NICE reference costs and informed by expert opinion.[40]

ERG comment: The main concerns of the ERG relate to: a) time to treatment discontinuation; b) the source for and estimates of acute and post-event health state costs; c) the period the costs of an event were considered; and d) inconsistencies in drug costs and assumptions about compliance.

a) The company clarified that in absence of clinical practice experience with icosapent ethyl, the exponential distribution for the TTD curve was chosen based on statistical fit. Indeed, this distribution showed the best fit, but Weibull, Gompertz, Log-Logistic and Log-normal were all ranked with second-best fit. The company provided scenario analyses with the other distributions (Table 4.12). This showed that the choice for one of the distributions with second best fit (log-normal) could increase the ICER up to £33,805 (log-normal distribution). In the subgroups using this distribution resulted in ICERs of £26,430 and £117,034 for the secondary and primary prevention population, respectively (response to clarification questions Table 42 and 43).[4]

Table 4.12: Scenario analyses with all distributions considered treatment discontinuation (ITT population)

Parametric survival model	Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Exponential	Placebo	9,961	10.553	7.526	-	-	-	-
	Icosapent ethyl	20,619	10.851	7.890	10,658	0.299	0.364	29,317
Weibull	Placebo	9,961	10.553	7.526	-	-	-	-
	Icosapent ethyl	21,268	10.851	7.890	11,307	0.299	0.364	31,102
Gompertz	Placebo	9,961	10.553	7.526	-	-	-	-
	Icosapent ethyl	22,017	10.851	7.890	12,056	0.299	0.364	33,163
Log-logistic	Placebo	9,961	10.553	7.526	-	-	-	-
	Icosapent ethyl	21,810	10.851	7.890	11,849	0.299	0.364	32,594
Lognormal	Placebo	9,961	10.553	7.526	-	-	-	-
	Icosapent ethyl	22,250	10.851	7.890	12,289	0.299	0.364	33,805

Parametric survival model	Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Generalised gamma	Placebo	9,961	10.553	7.526	-	-	-	-
	Icosapent ethyl	21,014	10.851	7.890	11,053	0.299	0.364	30,404

Source: Table 41 Response to the Clarification Letter [4]

£ = UK pounds sterling; ICER = incremental cost effectiveness ratio; Incr. = incremental; LYG = life years gained; QALY = quality adjusted life year.

b) The company justified the use of Danese et al., 2016[24] as a source for the acute and post-event health states by stating it used real-world data for the UK, from a population that received lipid-modifying therapy, maximising the relevance for the population in their submission. Also, the company stated they preferred to use Danese et al., 2016 because it enabled the company to retrieve all the cost inputs for their analyses from a single source.[24] The company provided scenario analyses with cost inputs based on NICE CG181 and sources mentioned in Ryder et al. 2019.[26, 41] These analyses showed lower ICERs than in the company's base-case (NICE CG181 ICER £28,899, Ryder et al. ICER £26,894).[26, 41] It was unclear to the ERG how the cost estimates in these scenario analyses were derived:

- A figure quoted for cardiovascular death costs was attributed to Danese et al., 2016.[24] However, that figure cannot be found in the publication. An alternative figure derived from Walker 2016[42] could be used.

- Costs for non-fatal stroke, in the scenario run by the company to reflect evidence from Ryder et al., 2019[41] were taken from Ali 2015[43] for acute costs of nonfatal stroke and Walker 2016[42] for post-event costs for nonfatal stroke. No rationale was provided for this so the ERG would prefer to use estimates from Danese et al., 2016 to maintain consistency with other estimates (for non-fatal MI and unstable angina).[24]

Additionally, acute costs in the model which were taken from Danese et al., 2016 related to the first six months after the event.[24] Much of this period will have been associated with ongoing post-event costs. The model assumes all costs occur on the day of the event, so it will be prudent to subtract post-event costs for six months minus the day of the event from the acute cost. This can be achieved by subtracting an element for daily post event costs (i.e. 181 days multiplied by the daily post event cost from Danese et al., 2016).[24] The ERG has adjusted cost estimates found in Danese et al., 2016 and Walker 2016 (identified in Ryder et al., 2019) by using a simple inflation calculator[44] so that prices can reflect 2018/19 values (as used in the report and economic model). The ERG has re-worked these estimates as derived from information in Ryder et al., 2019.[41] The ERG has also re-calculated acute costs of revascularisation as the methods used by the company to derive a value are not clear. Application of these adjustments produces the following cost inputs for first event (Table 4.13), which will be used in the ERG base-case analysis. With reference to Table 4.13, it is noteworthy that the main differences between the company and the re-worked scenario based on evidence identified in Ryder et al., 2019 (ERG base case) inputs relate to:[41]

- The incremental post event costs of coronary revascularisation (where the company suggest that post event costs are higher than for any other event whereas Danese et al., 2016 suggested

a negative cost, presumably reflecting effectiveness of the procedures in terms of reduced probability of other cardiac events).[24]

- The costs associated with cardiovascular deaths (where the company provided an estimate that could not be found in Danese et al., 2016 (the attributed source) compared to the ERG estimate based on data presented in Walker 2016).[24, 42]

Table 4.13: Company and ERG calculation of acute event and post event costs

Event	Company base-case	ERG base-case	Comments
Nonfatal MI			
Acute period	£4,678.22	£4,307.04	From Danese et al., 2016: Figure of £4275 adjusted for inflation with post event daily costs subtracted from acute cost (181 days assumed)[24]
Post event	£2.87	£2.85	From Danese et al., 2016:[24] Figure of £922 adjusted for inflation
Nonfatal Stroke			
Acute period	£3,978.91	£3,418.14	From Danese 2016:[24] Figure of £3,512 adjusted for inflation with post event daily costs subtracted from acute cost (181 days assumed)
Post event	£2.86	£3.00	From Danese 2016:[24] Figure of £973 adjusted for inflation
Coronary revascularisation			
Acute period	£6,147.04	£4,353.01	Based on 2018/19 reference costs with a 83%/17% split between PCI/CABG. Estimates for CABG are based on weighted values for HRG codes ED22A , ED22B , ED22C, ED23A, ED23B , ED23C, ED26A, ED26B , ED26C, ED27A, ED27B , ED27C, ED28A, ED28B , ED28C Estimates for PCI are based on weighted values for HRG codes of EY40A , EY40B , EY40C, EY41A, EY41B , EY41C, EY41D. Using these values, different estimates are derived
Percutaneous coronary intervention (PCI)	£4,406.97	£2,836.25	
Coronary artery bypass graft surgery (CABG)	£13,107.34	£11,758.34	
Post event	£5.19	-£1.14	
Unstable angina			
Acute period	£2,438.43	£2,274.59	From Danese et al., 2016:[24] Figure of £2179 adjusted for inflation with post event daily costs subtracted from acute cost (181 days assumed)
Post event	£1.12	£1.01	From Danese et al., 2016:[24] Figure of £328 adjusted for inflation
Cardiovascular death			

Event	Company base-case	ERG base-case	Comments
Total	£3,719.02	£2,543.19	From Walker 2016[42] adjusted for currency and inflation
Fatal MI - hospitalisation without procedure	£3,719.02		No estimate available
Fatal stroke - hospitalisation without procedure	£3,719.02		

CABG = coronary artery bypass graft; ERG = Evidence Review Group; MI = myocardial infarction; PCI = percutaneous coronary intervention.

c) The ERG asked the company to explain and justify for each acute event, for which period post-event costs were considered in the model, and how it was prevented that these costs were overestimated if another acute event (including a fatal event) would take place within this period. The company acknowledged in their response that this could be considered a limitation of their model approach. They argued that the majority of acute costs would be incurred immediately when an event occurs due to hospitalisation and treatment for a non-fatal event. Which would imply that the bias would be limited. The company did not further justify or explain for which duration event costs were considered. With regard to the acute event health state costs: these are based on Danese et al., 2016 who used a duration of six months to account for acute event costs.[24] Also, Danese et al., 2016[24] adopted an event hierarchy to assign patients to an event category to ensure that temporally close events did not lead to double-counting in the cost estimates of acute events. They give the following example: *"For example, someone with a TIA followed by MI, then CABG within a 30-day window would be assigned to the MI group."* As the company has argued that events are missed also if a cycle duration of a month is used, it seems plausible to assume that in the current model with a daily cycle, for a proportion of the events, the acute event costs are considered in full (in the one-day acute event tunnel state) while another event, including a fatal event, takes place within six months. According to the ERG, this structural feature of the model leads to an overestimation of the cost consequences of acute events in the model. With the current model structure it is not possible to determine how large the overestimation of the cost consequences of acute events is. For a detailed description of issues with the structure see section 4.2.2.

d) Compliance with icosapent ethyl treatment obtained from the REDUCE-IT trial was included in the model (98.3%, Table 15 of the CS), however, compliance with placebo treatment (99.2%, Table 15 of the CS) was not incorporated and instead assumed to be perfect. This causes a slight bias in favour of icosapent ethyl, but the ERG can confirm that the impact on cost effectiveness outcomes is very small.

5. COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

The parameters used in the model, including the distributions used in the probabilistic analysis (with 5,000 iterations), are listed in Table 49 in the CS. The CS base-case cost effectiveness results (probabilistic) indicated that icosapent ethyl is both more effective (0.335 incremental QALYs) and more costly (additional costs of £9,893) than current care amounting to a ICER of £27,875 per QALY gained. These results are similar to the deterministic results (Table 5.1).

Table 5.1: Base-case results (probabilistic)

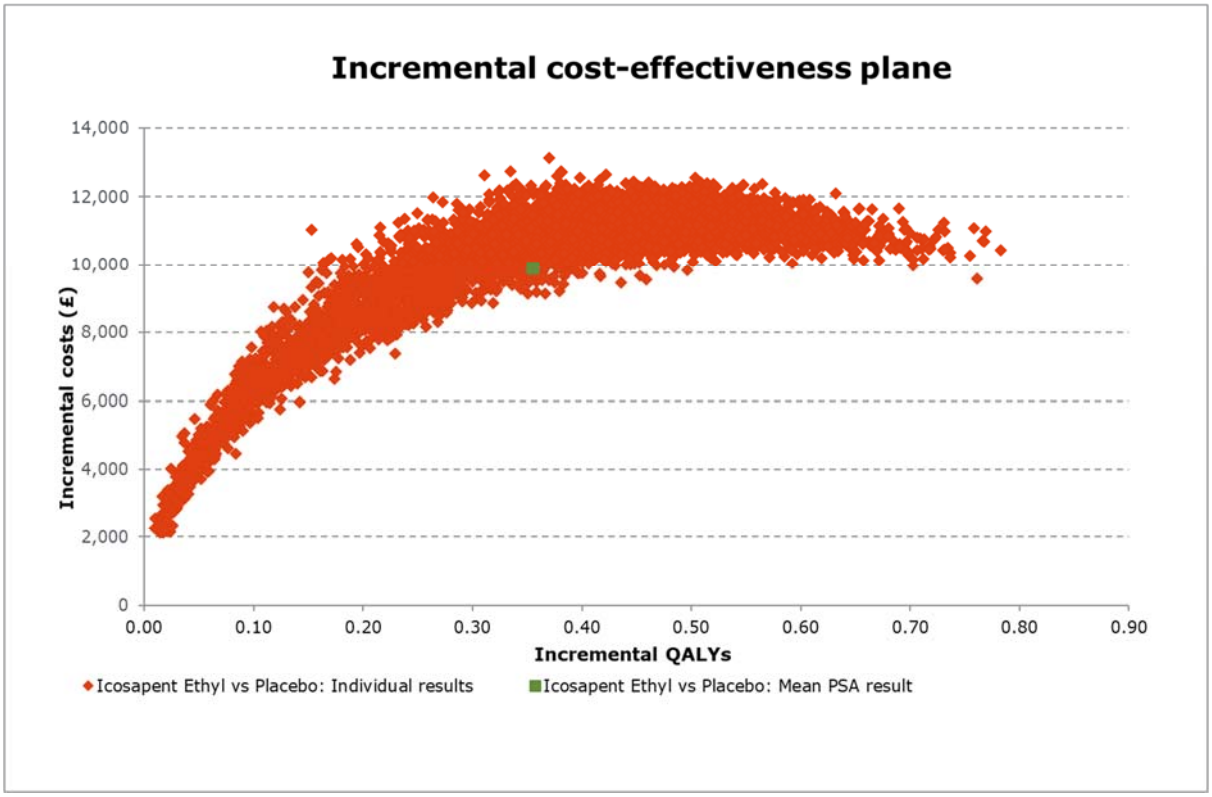
Technologies	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	Cost per QALY (£)
Placebo	10,195	7.353	-	-	-
Icosapent ethyl	20,088	7.708	9,893	0.355	27,875

Source: Table 52 CS[1]

£ = UK pounds sterling; CS = company submission; QALY = quality adjusted life year.

The probability of icosapent ethyl being cost effective, at a threshold of £20,000 per QALY gained, compared to current care is 10% (Figures 5.1 and 5.2).

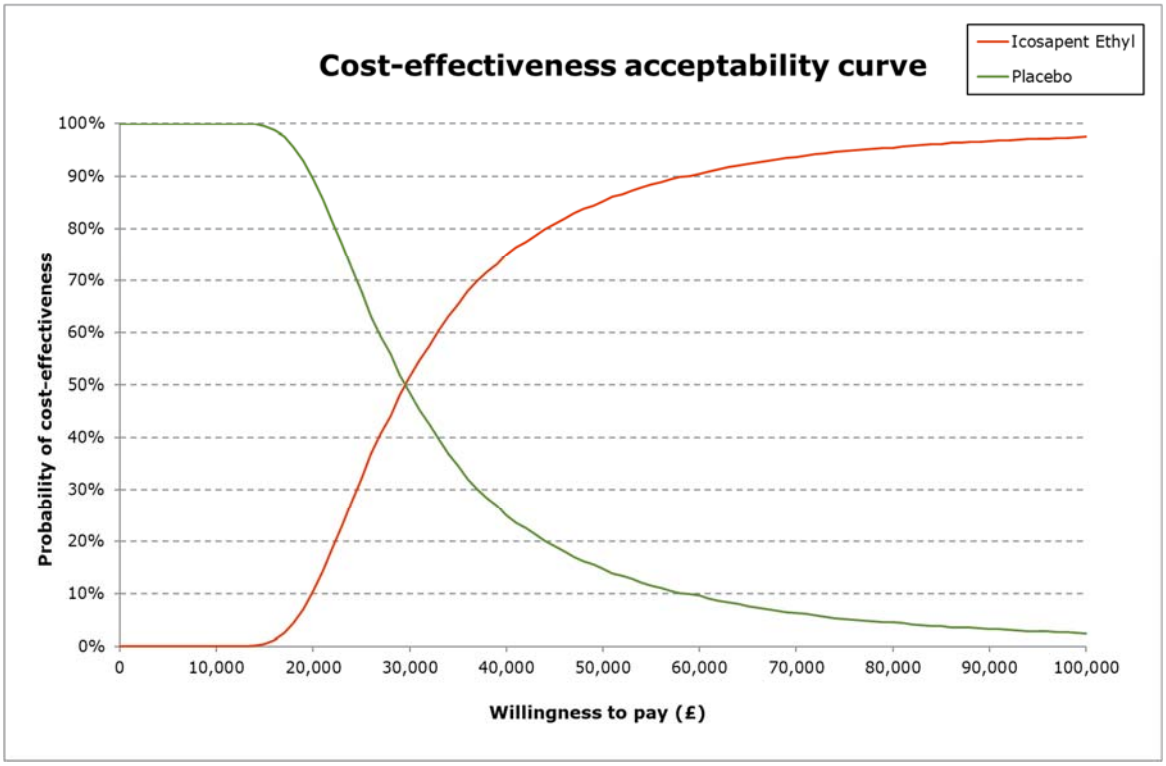
Figure 5.1: Cost effectiveness plane



Source: Figure 29 of the CS[1]

£ = UK pounds sterling; CS = company submission; PSA = probabilistic sensitivity analysis; QALY = quality adjusted life year; vs = versus.

Figure 5.2: Cost effectiveness acceptability curve



Source: Figure 30 of the CS[1]

£ = UK pounds sterling

Overall, the technology is modelled to affect QALYs by:

- Reduced risk of cardiovascular events.

Overall, the technology is modelled to affect costs by:

- Additional costs of icosapent ethyl,
- Reduced risk of cardiovascular events.

ERG comment: The main concerns of the ERG relate to: a) the curvilinear relationship between the incremental costs and QALYs; b) not always using empirical estimates to inform the standard errors in the probabilistic analysis; and c) not providing a breakdown of costs and QALYs.

a) Figure 29 of the CS seems to indicate that there is a curvilinear relationship between the incremental costs and incremental effects. The ERG asked the company to explain this and elaborate on the plausibility of this relationship between the incremental costs and QALYs. The company responded by stating that there was no reason to believe the PSA is incorrect, as the model had been through a full quality check. This did not exactly answer the ERG's questions. We see a positive correlation between incremental costs and QALYs for lower incremental QALYs, and no relation for higher incremental QALYs. So, with higher QALY increments, the incremental costs do not increase. This could be a result of the icosapent ethyl treatment cost being the main driver of incremental costs, and maintenance of the treatment effect after treatment discontinuation. However, further explanation by the company appears warranted.

b) The ERG noted that the company did not always use available empirical estimates to inform the standard errors in the probabilistic analyses. The company corrected this and provided an adjusted model file.

c) The company did not present a break-down of results in their report. The ERG obtained a break-down of costs (per cost category and per health state) and QALYs (per health state). These are presented in Table 5.2.

Table 5.2: Breakdown of the company's base case results (deterministic)

Outcomes	Icosapent ethyl	Placebo	Increment
Cost categories			
Treatment costs	£13,037	£197	£12,841
Health state costs	£7,169	£9,427	-£2,258
Adverse event costs	£412	£337	£75
Total costs	£20,619	£9,961	£10,658
Costs per health state			
First event	£1,666	£1,990	-£324
Post first event	£3,042	£1,794	£1,248
Second event	£792	£1,170	-£379
Post second event	£1,825	£1,591	£233
Third event	£429	£860	-£431
Post third event	£1,199	£1,850	-£651
No Event	£11,667	£705	£10,962
Total costs	£20,619	£9,961	£10,658
QALYs per health state			
First event	0.000	0.001	0.000
Post first event	0.884	0.876	0.007
Second event	0.000	0.000	0.000
Post second event	0.402	0.519	-0.117
Third event	0.000	0.000	0.000
Post third event	0.161	0.313	-0.151
No Event	6.441	5.816	0.625
Total QALYs	7.890	7.526	0.364

Source: Company clarification response model[4]

£ = UK pounds sterling; QALY = quality adjusted life year.

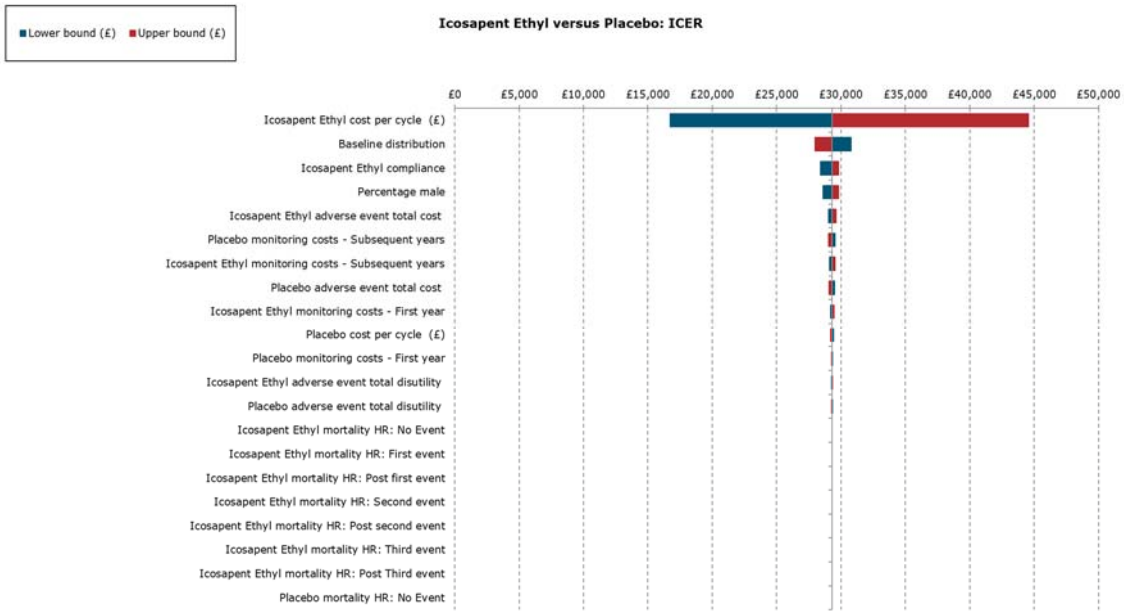
5.2 Company's sensitivity analyses

The company performed and presented the results of deterministic sensitivity analyses (DSA) as well as scenario analyses and subgroup analysis.

5.2.1 Deterministic sensitivity analysis

The DSA considered upper and lower confidence intervals sourced from the literature or calculated from the pre-specified probabilistic distributions assigned to each parameter as an alternative. Where the standard error was unavailable, this was assumed to be 10% of the mean value. The parameters that had the greatest effect on the ICER (based on the company's sensitivity analyses) was the costs of icosapent ethyl per cycle, followed by the baseline distribution of the characteristics age and gender (Figure 5.3).

Figure 5.3: Tornado diagram



Source: Figure 32 of the CS[1]

£ = UK pounds sterling; CS = company submission; HR = hazard ratio; ICER = incremental cost effectiveness ratio.

5.2.2 Scenario analyses

The company performed scenario analyses for discount rate, and the duration of the application of utility for acute events. A discount rate of 0% or 5% (instead of 3% in the base case) led to ICERs of £21,658 and £32,990, respectively. A 30- or 90-day duration of the utility for acute events (instead of 60 days in the base case) led to ICERs of £29,336 and £29,282, respectively.

5.2.3 Subgroup analyses

The company conducted subgroup analysis for the primary and secondary prevention populations. The ICERs amount to £101,828 and £22,999, respectively. The higher ICER in the primary prevention population is driven by fewer first events in this population (Table 5.3).

Table 5.3: Subgroup analysis results

Population	Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
	Placebo	11,371	10.322	7.336	-	-	-	-

Population	Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Secondary prevention	Icosapent ethyl	21,853	10.707	7.791	10,481	0.384	0.456	22,999
Primary prevention	Placebo	6,131	11.119	8.003	-	-	-	-
	Icosapent ethyl	17,628	11.190	8.116	11,497	0.071	0.113	101,828

Source: Table 56 of the CS[1]

£ = UK pounds sterling; CS = company submission; ICER = incremental cost effectiveness ratio; Incr. = incremental; LYG = life years gained; QALY = quality adjusted life year.

ERG comment: The main concerns of the ERG relate to: a) lack of transparency regarding the subgroup analysis, b) the absence of a probabilistic analysis and limited DSA and scenario analyses for the subgroups.

a) The ERG asked the company to clarify exactly which model inputs were different for the subgroup analyses. The company explained that the model inputs that were adjusted in the subgroup analyses were baseline characteristics (age and gender), clinical inputs (the survival models used to estimate and extrapolate the proportion of persons with an event) and the distribution of the types of CV events experienced per event, as reported in the REDUCE-IT trial. These changes impact the hazard ratios informing non-CV related mortality, the average costs and utilities associated with icosapent ethyl and the comparator, and ultimately the ICER.

b) The ERG requested and the company provided additional probabilistic and DSA and scenario analyses for the subgroups. The ICERs for the subgroups based on the probabilistic analysis amounted to £21,650 and £104,740, for the secondary and primary prevention population, respectively (Table 8 response to the clarification questions[4]). The DSA for the subgroups showed that also in both subgroups the parameter with the greatest effect on the ICER was the costs of icosapent ethyl per cycle, followed by the baseline distribution of the characteristics age and gender (Table 9 and 10 in the response to the clarification questions[4]). The company performed scenario analyses for discount rate, and the duration of the application of utility for acute events for both subgroups. A discount rate of 0% or 5% (instead of 3.5% in the base case) lead to ICERs of £17,283 and £25,733 for the secondary prevention population, and ICERs of £71,694 and £116,579 for the primary prevention population, respectively. A 30- or 90-day duration of the utility for acute events (instead of 60 days in the base case) led to ICERs of £23,024 and £22,98 for the secondary prevention population, and £101,762 and £101,529 for the primary prevention population, respectively (Table 11 to Table 14 in the response to the clarification questions[4]).

5.3 Model validation and face validity check

5.3.1 Face validity assessment

Two UK clinical experts were involved (1:1 interviews) in informing the key model assumptions.

5.3.2 Technical verification

The model was internally developed by a health economist and quality checked by multiple internal health economists.

5.3.3 Comparisons with other technology appraisals

No cross validation was reported in CS section B.3.10 (considering validation).[1]

5.3.4 Comparison with external data used to develop the economic model

No details on a comparison with data used to develop the economic model was reported in CS section B.3.10. However, Figures comparing the observed (Kaplan-Meier data) and estimated (parametric survival models) time to cardiovascular events were provided in CS section B.3.3.2.[1]

5.3.5 Comparison with external data not used to develop the economic model

No details on a comparison with data not used to develop the economic model was reported in CS section B.3.10.[1]

ERG comment: The main concerns of the ERG relate to: a) the technical validation; b) model efficiency; and c) cross validity and external validity assessments.

a) The ERG identified multiple issues that potentially would indicate a lack of technical (or internal) validity of the model as well as inconsistencies between the CS and the economic model (see clarification question C18).[4] These issues were resolved by the company during the clarification phase. Additionally, the ERG asked the company to use the TECH-VER checklist to further assess the technical validity. However, this was not provided by the company due to time constraints, instead an additional internal quality assessment checklist was completed by an internal health economist not involved in the development of the model. Although the ERG appreciates the company's efforts to further assess the technical validity, and it is to some degree reassuring that no additional errors were identified, this internal checklist was, according to the ERG, not optimal for assessing the technical validity. For instance, the item *"Verify key equations using the formula auditing tool (trace dependents of inputs, trace precedents of results)"* does not specify what was exactly checked and how. Consequently, the rigour of this additional quality assessment is unclear (especially given that the company mentioned constraint time as a justification not to use the TECH-VER checklist). Moreover, the technical plausibility of the results is still unclear to the ERG. Specifically, in clarification question C19b the ERG asked the company to clarify what causes the curvilinear relationship between the incremental costs and effects and to elaborate on the plausibility.[4] Unfortunately this was not clarified by the company. Additionally, the incremental cost effectiveness plane seems to indicate that [redacted] Given the above, the status of the technical model validity is unclear.

b) The internal health economist that completed the company's internal checklist, commented on the ease-of-use that "*Model very slow, >400k VLOOKUPs and HLOOKUPs which are semi-volatile meaning that if any of the cells in their arguments change the formulae will re-calculate. Also they are slow compared to INDEX/MATCH formula (XLOOKUP can also be used). ... Societal costs are hidden but include a lot of formulae, consider deleting these to improve the speed of the model.*".[1] Although this might not interfere with model functioning this hampers the ERG in assessing model validity and performing analyses. This is also illustrated in further comments by the internal reviewer: "*OWSA/PSA very slow. Consider reviewing code to increase efficiency*".[1]

c) In clarification question C17, the ERG asked the company to conduct a cross validation with other economic models focusing on a related decision problem (considering the model structure, model assumptions, model inputs, intermediate outcomes and final outcomes). Unfortunately this was not

provided by the company (only a brief summary of similar appraisals was provided in response to this question). Similarly, the external validity assessment (considering model inputs, intermediate outcomes as well as final outcomes) requested by the ERG was not provided in response to question C17[4]. This hampers the validity assessment of the cost effectiveness results.

6. EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the ERG

Table 6.1 summarises the key issues related to the cost effectiveness categorised according to the sources of uncertainty as defined by Grimm et al. 2020:[45]

- Transparency (e.g. lack of clarity in presentation, description, or justification)
- Methods (e.g. violation of best research practices, existing guidelines, or the reference case)
- Imprecision (e.g. particularly wide confidence intervals, small sample sizes, or immaturity of data)
- Bias and indirectness (e.g. there is a mismatch between the decision problem and evidence used to inform it in terms of population, intervention/comparator and/or outcomes considered)
- Unavailability (e.g. lack of data or insight)

Identifying the source of uncertainty can help determine what course of action can be taken (i.e. whether additional clarifications, evidence and/ or analyses might help to resolve the key issue). Moreover, Table 6.1 lists suggested alternative approaches, expected effects on the cost effectiveness, whether it is reflected in the ERG base-case as well as additional evidence or analyses that might help to resolve the key issues.

Based on all considerations in the preceding sections of this ERG report, the ERG defined a new base-case. This base-case included multiple adjustments to the original base-case presented in the previous sections. These adjustments made by the ERG form the ERG base-case and were subdivided into three categories (derived from Kaltenthaler 2016):[46]

- Fixing errors (FE) (correcting the model where the company's submitted model was unequivocally wrong)
- Fixing violations (FV) (correcting the model where the ERG considered that the NICE reference case, scope or best practice had not been adhered to)
- Matters of judgement (MJ) (amending the model where the ERG considers that reasonable alternative assumptions are preferred)

6.1.1 ERG base-case

The adjustments made by the ERG, to derive the ERG base-case (using the CS base-case as starting point) are listed below. Table 6.2 shows how individual adjustments impact the results plus the combined effect of all abovementioned adjustments simultaneously, resulting in the ERG base-case.

Fixing errors

There were errors identified by the ERG.

Fixing violations

1. The ERG has made changes to the calculation of acute event and post-event costs (Section 4.2.9)

Matters of judgement

2. Use of treatment-dependent non-CV related hazard ratios (Section 4.2.6): Assume the mean of the weighted hazard ratios for non-CV death by health state for the two treatments and apply these hazard ratios to both treatments equally.

3. Assuming the log-logistic parametric survival curve to estimate time to treatment discontinuation (Section 4.2.9).
4. Assuming waning of treatment effect over 10-years post trial completion after first, second and third events (Section 4.2.6).

6.1.2 ERG exploratory scenario analyses

The ERG performed the following exploratory scenario analyses to explore the impact of alternative assumptions conditional on the ERG base-case.

1. Assuming waning of treatment effect over 20-years post trial completion after first, second and third events (Section 4.2.6).
2. Assuming the exponential parametric survival curve to estimate time to treatment discontinuation which was used in the CS base-case (Section 4.2.9).

Table 6.1: Overview of key issues related to the cost effectiveness (conditional on fixing errors highlighted in Section 5.1)

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER[a]	Resolved in ERG base-case[b]	Required additional evidence or analyses
5 – Model structure	4.2.2	Methods	Longer cycle length or individual patient level model	+/-	No	Yes
6 – Use of reconstituted data	4.2.6	Methods	Re-estimate parametric survival curves using complete KM data	+/-	No	Yes
7 – Limited evidence available for (long-term) validation of survival curves	4.2.6	Unavailability	Collecting long-term observational data	+/-	No	No
8 – Use of stratified parametric models, guidance not followed	4.2.6	Methods	Follow NICE DSU TSD 14 on survival analysis and explore dependent modelling[47]	+/-	No	Yes
9 – Long-term extrapolation, no treatment waning assumed	4.2.6	Unavailability	Company provided treatment waning scenarios. Explore treatment waning further, potentially with expert opinion. Long-term observational data	+	MJ	Yes
10 – Use of treatment-dependent non-CV related hazard ratios	4.2.6	Methods, Unavailability	Use treatment-independent non-CV related death hazard ratios, provide further evidence to justify use of treatment-dependent non-CV related death hazard ratios	+	MJ	Yes
11 – Health-related quality of life sensitive to choice of utility source	4.2.8	Methods	Provide further justification for appropriateness of utility value source	+	No	Yes
12 – The duration event costs are considered in the model	4.2.9	Methods	Alternative model structure, alternative estimation of post-event costs	+/-	No	Yes

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER[a]	Resolved in ERG base-case[b]	Required additional evidence or analyses
13 – The distribution to extrapolate time to discontinuation	4.2.9	Methods	Expert opinion on long-term number of patients on treatment. Data on long-term use in clinical practice.	+	MJ	Yes
14 – Sources and calculation of event costs	4.2.9	Methods	Provide further justification and re-estimation of event costs	+	FV	Yes
15 – Model validation and face validity check	5.3	Methods	Appropriately conducting and describing validity assessments	+/-	No	Yes

[a] Likely conservative assumptions (of the intervention versus all comparators) are indicated by '-'; while '+/-' indicates that the bias introduced by the issue is unclear to the ERG and '+' indicates that the ERG believes this issue likely induces bias in favour of the intervention versus at least one comparator; [b] Explored in Section 6.1
CV = cardiovascular; DSU = Decision Support Unit; ERG = Evidence Review Group; FE = Fixing errors; FV = fixing violations; ICER = incremental cost effectiveness ratio; KM = Kaplan Meier; MJ = matters of judgement; NICE = National Institute for Health and Care Excellence; TSD = Technical Support Document.

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

In Section 6.1 the ERG base-case was presented, which was based on various changes compared to the company base-case. Table 6.2 shows how individual changes impact the results plus the combined effect of all changes simultaneously. The exploratory scenario analyses are presented in Table 6.3. These are all conditional on the ERG base-case. The analyses numbers in Tables 6.2 and 6.3 correspond to the numbers reported in Section 6.1. Tables 6.4 and 6.5 provide the deterministic results of the subgroup analyses, Tables 6.6 and 6.7 show the scenarios for the subgroup analyses, and Table 6.8 the probabilistic results for ERG base-case for the whole population and subgroups. The submitted model file contains technical details on the analyses performed by the ERG (e.g., the *"ERG"* sheet provides an overview of the cells that were altered for each adjustment).

Table 6.2: Deterministic ERG base-case – whole population

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
ERG base-case (ERG_1-4)					
Placebo	£4,926	7.539			
Icosapent ethyl	£18,588	7.651	£13,663	0.111	£122,598
Fixing violation: adjustments to cost inputs (ERG_1)					
Placebo	£4,916	7.526			
Icosapent ethyl	£16,947	7.890	£12,030	0.364	£33,092
Matter of judgement: Use of treatment-dependent non-CV related hazard ratios (ERG_2)					
Placebo	£9,989	7.539			
Icosapent ethyl	£20,595	7.879	£10,606	0.340	£31,225
Matter of judgement: Log-logistic TTD (ERG_3)					
Placebo	£9,961	7.526			
Icosapent ethyl	£21,810	7.890	£11,849	0.364	£32,594
Matter of judgement: Assuming waning of treatment effect over 10-years post trial completion after first, second and third events (ERG_4)					
Placebo	£9,961	7.526			
Icosapent ethyl	£21,876	7.663	£11,915	0.137	£87,240

£ = UK pounds sterling; CV = cardiovascular; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality adjusted life year; TTD = time to treatment discontinuation.

Table 6.3: Deterministic scenario analyses (conditional on ERG base-case) – whole population

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
ERG scenario 1: Assuming waning of treatment effect over 20-years post trial completion after first, second and third events.					
Placebo	£4,926	7.539			
Icosapent ethyl	£18,423	7.729	£13,498	0.190	£71,169
ERG scenario 2: Exponential TTD conditional on ERG base-case					
Placebo	£4,926	7.539			
Icosapent ethyl	£17,471	7.651	£12,546	0.111	£112,577

£ = UK pounds sterling; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality adjusted life year; TTD = time to treatment discontinuation.

Table 6.4: Deterministic ERG base-case – CV1 (secondary prevention) population

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
ERG base-case (ERG_1, ERG_2, ERG_3)					
Placebo	£5,490	7.333			
Icosapent ethyl	£19,398	7.489	£13,908	0.156	£88,888
Fixing violation: adjustments to cost inputs (ERG_1)					
Placebo	£5,495	7.340			
Icosapent ethyl	£17,765	7.795	£12,269	0.456	£26,933
Matter of judgement: Use of treatment-dependent non-CV related hazard ratios (ERG_2)					
Placebo	£11,368	7.333			
Icosapent ethyl	£21,770	7.759	£10,402	0.426	£24,403
Matter of judgement: Log-logistic TTD (ERG_3)					
Placebo	£11,382	7.340			
Icosapent ethyl	£23,005	7.795	£11,623	0.456	£25,514
Matter of judgement: Assuming waning of treatment effect over 10-years post trial completion after first, second and third events (ERG_4)					
Placebo	£11,382	7.340			
Icosapent ethyl	£23,386	7.527	£12,004	0.188	£63,920

£ = UK pounds sterling; CV = cardiovascular; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality adjusted life year; TTD = time to treatment discontinuation.

