Familial Hypercholesteraemia – Comments from consultation on 1st draft

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SH	AstraZeneca UK Ltd	1	Full	0	General	AstraZeneca appreciates being provided with the opportunity to comment upon the Familial Hypercholesterolaemia guideline. Kindly see our comments on individual aspects of the guideline below.	**Noted with thanks.**
SH	AstraZeneca UK Ltd	2	Full	5210	1.3.1.1 1.3.1.2	Given the baseline lipid characteristics exhibited by FH patients, AstraZeneca strongly supports the recommendations that "Statins should be the initial treatment for all adults with FH" and "Prescription of a potent statin should usually be considered when trying to achieve a reduction of LDL-C concentrations of greater than 50% (from baseline)".	**Noted with thanks**
SH	AstraZeneca UK Ltd	3	Full	5210	1.3.1.2 1.3.1.10	AstraZeneca wishes to highlight the following implementational issue concerning 1.3.1.2: Following the publication of NICE Technology Appraisal TA094 Cardiovascular Disease – Statins, a significant infrastructure is now in place in primary care to drive the prescribing of “low cost” statins (simvastatin, pravastatin). Some of the methods adopted include prescribing incentive schemes, prescribing league tables and add-on software to clinical systems that provide simvastatin as the default statin treatment. These tools take no account of clinical diagnosis. A related point is that almost all local treatment protocols at Primary Care Trust & Local Health Board level now include the recommendation that where statin therapy is required, dyslipidaemic patients be started on a low cost statin (almost universally simvastatin) before moving on to other lipid-lowering therapies that offer greater LDL-C efficacy. Rarely do local protocols include specific recommendations for the management	**Thank you.** **The GDG’s consideration of this issue has now been addressed with the chapter ‘Drug Treatment’.**

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						of patients with familial hypercholesterolaemia. Patients with FH usually require greater lowering in LDL-C concentration than is offered by simvastatin. We would highlight to the GDG that the tools in place to drive low cost statin use may delay or even prevent FH patients from receiving optimal statin therapy that would provide the appropriate level of cholesterol lowering required for their condition. Towards ensuring that patients receive optimal therapy in a timely manner, AstraZeneca suggests that the GDG include a specific recommendation regarding the timing of a follow-up lipid assessment at 1.3.1.10: "Blood lipids should be measured again at 6 weeks after initiation of lipid therapy. Individuals not achieving a reduction of LDL-C concentrations of greater than 50% from baseline should be referred to a specialist with expertise in FH".	
SH	AstraZeneca UK Ltd	4	Full	5210	1.3.1.7	"….appropriate control of cholesterol concentrations should be based on individualised risk assessment…". This statement appears to be at odds with recommendation 1.1.10: "...Risk estimation tools such as those based on the Framingham algorithm should not be used to assess their risk". Over and above stating that cardiovascular disease risk is inherently "high" in FH patients generally, AstraZeneca is not aware of a specific algorithm by which individualised risk can be estimated in FH patients, therefore a suggestion would be to remove statement 1.3.1.7 to avoid any possible confusion.	**Thank you. Individualised 'risk assessment' based on risk factor stratification is appropriate and recommended in this guideline in accordance with TA132. Where appropriate, specific clinical criteria have been added as examples.** **The use of specific formal risk assessment tools such as those based on the Framingham algorithm are not and the recommendation has been made clearer by 'adding already at high risk'..**
SH	AstraZeneca UK Ltd	5	NICE	12200	1.2.2	We notice that recommendation 1.2.2 is not reflected in the algorithm for "FH Diagnosis" at Appendix C. Given	**Thank you, this has been done.**

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						that initial presentation and diagnosis for most FH patients is expected to be via general practice, it would be appropriate to reflect the recommendation for referral to FH specialist for confirmation of diagnosis and initiation of cascade testing within the FH Diagnosis algorithm. General practioners are likely to refer to the algorithms over the main body of the guideline, inclusion of 1.2.2 within the diagnosis algorithm would provide clarity in the appropriate management of FH patients.	
SH	AstraZeneca UK Ltd	6	Full	0	General	We would like to bring to your attention recently published evidence from the ENHANCE trial, which studied change in carotid intima–media thickness in patients with familial hypercholesterolemia. Data is available from the New England Journal of Medicine, 30th March 2008.	**Thank you. The GDG has now considered this evidence. Please refer to the drug treatment chapter for consideration of this evidence.**
SH	Bedfordshire PCT	1	Full	0	general	A systematic review done by the University of British Columbia in 2007 on Ezitimibe reveals the following disturbing findings: (Ballantyne CM, Lipka LJ, Sager PT, Strony J, Alizadeh J, Suresh R et al. Long-term safety and tolerability profile of ezetimibe and atorvastatin coadministration therapy in patients with primary hypercholesterolaemia. International Journal of Clinical Practice Vol 58(7)()(pp 653-658), 2004 2004;(7):653-658) - The 9-month DBRCT demonstrated a 0.4mmol/l difference in LDL-C change from baseline with ezetimibe (dose) plus atorvastatin(dose or range used) vs. atorvastatin (dose) monotherapy;. Serious morbidity, mortality or other health outcomes were not reported according to the allocated treatment group. Therefore, it was not possible to assess the benefits or harm of ezetimibe therapy. Masana et al 2005 (Masana L et al. Long-term safety and tolerability profiles and lipid-modifying efficacy of ezetimibe coadministered with ongoing simvastatin	**Thank you. The recommendations regarding Ezetimibe are made in accordance with the NICE Ezetimibe Technology Appraisal and from evidence continuously identified through systematic review. Please refer to the drug treatment chapter for consideration of this evidence.**

