Familial Hypercholesteraemia – Comments from consultation on 1st draft

Status	Organisation	Order no.	Version	Chapter/Section	Sec-tion	Comment	**Response**
SH	Merck Sharp & Dohme Ltd 1	1	Full	0	General	Merck Sharp & Dohme Limited (MSD) is pleased that the Guideline Development Group (GDG) recognises that Familial Hypercholesterolaemia (FH) is a severe and prevalent disease within the UK.	**Noted with thanks**
SH	Merck Sharp & Dohme Ltd 1	2	Full	0	General	We are disappointed that the guideline focuses exclusively on low-density lipoproteins (LDL) cholesterol. With the current high prevalence of obesity, metabolic syndrome and diabetes, FH patients are increasingly presenting with mixed type hyperlipidaemia, as opposed to the classical presentation of total cholesterol (TC) and LDL cholesterol elevation. We would urge the GDG to recognise that high-density lipoproteins (HDL) and triglycerides (TGs) are important additional cardiovascular risk factors in such a patient population.	**Noted. Please refer to chapter 1 regarding the diagnosis of FH and the drug treatment chapters for risk factor stratification. We regret that mixed hyperlipidaemia is outside the remit of this guideline.**
SH	Merck Sharp & Dohme Ltd 1	3	Full	0	General	We are pleased to note that the treatment algorithm includes nicotinic acid as a recommended treatment option for use in patients who are not adequately controlled on the maximum dose of statin therapy.	**Noted with thanks**
SH	Merck Sharp & Dohme Ltd 1	4	Full	5210	1.3.1.12	Nicotinic acid was the first agent demonstrated to have cholesterol lowering effects (Altschul R et al, Arch Biochem 1055). It was also the first agent demonstrated to be associated with a reduction of atherosclerotic cardiovascular events in high risk patients (The Coronary Drug Research Group, JAMA 1975). Since then data from 30 trials (4,749 subjects) using niacin showed a comprehensive lipid modification effects and a significant reduction in risk of major coronary events by (Birjmohun RS, et al, J Am Coll Cardiol 2005). Trials have demonstrated nicotinic acid is an effective treatment not only for reducing LDL-C and TG's, but	**Repeated from before**

Status	Organisation	Order no.	Version	Chapter/Section	Sec-tion	Comment	**Response**
						also currently the most effective agent for raising HDL-C.Given the severity and prevalence of familial hypercholesterolaemia in the UK, combined with the high prevalence of obesity, metabolic syndrome and diabetes with mixed dyslipidaemia, we believe that clinicians should have access to a full range of treatment options that meet the individual patient need, which includes an effective treatment option at the second line therapeutic stage that provides a comprehensive approach of lipid lowering therapy. The treatment algorithm in section 1.7 clearly and appropriately states nicotinic acid as a second line therapeutic alternative to statin therapy. We would recommend section 1.3.12 is rectified to be in line with section 1.7. Furthermore, with the exception of flushing, which is being addressed by compounds in development, nicotinic acid is not associated with any significant additional adverse events to what is seen with statins. Therefore, it is not clear why the GDG recommend that the decision to add nicotinic acid should be made in a specialist centre.	
SH	Merck Sharp & Dohme Ltd 1	5	Full	5210	1.3.1.23	With the exception of flushing, nicotinic acid is not associated with any clinically significant additional adverse events to what is seen with statins. Therefore, it is not clear why the GDG recommend that the decision to add nicotinic acid should be made in a specialist centre. Nicotinic acid was the first agent demonstrated to have cholesterol lowering effects (Altschul R et al, Arch Biochem 1055). It was also the first agent demonstrated to be associated with a reduction of atherosclerotic	**Noted with thanks**

Status	Organisation	Order no.	Version	Chapter/Section	Sec-tion	Comment	**Response**
						cardiovascular events in high risk patients (The Coronary Drug Research Group, JAMA 1975). Since then data from 30 trials (4,749 subjects) using niacin showed comprehensive lipid modification effects and a significant reduction in risk of major coronary events by (Birjmohun RS, et al, J Am Coll Cardiol 2005). Though niacin induced flushing, the main limitation of niacin use, has been overcome to some extent by using modified or extended release forms of the molecule; there still is some residual flushing that limits its use. Niacin induced flushing has been shown to be mainly due to the release of prostaglandin D2 and binding to its receptor (DP1) on epidermal blood vessels. MSD has an agent which is currently in phase III development which addresses the flushing tolerability to a large degree by combining an Extended Release (ER) niacin with a prostaglandin D2 receptor (DP1) inhibitor, laropiprant.	
SH	Merck Sharp & Dohme Ltd 1	6	Full	5210	1.3.1.26	We appreciate that nicotinic acid is traditionally associated with flushing. However, we would advise the GDG that developments in this therapeutic area will be available within the timeframe of this guideline. MSD has an agent currently in phase III development which is a fixed dose combination of ER niacin/laropiprant. This agent has been shown to overcome most of the tolerability issues related to flushing. ER niacin/laropiprant has already been assessed in a number of lipid modification & tolerability/safety trials and is also being assessed in a long term outcome study, the HPS2-THRIVE study (Heart Protection Study	**Noted with thanks**

Status	Organisation	Order no.	Version	Chapter/Section	Sec-tion	Comment	**Response**
						2–Treatment of HDL to Reduce the Incidence of Vascular Events) to assess the effects of treatment with niacin, together with the prostaglandin D2 (DP1) inhibitor laropiprant (to reduce niacin-induced flushing), vs placebo in approximately 20,000 British, Scandinavian, and Chinese patients with pre-existing vascular disease managed using statins on first "major vascular event" (defined as non-fatal myocardial infarction or coronary death, non-fatal or fatal stroke, or revascularisation). LDL cholesterol levels will be controlled in all participants by simvastatin 40 mg plus ezetimibe 10 mg daily, if required. Secondary aims include assessment of the effects of ER niacin/laopiprant on early safety outcomes; on the separate components of the primary endpoint; and on the primary endpoint within major baseline disease subgroups. All patients will be followed up for 4 years.	
SH	Merck Sharp & Dohme Ltd 1	7	Full	1700	1.7	We are pleased to note the treatment algorithm includes nicotinic acid as a recommended treatment option for use in patients who are not adequately controlled on the maximum dose of statin therapy.	**Noted with thanks.**
SH	Merck Sharp & Dohme Ltd 1	8	Full	5100	5.1	We are pleased to note that the GDG has recognised the use of nicotinic acid as a therapy option for patients not tolerating statins in clinical practice.	**Noted with thanks**
SH	Merck Sharp & Dohme Ltd 1	9	Full	5100	5.1.3.1.12	Nicotinic acid was the first agent demonstrated to have cholesterol lowering effects (Altschul R et al, Arch Biochem 1055). It was also the first agent demonstrated to be associated with a reduction of atherosclerotic cardiovascular events in high risk patients (The Coronary Drug Research Group, JAMA 1975). Since then data from 30 trials (4,749 subjects) using niacin showed comprehensive lipid modification effects and a significant reduction in risk of major coronary events by (Birjmohun RS, et al, J Am Coll Cardiol 2005).	**Thank you.** **Details have now been added to the relevant evidence to recommendations section for chapter 5.**