Table 6.5: Deterministic scenario analyses (conditional on ERG base-case) – CV1 (secondary prevention) population

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
ERG scenario 1: Assuming waning of treatment effect over 20-years post trial completion after first, second and third events.					
Placebo	£5,490	7.333			
Icosapent ethyl	£19,197	7.585	£13,707	0.252	£54,396
ERG scenario 2: Exponential TTD conditional on ERG base-case					
Placebo	£5,490	7.333			

Icosapent ethyl	£18,352	7.489	£12,861	0.156	£82,199

£ = UK pounds sterling; CV = cardiovascular; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality adjusted life year; TTD = time to treatment discontinuation.

Table 6.6: Deterministic ERG base-case – CV2 (primary prevention) population

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
ERG base-case (ERG_1, ERG_2, ERG_3)					
Placebo	£3,423	8.096			
Icosapent ethyl	£16,560	8.113	£13,137	0.017	£758,717
Fixing violation: adjustments to cost inputs (ERG_1)					
Placebo	£3,379	8.007			
Icosapent ethyl	£15,022	8.120	£11,643	0.113	£102,932
Matter of judgement: Use of treatment-dependent non-CV related hazard ratios (ERG_2)					
Placebo	£6,244	8.096			
Icosapent ethyl	£17,737	8.183	£11,494	0.087	£132,714
Matter of judgement: Log-logistic TTD (ERG_3)					
Placebo	£6,137	8.007			
Icosapent ethyl	£18,915	8.120	£12,779	0.113	£112,968
Matter of judgement: Assuming waning of treatment effect over 10-years post trial completion after first, second and third events (ERG_4)					
Placebo	£6,137	8.007			
Icosapent ethyl	£18,018	8.047	£11,881	0.040	£300,727

£ = UK pounds sterling; CV = cardiovascular; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality adjusted life year; TTD = time to treatment discontinuation.

Table 6.7: Deterministic scenario analyses (conditional on ERG base-case) – CV2 (primary prevention) population

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
ERG scenario 1: Assuming waning of treatment effect over 20-years post trial completion after first, second and third events.					
Placebo	£3,423	8.096			
Icosapent ethyl	£16,502	8.134	£13,079	0.038	£345,421

ERG scenario 2: Exponential TTD conditional on ERG base-case					
Placebo	£3,423	8.096			
Icosapent ethyl	£15,273	8.113	£11,850	0.017	£684,348

£ = UK pounds sterling; CV = cardiovascular; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality adjusted life year; TTD = time to treatment discontinuation.

Table 6.8: Probabilistic ERG base-case analyses

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Whole population					
Placebo	£4,826	7.366			
Icosapent ethyl	£17,949	7.463	£13,124	0.097	£135,066
CV1 (secondary prevention) population					
Placebo	£5,361	7.157			
Icosapent ethyl	£18,708	7.295	£13,347	0.138	£96,924
CV2 (primary prevention) population					
Placebo	£3,420	7.982			
Icosapent ethyl	£16,077	7.996	£12,657	0.014	£905,132

£ = UK pounds sterling; CV = cardiovascular; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality adjusted life year.

6.3 ERG's preferred assumptions

The estimated ERG base-case ICER (probabilistic), based on the ERG preferred assumptions highlighted in Section 5.1, was £135,066 per QALY gained in the whole population. The probabilistic ERG base-case analyses indicated cost effectiveness probabilities of 0% and 0% at willingness to pay thresholds of £20,000 and £30,000 per QALY gained. The most influential adjustment was the treatment waning at 10-year assumption. The ICER increased most in the scenario analysis with alternative assumptions regarding treatment waning.

6.4 Conclusions of the cost effectiveness section

The company's cost effectiveness submission was partly in line with the NICE reference case. Elements not in line with the reference case include the estimation of health effects (guidance not followed), and estimation of health-related quality of life (only partly based on EQ-5D). The ERG identified several methodological issues in this submission. First, the model structure was not in line with other assessments considering related decision problems and there were significant doubts over the appropriateness of the chosen modelling approaches, including the daily cycle length and the estimation of event costs, which are estimated in full for all patients including those with subsequent events soon after. Secondly, the company did not follow available and widely used guidance on survival analysis and as a result there was uncertainty that could not be resolved by the ERG (e.g. the use of reconstituted data, and of stratified survival models without ruling out the proportional hazards assumption). Thirdly, there were issues in the estimation of costs that were corrected by the ERG as much as possible. Lastly, the company's model validation efforts were incomplete. The ERG's additional validation efforts were hampered by a cumbersome, computationally expensive model. The ERG considers that a considerable part of the uncertainty caused by these issues can likely be resolved by the company exploring

alternative methods and approaches. Further key uncertainties stem from the lack of knowledge on future treatment effectiveness / waning and time to treatment discontinuation.

The ERG adjusted the company's model by correcting costs, assuming treatment-independent non-CV death hazard ratios, choosing an alternative time to treatment discontinuation distribution, and assuming treatment waning from the end of the trial period up to 10 years. These changes significantly increased the ICER in the overall population. The subgroup analyses showed that icosapent ethyl has a significantly lower probability of being cost effective in the primary prevention subgroup (both company's and ERG analyses) compared with the secondary prevention subgroup. Model outcomes are sensitive to many inputs and settings, most notably treatment waning, model choice for time to treatment discontinuation, non-CV death hazard ratios and utilities.

In conclusion, there is currently significant uncertainty about the cost effectiveness of icosapent ethyl for the treatment of hypertriglyceridaemia. The ERG considers that part of this uncertainty can probably be resolved by exploring alternative methods and approaches adhering to commonly accepted practices.

7. END OF LIFE

The CS did not include any statements regarding icosapent ethyl meeting the end of life criteria defined by NICE, therefore this is not applicable.[1]

8. REFERENCES

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National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Icosapent ethyl with statin therapy for reducing the risk of cardiovascular events in adults with elevated triglycerides [ID3831]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Thursday 30 September 2021** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1 Factually incorrect statement in key issue 3

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 15, Table 1.4: Incorrect statement in the description of the issue identified by the ERG. Death from any cause is not part of the 5-point MACE.	Update wording from: 'It is possible that using the 5-point MACE masks the treatment effect in relation to individual outcomes such CV death and death from any cause.' To: 'It is possible that using the 5-point MACE masks the treatment effect in relation to individual outcomes such as CV death.'	Factually incorrect statement	Corrected.

Issue 2 Factually incorrect statement in Table 2.1

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 26, Table 2.1: Incorrect statement in the ERG comment on the economic analysis.	Update wording from: 'Mostly in line with NICE scope, with the exceptions of estimation of health effects (methodological guidance not followed) and health-related quality of life (not all estimates based on EQ-5D).' To: 'Mostly in line with NICE scope, with the exceptions of estimation of health effects (methodological guidance not followed) and health-related quality of life (all estimates based on EQ-5D except one disutility for severe	Factually incorrect statement	Not a factual inaccuracy.

	bleeding).'		

Issue 3 Incorrect inequality

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 33, Section 3.1.2: Incorrect inequality used for LDL-C levels.	Update wording from: 'LDL-C levels (>40 mg/dL [1.04 mmol/L] and ≥100 mg/dL [2.60 mmol/L]).' To: 'LDL-C levels (>40 mg/dL [1.04 mmol/L] and ≤100 mg/dL [2.60 mmol/L]).'	Factually incorrect statement	Corrected.

Issue 4 Incorrect inequality

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 41, Table 3.4: Incorrect inequality used for LDL-C levels.	Update wording from: 'LDL-C >40 mg/dL (1.04 mmol/L) and ≥100 mg/dL (2.60 mmol/L)' To: 'LDL-C >40 mg/dL (1.04 mmol/L) and ≤100 mg/dL (2.60 mmol/L)'	Factually incorrect statement	Corrected.

Issue 5 Values provided in Table 3.8 and 3.9 need AIC mark-up

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 52 – 53, Tables 3.8 and 3.9: Data provided for secondary and	All data provided for secondary and primary prevention in Table 3.8 and 3.9 should be	Presents unpublished data	Amended.

primary prevention not marked as academic in confidence.	marked as academic in confidence.		

Issue 6 Incorrect inception date for Embase/MEDLINE

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 60, Table 4.1: Incorrect inception date for Embase/MEDLINE.	Update wording from: '2021/02/8' To: '2021/01/8'	Factually incorrect statement	Corrected.

Issue 7 Missing a study design 1 inclusion criteria (for cost-effectiveness analysis studies)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 63, Table 4.2: Missing a study design 1 inclusion criteria (cost-effectiveness analysis studies).	Include "Cost-benefit analysis" in inclusion criteria	Missing statement	Amended.

Issue 8 Incorrect description of methods for construction of third plus event curve

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 72, Incorrect description of methods for how the third plus event curve was constructed.	Update wording from: 'To estimate time to second event, all patients that were considered for the first event	Factually incorrect statement	Corrected.

	curve…..' To: 'To estimate time to third plus event, all patients that were considered for the first event curve…..'		

Issue 9 Values provided in Table 4.6 incorrect AIC mark-up

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 73, Table 4.6: Patients with third plus CV events values are not marked as academic in confidence.	All values in 'Table 4.6: Distribution of types of first, second and third plus events' need to be marked as academic in confidence.	Presents unpublished data	Amended.

Issue 10 Incorrect description of baseline utility sources and justification

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 79: Incorrect description of baseline utilities sources and justification.	Update wording from: 'The company considered baseline utilities by Stevanovic and O'Reilly appropriate as they had been used in NICE CG181[26] on CV disease and lipid modification and because they appropriately reflected the target population of icosapent ethyl. No further evidence was provided to support this statement.' To: 'The company considered baseline utilities sourced from Stevanovic and O'Reilly appropriate to inform patients in the secondary prevention	Factually incorrect statement. Baseline utility values were not sourced from NICE CG181 and the justification for use was provided on page 108 (section B.3.4.5) of the CS. Health state multipliers were sourced from NICE CG181.	The statement was corrected in the report by deleting the part from "as they had been used in NICE CG181. statement".

	and primary prevention cohorts, respectively, for the following reasons: • Stevanović *et al.* 2016 was a multivariate meta-analysis that included 40 studies providing preference-based values in post-acute coronary syndrome, stable angina and coronary heart disease, a comparable population to the secondary prevention cohort within REDUCE-IT. The average age of patients was 65.35 years which is similar to the average age of patients in REDUCE-IT. The study was considered applicable to a UK population as 10 of the 40 studies referred to the UK and 53% of the EQ-5D scoring values were based on the UK tariff. • O'Reilly *et al.* 2011 analysed HRQoL data from 1,147 patients with type II diabetes and estimated the disutility associated with experiencing a diabetes-related complication. A diabetes study was considered appropriate with it being an inclusion criterion in the primary prevention cohort within REDUCE-IT. Additionally, the mean age was 63.7 years which is comparable to the average age of patients in REDUCE-IT.'		

Issue 11 Missing fatal stroke acute cost from Table 4.10

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 82, Table 4.10: Fatal stroke acute costs are missing.	Fatal stroke costs to be added to Table 4.10 from company CS.	Missing data	Amended.

Issue 12 Values provided in Table 4.11 incorrect AIC mark-up

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 82, Table 4.11: All values in Table 4.11 are not marked as academic in confidence.	All values in 'Table 4.11: Acute and post-event health state costs as used in the model' should be marked as academic in confidence.	Presents unpublished data	Amended.

Issue 13 Costs in Table 5.2 need to contain commas

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 91, Table 5.2: All cost values in Table 5.2 currently contain full stops rather than commas.	All cost values in Table 5.2 need to contain commas rather than full stops. E.g. £13.037 needs to be written as £13,037	Factual inaccuracy	Corrected.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Icosapent ethyl with statin therapy for reducing the risk of cardiovascular events in adults with elevated triglycerides [ID3831]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments by **5pm** on **Tuesday 9 November 2021**.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Amarin**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Not applicable**

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses ?	Response
Key issue 1: Population of main clinical effectiveness evidence, REDUCE-IT trial, narrower than scope and decision problem	NO	The population in the decision problem should be the population as per the eligibility criteria for the REDUCE-IT trial and is therefore narrower than the population referred to in the licensed indication and in the NICE final scope. The clinical evidence presented in the submission only includes the REDUCE-IT trial as it is the only relevant trial for icosapent ethyl. The economic model is based on the REDUCE-IT trial population. As such, the entire submission is based on the REDUCE-IT trial, in line with the decision problem which has a narrower population than in the licensed indication.
Key issue 2: The period to determine a stable dose of statin in REDUCE-IT is likely to be less than in	YES	The table below summarises additional evidence from the REDUCE-IT trial for the period to determine a stable dose of statin. Statistic — AMR101 (N=4089) — Placebo (N=4090) — Overall (N=8179) Duration of Stable Statin Dose Before Randomization - n (%) At least 3 months — [redacted] — [redacted] — [redacted]

Key issue	Does this response contain new evidence, data or analyses ?	Response
clinical practice		Note: Five patients with missing visit information are excluded from the analysis. Note: Duration of Stable Statin Dose (defined by statin intensity on Atorvastatin, Fluvastatin, Lovastatin, Pitavastatin, Pravastatin, Rosuvastatin, or Simvastatin) in years before randomization was calculated as number of days between randomization and stable statin dose start plus one divided by 365.25. Duration in months was calculated as duration in years multiplied by 12. The analysis shows that approximately [redacted] of patients in the ITT cohort of the REDUCE-IT trial had a duration of stable statin dose of more than three months. Healthcare professionals at the most recent Royal College of General Practitioners (RCGP) conference (14th – 15th October 2021) confirmed that three months is the duration observed in UK clinical practice for determining a stable dose of statin. This matches with the duration observed in the majority of patients in the REDUCE-IT trial, indicating that the patients enrolled in this trial are generalisable to patients in the UK NHS setting.
Key issue 3: Composite outcomes (MACE) instead of disaggregated outcomes e.g. CV death used as primary	NO	Although the composite 5-point MACE was used to model the time of a first, second or three plus 5-point MACE, the distribution of the specific type of cardiovascular event (CV death, nonfatal MI, nonfatal stroke, coronary revascularization and unstable angina) experienced by patients in each treatment group was applied, as per Table 26 of company submission. Therefore, the effect of icosapent ethyl on each specific event occurring as a first, second or third plus event was taken into account. For example, if a higher proportion of the total events in the icosapent ethyl treatment group were CV death than the proportion observed in the placebo group, this is accounted for when informing the type of event occurred. These proportions are then

Key issue	Does this response contain new evidence, data or analyses ?	Response
outcome and used in the model		used to inform the costs and utilities applied in the model, hence, the treatment effect predicted in the model is in line with the occurrence of CV death in the REDUCE-IT trial. The company believes that using the composite 5-point MACE for the time to event and then the proportion of each specific event would not lead to a significant difference in the cost-effectiveness of icosapent ethyl in comparison to an approach solely based on disaggregated outcomes as mentioned by the ERG. To further support this point, a comparison of the predicted model outcomes obtained using the submission model and the individual patient simulation [redacted] model provided as new evidence for validation, shows a similar trend in clinical outcomes (see key issue 5).
Key issue 4: Unclear generalisability of the results to patients in the UK NHS setting	YES	The tables below provide a comparison of the baseline characteristics from the REDUCE-IT trial with those from Steen *et al.* (2016) for each subgroup (primary prevention and secondary prevention). There are many similarities between the baseline characteristics of REDUCE-IT and Steen *et al.* but there are also some differences, particularly in the disease-relevant and medication use characteristics. However, this is not unusual to see, as primary and secondary prevention patients in general can have a wide range of underlying/prior diseases. Furthermore, Steen *et al.* is a real-world study whereas REDUCE-IT is a randomised controlled trial, so by definition has stricter eligibility criteria upon enrolment. However, the general trend observed in the characteristics between the two studies is very similar, indicating that the population enrolled in the REDUCE-IT trial is generalisable to patients in the UK NHS setting. **<u>Primary prevention population</u>**

The demographic characteristics (age, gender, BMI and systolic BP) were similar between studies. Both studies included patients with a mean age of ~60 years of age, and a similar proportion of male patients. Mean BMIs in both studies fall within the "obese" category, whilst mean systolic BP is also elevated (~130) in both studies.

In the REDUCE-IT trial, a larger proportion of patients suffer from diabetes, hypertension, a history of CHF, or CKD stage IV-V, though CKD stage III incidence is larger in Steen *et al*.

A larger proportion of patients in the REDUCE-IT trial were treated with a low or medium intensity statin, ACE inhibitor or ARB. However, the proportion of patients treated with a high-intensity statin was similar between both studies.

	REDUCE-IT (N=2,394)	**Steen *et al.* (N=92,086)**
Demographic characteristics		
Age (years), Mean	[redacted]	69.7
Male, %	[redacted]	50.3
BMI (kg/m^2), Mean	[redacted]	30.1
Systolic BP, Mean	[redacted]	134.3
Disease-relevant baseline characteristics		
Recent ACS, %	[redacted]	N/A
Other CHD, %	[redacted]	N/A
Ischaemic stroke/TIA, %	[redacted]	N/A
PAD, %	[redacted]	N/A
DM, %	[redacted]	76.3
Hypertension, %	[redacted]	66.0
History of CHF, %	[redacted]	2.4
CKD, stage III, %	[redacted]	38.2
CKD, stage IV-V, %	[redacted]	0.3
Statin Intensity		

Key issue	Does this response contain new evidence, data or analyses ?	Response

Low-intensity statin, %	[redacted]	5.0
Medium-intensity statin, %	[redacted]	40.4
High-intensity statin, %	[redacted]	17.0
Medications taken at baseline		
Anti-Platelet, %	[redacted]	N/A
ACE or ARB, %	[redacted]	61.1
Beta Blockers, %	[redacted]	N/A

Secondary prevention population

In the secondary prevention population, the BMI and systolic BP were similar between studies, though the mean age was higher in Steen *et al* and the percentage of male patients was higher in REDUCE-IT.

In the REDUCE-IT trial, a larger proportion of patients had recent ACS, other CHD, diabetes, hypertension, or a history of CHF. However, ischaemic stroke/TIA and PAD were slightly more common in Steen *et al*. CKD incidence was similar in both studies.

The proportion of patients treated with a low or high intensity statin was very similar between studies, though a larger proportion of patients were treated with a medium intensity statin, anti-platelet, ACE inhibitor, ARB, or beta-blocker in the REDUCE-IT trial.

Key issue	Does this response contain new evidence, data or analyses ?	Response

	REDUCE-IT (N=5,785)	Steen *et al.* (N=91,497)
Demographic characteristics		
Age (years), Mean	[redacted]	72.6
Male, %	[redacted]	60.7
BMI (kg/m^2), Mean	[redacted]	28.3
Systolic BP, Mean	[redacted]	132.1
Disease-relevant baseline characteristics		
Recent ACS, %	[redacted]	3.4
Other CHD, %	[redacted]	66.0
Ischaemic stroke/TIA, %	[redacted]	28.6
PAD, %	[redacted]	21.7
DM, %	[redacted]	29.4
Hypertension, %	[redacted]	61.5
History of CHF, %	[redacted]	9.1
CKD, stage III, %	[redacted]	23.5
CKD, stage IV-V, %	[redacted]	0.2
Statin Intensity		
Low-intensity statin, %	[redacted]	5.6
Medium-intensity statin, %	[redacted]	42.1
High-intensity statin, %	[redacted]	31.4

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<tr><th>Key issue</th><th>Does this response contain new evidence, data or analyses ?</th><th>Response</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><th colspan="3">Medications taken at baseline</th></tr>
<tr><td>Anti-Platelet, %</td><td>[redacted]</td><td>18.5</td></tr>
<tr><td>ACE or ARB, %</td><td>[redacted]</td><td>61.7</td></tr>
<tr><td>Beta Blockers, %</td><td>[redacted]</td><td>48.7</td></tr>
</table>
</td></tr>
<tr><td>Key issue 5: Model structure – partitioned survival analysis (partSA)</td><td>YES</td><td>A state-transition model in TreeAge, developed by the [redacted], has been provided to validate the outcomes of the company's partSA approach. The state-transition model and accompanying manuscript, submitted for publication, have been uploaded as new evidence to be used strictly for validation purposes and must be treated confidentially. The state-transition model is not intended to replace the company's original partSA model.

The objective of the state-transition model was to estimate the cost-effectiveness of icosapent ethyl compared with standard of care, using patient-level data from REDUCE-IT for the in-trial period, and using a microsimulation model and data from published literature for the lifetime analysis. The original model used a US healthcare sector perspective and was then adapted to the UK NHS setting (using the same costs, utilities and background mortality) by the model developer so that a comparison of the outcomes could be made with the partSA model submitted by the company. The state-transition model uses a 6-month cycle length.</td></tr>
</table>

Key issue	Does this response contain new evidence, data or analyses ?	Response
		  It is important to note that some events were disregarded in this analysis when multiple events occurred within three days, since only the costliest event was included. The table below highlights the proportions of each type of event disregarded throughout the state-transition model analysis at various timepoints:

Key issue	Does this response contain new evidence, data or analyses ?	Response

	1 year		5 years		10 years		20 years		30 years	
	Icosapent ethyl	BSC	Icosapent ethyl	BSC	Icosapent ethyl	BSC	Icosapent ethyl	BSC	Icosapent ethyl	BSC
Total (%)	[redacted]									
CV Death (%)	[redacted]									
MI (%)	[redacted]									
Stroke (%)	[redacted]									
Unstable Angina (%)	[redacted]									
Revascularization (%)	[redacted]									

A direct comparison of the clinical outcomes from the state-transition and partSA models was conducted. The table below shows the proportion of patients for each of the following: experiencing a first event, experiencing a second event, experiencing a third plus event, patients discontinuing icosapent ethyl, patients alive and patients who are event free.

	1 year		5 years		10 years		20 years		30 years	
	Icosapent ethyl	BSC	Icosapent ethyl	BSC	Icosapent ethyl	BSC	Icosapent ethyl	BSC	Icosapent ethyl	BSC
First event: Total										

Key issue	Does this response contain new evidence, data or analyses ?	Response									
		State-transition model	[redacted]								
		PartSA model – old base case	[redacted]								
		PartSA with HR – new preferred base case	[redacted]								
		Bhatt *et al.* 2019	-	-	17.2%	22.0%	-	-	-	-	-
		Second event: Total									
		State-transition model	[redacted]								
		PartSA model – old base case	[redacted]								
		PartSA with HR – new preferred base case	[redacted]								
		Bhatt *et al.* 2019	-	-	5.8%	9.2%	-	-	-	-	-
		Third & plus event: Total									
		State-transition model	[redacted]								
		PartSA model – old base case	[redacted]								
		PartSA with HR – new preferred base case	[redacted]								
		Bhatt *et al.* 2019	-	-	1.8%	3.5%	-	-	-	-	-
		Discontinuing icosapent ethyl									
		State-transition model	[redacted]								

Key issue	Does this response contain new evidence, data or analyses ?	Response

PartSA model – old base case	[redacted]										
PartSA with HR – new preferred base case	[redacted]										
Patients alive											
State-transition model	[redacted]										
PartSA model – old base case	[redacted]										
PartSA with HR – new preferred base case	[redacted]										
Event free											
State-transition model	[redacted]										
PartSA model – old base case	[redacted]										
PartSA with HR – new preferred base case	[redacted]										

As mentioned, the state-transition model disregarded some events whereas the partSA model submitted by the company included all the events observed throughout the REDUCE-IT trial. As a result, there are differences observed between the proportions of patients in the table above and these differences get larger as the time horizon increases. This is expected because the number of events patients experience during the in-trial period directly informs the long-term extrapolations used in both models, therefore any differences in the number of events in the first five years will lead to larger incremental differences in the extrapolations as the time horizon

Key issue	Does this response contain new evidence, data or analyses ?	Response

increases. However, although some events were missed in the state-transition model, it is important to note that the general trend observed in the proportions is the same across both models. This can be further ratified by looking at the ICERs of both models:

	Population	Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
State-transition model	ITT	Icosapent ethyl	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PartSA model – new preferred base case		Icosapent ethyl	20,276	10.931	7.995	10,630	0.377	0.468	22,709
		BSC	9,647	10.554	7.527	-	-	-	-
State-transition model	Primary prevention	Icosapent ethyl	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PartSA model – new preferred base case		Icosapent ethyl	17,521	11.240	8.174	11,228	0.117	0.168	66,952
		BSC	6,293	11.123	8.006	-	-	-	-
State-transition model	Secondary prevention	Icosapent ethyl	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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<tr><th>Key issue</th><th>Does this response contain new evidence, data or analyses ?</th><th>Response</th></tr>
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<tr><td></td><td></td><td>BSC</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td rowspan="3">PartSA model – new preferred base case</td><td rowspan="3"></td><td>Icosapent ethyl</td><td>21,584</td><td>10.763</td><td>7.876</td><td>10,680</td><td>0.434</td><td>0.535</td><td>19,981</td></tr>
<tr><td>BSC</td><td>10,904</td><td>10.329</td><td>7.341</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
</table>
A similar trend of results across populations and technologies is observed in the state-transition model and the partSA model. The total LYG, total QALYs and total costs are similar in the state-transition model and partSA model, however, there are some differences between the ICERs. This is expected, as the state-transition model disregards some events whereas the partSA model includes all the events observed throughout the REDUCE-IT trial. Despite the minor discrepancies, the results show that the partSA model is appropriate, as the observed results are comparable to results produced using a different modelling approach.
</td></tr>
<tr><td>Key issue 6: Use of reconstituted data</td><td>YES</td><td>In a scenario analysis on the company’s old base case, the parametric survival curves were re-estimated using the complete Kaplan-Meier data resulting in the ICER increasing from £29,316 to £29,854. Results are presented in the summary table below.
Company’s new preferred base-case, presented below, includes the complete Kaplan-Meier data.</td></tr>
<tr><td>Key issue 7: Limited evidence available for (long-term)</td><td>YES</td><td>As provided previously, scenario analyses for all the distributions considered for the time to event curves were tested statistically. There was little impact on the ICER when the choice of parametric survival model was varied. Due to a lack of long-term observational data and UK clinical experience, the choice of distribution cannot be informed by criteria other than the statistical fit. However, to further test the validity of the long-term</td></tr>
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<table>
<tr><th>Key issue</th><th>Does this response contain new evidence, data or analyses ?</th><th>Response</th></tr>
<tr><td>validation of survival curves</td><td></td><td>extrapolations of survival curves for icosapent ethyl, the company has taken an alternative approach of using proportional hazards, sourced from Bhatt et al. (2019), to estimate the long-term curves. The placebo curve for all distributions was ratified by UK clinical experts. The company has then used the extrapolation of the placebo curve and applied a HR to derive the icosapent ethyl curve. The HRs for the ITT population as well as for the CV1 and CV2 subgroups are presented below. Results of this scenario applied to the old base case are presented in the summary table below for the ITT, CV1 and CV2 populations. As the proportional hazard assumption holds (see response to key issue 8), the hazard ratios approach is used in the new preferred company’s base case.

<table>
<tr><td></td><td colspan="3">Icosapent ethyl versus placebo – HR or RR* (95% CI)</td><td>Source</td></tr>
<tr><td></td><td>1st event</td><td>2nd event</td><td>3+ event</td><td></td></tr>
<tr><td>ITT</td><td>0.75 (0.68, 0.83)</td><td>0.68 (0.60, 0.78)</td><td>0.69 (0.59, 0.82) for 3rd event</td><td>Bhatt et al. 2019</td></tr>
<tr><td>CV1</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>Amarin</td></tr>
<tr><td>CV2</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>Amarin</td></tr>
<tr><td colspan="5">* Presented as a relative risk</td></tr>
</table>
</td></tr>
<tr><td>Key issue 8: Use of stratified parametric models, methodologica</td><td>YES</td><td>Following issues raised by the ERG in their report, the company have re-evaluated the choice of survival models using the selection process algorithm as mentioned in NICE DSU TSD 14.

To test for the acceptability of using proportional hazards, the log cumulative hazard plot, Schoenfeld residual plot and Cox-Snell residual plots were evaluated (Appendix A below; Key issue 8). The log-cumulative hazard plot lines for icosapent ethyl and placebo remain parallel for the majority of the time period in all three events. However, the plot lines do cross towards the start in events 1 and 2 and towards the end of event 3+. This</td></tr>
</table>

Key issue	Does this response contain new evidence, data or analyses ?	Response
I guidance not followed		could be due to the treatment not showing full effect at the beginning of the time period and few patients remaining at risk towards the end of the time period. The Schoenfeld residual plot shows a linear curve with a zero slope for events 1 and 2 and shows a p-value >0.05 for all events, giving evidence that the proportional hazards assumption holds. The plot of the Cox-Snell residuals against the estimated cumulative hazard rate shows a relatively straight line with zero intercept and unit slope for events 1 and 2. Therefore, it can be assumed that the proportional hazards assumption holds between icosapent ethyl and placebo. The results of using proportional hazards are presented in the summary of key changes, under Key issue 7.
Key issue 9: Long-term extrapolation, assumption of no treatment waning	NO	No treatment waning effect was applied in the base case analysis. In response to the ERG clarification questions, two scenario analyses were provided with arbitrary waning assumptions. The company acknowledges that there are no long-term studies to inform the long-term efficacy of icosapent ethyl. However, the Kaplan-Meier event curves for the primary efficacy 5-point MACE composite endpoint (figure 5 in the company submission), shows that the treatment effect increases over time before stabilising. This treatment effect is further demonstrated in a landmark analysis for which results have been presented in the new evidence form. [redacted]

Key issue	Does this response contain new evidence, data or analyses ?	Response
		In addition, despite the absence of long-term studies to inform whether or not the treatment effect is maintained, no waning was applied in the appraisals of alirocumab TA393, evolucumab TA394 and inclisiran TA733, which are in a similar disease area (hypercholesterolaemia and mixed dyslipidaemia). The company therefore believes it is reasonable to assume that the treatment benefit of icosapent ethyl would be maintained beyond the trial period, and therefore no treatment waning should be applied in the base-case.
Key issue 10: Use of treatment-dependent non-CV related death hazard ratios	YES	The method that the ERG used to calculate the treatment-independent non-CV related death hazard ratios does not account for the differences between the ITT, CV1 and CV2 subpopulations. The ERG methodology took an average of the treatment dependent hazard ratios per health state and then applied this to both treatments making the hazard ratios treatment independent. However, these averages were only calculated for the ITT population and more specifically, when the split of the subgroups were 71.7% (CV1) and 28.3% (CV2). They did not account for the proportion of individuals that were CV1 vs. CV2. A patient in the CV1 subgroup cannot be considered comparable to an individual in the CV2 subgroup so it is not appropriate to apply a single hazard ratio per health state across the ITT, CV1 and CV2 subgroups. When comparing the type of individual likely to be observed in the two subgroups, a CV1 individual is required to have experienced a prior CV related event before entering the model at baseline, therefore a CV1 individual within the model, in the post-first event state, in fact has experienced at least two prior events. Additionally, they are not required to be diabetic. In comparison, an individual in the CV2 group in the post-first event state within the model, is only required to have experienced one event in their lifetime but will be diabetic. Both diabetes and number of prior events have been identified as non-CV related mortality modifiers so cannot be ignored.

Key issue	Does this response contain new evidence, data or analyses ?	Response
		We believe a more appropriate methodology to calculate the treatment-independent non-CV related death hazard ratios would be to use our current methodology, however, instead of using treatment independent distributions of events to inform the type of event that occurred, use the distribution of events that occurred across both treatment arms. The appropriate distributions are provided in the table below.

	Icosapent ethyl	Placebo	Total
First event			
CV death	[redacted]	[redacted]	[redacted]
MI	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]
Unstable angina	[redacted]	[redacted]	[redacted]
Revascularisation	[redacted]	[redacted]	[redacted]
Total	705	901	1606
Second event			
CV death	[redacted]	[redacted]	[redacted]
MI	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]
Unstable angina	[redacted]	[redacted]	[redacted]
Revascularisation	[redacted]	[redacted]	[redacted]
Total	236	376	612
Third plus event			
CV death	[redacted]	[redacted]	[redacted]
MI	[redacted]	[redacted]	[redacted]

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<tr><th>Key issue</th><th>Does this response contain new evidence, data or analyses ?</th><th>Response</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td>Stroke</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Unstable angina</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Revascularisation</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Total</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
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To assist with the correction of the ERGs preferred assumption of using treatment independent non-CV-related mortality hazard ratios, we have provided a scenario with our suggestions as described above implemented correcting the methodology used in their report. This scenario led to an ICER of £31,278 when implemented with the original company base case assumptions.
However, it is the company’s position that using dependent hazard ratios is the most approach to use due to patients experiencing a different distribution of events per treatment group in the REDUCE-IT trial which were non-CV death related modifiers.</td></tr>
<tr><td>Key issue 11: Health-related quality of life sensitive to choice of utility source</td><td>NO</td><td>Health-related quality of life utility values were based on multipliers sourced from NICE CG181 as they are considered appropriate by NICE, and also appropriately reflect the target population of icosapent ethyl.

The model is sensitive to the choice of utility values used as each of the events comprising the 5-point MACE is associated with a corresponding utility value based on the multipliers from NICE CG181. Therefore patients experiencing multiple events in the model will subsequently experience variations in their quality of life following each type of event. This is further impacted by the severity of the type of events experienced too.</td></tr>
</table>

Key issue	Does this response contain new evidence, data or analyses ?	Response
		This variation in quality of life following multiple events therefore makes the model very sensitive to the choice of utility source used. The disutilities in the model were sourced from multiple references in order to accurately capture the loss of quality of life experienced by patients following an adverse event. The disutilities for peripheral oedema and constipation were applied for seven days. The disutility for serious bleeding was applied for one month. The duration of each of these adverse events was informed by UK clinical expert input.
Key issue 12: Event costs not adjusted for time since previous event	YES	To address concerns surrounding the duration of acute and post-event costs, a scenario that estimates costs adopting the same approach used for estimating utilities within the post-event states is provided in the summary of key changes, under key issue 12. The acute event cost has been adjusted to reflect the cost associated with a single day. For example, Danese 2016 estimates the acute cost of a myocardial infarction to be £4,275.41 within the first six months, so we have inflated and adjusted this to a cost per day calculated as £4,678.22 / (365.25/2). In the scenario, the cost is applied for the first 60 days post-event (one day of cost is applied in the event states and then the remaining cost is applied in the post-event states) and then a long-term cost is applied beyond 60 days.
Key issue 13: The distribution to extrapolate time to	NO	As previously stated in the both the company submission and within the ERG clarification response, the exponential distribution for the TTD curve was chosen based on statistical fit in the absence of clinical experience with icosapent ethyl.

Key issue	Does this response contain new evidence, data or analyses ?	Response
discontinuation		There is no evidence to suggest that any of the alternative distributions should be preferred and implemented. However, the range of ICER previously presented did not show any of the distributions to have a significant impact on the ICER, with all scenarios for the ITT company base-case in the range of £29,316 – £33,805.
Key issue 14: Inconsistent use of sources and calculation of event costs	YES	In an attempt to minimise the over estimation of costs associated with events caused by an overlap of costs in the acute/post-event costs, we have implemented the methodology suggested by the ERG to estimate the costs applied in the economic model. Acute event costs were estimated using the following steps 1) identified in the literature, 2) inflated to 2021 using the CPI, 3) removal of any general post-event daily cost beyond 60 days from the acute cost, 4) divided by 60 to get a daily cost. Please find a summary of the updated costs and the calculations associated with them in the Appendix A under key issue 14.
Key issue 15: Incomplete model validation and face validity check	YES	The two checklists requested by the ERG to assess the technical verification of the economic model, AdViSHE and TECH-VER, have been completed and the results are provided in Appendix A below. Following the ERG clarification questions, it was discovered that the one-way sensitivity analysis in the model was not appropriately capturing variation in some parameters. The model was adapted to provide a more granular OWSA by varying disaggregated model parameters, this is provided in Appendix A below. The AdViSHE and TECH-VER checklists were conducted using the updated model.

Summary of changes to the company's cost-effectiveness estimate(s)

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER
Key issue 6: Use of reconstituted data	Use of reconstituted data in which observations which took place after the point that only 10% of patients were remaining at risk were removed from the dataset.	The complete Kaplan-Meier curve is used.	This change increases the old base case ICER from £29,195* to £29,731.
Key issue 7: Limited evidence available for (long-term) validation of survival curves	Independent Kaplan-Meier curves from the REDUCE-IT trial were used for the placebo and icosapent ethyl arms and extrapolated beyond the trial period. Statistical fit was used to inform the choice of distribution for the long-term extrapolations.	Hazard ratios, sourced from Bhatt *et al.* (2019), were used to estimate the long-term curves. The extrapolation of the Kaplan-Meier placebo curve was ratified by UK clinical experts. Hazard ratios were then applied to the placebo curve to derive the icosapent ethyl curve.	This change decreases the old base case ICER from £29,195* to £21,582.
Key issue 12: Event costs not adjusted for time since previous event	The event costs were not adjusted to account for the length of time since a previous CV event was experienced within the CE model. All acute event costs were applied in a single day.	The same methodology used in the utility calculations to estimate the proportion of individuals in the post-event states that have experienced an event in the last 60 days is implemented. Therefore, we have applied a daily cost for the acute stage to be applied for 60 days post-event rather than a one-off acute event cost.	This change increased the old base case ICER from £29,195* to £31,728.