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						treatment: A multicenter, randomized, double-blind, placebo-controlled, 48-week extension study. Clinical Therapeutics. 27(2): 174-184, 2005 (5) Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet 360(9346):1623-30, 2002)is a 48-week extension study of Gagne 2002 (Gagne C. Efficacy and safety of ezetimibe added to ongoing statin therapy for treatment of patients with primary hypercholesterolemia. American Journal of Cardiology 90(10):1084-91, 2002). On enrollment in the extension study, patients entered a 6-week open-label simavastatin run-in phase before they were randomized to receive ezetimibe 10mg or placebo once daily in addition to the ongoing simvastatin for 48 weeks. This extension study includes 56.3% of the originally randomized patients in the Gagne et al study. Almost half of the patients were lost to follow-up; therefore it is not possible to draw conclusions regarding long-term health outcomes. 1. Knopp RH GH. Effects of ezetimibe, a new cholesterol absorption inhibitor, on plasma lipids in patients with primary hypercholesterolemia. European Heart Journal 24(8):729-41, 2003. 2. Dujovne CA, Ettinger MP, McNeer JF. Efficacy and safety of a potent new selective cholesterol absorption inhibitor, ezetimibe, in patients with primary hypercholesterolemia. American Journal of Cardiology 90(10):1092-7, 2002. 3. Goldberg AC, Sapre A, Liu J, Capece R, Mitchel YB, Ezetimibe Study Group. Efficacy and safety of ezetimibe coadministered with simvastatin in	

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						patients with primary hypercholesterolemia: a randomized, double-blind, placebo-controlled trial. Mayo Clinic Proceedings 79(5):620-9, 2004. 4. Bays HE, Ose L, Fraser N, Tribble DL, Quinto K, Reyes R et al. A multicenter, randomized, double-blind, placebo-controlled, factorial design study to evaluate the lipid-altering efficacy and safety profile of the ezetimibe/simvastatin tablet compared with ezetimibe and simvastatin monotherapy in patients with primary hypercholesterolemia. Clinical Therapeutics Vol 26(11)()(pp 1758-1773), 2004 2004;(11):1758-1773. 5. Farnier M et al. Efficacy and safety of the coadministration of ezetimiibe with fenofibrate in patients with mixed byperlipdemia. European Heart Journal. 26: 897- 905 6. Gonzalez-ortiz M et al. Effect of ezetimibe on insulin sensitivity and lipid profile in obese and dyslipidaemic patients. Cardiovascular Drugs and Therapy 20 143-6, 2006 7. Jakulj L. Trip MD. Sudhop T. von Bergmann K. Kastelein JJ. Vissers MN. Inhibition of cholesterol absorption by the combination of dietary plant sterols and ezetimibe: effects on plasma lipid levels. Journal of Lipid Research. 46(12):2692- 8, 2005 8. Kerzner B. Efficacy and safety of ezetimibe coadministered with lovastatin in primary hypercholesterolemia. American Journal of Cardiology 91(4):418-24, 2003. 9. Melani L. Efficacy and safety of ezetimibe coadministered with pravastatin in patients with primary hypercholesterolemia: a prospective,	

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						randomized, double-blind trial.[see comment]. European Heart Journal 24(8):717-28, 2003. 10. Davidson MH MT. Ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia.[see comment]. Journal of the American College of Cardiology 40(12):2125-34, 2002. 11. Ballantyne CM HJ. Effect of ezetimibe coadministered with atorvastatin in 628 patients with primary hypercholesterolemia: a prospective, randomized, double-blind trial.[see comment]. Circulation 107(19):2409-15, 2003. 12. Gagne C. Efficacy and safety of ezetimibe added to ongoing statin therapy for treatment of patients with primary hypercholesterolemia.[see comment]. American Journal of Cardiology 90(10):1084-91, 2002. 13. Ballantyne CM, Blazing MA, King TR, Brady WE, Palmisano J. Efficacy and safety of ezetimibe co-administered with simvastatin compared with atorvastatin in adults with hypercholesterolemia. American Journal of Cardiology 93(12):1487-94, 2004. 14. Goldberg AC, Sapre A, Liu J, Capece R, Mitchel YB, Ezetimibe Study Group. Efficacy and safety of ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia: a randomized, double-blind, placebo-controlled trial. Mayo Clinic Proceedings 79(5):620-9, 2004. 15. Bays HE, Ose L, Fraser N, Tribble DL, Quinto K, Reyes R et al. A multicenter, randomized, double-blind, placebo-controlled, factorial design study to evaluate the lipid-altering efficacy and safety profile of the	