Status	Organisation	Order no.	Version	Chapter/Section	Sec-tion	Comment	**Response**
						Trials have demonstrated nicotinic acid is an effective treatment not only for reducing LDL-C and TG's, but also currently the most effective agent for raising HDL-C .Given the severity and prevalence of familial hypercholesterolaemia in the UK, combined with the high prevalence of obesity, metabolic syndrome and diabetes with mixed dyslipidaemia, we believe that clinicians should have access to a full range of treatment options that meet the individual patient need, which includes an effective treatment option at the second line therapeutic stage that provides a comprehensive approach of lipid lowering therapy. The treatment algorithm in section 1.7 clearly and appropriately states nicotinic acid as a second line therapeutic alternative to statin therapy. We would recommend this section is rectified to be in line with section 1.7. Furthermore, with the exception of flushing, which is being addressed by compounds in development, nicotinic acid is not associated with any clinically significant additional adverse events to what is seen with statins. Therefore, it is not clear why the GDG recommend that the decision to add nicotinic acid should be made in a specialist centre.	
SH	Merck Sharp & Dohme Ltd 1	10	Full	5100	5.1.3.1.23	With the exception of flushing, nicotinic acid is not associated with any clinically significant additional adverse events to what is seen with statins. Therefore, it is not clear why the GDG recommend that the decision to add nicotinic acid should be made in a specialist centre. Nicotinic acid was the first agent demonstrated to have	**Noted with thanks**

Status	Organisation	Order no.	Version	Chapter/Section	Sec-tion	Comment	**Response**
						cholesterol lowering effects (Altschul R et al, Arch Biochem 1055). It was also the first agent demonstrated to be associated with a reduction of atherosclerotic cardiovascular events in high risk patients (The Coronary Drug Research Group, JAMA 1975). Since then data from 30 trials (4,749 subjects) using niacin showed comprehensive lipid modification effects and a significant reduction in risk of major coronary events by (Birjmohun RS, et al, J Am Coll Cardiol 2005). Though niacin induced flushing, the main limitation of niacin use, has been overcome to some extent by using modified or extended release forms of the molecule; there still is some residual flushing that limits its use. Niacin induced flushing has been shown to be mainly due to the release of prostaglandin D2 and binding to its receptor (DP1) on epidermal blood vessels. MSD has an agent which is currently in phase III development which addresses the flushing tolerability to a large degree by combining an ER niacin with a prostaglandin D2 receptor (DP1) inhibitor, laropiprant.	
SH	Merck Sharp & Dohme Ltd 1	11	Full	5100	5.1.3.1.26	We appreciate that nicotinic acid is traditionally associated with flushing. However, we would advise the GDG that developments in this therapeutic area are imminent. Please refer to our response to section 1.3.1.26.	**Noted with thanks**
SH	Merck Sharp & Dohme Ltd 1	12	Full	5220	5.2.2 (page 103)	We are pleased to note that the GDG has recognised that nicotinic acid has clinical benefit, not only on LDL, but also on HDL and TG. FH patients are increasingly presenting with mixed dyslipidemia (as opposed to the classical presentation of TC and LDL elevation), largely due to the increasing prevalence of obesity, metabolic syndrome and	**Noted with thanks**

Status	Organisation	Order no.	Version	Chapter/Section	Sec-tion	Comment	**Response**
						diabetes. Given this change in presentation, and the risk associated with low HDL and raised TG, we would anticipate a possible wider place for agents affecting LDL-only in the guideline.	
SH	Merck Sharp & Dohme Ltd 1	13	Full	5232	5.2.3.2 (page 107-8)	We are pleased to note that the GDG has identified studies which show the clinical benefit of nicotinic acid in the treatment of lipid levels, whether used as monotherapy, or in combination with a statin. Given this clinical benefit, we support the GDGs positioning of nicotinic acid in the treatment algorithm (section 1.7).	**Noted with thanks**
SH	Merck Sharp & Dohme Ltd 1	14	Full	6120	6.1.2	We are pleased that the GDG recognises the primary importance of pharmacological treatment in familial hypercholesterolaemia patients. The prevalence of diabetes in FH population is similar to that in the general population. Therefore, while we recognise the importance of lowering LDL-C, we would urge the GDG to also consider HDL-C and TG's when identifying the need for treatment given the rising prevalence of obesity, metabolic syndrome and diabetes and a consequent presentation of mixed dyslipidaemia among FH patients.	**Thank you. We have added the rationale for treatment to page 73 of 193 of the Full Guideline.**
SH	Merck Sharp & Dohme Ltd 2 (Helen Johnson)	1	Full	0	General	There are occasions throughout the draft guideline where the NICE guidance on the use of ezetimibe for primary hypercholesterolaemia (NICE TA 132) is referred to inaccurately or incompletely. We would therefore urge the Guideline Development Group (GDG) to check all references to TA 132 in the final guideline for consistency, so as to ensure that TA 132 is fully incorporated into the final guideline.	**The GDG has worked collaboratively with the developers of TA132 and has taken care to incorporate the recommendations for ezetimibe in primary heterozygous FH into the guidance. Differences may occur in the case of homozygotes and children. These populations were outside the scope of TA 132.**

Status	Organisation	Order no.	Version	Chapter/Section	Sec-tion	Comment	**Response**
SH	Merck Sharp & Dohme Ltd 2 (Helen Johnson)	2	Full	.25	Key priorities for implementation - Management	We would question the GDG's conclusion that a "more potent statin" is the only treatment option in a situation where the goal is to achieve LDL-C reductions of greater than 50% from baseline. First, NICE guidance TA 132 clearly states that ezetimibe, coadministered with initial statin therapy, is recommended as an option in these circumstances, as per its licensed indications, and we are pleased to note that this recommendation is reflected in section 1.3.1.5 of the draft guideline. Secondly, NICE TA 132 recommends ezetimibe as an option in circumstances where consideration is being given to changing, not to a "more potent" statin, but to an "alternative statin". We would suggest that this key priority is reworded to take account of these two points.	**Thank you. Recommendation 1.3.1.2 refers to initial statin drug therapy and not change from existing statin therapy. The NICE Technology Appraisal 132 advises that it should be read in the context of the clinical guideline for the relevant area. TA 132 and the guideline recommendations are complementary and subject to stakeholder comment by NICE. We have also considered the results of the ENHANCE study, although this has not been raised in this instance.**
SH	Merck Sharp & Dohme Ltd 2 (Helen Johnson)	3	Full	5210	1.3.1.1	NICE guidance TA 94 recommends that, where statin therapy is initiated in patients at risk of cardiovascular events, the prescriber should use a statin of low acquisition cost. We appreciate that NICE TA 94 applies to patients with non-familial hypercholesterolaemia, but would suggest that the same caveat should apply here, in the interests of ensuring consistency of guidance.	**Comment noted. Please see the economic modelling re high dose low dose statins.**
SH	Merck Sharp & Dohme Ltd 2 (Helen Johnson)	4	Full	5210	1.3.1.2	We would question the GDG's conclusion that a "more potent statin" is the only treatment option in a situation where the goal is to achieve LDL-C reductions of greater than 50% from baseline. First, NICE TA 132 clearly states that ezetimibe, coadministered with initial statin therapy, is recommended as an option in these circumstances, as per its licensed indications, and we are pleased to note	**Thank you.** **NICE TA 132 also advises that it should be read in the context of the clinical guideline for the relevant area.** **Technology Appraisal 132 and the the guideline recommendations are complementary and subject to stakeholder comment by NICE.**