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER
Key issue 14: Inconsistent use of sources and calculation of event costs	Event cost calculations were inconsistent.	The methodology suggested by the ERG has been implemented to remove costs that were being double counted in both the post-event and acute event stages.	This change decreases the old base case ICER from £29,195* to £29,071.
Key issue 15: Incomplete model validation and face validity check	Error in formula	During the model validation, it was identified that there was an error due to an inconsistent formula from row 375 in the icosapent Ethyl Markov trace sheet. This was corrected in the model.	This change decreases the old base case ICER from £29,316 to £29,195.
Company's preferred base case following technical engagement	Incremental QALYs: ITT: 0.468 CV1: 0.535 CV2: 0.168	Incremental costs: ITT: £10,630 CV1: £10,680 CV2: £11,228	The company base-case ICER resulting from combining the changes described above decreases from £29,316 to £22,709. ITT: £22,709 CV1: £19,981 CV2: £66,952

*Old company base-case ICER with the correction described in issue 15.

APPENDIX A

Key issue 8: Use of stratified parametric models, methodological guidance not followed

Log cumulative hazard plots for the ITT population

Schoenfeld residual plots for the ITT population

Cox-Snell plots for the ITT population

Key issue 14: Inconsistent use of sources and calculation of event costs

Event	Company base-case	Revised base-case	Comments
Nonfatal MI			
Acute period	£4,678.22	£66.23	£4,275.41 (Source Danese 2016 using 2014 NHS reference costs) £4,678.22 (Once inflated to 2021 using CPI) Cost per day in acute phase = (£4,678.22 -(£1048.66 / (365.25*0.5))*((365.25*0.5)-60))/60 = £66.23 Assumption – daily cost applied for 60 days following an event

Event	Company base-case	Revised base-case	Comments
Post event	£2.87	£5.74	£922.43 (Source Danese 2016 using 2014 NHS reference costs) £1,048.66 (Once inflated to 2021 using CPI) £1,048.66*((365.25*0.5)) = £5.74
Nonfatal Stroke			
Acute period	£3,978.91	£54.64	£3,512.25 (Source Danese 2016 using 2014 NHS reference costs) £3,978.91 (Once inflated to 2021 using CPI) Cost per day in acute phase = (£3,978.91 -(£1,042.87 /(365.25*0.5))*((365.25*0.5)-60))/60 = £54.64 Assumption – daily cost applied for 60 days following an event
Post event	£2.86	£5.71	£972.62 (Source Danese 2016 using 2014 NHS reference costs) £1,042.87 (Once inflated to 2021 using CPI) £1,042.87*((365.25*0.5)) = £5.71
Coronary revascularisation			
Acute period	£6,147.04	£76.03	Daily acute cost of CR PCI acute cost*0.8+CABG acute cost*0.2 = (£47.03*0.8) + (£192.04*0.2) = £76.03 Assumption: 80% of individuals will receive PCI and remain 20% will receive CABG informed by UK clinical expert opinion
Percutaneous coronary intervention (PCI)	£4,406.97	£47.03	Source average of EY40A, EY40B, EY40C, EY40D, EY41A, EY41B, EY41C, EY41D, EY44A, EY44B, EY44C, EY44D NHS reference costs 2018/19 £4,406.97 (Once inflated to 2021 using CPI)

Event	Company base-case	Revised base-case	Comments
			Cost per day in acute phase = (£4,406.97-(£1,896.67/(365.25))*((365.25)-60))/60
Coronary artery bypass graft surgery (CABG)	£13,107.34	£192.04	Source average of ED26A, ED26B, ED26C, ED27A, ED27B, ED27C, ED28A, ED28B, ED28C NHS reference costs 2018/19 £13,107.34 (Once inflated to 2021 using CPI) Cost per day in acute phase = (£13,107.34 - (£1,896.67/(365.25))*((365.25)-60))/60
Post event	£5.19	£5.19	£1,896.67 (Once inflated to 2021 using CPI) Cost per day in acute phase = £1,896.67/365.25 = £5.19
Unstable angina			
Acute period	£2,438.43	£36.07	£2,179.24 (Source Danese 2016 using 2014 NHS reference costs) £2,438.43 (Once inflated to 2021 using CPI) Cost per day in acute phase = (£2,438.43 - (£408.13/(365.25*0.5))*((365.25*0.5)-60))/60 = £36.07 Assumption – daily cost applied for 60 days following an event
Post event	£1.12	£2.23	£328.45 (Source Danese 2016 using 2014 NHS reference costs) £408.13 (Once inflated to 2021 using CPI) £408.13*((365.25*0.5)) = £5.71
Cardiovascular death			
Total	£3,719.02	£3,719.02	£3,400.25 (Source Danese 2016 using 2014 NHS reference costs) £3,719.02 (Once inflated to 2021 using CPI)
Fatal MI - hospitalisation without procedure	£3,719.02	-	

Event	Company base-case	Revised base-case	Comments
Fatal stroke - hospitalisation without procedure	£3,719.02	-	Assumption CV death equal to hospitalisation cost

Key issue 15: Incomplete model validation and face validity check

Validation assessment using AdViSHE: A Validation-Assessment Tool of Health-Economic Models for Decision Makers and Model Users

Part A: Validation of the conceptual model

The conceptual model was presented in section B3.2 of the company's submission.

1. **A1/ Face validity testing (conceptual model): Have experts been asked to judge the appropriateness of the conceptual model? If yes, please provide information on the following aspects: -Who are these experts?-What is your justification for considering them experts?-To what extent do they agree that the conceptual model is appropriate? If no, please indicate why not.**

The conceptual model along with the model assumptions and inputs were validated by two UK clinical experts. The experts used to derive the expert opinion to support assumptions and decisions made with regard to the economic model were: [redacted]. They both qualify as clinical experts due to their expertise within this disease area. 1:1 interviews were conducted with each clinical expert with interview summary/notes taken for each interview and responses combined. The expert responses were previously provided to NICE ("Validation of assumptions in the UK cost-effectiveness model_v1.0_05_July_2021 – responses").

2. **A2/ Cross validity testing (conceptual model): Has this model been compared to other conceptual models found in the literature or clinical textbooks? If yes, please indicate where this comparison is reported. If no, please indicate why not.**

An internal review of the economic model submitted to CADTH was undertaken. It was considered that the Canadian model did not capture the full value of icosapent ethyl as it did not include all the events occurring in the REDUCE-IT trial. Hence, an alternative model was considered to capture the full benefit of icosapent ethyl.

The economic model from the [redacted] came to our attention too late in the technology appraisal process to be considered for submission. As an alternative, a comparison of the outcomes between the company and [redacted] models was undertaken in response to Key issue 5.

Part B: Input data validation

1. **B1/ Face validity testing (input data): Have experts been asked to judge the appropriateness of the input data? If yes, please provide information on the following aspects: -Who are these experts?-What is your justification for considering them experts?-To what extent do they agree that appropriate data have been used? If no, please indicate why not.**

As mentioned in section C17 of the response to the ERG questions, the model assumptions and inputs were validated by two UK clinical experts. The experts used to derive the expert opinion to support assumptions and decisions made with regard to the economic model were: [redacted]. They both qualify as clinical experts due to their expertise within this disease area. 1:1 interviews were conducted with each clinical expert with interview summary/notes taken for each interview and responses combined. The expert responses were previously provided to NICE ("Validation of assumptions in the UK cost-effectiveness model_v1.0_05_July_2021 – responses").

2. **B2/ Model fit testing: When input parameters are based on regression models, have statistical tests been performed? If yes, please indicate where the description, the justification and the outcomes of these tests are reported. If no, please indicate why not.**

As discussed in document B of the original company submission, in order to extrapolate the clinical data beyond the trial follow-up period, a series of parametric survival models (as published in NICE DSU Technical Support Document 14) were fitted to the reconstituted first, second and third + event IPD using the Flexsurv for R package for time-to-event data. To account for the range in follow-up data among individuals, data was extrapolated using IPD up until the point that 10% of patients at risk were left in the trial. A wide range of parametric survival models were fitted to the reconstituted data to match the placebo arm. To determine the most appropriate survival functions, model fit was assessed as follows:

- Graphic comparison of the predicted curve from a given parametric function to the Kaplan-Meier curve from the patient data
- Comparison of Akaike information criterion (AIC) statistics and Bayesian information criterion (BIC) statistics
- UK clinical expert opinion

As discussed in section C14 of the response to the ERG clarification questions, in the absence of clinical practice experience with icosapent ethyl, the distribution for the event and TTD curves were selected based on the best fitting curves using the AIC, BIC and visual inspection.

Part C: Validation of the computerized model

1. **C1/External review: Has the computerized model been examined by modelling experts? If yes, please provide information on the following aspects:-Who are these experts?-What is your justification for considering them experts?-Can these experts be qualified as independent?-Please indicate where the results of this review are reported, including a discussion of any unresolved issues. If no, please indicate why not.**

The model has been validated by an independent internal modelling expert, who was not working on the project. This individual was regarded as an expert as they have developed and reviewed a number of economic models before. The results of this review have been provided to NICE previously: “CEM QC_Final version_18Aug21”.

In addition, as part of the engagement with the [redacted] to assess if and how their model could be used in this technology appraisal, the company’s model was shared with the [redacted] for review along with the UK costs and utilities used in the company’s model. Modelling experts from the [redacted] included [redacted], who both co-developed the [redacted] model alongside a number of experts (see authorship for the draft manuscript). The difference in modelling approach was acknowledged however, no fundamental issues were raised.

2. **C2/Extreme value testing: Has the model been run for specific, extreme sets of parameter values in order to detect any coding errors? If yes, please indicate where these tests and their outcomes are reported. If no, please indicate why not.**

As discussed in question C1, the model was validated by an internal health economics expert. As part of this validation, it was found that the total costs and QALYs increased/decreased reasonably in accordance with longer/shorter durations up to the 36 years-time horizon. Tests were carried out and the model was validated with regard to: scope, ease of use, inputs, model accuracy, survival analyses, sensitivity analyses, VBA code, common errors, Markov traces, and results. Extreme sets of parameter values were specifically tested.

3. **C3/Testing of traces: Have patients been tracked through the model to determine whether its logic is correct? If yes, please indicate where these tests and their outcomes are reported. If no, please indicate why not.**

As stated in Appendix J of the original company submission, patients were tracked through the model, and the outcome of this was logical because it is expected that the number of patients with no events will decrease over time, while the number of patients in the “dead” state will increase over time. The number of patients in each state over time are as follows:

Figure 1. Icosapent ethyl results: number of patients in each state over time

Figure 2. Placebo results: number of patients in each state over time

4. **C4/Unit testing: Have individual sub-modules of the computerized model been tested? If yes, please provide information on the following aspects: -Was a protocol that describes the tests, criteria, and acceptance norms defined beforehand? -Please indicate where these tests and their outcomes are reported. If no, please indicate why not.**

As discussed in question C1 above, the model has been validated by an independent internal modelling expert, who was not working on the project. The tests conducted and the outcomes of this review have been provided to NICE previously: "CEM QC_Final version_18Aug21".

Part D: Operational validation

1. **D1/Face validity testing (model outcomes): Have experts been asked to judge the appropriateness of the model outcomes? If yes, please provide information on the following aspects: -Who are these experts? -What is your justification for considering them experts? -To what extent did they conclude that the model outcomes are reasonable? If no, please indicate why not.**

The company's model was shared with the [redacted] for review along with the UK costs and utilities used in the company's model. Modelling experts from the [redacted] included [redacted], who both co-developed the [redacted]

model alongside a number of experts (see authorship for the draft manuscript). They indicated that the modelled outcomes were in the same ballpark. The overall trend still translates into similar ICERs/QALYs/costs, indicating that the partSA approach produces results as expected (even if we were to use a different modelling approach) i.e., both models still show that patients taking icosapent ethyl experience fewer events than those on BSC, and that this translates into better LYG and QALYs when comparing icosapent ethyl to BSC.

2. **D2/Cross validation testing (model outcomes): Have the model outcomes been compared to the outcomes of other models that address similar problems? If yes, please provide information on the following aspects: -Are these comparisons based on published outcomes only, or did you have access to the alternative model? -Can the differences in outcomes between your model and other models be explained? -Please indicate where this comparison is reported, including a discussion of the comparability with your model. If no, please indicate why not.**

As discussed in the response to ERG clarification questions, our model is a *de novo* health state cohort model. After considering previous appraisals and the CADTH's submission for icosapent ethyl, we concluded that they all failed to model one key aspect, multiple subsequent events, which we believe to be pivotal in demonstrating the full value of icosapent ethyl in terms of the impact of reducing CV events on QoL and costs. Therefore, other submissions were not suitable to compare against and could not be used to validate our model.

Outcomes from the company model were validated against the outcomes from the state transition model and the comparison has been provided in response to Key issue 5. The company did not have access to the economic model and did not review it. This guarantees the independence of the [redacted] model and the validity of the comparison between the two different models.

3. **D3/Validation against outcomes using alternative input data: Have the model outcomes been compared to the outcomes obtained when using alternative input data? If yes, please indicate where these tests and their outcomes are reported. If no, please indicate why not.**

As discussed in the ERG clarification questions, sensitivity analyses for using alternative literature sources for utility values (ODYSSEY [TA 393]) were conducted to examine the impact on the ICER. Sensitivity analyses exploring alternative survival models to estimate time to event probabilities were also run (Table 16–Table 24 of the response to ERG clarification questions).

No alternative clinical input data, other than the REDUCE-IT trial, was retrieved in the literature.

4. **D4/Validation against empirical data: Have the model outcomes been compared to empirical data? If yes, please provide information on the following aspects: -Are these comparisons based on summary statistics, or patient-level datasets? -Have**

you been able to explain any difference between the model outcomes and empirical data?-Please indicate where this comparison is reported. If no, please indicate why not.

a. D4.A/Comparison against the data sources on which the model is based (dependent validation).

Results of the partSA model are in line with the Bhatt *et al.* 2019 (JACC) publication, as shown in Key issue 5: Model structure – partitioned survival analysis.

	Source at 4.9 years follow-up	First event	Second event	Third event
Icosapent ethyl	Bhatt *et al.* 2019	17.2%	5.8%	1.8%
	CE model	[redacted]	[redacted]	[redacted]
BSC	Bhatt *et al.* 2019	22.0%	9.2%	3.5%
	CE model	[redacted]	[redacted]	[redacted]

b. D4.B/Comparison against a data source that was not used to build the model (independent validation).

No clinical data other than that from REDUCE-IT were available to inform our model, so it is not possible to conduct this validation.

Part E: Other validation techniques

1. **E1/Other validation techniques: Have any other validation techniques been performed? If yes, indicate where the application and outcomes are reported, or else provide a short summary here.**

Not applicable.

Validation assessment using TECH-VER

Verification Stages 1-4: Black-box tests

Test description (please also document how the test is conducted)	**Expected result of the test**	**Company result of the test**
Pre-analysis calculations		

Test description (please also document how the test is conducted)	Expected result of the test	Company result of the test
Does the technology (drug/device, etc.) acquisition cost increase with higher prices?	Yes	Yes
Does the drug acquisition cost increase for higher weight or body surface area?	Yes	Not applicable
Does the probability of an event, derived from an OR/RR/HR and baseline probability, increase with higher OR/RR/HR?	Yes	Yes
In a partitioned survival model, does the progression-free survival curve or the time on treatment curve cross the overall survival curve?	No	Not applicable
If survival parametric distributions are used in the extrapolations or time-to-event calculations, can the formulae used for the Weibull (generalized gamma) distribution generate the values obtained from the exponential (Weibull or Gamma) distribution(s) after replacing/transforming some of the parameters?	Yes	Yes, when the shape of the Weibull distribution was set to 1 and the rate of the exponential was set to '1/scale of Weibull' the curves were identical.
Is the HR calculated from Cox proportional hazards model applied on top of the parametric distribution extrapolation found from the survival regression?	No, it is better if the treatment effect that is applied to the extrapolation comes from the same survival regression in which the extrapolation parameters are estimated	No
For the treatment effect inputs, if the model uses outputs from WINBUGS, are the OR, HR, and RR values all within plausible ranges? (Should all be non-negative and the average of these WINBUGS outputs should give the mean treatment effect)	Yes	Not applicable
Event-state calculations		
Calculate the sum of the number of patients at each health state	Should add up to the cohort size	Markov trace sheets contain a 'Check' column. Sum of the health state populations = starting population
Check if all probabilities and number of patients in a state are greater than or equal to 0	Yes	Yes
Check if all probabilities are smaller than or equal to 1	Yes	Yes
Compare the number of dead (or any absorbing state) patients in a period with the number of dead (or any absorbing state) patients in the previous periods?	Should be larger	Number of dead patients increases each period
In case of lifetime horizon, check if all patients are dead at the end of the time horizon	Yes	Yes
Discrete event simulation specific: Sample one of the 'time to event' types used in the simulation from the specified distribution. Plot the samples and compare the mean and the variance from the sample	Sample mean and variance, and the simulation outputs, should reflect the distribution it is sampled from	Not applicable
Set all utilities to 1	The QALYs accumulated at a given time would be the same as the life-years accumulated at that time	Life-years are equal to QALYs
Set all utilities to 0	No utilities will be accumulated in the model	QALYs are equal to 0

Test description (please also document how the test is conducted)	Expected result of the test	Company result of the test
Decrease all state utilities simultaneously (but keep event-based utility decrements constant)	Lower utilities will be accumulated each time	QALYs decrease
Set all costs to 0	No costs will be accumulated in the model at any time	No costs accumulated in the model
Put mortality rates to 0	Patients never die	No patients die
Put mortality rate at extremely high	Patients die in the first few cycles	Patients die in the early cycles
Set the effectiveness-, utility-, and safety-related model inputs for all treatment options equal	Same life-years and QALYs should be accumulated for all treatment at any time	Same life-years and QALYs are accumulated for all treatments at any time
In addition to the inputs above, set cost-related model inputs for all treatment options equal	Same costs, life-years, and QALYs should be accumulated for all treatment at any time	When the cost-related model inputs for treatment option were set to be equal an error was identified in the Markov trace (Icosapent Ethyl) sheet. The error was due to an inconsistent formula being used from row 375. After correction, the model showed to have the same costs, life-years, and QALYs accumulated for all treatments at any time.
Change around the effectiveness-, utility- and safety-related model inputs between two treatment options	Accumulated life-years and QALYs in the model at any time should also be reversed	Accumulated life-years and QALYs in the model are reversed
Check if the number of alive patients estimated at any cycle is in line with general population life-table statistics	At any given age, the percentage alive should be lower or equal in comparison with the general population estimate	Percentage of patients alive is lower than the general population estimate at any age
Check if the QALY estimate at any cycle is in line with general population utility estimates	At any given age, the utility assigned in the model should be lower or equal in comparison with the general population utility estimate	Lower
Set the inflation rate for the previous year higher	The costs (which are based on a reference from previous years) assigned at each time will be higher	Not applicable - No option to change the inflation rate in model
Calculate the sum of all ingoing and outgoing transition probabilities of a state in a given cycle	Difference of ingoing and outgoing probabilities at a cycle in a state times the cohort size will yield the change in the number of patients at that state in that cycle	Not applicable – no transition probabilities used in the model

Test description (please also document how the test is conducted)	Expected result of the test	Company result of the test
Calculate the number of patients entering and leaving a tunnel state throughout the time horizon	Numbers entering = numbers leaving	Not applicable
Check if the time conversions for probabilities were conducted correctly.	Yes	Not applicable
Decision tree specific: Calculate the sum of the expected probabilities of the terminal nodes	Should sum up to 1	Not applicable
Patient-level model specific: Check if common random numbers are maintained for sampling for the treatment arms	Yes	Not applicable
Patient-level model specific: Check if correlation in patient characteristics is taken into account when determining starting population	Yes	Not applicable
Increase the treatment acquisition cost	Costs accumulated at a given time will increase during the period when the treatment is administered	Validated
Population model specific: Set the mortality and incidence rates to 0	Prevalence should be constant in time	Validated
Result calculations		
Check the incremental life-years and QALYs gained results. Are they in line with the comparative clinical effectiveness evidence of the treatments involved?	If a treatment is more effective, it generally results in positive incremental LYs and QALYs in comparison with the less-effective treatments	Validated
Check the incremental cost results. Are they in line with the treatment costs?	If a treatment is more expensive, and if it does not have much effect on other costs, it generally results in positive incremental costs	Validated
Total life years greater than the total QALYs	Yes	Yes
Undiscounted results greater than the discounted results	Yes	Yes
Divide undiscounted total QALYs by undiscounted life years	This value should be within the outer ranges (maximum and minimum) of all the utility value inputs	Value within the ranges of all utility value inputs
Subgroup analysis results: How do the outcomes change if the characteristics of the baseline change?	Better outcomes for better baseline health conditions, and worse outcomes for worse health conditions, are expected	Primary prevention and secondary prevention subgroups were tested. Patients in the primary prevention subgroup had better baseline characteristics and better outcomes were observed
Could you generate all the results in the report from the model (including the uncertainty analysis results)?	Yes	Yes
Do the total life-years, QALYs, and costs decrease if a shorter time horizon is selected?	Yes	Yes

Test description (please also document how the test is conducted)	Expected result of the test	Company result of the test
Is the reporting and contextualization of the incremental results correct?	The use of terms such as 'dominant'/'dominated'/'extendedly dominated'/'cost effective'. etc.. should be in line with the results In the incremental analysis table involving multiple treatments, ICERs should be calculated against the next non-dominated treatment	Yes
Are the reported ICERs in the fully incremental analysis non-decreasing?	Yes	Yes
If disentangled results are presented, do they sum up to the total results (e.g. different cost types sum up to the total costs estimate)?	Yes	Yes
Check if half-cycle correction is implemented correctly (total life-years with half-cycle correction should be lower than without)	The half-cycle correction implementation should be error-free. Also check if it should be applied for all costs, for instance if a treatment is administered at the start of a cycle, half-cycle correction might be unnecessary	Half-cycle is implemented correctly although this has been removed in response to the ERG clarification questions.
Check the discounted value of costs/QALYs after 2 years	Discounted value = undiscounted/$(1 + r)^2$	Validated
Set discount rates to 0	The discounted and undiscounted results should be the same	Not applicable as undiscounted results are not presented
Set mortality rate to 0	The undiscounted total life-years per patient should be equal to the length of the time horizon	Undiscounted total life-years per patient are equal to the length of the time horizon when mortality rate is equal to 0
Put the consequence of adverse event/discontinuation to 0 (0 costs and 0 mortality/utility decrements)	The results would be the same as the results when the AE rate is set to 0	Validated
Divide total undiscounted treatment acquisition costs by the average duration on treatment	This should be similar to treatment-related unit acquisition costs	Validated
Set discount rates to a higher value	Total discounted results should decrease	Total results decrease
Set discount rates of costs/effects to an extremely high value	Total discounted results should be more or less the same as the discounted results accrued in the first cycles	Validated

Test description (please also document how the test is conducted)	Expected result of the test	Company result of the test
Put adverse event/discontinuation rates to 0 and then to an extremely high level	Less costs and higher QALYS/LYs when adverse event rates are 0, higher costs and lower QALYS/LYs when AE rates are extreme	Validated
Double the difference in efficacy and safety between the new intervention and comparator, and report the incremental results	Approximately twice the incremental effect results of the base case. If this is not the case, report and explain the underlying reason/mechanism	The incremental effect results are approximately twice of the base case.
Do the same for a scenario in which the difference in efficacy and safety is halved	Approximately halve of the incremental effect results of the base case. If this is not the case, report and explain the underlying reason/mechanism	The incremental effect results are approximately half of the base case.
Uncertainty analysis calculations		
Are all necessary parameters subject to uncertainty included in the OWSA?	Yes	Yes
Check if the OWSA includes any parameters associated with joint uncertainty (e.g. parts of a utility regression equation, survival curves with multiple parameters)	No	No, due to using independent parametric curves
Are the upper and lower bounds used in the one-way sensitivity analysis using confidence intervals based on the statistical distribution assumed for that parameter?	Yes	Yes
Are the resulting ICER, incremental costs/QALYs with upper and lower bound of a parameter plausible and in line with a priori expectations?	Yes	Yes
Check that all parameters used in the sensitivity analysis have appropriate associated distributions – upper and lower bounds should surround the deterministic value (i.e. upper bound ≥ mean ≥ lower bound)	Yes	Yes
Standard error and not standard deviation used in sampling	Yes	Yes, standard error was used where available, alternatively it assumed to be 20%
Lognormal/gamma distribution for HRs and costs/resource use	Yes	Yes lognormal/ gamma distribution used for HRs and costs/resource use except for compliance costs which used Beta
Beta for utilities and proportions/probabilities	Yes	Yes
Dirichlet for multinomial	Yes	Not applicable
Multivariate normal for correlated inputs (e.g. survival curve or regression parameters)	Yes	Yes
Normal for other variables as long as samples do not violate the requirement to remain positive when appropriate	Yes	Yes
Check PSA output mean costs, QALYs, and ICER compared with the deterministic results. Is there a large discrepancy?	No (in general)	No

Test description (please also document how the test is conducted)	Expected result of the test	Company result of the test
If you take new PSA runs from the Microsoft Excel model do you get similar results?	Yes	Yes
Is(are) the CEAC line(s) in line with the CE scatter plots and the efficient frontier?	Yes	Yes
Does the PSA cloud demonstrate an unexpected behavior or have an unusual shape?	No	No
Is the sum of all CEAC lines equal to 1 for all WTP values?	Yes	Yes
Do the explored scenario analyses provide a balanced view on the structural uncertainty (i.e. not always looking at more optimistic scenarios)?	Yes	Yes
Are the scenario analysis results plausible and in line with a priori expectations?	Yes	Yes
Check the correlation between two PSA results (i.e. costs/QALYs under the SoC and costs/QALYs under the comparator)	Should be very low (very high) if different (same) random streams are used for different arms	Validated
If a certain seed is used for random number generation (or previously generated random numbers are used), check if they are scattered evenly between 0 and 1 when they are plotted	Yes	Yes
Compare the mean of the parameter samples generated by the model against the point estimate for that parameter; use graphical methods to examine distributions, functions	The sample means and the point estimates will overlap, the graphs will be similar to the corresponding distribution functions (e.g. normal, gamma, etc.)	Validated
Check if sensitivity analyses include any parameters associated with methodological/structural uncertainty (e.g. annual discount rates, time horizon)	No	No
Value of information analysis if applicable: Was this implemented correctly?	Yes	Not applicable
Which types of analysis? Were aggregated parameters used? Which parameters are grouped together? Does it match the write-up's suggestions?	Yes	Not applicable
Is EVPI larger than all individual EVPPIs?	Yes	Not applicable
Is EVPPI for a (group of) parameters larger than the EVSI of that (group) of parameter(s)?	Yes	Not applicable
Are the results from EVPPI in line with OWSA or other parameter importance analysis (e.g. ANCOVA)?	Yes	Not applicable
Did the electronic model pass the black-box tests of the previous verification stages in all PSA iterations and in all scenario analysis settings? (Additional macro can be embedded to the PSA code, which stops the PSA when an error such as negative transition probability is detected)	Yes	Yes
Check if all sampled input parameters in the PSA are correctly linked to the corresponding event/state calculations	Yes	Yes

Calculations of the cycle-based technology acquisition costs, transition probabilities, and how these probabilities informed the transitions in certain cycles were tested in the previous quality checks conducted by the company.

Verification Stage 5: Overall Validation/Other Supplementary Tests

The model interface and model performance were tested in previous quality checks conducted by the company. It was highlighted that the model was slow due to the chosen formula, however, this did not interfere with the functioning of the model. Further validation of the model was conducted in the AdViSHE checklist above.

Updated OWSA for revised base case

OWSA results for icosapent ethyl versus placebo – ITT

Parameter	Lower bound (£) ICER	Upper bound (£) ICER	Difference (£) ICER
Treatment cost - Icosapent Ethyl cost per cycle	£12,860	£34,667	£21,807
Baseline utility: CV1	£34,125	£19,013	£15,112
Event 1 Icosapent Ethyl vs. Placebo HR - ITT	£30,488	£17,968	£12,520
Utility: Post CR	£16,081	£25,735	£9,654
Utility: Post non-fatal MI	£17,531	£24,668	£7,137
Utility: Post UA	£18,432	£24,146	£5,715
Baseline utility: CV2	£26,147	£20,960	£5,187
Event 2 Icosapent Ethyl vs. Placebo HR - ITT	£24,914	£21,210	£3,704
Event 3 Icosapent Ethyl vs. Placebo HR - ITT	£24,912	£21,459	£3,453
Type of CV event - Event 2 - Placebo	£24,680	£21,359	£3,321
Type of CV event - Event 2 - Icosapent Ethyl	£21,266	£24,330	£3,064
Non CV related mortality HR - Diabetes: CV1	£21,379	£24,305	£2,927
Non CV related mortality HR - Diabetes: CV2	£21,591	£24,136	£2,544
Utility: Post non-fatal Stroke	£21,513	£23,909	£2,396
Type of CV event - Event 1 - Placebo	£23,944	£21,851	£2,093
Long-term CR health state cost	£23,623	£21,599	£2,023

Parameter	Lower bound (£) ICER	Upper bound (£) ICER	Difference (£) ICER
Type of CV event - Event 3 - Placebo	£23,793	£21,801	£1,992
TTD curve - Icosapent Ethyl	£23,419	£22,030	£1,389
Acute Nonfatal MI health state cost	£22,955	£21,589	£1,366
Non CV related mortality HR - Diabetes and MI: CV1	£23,359	£22,021	£1,339

OWSA tornado - ITT

[redacted]

NICE National Institute for Health and Care Excellence

Technical engagement proposed new evidence form (company only)

Icosapent ethyl with statin therapy for reducing the risk of cardiovascular events in adults with elevated triglycerides [ID3831]

As the company for this appraisal, you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses will be used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting. As part of your response, you may intend to provide new evidence to address some or all of the key issues identified in the executive summary of the ERG report (that is, evidence that has not already been provided during the appraisal).

We would like to understand the extent of new evidence that you propose to provide in your response to technical engagement. This will help the ERG to plan its critique of your response. You do not have to provide new evidence in response to every issue. However, in general, any new evidence provided should have the purpose of addressing a key issue identified in the executive summary of the ERG report. Decisions about whether NICE will accept new evidence will be made on a case by case basis. Please note that NICE may need to extend timelines and reschedule the appraisal committee meeting to allow new evidence to be considered. Therefore, it is important that you notify NICE about new evidence in advance by completing this form as comprehensively as possible. Please be aware that NICE will not routinely accept new evidence provided after the deadline for technical engagement responses.

Deadline for returning this form: **5pm on Tuesday 26 October 2021**.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses.
- Please ensure your response clearly identifies which key issue from the executive summary of the ERG report your proposed new evidence is intended to address. Please use the same issue numbers that have been used in the executive summary of the ERG report.
- If you intend to provide new evidence to address issues in the ERG report that have not been identified as key issues, please make this clear.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink.

NICE National Institute for Health and Care Excellence

Summary of proposed new evidence

Please use the table below to provide details of any proposed new evidence that you intend to submit in response to technical engagement.

Please be as comprehensive as possible.

Key issue(s) that the new evidence will address	Summary of the proposed new evidence (short title)	How will the new evidence address the key issue(s)?	Is the new evidence expected to alter the company's base-case ICER?	Additional details about the proposed new evidence (if available)
Issue 2	**Analysis from REDUCE-IT showing the period to determine a stable dose of statin**	The additional evidence that will be provided regarding the period to determine a stable dose of statin from REDUCE-IT will show that this aligns with current clinical practice in the UK. I.e., that patients enrolled in	**NO**	The analysis shows that approximately [redacted] of patients in the ITT cohort have a duration of stable statin dose of more than three months, which aligns with the duration observed in UK clinical practice. Statistic — AMR101 (N=4089) — Placebo (N=4090) — Overall (N=8179) Duration of Stable Statin Dose Before Randomization - n (%) At least 3 months — [redacted] — [redacted] — [redacted] Note: Five patients with missing visit information are excluded from the analysis. Note: Duration of Stable Statin Dose (defined by statin intensity on Atorvastatin, Fluvastatin, Lovastatin, Pitavastatin, Pravastatin, Rosuvastatin, or Simvastatin) in years before randomization was calculated as number of days between randomization and stable statin dose start plus one divided by 365.25. Duration in months was calculated as duration in years multiplied by 12.

<table>
<tr><td></td><td></td><td>the REDUCE-IT trial are generalisable to patients in the UK NHS setting.</td><td></td><td></td></tr>
<tr><td>Issue 4</td><td>Baseline characteristics for primary and secondary prevention subgroups from REDUCE-IT</td><td>The baseline characteristics for the primary and secondary prevention subgroups from REDUCE-IT will be compared with the corresponding patients in Steen et al. (2016) to demonstrate that patients in the REDUCE-IT trial are generalisable to patients in the UK NHS setting.</td><td>NO</td><td>The below tables show the baseline characteristics for the primary and secondary prevention cohorts, respectively.