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						ezetimibe/simvastatin tablet compared with ezetimibe and simvastatin monotherapy in patients with primary hypercholesterolemia. Clinical Therapeutics Vol 26(11)()(pp 1758-1773), 2004 2004;(11):1758-1773. 16. Gaudiani LM, Lewin A, Meneghini L, Perevozskaya I, Plotkin D, Mitchel Y et al. Efficacy and safety of ezetimibe co-administered with simvastatin in thiazolidinedione-treated type 2 diabetic patients. Diabetes, Obesity & Metabolism 7(1):88-97, 2005. 17. Patel JV. Hughes EA. Efficacy, safety and LDL-C goal attainment of ezetimibe 10mg-simvastatin 20 mg vs. placebo-simvastatin 20 mg in UK-based adults with coronary heart disease and hypercholesterolaemia. International Journal of Clinical Practice. 60(8):914-21, 2006 18. Ballantyne CM. Abate N. Yuan Z. King TR. Palmisano J. Dose-comparison study of the combination of ezetimibe and simvastatin (Vytorin) versus atorvastatin in patients with hypercholesterolemia: the Vytorin Versus Atorvastatin (VYVA) study. American Heart Journal. 149(3):464-73, 2005 Mar. 19. Barrios V. Amabile N. Paganelli F. Chen JW. Allen C. Johnson-Levonas AO. Massaad R. Vandormael K. Lipid-altering efficacy of switching from atorvastatin 10 mg/day to ezetimibe/simvastatin 10/20 mg/day compared to doubling the dose of atorvastatin in hypercholesterolaemic patients with atherosclerosis or coronary heart disease. International Journal of Clinical Practice.	

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						59(12):1377-86, 2005 20. Goldberg, Ronald B. Guyton, John R. Mazzone, Theodore. Weinstock, Ruth S. Polis, Adam. Edwards, Patricia. Tomassini, Joanne E. Tershakovec, Andrew M. Ezetimibe/simvastatin vs atorvastatin in patients with type 2 diabetes mellitus and hypercholesterolemia: the VYTAL study. Mayo Clinic Proceedings. 81(12):1579-88, 2006 Dec. 21. Rodney RA. Sugimoto D. Wagman B. Zieve F. Kerzner B. Strony J. Yang B. Suresh R. Veltri E. Efficacy and safety of coadministration of ezetimibe and simvastatin in African-American patients with primary hypercholesterolemia. Journal of the National Medical Association. 98(5):772-8, 2006 May. 22. Catapano AL. Davidson MH. Ballantyne CM. Brady WE. Gazzara RA. Tomassini JE. Tershakovec AM. Lipid-altering efficacy of the ezetimibe/simvastatin single tablet versus rosuvastatin in hypercholesterolemic patients. Current Medical Research & Opinion. 22(10):2041-53, 2006 Oct. 23. Geiss HC. Otto C. Parhofer KG. Effect of ezetimibe on low-density lipoprotein subtype distribution: results of a placebo-controlled, double-blind trial in patients treated by regular low-density lipoprotein apheresis and statins. Metabolism: Clinical & Experimental. 55(5):599-604, 2006 May. 24. Pearson TA. Denke MA. McBride PE. Battisti WP. Brady WE. Palmisano J.A community-based, randomized trial of ezetimibe added to statin therapy to attain NCEP ATP III goals for LDL cholesterol in hypercholesterolemic	

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						patients: the ezetimibe add-on to statin for effectiveness (EASE) trial. Mayo Clinic Proceedings. 80(5):587-95, 2005 May. 25. Cruz-Fernandez JM. Bedarida GV. Adgey J. Allen C. Johnson-Levonas AO. Massaad R. Efficacy and safety of ezetimibe co-administered with ongoing atorvastatin therapy in achieving low-density lipoprotein goal in patients with hypercholesterolemia and coronary heart disease. International Journal of Clinical Practice. 59(6):619-27, 2005 Jun. 26. Brohet C. Banai S. Alings AM. Massaad R. Davies MJ. Allen C. LDL-C goal attainment with the addition of ezetimibe to ongoing simvastatin treatment in coronary heart disease patients with hypercholesterolemia. Current Medical Research & Opinion. 21(4):571-8, 2005 Apr. 27. Farnier M. Volpe M. Massaad R. Davies MJ. Allen C. Effect of co-administering ezetimibe with on-going simvastatin treatment on LDL-C goal attainment in hypercholesterolemic patients with coronary heart disease. International Journal of Cardiology. 102(2):327-32, 2005 Jul 10 28. Stein E, Stender S, Mata P, Sager P, Ponsonnet D, Melani L et al. Achieving lipoprotein goals in patients at high risk with severe hypercholesterolemia: efficacy and safety of ezetimibe co-administered with atorvastatin. American Heart Journal 148(3):447-55, 2004. 29. Gagne C. Efficacy and safety of ezetimibe coadministered with atorvastatin or simvastatin in patients with homozygous familial hypercholesterolemia. Circulation 105(21):2469-	