Status	Organisation	Order no.	Version	Chapter/Section	Sec-tion	Comment	**Response**
						that this recommendation is reflected in section 1.3.1.5 of the draft guideline. As currently worded, section 1.3.1.2 is inconsistent with section 1.3.1.5 which makes it clear that ezetimibe can be considered in situations where serum LDL-C concentration is not appropriately controlled by a statin alone and when consideration is being given to changing from initial statin therapy to an alternative statin. In NICE TA 132, the Appraisal Committee concluded that: "whereas doubling the dose of statin therapy or switching to an alternative statin generally leads to a further reduction in baseline LDL cholesterol concentrations of approximately 6% and 8%, respectively, the Committee concluded that the addition of ezetimibe to statin therapy is likely to lead to greater incremental reductions in LDL cholesterol concentrations" (NICE TA 132, section 4.3.2). Moreover, the Appraisal Committee also concluded that: "adding ezetimibe to initial statin therapy as a treatment option is a cost-effective use of NHS resources when compared with switching to an alternative statin (NICE TA 132, section 4.3.11). Secondly, NICE TA 132 recommends ezetimibe as an option in circumstances where consideration is being given to changing, not to a "more potent" statin, but to an "alternative statin".	**Please see the updated consideration of the ENHANCE study.** **The drug treatment recommendations guide selection of initial drug therapy for this population.**

Status	Organisation	Order no.	Version	Chapter/Section	Sec-tion	Comment	**Response**
						We would suggest that section 1.3.1.2 is reworded accordingly.	
SH	Merck Sharp & Dohme Ltd 2 (Helen Johnson)	5	Full	5210	1.3.1.5 Line 7	This sentence should be amended to read "when serum total or LDL-C concentration is not appropriately controlled…" in accordance with NICE TA 132.	**The focus of FH treatment is LDL-C lowering as FH is specifically a condition which affects LDL-C absorption.**
SH	Merck Sharp & Dohme Ltd 2 (Helen Johnson)	6	Full	5210	1.3.1.12	This section infers that resins, nicotinic acids and fibrates should only be considered as management options in patients who are otherwise intolerant to statins and ezetimibe, or in whom both statins and ezetimibe are contraindicated. We believe that this is the correct inference and is in line with existing NICE and national guidance. However, we do feel that there is some potential for confusion here, particularly when one compares the wording of section 1.3.1.12 to the treatment algorithm on page 31. We would strongly recommend that the GDG makes the sequence of treatments more explicit in this section.	**Thank you. Recommendation 1.3.1.12 indicates when referral should be undertaken when prescribing specific drugs.** **Selection of drug treatment is individualised to the patient in accordance with recommendation 1.3.1.16 and as described in the treatment algorithm.**
SH	Merck Sharp & Dohme Ltd 2 (Helen Johnson)	7	Full	Section 1.3.1.20	1.3.1.23	Section 1.3.1.20 seems to be inconsistent with section 1.3.1.23	**Thank you. The recommendation has been moved to the adult treatment section.**
SH	Merck Sharp & Dohme Ltd 2 (Helen Johnson)	8	Full	1700	1.7 Care Pathways	The drug therapy box (adults) of the FH management algorithm on page 31 of the guideline does not accurately reflect the recommendation in section 1.3.1.12, namely that ezetimibe can be considered as a treatment option after initial statin therapy, but that resins, nicotinic acids and fibrates should only be considered by a specialist in FH if both statins and ezetimibe are contraindicated or not tolerated. The same comment applies to the box titled "optimising	**Thank you. The recommendations for lipid lowering drug therapy do not specify the sequence of drugs that should be adopted in all healthcare settings, only the point of referral for particular drugs. We have not made any recommendations for sequencing in relation to any drug other than statins.**

Status	Organisation	Order no.	Version	Chapter/Section	Sec-tion	Comment	**Response**
						drug therapy (adults)".	**We have changed the algorithm to ensure the recommendations are congruent.**
SH	Merck Sharp & Dohme Ltd 2 (Helen Johnson)	9	Full	5273	5.2.7.3	We are concerned that the GDG has taken a somewhat selective approach to its health economic analysis. In particular, we do not believe it is helpful to compare, and make recommendations about, the cost effectiveness of high intensity statins with low intensity statins exclusively without a) undertaking a direct comparison of all the treatment options for FH, including ezetimibe, and b) conducting a comprehensive economic analysis, commensurate with the analyses that have been conducted on statins and ezetimibe as part of TA 94 and TA 132, respectively. In NICE TA 132, a comprehensive pharmacoeconomic evaluation was carried out, comparing ezetimibe as monotherapy and as an add-on to statin therapy in five different treatment scenarios. The Appraisal Committee concluded that "adding ezetimibe to initial statin therapy as a treatment option is a cost-effective use of NHS resources when compared with switching to an alternative statin (NICE TA 132, section 4.3.11). We believe that this recommendation should be taken fully into account in the final guideline.	**NICE TA 132 is fully incorporated within this guideline.** **Although you have not raised the ENHANCE study, the GDG have considered this evidence at the request of multiple stakeholders.**
SH	Newcastle Upon Tyne Hospitals NHS Foundation Trust	1	NICE Version	1	1 Introduction	It should be emphasised in the opening paragraphs of the Introduction or under Patient Centred Care that as Familial Hypercholesterolaemia is clearly recognised to be an autosomal co-dominant inherited condition, this knowledge places an obligation on the National Health Service to ensure that patients and their close relatives, who are at 50% (first degree) or 25% (second degree) risk of inheriting the condition, should be identified	**Noted. The recommendations for identification, management and referral are made throughout the guideline, and are supported by clinical and cost effectiveness evidence available. Where appropriate, heterogeneity in clinical and cost effectiveness has been highlighted.**

Status	Organisation	Order no.	Version	Chapter/Section	Sec-tion	Comment	**Response**
						without unnecessary delay and offered diagnostic testing and treatment if affected, to prevent avoidable morbidity and mortality.	**Several research questions have also been identified that address areas where important evidence was lacking.**
SH	Newcastle Upon Tyne Hospitals NHS Foundation Trust	2	NICE Version	1	1 Introduction	Line 14: Change serum cholesterol to serum LDL-cholesterol. Total cholesterol is less specific, being elevated in several other primary hyperlipidaemias.	**Incompletely referenced LDL-C has now been used throughout , except where specifically appropriate.**
SH	Newcastle Upon Tyne Hospitals NHS Foundation Trust	3	NICE Version	2	1 Key Priorities	Page 7, Line 10: "young people" should be defined by an upper age limit.	**Definition added – please see glossary.**
SH	Newcastle Upon Tyne Hospitals NHS Foundation Trust	4	NICE Version	2	1 Key Priorities	Page 7. Line 19. (and also section 1.5.1.1 likewise). Take out the word "treated" since a patient with FH may not be on treatment because of side effects or at their request.	**Change made.**
SH	Newcastle Upon Tyne Hospitals NHS Foundation Trust	5	NICE Version	111, 115	1.1.1 & 1.1.5	Corneal arcus is not part of the Simon Broome Diagnostic criteria for FH diagnosis and it should be omitted from this section.	**Change made.**
SH	Newcastle Upon Tyne Hospitals NHS Foundation Trust	6	NICE Version	11100	1.1.1	Suggest DNA testing instead of "molecular techniques"	**Change made.**
SH	Newcastle Upon Tyne	7	NICE Version	11600	1.1.6	Precisely what information should be recorded?	**Rec 1.1.0, change undertaken refer to Simon broome criteria added.**