<table>
<tr><th></th><th colspan="3">Primary Prevention (N=2394)</th></tr>
<tr><th></th><th>Icosapent Ethyl (N=1197)</th><th>Placebo (N=1197)</th><th>P-value *</th></tr>
<tr><td>Age (years), Median (Q1-Q3)</td><td></td><td></td><td></td></tr>
<tr><td>Age >=65 years, n(%)‡</td><td></td><td></td><td></td></tr>
<tr><td>Female, n(%)</td><td></td><td></td><td></td></tr>
<tr><td>Hispanic or Latino Ethnicity, n(%)</td><td></td><td></td><td></td></tr>
<tr><td>Race, n(%)†</td><td></td><td></td><td></td></tr>
<tr><td>White</td><td></td><td></td><td></td></tr>
<tr><td>Black Or African American</td><td></td><td></td><td></td></tr>
<tr><td>Asian</td><td></td><td></td><td></td></tr>
<tr><td>Other or Multiple</td><td></td><td></td><td></td></tr>
<tr><td>USA, n(%)</td><td></td><td></td><td></td></tr>
<tr><td>BMI (kg/m^2), Median (Q1-Q3)</td><td></td><td></td><td></td></tr>
<tr><td>BMI >=30 kg/m^2, n(%)‡</td><td></td><td></td><td></td></tr>
<tr><td>Stratification Factors</td><td></td><td></td><td></td></tr>
<tr><td>Location, n(%)</td><td></td><td></td><td></td></tr>
<tr><td>Westernized</td><td></td><td></td><td></td></tr>
<tr><td>Eastern Europe</td><td></td><td></td><td></td></tr>
<tr><td>Asia Pacific</td><td></td><td></td><td></td></tr>
<tr><td>Ezetimibe Use, n(%)</td><td></td><td></td><td></td></tr>
<tr><td>Statin Intensity and Diabetes Status</td><td></td><td></td><td></td></tr>
</table></td></tr>
</table>

				Statin Intensity, n(%)	[redacted]	[redacted]	[redacted]
				Low	[redacted]	[redacted]	[redacted]
				Moderate	[redacted]	[redacted]	[redacted]
				High	[redacted]	[redacted]	[redacted]
				Missing	[redacted]	[redacted]	[redacted]
				Diabetes, n(%)	[redacted]	[redacted]	[redacted]
				Type I	[redacted]	[redacted]	[redacted]
				Type II	[redacted]	[redacted]	[redacted]
				No Diabetes at Baseline	[redacted]	[redacted]	[redacted]
				Missing	[redacted]	[redacted]	[redacted]
				Laboratory Measurements	[redacted]	[redacted]	[redacted]
				Creatinine Clearance >30 and < 60 mL/min	[redacted]	[redacted]	[redacted]
				hsCRP (mg/L), Median (Q1-Q3)	[redacted]	[redacted]	[redacted]
				Triglycerides (mg/dL), Median (Q1-Q3)	[redacted]	[redacted]	[redacted]
				Triglycerides Category, n(%)	[redacted]	[redacted]	[redacted]
				< 150 mg/dL	[redacted]	[redacted]	[redacted]
				150 - <200 mg/dL	[redacted]	[redacted]	[redacted]
				>=200 mg/dL	[redacted]	[redacted]	[redacted]
				Missing	[redacted]	[redacted]	[redacted]
				Triglycerides Tertiles, n(%)	[redacted]	[redacted]	[redacted]
				Lowest (>=81.25 - <=190 mg/dL)	[redacted]	[redacted]	[redacted]
				Middle (>190 - <=250 mg/dL)	[redacted]	[redacted]	[redacted]
				Upper (>250 - <=1401 mg/dL)	[redacted]	[redacted]	[redacted]
				Triglycerides >=200 mg/dL and HDL-C <=35 mg/dL, n(%)	[redacted]	[redacted]	[redacted]
				HDL-C (mg/dL), Median (Q1-Q3)	[redacted]	[redacted]	[redacted]
				LDL-C (mg/dL), Median (Q1-Q3)	[redacted]	[redacted]	[redacted]
				LDL-C Tertiles, n(%)	[redacted]	[redacted]	[redacted]
				Lowest (>=1 - <=67 mg/dL)	[redacted]	[redacted]	[redacted]

				Middle (>67 - <=84 mg/dL)	[redacted]	[redacted]
				Upper (>84 - <=222 mg/dL)	[redacted]	[redacted]
				EPA (µg/mL), Median (Q1-Q3)	[redacted]	[redacted]
				Medications Taken at Baseline, n (%)	[redacted]	[redacted]
				Anti-Diabetic	[redacted]	[redacted]
				Anti-Hypertensive	[redacted]	[redacted]
				Anti-Platelet[#]	[redacted]	[redacted]
				One Anti-platelet	[redacted]	[redacted]
				Two or more Anti-platelets	[redacted]	[redacted]
				Anticoagulant	[redacted]	[redacted]
				Anticoagulant plus Anti-platelet	[redacted]	[redacted]
				No Antithrombotic	[redacted]	[redacted]
				ACE	[redacted]	[redacted]
				ARB	[redacted]	[redacted]
				ACE or ARB	[redacted]	[redacted]
				Beta Blockers	[redacted]	[redacted]
				Statin	[redacted]	[redacted]

	Secondary Prevention (N=5785)		
	Icosapent Ethyl (N=2892)	**Placebo (N=2893)**	**P-value** [*]
Age (years), Median (Q1-Q3)	[redacted]	[redacted]	[redacted]
Age >=65 years, n(%)[‡]	[redacted]	[redacted]	[redacted]
Female, n(%)	[redacted]	[redacted]	[redacted]
Hispanic or Latino Ethnicity, n(%)	[redacted]	[redacted]	[redacted]
Race, n(%)[†]	[redacted]	[redacted]	[redacted]
White	[redacted]	[redacted]	[redacted]
Black Or African American	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]

				Other or Multiple	[redacted]	[redacted]	[redacted]
				USA, n(%)	[redacted]	[redacted]	[redacted]
				BMI (kg/m^2), Median (Q1-Q3)	[redacted]	[redacted]	[redacted]
				BMI >=30 kg/m^2, n(%)‡	[redacted]	[redacted]	[redacted]
				Stratification Factors	[redacted]	[redacted]	[redacted]
				Location, n(%)	[redacted]	[redacted]	[redacted]
				Westernized	[redacted]	[redacted]	[redacted]
				Eastern Europe	[redacted]	[redacted]	[redacted]
				Asia Pacific	[redacted]	[redacted]	[redacted]
				Ezetimibe Use, n(%)	[redacted]	[redacted]	[redacted]
				Statin Intensity and Diabetes Status	[redacted]	[redacted]	[redacted]
				Statin Intensity, n(%)	[redacted]	[redacted]	[redacted]
				Low	[redacted]	[redacted]	[redacted]
				Moderate	[redacted]	[redacted]	[redacted]
				High	[redacted]	[redacted]	[redacted]
				Missing	[redacted]	[redacted]	[redacted]
				Diabetes, n(%)	[redacted]	[redacted]	[redacted]
				Type I	[redacted]	[redacted]	[redacted]
				Type II	[redacted]	[redacted]	[redacted]
				No Diabetes at Baseline	[redacted]	[redacted]	[redacted]
				Missing	[redacted]	[redacted]	[redacted]
				Laboratory Measurements	[redacted]	[redacted]	[redacted]
				Creatinine Clearance >30 and < 60 mL/min	[redacted]	[redacted]	[redacted]
				hsCRP (mg/L), Median (Q1-Q3)	[redacted]	[redacted]	[redacted]
				Triglycerides (mg/dL), Median (Q1-Q3)	[redacted]	[redacted]	[redacted]
				Triglycerides Category, n(%)	[redacted]	[redacted]	[redacted]
				< 150 mg/dL	[redacted]	[redacted]	[redacted]
				150 - <200 mg/dL	[redacted]	[redacted]	[redacted]
				>=200 mg/dL	[redacted]	[redacted]	[redacted]

				Missing	[redacted]	[redacted]	[redacted]
				Triglycerides Tertiles, n(%)	[redacted]	[redacted]	[redacted]
				Lowest (>=81.25 - <=190 mg/dL)	[redacted]	[redacted]	[redacted]
				Middle (>190 - <=250 mg/dL)	[redacted]	[redacted]	[redacted]
				Upper (>250 - <=1401 mg/dL)	[redacted]	[redacted]	[redacted]
				Triglycerides >=200 mg/dL and HDL-C <=35 mg/dL, n(%)	[redacted]	[redacted]	[redacted]
				HDL-C (mg/dL), Median (Q1-Q3)	[redacted]	[redacted]	[redacted]
				LDL-C (mg/dL), Median (Q1-Q3)	[redacted]	[redacted]	[redacted]
				LDL-C Tertiles, n(%)	[redacted]	[redacted]	[redacted]
				Lowest (>=1 - <=67 mg/dL)	[redacted]	[redacted]	[redacted]
				Middle (>67 - <=84 mg/dL)	[redacted]	[redacted]	[redacted]
				Upper (>84 - <=222 mg/dL)	[redacted]	[redacted]	[redacted]
				EPA (µg/mL), Median (Q1-Q3)	[redacted]	[redacted]	[redacted]
				Medications Taken at Baseline, n (%)	[redacted]	[redacted]	[redacted]
				Anti-Diabetic	[redacted]	[redacted]	[redacted]
				Anti-Hypertensive	[redacted]	[redacted]	[redacted]
				Anti-Platelet[#]	[redacted]	[redacted]	[redacted]
				One Anti-platelet	[redacted]	[redacted]	[redacted]
				Two or more Anti-platelets	[redacted]	[redacted]	[redacted]
				Anticoagulant	[redacted]	[redacted]	[redacted]
				Anticoagulant plus Anti-platelet	[redacted]	[redacted]	[redacted]
				No Antithrombotic	[redacted]	[redacted]	[redacted]
				ACE	[redacted]	[redacted]	[redacted]
				ARB	[redacted]	[redacted]	[redacted]
				ACE or ARB	[redacted]	[redacted]	[redacted]
				Beta Blockers	[redacted]	[redacted]	[redacted]
				Statin	[redacted]	[redacted]	[redacted]

Issue 5	**A state transition model for verifying outcomes of the partSA approach**	A state transition model for icosapent ethyl will be provided for validating the outcomes of the partSA approach. In addition, a manuscript which gives a summary of the methodology and results of the model will be provided (both the model and manuscript to be treated confidentially).	**NO**	The state transition model has been developed in TreeAge. As this software may not be readily available at NICE, we will also provide a manuscript (not yet published) which will provide an overview of the methodology behind the model along with the results. This model should strictly only be used to validate the outcomes of the partSA approach, it is not intended to replace it.
Issue 6	**Re-estimation of the parametric survival curves using the complete KM data**	The parametric survival curves will be re-estimated using the complete KM data to inform the long-term	**YES**	The updated parametric survival curves will be provided in an updated version of the cost-effectiveness model with these curves implemented.

		extrapolations .		
Issue 7	**All distributions ran for survival curves**	Results for the different types of distributions for the survival curves will be provided, to show that these do not have a large impact on the ICER.	**NO**	The results will be provided as scenarios only in the appendix of the response to technical engagement. These are not intended to replace the base case distributions since these have previously been ratified by UK clinical experts.
Issue 7 (added since 26th October)	**Hazard ratios for the 1st event, 2nd event and 3+ event for CV1 and CV2**	The proportional hazard assumption has been tested and holds. Therefore hazard ratios will be applied for the new preferred base case for the ITT as well as for the CV1 and CV2 subgroups	**YES**	Analyses for CV1 and CV2 have been conducted by Amarin, in line with the published analysis done for the ITT population (Bhatt *et al.* J Am Coll Cardiol 2019;73:2791–802). Both figures, in bigger size, are also included below this table. Hazard ratios for CV1 (secondary prevention) [redacted] Hazard ratios for CV2 (primary prevention)

				[redacted]
Issue 8	**Use of stratified parametric models**	Stratified parametric models will be ran following the model selection process algorithm as mentioned in NICE DSU TSD 14.	**UNKNOWN**	We are currently in the process of running these models and so at this stage are unsure if this will impact the base-case ICER. This evidence will be provided in the appendix of the response to technical engagement. If any changes need to be made, these will be provided in an updated version of the cost-effectiveness model.
Issue 9	**Landmark analyses for the primary efficacy 5-point MACE composite endpoint – ITT, primary and secondary**	The landmark analyses provide supportive evidence for the treatment benefit of icosapent ethyl to be maintained beyond the trial period.	**NO**	The analysis shows that no treatment waning was observed over the course of the REDUCE-IT trial up to the maximum study duration of 75 months (i.e., 6.2 years) across all the populations. **<u>ITT population:</u>** The icosapent ethyl benefit reached statistical significance starting at Month 21 with an estimated HR of [redacted] and the corresponding p value of [redacted]. The treatment benefit continued to increase thereafter, and reached its steady state with the HRs in the [redacted] after approximately 24 months of treatment till the maximum study duration of 75 months (i.e. 6.2 years). Similar patterns were observed for the primary and secondary prevention subgroups (see below).

	prevention populations			[redacted]

Endpoint	AMR101 (N=4089)	Placebo (N=4090)	HR (95% CI)[1]	Log-Rank P-value
Primary Composite Endpoint	705 (17.2%)	901 (22.0%)	0.75 (0.68, 0.83)	<.0001

[redacted]

Note: Events occurred after timepoint are censored to timepoint
[1] Hazard ratio, 95% CI are from a Cox proportional hazard model with treatment as factor and stratified by geographic region,
CV risk category, and use of ezetimibe.

Primary prevention population:

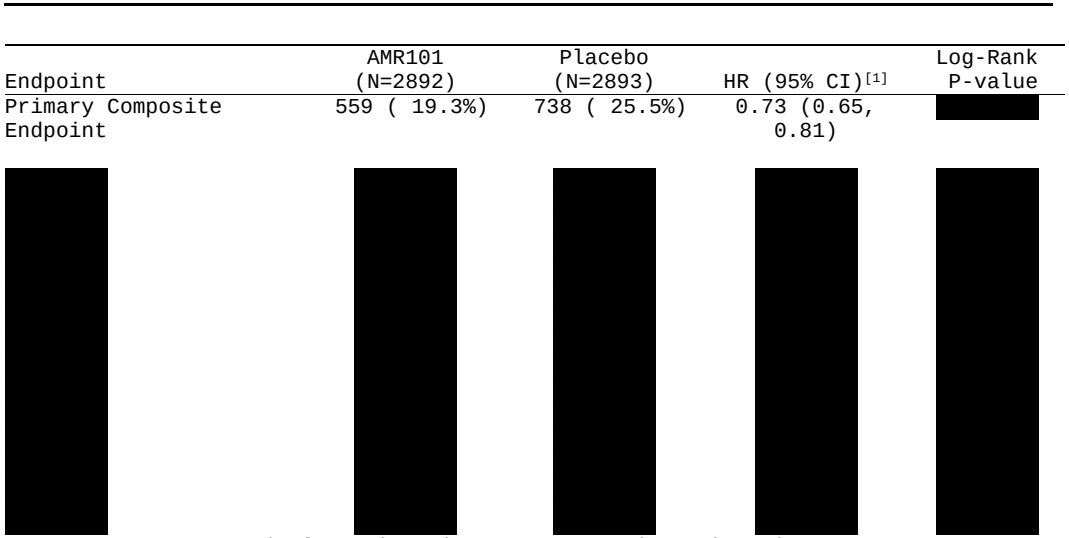
[redacted]

Endpoint	AMR101 (N=1197)	Placebo (N=1197)	HR (95% CI)[1]	Log-Rank P-value
Primary Composite Endpoint	146 (12.2%)	163 (13.6%)	0.88 (0.70, 1.10)	[redacted]

[redacted]

Note: Events occurred after timepoint are censored to timepoint
[1] Hazard ratio, 95% CI are from a Cox proportional hazard model with treatment as factor and stratified by geographic region,
CV risk category, and use of ezetimibe.

Secondary prevention population:

				[redacted]  [redacted] Endpoint / AMR101 (N=2892) / Placebo (N=2893) / HR (95% CI)[1] / Log-Rank P-value Primary Composite Endpoint: 559 (19.3%) / 738 (25.5%) / 0.73 (0.65, 0.81) / [redacted] Note: Events occurred after timepoint are censored to timepoint [1] Hazard ratio, 95% CI are from a Cox proportional hazard model with treatment as factor and stratified by geographic region, CV risk category, and use of ezetimibe.
Issue 12	**Event costs adjusted for time since**	Event costs will be adjusted and calculated in a similar fashion to	**UNKNOWN**	We are currently in the process of making this adjustment, so at this stage are unsure if this will impact the base-case ICER. If any changes need to be made, these will be provided in an updated version of the cost-effectiveness model.

	previous event	event utilities (which accrue 60-days post-event).		
Issue 14	**Updated cost calculations for events**	Event costs will be recalculated so that these can be easily verified by the ERG.	**UNKNOWN**	We are currently in the process of making this adjustment, so at this stage are unsure if this will impact the base-case ICER. If any changes need to be made, these will be provided in an updated version of the cost-effectiveness model.
Issue 15	**Completed model validation and face validity check**	Complete responses to clarification questions C17, C18 and C19 will be provided considering validation and transparency.	**UNKNOWN**	We are in the process of running this validation. This may only alter the base-case ICER if errors are picked up in the model during the validation and face validity checks.

Analyses for CV1 and CV2 have been conducted by Amarin, in line with the published analysis done for the ITT population (Bhatt et al. J Am Coll Cardiol 2019;73:2791–802).

Hazard ratios for CV1 (secondary prevention)

Hazard ratios for CV2 (primary prevention)

[redacted]

NICE National Institute for Health and Care Excellence

Technical engagement response form

Icosapent ethyl with statin therapy for reducing the risk of cardiovascular events in adults with elevated triglycerides [ID3831]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments by **5pm** on **Tuesday 9 November 2021**.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Amarin**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Not applicable**

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

<table>
<tr><th>Key issue</th><th>Does this response contain new evidence, data or analyses?</th><th>Response</th></tr>
<tr><td>Key issue 5: Model structure – partitioned survival analysis (partSA)</td><td>YES</td><td>Following the ERG's concerns regarding the large differences between the long-term clinical outcomes of the company's model and the state-transition model (for cross-validation purposes), the company has revisited the estimates of its model and reached out to the [redacted] to clarify calculations. It was noted that there was a discrepancy in the way the proportions were calculated for the cross-validation model. Rather than calculating the proportions based on the total cohort entering the model, the proportions were previously calculated based on the number of patients left in the model each year. This has now been corrected, and an update of the estimates is provided in Table 1 below:

Table 1: Clinical estimates from company model and cross-validation model
<table>
<tr><th></th><th colspan="2">1 year</th><th colspan="2">5 years</th><th colspan="2">10 years</th><th colspan="2">20 years</th><th colspan="2">30 years</th></tr>
<tr><th></th><th>Icosapent ethyl</th><th>BSC</th><th>Icosapent ethyl</th><th>BSC</th><th>Icosapent ethyl</th><th>BSC</th><th>Icosapent ethyl</th><th>BSC</th><th>Icosapent ethyl</th><th>BSC</th></tr>
<tr><td colspan="11">First event: Total</td></tr>
<tr><td>State-transition model</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>PartSA model - new preferred base case</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
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		Bhatt *et al.* 2019 (digitised)	4.4%	5.3%	19.3%	24.7%	-	-	-	-	-	-
		Second event: Total										
		State-transition model	[redacted]									
		PartSA model - new preferred base case	[redacted]									
		Bhatt *et al.* 2019	-	-	5.8%	9.2%	-	-	-	-	-	-
		Third & plus event: Total										
		State-transition model	[redacted]									
		PartSA model - new preferred base case	[redacted]									
		Bhatt *et al.* 2019	-	-	1.8%	3.5%	-	-	-	-	-	-
		Discontinuing icosapent ethyl										
		State-transition model	[redacted]									
		PartSA model - new preferred base case	[redacted]									
		Patients alive										
		State-transition model	[redacted]									
		PartSA model - new preferred base case	[redacted]									
		Event free										

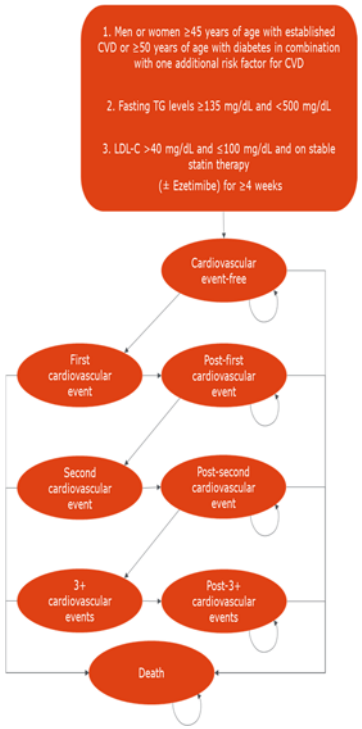
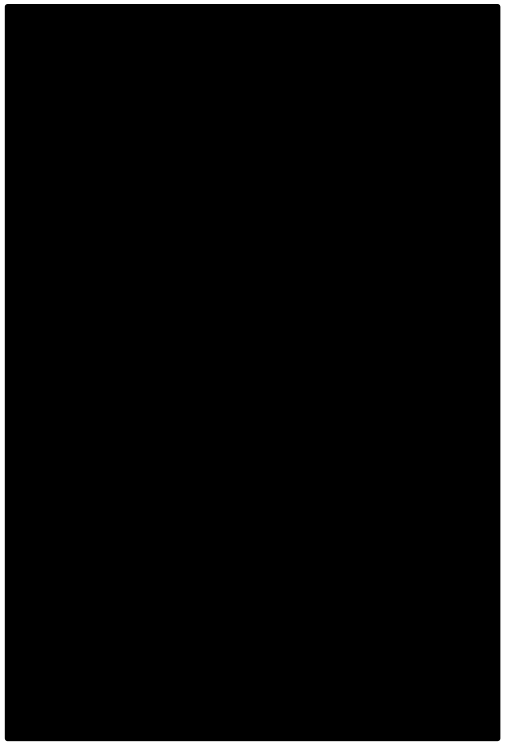
State-transition model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
PartSA model - new preferred base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

The updated table shows that the clinical estimates produced from both the company model and the cross-validation model are very similar, despite the model structures being different (partitioned-survival vs. Markov/micro-simulation). Please note that the best fitting curves were selected for the event curves in the base case of the company model, following the amends made to the survival analysis under key issues 6, 7 and 8 (see below). The proportion of patients alive in the company model are slightly lower than the estimates from the cross-validation model because non-CV related mortality hazard ratios are applied in the company model to account for the additional risk of death in patients following a CV event, but not in the cross-validation model.

Other key differences between the two models are highlighted in Table 2 below as per the ERG's request:

Table 2: Model specifications

	Company model	**Cross-validation model**	**Comparison**
Model structure summary	• *De novo* health state cohort model • **Key assumption:** A partitioned survival (partSA) approach was used to estimate the proportion of patients experiencing a first, second and third+ event • **Key assumption:** Individual non-fatal CV events were not explicitly modelled. Events were grouped by first, second and third+ CV events	• Micro-simulation/Markov model approach used to estimate the proportion of patients experiencing individual non-fatal CV events • **Key assumption:** a lifetime analysis using a microsimulation model and data from published literature, to estimate costs, clinical outcomes, and quality-adjusted life-years (QALYs) of patients in the REDUCE-IT trial • Accounted for health gained and lost to society due to intensive control and for payers' direct health care	Different methodology for estimating time of event and number of patients with an event: Markov vs. partSA.

				costs. Patients' indirect costs were not included	
		Model structure diagram			The cross-validation model explicitly models individual non-fatal CV events, whereas the company model considers health states which are grouped by first, second and third+ CV events.
		Software	• Programmed in Microsoft Excel	• Programmed in TreeAge	Different software used.
		Perspective	• NHS and PSS	• Payers' direct health care costs	Same perspective.
		Cycle length	• 1 day	• 6 months	Longer cycles in the cross-validation model, but still allowed for

					multiple events to occur within each cycle through the transition probabilities.
		Time horizon	• Lifetime (36 years)	• Lifetime (36 years)	Same assumption. Both models assume that patients do not live beyond 100 years old.
		Population	• The model considers a hypothetical cohort of 1,000 patients who are aligned with the licenced indication and the ITT population from REDUCE-IT: Males and females ≥45 years of age with established CVD (secondary prevention subgroup) or ≥50 years of age with diabetes in combination with one or more additional risk factor for CVD (primary prevention subgroup), with LDL-C levels >40 mg/dL and ≤100 mg/dL and fasting TG levels ≥135 mg/dL and <500 mg/dL, on stable statin therapy for at least four weeks	• The model considers a hypothetical cohort of 10,000 patients who share the same baseline characteristics inclusion criteria, and strategies of treatments with the participants from the REDUCE-IT trial	Same population.

		Baseline age	• 64 years old	• 63.3 years old	Same baseline age, as per the REDUCE-IT trial.
		Intervention	• Icosapent ethyl (four capsules taken as two 998 mg capsules twice daily) in combination with a stable dose of statin therapy with or without ezetimibe 10 mg	• Icosapent ethyl (four capsules taken as two 998 mg capsules twice daily) in combination with a stable dose of statin therapy with or without ezetimibe 10 mg	Same intervention.
		Comparator	• Best supportive care (stable dose of statin therapy with or without ezetimibe 10 mg)	• Best supportive care (stable dose of statin therapy with or without ezetimibe 10 mg)	Same comparator.
		Discount rate	• Costs and health outcomes were discounted at 3.5% per annum	• Costs and health outcomes were discounted at 3.5% per annum	Same discount rate as stated in the NICE reference case.
		Clinical effectiveness	• Long-term effectiveness informed by extrapolation of the treatment effect based on IPD from the REDUCE-IT trial, following survival analysis methodology from NICE TSD 14	• Derived baseline transition probabilities from the in-trial results of REDUCE-IT • Long-term effectiveness was estimated by applying multipliers to the baseline transition probabilities, which were adjusted by age-group and gender (Risha *et al.* 2020)	Company model uses extrapolated time to event curves, whereas the cross-validation model uses transition probabilities adjusted by age and gender.
		Safety	• Adverse events from the REDUCE-IT trial.	• Used all the safety outcomes from the REDUCE-IT trial.	Cross-validation model includes

			• **Key assumption:** Only the TEAEs that occurred in >5% of patients and with a statistically significant difference between the icosapent ethyl and placebo groups were included in the economic model		all AEs from the REDUCE-IT trial, whereas the company model only considers those that occurred in >5% of individuals that were significant in the icosapent ethyl group.
		Utilities	• Baseline utility sources: Stevanović *et al.* 2016 (CV1) and O'Reilly *et al.* 2011 (CV2) • Weighted average for ITT population • First event acute and post-event health states: Multipliers sourced from NICE CG181 were applied to the baseline utility values. • Second event acute and post-event health states: Multipliers sourced from NICE CG181 were applied to the post-first event utility value • Third+ event acute and post-event health states: Multipliers sourced from NICE CG181 were	• Baseline utility sources: Murray *et al.* 2012 and Moran *et al.* 2014 • The baseline utility values were based on a patient's history of CV events • Upon experiencing a CV event, a disutility associated with the event was applied to the baseline value for each patient • **Key assumption:** It was assumed patients experience an acute utility for the first three cycles (18 months) following an event, after which they experience a post-event utility.	Different sources used for the baseline utility values, and different duration of acute utility application.

			applied to the post-second event utility value • Acute and post event health states within the model are grouped by the number of events an individual has experienced since the beginning of the trial rather than the type of event. Therefore, a weighted average was calculated by multiplying the utility of each of the four non-fatal events by the distribution of type of event in the icosapent ethyl and placebo groups • **Key assumption:** It was assumed patients experience an acute utility for the first 60 days following an event, after which they experience a post-event utility		
		Intervention cost	• £173 for 120 capsules (998 mg) • Icosapent ethyl alone: £5.77 per day • Icosapent ethyl + concomitant therapies: £5.82 per day	• £173 for 120 capsules (998 mg) • Icosapent ethyl alone: £5.77 per day • Icosapent ethyl + concomitant therapies: £5.82 per day	Same intervention cost.
		Comparator cost	• £0.05 per day	• £0.05 per day	Same comparator cost.
		Discontinuation	• Discontinuation informed by extrapolation of the	• Discontinuation informed by extrapolation of the treatment effect	Both models extrapolate the

			treatment effect based on IPD from the REDUCE-IT trial	based on IPD from the REDUCE-IT trial	discontinuation KM curve from the REDUCE-IT trial.
		Health state costs	• Acute and long-term costs were sourced from Danese *et al.* 2016, and the costs were adjusted for the time since a previous event following key issue 12 as suggested by the ERG (i.e., acute costs were applied for the first 60 days following the CV event) • A weighted average was calculated by multiplying the cost of each of the five individual events by the distribution of type of event in the icosapent ethyl and placebo groups for first, second and third+ events • **Key assumption:** All acute event associated costs were applied on the day the event occurred • **Key assumption:** It was assumed 80% of individuals that receive revascularisation would receive a PCI, with the remaining 20% receiving CABG	• Acute and long-term costs were sourced from Danese *et al.* 2016, however, these have not been adjusted as per the company model • **Key assumption:** It was assumed patients experience an acute cost for the first three cycles (18 months) following an event, after which they experience a long-term cost • **Key assumption:** 30% of fatal events were estimated at the cost of the hospitalisation	Different methodology in application of costs, but same cost source used.

			• **Key assumption:** Fatal event costs were assumed equal to the cost of a hospitalisation • **Key assumption:** 90% of patient's management would be received by a GP		
		Mortality	• All-cause mortality informed using UK Office for National Statistics data • Non-CV related mortality hazard ratios were sourced from The Asia Pacific Cohort Studies Collaboration (2003) and The Emerging Risk Factors Collaboration (2015) to inform the increased risk of non-CV related mortality when modelled patients experienced multiple CV events	• All-cause mortality informed using age-specific death rates in the UK from Statista	Different reference used for all-cause mortality. Hazard ratios for non-CV related mortality were not applied in the cross-validation model.
		Although there are some differences in the structure, methodology and input values used, the overall estimated long-term clinical effectiveness parameters from both models are very similar, demonstrating that the partSA approach used by the company is appropriate. The cost-effectiveness results from both models are provided in Table 3 below:			

Table 3: Cost-effectiveness results

	Population	Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
State-transition model	ITT	Icosapent ethyl	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
New preferred base case		Icosapent ethyl	21,179	10.767	7.808	10,632	0.313	0.376	28,266
		BSC	10,546	10.454	7.432	-	-	-	-
State-transition model	Primary prevention	Icosapent ethyl	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
New preferred base case		Icosapent ethyl	17,816	11.104	8.035	11,276	0.097	0.132	85,438
		BSC	6,540	11.007	7.903	-	-	-	-
State-transition model	Secondary prevention	Icosapent ethyl	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
New preferred base case		Icosapent ethyl	22,589	10.618	7.703	10,534	0.392	0.462	22,796
		BSC	12,055	10.226	7.241	-	-	-	-

Key issue 6, 7 and 8: • Use of reconstituted data • Limited evidence available for (long-term) validation of survival curves • Use of stratified parametric models, methodological guidance not followed	YES	Following the ERG's comments in the technical engagement stage, we have revised the methodology used to estimate the long-term extrapolations informing clinical efficacy within the cost-effectiveness model to fully align with NICE DSU 14. Key changes include: • Use of the full REDUCE-IT dataset to estimate time-to-event curves (in line with initial response to the technical engagement) • Time-to-event curves estimated by fitting one parametric model to the entire dataset, with treatment group included as a covariate. Full details of our revised methodology used for estimating the long-term time-to-event curves for first, second and third plus events applied within the cost-effectiveness model are presented below. The REDUCE-IT trial was a randomised controlled trial and included both treatment arms required to inform the cost-effectiveness model, therefore the first, second and third plus time to event curves were fitted to the full patient-level data, as recommended in NICE DSU14 guidance. Parametric curves were fitted to the placebo and icosapent ethyl arms simultaneously, with a covariate for the icosapent ethyl group included. As per the NICE DSU14 guidelines, the following parametric curves were jointly fitted to the data: exponential, Weibull, gompertz, log-normal, log-logistic and generalised gamma. Extrapolations were carried out in R using the 'survival' package. For all curves, the following criteria were applied to select the baseline curves: • Inspection of log-cumulative hazard plots (to assess the behaviour of the hazard over time) • Visual inspection of the survival curve fit to KM data from the REDUCE-IT trial • Statistical model fit, as measured by AIC and BIC ***Assessment of proportional hazards assumption*** As discussed in the company response to key issue 8, to test for the acceptability of using proportional hazards, the log cumulative hazard plot, Schoenfeld residual plot and Cox-Snell residual plots were evaluated (Appendix A in original technical engagement response; Key issue 8). The log-cumulative

		hazard plot lines for icosapent ethyl and placebo remain parallel for the majority of the time period in all three events. However, the plot lines do cross towards the start in events 1 and 2 and towards the end of event 3+. This could be due to the treatment not showing full effect at the beginning of the time period and few patients remaining at risk towards the end of the time period. The Schoenfeld residual plot shows a linear curve with a zero slope for events 1 and 2 and shows a p-value >0.05 for all events, giving evidence that the proportional hazards assumption holds. The plot of the Cox-Snell residuals against the estimated cumulative hazard rate shows a relatively straight line with zero intercept and unit slope for events 1 and 2. Therefore, it can be assumed that the proportional hazards assumption holds between icosapent ethyl and placebo. Therefore, based on these findings and the algorithm in Figure 3 in NICE DSU14, dependent fitted extrapolation models were deemed most appropriate to extrapolate the first, second and third plus time-to-event curves for the ITT population. ***Selection of survival curves*** We attempted to fit the six standard parametric models to the study data, however, the Weibull distribution caused an error, and we were unable to obtain parameter coefficients for this distribution. Therefore, only five distributions were fitted: exponential, Weibull, gompertz, log-logistic, log-normal and generalised gamma, presented for the ITT population (see figures below). Each of the curves underwent visual inspection of the survival curve to assess whether they were as expected from the REDUCE-IT trial. The best fitting distribution was chosen by statistical consideration (AIC and BIC), visual inspection of the fitted curves against the KM data to ensure the survival distributions closely predicted the observed data. Additionally, comparison against the [redacted] cost-effectiveness model and clinical plausibility of the long-term extrapolations was considered. Lower AIC and BIC values are associated with better statistical fit to the observed data. Therefore, based on statistical fit, the most appropriate distributions to be used for our time-to-event curves were

determined to be exponential, log-logistic and log-logistic, for the first event, second event and third+ event, respectively.

In general, most of the parametric models fitted well to the data and produced reasonable visual predictions for placebo and icosapent ethyl within the observed period.

A summary of the goodness-of-fit statistics for the first, second and third+ event extrapolations is presented in Table 4.

Table 4. Goodness-of-fit statistics

Distribution	AIC	Rank	BIC	Rank	Diff rank
First event					
Exponential	***31740***	***=2***	***31754***	***1***	***1***
Weibull	NA	NA	NA	NA	NA
Gompertz	31742	4	31763	3	=2
Log-logistic	31738	1	31759	2	=2
Lognormal	31776	5	31797	5	=2
Generalised Gamma	31740	=2	31768	4	5
Second event					
Exponential	13325	5	13339	4	1
Weibull	NA	NA	NA	NA	NA
Gompertz	13317	4	13338	=2	=2
Log-logistic	***13310***	***1***	***13331***	***1***	***=2***
Lognormal	13316	3	13338	=2	4
Generalised Gamma	13312	2	13340	5	5
Third+ event					
Exponential	5132	5	5146	5	1

Weibull	NA	NA	NA	NA	NA
Gompertz	5095	4	5116	4	=2
Log-logistic	***5085***	***1***	***5106***	***1***	***=2***
Lognormal	5092	3	5113	2	=2
Generalised Gamma	5087	2	5115	3	5

Table 5, Table 6, and Table 7 present a 30-year time horizon comparison against the estimates provided from the [redacted] model, for the first, second and third+ event curves, respectively. Table 5 also presents a comparison of the first five years extrapolated data for the time to first event against the KM curve published in Bhatt 2019.

For the first event curve, the exponential distribution (best fitting chosen by statistical consideration) was very similar to the percentage of individuals experiencing the primary endpoint as reported in the KM curve in Bhatt 2019. Additionally, over a time horizon of 30 years, the estimates are similar to those observed in the [redacted] cost-effectiveness model.
There is still some uncertainty surrounding the second and third+ event curve distributions to inform the long-term estimates, with the best fitting curve chosen by statistical consideration being the one based on the log-logistic distribution, while the curve based on the exponential distribution results in estimates closer to those observed in the [redacted] model (KM curves were not generated separately for 2nd events and 3rd events). However, scenario analyses presented in Table 8, Table 9 and Table 10 show that the choice of distribution for the second and third+ events has minimal impact on the ICER.

Table 5. Comparison of extrapolation data for time to first event for a 30-year time horizon

	1 year		**5 years**		**10 years**		**20 years**		**30 years**	
	Icosapent ethyl	**BSC**	**Icosapent ethyl**	**BSC**	**Icosapent ethyl**	**BSC**	**Icosapent ethyl**	**BSC**	**Icosapent ethyl**	**BSC**
Bhatt 2019 (digitised)	4.4%	5.3%	19.3%	24.7%	-	-	-	-	-	-

[redacted] model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Extrapolation estimates from company model											
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Table 6. Comparison of extrapolation data for time to second event for a 30-year time horizon

	1 year		**5 years**		**10 years**		**20 years**		**30 years**	
	Icosapent ethyl	**BSC**	**Icosapent ethyl**	**BSC**	**Icosapent ethyl**	**BSC**	**Icosapent ethyl**	**BSC**	**Icosapent ethyl**	**BSC**
[redacted] model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Extrapolation estimates from company model										
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 7. Comparison of extrapolation data for time to third plus event for a 30-year time horizon

	1 year		**5 years**		**10 years**		**20 years**		**30 years**	
	Icosapent ethyl	**BSC**	**Icosapent ethyl**	**BSC**	**Icosapent ethyl**	**BSC**	**Icosapent ethyl**	**BSC**	**Icosapent ethyl**	**BSC**
[redacted] model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Extrapolation estimates from the company model										
Exponential	[redacted]									
Weibull	[redacted]									
Gompertz	[redacted]									
Log-logistic	[redacted]									
Lognormal	[redacted]									
Generalised Gamma	[redacted]									

Table 8. Scenario analysis varying distribution for the first event in the ITT population

Distribution	Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Exponential – Base case	BSC	10,546	10.454	7.432	-	-	-	-
	Icosapent ethyl	21,179	10.767	7.808	10,632	0.313	0.376	28,266
Gompertz	BSC	10,525	10.460	7.438	-	-	-	-
	Icosapent ethyl	21,160	10.774	7.814	10,635	0.314	0.377	28,224
Log-logistic	BSC	10,205	10.549	7.521	-	-	-	-
	Icosapent ethyl	20,996	10.838	7.872	10,791	0.289	0.351	30,733
Lognormal	BSC	9,705	10.669	7.639	-	-	-	-
	Icosapent ethyl	20,660	10.945	7.973	10,955	0.275	0.335	32,747
Generalised Gamma	BSC	10,332	10.510	7.485	-	-	-	-
	Icosapent ethyl	21,056	10.811	7.848	10,725	0.301	0.363	29,517

Table 9. Scenario analysis varying distribution for the second event in the ITT population

Distribution	Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Exponential	BSC	10,522	10.472	7.452	-	-	-	-
	Icosapent ethyl	21,163	10.785	7.829	10,641	0.313	0.376	28,282
Gompertz	BSC	10,525	10.370	7.344	-	-	-	-
	Icosapent ethyl	21,177	10.704	7.741	10,652	0.334	0.397	26,810
Log-logistic – Base case	BSC	10,546	10.454	7.432	-	-	-	-
	Icosapent ethyl	21,179	10.767	7.808	10,632	0.313	0.376	28,266
Lognormal	BSC	10,491	10.525	7.502	-	-	-	-
	Icosapent ethyl	21,193	10.797	7.840	10,702	0.272	0.338	31,688
Generalised Gamma	BSC	10,548	10.462	7.441	-	-	-	-
	Icosapent ethyl	21,181	10.772	7.814	10,633	0.311	0.373	28,498

Table 10. Scenario analysis varying distribution for the third plus event in the ITT population

Distribution	Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Exponential	BSC	9,667	10.536	7.507	-	-	-	-
	Icosapent ethyl	20,664	10.829	7.865	10,997	0.294	0.358	30,723

Gompertz	BSC	11,132	10.417	7.390	-	-	-	-
	Icosapent ethyl	21,729	10.712	7.753	10,597	0.294	0.363	29,231
Log-logistic – Base Case	BSC	10,546	10.454	7.432	-	-	-	-
	Icosapent ethyl	21,179	10.767	7.808	10,632	0.313	0.376	28,266
Lognormal	BSC	9,938	10.515	7.488	-	-	-	-
	Icosapent ethyl	20,947	10.798	7.836	11,009	0.283	0.348	31,623
Generalised Gamma	BSC	10,650	10.444	7.423	-	-	-	-
	Icosapent ethyl	21,204	10.763	7.805	10,554	0.319	0.382	27,664

The different distributions fitted to each event curve (KM data) for icosapent ethyl and placebo can be seen in Figure 1 to Figure 6 below.