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						75, 2002. 30. Salen G, von Bergmann K, Lutjohann D, Kwiterovich P, Kane J, Patel SB et al. Ezetimibe effectively reduces plasma plant sterols in patients with sitosterolemia. Circulation 109(8):966-71, 2004. None of the above 30 trials over 24 weeks duration studied the effectiveness of ezetimibe therapy on mortality and/or morbidity in adult patients with primary hypercholesterolemia, familial homozygous hypercholesterolemia and sitosterolemia. All trials focused on a decrease in LDL-C level, which is a surrogate outcome measure for ezetimibe and has not been validated to predict clinically relevant outcomes. In these trials the percentage decrease in LDL –C levels from baseline ranged from 3% to 34% over a duration of 6 to 24 weeks. In addition, the manufacturers of Ezitimibe have withheld data on the drug for the past two years and only released them recently on threat of a subpoena from the US Senate. The negative findings of the ENHANCE Trial further question the effectiveness of Ezitimibe. CONCLUSIONs: • There is insufficient evidence that ezetimibe 10mg/day as monotherapy provides a therapeutic advantage over placebo or other cholesterol lowering drug monotherapy for the treatment primary hypercholesterolemia, HoFH or sitosterolemia. • There is insufficient evidence that ezetimibe 10mg/day as adjunctive therapy to statin	

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						provides a therapeutic advantage over statins alone for the treatment primary hypercholesterolemia, HoFH or sitosterolemia. • There are no double-blind randomized clinical trials that compare the combination ezetimibe 10mg/day plus statin with other statin combination therapies for the treatment primary hypercholesterolemia, HoFH or sitosterolemia.	
SH	British Heart Foundation	1	Full version	0	General	BHF warmly welcomes the NICE draft guidelines on the identification and management of Familial Hypercholesterolaemia (FH). The BHF is the UK's leading research charity in cardiovascular disease. Each year we commit some £60-70m to support cardiovascular research in UK universities and health departments. The BHF is proud to be funding Prof Steve Humphries and much of his research on FH.	**Noted with thanks.**
SH	British Heart Foundation	2	Full version	3200	1.2 line 18	BHF strongly supports identification of individuals with FH through cascade screening. We also strongly support the establishment and use of a nationwide family based follow up system (page 10, line 9)	**Noted with thanks**
SH	British Heart Foundation	3	Full version	5200	1.3.1.3 line 18	BHF supports the use of ezetemibe either as monotherapy for FH patients who cannot take statins or in combination with statins to achieve adequate LDL reductions. This is despite the recent announcement of the ENHANCE trial results at the American College of Cardiology which showed that the combination of ezetimibe with simvastatin did not have any beneficial effect on a surrogate marker, carotid intima media thickening. However, ENHANCE was not an outcome study and the committee is reminded that early studies	**Thank you. This has now been incorporated into the guideline.**

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						on the effects of statins on angiographic descriptions of atheroma also failed to demonstrate any benefit, yet subsequent outcome studies demonstrated unequivocal reductions in cardiovascular events.	
SH	British Heart Foundation	4	Full version	3200	1.3.1.1 1 line 8,	The statement that individuals with FH should be referred to a specialist with expertise in FH if they are assessed to be at high risk is inconsistent with the statements earlier in the guidance that ' a clinical diagnosis of FH should be considered in individuals with LDL-C concentrations greater than 13 mmol/l and they should be referred to a specialist centre' (point 1.1.2), and 'individuals with FH are at a very high risk of coronary heart disease' (point 1.1.10).	**Thank you. We have amended the terms used through out these recommendations and also specified the clinical criteria where appropriate.**
SH	Department of Health	1	Full	.25	3. KPs	Line 16: We agree; however, most GPs, practice nurses, lipidologists and lipid clinic nurses cannot take and record a three-generation family history, required to identify autosomal dominant inheritance. We have funded service development pilots, which demonstrate that general (i.e. non-genetics specialist) staff - including administrative staff - can be trained to do this. You may be aware that the NHS genetics education and development centre has produced a generic family history tool, and that advice is available on its website.	**Comment referred to NICE implementation team**
SH	Department of Health	2		0		In the history taking process, we feel that time needs to be allowed for the gathering and verifying of family history information, including diagnosis. In our opinion, this is often underestimated, and has implications for waiting time targets and staff resources in clinics.	**Thank you. Comment noted and will be referred to the NICE implementation team.**
SH	Department of Health	3	Full	.25	3 KPs	Line 21: We agree; however, we believe that an educational programme is necessary, along with the implementation of section 4.3 of the guideline on cardiovascular risk assessment.	**Comment referred to NICE implementation team**
SH	Department of Health	4		0 -		Line 26: Our pilots have tested the feasibility of this approach; please see references 41and 45. In our view, the text does not appear to explain exactly what	**Thank you. The definition in the text has now been expanded and we have added a definition in the glossary**