Status	Organisation	Order no.	Version	Chapter/Section	Sec-tion	Comment	**Response**
	Hospitals NHS Foundation Trust						
SH	Newcastle Upon Tyne Hospitals NHS Foundation Trust	8	NICE Version	11700	1.1.7	Page 9, Line 8: "coronary heart disease" should be cardiovascular disease. Also applies in many places throughout. A variety of abbreviations are used in the document including CHD, CAD, CVD and could be defined in the glossary	**The GDG has purposely used CHD as this is the site of FH morbidity. Rates of stroke and peripheral does not increase in these individuals , this is consistent with the Simon Broome definition. See evidence to recommendaiton page 31 of 193. Abbreviations will be added to the glossary**
SH	Newcastle Upon Tyne Hospitals NHS Foundation Trust	9	NICE Version	11110	1.1.11	What should be included in the DNA test, precisely? This is addressed in the main document (Section 3.1.1.2) but deserves a brief mention here.	**The specific varieties of DNA tests was outside the scope of the guideline. The full guideline gives a brief outline of the principles behind the test but this is not appropriate for the NICE version due to the need for brevity.**
SH	Newcastle Upon Tyne Hospitals NHS Foundation Trust	10	NICE Version	11120	1.1.12	The use of the term "unequivocal FH" risks implying an additional category of FH in addition to those defined in the Simon Broome Criteria. Some relatives of an FH proband may be found to have the family mutation but may not have typically elevated LDL-Cholesterol. If these relatives are to be diagnosed with FH in all cases the phrase "regardless of LDL-Cholesterol concentration" should be added. It should also be stated here, as in the main document, that in individuals who have a clinical diagnosis of FH the absence of a diagnostic mutation does not exclude the diagnosis. They should be given a clinical diagnosis of FH (either Definite or Possible) according to the Simon Broome Criteria and managed accordingly.	**Changes made.** **We have added a new recommendation for the clinical diagnosis of Fh in the absence of a mutation see rec 1.1.4.**

Status	Organisation	Order no.	Version	Chapter/Section	Sec-tion	Comment	**Response**
SH	Newcastle Upon Tyne Hospitals NHS Foundation Trust	11	NICE Version	124000	1.2.4	We agree this is important as other forms of hyperlipidaemia are frequently found in families with premature coronary disease and may co-exist with FH.	**Noted with thanks**
SH	Newcastle Upon Tyne Hospitals NHS Foundation Trust	12	NICE Version	125	1.2.5	Change to "the mutation and not LDL-cholesterol should be used to identify affected relatives." See previous point under 1.2.4	**Change made.**
SH	Newcastle Upon Tyne Hospitals NHS Foundation Trust	13	NICE Version	12800	1.2.8	There is mention of the creation of a national system for co-ordinating cascade testing, this of course already exists and is called the regional genetic services, who already do this very effectively for other heritable diseases. Why should FH be any different? In fact there is no mention in this of the role of genetic services in the management of cascade testing. I am surprised at this given that there was a clinical geneticist on the panel who wrote the draft. It is likely that a typical lipidologist will know no more about cascade screening than a typical geneticist knows about FH. In the same way that there is mention of the role of cardiologists and obstetricians in the management of FH there surely needs to be acknowledgement that it makes sense to involve genetic services in the management of an archetypal single gene disease	**The GDG did consider the issue of genetic counselling . See page 119 of 193. We have not attempted to undertake service specification, the 'term healthcare with expertise in FH' is inclusive of all people with the competence to undertake this role.**
SH	Newcastle Upon Tyne Hospitals NHS Foundation Trust	14	NICE Version	13120	1.3.1.2	In most cases the decision to treat FH is not difficult one, however in some cases carriers of FH mutations may not have typically elevated LDL-Cholesterol concentrations. We would suggest that where there is doubt about the diagnosis or the need to initiate statin treatment in such cases, this should prompt referral to a specialist with expertise in FH	**Thank you. The recommendations for diagnosis assume that the patients meet the Simon Broome criteria at the outset, and therefore all index individuals will have an elevated cholesterol. Recommendations have been made for family members who do**

Status	Organisation	Order no.	Version	Chapter/Section	Sec-tion	Comment	**Response**
							not have raised cholesterol but carry a mutation – equivocal diagnosis of FH.
SH	Newcastle Upon Tyne Hospitals NHS Foundation Trust	15	NICE Version	13120	1.3.1.2	The full range of available statins should be open to consideration as an alternative to low acquisition cost statins in these are ineffective of not tolerated. The ascertainment of a greater than 50% reduction is dependent on establishing an accurate baseline, pre-treatment LDL-cholesterol for the purpose of goal setting. This is often unavailable and unless treatment is withdrawn temporarily to establish it, in practice it is necessary to work towards an absolute LDL-Cholesterol target (see below under 1.3.1.10).	**Examples of statins now given.** **The GDG considered the issue of what should be done for patients already taking treatment. Expert advice suggested that a phone call to the relevant biochemical laboratory would be usually being sufficient to confirm the diagnosis. Expert opinion also suggested that treatment and referral for subsequent cascade testing without confirmation of the diagnosis would be poor practice. See page 73 Full Guideline.**
SH	Newcastle Upon Tyne Hospitals NHS Foundation Trust	16	NICE Version	13110	1.3.1.10	A reduction of 51% may be far from sufficient in severe cases. Instead recommend in addition the same absolute targets as for non-FH i.e. LDL-C < 3 (or ideally <2), to achieve whichever represents the greater reduction.	**We note you have not provided any scientific evidence. A risk stratification approach to treatment is described in the treatment recommendations. Rec 1.3.1.13**
SH	Newcastle Upon Tyne Hospitals NHS Foundation Trust	17	NICE Version	13110	1.3.1.11-12	It is not clear what (See 'At least five a week') is referring to. Superscript 4 referring to footnote required	**This is unclear, we were unable to determine the purpose of this comment.**
SH	Newcastle Upon Tyne Hospitals NHS Foundation Trust	18	NICE Version	13114	1.3.1.14	The term child-focussed setting is unclear and requires definition	**Added to glossary**

Status	Organisation	Order no.	Version	Chapter/Section	Sec-tion	Comment	**Response**
SH	Newcastle Upon Tyne Hospitals NHS Foundation Trust	19	NICE Version	13124	1.3.1.24	Please specify which vitamin supplements should be considered.	**We have added details of the vitamins required. The BNF states that resins may affect vitamin absorption and that vitamins A, D and K may be required with long term use.**
SH	Newcastle Upon Tyne Hospitals NHS Foundation Trust	20	NICE Version	14130	1.4.1.3	It is most important that relatives are be provided with appropriate documentation including contact letters. A direct approach should be offered as an alternative where estranged relatives may not wish to make personal contact.	**We have used the term 'facilitate' to capture the sensitivities of the numerous variations in personal circumstances. See page 119.**
SH	Newcastle Upon Tyne Hospitals NHS Foundation Trust	21	NICE Version	14220	1.4.2.2	There is little evidence to justify avoidance of combined oral contraception which is usually more secure and better tolerated than other forms of contraception. Suggest include here the evidence statement from the Full guideline, Section 8.3.2. "If treated optimally, women with FH will have normalised lipid concentrations, so combined oral contraception is not routinely contraindicated"	**Absence of evidence is not evidence of absence - see evidence to recommendations page 172 for the GDGs updated and detailed analysis of this area..**
SH	Newcastle Upon Tyne Hospitals NHS Foundation Trust	22	NICE Version	15110	1.5.1.1	We agree that a structured review should be required annually as a minimum once the patient is stable on maintenance therapy.	**Change made.**
SH	Newcastle Upon Tyne Hospitals NHS Foundation Trust	23	NICE Version	15140	1.5.1.4	A fasting blood specimen is not essential for monitoring lipid concentrations in typical FH patients in whom triglyceride concentration are low normal but it should be recognised that calculated LDL-Cholesterol is subject to negative bias in non-fasting specimens (in inverse proportion to the post-prandial triglyceride increase) and might lead to under-treatment if used inappropriately. Total and HDL-cholesterol can be estimated on a non-fasting specimen and are usually sufficient for	**Noted. A fasting sample is not unreasonable given that the patient may only have an annual review and that LDL-C concentrations are the basis of this condition. See page 136.**