Figure 1. Long-term extrapolations based on the parametric models fitted to the first event: ITT population (Icosapent ethyl)

		Figure 2. Long-term extrapolations based on the parametric models fitted to the first event: ITT population (Placebo)  **Figure 3. Long-term extrapolations based on the parametric models fitted to the second event: ITT population (Icosapent Ethyl)**  **Figure 4. Long-term extrapolations based on the parametric models fitted to the second event: ITT population (Placebo)**

Figure 5. Long-term extrapolations based on the parametric models fitted to the third plus event: ITT population (Icosapent Ethyl)

		Figure 6. Long-term extrapolations based on the parametric models fitted to the third plus event: ITT population (Placebo) 

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: The ERG states the following: "We've noticed that the company's name of the validation model is marked CIC, however other information relating to the model is marked AIC. Our understanding is this marking is to protect the company's name. We would be grateful if you could confirm that's the case and let us know if there's any other reason for the differences in marking."	N/A	NO	We can confirm that the company's name of the validation model has been marked as CIC in order to protect the company's name only.

Additional issue 2: The ERG states the following: "The hazard ratios used in the technical engagement model are marked AIC ('clinical inputs' D19, D44, D72). However, these values appear in the published Bhatt et al. 2019 paper. We would remind you that values that appear in the public domain cannot be marked as confidential. Please remove the marking from these values and submit an updated model."	N/A	NO	The ERG is correct that the hazard ratios in cells D19, D44 and D72 in the "Clinical Inputs" tab are published in Bhatt et al. 2019 in the base case (ITT population). However, these values change when selecting the subgroups CV1 or CV2 in the model, and the hazard ratios associated with each of these subgroups are not published in the public domain hence, these cells have been marked as AIC in the model.

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement update	Change(s) made in response to technical engagement update	Impact on the company's base-case ICER
Key issue 6, 7 and 8: • Use of reconstituted data	The ERG considered that details were lacking around the survival analyses conducted, and felt that it is not	Methodological guidance from NICE DSU14 followed to conduct survival	This change increases the previous base case ICER from £22,709 to £28,266

• Limited evidence available for (long-term) validation of survival curves • Use of stratified parametric models, methodological guidance not followed	appropriate to use hazard ratios from publications to estimate the treatment effect when IPD is available and considered in the model	analyses and full details of analyses provided	
Company's preferred base case following technical engagement updates	Incremental QALYs: ITT: 0.376 CV1: 0.462 CV2: 0.132	Incremental costs: ITT: £10,632 CV1: £10,534 CV2: £11,276	The company base-case ICER resulting from combining the changes described above increases from £22,709 to £28,266. ITT: £28,266 CV1: £22,796 CV2: £85,438

Additional information request: Icosapent ethyl with statin therapy for reducing the risk of cardiovascular events in adults with elevated triglycerides [ID3831]

Please find below the additional analyses in the **secondary prevention (CV1) population** as requested by the NICE technical team.

As explained during the technical engagement stage, we believe that the exponential curve is the most appropriate curve to use in order to extrapolate TTD, as this curve has the best fit to the trial data based on the AIC, BIC and visual inspection (in the absence of clinical practice experience with icosapent ethyl).

Furthermore, we believe treatment waning should not be applied in the base case, since the Kaplan-Meier event curves for the primary efficacy 5-point MACE composite endpoint show that the treatment effect increases over time before stabilising. This treatment effect is further demonstrated in a landmark analysis for which results have been presented in the new evidence form, previously submitted to NICE. In addition, no waning was applied in the appraisals of alirocumab TA393, evolucumab TA394 and inclisiran TA733, which are in a similar disease area (hypercholesterolaemia and mixed dyslipidaemia). The company therefore believes it is reasonable to assume that the treatment benefit of icosapent ethyl would be maintained beyond the trial period, and therefore no treatment waning should be applied in the base case.

We confirm that the updated company base case already includes updates to event cost calculations and treatment-dependent non-CV related mortality hazard ratios.

Table 1 below provides a summary of the cost-effectiveness results in the secondary prevention population for the scenario analyses requested by the NICE technical team.

Scenarios

Table 1: Additional scenarios requested by the NICE technical team

Scenario number	Scenario description	Population	Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
1	***Company new base case (exponential extrapolation for TTD and no treatment waning applied)***	***Deterministic results***								
		Secondary prevention	Icosapent ethyl	22,589	10.618	7.703	10,534	0.392	0.462	22,796
			BSC	12,055	10.226	7.241	-	-	-	-
		Probabilistic results								
		Secondary prevention	Icosapent ethyl	22,103	-	7.602	9,978	-	0.452	22,075
			BSC	12,125	-	7.150	-	-	-	-
2	***Log-logistic extrapolation for TTD (1+2)***	Secondary prevention	Icosapent ethyl	23,697	10.618	7.703	11,642	0.392	0.462	25,193
			BSC	12,055	10.226	7.241	-	-	-	-
3	***10-year post trial treatment waning* (1+3)***	Secondary prevention	Icosapent ethyl	23,132	10.564	7.650	11,078	0.338	0.409	27,086
			BSC	12,055	10.226	7.241	-	-	-	-
4	***Combined scenario (1+2+3)***	Secondary prevention	Icosapent ethyl	24,224	10.564	7.650	12,170	0.338	0.409	29,756
			BSC	12,055	10.226	7.241	-	-	-	-

*Applied to the third plus events only

Sensitivity analyses (ran using scenario 4 above)

Table 2 below provides a summary of the cost-effectiveness results in the secondary prevention population for the sensitivity analyses requested by the NICE technical team.

Please note that for sensitivity analyses 2-4 below, it was not possible to apply the Weibull distribution to the trial data as this causes an error which does not allow the parameter coefficients to be obtained for this distribution. An error is also produced in sensitivity analysis 4 when selecting the generalised gamma distribution, due to the fact that the curve does not fit the trial data appropriately.

Table 2: Additional sensitivity analyses requested by the NICE technical team

Sensitivity analysis number	Sensitivity analysis description	Population	Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
1	***20-year post trial treatment waning****	Secondary prevention	Icosapent ethyl	24,088	10.577	7.664	12,034	0.351	0.423	28,455
			BSC	12,055	10.226	7.241	-	-	-	-
2	***Time to event curve for the first event***									
	Exponential (base case)	Secondary prevention	Icosapent ethyl	24,224	10.564	7.650	12,170	0.338	0.409	29,756
			BSC	12,055	10.226	7.241	-	-	-	-
	Gompertz		Icosapent ethyl	24,134	10.601	7.684	12,198	0.343	0.413	29,547
			BSC	11,936	10.258	7.271	-	-	-	-
	Log-logistic		Icosapent ethyl	24,026	10.648	7.727	12,392	0.311	0.380	32,582
			BSC	11,633	10.337	7.346	-	-	-	-
	Lognormal		Icosapent ethyl	23,735	10.746	7.821	12,587	0.294	0.361	34,821
			BSC	11,148	10.452	7.460	-	-	-	-
			Icosapent ethyl	24,099	10.613	7.695	12,286	0.327	0.397	30,976

Sensitivity analysis number	Sensitivity analysis description	Population	Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
	Generalised Gamma		BSC	11,813	10.286	7.298	-	-	-	-
3	***Time to event curve for the second event***									
	Exponential	Secondary prevention	Icosapent ethyl	24,070	10.598	7.685	12,052	0.359	0.429	28,090
			BSC	12,018	10.238	7.255	-	-	-	-
	Gompertz		Icosapent ethyl	24,392	10.460	7.545	12,361	0.326	0.404	30,623
			BSC	12,031	10.134	7.142	-	-	-	-
	Log-logistic (base case)		Icosapent ethyl	24,224	10.564	7.650	12,170	0.338	0.409	29,756
			BSC	12,055	10.226	7.241	-	-	-	-
	Lognormal		Icosapent ethyl	24,022	10.624	7.708	12,050	0.318	0.389	30,984
			BSC	11,972	10.306	7.319	-	-	-	-
	Generalised Gamma		Icosapent ethyl	24,244	10.556	7.642	12,201	0.344	0.416	29,357
			BSC	12,044	10.212	7.227	-	-	-	-
4	***Time to event curve for the third plus events***									
	Exponential	Secondary prevention	Icosapent ethyl	23,550	10.633	7.716	12,621	0.316	0.390	32,353
			BSC	10,929	10.317	7.326	-	-	-	-
	Gompertz		Icosapent ethyl	24,312	10.566	7.646	11,567	0.374	0.448	25,797
			BSC	12,745	10.192	7.197	-	-	-	-
	Log-logistic (base case)		Icosapent ethyl	24,224	10.564	7.650	12,170	0.338	0.409	29,756
			BSC	12,055	10.226	7.241	-	-	-	-

Sensitivity analysis number	Sensitivity analysis description	Population	Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
	Lognormal		Icosapent ethyl	23,854	10.604	7.688	12,575	0.310	0.384	32,739
			BSC	11,279	10.294	7.304	-	-	-	-

*Applied to the third plus events only

Additional information request: Icosapent ethyl with statin therapy for reducing the risk of cardiovascular events in adults with elevated triglycerides [ID3831]

Please find below the additional sensitivity analyses in the **secondary prevention (CV1) population** as requested by the NICE technical team, using treatment independent non-CV related death hazard ratios.

However, as mentioned in the responses to the technical engagement, the company believes that the most appropriate choice is to use treatment dependent hazard ratios, due to patients experiencing a different distribution of events per treatment group in the REDUCE-IT trial which were non-CV death related modifiers.

We also believe that the exponential curve is the most appropriate curve to use in order to extrapolate TTD, as this curve has the best fit to the trial data based on the AIC, BIC and visual inspection (in the absence of clinical practice experience with icosapent ethyl).

Furthermore, it is the company's position that treatment waning should not be applied in the base case, since the Kaplan-Meier event curves for the primary efficacy 5-point MACE composite endpoint show that the treatment effect increases over time before stabilising. This treatment effect is further demonstrated in a landmark analysis for which results have been presented in the new evidence form, previously submitted to NICE. In addition, no waning was applied in the appraisals of alirocumab TA393, evolucumab TA394 and inclisiran TA733, which are in a similar disease area (hypercholesterolaemia and mixed dyslipidaemia). The company therefore believes it is reasonable to assume that the treatment benefit of icosapent ethyl would be maintained beyond the trial period, and therefore no treatment waning should be applied in the base case.

Table 1 below provides a summary of the cost-effectiveness results in the secondary prevention population for the sensitivity analyses requested by the NICE technical team.

Table 1: Additional scenarios requested by the NICE technical team

Scenario number	Scenario description	Population	Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
1	***Company new base case (exponential extrapolation for TTD and no treatment waning applied)***	***Deterministic results***								
		Secondary prevention	Icosapent ethyl	22,589	10.618	7.703	10,534	0.392	0.462	22,796
			BSC	12,055	10.226	7.241	-	-	-	-
		Probabilistic results								
		Secondary prevention	Icosapent ethyl	22,103	-	7.602	9,978	-	0.452	22,075
			BSC	12,125	-	7.150	-	-	-	-
2	***Log-logistic extrapolation for TTD (1+2)***	Secondary prevention	Icosapent ethyl	23,697	10.618	7.703	11,642	0.392	0.462	25,193
			BSC	12,055	10.226	7.241	-	-	-	-
3	***10-year post trial treatment waning* (1+3)***	Secondary prevention	Icosapent ethyl	23,132	10.564	7.650	11,078	0.338	0.409	27,086
			BSC	12,055	10.226	7.241	-	-	-	-
4	***Treatment independent non-CV related death HRs (1+4)***	Secondary prevention	Icosapent ethyl	22,554	10.602	7.692	10,456	0.354	0.438	23,899
			BSC	12,098	10.247	7.254	-	-	-	-
5	***Combined scenario (1+2+3+4)***	Secondary prevention	Icosapent ethyl	24,200	10.555	7.643	12,102	0.307	0.389	31,121
			BSC	12,098	10.247	7.254	-	-	-	-

*Applied to the third plus events only

NICE National Institute for Health and Care Excellence

Clinical expert statement & technical engagement response form

Icosapent ethyl with statin therapy for reducing the risk of cardiovascular events in adults with elevated triglycerides [ID3831]

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

Please return this form by **5pm** on **Tuesday 9 November 2021**.

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

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- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with elevated triglycerides at risk of cardiovascular events and current treatment options	
About you	
1. Your name	**Dr Peter Howard Winocour**
2. Name of organisation	**Representing ABCD**
3. Job title or position	**Consultant Diabetologist**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? **X**☐ a specialist in the treatment of people with elevated triglycerides at risk of cardiovascular events? ☐ a specialist in the clinical evidence base for people with elevated triglycerides at risk of cardiovascular events or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	**X**☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	**X**☐ yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Nil**
The aim of treatment for people with elevated triglycerides at risk of cardiovascular events	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To reduce the risk of developing CVD, diabetes and on occasion pancreatitis . Potential improvement in glycaemic control
9. What do you consider a clinically significant treatment response? (For example, a	Reduction in trigs by 15% + NB The CVD outcome benefits of EPA in REDUCE-IT (eg similar with eg gliflozin CVD outcomes) may be greater than expected from reduction in trigs and as suggested reflect additional mechanisms of action-benefit

reduction in disease activity by a certain amount.)	
10. In your view, is there an unmet need for patients and healthcare professionals in patients with elevated triglycerides at risk of cardiovascular events?	Yes
What is the expected place of icosapent ethyl in current practice?	
11. How is the condition currently treated in the NHS?	Apart from fibrates and very high doses of fish oils the loss of nicotinates from care means that there is no effective treatment once statins optimised for residual hypertrig – NB this study showed CVD benefit which is a harder outcome than simply managing the dyslipidaemia
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	ESC /EAS and ABCD UKKA renal lipid guidelines
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Not really well defined – within primary care, lipid , cardiology diabetes services there may be less clear protocols

• What impact would icosapent ethyl have on the current pathway of care?	Would in the range of clinic settings stated enable IcosaPentEthyl introduction if criteria met
12. Will icosapent ethyl be used (or is it already used) in the same way as current care in NHS clinical practice?	It would be additive to statins as stated in REDUCE IT – not being used at present
• How does healthcare resource use differ between icosapent ethyl and current care?	There is no effective management of the residual dyslipidaemia at present unless high dose eg Fish Oil Maxepa used where there is no CVD benefit . in addition combination DHA EPA does not show the same clinical outcomes as high dose EPA alone
• In what clinical setting should icosapent ethyl be used? (For example, primary or secondary care, specialist clinics.)	All settings – primary care , lipid , cardio and DM clinics. By definition there will be more suitable patients in the primary care setting
• What investment is needed to introduce icosapent ethyl? (For example, for facilities, equipment, or training.)	Modest educational on line support
13. Do you expect icosapent ethyl to provide clinically meaningful	Yes

benefits compared with current care?	
• Do you expect icosapent ethyl to increase length of life more than current care?	Yes – but main impact morbidity
• Do you expect icosapent ethyl to increase health-related quality of life more than current care?	Yes
14. Are there any groups of people for whom icosapent ethyl would be more or less effective (or appropriate) than the general population?	DM with CVD esp + role Issues in those with AF-bleeding diathesis
The use of icosapent ethyl	
15. Will icosapent ethyl be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional	The issues around bleeding tendency and AF need assessment and may preclude use in such cases

clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
16. Will any rules (informal or formal) be used to start or stop treatment with icosapent ethyl? Do these include any additional testing?	If develops AF or bleeding issues ? withdraw permanently
17. Do you consider that the use of icosapent ethyl will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Possible impact on insulin resistance ?? fatty liver , diabetes control
18. Do you consider icosapent ethyl to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	Yes – no other effective high dose EPA with evidence base and on top of usual standard of care of high risk cases

improve the way that current need is met?	
• Is icosapent ethyl a 'step-change' in the management of the condition?	Yes
• Does the use of icosapent ethyl address any particular unmet need of the patient population?	Raised trigs and linked residual CVD metabolic risk
19. How do any side effects or adverse effects of icosapent ethyl affect the management of the condition and the patient's quality of life?	Bleeding and AF risk both impt and detectable issues although modest rates of increase
Sources of evidence	
20. Do the clinical trials on icosapent ethyl reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	

• What, in your view, are the most important outcomes, and were they measured in the trials?	Key MACE measured DM control , fatty liver , Insulin resistance issues potential measures
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Hard CVD outcomes were assessed
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not to my knowledge
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	Many surveys of T2DM care show residual dyslipidaemia wrt triglycerides

Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	Impt to ensure access to all ethnic groups – study may have limited representation from BAME
23b. Consider whether these issues are different from issues with current care and why.	

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the issues below, but you do not have to answer every issue. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Key issue 1: Population of main clinical effectiveness evidence, REDUCE-IT trial, narrower than scope and decision problem	Appropriated
Key issue 2: The period to determine a stable dose of statin in REDUCE-IT is likely to be less than in clinical practice	To all intents and purposes the minimum period stated is adequate as triglyceride reduction less evdientr with statin use

Key issue 3: Composite outcomes (MACE) instead of disaggregated outcomes e.g. CV death used as primary outcome and used in the model	In line with other CVD outcome studies re composite MACE
Key issue 4: Unclear generalisability of the results to patients in the UK NHS setting	Fully generalizable to NHS high risk Did NDA have this info re T2DM wrt more lipid abno than just cholesterol ? HDL as well as ?? trigs
Key issue 5: Model structure – partitioned survival analysis (partSA)	
Key issue 6: Use of reconstituted data	
Key issue 7: Limited evidence available for (long-term) validation of survival curves	Acceptable

Key issue 8: Use of stratified parametric models, methodological guidance not followed	
Key issue 9: Long-term extrapolation, assumption of no treatment waning	Takes account of likely drop off an mortality
Key issue 10: Use of treatment-dependent non-CV related death hazard ratios	
Key issue 11: Health-related quality of life sensitive to choice of utility source	
Key issue 12: Event costs not adjusted for time since previous event	

Key issue 13: The distribution to extrapolate time to discontinuation	Given the high risk population and long term extrapolation the exponential curve would seem a reasonable expectation of continued use of therapy
Key issue 14: Inconsistent use of sources and calculation of event costs	
Key issue 15: Incomplete model validation and face validity check	
Are there any important issues that have been missed in ERG report?	

PART 3 -Key messages

24. In up to 5 sentences, please summarise the key messages of your statement:

- High risk CVD cases on current statin use still have high residual risk in part attributable tpo residual hypertriglyceridaemia
- EPA manages this and importantly those with and without the frequent linked low HDL

- The benefits are clear on MACE and this of value for high risk cases
- The REDUCE-It outcome data raise important possibility there may be additional mechanisms for the beneficial CVD outcomes
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

.....

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The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

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NICE National Institute for Health and Care Excellence

Clinical expert statement & technical engagement response form

Icosapent ethyl with statin therapy for reducing the risk of cardiovascular events in adults with elevated triglycerides [ID3831]

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  OR
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NICE National Institute for Health and Care Excellence

PART 1 – Treating a patient with elevated triglycerides at risk of cardiovascular events and current treatment options	
About you	
1. Your name	**Riyaz Patel**
2. Name of organisation	**University College London**
3. Job title or position	**Professor of Cardiology and Consultant Cardiologist**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with elevated triglycerides at risk of cardiovascular events? ☒ a specialist in the clinical evidence base for people with elevated triglycerides at risk of cardiovascular events or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
The aim of treatment for people with elevated triglycerides at risk of cardiovascular events	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The aim of treatment is to reduce residual cardiovascular risk in people at high risk of CVD events. Currently, in secondary prevention, even optimally treated patients surviving from CVD, remain at very high risk of further CVD events and progression of vascular disease. Some estimates suggest between 5-10% per year experience a MACE for example after a non-fatal ACS. For primary prevention those with diabetes and other risk factors are also at high risk despite contemporary therapy. The expanding literature base on triglyceride rich lipoproteins, suggests that in people with high triglyceride concentrations, there remains an untreated risk, potentially due to a pool of cholesterol not contained within LDL particles, but in other potentially atherogenic apoB containing particles like VLDL and IDL (which contain both TGs and cholesterol) and also possibly due to co-existing inflammation. The expectation is that is that by reducing these triglyceride rich lipoproteins (in size and number) and the TG & cholesterol within them, this could help tackle some of the residual risk mentioned above. Historically it has been uncertain whether triglycerides themselves are causal for atherosclerosis. From observational studies we know that high TG levels associate with pancreatitis and pancreatic insufficiency. Severely elevated TGs are often treated to reduce risk of pancreatitis, especially when levels exceed 10mmol/L, although emerging data suggests a lower threshold at 5mmol/L may be needed. Observational data also suggests that at more moderate

	elevations of TGs, <10mmol/L, the risk of CVD also increases. At higher TG levels there is no increase in risk likely due to high lipoprotein particle size limiting entry into the intima. As such, using the totality of evidence, circulating Triglyceride concentrations at moderate levels can reasonably be considered as a marker of untreated risk. However, whether triglycerides per se, play a direct role in plaque development is still unclear and not yet widely accepted. The main aim of treatment is thus to reduce CVD risk in patients who have high TG levels, which identifies those patients at raised CVD risk.
9. What do you consider a clinically significant treatment response? (For example, a reduction in disease activity by a certain amount.)	Any relative risk reduction in MACE, within 5 years close to 15-20% would be clinically significant. Or absolute event rate reduction of ~2-3%
10. In your view, is there an unmet need for patients and healthcare professionals in patients with elevated triglycerides at risk of cardiovascular events?	There is certainly an unmet need for residual risk lowering in this population. The prevalence of people with co-existing moderately raised triglycerides and high CVD risk is rising everyday with increasing diabetes and obesity rates. Currently we treat such patients with statins to lower LDL, lifestyle changes, manage any secondary causes of high TGs and then if TGs remain raised, we have no option but to leave them as they are. In the past there was a tendency to use TG lowering agents for moderate elevations of TG, but these have not shown any CVD risk reduction benefits and are not recommended by current NICE guidance. I suspect the need may be greater in those with established CVD (~6M in the UK live with CVD), where even optimally treated patients with the best antithrombotic and most intensive LDL lowering still have high risk of recurrent CVD events. Any new drug that can target different pathways to these, are sorely needed to tackle residual CVD risk as we may have hit a ceiling of effect with the existing pathways.
What is the expected place of icosapent ethyl in current practice?	

11. How is the condition currently treated in the NHS?	This specific condition or patient group (raised CVD risk with elevated TGs) is not currently treated in the NHS. We treat all patients with elevated CVD risk with high intensity statin therapy (+other LDL lowering agents) but do not offer anything further to those who also have high TGs and may be at higher risk.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	None in the UK that I am aware of. The 2021 ESC guidelines on CVD prevention, propose use of statins in people with high TG levels for reducing risk with a class I/level A recommendation. The same guidance advocates use of fibrates if TG levels are >2.3mmol/L, giving this a IIb/B recommendation and similarly gives icosapentyl ethyl a IIb/B recommendation if TG levels are >1.5mmol/L. The 2019 ESC guidelines on dyslipidaemia gives a class IIa/B recommendation for use of icosapentyl ethyl in patients at high risk with TG levels 1.5-5.6 in combination with a statin.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The management of LDL is well defined and there is an AAC pathway that spells out very nicely how to manage lipids for primary and secondary prevention of CVD. However, this does not cover treatment of those with raised TG levels and at high CVD risk. As a side note, there is a difference of opinion between international guidelines on how to manage very high TG levels for reducing the risk of acute pancreatitis, with some suggesting treatment with TG lowering agents at higher (~>10) or lower (~>5) thresholds. For CVD risk reduction the focus is on the lower range between 1.7- ~5mmol/L
• What impact would icosapent ethyl have on the current pathway of care?	I would imagine that the AAC pathway would need to be modified with a new decision branch to propose that once LDL has been optimised, and if TGs remain high (1.5-5.6mmol/L) on a fasting sample then icosapentyl ethyl could be added for additional CVD risk reduction. In theory as the benefit was independent of LDL levels, the LDL optimization requirement could be omitted and just state once on high intensity statin therapy and if TGs raised consider the agent. My view though is that there is much more robust data on LDL lowering and so this should be optimized first and then icosapentyl ethyl could be considered as add on therapy for additional risk lowering.
12. Will icosapent ethyl be used (or is it already used) in the same	The drug is not currently used and the patient population not treated in any different way to others at high risk without TG elevation. It would be used as an additional agent to existing clinical practice.

way as current care in NHS clinical practice?	
• How does healthcare resource use differ between icosapent ethyl and current care?	It is a new agent to be added to standard care. A major difference will be the need to assess TG levels to ensure eligibility for the drug. As per NICE CG181, at 3 months after starting a statin, only a non-HDL is measured, (TC and HDL are measured, not a full lipid panel). This is also done for cost reasons with many CCGs refusing to measure lipid profiles. Annual reviews for people with CVD or at high risk also only include a non-fasting non-HDL assessment. Therefore, based on current practice, many people will not be identified as having raised TGs at the 3month post statin or annual review stages. If this drug is recommended, then a full fasting lipid profile will need to be assessed and existing guidance modified to advise this.
• In what clinical setting should icosapent ethyl be used? (For example, primary or secondary care, specialist clinics.)	For maximum impact on CVD risk reduction, and in line with population health management, I would expect it to be available to both primary and secondary care. In secondary care, after a CVD event the focus is usually on initiating a statin. The trial did not administer the drug to patients immediately after a CVD event, and required at least 4 weeks of statin stabilization, so most patients were stable at recruitment. However, patients could be flagged in secondary care for potential consideration of icosapentyl ethyl in due course, on the discharge summary. Drug initiation in hospitals would be in outpatient settings in cardiology clinics where patients with CVD or those at high risk are seen and managed or by specialist lipid clinics advising on similar patients. I would anticipate that the majority of initiation would be in primary care for stable patients at high CVD risk. However, the biggest challenge is education of the primary care workforce on the place and role of this agent. Currently, primary care as a whole still struggles with lipid management (and especially TG management), and personal interaction with GP colleagues suggests many are feeling overwhelmed at the different drugs and guidance available in this space. On top of that, there is pushback from more people about the value of managing lipids and CVD risk. On top of this, many areas still have large swathes of eligible people not on high dose statins (eg ~50% of people with CVD are not on high intensity statin in our local area), who probably ought to be managed with LDL lowering first

	For it to work, the AAC pathway will need to be updated, ongoing education continued in primary care along with a strong steer provided from secondary care and specialist clinics for which patients to be started on this agent. Robust advice and guidance set up may also be needed to support GPs and regular audit to ensure appropriate use of the drug.
• What investment is needed to introduce icosapent ethyl? (For example, for facilities, equipment, or training.)	Training and education of healthcare practitioners about the benefit of this drug and its place in the lipid management pathway – when and when not to use it. Consideration of the need for measuring a full fasting lipid profile – not routinely performed- to assess eligibility for the drug and the cost of this
13. Do you expect icosapent ethyl to provide clinically meaningful benefits compared with current care?	As there is no current treatment for this group of patients and given the impressive relative risk reduction seen in the trials, I would expect to see a benefit. However, this is caveated by the concerns about the trial and whether the benefit may have been to some extent exaggerated. Looking at the STRENGTH study data alongside REDUCE IT and factoring in the differences and potential non TG mediated changes, my feeling is there will be a benefit but perhaps not as high as in the trial, once a real world population without a mineral oil placebo is considered.
• Do you expect icosapent ethyl to increase length of life more than current care?	Potentially, but not certain. In the study with hierarchical testing, there was a borderline reduction in CVD death (HR 0.80 (0.66-0.98)) and marginal for all cause death HR 0.87 (0.74-1.02).
• Do you expect icosapent ethyl to increase health-related quality of life more than current care?	Yes, if CVD events are reduced as anticipated, especially stroke, which was significantly reduced.

14. Are there any groups of people for whom icosapent ethyl would be more or less effective (or appropriate) than the general population?	The study showed a consistent benefit for almost all prespecified subgroups. What is interesting is that the baseline level of TG or LDL had no bearing on the risk reduction, suggesting its mechanism may be independent of lipid pathway modulation. There may be greater benefit for secondary prevention (those with CVD), but this may be power related due to fewer events in the primary prevention subgroup. Of note those <65 may have gained greater benefit (p for interaction 0.004). As the lower age limit was 45, this is an age group enriched for premature CVD and so may have more people with genetically driven dyslipidaemias such as FCH. Finally, the subgroup analysis suggested a possible greater benefit for those with a more metabolic syndrome picture with low HDL (<0.9mmol/L) and high TG (>2.25mmol/L). This is consistent with other studies on fish oils.
The use of icosapent ethyl	
15. Will icosapent ethyl be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	No current care so it will be added as an additional medication for eligible patients A practical implication will be the need to assess TG levels to ensure eligibility for the drug. As per NICE CG181, at 3 months after starting a statin, only a non-HDL is recommended, (TC and HDL are measured, not a full lipid panel). This is also done for cost reasons with many CCGs not supporting measurement of full lipid profiles. Annual reviews for people with CVD or at high risk also only include a non-fasting non-HDL assessment or in some areas just a TC Therefore, based on current practice, many people will not easily be identified as having raised TGs at the 3month post statin or annual review stages. If this drug is recommended, then a full fasting lipid profile will need to be assessed and existing guidance modified. I am not aware that any additional monitoring is needed. Certainly, TGs do not need to be monitored to gauge effectiveness as the effect seems independent of baseline and treated TG values.

	From a patient acceptability, the risk of constipation may be an issue, as would the potential risks of AF and bleeding. Also, the product is made from fish oil so some patients may not be willing to take it.
16. Will any rules (informal or formal) be used to start or stop treatment with icosapent ethyl? Do these include any additional testing?	The definition of high-risk patients will need be carefully defined as the definition differs slightly in different guidelines, or the same strict definition used in the study is applied – but may complicate things. Ideally it would be better to have a single definition of "high risk" applied across the suite of NICE CVD prevention guidance and TAs. Perhaps one rule may be to first ensure LDL has been optimally lowered and patients are statin compliant. Importantly, I am unclear if the drug would be denied to those unable to take a statin given the trial only included those on a statin and had a run-in period thereby excluding those who were stain intolerant. There may be people who are statin intolerant on a PCSK9 inhibitor (either mAB or inclisiran) and have raised TGs. It would seem strange to deny them the drug and I cannot see any biological reason for doing so. Whether bleeding and AF are considered in decision making around whether to use the drug needs to be assessed. For example, there may need to be caution in those with diagnosed PAF.
17. Do you consider that the use of icosapent ethyl will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	None that would be outside the QALY calculations Possibly acute pancreatitis reduction although this would be a small benefit as incidence is low especially at these moderately raised TG levels.
18. Do you consider icosapent ethyl to be innovative in its potential to make a significant and	It is innovative as it appears to work on a pathway that is as yet undefined yet with a substantial benefit. As the current need is not met with any other similar drug it will provide new health benefits.

substantial impact on health-related benefits and how might it improve the way that current need is met?	I would make the comparison with SGLT2 / GLP1, which were designed for diabetes yet have dramatic CVD benefits and we still don't know for sure the mechanism by which they do this.
• Is icosapent ethyl a 'step-change' in the management of the condition?	I would hesitate to call it a "step-change" as other fish oils are available and it will not be viewed by the public as a completely novel treatment (the subtlety of purified EPA and EPA/DHA will be lost on most). This is the first to prove a large CV risk benefit, so it is novel in that sense – albeit with a cloud over the trial.
• Does the use of icosapent ethyl address any particular unmet need of the patient population?	Yes, those with residual CVD risk and high TG levels.
19. How do any side effects or adverse effects of icosapent ethyl affect the management of the condition and the patient's quality of life?	It seems to be a generally well tolerated drug with few significant side effects. There are some concerns: AF risk – this is an important signal as hospitalization for AF is not trivial. It carries with it patient symptoms, admission, medication usage, potential DC cardioversion and anticoagulation. This I suspect would need to be considered when prescribing and should be used with caution in people with known PAF or prior AF Bleeding – possible increased risk but again might just be used as a caution in those with bleeding tendencies. Most people with CVD are on antiplatelets as in the trial and did not experience very high bleeding rates so this should not be a major concern. However more data would be needed especially for those on multiple antithrombotic agents – eg DOAC + clopidogrel

	Constipation – of note this could be a factor that reduces compliance. Diarrhoea was less in the treatment arm, perhaps due to the constipating effect of the drug. Peripheral oedema – this could lead to drug discontinuation and impair quality of life. Might lead to empirical use of diuretics.
Sources of evidence	
20. Do the clinical trials on icosapent ethyl reflect current UK clinical practice?	To some extent, the population in the trial can be found in the UK, if we looked for it. However, the UK was not represented in the study, so our populations were not included in the study itself. This is relevant especially for ethnic minority groups, who have higher levels of CVD, and TGs and insulin resistance and might have benefitted more. The biggest difference is that current UK practice does not incorporate assessment of TGs routinely during the care pathway and also does not stipulate an LDL target. As such both parameters are not routinely assessed and therefore the eligible population based on the trial criteria (TG and LDL levels) would not be easily identified in routine care.
• If not, how could the results be extrapolated to the UK setting?	Exploring the demographic and risk factor profiles of those in the study in more detail and comparing to the UK population from information such as CPRD or Health survey England etc. This would need the trial data to be split by secondary and primary prevention as this data is aggregated in the paper. After that assuming they are similar, we can only extrapolate from the included US population and make the assumption that there are no significant biological differences in factors that might affect the efficacy of the drug.

• What, in your view, are the most important outcomes, and were they measured in the trials?	Major CVD outcomes – yes, all were measured
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Additional biomarker changes were assessed but they were used more to explore the mechanism of action
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	None that I'm aware of
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	I presume all relevant studies for the concept have been examined? Relevant studies to REDUCE-IT = JELIS trial, EVAPORATE, STRENGTH, CHERRY Observational data and Mendelian randomization on TG associations with CVD may be of interest
22. How do data on real-world experience compare with the trial data?	I don't have any real-world experience of this agent and am not aware of any data on this.
Equality	

23a. Are there any potential equality issues that should be taken into account when considering this treatment?	TG levels are higher in BAME patients, due to diabetes, obesity and insulin resistance, and they also have more CVD so this group may benefit more from the drug. More people are or becoming Vegan or Vegetarian and therefore may not be able or willing to take this drug which I think is made from sardines and anchovies. Similarly, there might be religious restrictions on seafood for some people.
23b. Consider whether these issues are different from issues with current care and why.	Usual medicines are not made from animal products, so most people do not object to them.

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the issues below, but you do not have to answer every issue. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Key issue 1: Population of main clinical effectiveness evidence, REDUCE-IT trial, narrower than scope and decision problem	The ERG suggest the scope should be in line with the study criteria and propose 135mg/dL as the definition of high triglycerides (not sure where this comes from as the NEJM paper states the initial cut point was 150 and then increased to 200mg/dL)). NICE just states hypertriglyceridaemia. The accepted definition of this is 1.7mmol/L (150mg/dL), which fits with the initial TG cut point used in the trial. It was later increased to 2.2mmol/L, but there was no difference in efficacy when stratified by baseline TG. Given that 1.7mmol/L is an accepted threshold for defining hypertriglyceridaemia, I would keep it as it is. With regards to age, the study did restrict to >45 for secondary prevention. There was an age interaction with a trend to greater benefit in younger patients. This could be because more genetically driven raised TGs are present in younger people rather than secondary causes. In my view, there is no biological reason to restrict use of the drug to those over 45. We certainly see many younger people with CVD or diabetes who have raised TGs, especially among the South Asian population. As such restricting to age >45 or >50 may disadvantage people at risk.

	Restricting to LDL levels to 1-2.6mmol/L, could add a layer of complexity to use of the drug in the UK as LDL is not routinely measured and only non-HDL is advocated by NICE guidance. It should be sufficient to ensure that a high intensity statin is used (or proven intolerance) before the agent is offered. LDL lowering and management should continue thereafter in parallel with other agents like ezetimibe, bempedoic acid or PCSK9i. As efficacy again did not vary by baseline LDL levels, this would not make sense and would just add more cost and complexity to initiation.
Key issue 2: The period to determine a stable dose of statin in REDUCE-IT is likely to be less than in clinical practice	I agree that in clinical practice, and based on NICE guidance, we check LFTs and non-HDL at 3 months after statin initiation. Doing so any sooner is unlikely to be pragmatic and would introduce cost. In my view if a patient is on statin therapy for longer than 4 weeks, this is not an issue as there is no biological reason to assume it would have any impact on the efficacy of the drug. Possibly LDL may be a bit lower if assessed later but as we have seen the effect was not related to baseline LDL concentration. Pragmatically I would expect patients to be started on a statin, have a 3 month blood test (would need to be a fasting lipid profile - a change to current practice) and if at that time they also have high TGs (>1.7), the doctor would start the agent. If this was an even longer time frame, perhaps as it happened in an outpatient consultation, it should make no material difference.
Key issue 3: Composite outcomes (MACE) instead of disaggregated outcomes e.g. CV death used as primary outcome and used in the model	It is fair to say most major trials use a composite MACE outcome. Individual endpoints on hierarchical testing are provided and could be used as needed by the NICE team.

