National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

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

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

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Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	British Cardiovascular Society	Yes, this is an appropriate topic given the large beneficial effects seen in the REDUCE-IT trial. The drug is also listed for consideration in the current 2019 ESC CVD prevention guidelines and will likely feature in the next guidelines too. It is available in the US so clinicians in the UK will be looking at this within the next year or so too. I am not aware that the EMA has granted a license yet but assume as FDA gave this last year it will also be granted soon.	Thank you for your comment. This topic has been scheduled into the work programme.
Wording	Amarin Corporation	**Current wording:** **"**To appraise the clinical and cost effectiveness of icosapent ethyl within its marketing authorisation for preventing cardiovascular events due to elevated triglycerides." **Suggested new wording:** **"**To appraise the clinical and cost effectiveness of icosapent ethyl within its marketing authorisation for reducing the risk of cardiovascular events as an	Thank you for your comment. The wording of the remit has been updated.

Section	Consultee/ Commentator	Comments [sic]	Action
		adjunct to statin therapy in adult patients with elevated triglycerides, who are at high risk of cardiovascular events **Rationale** To reflect the anticipated marketing authorisation.	
	British Cardiovascular Society	Yes	Thank you for your comment.
Timing Issues	Amarin Corporation	As noted in the draft scope, cardiovascular disease is one of the main causes of mortality in England, resulting in an estimated 136,317 deaths in 2018. These deaths occur in spite of very widespread use of existing therapies – including statins – to reduce cardiovascular risk. Some patients remain at high-risk of ischaemic events in spite of optimised statin therapy. Residual risk is particularly high in patients with documented CVD and those with diabetes and additional cardiovascular risk factors. Elevated triglyceride levels have been associated with increased risk of CV events in statin-treated patient populations. In this well identified population, CV risk remains high. In the control arm of the REDUCE-IT study 22 % of patients experienced a CV endpoint over a median follow up of 4.9 years, in spite of optimal statin therapy.[1] In a population of high-risk patients with moderately elevated triglycerides on statin therapy, icosapent ethyl demonstrated a 25% relative risk reduction compared to placebo in the primary composite endpoint of 5-point MACE (CV death, nonfatal myocardial infarction [MI], nonfatal stroke, coronary revascularization, hospitalization for unstable angina).[1] The risk reduction was statistically significant (P<0.001) and consistent across secondary endpoints including the key secondary endpoint of a 3-point MACE (CV death, nonfatal	Thank you for your comment. This topic has been scheduled into the work programme.

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		MI, or nonfatal stroke - HR 0.74, 95% CI, 0.65 to 0.83; P<0.001).[1] No other similar product has been shown to reduce “hard” cardiovascular endpoints in this population. The most recent European guidelines state that in high-risk (or above) patients with TG between 1.5 and 5.6 mmol/L despite statin treatment, icosapent ethyl should be considered in combination with statins (recommendation class IIa).[2] Icosapent ethyl, as reflected offers the NHS the opportunity to reduce major cardiovascular events in a well identifiable group of patients at high risk of cardiac morbidity and mortality. This benefit has not been shown by other products. In order to make these benefits available to patients, an appraisal should be conducted as soon as evidence of clinical and cost-effectiveness can be made available. Amarin is working to gather the necessary information and expects to be able to provide a full submission by April 2021.	
	British Cardiovascular Society	Given that ESC guidelines are mentioning this drug already, there will be some urgency in deciding its place in UK guidance	Thank you for your comment. This topic has been scheduled into the work programme.
Additional comments on the draft remit	Amarin Corporation	No additional comments	Thank you.
	British Cardiovascular Society	No comment.	Thank you.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Amarin Corporation	**Current wording:** Hypertriglyceridemia is a form of dyslipidaemia characterised by high concentrations of triglycerides in the blood and is a risk factor for CVD[1]. Triglyceride levels can be raised due to either primary causes (an inherited genetic condition) or secondary causes (other influences on triglycerides such as diet, lifestyle and medical conditions such as kidney disease, non-alcoholic fatty liver disease, gout, obesity and type 2 diabetes)[2]. Some people with hypertriglyceridemia have normal levels of high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol. Others have mixed dyslipidaemia, defined as elevations in triglyceride and LDL cholesterol levels that are often accompanied by low levels of HDL cholesterol[3]. People with hypertriglyceridemia are at increased risk of cardiovascular disease (CVD) because of the build-up of fatty deposits in arteries (atherosclerosis) which can lead to angina, and an increased risk of blood clots, myocardial infarction and stroke[4]. It can be associated with damage to arteries in organs such as the brain, heart, kidneys and eyes. CVD is a common cause of death in England, accounting for approximately 136,317 deaths in 2018, and it is a major cause of disability and reduced quality of life[3]. NICE guideline CG181 recommends advising people at high risk of, or with, CVD to eat a cardioprotective diet, engage in physical activity and stop smoking. 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 cardiovascular events in people with CVD. Fibrates, nicotinic acid, bile sequestrants and omega-3 fatty acids are not currently recommended for the primary or secondary prevention of CVD. There are around 6.1 million people living with CVD in England and	Thank you for your comment. The scope has been updated to focus only on people with hypertriglyceridemia. The recommended treatment options have been updated.