Status	Organisation	Order no.	Version	Chapter/Section	Sec-tion	Comment	**Response**
						monitoring patients on stable maintenance therapy.	
SH	Newcastle Upon Tyne Hospitals NHS Foundation Trust	24	NICE Version	15210	1.5.2.1	Appropriate specialist referral should be arranged if there are signs or symptoms of ANY cardiovascular disease. (NB Already changed in care pathway on page 31).	**The term CHD has been used based on the Simon Broome data. See evidence to recommendation page 31 of 193.**
SH	Newcastle Upon Tyne Hospitals NHS Foundation Trust	25	NICE Version	15220	1.5.2.2	A more explicit definition is required for "a family history of coronary heart disease in early adulthood" with an upper age limit if this criterion is to be applied in clinical practice. Coronary heart disease should be changed to cardiovascular disease. As diabetes is unusual in association with FH and is a potent cardiovascular risk factor which overcomes gender related risk differentials, diabetes by itself should be considered as an indication for specialist referral. Diagnosis of FH may be poorly recognised among patients attending diabetes services.	**See Full Guideline page 136 for explanation fo why this has been used.**
SH	Newcastle Upon Tyne Hospitals NHS Foundation Trust	26	NICE Version	20003	Appendix C	Page 34. Corneal arcus is not included in the Simon Broome diagnostic criteria and it is not possible to examine for symptoms. Suggest replace "Examine for clinical signs and symptoms including corneal arcus and tendon xanthomata" with "Examine for tendon xanthomata and clinical signs of cardiovascular disease". "Take personal and family medical history, especially CHD" should be placed before the clinical examination. Note that there are some differences between the information in the boxes and in the related body text of the guidelines.	**Changes have been made.**
SH	Newcastle Upon Tyne Hospitals NHS	27	NICE Version	20004	Appendix D	LDL-cholesterol calculation by the Friedewald formula is invalid unless the lipid measurements are performed on a fasting specimen.	**Noted with thanks**

Status	Organisation	Order no.	Version	Chapter/Section	Sec-tion	Comment	**Response**
	Foundation Trust						
SH	Newcastle Upon Tyne Hospitals NHS Foundation Trust	28	NICE Version	20005	Appendix E	As presented, diagnosis of Possible Familial Hypercholesterolaemia requires 2 of the 3 bulleted criteria as for Definite Familial Hypercholesterolaemia AND one or the two bulleted family history criteria. It would be clearer if the criteria were not bulleted but numbered 1-5; then Definite FH is 1 + (2or 3) and possible is 1 + (4 or 5).	**Noted with thanks**
SH	Newcastle Upon Tyne Hospitals NHS Foundation Trust	29	Full	0	General	The guidelines will be of considerable practical value if they are used to form the basis for commissioning of an integrated care pathway which links together the existing secondary care services (including Adult and Paediatric Lipid Clinic Services, Clinical Genetics and Cardiology) and primary care services.	**Noted and will be passed to the NICE implementation team.**
SH	Newcastle Upon Tyne Hospitals NHS Foundation Trust	30	Full	0	General	Abbreviations are not used consistently throughout and are frequently not defined at first use. Tables are given numbers and titles in some cases and not others in an inconsistent fashion, especially see Sections 3 and 8.	**Noted and corrections made.**
SH	Royal College of Nursing	1	Introduction	0		With a membership of over 400,000 registered nurses, midwives, health visitors, nursing students, health care assistants and nurse cadets, the Royal College of Nursing (RCN) is the voice of nursing across the UK and the largest professional union of nursing staff in the world. RCN members work in a variety of hospital and community settings in the NHS and the independent sector. The RCN promotes patient and nursing interests on a wide range of issues by working closely with the Government, the UK parliaments and other national and European political institutions, trade unions, professional bodies and voluntary organisations. The RCN welcomes this guideline.	**Noted with thanks**

Familial Hypercholesteraemia – Comments from consultation on 1st draft

Status	Organisation	Order no.	Version	Chapter/Section	Sec-tion	Comment	**Response**
SH	Royal College of Nursing	2	General	0		This guideline is much needed. We feel it is easy to follow and it should be easy for healthcare professionals to decide what to do when following the guideline. It will also hopefully result in better and more uniform care of patients with Familial Hypercholesterolaemia and those with suspected Familial Hypercholesterolaemia.	**Noted with thanks**
SH	Royal College of Nursing	3	NICE	1111	1.1.11	If DNA testing is carried out on both possible a definite FH patients and a mutation is not identified there could be potential for confusion on the part of the individual and the possibility that they may then underestimate their risk.	**We agree. Both clinical and molecular testing are recommended in 1.1.1**
SH	Royal College of Nursing	4	NICE	13114	1.3.1.14	Where paediatric/child focused services are not available where should children be seen? Could there not be family FH clinics?	**Comment will be passed to the NICE implementation team.**
SH	Royal College of Paediatrics and Child Health	0	Full version	5240	5.2.4	No studies found on the use of nicotinamide. There are no RCTs but Colletti et al reported in Pediatrics 1993 92:78-82.	**Our searches were limited to RCTs with regard to drug interventions.**
SH	Royal College of Paediatrics and Child Health	1	Full	0	General	Including children's guidelines in the body of an adult guideline is generally not good practice. It would be better for the Paediatric guidance to be separate and easily identifiable. It would also limit confusion.	**Thank you. The recommendations will be colour coded in the final guideline, and recommendations that are specific to children/young people only are clearly marked.**
SH	Royal College of Paediatrics and Child Health	2		0	General	The paediatric guidelines are not specific enough and could be confusing and do not have enough precautions to safeguard children. Holistic paediatric care may also not be possible if this service is delivered by adult trained specialists; shared care with a general practitioner/paediatrician may provide the solution.	**Thank You. The recommendations for children were based on the best available (limited) evidence in this age group. The role of the National Service Framework for Children, Young People and Maternity Services in the delivery of care for children and young people has now been emphasised. We regret**

Status	Organisation	Order no.	Version	Chapter/Section	Sec-tion	Comment	**Response**
							that are unable to offer advice of service specification.
SH	Royal College of Paediatrics and Child Health	3		0	General	Excluding the post mortem data collected from children is an error in my view as the evidence for early onset disease is eliminated by this assumption.	**Our searches did not exclude post mortem data but non was identified. We do have evidence of early onset disease from studies of carotid intima thickness.**
SH	Royal College of Paediatrics and Child Health	4		0	General	I find it disappointing that the American NCEP program was not used in the process especially as this is the longest running Cholesterol program for children and they have recently reviewed it after being in use for nearly 515 years. Their reviewers felt that children were not diagnosed early enough and not treated adequately, and that was using guidelines much stricter than those suggested here. See: http://www.nhlbi.nih.gov/about/ncep/ncep_pd.htm and Julia Steinberger and Aaron S. Kelly. Challenges of Existing Pediatric Dyslipidemia Guidelines: Call for Reappraisal Circulation, January 1/8, 2008; 117: 9 - 10.	**We have excluded studies in the general population and looked instead at studies specific to children with FH. We have recommended treatment as early as age 10 in children with known FH. Although we appreciate the opinions of Steinberger and Kelly our process is to review the original research which underpins the recommendations.**
SH	Royal College of Paediatrics and Child Health	5	Full	0	General	The guideline highlights throughout the document where there are gaps in the evidence to support clinical practice. Although these areas are in the main text of the document, it would be helpful if there could be an additional section at the end of each chapter with areas where further research would be helpful. This would support the research agenda and maximise resources.	**Please refer to the guideline research recommendations.**
SH	Royal College of Paediatrics and Child Health	6	Full	0	General	There needs to be more mention of patient /parent organisations who play an important part of support in managing families	**This will appear in the Understanding NICE Guidance (UNG) publication.**
SH	Royal College of Paediatrics	7	Full version and	3200	1.1.8	It would be detrimental to only confirm the diagnosis of FH after puberty, especially as children with Homozygous status therapy should be initiated before	**Thank you. We have now provided advice for children at risk of homozygous FH (see**