Key issue 4: Unclear generalisability of the results to patients in the UK NHS setting	I agree with the ERG on this point. For example, the UK population has a high proportion of BAME patients and a population overall with a slightly different risk profile for metabolic disease compared to the populations studied in the trial. My suspicion is that it may not be so important, and we can extrapolate from the US but certainly some more clarity on the demographics and risk profile of the US population would help. The data would need to be separated by secondary prevention and primary prevention cohorts. This could then be compared with the Steen data or to UK health survey data or information from other UK sources (e.g. CPRD). This would allay any fears about generalizability or demonstrate significant differences.
Key issue 5: Model structure – partitioned survival analysis (partSA)	Apologies, unable to comment
Key issue 6: Use of reconstituted data	Apologies, unable to comment
Key issue 7: Limited evidence available for (long-term) validation of survival curves	Apologies, unable to comment
Key issue 8: Use of stratified parametric models,	Apologies, unable to comment

methodological guidance not followed	
Key issue 9: Long-term extrapolation, assumption of no treatment waning	There is not much data to guide the assumption that treatment does not wane. Statin therapy appears to have a long-term effect based on available studies such as long term follow up of WOSCOPS. This could be extrapolated, biologically, to other LDL lowering agents. However, as icosapentyl ethyl has a mechanism that is as yet uncertain I am not sure we can use the same assumption. There is a suggestion in the literature that icosapentyl ethyl works by affecting oxidative stress or inflammation, endothelial function etc, which may be more short-term effects or ones that could vary over time or with intercurrent illnesses or non CVD drugs or recurrent events. I note the JACC study by Bhatt et al in 2019 on subsequent events in REDUCE IT, where they report that 1606 primary outcome first events took place as reported in NEJM, but after this another 1303 recurrent events also occurred. The authors state that the drug reduced the rate of these recurrent events too, compared to placebo, suggesting the drug has an effect on first and subsequent event reduction. I believe the company use this to extrapolate on longer term effects of the drug. I don't think this is unreasonable.
Key issue 10: Use of treatment-dependent non-CV related death hazard ratios	Apologies, unable to comment
Key issue 11: Health-related quality of life sensitive to choice of utility source	Apologies, unable to comment

Key issue 12: Event costs not adjusted for time since previous event	Apologies, unable to comment
Key issue 13: The distribution to extrapolate time to discontinuation	Given the mean age of REDUCE-IT participants was 65, extrapolating to 40 years is somewhat artificial. Most people would take the drug until perhaps 80 yrs, after which medications like this would likely be stopped. Nonetheless, most CVD drugs seem to have a long-term adherence rate of about 60%. As such the models in figure 4.2 seem a bit conservative and the Gompertz or Lognormal models may be closest to expectations. For example: Wei L, Fahey T, MacDonald TM. Adherence to statin or aspirin or both in patients with established cardiovascular disease: exploring healthy behaviour vs. drug effects and 10-year follow-up of outcome. Br J Clin Pharmacol. 2008;66:110–116 For primary prevention discontinuation may be greater, especially if used in younger people with polypharmacy
Key issue 14: Inconsistent use of sources and calculation of event costs	Apologies, unable to comment
Key issue 15: Incomplete model validation and face validity check	Apologies, unable to comment

Are there any important issues that have been missed in ERG report?	

PART 3 -Key messages

24. In up to 5 sentences, please summarise the key messages of your statement:

- There is an unmet need to help those at highest CVD risk, who remain vulnerable to more CVD events despite optimal contemporary treatments and people with high CVD risk and raised triglycerides represent a potential group of people in whom we could do more.
- In UK practice, especially primary care, there has been a big move away from measuring lipid profiles and TG levels, in favour of non-HDL, so for this drug to be used widely there would need to be a move back towards checking the full lipid profile at some stage in the patient journey
- There is a growing population of people with raised TGs and CVD risk, as a result of rising diabetes and obesity levels and confusion around how to deal with this, so a large piece of work on education of healthcare professionals on the role of TGs in disease will be needed.
- There may be some issues around patient acceptability as the drug is extracted from fish, affecting those with dietary or religious restrictions
- I think the drug could have a meaningful impact in clinical practice and it would be helpful to have available for the many patients who continue to have events, but as with most colleagues, my confidence would be greater if we didn't have the limitations/concerns of the JELIS/REDUCE-IT trials and we had a better mechanistic understanding of how the benefit arises.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

.....

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Icosapent ethyl with statin therapy for reducing the risk of cardiovascular events in adults with elevated triglycerides [ID3831]

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

About this Form

In **part 1** we are asking you to complete questions about living with or caring for a patient with the condition.

In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.

The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a patient perspective could help either:

- resolve any uncertainty that has been identified
  or
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

If you have any questions or need help with completing this form please email the public involvement team via pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

NICE National Institute for Health and Care Excellence

Please return this form by **5pm** on **Tuesday 9 November 2021**.

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee. The text boxes will expand as you type.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 15 pages.

PART 1 – Living with or caring for a patient with elevated triglycerides at risk of cardiovascular events and current treatment options	
About you	
1.Your name	**Jules Payne**
2. Are you (please tick all that apply):	☐ a patient with elevated triglycerides at risk of cardiovascular events? ☐ a patient with experience of the treatment being evaluated? ☐ a carer of a patient with elevated triglycerides at risk of cardiovascular events? ☐ X a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation.	HEART UK – The Cholesterol Charity
4. Has your nominating organisation provided a submission? Please tick all options that apply.	☐ No, (please review all the questions below and provide answers where possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement

	☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience. ☐ **X** I have other relevant knowledge/experience (e.g. I am drawing on others' experiences). Please specify what other experience: experience from our helpline ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
Living with the condition	
6. What is your experience of living with elevated triglycerides at risk of cardiovascular events? If you are a carer (for someone with elevated triglycerides at risk of cardiovascular events) please share your experience of caring for them.	The biggest challenge currently is to get a test done, especially in primary care. Testing is important as the condition, if raised, often doesn't show symptoms. When patients are diagnosed they need to adjust their diet and lifestyle in the first instance. This can often be challenging but HEART UK can assist with this. For some a change in diet and lifestyle works but others may need more help. In the extreme patients at the higher end they can suffer from pancreatitis and the condition is often misdiagnosed initially which may cause anxiety. The higher end has a significant impact on patients lives causing much distress, pain and sometimes hospitalisation, often having to take time out of work. Primary care would be a good place for this to be prescribed due to the patient population it can help.

Current treatment of the condition in the NHS	
7a. What do you think of the current treatments and care available for people with elevated triglycerides at risk of cardiovascular events on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	Statins help. Fibrates are not routinely given and are obviously for the more extreme end of high triglycerides. However, having another treatment between the two would be a good source for patients struggling to reduce their level.
8. If there are disadvantages for patients of **current NHS treatments** for elevated triglycerides at risk of cardiovascular events (for example how the treatment is given or taken, side effects of treatment etc) please describe these	
Advantages of this treatment	
9a. If there are advantages of icosapent ethyl over current treatments on the NHS please describe these. For example, the impact on your Quality of Life, your ability to continue work, education, self-care, and care for others?	

9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does icosapent ethyl help to overcome/address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these.	
Disadvantages of this treatment	
10. If there are disadvantages of icosapent ethyl over current treatments on the NHS please describe these? For example, are there any risks with icosapent ethyl? If you are concerned about any potential side affects you have heard about, please describe them and explain why.	
Patient population	
11. Are there any groups of patients who might benefit more from icosapent ethyl or any who may	

benefit less? If so, please describe them and explain why. Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	
Equality	
12. Are there any potential equality issues that should be taken into account when considering people with elevated triglycerides at risk of cardiovascular events and icosapent ethyl? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics	Consistent access to testing is important in order to ensure equity.

More information on how NICE deals with equalities issues can be found in the NICE equality scheme More general information about the Equality Act can and equalities issues can be found at https://www.gov.uk/government/publications/easy-read-the-equality-act-making-equality-real and https://www.gov.uk/discrimination-your-rights.	
Other issues	
13. Are there any other issues that you would like the committee to consider?	

PART 2 – Technical engagement questions for patient experts
Issues arising from technical engagement
We welcome your response to the issues below, but you do not have to answer every issue. If you think an issue that is important to patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.

For information: the patient organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Key issue 1: Population of main clinical effectiveness evidence, REDUCE-IT trial, narrower than scope and decision problem	
Key issue 2: The period to determine a stable dose of statin in REDUCE-IT is likely to be less than in clinical practice	
Key issue 3: Composite outcomes (MACE) instead of disaggregated outcomes e.g. CV death used as primary outcome and used in the model	

Key issue 4: Unclear generalisability of the results to patients in the UK NHS setting	
Key issue 5: Model structure – partitioned survival analysis (partSA)	
Key issue 6: Use of reconstituted data	
Key issue 7: Limited evidence available for (long-term) validation of survival curves	
Key issue 8: Use of stratified parametric models, methodological guidance not followed	

Key issue 9: Long-term extrapolation, assumption of no treatment waning	
Key issue 10: Use of treatment-dependent non-CV related death hazard ratios	
Key issue 11: Health-related quality of life sensitive to choice of utility source	
Key issue 12: Event costs not adjusted for time since previous event	
Key issue 13: The distribution to extrapolate time to discontinuation	

Key issue 14: Inconsistent use of sources and calculation of event costs	
Key issue 15: Incomplete model validation and face validity check	
15. Are there any important issues that have been missed in ERG report?	

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- An additional treatment to help with raised triglycerides would be really helpful
- Prescribed in primary care would be ideal
- Access to testing will be key
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

……

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

……

NICE National Institute for Health and Care Excellence

Technical engagement response form

Icosapent ethyl with statin therapy for reducing the risk of cardiovascular events in adults with elevated triglycerides [ID3831]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments by **5pm** on **Tuesday 9 November 2021**.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**British Cardiovascular Society**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

NICE National Institute for Health and Care Excellence

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	**Does this response contain new evidence, data or analyses?**	Response
Key issue 1: Population of main clinical effectiveness evidence, REDUCE-IT trial, narrower than scope and decision problem	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 2: The period to determine a stable dose of statin in REDUCE-IT is likely to be less than in clinical practice	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 3: Composite outcomes (MACE) instead of disaggregated outcomes e.g. CV death used as primary outcome and used in the model	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 4: Unclear generalisability of the results to patients in the UK NHS setting	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 5: Model structure – partitioned survival analysis (partSA)	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses

Key issue 6: Use of reconstituted data	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 7: Limited evidence available for (long-term) validation of survival curves	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 8: Use of stratified parametric models, methodological guidance not followed	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 9: Long-term extrapolation, assumption of no treatment waning	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 10: Use of treatment-dependent non-CV related death hazard ratios	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 11: Health-related quality of life sensitive to choice of utility source	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 12: Event costs not adjusted for time since previous event	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 13: The distribution to extrapolate time to discontinuation	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 14: Inconsistent use of sources and calculation of event costs	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses

Key issue 15: Incomplete model validation and face validity check	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response

Additional issue 1: Results of REDUCE it trial	3.2.5	YES	BSC would like to raise some additional points relating to the results of REDUCE-IT. The basic issue is do we believe the results. As a trial with respect to conduct - no issues. But the control group is not neutral, so not placebo like. If it has harmful effects then the magnitude of the treatment effect for EPA is much lower and uncertain at best. 1. EPA lowers TG modestly about 17%. So the level of risk reduction is disproportionate to the level of TG lowering when looking at genetics and observational epidemiology 2. Mineral oil increases inflammatory markers and lipids. Thus increasing risk of harm. If we look at lipids and inflammatory benefits of EPA and compare the two see attached paper, then the relative risk reduction is about half the reported benefit in the trial. This impacts Health economic assessment. 3. If the drug does not work through traditional lipids then it has to do so by some other mechanism we can't measure. 4. A relevant publication is the Attached STRENGTH analysis where the on treatment EPA level levels with epanova which contains both EPA and DHA were measured. The comparator was a truly neutral compound corn oil. The overall trial was neutral. On treatment EPA levels and DHA levels from pharmaceutical elevation had no association with outcomes. This calls into question the theory that EPA in REDUCE high EPA levels associated with better outcomes. It could be that the mineral oil just causes harm.

			5. Patients with high TG, can have their risk mitigated by greater non HDL-C lowering and greater BP lowering and control of traditional risk factors. We understand how these mechanisms work. 6. I would be more convinced if EPA were tested against corn oil and showed benefit. Please see attached papers from Takahito et al. 2021 and Nissen et al. 2021.

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER
Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER

NICE National Institute for Health and Care Excellence

Technical engagement response form

Icosapent ethyl with statin therapy for reducing the risk of cardiovascular events in adults with elevated triglycerides [ID3831]

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- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

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About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Amarin**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Not applicable**

NICE National Institute for Health and Care Excellence

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response	ERG response
Key issue 1: Population of main clinical effectiveness evidence, REDUCE-IT trial, narrower than scope and decision problem	NO	The population in the decision problem should be the population as per the eligibility criteria for the REDUCE-IT trial and is therefore narrower than the population referred to in the licensed indication and in the NICE final scope. The clinical evidence presented in the submission only includes the REDUCE-IT trial as it is the only relevant trial for icosapent ethyl. The economic model is based on the REDUCE-IT trial population. As such, the entire submission is based on the REDUCE-IT trial, in line with the decision problem which has a narrower population than in the licensed indication.	The company have provided clarification on the relevant population as suggested by the ERG.
Key issue 2: The period to determine a stable dose of statin in REDUCE-IT is likely to be less	YES	The table below summarises additional evidence from the REDUCE-IT trial for the period to determine a stable dose of statin.	The ERG consider that this new evidence does appear to support the applicability of the duration of stable dose of

Key issue	Does this response contain new evidence, data or analyses?	Response	ERG response
than in clinical practice			statin to UK clinical practice.

Statistic	AMR101 (N=4089)	Placebo (N=4090)	Overall (N=8179)
Duration of Stable Statin Dose Before Randomization - n (%)			
At least 3 months	[redacted]	[redacted]	[redacted]

Note: Five patients with missing visit information are excluded from the analysis.
Note: Duration of Stable Statin Dose (defined by statin intensity on Atorvastatin, Fluvastatin, Lovastatin, Pitavastatin, Pravastatin, Rosuvastatin, or Simvastatin) in years before randomization was calculated as number of days between randomization and stable statin dose start plus one divided by 365.25. Duration in months was calculated as duration in years multiplied by 12.

The analysis shows that approximately [redacted] of patients in the ITT cohort of the REDUCE-IT trial had a duration of stable statin dose of more than three months. Healthcare professionals at the most recent Royal College of General Practitioners (RCGP) conference (14th – 15th October 2021) confirmed that three months is the duration observed in UK clinical practice for determining a stable dose of statin. This matches with the duration observed in the majority of patients in the REDUCE-IT trial, indicating that the patients enrolled in this trial are generalisable to patients in the UK NHS setting.

Key issue	Does this response contain new evidence, data or analyses?	Response	ERG response
Key issue 3: Composite outcomes (MACE) instead of disaggregated outcomes e.g. CV death used as primary outcome and used in the model	NO	Although the composite 5-point MACE was used to model the time of a first, second or three plus 5-point MACE, the distribution of the specific type of cardiovascular event (CV death, nonfatal MI, nonfatal stroke, coronary revascularization and unstable angina) experienced by patients in each treatment group was applied, as per Table 26 of company submission. Therefore, the effect of icosapent ethyl on each specific event occurring as a first, second or third plus event was taken into account. For example, if a higher proportion of the total events in the icosapent ethyl treatment group were CV death than the proportion observed in the placebo group, this is accounted for when informing the type of event occurred. These proportions are then used to inform the costs and utilities applied in the model, hence, the treatment effect predicted in the model is in line with the occurrence of CV death in the REDUCE-IT trial. The company believes that using the composite 5-point MACE for the time to event and then the proportion of each specific event would not lead to a significant difference in the cost-effectiveness of icosapent ethyl in comparison to an approach solely based on disaggregated outcomes as mentioned by the ERG. To further support this point, a comparison of the predicted model outcomes obtained using the submission model and the individual patient simulation [redacted] model provided as new evidence for validation, shows a similar trend in clinical outcomes (see key issue 5).	The ERG would argue that applying direct estimates of time to each event is not necessarily equivalent to the combination of time to the composite and proportion of the composite attributed to each event given the potential for differential effect on time to each separate event.

Key issue	Does this response contain new evidence, data or analyses?	Response	ERG response
Key issue 4: Unclear generalisability of the results to patients in the UK NHS setting	YES	The tables below provide a comparison of the baseline characteristics from the REDUCE-IT trial with those from Steen *et al.* (2016) for each subgroup (primary prevention and secondary prevention). There are many similarities between the baseline characteristics of REDUCE-IT and Steen *et al.* but there are also some differences, particularly in the disease-relevant and medication use characteristics. However, this is not unusual to see, as primary and secondary prevention patients in general can have a wide range of underlying/prior diseases. Furthermore, Steen *et al.* is a real-world study whereas REDUCE-IT is a randomised controlled trial, so by definition has stricter eligibility criteria upon enrolment. However, the general trend observed in the characteristics between the two studies is very similar, indicating that the population enrolled in the REDUCE-IT trial is generalisable to patients in the UK NHS setting. **<u>Primary prevention population</u>** The demographic characteristics (age, gender, BMI and systolic BP) were similar between studies. Both studies included patients with a mean age of ~60 years of age, and a similar proportion of	It is clear that there are substantial differences in some patient characteristics that might be treatment effect modifying between REDUCE-IT and Steen et al. What is unclear is the extent to which Steen et al itself is relevant to current UK clinical practice for the type of patients eligible for the REDUCE-IT trial, particularly given that Steen et al is five years old. What does seem clear is that the patients in UK clinical practice for

male patients. Mean BMIs in both studies fall within the "obese" category, whilst mean systolic BP is also elevated (~130) in both studies.

In the REDUCE-IT trial, a larger proportion of patients suffer from diabetes, hypertension, a history of CHF, or CKD stage IV-V, though CKD stage III incidence is larger in Steen *et al*.

A larger proportion of patients in the REDUCE-IT trial were treated with a low or medium intensity statin, ACE inhibitor or ARB. However, the proportion of patients treated with a high-intensity statin was similar between both studies.

	REDUCE-IT (N=2,394)	**Steen *et al.* (N=92,086)**
Demographic characteristics		
Age (years), Mean	[redacted]	69.7
Male, %	[redacted]	50.3
BMI (kg/m^2), Mean	[redacted]	30.1
Systolic BP, Mean	[redacted]	134.3
Disease-relevant baseline characteristics		
Recent ACS, %	[redacted]	N/A
Other CHD, %	[redacted]	N/A
Ischaemic stroke/TIA, %	[redacted]	N/A
PAD, %	[redacted]	N/A
DM, %	[redacted]	76.3
Hypertension, %	[redacted]	66.0
History of CHF, %	[redacted]	2.4
CKD, stage III, %	[redacted]	38.2
CKD, stage IV-V, %	[redacted]	0.3
Statin Intensity		
Low-intensity statin, %	[redacted]	5.0
Medium-intensity statin, %	[redacted]	40.4

whom the company submission would be most appropriate would be those who most resemble the patients in the REDUCE-IT trial, for example with diabetes in the primary prevention population and with hypertension regardless of population.

Key issue	Does this response contain new evidence, data or analyses?	Response	ERG response

High-intensity statin, %	[redacted]	17.0
Medications taken at baseline		
Anti-Platelet, %	[redacted]	N/A
ACE or ARB, %	[redacted]	61.1
Beta Blockers, %	[redacted]	N/A

Secondary prevention population

In the secondary prevention population, the BMI and systolic BP were similar between studies, though the mean age was higher in Steen *et al* and the percentage of male patients was higher in REDUCE-IT.

In the REDUCE-IT trial, a larger proportion of patients had recent ACS, other CHD, diabetes, hypertension, or a history of CHF. However, ischaemic stroke/TIA and PAD were slightly more common in Steen *et al*. CKD incidence was similar in both studies.

The proportion of patients treated with a low or high intensity statin was very similar between studies, though a larger proportion of patients were treated with a medium intensity statin, anti-platelet, ACE inhibitor, ARB, or beta-blocker in the REDUCE-IT trial.

Key issue	Does this response contain new evidence, data or analyses?	Response	ERG response

	REDUCE-IT (N=5,785)	Steen *et al.* (N=91,497)
Demographic characteristics		
Age (years), Mean	[redacted]	72.6
Male, %	[redacted]	60.7
BMI (kg/m^2), Mean	[redacted]	28.3
Systolic BP, Mean	[redacted]	132.1
Disease-relevant baseline characteristics		
Recent ACS, %	[redacted]	3.4
Other CHD, %	[redacted]	66.0
Ischaemic stroke/TIA, %	[redacted]	28.6
PAD, %	[redacted]	21.7
DM, %	[redacted]	29.4
Hypertension, %	[redacted]	61.5
History of CHF, %	[redacted]	9.1
CKD, stage III, %	[redacted]	23.5
CKD, stage IV-V, %	[redacted]	0.2
Statin Intensity		

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<tr><th>Key issue</th><th>Does this response contain new evidence, data or analyses?</th><th>Response</th><th>ERG response</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td>Low-intensity statin, %</td><td>[redacted]</td><td>5.6</td></tr>
<tr><td>Medium-intensity statin, %</td><td>[redacted]</td><td>42.1</td></tr>
<tr><td>High-intensity statin, %</td><td>[redacted]</td><td>31.4</td></tr>
<tr><td colspan="3">Medications taken at baseline</td></tr>
<tr><td>Anti-Platelet, %</td><td>[redacted]</td><td>18.5</td></tr>
<tr><td>ACE or ARB, %</td><td>[redacted]</td><td>61.7</td></tr>
<tr><td>Beta Blockers, %</td><td>[redacted]</td><td>48.7</td></tr>
</table>
</td><td></td></tr>
<tr><td>Key issue 5: Model structure – partitioned survival analysis (partSA)</td><td>YES</td><td>A state-transition model in TreeAge, developed by the [redacted], has been provided to validate the outcomes of the company's partSA approach. The state-transition model and accompanying manuscript, submitted for publication, have been uploaded as new evidence to be used strictly for validation purposes and must be treated confidentially. The state-transition model is not intended to replace the company's original partSA model.

The objective of the state-transition model was to estimate the cost-effectiveness of icosapent ethyl compared with standard of care, using patient-level data from REDUCE-IT for the in-trial period, and using a microsimulation model and data from published literature for the lifetime analysis. The original model used a US healthcare sector perspective and was then adapted to the UK NHS setting (using the same costs, utilities and background mortality) by the model developer so that a comparison of the</td><td>The ERG appreciates the cross-validation model provided by the company. Unfortunately, the ERG's concerns have not been addressed with this cross -validation exercise:
• There are large differences between the company's new base-</td></tr>
</table>

Key issue	Does this response contain new evidence, data or analyses?	Response	ERG response
		outcomes could be made with the partSA model submitted by the company. The state-transition model uses a 6-month cycle length. 	case and validation model in patients alive, third events, and second events. The number of first events is also larger in the new base-case than in the validation model but differences are not as large as for the other events. Differences in number of patients alive are especially concerning. The company attributed differences in events to the fact that in the validation model, multiple events within 3 days would be counted

Key issue	Does this response contain new evidence, data or analyses?	Response	ERG response
		[redacted] It is important to note that some events were disregarded in this analysis when multiple events occurred within three days, since only the costliest event was included. The table below highlights the proportions of each type of event disregarded throughout the state-transition model analysis at various timepoints: **1 year** / **5 years** / **10 years** / **20 years** / **30 years** **Icosapent ethyl** / **BSC** (each timepoint) **Total (%)** [redacted] **CV Death (%)** [redacted] **MI (%)** [redacted]	as one (the costliest) event. If this were the only difference, then number of patients alive should not differ considerably between modelling approaches. • The difference between icosapent ethyl and BSC arms is generally larger in the company's model than the validation model, which works in favour of icosapent ethyl. As a result, the company's ICERs are much lower than those of the validation model.

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<tr><th>Key issue</th><th>Does this response contain new evidence, data or analyses?</th><th>Response</th><th>ERG response</th></tr>
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<table>
<tr><td>Stroke (%)</td><td>[redacted]</td></tr>
<tr><td>Unstable Angina (%)</td><td>[redacted]</td></tr>
<tr><td>Revascularization (%)</td><td>[redacted]</td></tr>
</table>
A direct comparison of the clinical outcomes from the state-transition and partSA models was conducted. The table below shows the proportion of patients for each of the following: experiencing a first event, experiencing a second event, experiencing a third plus event, patients discontinuing icosapent ethyl, patients alive and patients who are event free.
<table>
<tr><th></th><th colspan="2">1 year</th><th colspan="2">5 years</th><th colspan="2">10 years</th><th colspan="2">20 years</th><th colspan="2">30 years</th></tr>
<tr><th></th><th>Icosapent ethyl</th><th>BSC</th><th>Icosapent ethyl</th><th>BSC</th><th>Icosapent ethyl</th><th>BSC</th><th>Icosapent ethyl</th><th>BSC</th><th>Icosapent ethyl</th><th>BSC</th></tr>
<tr><td colspan="11">First event: Total</td></tr>
<tr><td>State-transition model</td><td colspan="10">[redacted]</td></tr>
<tr><td>PartSA model – old base case</td><td colspan="10">[redacted]</td></tr>
</table>
</td><td>The ERG therefore considers that discrepancies cannot solely be attributed to the one difference highlighted by the company: that the validation model considers multiple events that happen within 3 consecutive days as one event (the costliest). It is also unclear how the numbers in the tables align: over a 30-year time horizon, according to the company, only [redacted] of</td></tr>
</table>

Key issue	Does this response contain new evidence, data or analyses?	Response	ERG response

PartSA with HR – new preferred base case	[redacted]										
Bhatt *et al.* 2019	-	-	17.2%	22.0%	-	-	-	-	-	-	
Second event: Total											
State-transition model	[redacted]										
PartSA model – old base case	[redacted]										
PartSA with HR – new preferred base case	[redacted]										
Bhatt *et al.* 2019	-	-	5.8%	9.2%	-	-	-	-	-	-	
Third & plus event: Total											

events are missed. But the differences in proportions of patients with events in the modelling as presented by the company appear to be much larger.

In addition, the ERG also considers it more relevant to know what types of events were missed, rather than first, second or third events. It may be helpful if the company could provide a more detailed cross validation, and elaborate

Key issue	Does this response contain new evidence, data or analyses?	Response										ERG response
		State-transition model	[redacted]									on the identified differences regarding: • Model structure and assumptions • Input parameters related to: I. Clinical effectiveness ii. Health state utility values iii. Resource use and costs • Estimated (disaggregated) outcomes per comparator/ intervention i. Life years ii. QALYs iii. Costs
		PartSA model – old base case	[redacted]									
		PartSA with HR – new preferred base case	[redacted]									
		Bhatt *et al.* 2019	-	-	1.8%	3.5%	-	-	-	-	-	-
		Discontinuing icosapent ethyl										
		State-transition model	[redacted]									
		PartSA model – old base case	[redacted]									
		PartSA with HR – new	[redacted]									

Key issue	Does this response contain new evidence, data or analyses?	Response	ERG response
		preferred base case |	
		Patients alive |	
		State-transition model | [redacted]	
		PartSA model – old base case | [redacted]	
		PartSA with HR – new preferred base case | [redacted]	
		Event free |	
		State-transition model | [redacted]	
		PartSA model – old base case | [redacted]	

<table>
<tr><th>Key issue</th><th>Does this response contain new evidence, data or analyses?</th><th>Response</th><th>ERG response</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td>PartSA with HR – new preferred base case</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
As mentioned, the state-transition model disregarded some events whereas the partSA model submitted by the company included all the events observed throughout the REDUCE-IT trial. As a result, there are differences observed between the proportions of patients in the table above and these differences get larger as the time horizon increases. This is expected because the number of events patients experience during the in-trial period directly informs the long-term extrapolations used in both models, therefore any differences in the number of events in the first five years will lead to larger incremental differences in the extrapolations as the time horizon increases. However, although some events were missed in the state-transition model, it is important to note that the general trend observed in the proportions is the same across both models. This can be further ratified by looking at the ICERs of both models:
<table>
<tr><th></th><th>Population</th><th>Technologies</th><th>Total costs (£)</th><th>Total LYG</th><th>Total QALYs</th><th>Incr. costs (£)</th><th>Incr. LYG</th><th>Incr. QALYs</th><th>ICER (£/QALY)</th></tr>
<tr><td>State-transition model</td><td>ITT</td><td>Icosapent ethyl</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
</td><td></td></tr>
</table>

Key issue	Does this response contain new evidence, data or analyses?	Response								ERG response
				BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
		PartSA model – new preferred base case		Icosapent ethyl	20,276	10.931	7.995	10,630	0.377	0.468	22,709	
				BSC	9,647	10.554	7.527	-	-	-	-	
		State-transition model	Primary prevention	Icosapent ethyl	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
				BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
		PartSA model – new preferred base case		Icosapent ethyl	17,521	11.240	8.174	11,228	0.117	0.168	66,952	
				BSC	6,293	11.123	8.006	-	-	-	-	
		State-transition model	Secondary prevention	Icosapent ethyl	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
				BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
		PartSA model – new preferred base case		Icosapent ethyl	21,584	10.763	7.876	10,680	0.434	0.535	19,981	
				BSC	10,904	10.329	7.341	-	-	-	-	

Key issue	Does this response contain new evidence, data or analyses?	Response	ERG response
		A similar trend of results across populations and technologies is observed in the state-transition model and the partSA model. The total LYG, total QALYs and total costs are similar in the state-transition model and partSA model, however, there are some differences between the ICERs. This is expected, as the state-transition model disregards some events whereas the partSA model includes all the events observed throughout the REDUCE-IT trial. Despite the minor discrepancies, the results show that the partSA model is appropriate, as the observed results are comparable to results produced using a different modelling approach.	
Key issue 6: Use of reconstituted data	YES	In a scenario analysis on the company's old base case, the parametric survival curves were re-estimated using the complete Kaplan-Meier data resulting in the ICER increasing from £29,316 to £29,854. Results are presented in the summary table below. Company's new preferred base-case, presented below, includes the complete Kaplan-Meier data.	The company did not provide details on the new survival analysis, i.e. the whole process according to TSD 14, including model fit of the different distributions. The ERG would like to see this information

<table>
<tr><th>Key issue</th><th>Does this response contain new evidence, data or analyses?</th><th>Response</th><th>ERG response</th></tr>
<tr><td></td><td></td><td></td><td>before it considers this issue as resolved.</td></tr>
<tr><td>Key issue 7:
Limited evidence available for (long-term) validation of survival curves</td><td>YES</td><td>As provided previously, scenario analyses for all the distributions considered for the time to event curves were tested statistically. There was little impact on the ICER when the choice of parametric survival model was varied. Due to a lack of long-term observational data and UK clinical experience, the choice of distribution cannot be informed by criteria other than the statistical fit. However, to further test the validity of the long-term extrapolations of survival curves for icosapent ethyl, the company has taken an alternative approach of using proportional hazards, sourced from Bhatt et al. (2019), to estimate the long-term curves. The placebo curve for all distributions was ratified by UK clinical experts. The company has then used the extrapolation of the placebo curve and applied a HR to derive the icosapent ethyl curve. The HRs for the ITT population as well as for the CV1 and CV2 subgroups are presented below. Results of this scenario applied to the old base case are presented in the summary table below for the ITT, CV1 and CV2 populations. As the proportional hazard assumption holds (see response to key issue 8), the hazard ratios approach is used in the new preferred company’s base case.
<table>
<tr><td></td><td colspan="3">Icosapent ethyl versus placebo – HR or RR* (95% CI)</td><td>Source</td></tr>
<tr><td></td><td>1st event</td><td>2nd event</td><td>3+ event</td><td></td></tr>
</table>
</td><td>The ERG considers that the publication by Bhatt et al (2019) does not resolve the issue of lack of long-term evidence suitable for validation, as this article was again based on the REDUCE-IT trial.

In addition, the company still did not provide full survival analysis according to established guidance. Instead of estimating time-to-</td></tr>
</table>

Key issue	Does this response contain new evidence, data or analyses?	Response	ERG response

ITT	0.75 (0.68, 0.83)	0.68 (0.60, 0.78)	0.69 (0.59, 0.82) for 3rd event	Bhatt *et al.* 2019
CV1	0.73 (0.65, 0.81)	[redacted]	[redacted]	Amarin
CV2	0.88 (0.70, 1.10)	[redacted]	[redacted]	Amarin

* Presented as a relative risk

events by fitting one parametric model to the entire dataset, with treatment group included as a covariate in the analysis and assuming proportional hazards (as recommended in TSD 14), the company uses a published relative effectiveness estimate from Bhatt et al 2019. This goes against the advice in TSD 14 that *"care should be taken to ensure that only the HR obtained from the chosen parametric model is applied to the control*

Key issue	Does this response contain new evidence, data or analyses?	Response	ERG response
			group survival curve derived from the parametric model fitted with the treatment group as a covariate – it is theoretically incorrect to apply a HR derived from a different parametric model, or one derived from a Cox proportional hazards model". The ERG considers that, while the proportional hazard assumption likely holds (based on information provided in the appendix),

Key issue	Does this response contain new evidence, data or analyses?	Response	ERG response
			methodological guidance is still not followed.
Key issue 8: Use of stratified parametric models, methodological guidance not followed	YES	Following issues raised by the ERG in their report, the company have re-evaluated the choice of survival models using the selection process algorithm as mentioned in NICE DSU TSD 14. To test for the acceptability of using proportional hazards, the log cumulative hazard plot, Schoenfeld residual plot and Cox-Snell residual plots were evaluated (Appendix A below; Key issue 8). The log-cumulative hazard plot lines for icosapent ethyl and placebo remain parallel for the majority of the time period in all three events. However, the plot lines do cross towards the start in events 1 and 2 and towards the end of event 3+. This could be due to the treatment not showing full effect at the beginning of the time period and few patients remaining at risk towards the end of the time period. The Schoenfeld residual plot shows a linear curve with a zero slope for events 1 and 2 and shows a p-value >0.05 for all events, giving evidence that the proportional hazards assumption holds. The plot of the Cox-Snell residuals against the estimated cumulative hazard rate shows a relatively straight line with zero intercept and unit slope for events 1 and 2. Therefore, it can be assumed that the proportional hazards assumption holds between icosapent ethyl and placebo. The results of using proportional hazards are presented in the summary of key changes, under Key issue 7.	The ERG considers that the proportional hazard assumption is probably appropriate, but full survival analysis has not been conducted and reported (see response to Key issue 7). The ERG would like to see full survival analysis, with relative effectiveness estimates derived as per guidance in TSD 14, and full information provided,

Key issue	Does this response contain new evidence, data or analyses?	Response	ERG response
			e.g. on selection of distributions.
Key issue 9: Long-term extrapolation, assumption of no treatment waning	NO	No treatment waning effect was applied in the base case analysis. In response to the ERG clarification questions, two scenario analyses were provided with arbitrary waning assumptions. The company acknowledges that there are no long-term studies to inform the long-term efficacy of icosapent ethyl. However, the Kaplan-Meier event curves for the primary efficacy 5-point MACE composite endpoint (figure 5 in the company submission), shows that the treatment effect increases over time before stabilising. This treatment effect is further demonstrated in a landmark analysis for which results have been presented in the new evidence form. [redacted] In addition, despite the absence of long-term studies to inform whether or not the treatment effect is maintained, no waning was applied in the appraisals of alirocumab TA393, evolucumab TA394 and inclisiran TA733, which are in a similar disease area (hypercholesterolaemia and mixed dyslipidaemia).	The ERG notes the company's statement that [redacted]. Evidence was supplied to support this, [redacted] The ERG would also like to see smoothed hazard plots over time per arm and for subgroups (with numbers of patients at

Key issue	Does this response contain new evidence, data or analyses?	Response	ERG response
		The company therefore believes it is reasonable to assume that the treatment benefit of icosapent ethyl would be maintained beyond the trial period, and therefore no treatment waning should be applied in the base-case.	risk) and expert opinion was equivocal on treatment waning (see additional TE responses). Whether treatment waning applies or not remains an area of uncertainty.
Key issue 10: Use of treatment-dependent non-CV related death hazard ratios	YES	The method that the ERG used to calculate the treatment-independent non-CV related death hazard ratios does not account for the differences between the ITT, CV1 and CV2 subpopulations. The ERG methodology took an average of the treatment dependent hazard ratios per health state and then applied this to both treatments making the hazard ratios treatment independent. However, these averages were only calculated for the ITT population and more specifically, when the split of the subgroups were 71.7% (CV1) and 28.3% (CV2). They did not account for the proportion of individuals that were CV1 vs. CV2. A patient in the CV1 subgroup cannot be considered comparable to an individual in the CV2 subgroup so it is not appropriate to apply a single hazard ratio per health state across the ITT, CV1 and CV2	The ERG agrees with the company that non-CV related death hazard ratios should be calculated for each population separately. The company also emphasize that diabetes and a number of prior

subgroups. When comparing the type of individual likely to be observed in the two subgroups, a CV1 individual is required to have experienced a prior CV related event before entering the model at baseline, therefore a CV1 individual within the model, in the post-first event state, in fact has experienced at least two prior events. Additionally, they are not required to be diabetic. In comparison, an individual in the CV2 group in the post-first event state within the model, is only required to have experienced one event in their lifetime but will be diabetic.