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		around 6.5 million adults in England are currently taking lipid-lowering drugs such as statins[3]. **Suggested new wording:** People with dyslipidaemia are at increased risk of cardiovascular disease (CVD) because of the build-up of fatty deposits in arteries (atherosclerosis) which can lead to angina, and an increased risk of blood clots, myocardial infarction and stroke[4]. Epidemiological and genetic studies have demonstrated an independent correlation between increased TG levels and increased CV events, with increases in risk being observed starting at TG levels less than 100 mg/dL [3,4,5,6]. CVD is a common cause of death in England, accounting for approximately 136,317 deaths in 2018, and it is a major cause of disability and reduced quality of life[3]. NICE guideline CG181 recommends advising people at high risk of, or with, CVD to eat a cardioprotective diet, engage in physical activity and stop smoking. 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 cardiovascular events in people with CVD. There are around 6.1 million people living with CVD in England and around 6.5 million adults in England are currently taking lipid-lowering drugs such as statins[3]. Some patients remain dyslipidaemic in spite of statin therapy. Evolocumab and Alirocumab are recommended as options for treating hypercholesteremia in some high risk groups of patients with low-density lipoprotein concentrations that are persistently elevated despite maximal tolerated lipid‑lowering therapy. No therapies are currently recommended by NICE specifically for the management of the patients included in the REDUCE-IT study, i.e. with persistently moderately elevated triglyceride levels despite statin therapy.	

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		Rationale: Icosapent ethyl is expected to be indicated for reducing the risk of cardiovascular events as an adjunct to statin therapy in adult patients with elevated triglycerides, who are at high risk of cardiovascular events. To better align with the anticipated indication, the suggested wording changes the focus towards cardiovascular event prevention rather than triglyceride reduction and discusses options available for patients with residual CVD risk who are already receiving statins. We also suggest clarifying that there are no NICE recommended therapies for the patient group of interest, rather than listing some therapies that NICE does not recommend.	
	British Cardiovascular Society	We would suggest some caution about stating that there is a causal role for triglycerides in atherosclerosis as this is a topic of ongoing debate. Perhaps say “possible” causal role?	Thank you for your comment. The scope has been updated.
The technology/ intervention	Amarin Corporation	**Current wording:** “Icosapent ethyl (Vascepa, Amarin Corporation) is an omega-3 fatty acid agent. Icosapent ethyl is thought to reduce hepatic very low-density lipoprotein triglyceride synthesis and secretion and enhance triglyceride clearance. It is administered orally. Icosapent ethyl does not currently have a marketing authorisation in the UK. It has been studied in combination with statins in clinical trials in adults with established CVD or high risk for CVD and hypertriglyceridemia for the prevention of cardiovascular events.” **Suggested wording:**	Thank you for your comment. The description of the technology has been updated to refer to icosapent ethyl being a highly purified ethyl ester of eicosapentaenoic acid. The description of the mechanism of action and clinical trial description is a succinct