Status	Organisation	Order no.	Version	Chapter/Section	Sec-tion	Comment	**Response**
	and Child Health		NICE			the age of 5. Please see: Atherosclerosis. 2008 Feb 19. Recommendations for the use of LDL apheresis. Thompson GR; HEART-UK LDL Apheresis Working Group.	**recommendation 1.1.16).**
SH	Royal College of Paediatrics and Child Health	8	IFP	1300	1.3	A second paragraph should state 'This should include…'	**The general inclusions for the FH guideline are identified in paragraph 2. Further detail is available in the scope.**
SH	Royal College of Paediatrics and Child Health	9	Full	5210	1.3.1.14	What exactly is a "specialist with expertise in FH" for children? This should be a paediatrician (preferably with metabolic expertise) at least. This recommendation needs to be considerably strengthened to ensure that children are seen by paediatricians who then have extra expertise. There is reference to patients being seen in a child friendly area, but that needs to be with a paediatrician. This has to be taken seriously as we have concerns that adult practitioners may feel that a paediatrician is not essential from the way this guidance is written at present, which cannot be allowed.	**Thank you.** **We are unable to address service specification however the standards for service delivery within the National Service Framework for Children, Young People and Maternity Services are signposted.**
SH	Royal College of Paediatrics and Child Health	10	Full version and NICE	5200	1.3.1.14	Specialist with expertise in child focused setting should be expanded to protect children. The specialist would need to be actively managing at least 25 children with FH, should have experience in prescribing drugs in children, should be enhanced CRB checked to work with children and have received child protection training at level 2 as a minimum. Facilities should be available to have access to paediatric dieticians as the needs and management of dietary intervention are different in children.	**This comment will be referred to the NICE implementation team**
SH	Royal College of Paediatrics and Child Health	11	Full version and NICE	5200	1.3.1.15	How did the team arrive at this value of LDL-C as most of the quoted evidence in children looked at total cholesterol? Is this typing error? Total Cholesterol of 6mmol/l would be more appropriate for children. Especially as that would be way above the 95th centile	**This is an incorrect recommendation and has been revised.**

Status	Organisation	Order no.	Version	Chapter/Section	Sec-tion	Comment	**Response**
						for children of all ages.	
SH	Royal College of Paediatrics and Child Health	12	Full version and NICE	5200	1.3.1.16	Pravastatin have a licence from the age of 8, but all statin therapy should be initiated by an expert in lipid disorders in children.	**Noted. This is also the GDG recommendation.**
SH	Royal College of Paediatrics and Child Health	13	Full	6000	1.3.2	More emphasis is needed on educating of children about FH lifestyle/diet as this is one of the main aims of early intervention.	**Thank you. The GDG have specifically considered this issue and this is explained within the evidence to recommendations on page 125 of the Full Guideline.**
SH	Royal College of Paediatrics and Child Health	14	Full version and NICE	6300	1.3.2.7	The use of stanols in children may lead to Vitamin deficiencies and their use is generally not encouraged in children under the age of 8.This is not clear from current guidance.	**There was no evidence re children with FH and stanols or of vitamin deficiencies in the paediatric population. See page 125 of the Full Guideline.**
SH	Royal College of Paediatrics and Child Health	15	Full	8300	1.4.2	Whilst we agree in principle with ... example and comment.	**Comment is incomplete**
SH	Royal College of Paediatrics and Child Health	16	Full	6400	1.5	There is no recommendation regarding the frequency of monitoring cholesterol levels , what to monitor and what target levels to aim for in the paediatric population	**Thank you. The guideline provides monitoring recommendations for all people with FH (including children). Target levels were not specified in this guideline for children as values change with growth. This information has been added to page 81 of 193.**
SH	Royal College of Paediatrics and Child Health	17	Full version and NICE	1800	1.8.2	Lifestyle changes should be started earlier in children and change during adolescence is not well tolerated. Identifying children at younger age may be a greater benefit in view of the lack of evidence. Lifestyle changes before the age of 5 are more likely to have an impact.	**Thank you.** **The GDG considered this specific issue and their consensus view is now described in the guideline. Please page 125 of Full Guideline.**

Status	Organisation	Order no.	Version	Chapter/Section	Sec-tion	Comment	**Response**
						Multiple paediatric references can be found on this topic. The sensitivity of cholesterol value is also higher in the pre-pubertal age, supporting the fact that children should be diagnosed earlier than suggested in the guidance.	
SH	Royal College of Paediatrics and Child Health	18	Full version	2111	2.11.1	The NSF for children should have been consulted for the paediatric guidelines.	**The need to refer to this has now been made clear within the Introduction and the relevant recommendations.**
SH	Royal College of Paediatrics and Child Health	19	Full	3120	3.1.2 3.1.3	Who should organise mutation analysis? Has full consideration been given to genetic consequences of this investigation and need for genetic counselling? Who would pay for testing?	**The issue of genetic counselling was considered by the GDG and a recommendation made that information and education should be given by an individual with expertise in FH. Please see page 119 of the Full Guideline for the evidence to recommendation for this area. The organisation and funding of services is beyond our remit. Your query will be referred to the NICE implementation team.**
SH	Royal College of Paediatrics and Child Health	20	Full version	3130	3.1.3	This statement is not true. Most children with Homozygous hypercholesterolaemia actually have lower values than the adults. The younger they are the lower the concentration, and with this value many children will be missed. A value of 12mmol/l for total cholesterol has previously been agreed by consensus for the trials in children. See: The Metabolic& Molecular Bases of inherited Disease 8th edition Volume 11 p 2865 table 120-1. Goldstein, Hobbs and Brown.	**Thank you. We have now adopted a recommendation that defines a LDL-C level in children with homozygous FH. Please also see page 28 and 31of the Full Guideline for the explanation for this figure.**
SH	Royal College of Paediatrics and Child	21	Full version	5250	5.2.5	How were 8 studies identified as there are 12 RCT studies on the subject in Paediatrics? It may not influence the guidance but the RCT studies published by Couture et al, Koeijvoets et al, Rodenburg et al and	**These were studies which met the inclusion criteria for the Arambepola et al systematic review. This well conducted systematic review**

Status	Organisation	Order no.	Version	Chapter/Section	Sec-tion	Comment	**Response**
	Health					Kwiterovich et al seem to have been excluded. As they represent RCT's and, except for Couture et al, the others have follow up in excess of 2 years it seems strange not to mention them.	**represents the highest level of evidence and therefore individual RCTs were not extracted.**
SH	Royal College of Pathologists	1	NICE	0		The College recommends an interpretative comment on any cholesterol of 7.5 mmol/L or above recommending family history screening and screening of family members if there is a family history of IHD. This is supported by the HEART UK laboratory sub-committee.	**Thank you. A new recommendation has been made that addresses this issue (see first recommendation under 'diagnosis').**
SH	South Asian Health Foundation	1	NICE	0	Genera l	A comprehensive guideline for which the GDG must be congratulated. We are pleased to particularly see the low threshold for investigation coupled to the fact that symptoms and signs signal the need for further non invasive investigation of coronary disease and that asymptomatic individuals should not automatically be investigated. We are also delighted to see emphasised that the use of standard risk prediction charts is not advocated in FH. This will need significant education as relatively young patients with FH will score low in terms of CV risk and therefore receive inappropriate reassurance and neglect if practitioners are unaware of the possible diagnosis of FH. Thus, education is key to this guideline.	**Noted with thanks. Will pass comments to the NICE Implementation team.**
SH	Trafford Primary Care Trust	1	Full	7 7.1.3	7 7.1.3; 7.1.4.2	We would like to have seen a statement regarding the place of the resting ECG in management. Although the exercise ECG is mentioned, there is no statement (positive or negative) regarding the resting ECG.	**A recommendation has made in the monitoring section that this should be considered and please also see page 136 of the Full Guideline.**
SH	Trafford Primary Care Trusts	2	Full	25	Appen dix E	We feel there is an error in "Appendix E: Diagnostic criteria for probands (Simon Broome) and relatives". We don't understand how "Possible FH" can require more criteria than "Definite FH". Going back to earlier	**Thank you. This has been amended.**

Status	Organisation	Order no.	Version	Chapter/Section	Sec-tion	Comment	**Response**
						publications of the Simon Broome criteria these show possible FH to include the FIRST bullet point in the "Definite" list plus one of the bullet points in the "Possible" list. We think there may have been a transcription error and would like NICE to review the appendix and compare it to published Simon Broome criteria.	
SH	UK National Screening Committee	1	Full	0	General	The UK NSC notes that population screening is outside the remit of this guideline. The Committee welcomes the guideline's distinction between 'targeted testing' or 'cascade testing' of relatives positively diagnosed with FH which is recommended and population screening which is not. This helpful distinction is maintained within the guideline's recommendations. However the glossary definition of 'targeted testing' refers to 'targeted cascade screening'. We would be grateful if this could be replaced with 'targeted cascade testing'. There are other examples of this sliding terminology, eg page 23 line 2/3 refers to 'cascade screening'. We would be grateful if the Guideline Development Group could refer to 'testing', targeted or cascade consistently throughout the document.	**Corrections made.**
SH	Welsh Endocrine and Diabetes Society	1	NICE version	1	1 Introduction	Line 11: It is stated that "rarely an individual will inherit a genetic defect from both parents and will have homozygous FH". As inheritance of two different defects from each parent (compound heterozygosity) is likely to occur at least as often as inheriting the same defect from both patients (homozygosity). The clinical equivalence of these is noted in the Full Guideline Section 1.10, Glossary, but for clarity this paragraph	**Thank you. This has been amended.**

Status	Organisation	Order no.	Version	Chapter/Section	Sec-tion	Comment	**Response**
						could be reworded to state "rarely an individual will inherit a genetic defect from each parent and will have homozygous or compound heterozygous FH, which will be collectively termed homozygous FH for the purpose of this guideline."	
SH	Welsh Endocrine and Diabetes Society	2	NICE version	1	1 Introduction	Line 14: The statement "The elevated serum cholesterol concentrations that characterise heterozygous FH" should be modified to read "The elevated serum LDL-cholesterol concentrations that characterise heterozygous FH" as the latter are much more specific for FH.	**We appreciate this is true, however this section is the introduction to the guideline and therefore for reasons of ease of comprehension we have used the term cholesterol here, but in all evidence appraisal through the guideline, and in recommendations, we have used LDL-cholesterol where possible.**
SH	Welsh Endocrine and Diabetes Society	3	NICE version	2	1 Key Priorities	Page 7. Line 19. (and also section 1.5.1.1 likewise). Take out the word "treated" since a patient with FH may not be on treatment because of side effects or at their request.	**Change made.**
SH	Welsh Endocrine and Diabetes Society	4	NICE version	11100	1.1.1 & 1.1.5	"Arcus" is listed with tendon xanthoma as a clinical sign for FH, Tendon xanthoma is considered pathognomic for FH, but corneal arcus lipidus lacks specificity and is therefore not part of the Simon Broome Diagnostic criteria for FH diagnosis.	**Change made.**
SH	Welsh Endocrine and Diabetes Society	5	NICE version	111	1.1.1	Rather than "molecular techniques" why not just say DNA testing?	**Change made.**
SH	Welsh Endocrine and Diabetes Society	6	NICE version	11700	1.1.7	Page 9. Line 8. "coronary heart disease" should be cardiovascular disease. Also applies in many places throughout.	**The GDG has purposely used CHD as this is the site of FH morbidity. Rates of stroke and peripheral does not increase in these individuals, this is consistent with the Simon Broome definition. See evidence to recommendation page 31 of 193.**

Familial Hypercholesteraemia – Comments from consultation on 1st draft

Status	Organisation	Order no.	Version	Chapter/Section	Sec-tion	Comment	**Response**
SH	Welsh Endocrine and Diabetes Society	7	NICE version	11120	1.1.12	The phrase "relatives who have a detected mutation" would be more clearly expressed as "relatives who have a diagnostic FH mutation detected on DNA testing". The use of the term "unequivocal FH" is appropriate in this context but there is a risk of implying an additional category of FH in addition to those defined in the Simon Broome Criteria. It should also be stated here, as in the main document, that in individuals who have a clinical diagnosis of FH the absence of a diagnostic mutation does not exclude the diagnosis. They should be given a clinical diagnosis of FH according to the Simon Broome Criteria and managed accordingly.	**Change made.**
SH	Welsh Endocrine and Diabetes Society	8	NICE version	12400	1.2.4	We agree this is important as other forms of hyperlipidaemia are frequent in families with premature coronary disease and may co-exist with FH.	**Comment noted.**
SH	Welsh Endocrine and Diabetes Society	9	NICE version	12500	1.2.5	The intention of statement would be clearer if modified to read "In families in which a mutation has been identified, the mutation and not LDL-cholesterol should be used to identify affected relatives. See previous point under 1.2.4	**Thank you. Incorporated.**
SH	Welsh Endocrine and Diabetes Society	10	NICE version	13110	1.3.1.10	A reduction of 51% may be far from sufficient. Instead recommend in addition the same absolute targets as for non-FH ie LDL-C < 3 (or ideally <2), to achieve whichever represents the greater reduction.	**We note you have not provided any scientific evidence. A risk stratification approach to treatment is described in the treatment recommendations. Rec 1.3.1.13.**
SH	Welsh Endocrine and Diabetes Society	11	NICE version	13290	1.3.2.9	Shouldn't limit exercise to 30 mins i.e. change to "at least 30 mins"."	**Change undertaken.**
SH	Welsh Endocrine	12	NICE version	13330	1.3.3.3	Specify "arterio-venous" fistulae. There are other varieties. Also in Full Guideline Page 186, Line 17:	**Change undertaken.**

Status	Organisation	Order no.	Version	Chapter/Section	Sec-tion	Comment	**Response**
	and Diabetes Society						
SH	Welsh Endocrine and Diabetes Society	13	NICE version	15110	1.5.1.1	Structured review should be required annually as a minimum once the patient is stable on maintenance therapy.	**Change made.**
SH	Welsh Endocrine and Diabetes Society	14	NICE version	15140	1.5.1.4	A fasting blood specimen is only essential for assessment of LDL-Cholesterol using the Friedewald calculation, as required for the application of the Simon Broome criteria in order to establish a diagnosis. A fasting blood specimen is seldom essential for monitoring lipid concentrations in typical FH patients in whom triglyceride concentration are low normal and to insist on fasting may be detrimental to patient compliance and overall service delivery. HDL-Cholesterol remains important but can be estimated on a non-fasting specimen. As any reduction in total cholesterol in the absence of hypertriglyceridaemia is likely to be due to reduction of LDL-Cholesterol or increase of HDL-cholesterol, estimation of VLDL cholesterol (by Friedewald calculation on a fasting specimen) is not required routinely.	**Noted. A fasting sample is not unreasonable given that the patient may only have an annual review and that LDL-C concentrations are the basis of this condition. See page 136.**
SH	Welsh Endocrine and Diabetes Society	15	NICE version	15220	1.5.2.2	This statement is vague and requires a more explicit definition of what is meant by “a family history of coronary heart disease in early adulthood”. Coronary heart disease should be changed to cardiovascular disease. As diabetes is unusual in association with FH and is a potent cardiovascular risk factor which overcomes gender related risk differentials, diabetes by itself should be considered as an indication for specialist referral	**See Full Guideline page 136 for explanation fo why this has been used.**
SH	Welsh Endocrine and Diabetes Society	16	NICE version	20003	Appen dix C	Page 34. Corneal arcus is not included in the Simon Broome diagnostic criteria and it is not possible to examine for symptoms. Suggest replace “Examine for clinical signs and symptoms including corneal arcus and	**Changes have been made.**

Status	Organisation	Order no.	Version	Chapter/Section	Sec-tion	Comment	**Response**
						tendon xanthomata" with "Examine for tendon xanthomata and clinical signs of cardiovascular disease". "Take personal and family medical history, especially CHD" should be placed before the clinical examination. a. Recommendation 1.2.2 i.e. "All individuals with FH should be referred to a specialist with expertise in FH for confirmation of diagnosis and initiation of cascade testing" is not included in the pathway . Should be in first right hand box. b. No mention of recommendation 1.5.1.1 i.e. "All treated individuals with FH should have a regular structured review carried out at least annually". (NB word "treated" should be removed – see comment 2). Should be placed as first bullet point in second last management box which should be retitled as "On-going monitoring of FH patients". There is a need to ensure consistency.	
SH	Welsh Endocrine and Diabetes Society	17	NICE version	20004	Appendix D	LDL-cholesterol calculation by the Friedewald formula is invalid unless the lipid measurements are performed on a fasting specimen.	**Noted with thanks**
SH	Welsh Endocrine and Diabetes Society	18	Full	0	General	No guidance is given on anti-platelet therapy except in relation to LDL apheresis (1.3.3.8). When and for whom is it considered appropriate to prescribe aspirin or clopidogrel?	**The specifics indications foraspirin treatment are outside the scope of this guidance.**
SH	Welsh Endocrine and Diabetes Society	19	Full	3110	3.1.1	Line 25: "Simon Broom" should be "Simon Broome".	**Correction made.**

Familial Hypercholesteraemia – Comments from consultation on 1st draft

Status	Organisation	Order no.	Version	Chapter/Section	Sec-tion	Comment	**Response**
SH	Welsh Endocrine and Diabetes Society	20	Full	3120	3.1.2	Line 2/3: "in individuals of the proband" should be in relatives of the proband. Line 11: "between FH and non-FH relatives" – "affected and unaffected relatives" or "mutation carriers and non-carriers" might be clearer.	**Corrections made**
SH	Welsh Endocrine and Diabetes Society	21	3220	3220	3.2.2	"Simon Broome criteria allow for a diagnosis of 'probable' or 'definite' FH." The use of the term probable rather than possible, as used in Appendix E, may cause confusion. If these terms are considered synonymous this should be made clear and one or other used throughout.	**We have amended Appendix E. The GDG agreed to use the term 'possible FH' as this is consistent with the Simon Broome criteria. We have . Consistency will be checked.**
SH	Welsh Endocrine and Diabetes Society	22	Full	3232	3.2.5.2	P76, Line 1: PCSK9 p.Y374 appears incorrect.	**Correction made**
SH	Welsh Endocrine and Diabetes Society	23	Full	5220	5.2.2	P103: ASAP not ASAPS study, requires reference number. P104. Are high potency statins considered cost effective in FH patients who are not <60years?	**Correction made.**
SH	Welsh Endocrine and Diabetes Society	24	Full	5220	5.2.3.2	P108, last line "ciprofibrate50mg or 10mg" should be "50 mg or 100mg"	**Correction made**
SH	Welsh Endocrine and Diabetes Society	25	Full	5272	5.2.7.2	P130 Line 13: "gemfibrozil 60 mg twice daily"should be gemfibrozil 600 mg twice daily. Line 14/15: "Pravastatin reduced total cholesterol more than gemfibrozil (26.3% versus 15.2%, p≤0.01) and LDL-C (16.8%, p≤0.01)" – data item missing for LDL-C comparison. P131 Line 18/19: "received 40 mg bezafibrate" should be received 400 mg bezafibrate", specified as plain of modified release (which are not bioequivalent).	**All changes made. Thank you.**
SH	Welsh Endocrine and Diabetes	26	Full	8110	8.1.1	Page 185, Line 4 states: "Individuals with homozygous FH and, in exceptional circumstances, those with homozygous FH" – should read "Individuals with	**Change made. Thank you**

Status	Organisation	Order no.	Version	Chapter/Section	Sec-tion	Comment	**Response**
	Society					homozygous FH and, in exceptional circumstances, those with heterozygous FH"	
SH	Welsh Endocrine and Diabetes Society	27	Full	8200	1.3.3.3	Page 186, Line 17: Specify "arterio-venous" fistulae. There are other varieties.	**Change made.**
SH	Welsh Endocrine and Diabetes Society	28	Full	8232	8.2.3.2	Page 191, Clinical evidence: The important and informative study of Thompson et. al., [Thompson, G.R., Miller, J.P. and Breslow, J.L. (l985) Improved survival of patients with homozygous familial hypercholesterolaemia treated by plasma exchange. Br. Med. J., 29l, l67l-l673] should have been considered and cited. This provided unique and statistically significant data on the survival of 5 untreated versus 5 plasmapheresed homozygous siblings whereas the study by Borberg et al (ref 142), which is cited, simply compared the ages of 8 treated homozygotes with the published ages of death of unrelated homozygotes, many of whom had been treated.	**Comment noted. Our remit was to review LDL apheresis rather than plasmapheresis.**
SH	Welsh Endocrine and Diabetes Society	29	Full	8232	8.2.3.2	Page 204, Line 5: Apheresis, statins and ezetimibe versus apheresis and statins alone: Reference 159 is not the only information on the treatment of homozygotes with LDL apheresis with statins ± ezetimibe. A much better and earlier study was that of Gagné et al, [Gagne, C., Gaudet, D., Bruckert, E. Efficacy and safety of ezetimibe coadministered with atorvastatin or simvastatin in patients with homozygous familial hypercholesterolemia, Circulation. 2002;105:2469-75.]	**This study was cited for question 9: What is the effectiveness of the following adjunctive pharmacotherapy with statins in individuals with FH: statins with any of resins, fibrates, niacin, fish oils, nicotinic acid and ezetimbe (alone or in combination)?**
SH	Welsh Endocrine and Diabetes Society	30	Full	8232	8.2.3.2	P206, Line 6: The quoted cost of LDL apheresis is out of date. A more recent estimate is £1000-1200, as provided by the HEART UK Working Group on LDL Apheresis in its Recommendations for the use of LDL apheresis (Atherosclerosis, in press doi:10.1016/j.atherosclerosis.2008.02.009). Many of the	**Thank you. We have now incorporated actual costs from 3 NHS centres and this is now included within the Full Guideline (see page 64 of Full Guideline)..**

Status	Organisation	Order no.	Version	Chapter/Section	Sec-tion	Comment	**Response**
						recommendations in this document are relevant to deciding which FH patients should be treated with LDL apheresis and it should be cited in the Guidelines.	
SH	Welsh Endocrine and Diabetes Society	31	Full	21	Appendix A:	The Guideline Development Group: XXXX is cited as Clinical Advisor, implying medical qualifications. Should this not be Scientific Advisor reflecting his undoubted scientific expertise?	**Thank you.** **This has now been revised.**