Both diabetes and number of prior events have been identified as non-CV related mortality modifiers so cannot be ignored.

We believe a more appropriate methodology to calculate the treatment-independent non-CV related death hazard ratios would be to use our current methodology, however, instead of using treatment independent distributions of events to inform the type of event that occurred, use the distribution of events that occurred across both treatment arms. The appropriate distributions are provided in the table below.

	Icosapent ethyl	Placebo	Total
First event			
CV death	[redacted]	[redacted]	[redacted]
MI	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]
Unstable angina	[redacted]	[redacted]	[redacted]
Revascularisation	[redacted]	[redacted]	[redacted]
Total	705	901	1606
Second event			
CV death	[redacted]	[redacted]	[redacted]
MI	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]
Unstable angina	[redacted]	[redacted]	[redacted]
Revascularisation	[redacted]	[redacted]	[redacted]
Total	236	376	612
Third plus event			

events have been identified as non-CV related mortality modifiers. The ERG would like to see evidence for this, especially as it remains unclear to what extent the CV events reported in the company's table will have an effect on non-CV related death.

Key issue	Does this response contain new evidence, data or analyses?	Response	ERG response
		CV death [redacted] MI [redacted] Stroke [redacted] Unstable angina [redacted] Revascularisation [redacted] Total [redacted] To assist with the correction of the ERGs preferred assumption of using treatment independent non-CV-related mortality hazard ratios, we have provided a scenario with our suggestions as described above implemented correcting the methodology used in their report. This scenario led to an ICER of £31,278 when implemented with the original company base case assumptions. However, it is the company's position that using dependent hazard ratios is the most approach to use due to patients experiencing a different distribution of events per treatment group in the REDUCE-IT trial which were non-CV death related modifiers.	

Key issue	Does this response contain new evidence, data or analyses?	Response	ERG response
Key issue 11: Health-related quality of life sensitive to choice of utility source	NO	Health-related quality of life utility values were based on multipliers sourced from NICE CG181 as they are considered appropriate by NICE, and also appropriately reflect the target population of icosapent ethyl. The model is sensitive to the choice of utility values used as each of the events comprising the 5-point MACE is associated with a corresponding utility value based on the multipliers from NICE CG181. Therefore patients experiencing multiple events in the model will subsequently experience variations in their quality of life following each type of event. This is further impacted by the severity of the type of events experienced too. This variation in quality of life following multiple events therefore makes the model very sensitive to the choice of utility source used. The disutilities in the model were sourced from multiple references in order to accurately capture the loss of quality of life experienced by patients following an adverse event. The disutilities for peripheral oedema and constipation were applied for seven days. The disutility for serious bleeding was applied for one month. The duration of each of these adverse events was informed by UK clinical expert input.	No further justification for using utility values by Stevanovic and O'Reilly was provided. Justification may be useful to decide whether the company's choice of utility values was appropriate, especially given that utilities by Ara et al increased the ICERs. The ERG therefore considers there is uncertainty about the appropriate utility values to use.

Key issue	Does this response contain new evidence, data or analyses?	Response	ERG response
Key issue 12: Event costs not adjusted for time since previous event	YES	To address concerns surrounding the duration of acute and post-event costs, a scenario that estimates costs adopting the same approach used for estimating utilities within the post-event states is provided in the summary of key changes, under key issue 12. The acute event cost has been adjusted to reflect the cost associated with a single day. For example, Danese 2016 estimates the acute cost of a myocardial infarction to be £4,275.41 within the first six months, so we have inflated and adjusted this to a cost per day calculated as £4,678.22 / (365.25/2). In the scenario, the cost is applied for the first 60 days post-event (one day of cost is applied in the event states and then the remaining cost is applied in the post-event states) and then a long-term cost is applied beyond 60 days.	The ERG considers that this change likely explores the bias introduced by the daily cycle lengths and applying a one-off cost, which may over-estimate costs of those patients that quickly move to the next event / death state.
Key issue 13: The distribution to extrapolate time to discontinuation	NO	As previously stated in the both the company submission and within the ERG clarification response, the exponential distribution for the TTD curve was chosen based on statistical fit in the absence of clinical experience with icosapent ethyl. There is no evidence to suggest that any of the alternative distributions should be preferred and implemented. However, the range of ICER previously presented did not show any of the distributions to	This remains an area of uncertainty, given that there is a lack of clinical experience with icosapent ethyl.

Key issue	Does this response contain new evidence, data or analyses?	Response	ERG response
		have a significant impact on the ICER, with all scenarios for the ITT company base-case in the range of £29,316 – £33,805.	
Key issue 14: Inconsistent use of sources and calculation of event costs	YES	In an attempt to minimise the over estimation of costs associated with events caused by an overlap of costs in the acute/post-event costs, we have implemented the methodology suggested by the ERG to estimate the costs applied in the economic model. Acute event costs were estimated using the following steps 1) identified in the literature, 2) inflated to 2021 using the CPI, 3) removal of any general post-event daily cost beyond 60 days from the acute cost, 4) divided by 60 to get a daily cost. Please find a summary of the updated costs and the calculations associated with them in the Appendix A under key issue 14.	The ERG considers this issue as resolved.
Key issue 15: Incomplete model validation and face validity check	YES	The two checklists requested by the ERG to assess the technical verification of the economic model, AdViSHE and TECH-VER, have been completed and the results are provided in Appendix A below. Following the ERG clarification questions, it was discovered that the one-way sensitivity analysis in the model was not appropriately capturing variation in some parameters. The model was adapted to provide a more granular OWSA by varying disaggregated model parameters, this is provided in Appendix A below. The AdViSHE and TECH-VER checklists were conducted using the updated model.	The ERG appreciates the company's additional efforts in model validation and considers this issue as resolved.

Summary of changes to the company's cost-effectiveness estimate(s)

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER	ERG comment
Key issue 6: Use of reconstituted data	Use of reconstituted data in which observations which took place after the point that only 10% of patients were remaining at risk were removed from the dataset.	The complete Kaplan-Meier curve is used.	This change increases the old base case ICER from £29,195* to £29,731.	Full details on survival analysis are not provided, hence there remains uncertainty over whether the selected distributions are now appropriate.
Key issue 7: Limited evidence available for (long-term) validation of survival curves	Independent Kaplan-Meier curves from the REDUCE-IT trial were used for the placebo and icosapent ethyl arms and extrapolated beyond the trial period. Statistical fit was used to inform the choice of distribution for the long-term extrapolations.	Hazard ratios, sourced from Bhatt *et al.* (2019), were used to estimate the long-term curves. The extrapolation of the Kaplan-Meier placebo curve was ratified by UK clinical experts. Hazard ratios were then applied to the placebo curve to derive the icosapent ethyl curve.	This change decreases the old base case ICER from £29,195* to £21,582.	As detailed above, the ERG considers that methodological guidance has still not been followed and using hazard ratios from Bhatt et al is probably inappropriate.

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER	ERG comment
Key issue 12: Event costs not adjusted for time since previous event	The event costs were not adjusted to account for the length of time since a previous CV event was experienced within the CE model. All acute event costs were applied in a single day.	The same methodology used in the utility calculations to estimate the proportion of individuals in the post-event states that have experienced an event in the last 60 days is implemented. Therefore, we have applied a daily cost for the acute stage to be applied for 60 days post-event rather than a one-off acute event cost.	This change increased the old base case ICER from £29,195* to £31,728.	The ERG considers that this change is probably appropriate.
Key issue 14: Inconsistent use of sources and calculation of event costs	Event cost calculations were inconsistent.	The methodology suggested by the ERG has been implemented to remove costs that were being double counted in both the post-event and acute event stages.	This change decreases the old base case ICER from £29,195* to £29,071.	The ERG considers that this change is likely appropriate.

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER	ERG comment
Key issue 15: Incomplete model validation and face validity check	Error in formula	During the model validation, it was identified that there was an error due to an inconsistent formula from row 375 in the icosapent Ethyl Markov trace sheet. This was corrected in the model.	This change decreases the old base case ICER from £29,316 to £29,195.	The ERG considers this issue as resolved.
Company's preferred base case following technical engagement	Incremental QALYs: ITT: 0.468 CV1: 0.535 CV2: 0.168	Incremental costs: ITT: £10,630 CV1: £10,680 CV2: £11,228	The company base-case ICER resulting from combining the changes described above decreases from £29,316 to £22,709. ITT: £22,709 CV1: £19,981 CV2: £66,952	The ERG considers that these ICERs may change once appropriate methodological guidance is followed.

*Old company base-case ICER with the correction described in issue 15.

APPENDIX A

Key issue 8: Use of stratified parametric models, methodological guidance not followed

Log cumulative hazard plots for the ITT population

Schoenfeld residual plots for the ITT population

Cox-Snell plots for the ITT population

Key issue 14: Inconsistent use of sources and calculation of event costs

Event	Company base-case	Revised base-case	Comments
Nonfatal MI			
Acute period	£4,678.22	£66.23	£4,275.41 (Source Danese 2016 using 2014 NHS reference costs) £4,678.22 (Once inflated to 2021 using CPI) Cost per day in acute phase = (£4,678.22 -(£1048.66 / (365.25*0.5))*((365.25*0.5)-60))/60 = £66.23 Assumption – daily cost applied for 60 days following an event

Event	Company base-case	Revised base-case	Comments
Post event	£2.87	£5.74	£922.43 (Source Danese 2016 using 2014 NHS reference costs) £1,048.66 (Once inflated to 2021 using CPI) £1,048.66*((365.25*0.5)) = £5.74
Nonfatal Stroke			
Acute period	£3,978.91	£54.64	£3,512.25 (Source Danese 2016 using 2014 NHS reference costs) £3,978.91 (Once inflated to 2021 using CPI) Cost per day in acute phase = (£3,978.91 -(£1,042.87 /(365.25*0.5))*((365.25*0.5)-60))/60 = £54.64 Assumption – daily cost applied for 60 days following an event
Post event	£2.86	£5.71	£972.62 (Source Danese 2016 using 2014 NHS reference costs) £1,042.87 (Once inflated to 2021 using CPI) £1,042.87*((365.25*0.5)) = £5.71
Coronary revascularisation			
Acute period	£6,147.04	£76.03	Daily acute cost of CR PCI acute cost*0.8+CABG acute cost*0.2 = (£47.03*0.8) + (£192.04*0.2) = £76.03 Assumption: 80% of individuals will receive PCI and remain 20% will receive CABG informed by UK clinical expert opinion
Percutaneous coronary intervention (PCI)	£4,406.97	£47.03	Source average of EY40A, EY40B, EY40C, EY40D, EY41A, EY41B, EY41C, EY41D, EY44A, EY44B, EY44C, EY44D NHS reference costs 2018/19 £4,406.97 (Once inflated to 2021 using CPI)

Event	Company base-case	Revised base-case	Comments
			Cost per day in acute phase = (£4,406.97-(£1,896.67/(365.25))*((365.25)-60))/60
Coronary artery bypass graft surgery (CABG)	£13,107.34	£192.04	Source average of ED26A, ED26B, ED26C, ED27A, ED27B, ED27C, ED28A, ED28B, ED28C NHS reference costs 2018/19 £13,107.34 (Once inflated to 2021 using CPI) Cost per day in acute phase = (£13,107.34 - (£1,896.67/(365.25))*((365.25)-60))/60
Post event	£5.19	£5.19	£1,896.67 (Once inflated to 2021 using CPI) Cost per day in acute phase = £1,896.67/365.25 = £5.19
Unstable angina			
Acute period	£2,438.43	£36.07	£2,179.24 (Source Danese 2016 using 2014 NHS reference costs) £2,438.43 (Once inflated to 2021 using CPI) Cost per day in acute phase = (£2,438.43 - (£408.13/(365.25*0.5))*((365.25*0.5)-60))/60 = £36.07 Assumption – daily cost applied for 60 days following an event
Post event	£1.12	£2.23	£328.45 (Source Danese 2016 using 2014 NHS reference costs) £408.13 (Once inflated to 2021 using CPI) £408.13*((365.25*0.5)) = £5.71
Cardiovascular death			
Total	£3,719.02	£3,719.02	£3,400.25 (Source Danese 2016 using 2014 NHS reference costs) £3,719.02 (Once inflated to 2021 using CPI)
Fatal MI - hospitalisation without procedure	£3,719.02	-	

Event	Company base-case	Revised base-case	Comments
Fatal stroke - hospitalisation without procedure	£3,719.02	-	Assumption CV death equal to hospitalisation cost

Key issue 15: Incomplete model validation and face validity check

Validation assessment using AdViSHE: A Validation-Assessment Tool of Health-Economic Models for Decision Makers and Model Users

Part A: Validation of the conceptual model

The conceptual model was presented in section B3.2 of the company's submission.

1. **A1/ Face validity testing (conceptual model): Have experts been asked to judge the appropriateness of the conceptual model? If yes, please provide information on the following aspects: -Who are these experts?-What is your justification for considering them experts?-To what extent do they agree that the conceptual model is appropriate? If no, please indicate why not.**

The conceptual model along with the model assumptions and inputs were validated by two UK clinical experts. The experts used to derive the expert opinion to support assumptions and decisions made with regard to the economic model were: [redacted]. They both qualify as clinical experts due to their expertise within this disease area. 1:1 interviews were conducted with each clinical expert with interview summary/notes taken for each interview and responses combined. The expert responses were previously provided to NICE ("Validation of assumptions in the UK cost-effectiveness model_v1.0_05_July_2021 – responses").

2. **A2/ Cross validity testing (conceptual model): Has this model been compared to other conceptual models found in the literature or clinical textbooks? If yes, please indicate where this comparison is reported. If no, please indicate why not.**

An internal review of the economic model submitted to CADTH was undertaken. It was considered that the Canadian model did not capture the full value of icosapent ethyl as it did not include all the events occurring in the REDUCE-IT trial. Hence, an alternative model was considered to capture the full benefit of icosapent ethyl.

The economic model from the [redacted] came to our attention too late in the technology appraisal process to be considered for submission. As an alternative, a comparison of the outcomes between the company and [redacted] models was undertaken in response to Key issue 5.

Part B: Input data validation

1. **B1/ Face validity testing (input data): Have experts been asked to judge the appropriateness of the input data? If yes, please provide information on the following aspects: -Who are these experts?-What is your justification for considering them experts?-To what extent do they agree that appropriate data have been used? If no, please indicate why not.**

As mentioned in section C17 of the response to the ERG questions, the model assumptions and inputs were validated by two UK clinical experts. The experts used to derive the expert opinion to support assumptions and decisions made with regard to the economic model were: [redacted]. They both qualify as clinical experts due to their expertise within this disease area. 1:1 interviews were conducted with each clinical expert with interview summary/notes taken for each interview and responses combined. The expert responses were previously provided to NICE ("Validation of assumptions in the UK cost-effectiveness model_v1.0_05_July_2021 – responses").

2. **B2/ Model fit testing: When input parameters are based on regression models, have statistical tests been performed? If yes, please indicate where the description, the justification and the outcomes of these tests are reported. If no, please indicate why not.**

As discussed in document B of the original company submission, in order to extrapolate the clinical data beyond the trial follow-up period, a series of parametric survival models (as published in NICE DSU Technical Support Document 14) were fitted to the reconstituted first, second and third + event IPD using the Flexsurv for R package for time-to-event data. To account for the range in follow-up data among individuals, data was extrapolated using IPD up until the point that 10% of patients at risk were left in the trial. A wide range of parametric survival models were fitted to the reconstituted data to match the placebo arm. To determine the most appropriate survival functions, model fit was assessed as follows:

- Graphic comparison of the predicted curve from a given parametric function to the Kaplan-Meier curve from the patient data
- Comparison of Akaike information criterion (AIC) statistics and Bayesian information criterion (BIC) statistics
- UK clinical expert opinion

As discussed in section C14 of the response to the ERG clarification questions, in the absence of clinical practice experience with icosapent ethyl, the distribution for the event and TTD curves were selected based on the best fitting curves using the AIC, BIC and visual inspection.

Part C: Validation of the computerized model

1. **C1/External review: Has the computerized model been examined by modelling experts? If yes, please provide information on the following aspects:-Who are these experts?-What is your justification for considering them experts?-Can these experts be qualified as independent?-Please indicate where the results of this review are reported, including a discussion of any unresolved issues. If no, please indicate why not.**

The model has been validated by an independent internal modelling expert, who was not working on the project. This individual was regarded as an expert as they have developed and reviewed a number of economic models before. The results of this review have been provided to NICE previously: “CEM QC_Final version_18Aug21”.

In addition, as part of the engagement with the [redacted] to assess if and how their model could be used in this technology appraisal, the company’s model was shared with the [redacted] for review along with the UK costs and utilities used in the company’s model. Modelling experts from the [redacted] included [redacted]), who both co-developed the [redacted] model alongside a number of experts (see authorship for the draft manuscript). The difference in modelling approach was acknowledged however, no fundamental issues were raised.

2. **C2/Extreme value testing: Has the model been run for specific, extreme sets of parameter values in order to detect any coding errors? If yes, please indicate where these tests and their outcomes are reported. If no, please indicate why not.**

As discussed in question C1, the model was validated by an internal health economics expert. As part of this validation, it was found that the total costs and QALYs increased/decreased reasonably in accordance with longer/shorter durations up to the 36 years-time horizon. Tests were carried out and the model was validated with regard to: scope, ease of use, inputs, model accuracy, survival analyses, sensitivity analyses, VBA code, common errors, Markov traces, and results. Extreme sets of parameter values were specifically tested.

3. **C3/Testing of traces: Have patients been tracked through the model to determine whether its logic is correct? If yes, please indicate where these tests and their outcomes are reported. If no, please indicate why not.**

As stated in Appendix J of the original company submission, patients were tracked through the model, and the outcome of this was logical because it is expected that the number of patients with no events will decrease over time, while the number of patients in the “dead” state will increase over time. The number of patients in each state over time are as follows:

Figure 1. Icosapent ethyl results: number of patients in each state over time

Figure 2. Placebo results: number of patients in each state over time

4. **C4/Unit testing: Have individual sub-modules of the computerized model been tested? If yes, please provide information on the following aspects: -Was a protocol that describes the tests, criteria, and acceptance norms defined beforehand? -Please indicate where these tests and their outcomes are reported. If no, please indicate why not.**

As discussed in question C1 above, the model has been validated by an independent internal modelling expert, who was not working on the project. The tests conducted and the outcomes of this review have been provided to NICE previously: "CEM QC_Final version_18Aug21".

Part D: Operational validation

1. **D1/Face validity testing (model outcomes): Have experts been asked to judge the appropriateness of the model outcomes? If yes, please provide information on the following aspects: -Who are these experts? -What is your justification for considering them experts? -To what extent did they conclude that the model outcomes are reasonable? If no, please indicate why not.**

The company's model was shared with the [redacted] for review along with the UK costs and utilities used in the company's model. Modelling experts from the [redacted] included [redacted]), who both co-

developed the [redacted] model alongside a number of experts (see authorship for the draft manuscript). They indicated that the modelled outcomes were in the same ballpark. The overall trend still translates into similar ICERs/QALYs/costs, indicating that the partSA approach produces results as expected (even if we were to use a different modelling approach) i.e., both models still show that patients taking icosapent ethyl experience fewer events than those on BSC, and that this translates into better LYG and QALYs when comparing icosapent ethyl to BSC.

2. **D2/Cross validation testing (model outcomes): Have the model outcomes been compared to the outcomes of other models that address similar problems? If yes, please provide information on the following aspects: -Are these comparisons based on published outcomes only, or did you have access to the alternative model? -Can the differences in outcomes between your model and other models be explained? -Please indicate where this comparison is reported, including a discussion of the comparability with your model. If no, please indicate why not.**

As discussed in the response to ERG clarification questions, our model is a *de novo* health state cohort model. After considering previous appraisals and the CADTH's submission for icosapent ethyl, we concluded that they all failed to model one key aspect, multiple subsequent events, which we believe to be pivotal in demonstrating the full value of icosapent ethyl in terms of the impact of reducing CV events on QoL and costs. Therefore, other submissions were not suitable to compare against and could not be used to validate our model.

Outcomes from the company model were validated against the outcomes from the state transition model and the comparison has been provided in response to Key issue 5. The company did not have access to the economic model and did not review it. This guarantees the independence of the [redacted] model and the validity of the comparison between the two different models.

3. **D3/Validation against outcomes using alternative input data: Have the model outcomes been compared to the outcomes obtained when using alternative input data? If yes, please indicate where these tests and their outcomes are reported. If no, please indicate why not.**

As discussed in the ERG clarification questions, sensitivity analyses for using alternative literature sources for utility values (ODYSSEY [TA 393]) were conducted to examine the impact on the ICER. Sensitivity analyses exploring alternative survival models to estimate time to event probabilities were also run (Table 16–Table 24 of the response to ERG clarification questions).

No alternative clinical input data, other than the REDUCE-IT trial, was retrieved in the literature.

4. **D4/Validation against empirical data: Have the model outcomes been compared to empirical data? If yes, please provide information on the following aspects: -Are these comparisons based on summary statistics, or patient-level datasets? -Have**

you been able to explain any difference between the model outcomes and empirical data?-Please indicate where this comparison is reported. If no, please indicate why not.

a. D4.A/Comparison against the data sources on which the model is based (dependent validation).

Results of the partSA model are in line with the Bhatt *et al.* 2019 (JACC) publication, as shown in Key issue 5: Model structure – partitioned survival analysis.

	Source at 4.9 years follow-up	First event	Second event	Third event
Icosapent ethyl	Bhatt *et al.* 2019	17.2%	5.8%	1.8%
	CE model	[redacted]	[redacted]	[redacted]
BSC	Bhatt *et al.* 2019	22.0%	9.2%	3.5%
	CE model	[redacted]	[redacted]	[redacted]

b. D4.B/Comparison against a data source that was not used to build the model (independent validation).

No clinical data other than that from REDUCE-IT were available to inform our model, so it is not possible to conduct this validation.

Part E: Other validation techniques

1. **E1/Other validation techniques: Have any other validation techniques been performed? If yes, indicate where the application and outcomes are reported, or else provide a short summary here.**

Not applicable.

Validation assessment using TECH-VER

Verification Stages 1-4: Black-box tests

Test description (please also document how the test is conducted)	**Expected result of the test**	**Company result of the test**
Pre-analysis calculations		

Test description (please also document how the test is conducted)	Expected result of the test	Company result of the test
Does the technology (drug/device, etc.) acquisition cost increase with higher prices?	Yes	Yes
Does the drug acquisition cost increase for higher weight or body surface area?	Yes	Not applicable
Does the probability of an event, derived from an OR/RR/HR and baseline probability, increase with higher OR/RR/HR?	Yes	Yes
In a partitioned survival model, does the progression-free survival curve or the time on treatment curve cross the overall survival curve?	No	Not applicable
If survival parametric distributions are used in the extrapolations or time-to-event calculations, can the formulae used for the Weibull (generalized gamma) distribution generate the values obtained from the exponential (Weibull or Gamma) distribution(s) after replacing/transforming some of the parameters?	Yes	Yes, when the shape of the Weibull distribution was set to 1 and the rate of the exponential was set to '1/scale of Weibull' the curves were identical.
Is the HR calculated from Cox proportional hazards model applied on top of the parametric distribution extrapolation found from the survival regression?	No, it is better if the treatment effect that is applied to the extrapolation comes from the same survival regression in which the extrapolation parameters are estimated	No
For the treatment effect inputs, if the model uses outputs from WINBUGS, are the OR, HR, and RR values all within plausible ranges? (Should all be non-negative and the average of these WINBUGS outputs should give the mean treatment effect)	Yes	Not applicable
Event-state calculations		
Calculate the sum of the number of patients at each health state	Should add up to the cohort size	Markov trace sheets contain a 'Check' column. Sum of the health state populations = starting population
Check if all probabilities and number of patients in a state are greater than or equal to 0	Yes	Yes
Check if all probabilities are smaller than or equal to 1	Yes	Yes
Compare the number of dead (or any absorbing state) patients in a period with the number of dead (or any absorbing state) patients in the previous periods?	Should be larger	Number of dead patients increases each period
In case of lifetime horizon, check if all patients are dead at the end of the time horizon	Yes	Yes
Discrete event simulation specific: Sample one of the 'time to event' types used in the simulation from the specified distribution. Plot the samples and compare the mean and the variance from the sample	Sample mean and variance, and the simulation outputs, should reflect the distribution it is sampled from	Not applicable
Set all utilities to 1	The QALYs accumulated at a given time would be the same as the life-years accumulated at that time	Life-years are equal to QALYs
Set all utilities to 0	No utilities will be accumulated in the model	QALYs are equal to 0

Test description (please also document how the test is conducted)	Expected result of the test	Company result of the test
Decrease all state utilities simultaneously (but keep event-based utility decrements constant)	Lower utilities will be accumulated each time	QALYs decrease
Set all costs to 0	No costs will be accumulated in the model at any time	No costs accumulated in the model
Put mortality rates to 0	Patients never die	No patients die
Put mortality rate at extremely high	Patients die in the first few cycles	Patients die in the early cycles
Set the effectiveness-, utility-, and safety-related model inputs for all treatment options equal	Same life-years and QALYs should be accumulated for all treatment at any time	Same life-years and QALYs are accumulated for all treatments at any time
In addition to the inputs above, set cost-related model inputs for all treatment options equal	Same costs, life-years, and QALYs should be accumulated for all treatment at any time	When the cost-related model inputs for treatment option were set to be equal an error was identified in the Markov trace (Icosapent Ethyl) sheet. The error was due to an inconsistent formula being used from row 375. After correction, the model showed to have the same costs, life-years, and QALYs accumulated for all treatments at any time.
Change around the effectiveness-, utility- and safety-related model inputs between two treatment options	Accumulated life-years and QALYs in the model at any time should also be reversed	Accumulated life-years and QALYs in the model are reversed
Check if the number of alive patients estimated at any cycle is in line with general population life-table statistics	At any given age, the percentage alive should be lower or equal in comparison with the general population estimate	Percentage of patients alive is lower than the general population estimate at any age
Check if the QALY estimate at any cycle is in line with general population utility estimates	At any given age, the utility assigned in the model should be lower or equal in comparison with the general population utility estimate	Lower
Set the inflation rate for the previous year higher	The costs (which are based on a reference from previous years) assigned at each time will be higher	Not applicable - No option to change the inflation rate in model
Calculate the sum of all ingoing and outgoing transition probabilities of a state in a given cycle	Difference of ingoing and outgoing probabilities at a cycle in a state times the cohort size will yield the change in the number of patients at that state in that cycle	Not applicable – no transition probabilities used in the model

Test description (please also document how the test is conducted)	Expected result of the test	Company result of the test
Calculate the number of patients entering and leaving a tunnel state throughout the time horizon	Numbers entering = numbers leaving	Not applicable
Check if the time conversions for probabilities were conducted correctly.	Yes	Not applicable
Decision tree specific: Calculate the sum of the expected probabilities of the terminal nodes	Should sum up to 1	Not applicable
Patient-level model specific: Check if common random numbers are maintained for sampling for the treatment arms	Yes	Not applicable
Patient-level model specific: Check if correlation in patient characteristics is taken into account when determining starting population	Yes	Not applicable
Increase the treatment acquisition cost	Costs accumulated at a given time will increase during the period when the treatment is administered	Validated
Population model specific: Set the mortality and incidence rates to 0	Prevalence should be constant in time	Validated
Result calculations		
Check the incremental life-years and QALYs gained results. Are they in line with the comparative clinical effectiveness evidence of the treatments involved?	If a treatment is more effective, it generally results in positive incremental LYs and QALYs in comparison with the less-effective treatments	Validated
Check the incremental cost results. Are they in line with the treatment costs?	If a treatment is more expensive, and if it does not have much effect on other costs, it generally results in positive incremental costs	Validated
Total life years greater than the total QALYs	Yes	Yes
Undiscounted results greater than the discounted results	Yes	Yes
Divide undiscounted total QALYs by undiscounted life years	This value should be within the outer ranges (maximum and minimum) of all the utility value inputs	Value within the ranges of all utility value inputs
Subgroup analysis results: How do the outcomes change if the characteristics of the baseline change?	Better outcomes for better baseline health conditions, and worse outcomes for worse health conditions, are expected	Primary prevention and secondary prevention subgroups were tested. Patients in the primary prevention subgroup had better baseline characteristics and better outcomes were observed
Could you generate all the results in the report from the model (including the uncertainty analysis results)?	Yes	Yes
Do the total life-years, QALYs, and costs decrease if a shorter time horizon is selected?	Yes	Yes

Test description (please also document how the test is conducted)	Expected result of the test	Company result of the test
Is the reporting and contextualization of the incremental results correct?	The use of terms such as 'dominant'/'dominated'/'extendedly dominated'/'cost effective'. etc.. should be in line with the results In the incremental analysis table involving multiple treatments, ICERs should be calculated against the next non-dominated treatment	Yes
Are the reported ICERs in the fully incremental analysis non-decreasing?	Yes	Yes
If disentangled results are presented, do they sum up to the total results (e.g. different cost types sum up to the total costs estimate)?	Yes	Yes
Check if half-cycle correction is implemented correctly (total life-years with half-cycle correction should be lower than without)	The half-cycle correction implementation should be error-free. Also check if it should be applied for all costs, for instance if a treatment is administered at the start of a cycle, half-cycle correction might be unnecessary	Half-cycle is implemented correctly although this has been removed in response to the ERG clarification questions.
Check the discounted value of costs/QALYs after 2 years	Discounted value = undiscounted/$(1 + r)^2$	Validated
Set discount rates to 0	The discounted and undiscounted results should be the same	Not applicable as undiscounted results are not presented
Set mortality rate to 0	The undiscounted total life-years per patient should be equal to the length of the time horizon	Undiscounted total life-years per patient are equal to the length of the time horizon when mortality rate is equal to 0
Put the consequence of adverse event/discontinuation to 0 (0 costs and 0 mortality/utility decrements)	The results would be the same as the results when the AE rate is set to 0	Validated
Divide total undiscounted treatment acquisition costs by the average duration on treatment	This should be similar to treatment-related unit acquisition costs	Validated
Set discount rates to a higher value	Total discounted results should decrease	Total results decrease
Set discount rates of costs/effects to an extremely high value	Total discounted results should be more or less the same as the discounted results accrued in the first cycles	Validated

Test description (please also document how the test is conducted)	Expected result of the test	Company result of the test
Put adverse event/discontinuation rates to 0 and then to an extremely high level	Less costs and higher QALYS/LYs when adverse event rates are 0, higher costs and lower QALYS/LYs when AE rates are extreme	Validated
Double the difference in efficacy and safety between the new intervention and comparator, and report the incremental results	Approximately twice the incremental effect results of the base case. If this is not the case, report and explain the underlying reason/mechanism	The incremental effect results are approximately twice of the base case.
Do the same for a scenario in which the difference in efficacy and safety is halved	Approximately halve of the incremental effect results of the base case. If this is not the case, report and explain the underlying reason/mechanism	The incremental effect results are approximately half of the base case.
Uncertainty analysis calculations		
Are all necessary parameters subject to uncertainty included in the OWSA?	Yes	Yes
Check if the OWSA includes any parameters associated with joint uncertainty (e.g. parts of a utility regression equation, survival curves with multiple parameters)	No	No, due to using independent parametric curves
Are the upper and lower bounds used in the one-way sensitivity analysis using confidence intervals based on the statistical distribution assumed for that parameter?	Yes	Yes
Are the resulting ICER, incremental costs/QALYs with upper and lower bound of a parameter plausible and in line with a priori expectations?	Yes	Yes
Check that all parameters used in the sensitivity analysis have appropriate associated distributions – upper and lower bounds should surround the deterministic value (i.e. upper bound ≥ mean ≥ lower bound)	Yes	Yes
Standard error and not standard deviation used in sampling	Yes	Yes, standard error was used where available, alternatively it assumed to be 20%
Lognormal/gamma distribution for HRs and costs/resource use	Yes	Yes lognormal/ gamma distribution used for HRs and costs/resource use except for compliance costs which used Beta
Beta for utilities and proportions/probabilities	Yes	Yes
Dirichlet for multinomial	Yes	Not applicable
Multivariate normal for correlated inputs (e.g. survival curve or regression parameters)	Yes	Yes
Normal for other variables as long as samples do not violate the requirement to remain positive when appropriate	Yes	Yes
Check PSA output mean costs, QALYs, and ICER compared with the deterministic results. Is there a large discrepancy?	No (in general)	No

Test description (please also document how the test is conducted)	Expected result of the test	Company result of the test
If you take new PSA runs from the Microsoft Excel model do you get similar results?	Yes	Yes
Is(are) the CEAC line(s) in line with the CE scatter plots and the efficient frontier?	Yes	Yes
Does the PSA cloud demonstrate an unexpected behavior or have an unusual shape?	No	No
Is the sum of all CEAC lines equal to 1 for all WTP values?	Yes	Yes
Do the explored scenario analyses provide a balanced view on the structural uncertainty (i.e. not always looking at more optimistic scenarios)?	Yes	Yes
Are the scenario analysis results plausible and in line with a priori expectations?	Yes	Yes
Check the correlation between two PSA results (i.e. costs/QALYs under the SoC and costs/QALYs under the comparator)	Should be very low (very high) if different (same) random streams are used for different arms	Validated
If a certain seed is used for random number generation (or previously generated random numbers are used), check if they are scattered evenly between 0 and 1 when they are plotted	Yes	Yes
Compare the mean of the parameter samples generated by the model against the point estimate for that parameter; use graphical methods to examine distributions, functions	The sample means and the point estimates will overlap, the graphs will be similar to the corresponding distribution functions (e.g. normal, gamma, etc.)	Validated
Check if sensitivity analyses include any parameters associated with methodological/structural uncertainty (e.g. annual discount rates, time horizon)	No	No
Value of information analysis if applicable: Was this implemented correctly?	Yes	Not applicable
Which types of analysis? Were aggregated parameters used? Which parameters are grouped together? Does it match the write-up's suggestions?	Yes	Not applicable
Is EVPI larger than all individual EVPPIs?	Yes	Not applicable
Is EVPPI for a (group of) parameters larger than the EVSI of that (group) of parameter(s)?	Yes	Not applicable
Are the results from EVPPI in line with OWSA or other parameter importance analysis (e.g. ANCOVA)?	Yes	Not applicable
Did the electronic model pass the black-box tests of the previous verification stages in all PSA iterations and in all scenario analysis settings? (Additional macro can be embedded to the PSA code, which stops the PSA when an error such as negative transition probability is detected)	Yes	Yes
Check if all sampled input parameters in the PSA are correctly linked to the corresponding event/state calculations	Yes	Yes

Calculations of the cycle-based technology acquisition costs, transition probabilities, and how these probabilities informed the transitions in certain cycles were tested in the previous quality checks conducted by the company.

Verification Stage 5: Overall Validation/Other Supplementary Tests

The model interface and model performance were tested in previous quality checks conducted by the company. It was highlighted that the model was slow due to the chosen formula, however, this did not interfere with the functioning of the model. Further validation of the model was conducted in the AdViSHE checklist above.