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						"cascade testing" is, and our belief is that many lipidologists would not know.	
SH	Department of Health	5		0 -		Line 27: We agree that in most cases, DNA testing is helpful in the diagnosis of familial hypercholesterolaemia, and the identification of affected relatives. At present, most genetic tests are covered by specialist genetic centre budgets (specialised commissioning for these services) and, in most cases we feel, would involve referral to a specialist genetics centre to access the test. At present, there is not a commissioning mechanism in place to move the costs of genetic testing from specialised genetic services to secondary care. The Genetics White Paper "our inheritance, our future: realising the potential of genetics in the NHS" sets out a strategy to shift the management of common genetic conditions towards secondary care. In our opinion, having to involve specialist genetics services in this pathway, in every case where DNA testing is indicated, threatens to overburden these already overstretched services. We believe that implementation of this recommendation would have resource issues for regional genetic services, unless a commissioning mechanism to shift the costs of testing is found.	**Thank you. Comment will be referred to the NICE implementation team**
SH	Department of Health	6	Full	3200	1.1.7	Please see under KPs (line 16 above): in our view, there are implications for the education and support of NHS staff involved in the process.	**Comment referred to NICE implementation team**
SH	Department of Health	7	Full version and NICE	11700	1.1.7	We feel that special software is required to record family history and that Connecting for Health has yet to come up with a solution, compatible with the framework for the electronic health record.	**Comment will be passed to the NICE implementation team.**

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SH	Department of Health	8	Full version and NICE	11800	1.1.8	In our opinion this work may fall to primary care, necessitating the education of GPs.	**Comment will be passed to the NICE implementation team.**
SH	Department of Health	9	Full version and NICE	11100	1.1.10	We believe that this is new knowledge for most GPs.	**We shall alert the NICE implementation.**
SH	Department of Health	10	Full version and NICE	11110	1.1.11	In our view, there is a degree of complexity and sensitivity involved in discussing, offering and interpreting genetic tests, including family issues and ethical issues (especially in the consent for testing of children for adult-onset disease). We feel that most primary and secondary care staff would need intensive training and support, to implement this recommendation. You may be aware that, at present, regional genetics service are the only source of such training and support. Therefore, we feel that this would generate resource issues.	**We shall pass this comment to the NICE implementation team**
SH	Department of Health	11	Full version and NICE	12300	1.2.3	In our view, training is applicable.	**Comment will be passed to the NICE implementation team.**
SH	Department of Health	12	Full version and NICE	12800	1.2.8	At present there appears to be no funding or organisational framework, which would support a nationwide family-based follow-up system.	**Comment will be passed to the NICE implementation team.**
SH	Department of Health	13	Full version and NICE	12800	1.2.8	At present, the national electronic patient record does not appear to support family records.	**Comment will be passed to the NICE implementation team.**
SH	Department of Health	14	Full version and NICE	13121	1.3.1.21	We feel that this would have staffing issues, and that there are no universal helpful growth charts, to assist in monitoring.	**Comment will be passed to NICE implementation team**

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SH	Department of Health	15	Full version and NICE	14110	1.4.1.1	In our opinion, writing information leaflets for patients about genetics (including provision of translations for people whose first language is not English) is resource intensive, and requires skill. There are examples of good practice in writing genetic testing information for patients from Cancer Bacup. We believe that a respected national source, with expertise in writing for patients, should be commissioned to provide information. In our view, NHS direct/NHS choices should also be involved. We feel that there is no obvious source of public funding for the production and distribution of these resources.	**Comment passed to NICE implementation team**
SH	Department of Health	16	Full version and NICE	14310	1.4.3.1	We feel that guidance on preconception and antenatal counselling in primary care will need to include this, and that there could be educational implications for primary care staff.	**Comment passed to NICE implementation team**
SH	Heart UK	1	NICE Version	1	1 Introduction	The knowledge that Familial Hypercholesterolaemia is a condition which is inherited in an autosomal co-dominant fashion 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 without unnecessary delay and offered diagnostic testing and treatment if affected, to prevent avoidable morbidity and mortality. This should be emphasised in the opening paragraphs of the Introduction or under Patient Centred Care.	**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. Several research questions have also been identified that address areas where important evidence was lacking.**
SH	Heart UK	2	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	**This is a comment on the full guideline. Change made.**

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						equivalence of these is noted in the Full Guideline Section 1.10, Glossary, but for clarity this paragraph 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	Heart UK	3	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.	**This is a comment on the full guideline. Wording changed.**
SH	Heart UK	4	NICE Version	2	1 Key Priorities	Page 7. Line 10 (and 1.3.1.14 likewise). Why include words "young people". This begs the question of what age range. "Young people" may not wish to be seen in a "child" focussed setting . Use of "young people" in sections 1.3.1.14-21 on page 13 likewise unnecessary unless defined.	**Please see glossary for the definition of these terms. The sentence has been changed to incorporate both children/young people.**
SH	Heart UK	5	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	Heart UK	6	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 highly specific, even pathognomonic for FH, but corneal arcus lipidus lacks specificity and is therefore not part of the Simon Broome Diagnostic criteria for FH diagnosis. Inclusion of corneal arcus here could be confusing if mentioned here and it should be omitted from this section. It may be better to include it in Appendix D	**Change made.**
SH	Heart UK	7	NICE Version	11100	1.1.1	Rather than "molecular techniques" why not just say DNA testing?	**Change made.**
SH	Heart UK	8	NICE Version	11600	1.1.6	Precisely what information should be recorded?	**Rec 1.1.0, change undertaken.**

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SH	Heart UK	9	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 vascular disease does not increase in these individuals, this is consistent with the Simon Broome definition See evidence to recomemndaiton page 31 of 193.**
SH	Heart UK	10	NICE Version	11110	1.1.11	What DNA test, specifically? This is addressed in the main document (Section 3.1.1.2) but deserves a brief mention here.	**The specific varieties of DNA techniques was outside the scope of the guideline.**
SH	Heart UK	11	NICE Version	11120	1.1.12	The phrase "relatives who have a detected mutation" would be more clearly expressed as "relatives who have a mutation diagnostic of FH 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.	**Changes made.**
SH	Heart UK	12	NICE Version	11130	1.1.13	This may not always be true e.g. in the case of a different primary mutation or a de novo mutation.	**Please see evidence to reccomendations for explanation page 40 of 193.**
SH	Heart UK	13	NICE Version	124000	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.	**Noted with thanks**
SH	Heart UK	14	NICE Version	125000	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	**The statement has been revised accordingly**

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						point under 1.2.4	
SH	Heart UK	15	NICE Version	13120	1.3.1.2	The meaning of the term potent statin is not self-evident and requires definition. Perhaps "the full range of available statins" should be considered as an alternative. The ascertainment of a greater than 50% reduction is dependent on establishing a baseline, pre-treatment LDL-cholesterol for the purpose of goal setting.	**Examples now given.**
SH	Heart UK	16	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	Heart UK	17	NICE Version	13111	1.3.1.11	This section does not relate to drug management. Should be the first section under management ie. 1.3 before section on drug management.	**This has been revised to make it clear it relates to to referral for drug management.**
SH	Heart UK	18	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	Heart UK	19	NICE Version	13114	1.3.1.14	The term child-focussed setting is unclear and requires definition	**Added to glossary.**
SH	Heart UK	20	NICE Version	13124	1.3.1.24	The advice should specify which vitamin supplements should be considered and supporting evidence should be cited in the relevant section of the Full guideline.	**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	Heart UK	21	NICE Version	13290	1.3.2.9	Should not limit exercise to 30 mins i.e. change to "at least 30 mins".	**Change undertaken.**
SH	Heart UK	22	NICE Version	13310	1.3.3.1 & 1.3.3.2	The provision of LDL-apheresis for these indications (effectively primary prevention and secondary prevention) should be reimbursed appropriately under a suitably defined tariff code. At present centres being reimbursed differently for the same treatment under codes for "inborn error of metabolism" (approx. £300)	**Comment passed to NICE implementation team**

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						and “treatment for coronary disease” (approx. £1000).	
SH	Heart UK	23	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.**
SH	Heart UK	24	NICE Version	14130	1.4.1.3	Relatives should 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	Heart UK	25	NICE Version	14210	1.4.2.1 & 1.4.3.2	Ezetimibe is contraindicated during breastfeeding. Is there specific advice regarding pregnancy?	**The manufacturer advises use only if potential benefit outweighs risk – no information available. May cross placenta in small amounts.**
SH	Heart UK	26	NICE Version	14220	1.4.2.2	In view of the paucity of relevant evidence in FH women, there is little to justify avoidance of combined oral contraception which is usually more secure and better tolerated than other forms of contraception. It would be useful to 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	Heart UK	27	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	Heart UK	28	NICE Version	15140	1.5.1.4	A fasting blood specimen is 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 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	**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.**

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						might lead to undertreatment if used inappropriately. Total and HDL-cholesterol can be estimated on a non-fasting specimen and are usually sufficient for monitoring patients on stable maintenance therapy..	
SH	Heart UK	29	NICE Version	15210	1.5.2.1	Not just cardiology / symptoms of CHD but appropriate specialist if symptoms of 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	Heart UK	30	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 of why this has been used.**
SH	Heart UK	31	NICE Version	15200	1.5.2	Potential for confusion regarding the need for referral from GP's/ others to specialists involved in FH. Consider merging this section into 1.5.1	**Thank you. We believe that delay in diagnosis and investigation would be made more likely if the 'referral' section were made less explicit.**
SH	Heart UK	32	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 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.**

Status	Organisation	Order no.	Version	Chapter/Section	Sec-tion	Comment	**Response**
						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. Page 31, bottom left box. "adequate LDLC lowering (> 50%)" – this may be far from adequate. "referring if not achieving a reduction in LDLC > 50%" could mean no need to refer if 51% or more reduction achieved. NB Recommendation 1.3.1.2 ie "Prescription of a potent statin should usually be considered when trying to achieve a reduction of LDL-C concentrations of greater than 50% (from baseline)" is not saying the same thing – only relates to need for a potent statin. c. 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	Heart UK	33	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	Heart UK	34	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**

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SH	Heart UK	35	Full	0	General	The recommendations are practicable ones which would have the support of the majority of lipid clinic specialists and others involved in the management of FH, if the required resources were made available.	**Noted with thanks**
SH	Heart UK	36	Full	0	General	Abbreviations are not used consistently throughout 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	Heart UK	37	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 wider use and indications for aspirin therapy are outside the scope of this guidance.**
SH	Heart UK	38	Full	1800	1.8.5	Page 36, Line 19: LDFL-C should be LDL-C	**Correction made.**
SH	Heart UK	39	Full	1000	1.10	Page 40, last line: remove 2nd full stop	**Correction made.**
SH	Heart UK	40	Full	2300	2.3	Line 8: remove 2nd full stop	**Correction made.**
SH	Heart UK	41	Full	2112	2.11.2	Line 2: replace “followed” with following	**Correction made**
SH	Heart UK	42	Full	3000	3	Some of the data tables in this section are numbered and given titles, many are not. P-values are frequently omitted. A consistent style would be preferable.	**The tables have been numbered.**
SH	Heart UK	43	Full	3110	3.1.1	Line 25: “Simon Broom” should be “Simon Broome”.	**Correction made.**
SH	Heart UK	44	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	Heart UK	45	Full	3130	3.1.3	Line 27/28: This does not make sense, is a false negative, lower cholesterol the specific concern addressed by DNA testing?	**Corrections made**
SH	Heart UK	46	Full	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,	**We have amended Appendix E. The GDG agreed to use the term ‘possible FH’ as this is consistent with the**

Status	Organisation	Order no.	Version	Chapter/Section	Sec-tion	Comment	**Response**
						may cause confusion. If these terms are considered synonymous this should be made clear and one or other used throughout.	**Simon Broome criteria. We have . Consistency will be checked.**
SH	Heart UK	47	Full	3232	3.2.3.2	Page 60, line 2/3: "The LDLR plus group showed significantly higher concentrations of LDL-C, TC, and TG". This is incorrect. Table 2 shows that the LDLR plus group showed higher concentrations of total and LDL-C but lower triglycerides. Page 61, Table 3: No p-values are given. "LCL-C" should be LDL-C.	**Page 60 Correction made.** **Page 61 – P values not provided by the authors. LCL corrected.**
SH	Heart UK	48	Full	3232	3.2.3.2	Table 2: were there really 69% and 80% ever smokers in the groups? Is this not non-smokers?	**Figures were checked and found to be correct.**
SH	Heart UK	49	Full	3232	3.2.3.2	Table 3, first column: remove space in Lipids heading. No p values given.	**Corrrection made. P values not provided by the authors**
SH	Heart UK	50	Full	3232	3.2.3.2	Page 62, un-numbered table: The total cholesterol results appear incorrect and inconsistent with the LDL-Cholesterol data.	**Figures were checked and found to be correct.**
SH	Heart UK	51	Full	3232	3.2.3.2	Page 66, Line 22: "Among first degree relatives of confirmed cases in families with FH the new TC is much lower:" – this sentence does not make sense.	**Sentence corrected.**
SH	Heart UK	52	Full	3232	3.2.3.2	Page 69, Line 7: full stop required.	**Corrected.**
SH	Heart UK	53	Full	3232	3.2.3.2	Page age 71, Line 13: Replace US with ultrasound	**Corrected.**
SH	Heart UK	54	Full	3232	3.2.3.2	Page 71, Line 21: define "ns"	**Defined. (non significant)**
SH	Heart UK	55	Full	3232	3.2.3.2	Page 71, Line 22: define "sem"	**SEM is the standard error of measurement/mean and is a common statistical abbreviation, similar to SD for standard deviation.**
SH	Heart UK	56	Full	3232	3.2.5.2	Page 76, Line 1: PCSK9 p.Y374 appears incorrect.	**Correction made.**
SH	Heart UK	57	Full	3232	3.2.5.2	Page 78, Line 3: no Table number	**Table numbers added**
SH	Heart UK	58	Full	4.2.3.3	4.2.3.3	Page 92, Line 30: remove space before full stop	**Correction made.**

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SH	Heart UK	59	Full	4.2.3.3	4.2.3.3	Page 94, Line 13: commas should be superscript	**Correction will be made.**
SH	Heart UK	60	Full	5220	5.2.2	Page 103, Right hand column: ASAP not ASAPS study, requires reference number. Penultimate paragraph, LDL-c should be LDL-C	**Corrections made.**
SH	Heart UK	61	Full	5220	5.2.2	Page 104. Are high potency statins considered cost effective in FH patients who are not <60years? Last line – remone 2nd full stop	**Thank you.**
SH	Heart UK	62	Full	5232	5.2.3.2	Page 108, last line "ciprofibrate 50mg or 10mg" should be "50 mg or 100mg"	**Change made.**
SH	Heart UK	63	Full	5232	5.2.3.2	Page 109, Line 5: Insert space between % and (	**Change made**
SH	Heart UK	64	Full	5252	5.2.5.2	Page 122, Line 14: The unit is g	**Change made**
SH	Heart UK	65	Full	5252	5.2.5.2	Page 122, Line 14: The unit is g/l	**Change made**
SH	Heart UK	66	Full	5272	5.2.7.2	Page 128 Line 19: Remove "bile acid binding"	**Change made.**
SH	Heart UK	67	Full	5272	5.2.7.2	Page 130 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	Heart UK	68	Full	5273	5.2.7.3	Page 132 Line 25: de novo in italics	**Change made**
SH	Heart UK	69	Full	5273	5.2.7.3	Page 134 Table 9: include units in the table	**Change made**
SH	Heart UK	70	Full	5273	5.2.7.3	Page 134 Line 16: Should it not be Table 10 rather than Table 4?	**Section has been amended**
SH	Heart UK	71	Full	6232	6.2.3.2	Page 154 Line 12: Remove full stop	**Change made**
SH	Heart UK	72	Full	6332	6.3.3.2	Page 163, Line 15: remove space between 0.5 and g	**Change made**

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SH	Heart UK	73	Full	7.1.1.171	7.1.1	Page 171, Line 5: Replace "individual" with individuals	**Change made**
SH	Heart UK	74	Full	7.1.3.174	7.1.3	Page 174, "However, concern was expressed that asymptomatic coronary disease may not be detected up without routine investigation" – should be either "picked up" or "detected"	**Change made**
SH	Heart UK	75	Full	7.1.4.2	7.1.4.2	Page 176, Line 3: Replace calcium with calcification	**Change made**
SH	Heart UK	76	Full	7.1.4.2	7.1.4.2	Table 11: numerous misplaced spaces (Pages 178, 179, 182, 183) and capitals. Page 178, Third row, RH column: Replace "was" with "were" in "Baseline and follow up at 12 months with TEE was performed." Replace "significantly improved with "significant improvement". Page 181, Second row, RH column: Replace "cardiac cath" with "cardiac catheterisation"	**Table reviewed and changes made. Thank you.**
SH	Heart UK	77	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 homozygous FH and, in exceptional circumstances, those with heterozygous FH"	**Change made. Thank you.**
SH	Heart UK	78	Full	8110	8.1.1	Page 185, Line 4: Has liver transplantation ever been used to treat heterozygous FH?	**Yes, in the case of a double heterozygous mutation (see case studies).**
SH	Heart UK	79	Full	8200	1.3.3.3	Page 186, Line 17: Specify "arterio-venous" fistulae. There are other varieties.	**Change made.**
SH	Heart UK	80	Full	8220	8.2.2	Page 188, Line 1: To avoid confusion it would be clearer if the phrase "LDL apheresis" rather than "apheresis" was used throughout. Apheresis means "to take away" and needs a prefix such as "plasma" or "LDL".	**Changes made**
SH	Heart UK	81	Full	8232	8.2.3.2	Page 191: centre columns in untitled table	**Changes made and tables numbered.**
SH	Heart UK	82	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	**Comment noted. Our remit was to review LDL apheresis rather than plasmapheresis.**

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						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.	
SH	Heart UK	83	Full	8232	8.2.3.2	Page 193, Line 5: remove space before) and add after	**Change made**
SH	Heart UK	84	Full	8232	8.2.3.2	Page 193, Line 10: add space after tests	**Change made**
SH	Heart UK	85	Full	8232	8.2.3.2	Page 194, Line 6: give units for data	**Changes made**
SH	Heart UK	86	Full	8232	8.2.3.2	Page 197, Line 10: Don't start a sentence with a number	**Change made**
SH	Heart UK	87	Full	8232	8.2.3.2	Page 203, Line 3: Replace "hypercholesterolemi" with hypercholesterolemia	**Change made**
SH	Heart UK	88	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)?**

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SH	Heart UK	89	Full	8232	8.2.3.2	Page 206, 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 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.	**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)..**
SH	Heart UK	90	Full	8340	8.3.4	Page 222, RH column: remove extra full stop after "breast feed", Replace "LDL-c" with LDL-C in final paragraph	**Changes made.**
SH	Heart UK	91	Full	8343	8.3.4.3	Page 224, Line 28: Remove extra full stop after"life"	**Changes made**
SH	Heart UK	92	Full	21	Appendix A:	The Guideline Development Group: XXXX, who is an internationally renowned expert on the genetic basis of FH, 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.**