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		"Icosapent ethyl (Vascepa, Amarin Corporation) is a highly purified ethyl ester of eicosapentaenoic acid (EPA). Omega-3 fatty acid formulations contain compounds such as alpha-linolenic acid (ALA) and docosa-hexaenoic acid (DHA) which have no proven impact on cardiovascular events and are present in varying concentrations, mixed with various amounts of EPA. Vascepa is the only product to consist of a highly purified single active ingredient, EPA. The mechanisms of action of icosapent ethyl are not completely understood, but likely include improved lipoprotein profile, with reduction of triglyceride-rich lipoproteins as well as anti-inflammatory, antioxidant, and membrane stabilising effects, reduction of macrophage accumulation, improved endothelial function, increased fibrous cap thickness/stability, and antiplatelet effects. Icosapent ethyl does not currently have a marketing authorisation in the UK. It has been studied for the prevention of cardiovascular events in combination with statins in a multinational, double-blind, randomised, placebo controlled clinical trial with 5-year follow up in 8,179 adults with established CVD, or with diabetes and other high risk factors for CVD and hypertriglyceridemia. **Rationale** Fuller description of the product. Description of mechanism of action, aligned with expected label. Fuller description of the main clinical evidence source. Comparing the therapy with other omega-3 products is important in understanding the rationale for conducting this appraisal.	summary and is not exhaustive. This has not been amended.

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	British Cardiovascular Society	We would suggest mentioning the degree of reduction of triglyceride levels in older trials as well as the key trial.	Thank you for your comment. This section describes the clinical trials available for this technology and does not include trials on other technologies. No changes to the scope have been made.
Population	Amarin Corporation	**Is the population defined appropriately?** **Current wording:** "Adults with established cardiovascular disease or at high risk of cardiovascular disease with hypertriglyceridemia and on statin therapy" **Suggested new wording:** Adults receiving statin therapy and with elevated triglycerides, who are at high risk of cardiovascular events due to: • established cardiovascular disease, or • diabetes, and at least one other cardiovascular risk factor. **Rationale** To align with the anticipated marketing authorisation.	Thank you for your comment. The scope has been updated.
	British Cardiovascular Society	Yes, high risk patients although not all patients in the trial had established CVD, as many were included for primary prevention if they were older than 50 with diabetes + one other risk factor	Thank you for your comment. The scope has been updated.

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Comparators	Amarin Corporation	**Current wording:** • Statins: o atorvastatin o fluvastatin o pravastatin o rosuvastatin o simvastatin • When statins are contraindicated or not tolerated: o alirocumab o evolocumab • For people with hypertriglyceridemia and primary hypercholesterolaemia: o ezetimibe **Suggested new wording:** • Continuing therapy with a statin alone • alirocumab or evolocumab might be comparators, as adjuncts to statins in certain patient groups **Rationale** • Icosapent ethyl is expected to be indicated as an adjunct to optimal statin therapy, so statins are not a comparator. Icosapent ethyl is not expected to be indicated when statins are contraindicated or not tolerated: No other therapy has been shown to reduce cardiovascular events in this setting and we believe that the majority of patients with elevated triglycerides do not currently receive additional therapy.	Thank you for your comment. Comparators have been updated to established clinical management only (including low and high-dose intensity statins). Because the scope has been updated to exclude mixed dyslipidaemia, the drugs alirocumab, evolocumab and ezetimibe (which are all recommended for patients with mixed dyslipidemia) were removed from the scope as potential comparators.

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	British Cardiovascular Society	See below	Thank you for your comment.
Outcomes	Amarin Corporation	**Current wording:** • time to cardiovascular event (including myocardial infarction, stroke and unstable angina) • mortality • hospital admissions • adverse effects of treatment • health-related quality of life. **Suggested new wording:** • time to cardiovascular event (including cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularisation, or unstable angina) • time to 3-point MACE (including cardiovascular death, nonfatal myocardial infarction, nonfatal stroke) • mortality • coronary revascularization (CABG and PCI) • hospitalisation for unstable angina • adverse effects of treatment • health-related quality of life. **Rationale** To better align with evidence available from the REDUCE-IT trial. The primary endpoint of the REDUCE-IT trial was a 5 point MACE (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke,	Thank you for your comment. The outcomes included in the scope do not provide an exhaustive list. The scope has been updated to reflect the suggestions on defining cardiovascular events.

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		coronary revascularisation, or unstable angina). A key secondary endpoint was a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. Further secondary endpoints included components of the primary composite endpoint.	
	British Cardiovascular Society	See below	Thank you for your comment.
Economic analysis	Amarin Corporation	The economic analyses for icosapent ethyl for the reduction in risk of cardiovascular events in high risk patients with hypertriglyceridemia, will be expressed as incremental costs per quality-adjusted life years, following the reference case. The costs and effectiveness of icosapent ethyl vs the relevant comparator will be modelled over a lifetime horizon with ability for sensitivity analyses at different time horizons. The cost and utility impact of cardiovascular events and hospitalisations avoided will be considered.	Thank you for your comment. No changes to the scope have been made.
	British Cardiovascular Society	No comment.	Thank you.
Equality and Diversity	Amarin Corporation	Cardiovascular risk differs between ethnic groups. We do not anticipate that there will be sufficient evidence to support separate evaluations of the effectiveness and cost-effectiveness of icosapent ethyl for separate ethnic groups. We anticipate that NICE may issue guidance that allows physicians to take elevated risk in certain groups into consideration in practice. NHS funding would allow equal access in England to a product bringing major cardiovascular outcomes benefit, regardless of a patient's financial means.	Thank you for your comment. The committee will consider the impact of all equalities issues during

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		The availability of the icosapent ethyl would reduce risk of COVID-19 infection. The oral formulation allows home based treatment and less frequent visits to cardiovascular clinics than injectable therapies. Reduction in CV procedures and events will also reduce pressure on hospital facilties at a time of increased demand due to COVID-19.	the appraisal for this technology.
	British Cardiovascular Society	Triglyceride levels are high in patients with insulin resistance. Such patients have a higher proportion of BAME patients than the general population. BAME groups may therefore benefit more than others if the drug has a true benefit.	Thank you for your comment. The committee will consider the impact of all equalities issues during the appraisal for this technology.
Other considerations	Amarin Corporation	**Suggested wording (no change):** If the evidence allows the following subgroup will be considered: • adults at high risk of cardiovascular disease (primary prevention) • adults with established cardiovascular disease (secondary prevention) **Rationale** It is not yet clear if there is sufficient evidence to establish separate estimates of effectiveness or cost-effectiveness in these subgroups. If licensed and recommended by NICE, icosapent ethyl will be the first new therapy used as an adjunct to statin therapy to reduce the risk of cardiovascular events in patients with hypertriglyceridemia.	Thank you for your comment. Subgroups have been updated in the scope.

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	British Cardiovascular Society	The issues centre around mechanism of action. The drug does not seem to reduce TG sufficiently to explain the apparent benefit. There could be pleiotropic effects of this therapy, but it's unclear what that might be. We are unsure therefore if the drug should be described as one to benefit those with high tryglycerides or rather those at highest residual CV risk – the proportional reduction in TGs was modest compared to the effect obtained, while the benefit was the same at all levels of TGs, including those at very low values. The Evaporate trial suggested placebo(mineral oil)-exposed atheroma progresses at a 10 fold rate greater than expected over 18 months. Moreover, the interim analysis of atheroma increasing then decreasing is unheard of and perhaps suggests methodological issues. These difficult to explain changes make it hard to understand the potential mechanism of how this drug might have resulted in the apparent benefit reported. This then leaves the issue of is the placebo really placebo. Mineral oil increase LDL-C and hsCRP and apo B. The trial authors suggested that these increases do not account for the differences in the placebo arm. However these are only the measured effects . There could be intermediate effects we are not measuring. Hence if EPA is neutral or modest in its effect then the HR is not).75 for benefit but rather 1/0.75 or 1.33 mineral oil causes harm. Given these concerns, we are unsure whether the apparent benefits would be reproduced in a trial where the placebo arm was truly biologically inert. Such a trial, by independent researchers, finding the same benefit would likely	Thank you for your comment. The committee will consider the clinical efficacy of icosapent ethyl during the appraisal for this technology. No changes to the scope have been made.

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		reassure the lipid community greatly, although this may not be quickly available.	
Innovation	Amarin Corporation	**Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?** Unlike other omega-3 products which are composed of various mixtures of alpha-linolenic acid (ALA), docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA); icosapent ethyl (Vascepa, Amarin Corporation) contains a single active ingredient, a highly purified ethyl ester of EPA. Icosapent ethyl is the only agent to have shown significant reduction in cardiovascular events in high-risk patients with established cardiovascular disease or with diabetes and at high risk of cardiovascular disease with hypertriglyceridemia and on statin therapy. The opportunity to substantially reduce the occurrence of cardiovascular events will constitute a step change in the management of CVD in this population. Isolating EPA and purifying to the very high levels achieved in Vascepa constitutes a manufacturing innovation. This has been achieved after a decade of significant investment in manufacturing methodology and required development of proprietary technology and processes. **Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?** The company is not aware of major health-related benefits associated with icosapent ethyl that cannot be included in the QALY calculation.	Thank you for your comment. The committee will consider the innovative nature of this technology and any potential health-related benefits not captured in the QALY during the appraisal. No changes to the scope have been made.

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	British Cardiovascular Society	See above. Similar agents have not resulted in similar benefit, so the drug is not innovative, but may have a specific benefit not seen in other agents of a similar nature.	Thank you for your comment. The committee will consider the innovative nature of this technology during the appraisal. No changes to the scope have been made.
Questions for consultation	Amarin Corporation	Please find below Amarin Corporation's responses to the additional consultation questions. **Is it appropriate to refer to reducing cardiovascular events in the title? Is it more appropriate to refer to 'treating hypertriglyceridemia'?** It is more appropriate to refer to reducing the risk of cardiovascular events in high risk patients with hypertriglyceridemia in the title. This is better aligned with the population and methodology of the pivotal study and the anticipated indication for the product. **Should the remit and population in the scope also include people with mixed dyslipidaemia?** Icosapent ethyl is expected to be indicated as an adjunct to statin therapy in adult patients with elevated triglycerides, who are at high risk of cardiovascular events. Patients in REDUCE-IT were required to have a low-density lipoprotein cholesterol level of 1.06 to 2.59 mmol/l at baseline while receiving a stable dose of statin therapy. The analyses by subgroup consistently showed CV benefits	Thank you for your comment. The scope has been updated to reflect your comments.

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		in patients with high TG and low HDL-C at baseline. [1] We do not believe that separate consideration of a ”mixed dyslipidaemia” population is needed. **Have all relevant comparators for icosapent ethyl been included in the scope? Which treatments are considered to be established clinical practice in the NHS for prevention of cardiovascular events?** Icosapent ethyl (EPA) is an innovative therapy for a group of high risk patients for whom no currently available therapies have been shown to reduce cardiovascular event risk. We expect icosapent ethyl to be used in addition to continuing standard of care. **Are the outcomes listed appropriate?** We have proposed including a 5 point MACE, a 3 point MACE and individual cardiovascular events to align with the primary and secondary composite endpoints in the REDUCE-IT trial. **Are the subgroups suggested in ‘other considerations’ appropriate? Are there any other subgroups of people in whom icosapent ethyl is expected to be more clinically effective and cost effective or other groups that should be examined separately? Specifically, is it appropriate to add people with mixed dyslipidaemia as a subgroup?** See comments above.	
	British Cardiovascular Society	The company lost a major patent battle in the USA this year so that a generic version will be available – what are the chances and consequences of that happening here? This should be factored in the cost effectiveness analysis.	Thank you for your comment. The availability of generic versions of icosapent ethyl will be taken into account by the

Section	Consultee/ Commentator	Comments [sic]	Action
			committee during the appraisal. No changes to the scope have been made.
Additional comments on the draft scope	Amarin Corporation	References 1. Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, Doyle Jr RT, Juliano RA, Jiao L, Granowitz C, Tardif JC. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. New England Journal of Medicine. 2019 Jan 3;380(1):11-22. 2. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) Eur. Heart J. 2019 Aug 31. pii: ehz455. 3. Jacobson TA, Miller M, Schaefer EJ. Hypertriglyceridemia and cardiovascular risk reduction. Clin Ther. 2007;29(5):763-777. 4. Manninen V, Tenkanen L, Koskinen P, et al. Joint effects of serum triglyceride and LDL cholesterol and HDL cholesterol concentrations on coronary heart disease risk in the Helsinki Heart Study. Implications for treatment. Circulation. 1992;85(1):37-45. 5. Navar AM. The Evolving Story of Triglycerides and Coronary Heart Disease Risk. JAMA. 2019;321(4):347-349. 6. Sarwar N, Danesh J, Eiriksdottir G, et al. Triglycerides and the risk of coronary heart disease: 10,158 incident cases among 262,525 participants in 29 Western prospective studies. Circulation. 2007;115(4):450-458.	Thank you for your comment.
	British Cardiovascular Society	Questions for consultation Is it appropriate to refer to reducing cardiovascular events in the title? Yes Is it more appropriate to refer to 'treating hypertriglyceridemia'? No, the drug is specifically targeted at the cardiovascular consequences of hypertriglyceridemia in patients with known or at risk of cardiovascular	Thank you for your comment. The title has been updated.

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		disease. See above comments about relative lack of efficacy in lowering triglyceride levels. Should the remit and population in the scope also include people with mixed dyslipidaemia? Yes – in effect that is the population that has already been studied, since the main trial with this drug recruited patients who were already taking a statin (to reduce cholesterol). This is an underserved population who remain at high residual risk. Have all relevant comparators for icosapent ethyl been included in the scope? Which treatments are considered to be established clinical practice in the NHS for prevention of cardiovascular events? It would be interesting to know what the effect of this agent would be if compared specifically to **high intensity statin**. In the main trial, most patients recruited were on moderate intensity statin, which would be expected to be less effective in preventing cardiovascular events. There have been some concerns that the mineral oil placebo used in the REDUCE-IT trial might have had physiological effects and thus not really have been a placebo. I am not sure how that should be handled when considering comparators. Was mineral oil itself a comparator?	Comparators have been updated to established clinical management only (including low and high-dose intensity statins). Mineral oil and omega-3 supplements are not standard practice for treatment of this population and therefore have not been included as comparators. Subgroups of interest have been limited to those included in the trial. The committee will consider the innovative nature of this technology during the appraisal.

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		The closest comparators to this drug would be omega 3 supplements and other triglyceride lowering agents, although these are not NICE approved due to lack of outcome benefit in trials so far. Are the outcomes listed appropriate? Yes. I would use both all–cause mortality and cardiovascular mortality as endpoints. I would also use revascularisation procedures as an endpoint. There is a hypothetical effect on arrhythmia, so new AF and sudden cardiac death rates may also be worth recording. Are the subgroups suggested in 'other considerations' appropriate? Are there any other subgroups of people in whom icosapent ethyl is expected to be more clinically effective and cost effective or other groups that should be examined separately? Specifically, is it appropriate to add people with mixed dyslipidaemia as a subgroup? May be more or less effective in patients with familial hyperlipidemia where triglyceride levels may be extremely high. As noted above, most patients in the trial will have had mixed dyslipidemia, as they were already on a statin. I do not think it makes sense to consider mixed dyslipideima as a subgroup. It will not be possible to distinguish between patients with hypertriglyceridemia and those with mixed (unless historical data for each patient was obtained prior to them being initiated on a statin.)	

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		A subgroup analysis based on diabetic status (where triglyceride levels are relevant) may be useful. Where do you consider icosapent ethyl will fit into the existing NICE pathway, cardiovascular disease prevention? After use of a high intensity statin (with or without ezetimibe or evolucamab etc) when patients have well controlled LDL, but with tryglceride levels above 2.26mmol/l. Note exclusion criteria include those under age 45, those with severe heart failure (which is quite common in this population) and a history of pancreatitis. These groups should not therefore be considered for this treatment in general, although the effect would seem as likely to apply to younger patients as older ones and those under age 45 with especially aggressive premature atherosclerosis may still benefit, even though excluded from the trial. NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope: • could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which icosapent ethyl will be licensed; • could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;	

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		• could have any adverse impact on people with a particular disability or disabilities. Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts. Do you consider icosapent ethyl to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)? It probably is, since we currently have no treatments used to reduce cardiovascular endpoints that are based on the treatment of hypertriglyceridemia. As with most cardiovascular preventative treatments, the reduction in clinical events is modest (absolute reduction in events of around 3-5%, depending on which endpoints are considered important.) We agree that this level of benefit would give it an important place as another agent in reducing CV risk in secondary prevention. Do you consider that the use of icosapent ethyl can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? I suppose it is possible it could reduce pancreatitis episodes. Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.	

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		To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly. No, apart from cost (which may be less of an issue if a generic version is available)	

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Cardiac Risk in the Young
Different Strokes
Thrombosis UK
Pfizer