Updated OWSA for revised base case

OWSA results for icosapent ethyl versus placebo – ITT

Parameter	Lower bound (£) ICER	Upper bound (£) ICER	Difference (£) ICER
Treatment cost - Icosapent Ethyl cost per cycle	£12,860	£34,667	£21,807
Baseline utility: CV1	£34,125	£19,013	£15,112
Event 1 Icosapent Ethyl vs. Placebo HR - ITT	£30,488	£17,968	£12,520
Utility: Post CR	£16,081	£25,735	£9,654
Utility: Post non-fatal MI	£17,531	£24,668	£7,137
Utility: Post UA	£18,432	£24,146	£5,715
Baseline utility: CV2	£26,147	£20,960	£5,187
Event 2 Icosapent Ethyl vs. Placebo HR - ITT	£24,914	£21,210	£3,704
Event 3 Icosapent Ethyl vs. Placebo HR - ITT	£24,912	£21,459	£3,453
Type of CV event - Event 2 - Placebo	£24,680	£21,359	£3,321
Type of CV event - Event 2 - Icosapent Ethyl	£21,266	£24,330	£3,064
Non CV related mortality HR - Diabetes: CV1	£21,379	£24,305	£2,927
Non CV related mortality HR - Diabetes: CV2	£21,591	£24,136	£2,544
Utility: Post non-fatal Stroke	£21,513	£23,909	£2,396
Type of CV event - Event 1 - Placebo	£23,944	£21,851	£2,093
Long-term CR health state cost	£23,623	£21,599	£2,023

Parameter	Lower bound (£) ICER	Upper bound (£) ICER	Difference (£) ICER
Type of CV event - Event 3 - Placebo	£23,793	£21,801	£1,992
TTD curve - Icosapent Ethyl	£23,419	£22,030	£1,389
Acute Nonfatal MI health state cost	£22,955	£21,589	£1,366
Non CV related mortality HR - Diabetes and MI: CV1	£23,359	£22,021	£1,339

OWSA tornado - ITT

NICE National Institute for Health and Care Excellence

Clinical expert statement & technical engagement response form

Icosapent ethyl with statin therapy for reducing the risk of cardiovascular events in adults with elevated triglycerides [ID3831]

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

Please return this form by **5pm** on **Tuesday 9 November 2021**.

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

NICE National Institute for Health and Care Excellence

PART 1 – Treating a patient with elevated triglycerides at risk of cardiovascular events and current treatment options	
About you	
1. Your name	**Dr Peter Howard Winocour**
2. Name of organisation	**Representing ABCD**
3. Job title or position	**Consultant Diabetologist**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? **X**☐ a specialist in the treatment of people with elevated triglycerides at risk of cardiovascular events? ☐ a specialist in the clinical evidence base for people with elevated triglycerides at risk of cardiovascular events or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	**X**☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	**X**☐ yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Nil**
The aim of treatment for people with elevated triglycerides at risk of cardiovascular events	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To reduce the risk of developing CVD, diabetes and on occasion pancreatitis . Potential improvement in glycaemic control
9. What do you consider a clinically significant treatment response? (For example, a	Reduction in trigs by 15% + NB The CVD outcome benefits of EPA in REDUCE-IT (eg similar with eg gliflozin CVD outcomes) may be greater than expected from reduction in trigs and as suggested reflect additional mechanisms of action-benefit

reduction in disease activity by a certain amount.)	
10. In your view, is there an unmet need for patients and healthcare professionals in patients with elevated triglycerides at risk of cardiovascular events?	Yes
What is the expected place of icosapent ethyl in current practice?	
11. How is the condition currently treated in the NHS?	Apart from fibrates and very high doses of fish oils the loss of nicotinates from care means that there is no effective treatment once statins optimised for residual hypertrig – NB this study showed CVD benefit which is a harder outcome than simply managing the dyslipidaemia
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	ESC /EAS and ABCD UKKA renal lipid guidelines
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Not really well defined – within primary care, lipid , cardiology diabetes services there may be less clear protocols

• What impact would icosapent ethyl have on the current pathway of care?	Would in the range of clinic settings stated enable IcosaPentEthyl introduction if criteria met
12. Will icosapent ethyl be used (or is it already used) in the same way as current care in NHS clinical practice?	It would be additive to statins as stated in REDUCE IT – not being used at present
• How does healthcare resource use differ between icosapent ethyl and current care?	There is no effective management of the residual dyslipidaemia at present unless high dose eg Fish Oil Maxepa used where there is no CVD benefit . in addition combination DHA EPA does not show the same clinical outcomes as high dose EPA alone
• In what clinical setting should icosapent ethyl be used? (For example, primary or secondary care, specialist clinics.)	All settings – primary care , lipid , cardio and DM clinics. By definition there will be more suitable patients in the primary care setting
• What investment is needed to introduce icosapent ethyl? (For example, for facilities, equipment, or training.)	Modest educational on line support
13. Do you expect icosapent ethyl to provide clinically meaningful	Yes

benefits compared with current care?	
• Do you expect icosapent ethyl to increase length of life more than current care?	Yes – but main impact morbidity
• Do you expect icosapent ethyl to increase health-related quality of life more than current care?	Yes
14. Are there any groups of people for whom icosapent ethyl would be more or less effective (or appropriate) than the general population?	DM with CVD esp + role Issues in those with AF-bleeding diathesis
The use of icosapent ethyl	
15. Will icosapent ethyl be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional	The issues around bleeding tendency and AF need assessment and may preclude use in such cases

clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
16. Will any rules (informal or formal) be used to start or stop treatment with icosapent ethyl? Do these include any additional testing?	If develops AF or bleeding issues ? withdraw permanently
17. Do you consider that the use of icosapent ethyl will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Possible impact on insulin resistance ?? fatty liver , diabetes control
18. Do you consider icosapent ethyl to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	Yes – no other effective high dose EPA with evidence base and on top of usual standard of care of high risk cases

improve the way that current need is met?	
• Is icosapent ethyl a 'step-change' in the management of the condition?	Yes
• Does the use of icosapent ethyl address any particular unmet need of the patient population?	Raised trigs and linked residual CVD metabolic risk
19. How do any side effects or adverse effects of icosapent ethyl affect the management of the condition and the patient's quality of life?	Bleeding and AF risk both impt and detectable issues although modest rates of increase
Sources of evidence	
20. Do the clinical trials on icosapent ethyl reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	

• What, in your view, are the most important outcomes, and were they measured in the trials?	Key MACE measured DM control , fatty liver , Insulin resistance issues potential measures
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Hard CVD outcomes were assessed
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not to my knowledge
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	Many surveys of T2DM care show residual dyslipidaemia wrt triglycerides

Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	Impt to ensure access to all ethnic groups – study may have limited representation from BAME
23b. Consider whether these issues are different from issues with current care and why.	

PART 2 – Technical engagement questions for clinical experts		ERG comment
Issues arising from technical engagement		
We welcome your response to the issues below, but you do not have to answer every issue. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.		
Key issue 1: Population of main clinical effectiveness evidence, REDUCE-IT trial, narrower than	Appropriated	No comment.

scope and decision problem		
Key issue 2: The period to determine a stable dose of statin in REDUCE-IT is likely to be less than in clinical practice	To all intents and purposes the minimum period stated is adequate as triglyceride reduction less evdientr with statin use	No comment.
Key issue 3: Composite outcomes (MACE) instead of disaggregated outcomes e.g. CV death used as primary outcome and used in the model	In line with other CVD outcome studies re composite MACE	No comment.
Key issue 4: Unclear generalisability of the	Fully generalizable to NHS high risk	No comment.

results to patients in the UK NHS setting	Did NDA have this info re T2DM wrt more lipid abno than just cholesterol ? HDL as well as ?? trigs	
Key issue 5: Model structure – partitioned survival analysis (partSA)		No comment.
Key issue 6: Use of reconstituted data		No comment.
Key issue 7: Limited evidence available for (long-term) validation of survival curves	Acceptable	No comment.
Key issue 8: Use of stratified parametric models, methodological guidance not followed		No comment.

Key issue 9: Long-term extrapolation, assumption of no treatment waning	Takes account of likely drop off an mortality	No comment.
Key issue 10: Use of treatment-dependent non-CV related death hazard ratios		No comment.
Key issue 11: Health-related quality of life sensitive to choice of utility source		No comment.
Key issue 12: Event costs not adjusted for time since previous event		No comment.
Key issue 13: The distribution to	Given the high risk population and long term extrapolation the exponential curve would	No comment.

extrapolate time to discontinuation	seem a reasonable expectation of continued use of therapy	
Key issue 14: Inconsistent use of sources and calculation of event costs		No comment.
Key issue 15: Incomplete model validation and face validity check		No comment.
Are there any important issues that have been missed in ERG report?		No comment.

PART 3 -Key messages	
24. In up to 5 sentences, please summarise the key messages of your statement: • High risk CVD cases on current statin use still have high residual risk in part attributable tpo residual hypertriglyceridaemia • EPA manages this and importantly those with and without the frequent linked low HDL • The benefits are clear on MACE and this of value for high risk cases • The REDUCE-It outcome data raise important possibility there may be additional mechanisms for the beneficial CVD outcomes •	

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

……

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Clinical expert statement & technical engagement response form

Icosapent ethyl with statin therapy for reducing the risk of cardiovascular events in adults with elevated triglycerides [ID3831]

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

Please return this form by **5pm** on **Tuesday 9 November 2021**.

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

NICE National Institute for Health and Care Excellence

PART 1 – Treating a patient with elevated triglycerides at risk of cardiovascular events and current treatment options	
About you	
1. Your name	**Riyaz Patel**
2. Name of organisation	**University College London**
3. Job title or position	**Professor of Cardiology and Consultant Cardiologist**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with elevated triglycerides at risk of cardiovascular events? ☒ a specialist in the clinical evidence base for people with elevated triglycerides at risk of cardiovascular events or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
The aim of treatment for people with elevated triglycerides at risk of cardiovascular events	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The aim of treatment is to reduce residual cardiovascular risk in people at high risk of CVD events. Currently, in secondary prevention, even optimally treated patients surviving from CVD, remain at very high risk of further CVD events and progression of vascular disease. Some estimates suggest between 5-10% per year experience a MACE for example after a non-fatal ACS. For primary prevention those with diabetes and other risk factors are also at high risk despite contemporary therapy. The expanding literature base on triglyceride rich lipoproteins, suggests that in people with high triglyceride concentrations, there remains an untreated risk, potentially due to a pool of cholesterol not contained within LDL particles, but in other potentially atherogenic apoB containing particles like VLDL and IDL (which contain both TGs and cholesterol) and also possibly due to co-existing inflammation. The expectation is that is that by reducing these triglyceride rich lipoproteins (in size and number) and the TG & cholesterol within them, this could help tackle some of the residual risk mentioned above. Historically it has been uncertain whether triglycerides themselves are causal for atherosclerosis. From observational studies we know that high TG levels associate with pancreatitis and pancreatic insufficiency. Severely elevated TGs are often treated to reduce risk of pancreatitis, especially when levels exceed 10mmol/L, although emerging data suggests a lower threshold at 5mmol/L may be needed. Observational data also suggests that at more moderate

	elevations of TGs, <10mmol/L, the risk of CVD also increases. At higher TG levels there is no increase in risk likely due to high lipoprotein particle size limiting entry into the intima. As such, using the totality of evidence, circulating Triglyceride concentrations at moderate levels can reasonably be considered as a marker of untreated risk. However, whether triglycerides per se, play a direct role in plaque development is still unclear and not yet widely accepted. The main aim of treatment is thus to reduce CVD risk in patients who have high TG levels, which identifies those patients at raised CVD risk.
9. What do you consider a clinically significant treatment response? (For example, a reduction in disease activity by a certain amount.)	Any relative risk reduction in MACE, within 5 years close to 15-20% would be clinically significant. Or absolute event rate reduction of ~2-3%
10. In your view, is there an unmet need for patients and healthcare professionals in patients with elevated triglycerides at risk of cardiovascular events?	There is certainly an unmet need for residual risk lowering in this population. The prevalence of people with co-existing moderately raised triglycerides and high CVD risk is rising everyday with increasing diabetes and obesity rates. Currently we treat such patients with statins to lower LDL, lifestyle changes, manage any secondary causes of high TGs and then if TGs remain raised, we have no option but to leave them as they are. In the past there was a tendency to use TG lowering agents for moderate elevations of TG, but these have not shown any CVD risk reduction benefits and are not recommended by current NICE guidance. I suspect the need may be greater in those with established CVD (~6M in the UK live with CVD), where even optimally treated patients with the best antithrombotic and most intensive LDL lowering still have high risk of recurrent CVD events. Any new drug that can target different pathways to these, are sorely needed to tackle residual CVD risk as we may have hit a ceiling of effect with the existing pathways.
What is the expected place of icosapent ethyl in current practice?	

11. How is the condition currently treated in the NHS?	This specific condition or patient group (raised CVD risk with elevated TGs) is not currently treated in the NHS. We treat all patients with elevated CVD risk with high intensity statin therapy (+other LDL lowering agents) but do not offer anything further to those who also have high TGs and may be at higher risk.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	None in the UK that I am aware of. The 2021 ESC guidelines on CVD prevention, propose use of statins in people with high TG levels for reducing risk with a class I/level A recommendation. The same guidance advocates use of fibrates if TG levels are >2.3mmol/L, giving this a IIb/B recommendation and similarly gives icosapentyl ethyl a IIb/B recommendation if TG levels are >1.5mmol/L. The 2019 ESC guidelines on dyslipidaemia gives a class IIa/B recommendation for use of icosapentyl ethyl in patients at high risk with TG levels 1.5-5.6 in combination with a statin.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The management of LDL is well defined and there is an AAC pathway that spells out very nicely how to manage lipids for primary and secondary prevention of CVD. However, this does not cover treatment of those with raised TG levels and at high CVD risk. As a side note, there is a difference of opinion between international guidelines on how to manage very high TG levels for reducing the risk of acute pancreatitis, with some suggesting treatment with TG lowering agents at higher (~>10) or lower (~>5) thresholds. For CVD risk reduction the focus is on the lower range between 1.7- ~5mmol/L
• What impact would icosapent ethyl have on the current pathway of care?	I would imagine that the AAC pathway would need to be modified with a new decision branch to propose that once LDL has been optimised, and if TGs remain high (1.5-5.6mmol/L) on a fasting sample then icosapentyl ethyl could be added for additional CVD risk reduction. In theory as the benefit was independent of LDL levels, the LDL optimization requirement could be omitted and just state once on high intensity statin therapy and if TGs raised consider the agent. My view though is that there is much more robust data on LDL lowering and so this should be optimized first and then icosapentyl ethyl could be considered as add on therapy for additional risk lowering.
12. Will icosapent ethyl be used (or is it already used) in the same	The drug is not currently used and the patient population not treated in any different way to others at high risk without TG elevation. It would be used as an additional agent to existing clinical practice.

way as current care in NHS clinical practice?	
• How does healthcare resource use differ between icosapent ethyl and current care?	It is a new agent to be added to standard care. A major difference will be the need to assess TG levels to ensure eligibility for the drug. As per NICE CG181, at 3 months after starting a statin, only a non-HDL is measured, (TC and HDL are measured, not a full lipid panel). This is also done for cost reasons with many CCGs refusing to measure lipid profiles. Annual reviews for people with CVD or at high risk also only include a non-fasting non-HDL assessment. Therefore, based on current practice, many people will not be identified as having raised TGs at the 3month post statin or annual review stages. If this drug is recommended, then a full fasting lipid profile will need to be assessed and existing guidance modified to advise this.
• In what clinical setting should icosapent ethyl be used? (For example, primary or secondary care, specialist clinics.)	For maximum impact on CVD risk reduction, and in line with population health management, I would expect it to be available to both primary and secondary care. In secondary care, after a CVD event the focus is usually on initiating a statin. The trial did not administer the drug to patients immediately after a CVD event, and required at least 4 weeks of statin stabilization, so most patients were stable at recruitment. However, patients could be flagged in secondary care for potential consideration of icosapentyl ethyl in due course, on the discharge summary. Drug initiation in hospitals would be in outpatient settings in cardiology clinics where patients with CVD or those at high risk are seen and managed or by specialist lipid clinics advising on similar patients. I would anticipate that the majority of initiation would be in primary care for stable patients at high CVD risk. However, the biggest challenge is education of the primary care workforce on the place and role of this agent. Currently, primary care as a whole still struggles with lipid management (and especially TG management), and personal interaction with GP colleagues suggests many are feeling overwhelmed at the different drugs and guidance available in this space. On top of that, there is pushback from more people about the value of managing lipids and CVD risk. On top of this, many areas still have large swathes of eligible people not on high dose statins (eg ~50% of people with CVD are not on high intensity statin in our local area), who probably ought to be managed with LDL lowering first

	For it to work, the AAC pathway will need to be updated, ongoing education continued in primary care along with a strong steer provided from secondary care and specialist clinics for which patients to be started on this agent. Robust advice and guidance set up may also be needed to support GPs and regular audit to ensure appropriate use of the drug.
• What investment is needed to introduce icosapent ethyl? (For example, for facilities, equipment, or training.)	Training and education of healthcare practitioners about the benefit of this drug and its place in the lipid management pathway – when and when not to use it. Consideration of the need for measuring a full fasting lipid profile – not routinely performed- to assess eligibility for the drug and the cost of this
13. Do you expect icosapent ethyl to provide clinically meaningful benefits compared with current care?	As there is no current treatment for this group of patients and given the impressive relative risk reduction seen in the trials, I would expect to see a benefit. However, this is caveated by the concerns about the trial and whether the benefit may have been to some extent exaggerated. Looking at the STRENGTH study data alongside REDUCE IT and factoring in the differences and potential non TG mediated changes, my feeling is there will be a benefit but perhaps not as high as in the trial, once a real world population without a mineral oil placebo is considered.
• Do you expect icosapent ethyl to increase length of life more than current care?	Potentially, but not certain. In the study with hierarchical testing, there was a borderline reduction in CVD death (HR 0.80 (0.66-0.98)) and marginal for all cause death HR 0.87 (0.74-1.02).
• Do you expect icosapent ethyl to increase health-related quality of life more than current care?	Yes, if CVD events are reduced as anticipated, especially stroke, which was significantly reduced.

14. Are there any groups of people for whom icosapent ethyl would be more or less effective (or appropriate) than the general population?	The study showed a consistent benefit for almost all prespecified subgroups. What is interesting is that the baseline level of TG or LDL had no bearing on the risk reduction, suggesting its mechanism may be independent of lipid pathway modulation. There may be greater benefit for secondary prevention (those with CVD), but this may be power related due to fewer events in the primary prevention subgroup. Of note those <65 may have gained greater benefit (p for interaction 0.004). As the lower age limit was 45, this is an age group enriched for premature CVD and so may have more people with genetically driven dyslipidaemias such as FCH. Finally, the subgroup analysis suggested a possible greater benefit for those with a more metabolic syndrome picture with low HDL (<0.9mmol/L) and high TG (>2.25mmol/L). This is consistent with other studies on fish oils.
The use of icosapent ethyl	
15. Will icosapent ethyl be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	No current care so it will be added as an additional medication for eligible patients A practical implication will be the need to assess TG levels to ensure eligibility for the drug. As per NICE CG181, at 3 months after starting a statin, only a non-HDL is recommended, (TC and HDL are measured, not a full lipid panel). This is also done for cost reasons with many CCGs not supporting measurement of full lipid profiles. Annual reviews for people with CVD or at high risk also only include a non-fasting non-HDL assessment or in some areas just a TC Therefore, based on current practice, many people will not easily be identified as having raised TGs at the 3month post statin or annual review stages. If this drug is recommended, then a full fasting lipid profile will need to be assessed and existing guidance modified. I am not aware that any additional monitoring is needed. Certainly, TGs do not need to be monitored to gauge effectiveness as the effect seems independent of baseline and treated TG values.

	From a patient acceptability, the risk of constipation may be an issue, as would the potential risks of AF and bleeding. Also, the product is made from fish oil so some patients may not be willing to take it.
16. Will any rules (informal or formal) be used to start or stop treatment with icosapent ethyl? Do these include any additional testing?	The definition of high-risk patients will need be carefully defined as the definition differs slightly in different guidelines, or the same strict definition used in the study is applied – but may complicate things. Ideally it would be better to have a single definition of "high risk" applied across the suite of NICE CVD prevention guidance and TAs. Perhaps one rule may be to first ensure LDL has been optimally lowered and patients are statin compliant. Importantly, I am unclear if the drug would be denied to those unable to take a statin given the trial only included those on a statin and had a run-in period thereby excluding those who were stain intolerant. There may be people who are statin intolerant on a PCSK9 inhibitor (either mAB or inclisiran) and have raised TGs. It would seem strange to deny them the drug and I cannot see any biological reason for doing so. Whether bleeding and AF are considered in decision making around whether to use the drug needs to be assessed. For example, there may need to be caution in those with diagnosed PAF.
17. Do you consider that the use of icosapent ethyl will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	None that would be outside the QALY calculations Possibly acute pancreatitis reduction although this would be a small benefit as incidence is low especially at these moderately raised TG levels.
18. Do you consider icosapent ethyl to be innovative in its potential to make a significant and	It is innovative as it appears to work on a pathway that is as yet undefined yet with a substantial benefit. As the current need is not met with any other similar drug it will provide new health benefits.

substantial impact on health-related benefits and how might it improve the way that current need is met?	I would make the comparison with SGLT2 / GLP1, which were designed for diabetes yet have dramatic CVD benefits and we still don't know for sure the mechanism by which they do this.
• Is icosapent ethyl a 'step-change' in the management of the condition?	I would hesitate to call it a "step-change" as other fish oils are available and it will not be viewed by the public as a completely novel treatment (the subtlety of purified EPA and EPA/DHA will be lost on most). This is the first to prove a large CV risk benefit, so it is novel in that sense – albeit with a cloud over the trial.
• Does the use of icosapent ethyl address any particular unmet need of the patient population?	Yes, those with residual CVD risk and high TG levels.
19. How do any side effects or adverse effects of icosapent ethyl affect the management of the condition and the patient's quality of life?	It seems to be a generally well tolerated drug with few significant side effects. There are some concerns: AF risk – this is an important signal as hospitalization for AF is not trivial. It carries with it patient symptoms, admission, medication usage, potential DC cardioversion and anticoagulation. This I suspect would need to be considered when prescribing and should be used with caution in people with known PAF or prior AF Bleeding – possible increased risk but again might just be used as a caution in those with bleeding tendencies. Most people with CVD are on antiplatelets as in the trial and did not experience very high bleeding rates so this should not be a major concern. However more data would be needed especially for those on multiple antithrombotic agents – eg DOAC + clopidogrel

	Constipation – of note this could be a factor that reduces compliance. Diarrhoea was less in the treatment arm, perhaps due to the constipating effect of the drug. Peripheral oedema – this could lead to drug discontinuation and impair quality of life. Might lead to empirical use of diuretics.
Sources of evidence	
20. Do the clinical trials on icosapent ethyl reflect current UK clinical practice?	To some extent, the population in the trial can be found in the UK, if we looked for it. However, the UK was not represented in the study, so our populations were not included in the study itself. This is relevant especially for ethnic minority groups, who have higher levels of CVD, and TGs and insulin resistance and might have benefitted more. The biggest difference is that current UK practice does not incorporate assessment of TGs routinely during the care pathway and also does not stipulate an LDL target. As such both parameters are not routinely assessed and therefore the eligible population based on the trial criteria (TG and LDL levels) would not be easily identified in routine care.
• If not, how could the results be extrapolated to the UK setting?	Exploring the demographic and risk factor profiles of those in the study in more detail and comparing to the UK population from information such as CPRD or Health survey England etc. This would need the trial data to be split by secondary and primary prevention as this data is aggregated in the paper. After that assuming they are similar, we can only extrapolate from the included US population and make the assumption that there are no significant biological differences in factors that might affect the efficacy of the drug.

• What, in your view, are the most important outcomes, and were they measured in the trials?	Major CVD outcomes – yes, all were measured
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Additional biomarker changes were assessed but they were used more to explore the mechanism of action
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	None that I'm aware of
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	I presume all relevant studies for the concept have been examined? Relevant studies to REDUCE-IT = JELIS trial, EVAPORATE, STRENGTH, CHERRY Observational data and Mendelian randomization on TG associations with CVD may be of interest
22. How do data on real-world experience compare with the trial data?	I don't have any real-world experience of this agent and am not aware of any data on this.
Equality	

23a. Are there any potential equality issues that should be taken into account when considering this treatment?	TG levels are higher in BAME patients, due to diabetes, obesity and insulin resistance, and they also have more CVD so this group may benefit more from the drug. More people are or becoming Vegan or Vegetarian and therefore may not be able or willing to take this drug which I think is made from sardines and anchovies. Similarly, there might be religious restrictions on seafood for some people.
23b. Consider whether these issues are different from issues with current care and why.	Usual medicines are not made from animal products, so most people do not object to them.

PART 2 – Technical engagement questions for clinical experts		ERG comment
Issues arising from technical engagement		
We welcome your response to the issues below, but you do not have to answer every issue. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.		
Key issue 1: Population of main clinical effectiveness evidence, REDUCE-IT trial, narrower than scope and decision problem	The ERG suggest the scope should be in line with the study criteria and propose 135mg/dL as the definition of high triglycerides (not sure where this comes from as the NEJM paper states the initial cut point was 150 and then increased to 200mg/dL)). NICE just states hypertriglyceridaemia. The accepted definition of this is 1.7mmol/L (150mg/dL), which fits with the initial TG cut point used in the trial. It was later increased to 2.2mmol/L, but there was no difference in efficacy when stratified by baseline TG. Given that 1.7mmol/L is an accepted threshold for defining hypertriglyceridaemia, I would keep it as it is.	The ERG did not only suggest that the scope should be in line with the study criteria and nor did the ERG propose any definition of high triglycerides. The ERG suggested that the decision problem should be 'based on the eligibility criteria for REDUCE-IT' or that evidence needed to be provided if there was any discrepancy. Also, the main focus of any discrepancy between scope and trial that the ERG identified was in terms of age. The clinical expert acknowledges an age effect, although of course this was only in those

	With regards to age, the study did restrict to >45 for secondary prevention. There was an age interaction with a trend to greater benefit in younger patients. This could be because more genetically driven raised TGs are present in younger people rather than secondary causes. In my view, there is no biological reason to restrict use of the drug to those over 45. We certainly see many younger people with CVD or diabetes who have raised TGs, especially among the South Asian population. As such restricting to age >45 or >50 may disadvantage people at risk. Restricting to LDL levels to 1-2.6mmol/L, could add a layer of complexity to use of the drug in the UK as LDL is not routinely measured and only non-HDL is advocated by NICE guidance. It should be sufficient to ensure that a high intensity statin is used (or proven intolerance) before the agent is offered. LDL lowering and management should continue thereafter in parallel with other agents like ezetimibe, bempedoic acid or PCSK9i. As efficacy again did not vary by baseline LDL levels, this would not make sense and would just add more cost and complexity to initiation.	aged at least 50 or 45 for primary and secondary prevention populations. The clinical expert then asserts that there is no biological reason to restrict to those over 45. Unfortunately, no evidence has been presented for those younger than 50 or 45 for the primary and secondary prevention populations respectively.
Key issue 2: The period to determine a	I agree that in clinical practice, and based on NICE guidance, we check LFTs and non-HDL at 3 months	No comment.

stable dose of statin in REDUCE-IT is likely to be less than in clinical practice	after statin initiation. Doing so any sooner is unlikely to be pragmatic and would introduce cost. In my view if a patient is on statin therapy for longer than 4 weeks, this is not an issue as there is no biological reason to assume it would have any impact on the efficacy of the drug. Possibly LDL may be a bit lower if assessed later but as we have seen the effect was not related to baseline LDL concentration. Pragmatically I would expect patients to be started on a statin, have a 3 month blood test (would need to be a fasting lipid profile - a change to current practice) and if at that time they also have high TGs (>1.7), the doctor would start the agent. If this was an even longer time frame, perhaps as it happened in an outpatient consultation, it should make no material difference.	
Key issue 3: Composite outcomes (MACE) instead of disaggregated outcomes e.g. CV death used as primary outcome and used in the model	It is fair to say most major trials use a composite MACE outcome. Individual endpoints on hierarchical testing are provided and could be used as needed by the NICE team.	No comment.

Key issue 4: Unclear generalisability of the results to patients in the UK NHS setting	I agree with the ERG on this point. For example, the UK population has a high proportion of BAME patients and a population overall with a slightly different risk profile for metabolic disease compared to the populations studied in the trial. My suspicion is that it may not be so important, and we can extrapolate from the US but certainly some more clarity on the demographics and risk profile of the US population would help. The data would need to be separated by secondary prevention and primary prevention cohorts. This could then be compared with the Steen data or to UK health survey data or information from other UK sources (e.g. CPRD). This would allay any fears about generalizability or demonstrate significant differences.	No comment.
Key issue 5: Model structure – partitioned survival analysis (partSA)	Apologies, unable to comment	
Key issue 6: Use of reconstituted data	Apologies, unable to comment	
Key issue 7: Limited evidence available for	Apologies, unable to comment	

(long-term) validation of survival curves		
Key issue 8: Use of stratified parametric models, methodological guidance not followed	Apologies, unable to comment	
Key issue 9: Long-term extrapolation, assumption of no treatment waning	There is not much data to guide the assumption that treatment does not wane. Statin therapy appears to have a long-term effect based on available studies such as long term follow up of WOSCOPS. This could be extrapolated, biologically, to other LDL lowering agents. However, as icosapentyl ethyl has a mechanism that is as yet uncertain I am not sure we can use the same assumption. There is a suggestion in the literature that icosapentyl ethyl works by affecting oxidative stress or inflammation, endothelial function etc, which may be more short-term effects or ones that could vary over time or with intercurrent illnesses or non CVD drugs or recurrent events. I note the JACC study by Bhatt et al in 2019 on subsequent events in REDUCE IT, where they report that 1606 primary outcome first events took place as reported in NEJM, but after this another 1303 recurrent	No comment.

	events also occurred. The authors state that the drug reduced the rate of these recurrent events too, compared to placebo, suggesting the drug has an effect on first and subsequent event reduction. I believe the company use this to extrapolate on longer term effects of the drug. I don't think this is unreasonable.	
Key issue 10: Use of treatment-dependent non-CV related death hazard ratios	Apologies, unable to comment	No comment.
Key issue 11: Health-related quality of life sensitive to choice of utility source	Apologies, unable to comment	No comment.
Key issue 12: Event costs not adjusted for time since previous event	Apologies, unable to comment	No comment.
Key issue 13: The distribution to	Given the mean age of REDUCE-IT participants was 65, extrapolating to 40 years is somewhat artificial. Most	No comment.

extrapolate time to discontinuation	people would take the drug until perhaps 80 yrs, after which medications like this would likely be stopped. Nonetheless, most CVD drugs seem to have a long-term adherence rate of about 60%. As such the models in figure 4.2 seem a bit conservative and the Gompertz or Lognormal models may be closest to expectations. For example: Wei L, Fahey T, MacDonald TM. Adherence to statin or aspirin or both in patients with established cardiovascular disease: exploring healthy behaviour vs. drug effects and 10-year follow-up of outcome. Br J Clin Pharmacol. 2008;66:110–116 For primary prevention discontinuation may be greater, especially if used in younger people with polypharmacy	
Key issue 14: Inconsistent use of sources and calculation of event costs	Apologies, unable to comment	No comment.
Key issue 15: Incomplete model validation and face validity check	Apologies, unable to comment	No comment.

Are there any important issues that have been missed in ERG report?		
PART 3 -Key messages		
24. In up to 5 sentences, please summarise the key messages of your statement: • There is an unmet need to help those at highest CVD risk, who remain vulnerable to more CVD events despite optimal contemporary treatments and people with high CVD risk and raised triglycerides represent a potential group of people in whom we could do more. • In UK practice, especially primary care, there has been a big move away from measuring lipid profiles and TG levels, in favour of non-HDL, so for this drug to be used widely there would need to be a move back towards checking the full lipid profile at some stage in the patient journey • There is a growing population of people with raised TGs and CVD risk, as a result of rising diabetes and obesity levels and confusion around how to deal with this, so a large piece of work on education of healthcare professionals on the role of TGs in disease will be needed. • There may be some issues around patient acceptability as the drug is extracted from fish, affecting those with dietary or religious restrictions • I think the drug could have a meaningful impact in clinical practice and it would be helpful to have available for the many patients who continue to have		

events, but as with most colleagues, my confidence would be greater if we didn't have the limitations/concerns of the JELIS/REDUCE-IT trials and we had a better mechanistic understanding of how the benefit arises.	

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

.....

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The information that you provide on this form will be used to contact you about the topic above.

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NICE National Institute for Health and Care Excellence

Technical engagement response form

Icosapent ethyl with statin therapy for reducing the risk of cardiovascular events in adults with elevated triglycerides [ID3831]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments by **5pm** on **Tuesday 9 November 2021**.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**British Cardiovascular Society**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

NICE National Institute for Health and Care Excellence

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	**Does this response contain new evidence, data or analyses?**	Response
Key issue 1: Population of main clinical effectiveness evidence, REDUCE-IT trial, narrower than scope and decision problem	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 2: The period to determine a stable dose of statin in REDUCE-IT is likely to be less than in clinical practice	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 3: Composite outcomes (MACE) instead of disaggregated outcomes e.g. CV death used as primary outcome and used in the model	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 4: Unclear generalisability of the results to patients in the UK NHS setting	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 5: Model structure – partitioned survival analysis (partSA)	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses

Key issue 6: Use of reconstituted data	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 7: Limited evidence available for (long-term) validation of survival curves	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 8: Use of stratified parametric models, methodological guidance not followed	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 9: Long-term extrapolation, assumption of no treatment waning	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 10: Use of treatment-dependent non-CV related death hazard ratios	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 11: Health-related quality of life sensitive to choice of utility source	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 12: Event costs not adjusted for time since previous event	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 13: The distribution to extrapolate time to discontinuation	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 14: Inconsistent use of sources and calculation of event costs	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses

Key issue 15: Incomplete model validation and face validity check	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response	ERG comment

Additional issue 1: Results of REDUCE it trial	3.2.5	YES	BSC would like to raise some additional points relating to the results of REDUCE-IT. The basic issue is do we believe the results. As a trial with respect to conduct - no issues. But the control group is not neutral, so not placebo like. If it has harmful effects then the magnitude of the treatment effect for EPA is much lower and uncertain at best. 1. EPA lowers TG modestly about 17%. So the level of risk reduction is disproportionate to the level of TG lowering when looking at genetics and observational epidemiology 2. Mineral oil increases inflammatory markers and lipids. Thus increasing risk of harm. If we look at lipids and inflammatory benefits of EPA and compare the two see attached paper, then the relative risk reduction is about half the reported benefit in the trial. This impacts Health economic assessment.	The ERG would like to point out, as mentioned in the ERG report, that icosapent ethyl is not the same as EPA. It is also unclear what the source of the estimate of 17% TG lowering is or the risk reduction to which the BCS refer. The ERG has examined the paper referred to as 'Takahito et a.2021. It is true that this paper reports an analysis that seems to show that the difference between REDUCE-IT and another trial, STRENGTH, in treatment effect in terms of HR of MACE, the primary outcome, might be at least partly explained by difference in comparator i.e., mineral oil in the former vs. corn oil in the latter. This might suggest that the treatment effect of icosapent ethyl has been overestimated if it is believed that mineral oil increases the risk of MACE. The ERG would sound a note of caution as to what can be

			3. If the drug does not work through traditional lipids then it has to do so by some other mechanism we can't measure. 4. A relevant publication is the Attached STRENGTH analysis where the on treatment EPA level levels with epanova which contains both EPA and DHA were measured. The comparator was a truly neutral compound corn oil. The overall trial was neutral. On treatment EPA levels and DHA levels from pharmaceutical elevation had no association with outcomes. This calls into question the theory that EPA in REDUCE high EPA levels associated with better outcomes. It could be that the mineral oil just causes harm. 5. Patients with high TG, can have their risk mitigated by greater non HDL-C lowering and greater BP lowering and control of traditional risk factors. We understand how these mechanisms work.	inferred from the Takahito et a.2021 study: 1) A plausible explanation for the difference between mineral oil and corn oil is that corn oil decreases the risk of MACE and that the changes observed in the REDUCE-IT placebo arm are part of the natural history. 2) The Takahito et al .2021 conclusions regarding mineral oil versus corn oil are based on an analysis using surrogates for oil i.e., plasma triglycerides, low-density lipoprotein cholesterol, and C-reactive protein. It might be that the differences in these measures between the mineral oil arm of REDUCE-IT and the corn oil arm of STRENGTH are not attributable to the oil, but to differences in patient characteristics.

			6. I would be more convinced if EPA were tested against corn oil and showed benefit. Please see attached papers from Takahito et al. 2021 and Nissen et al. 2021.	The ERG also noted that an analysis of time to the primary outcome by LDL-C increase or not and by C-reactive protein increase or not showed no significant effect of either of these surrogates (see Figures 11-12 to 11-15, CSR). In addition, the ERG did find a systematic review by Olshansky et al 2020 (Mineral oil: safety and use as placebo in REDUCE-IT and other clinical studies, European Heart Journal Supplements, Volume 22, Issue Supplement, October 2020, Pages J34–J48) that examined the potential harmful effect of mineral oil as placebo, which concluded that it 'does not meaningfully affect study conclusions when used as a placebo at the quantities used in clinical trials.' However, the review was not well reported with some question as to whether all relevant trials had been included and one of the co-authors was employed by Amarin.

				In conclusion, it is unclear whether the placebo in REDUCE-IT was inert or not and therefore whether the treatment effect of icosapent ethyl has been overestimated.

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER
Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER