National Institute for Health and Care Excellence

Familial hypercholesterolaemia quality standard
Quality Standard Consultation Comments Table
28.02.13 - 28.03.13

ID	Stakeholder	Statement No	Comments Please insert each new comment in a new row.	Responses
1	Aegerion Pharmaceuticals Limited	General	The quality standard covers the identification and management of Familial Hypercholesterolemia (FH) in adults, young people and children. Although the quality standard mentions the condition of Homozygous Familial Hypercholesterolemia (HoFH), its management and treatment is considered under the general term of FH. The scope of the quality standards states that no patient subgroups have been identified as needing specific consideration. We believe that HoFH should be considered separately within the quality standard, due to its severity and prognosis with respect to CVD, life expectancy, and its management in specialist centres using treatments such as apheresis. **Homozygous Familial Hypercholesterolemia (HoFH)** HoFH is associated with much higher levels of low density lipoprotein cholesterol (LDL-C) than normally experienced with FH. Untreated, most individuals with HoFH die from accelerated atherosclerosis of the aortic root and coronary arteries before the age of 30. A study by Raal et al showed that even with current standard therapy with statins, the average age of death of patients with HoFH is 33 years[1]. HoFH is caused by two defective alleles in the LDL receptor gene, or genes known to affect LDL receptor function (LDLR). It is most commonly caused by mutations in both alleles of the LDLR gene, but can also be caused by mutations in other genes such as the apo B gene or proprotein convertase subtilsin/kexin type 9 (PCSK-9) genes.[2, 3, 4] Individuals with HoFH may have two identical mutations (true homozygous), two different mutations on the LDLR gene (compound heterozygous), two different mutations on two different genes (double heterozygous), or two mutations in the autosomal recessive LDLRAP1 gene (autosomal recessive hypercholesterolemia, or ARH).[5] Importantly, the mutations can impair the functioning of the LDLR and in some cases result in complete inactivity. As statins work by the up-regulation of the LDLR (see table 1), statins are	Thank you for your comment. The topic expert group recognised people with homozygous were a specific group who required special consideration however because of the low incidence of homozygous FH and the need for specialist care, this area was not progressed for statement development. The group agreed to exclude people with homozygous FH with the understanding that this group was still covered by the guideline recommendations.

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			much less effective in patients with HoFH than in the general population. **Table 1: Current cholesterol-lowering drugs are insufficient in HoFH** [6, 7] | Class	Major Effect	Typical LDL-C-Lowering Response
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Statins (e.g. atorvastatin, rosuvastatin)	↑ LDLR activity	<10 to 25%
Bile acid sequestrants (e.g. cholestyamine, colestipol)	↑ LDLR activity	<10%
Cholesterol absorption inhibitors (e.g. ezetimibe)	↑ LDLR activity	<10%
Nicotinic acid (ie, niacin)	Unknown	<10%	 In a recent meta-analysis of 21 statin trials encompassing >130,000 subjects, the weighted average LDL-C level of HC patients was 144 mg/dL at baseline.[8] Compared with HeFH patients and the normal population, patients with HoFH have significantly higher rates of LDL-C production and decreased rates of LDL-C breakdown.[10] This leads to significantly increased LDL-C levels in HoFH compared to HeFH (**Error! Reference source not found.**), with consequent increases in CVD and a more severe disease course.[9-11, 13, 14] For example, a study comparing a cohort of French-Canadian patients with familial hypercholesterolemia (FH) found that the onset of atherosclerosis was earlier in HoFH patients (14 years *vs* 34 years in HeFH patients), and those with HoFH had faster disease progression. In addition, 83% of patients had experienced a major CV event compared with 53% of HeFH patients, despite HoFH patients being younger (mean age of 34 *vs* 50 years).[9] The more severe disease course associated with HoFH leads to a greatly reduced life expectancy compared to the general population and patients with HeFH, with many patients dying in their early 30s even with modern lipid-lowering therapy.[12]	

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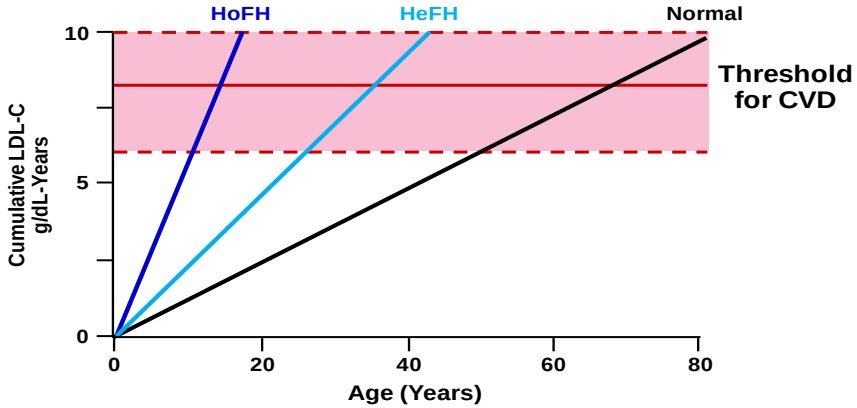
			Figure 1: Theoretical relationship between cumulative cholesterol years and age at CVD development (adapted from ref [15])  **Apheresis** As statins have lower efficacy in HoFH, there is a need to manage the condition with additional therapies. The current standard of care includes apheresis as discussed in CG71 - Identification and management of familial hypercholesterolaemia. This quality standard does not include recommendations on apheresis. Apheresis is an extracorporeal process for removal of atherogenic LDL-C and lipoprotein (a) (Lp(a)) particles from whole blood or plasma at weekly or bi-weekly intervals by adsorption, precipitation or differential filtration. The procedure commonly takes 3-4 hours per session. LDL-C levels rapidly rebound after an apheresis procedure and as such best criterion of long-term efficacy is the interval mean concentration between consecutive procedures.[18] Current guidelines stipulate that the mean LDL-C of patients with HoFH should be reduced to <6.5 mmol/l or by >65% from baseline,[18] which nearly always necessitates the use of apheresis. This is at odds with quality statement 5 which is therefore not relevant to HoFH. Currently, there are three main indications for undertaking long-term Lipoprotein	

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			apheresis: (1) Patients with homozygous familial hypercholesterolaemia (FH) whose serum cholesterol remains >9 mmol/l or decreases by < 50% despite treatment with high dose statin, plus ezetimibe and/or bile acid sequestrants and/or nicotinic acid-containing compounds.[16] (2) Patients with heterozygous FH or other forms of severe hypercholesterolaemia and with progressive coronary heart disease (CHD) whose LDL cholesterol remains > 5 mmol/l or decreases by < 40% on maximally tolerable doses of combined drug therapy. (3) Patients with a raised level of Lp(a) (> 600 mg/l, measured with a Kringle IV- independent assay) (HyperLp(a)) and with progressive CHD despite treatment with maximally tolerable combined drug therapy.	
2	AstraZeneca UK Limited	General	AstraZeneca UK Ltd would like to express thanks for the opportunity participate in this consultation on the Familial Hypercholesterolaemia Quality Standard	Thank you for your response.
3	AstraZeneca UK Limited	General	We would like to see aspirational targets for the draft quality measures that the TEG have identified to ensure the quality of care FH patients receive is consistent nationally	Thank you for your comment. The topic expert group felt the measures chosen were most reflective of the statement.
4	British Heart Foundation	General	The British Heart Foundation (BHF) is the largest single funder of cardiovascular research in the United Kingdom. As a funder of the first Familial Hypercholesterolaemia (FH) pilot family screening programme in the UK, and life-saving medical research to understand the causes of FH, the BHF has a strong vested interest in the draft quality standard and welcomes the opportunity to respond to the National Institute for Health and Clinical Excellence's consultation. Improving the processes for identifying inherited cardiac conditions, such as FH, has been identified as a priority in the National Cardiovascular Outcomes Strategy.	Thank you for your response. The topic expert group recognised the importance of the Cardiovascular Disease Outcomes Strategy and have included it as a key policy document.
5	British Heart Foundation	General	We are pleased to see a draft quality standard which provides DNA testing for children by the age of 10 through a nationwide cascade screening process. We are pleased with the draft quality standard overall, and believe that the seven draft quality statements are appropriate. Most importantly, we are keen to see that the national screening system is put into action as soon as possible.	Thank you for your response. The topic expert group agreed DNA testing for children under 10 years and the use of a national cascade screening process were important. Please see final statements 4 and 5.
6	British Hypertension Society	General	The BHS supports the statement	Thank you for your response.

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7	Genzyme	General	Genzyme welcomes the opportunity to participate in and respond to this consultation and would like to submit the following comments in response: Most of the quality statements in this Quality Standard refer to 'local data collection'. However, there is no reference to who will be responsible for collating this data. We are concerned that, without specifying who is responsible for collating data, there will be no accountability in the system to make this happen. We would call for a named organisation to collect the data or suggest that the QoF be used to facilitate this. We would also call for annual publication of the data, including a comparison of results across CCGs. This would help highlight any inequalities and encourage CCGs to address the issue if they are outliers. We also recommend that the data collected should contain information on patient characteristics, medical history, medications, LDL-C levels and documentation of cardiovascular events. We also recommend the inclusion of a requirement that healthcare professionals show evidence that they have Continuing Medical Education related to Familial Hypercholesterolaemia (FH), as this is an area of concern raised by a recent RCP audit on FH.	Thank you for your comment. It is expected that local data sources and audits where appropriate will be considered in order to measure the quality statements in full. It is not within the remit of the quality standard to advise who should collect the data nationally and how it should be published.
8	RCGP	General	I did a practice audit last year to see how many children of parents with known familial hypercholesterolaemia had been tested. The problem was that unless the consultant had specifically mentioned it, those concerned had not asked their families to be tested and were unwilling to get involved. Only a few children had been tested.	Thank you for your comment. The topic expert group recognised the importance of testing family members. Please see final statement 5.
9	RCN	General	The Royal College of Nursing welcomes proposals to develop these quality standards. We welcome the proposed draft quality statements for Familial Hypercholesterolaemia and consider that these services are very lacking in England.	Thank you for your response.
10	RCP	General	The RCP is grateful for the opportunity to respond to the QS consultation. Our experts in clinical genetics have returned the following comments. Overall, they believe that the draft quality standards would improve the care and outcomes for the common disorders 'familial hypercholesterolaemia'. However, they believe that not including a standard for dietetic input is a serious omission, and decreases the likely	Thank you for your comment. The topic expert group prioritised the areas of care where practice is variable, or where implementation could have a significant impact on patient care and improved outcomes, and where they represent key

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			benefits from specialist services. They also feel that the emphasis on molecular testing (particularly in adults) within the QS is perhaps misplaced. This is a diagnosis that is made on the basis of lipid assessment and family history. Again, particularly in adults, they believe that molecular genetic characterisation probably has little to offer in most cases. The biochemistry is likely to reflect the clinical phenotype more closely. Referral to a specialist for paediatric patients is quite important and the inclusion of this disorder within the service specification for metabolic disorders reflects this priority. Although Quality Standards are outwith resource implications, it should be noted that most specialist services currently are unable to offer mutation testing as it is unfunded, and it is unlikely to be prioritised when other clinical diagnostic methods are available. Lipid testing has the advantage of being diagnostic, and used in monitoring treatment. Our experts are also concerned with regard to the funding for all of the specialist clinics for this common condition i.e. where will it come from? One possible solution might be for assessment by a specialist service, with provision of information subsequently after the family have been assessed, to patient and GP for ongoing management. From the perspective of experts in clinical genetics the ranking of the standards should be; 1,5,3,6,4,2,7.	markers of clinical and cost effective care based on the development sources listed. The topic expert group considered the resource implications when prioritising areas for statement development and agreed DNA testing should be offered to everyone for confirmation of diagnosis and initiation of cascade testing. It will be for people with FH and their clinician to discuss jointly if it is appropriate. The topic expert group also agreed referral to a specialist was important and recognised that this would be different for adults and children. The group agreed to add further information to the definitions to highlight this issue. Please see final statement 2. A 'support for commissioners' document has been produced alongside the quality standard and considers the cost and commissioning implications of the statements. All quality statements were progressed to the final quality standard.
11	Sanofi	General	Sanofi welcomes the opportunity to participate in this consultation and would like to submit the following comments in response: Most of the quality statements in this Quality Standard refer to 'local data collection'. However, there is no reference to who will be responsible for collating this data. We are concerned that, without specifying who is responsible for collating data, there will be no accountability in the system to make this happen. We would call for a named organisation to collect the data. We would also call for annual publication of the data, including a comparison of results across CCGs. This would help highlight any inequalities and encourage CCGs to	Thank you for your comment. It is expected that local data sources and audits where appropriate will be considered in order to measure the quality statements in full. It is not within the remit of the quality standard to advise who should collect the data nationally and how it should be published.

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			address the issue if they are outliers. We also recommend that the data collected should contain a requirement for information on patient characteristics, medical history, medications, LDL-C levels and documentation of Cardiovascular (CV) events. We also recommend the inclusion of a requirement that healthcare professionals show evidence that they have Continuing Medical Education related to Familial Hypercholesterolaemia (FH), as this is an area of concern raised by a recent Royal College of Physicians (RCP) audit on FH.	
12	WEDS	General	This quality standard consultation is based on the All Wales FH Cascade Screening Service implemented by Dr Alan Rees and Dr Ian McDowell, both of whom are active members of WEDS WEDS strongly believes them to be comprehensive and to reflect Best Practice. They deserve to be supported. We have no caveats and no criticisms.	Thank you for your response. Dr Ian McDowell was part of the topic expert group who developed the quality standard.
13	ACP	Introduction	The often quoted statement “50% of men with heterozygous FH will develop coronary heart disease by the age of 50 years and at least 30% of women by the age of 60 years” is referenced neither here nor in CG71. Often when these same figures are quoted elsewhere they reference Slack’s paper in the Lancet (Slack J (1969) Risks of ischaemic heart-disease in familial hyperlipoproteinaemia stats. Lancet; 2:1380-1382.), but the figures are incorrect: That paper actually reports (in the summary section): “For men with type-II hyperbetalipoproteinaemia the chance of a first attack of I.H.D. was 5.4% by age thirty, 51.4% by age fifty, and 85.4% by age sixty. For women the risks were 0, 12.2%, and 57.5% respectively.”	Thank you for your comment. The introduction has been updated to reflect the figures from the Slack paper which is now referenced in the quality standard.
14	British Heart Foundation	Introduction	We are concerned that the introduction of the draft quality standard document says that FH is caused by an alteration in a gene –this is not true. As highlighted by the research of Professor Steve Humphries at University College London, in some cases the cause of FH is polygenic.	Thank you for your comment. The Lancet paper shows that in a significant proportion of people with a clinical diagnosis of FH but where no FH-causing mutation can be found, the likely explanation for their elevated LDL-C is a polygenic cause. The authors of the paper suggest that the diagnosis of “FH” should be restricted to those with an FH-causing mutation and the remainder be given the

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				diagnosis “polygenic hypercholesterolaemia”. The topic expert group agreed with the statements made in the introduction.
15	MSD	Introduction	Within the Introduction of the draft quality standard, paragraph 3 states that life expectancy is restored to near normal with “early preventative treatment, particularly statin treatment and smoking cessation”. MSD believe it is inappropriate for statin treatment to be specifically highlighted in this sentence, rather than referring to lipid-modifying therapy more generally. While it is recognised that statins should be the initial treatment for adults with FH to achieve a recommended reduction in LDL-C concentration of >50% from baseline (Ref 1), there will be certain patients for whom statin therapy is neither an appropriate nor adequate option to control serum total or low-density lipoprotein (LDL) cholesterol concentrations. MSD suggest it would be more appropriate for “particularly statin treatment” to be replaced with “particularly treatment with lipid-regulating therapy” in the above mentioned sentence. Such a modification would also ensure consistency with recommendations made in NICE TA132 (Ref 2) Ref 1: NICE Clinical guideline 71 “Identification and management of familial hypercholesterolaemia” - August 2008. Available at: http://www.nice.org.uk/nicemedia/live/12048/41697/41697.pdf (accessed 25/03/13) Ref 2: NICE Technology Appraisal guidance 132: “Ezetimibe for the treatment of primary (heterozygous–familial and non-familial) hypercholesterolaemia”– November 2007. Available at http://www.nice.org.uk/nicemedia/live/11886/38799/38799.pdf (accessed 25/03/13)	Thank you for your comment. Based on current available published evidence, The topic expert group have agreed to the wording in the introduction and felt that in most cases statin treatment would be used and so agreed this was an appropriate example to include.
16	ACB	Question 1	Comment about General Question 1: The following would be appropriate outcomes, measurable in the clinical setting Number of patients diagnosed with Definite FH, age at diagnosis, number referred (Standard 1, 3) Number of patients diagnosed with Possible FH, age at diagnosis, number	Thank you for your comment. The topic expert group considered all suggested measure. Outcome measures are stated where the topic expert group felt they are appropriate, measurable and specifically

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			referred (Standard 1, 3) Number of patients having DNA testing for FH (Standard 2) Number of patients with diagnostic mutation on DNA testing (Standard 2) Number of relatives identified, number cascade tested (Standard 4) Number of affected relatives identified on cascade testing (Standard 4) Number of patients achieving 50% reduction of LDL-cholesterol (or non-HDL-cholesterol) (Standard 5) Number of patients having a structured annual review in the past year (Standard 5)	attributable to the action stated in the statement.
17	ACP	Question 1	Suggested outcomes 1. No. of adults with [cholesterol >7.5 and (xanthomata or a family history of premature CVD)] and no. who have been referred 2. No. of above who have been offered genetic testing 3. No. of children at risk of FH, and no. who have been diagnosed by age 10 (noting comments above, possibly by age 7) 4. No of 'at risk' relatives and no diagnosed by cascade testing 5. No of patients with FH, and no. achieving 50% reduction of LDL-cholesterol (noting comments above – possibly a further outcome of no of patients with established CVD achieving LDL-cholesterol <1.7 mmol/l). 6. No of children with FH, no. who have been referred 7. No of individuals with FH, no. who have been offered a structured review within the last 15 months.	Thank you for your comment. The topic expert group considered all suggested measure. Outcome measures are stated where the topic expert group felt they are appropriate, measurable and specifically attributable to the action stated in the statement.
18	Genzyme	Question 1	In addition to the specific responses about, we also believe that a national register to record the incidence of CV events in FH patients may be useful in order to see if the measures being implemented are resulting in any decrease in CV events and improvements in survival.	Thank you for your comment. It is not within the remit of the quality standard to suggest the use of a national register.
19	Heart UK	Question 1	Comment about General Question 1: The following would be appropriate outcomes, measurable in the clinical setting Number of patients diagnosed with Definite FH, age at diagnosis, number referred (Standard 1, 3) Number of patients diagnosed with Possible FH, age at diagnosis, number referred (Standard 1, 3) Number of patients having DNA testing for FH (Standard 2) Number of patients with diagnostic mutation on DNA testing (Standard 2) Number of relatives identified, number cascade tested (Standard 4) Number of affected relatives identified on cascade testing (Standard 4) Number of patients achieving 50% reduction of LDL-cholesterol (or non-	Thank you for your comment. The topic expert group considered all suggested measure. Outcome measures are stated where the topic expert group felt they are appropriate, measurable and specifically attributable to the action stated in the statement.

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			HDL-cholesterol) (Standard 5) Number of patients having a structured annual review in the past year (Standard 5)	
20	Sanofi	Question 1	In addition to the specific responses above, we also believe that a national register to record the incidence of CV events in FH patients may be useful in order to see if the measures being implemented are resulting in a decrease in CV events.	Thank you for your comment. It is not within the remit of the quality standard to suggest the use of a national register.
21	ACB	Question 2	Comment about General Question 2: The following important quality issues have not been covered Provision on professional nutritional advice should be an essential quality standard as covered in Section 1.3.2 of CG 71 "1.3.2.2 All people with FH should be offered individualised nutritional advice from a healthcare professional with specific expertise in nutrition". Failure to include this standard could have a serious adverse effect on prioritisation of resources for nutritional support within specialist clinics Acute Cardiology - the identification of patients with FH among those admitted to hospital with acute coronary syndromes under the age of 60 years is a major area of weakness which should be addressed. All such patients should have a full non-fasting lipid profile at the time of hospital admission and if found to have hypercholesterolaemia >7.5 mmol/L should be examined for tendon xanthomas and have a family history taken. This could easily be incorporated into a quality standard. There should be a national register for confirmed homozygous and heterozygous FH, however the former numbers are small and the register should be easily established All patients with homozygous FH over 2 years should be offered apheresis within 3 months of diagnosis	Thank you for your comment. The topic expert group prioritised the areas of care where practice is variable, or where implementation could have a significant impact on patient care and improved outcomes, and where they represent key markers of clinical and cost effective care based on the development sources listed.
22	ACP	Question 2	Nutritional and other lifestyle advice (especially smoking) should be addressed, e.g. 'No of individuals with FH, no. who currently smoke'.	Thank you for your comment. The topic expert group felt lifestyle advice is important and agreed it should be one of the core components of a structured review. Please see final statement 8.
23	AstraZeneca UK Limited	Question 2	We support this quality standard and would additionally support the inclusion of monitoring growth and pubertal development in children. Cascade testing progress should be recorded and identified whether this is with 1st, 2nd or 3rd degree relatives. We would also recommend discussing lifestyle changes such as smoking and diet as a separate	Thank you for your comment. The topic expert group agreed the monitoring of growth and pubertal development in children, recording cascade testing and lifestyle changes are important and

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			bullet.	agreed these should be some of the core components of a structured review. Please see final statement 8.
24	Genzyme	Question 2	**Consideration for severe FH and/or compound HeFH patients** We believe the most significant omission is that the Quality Standard does not make reference to the need to ensure those patients who remain at risk despite maximally tolerated treatment , and those with severe disease, (eg some HoFH), have access to mechanical interventions such as apheresis. We believe consideration should be given as to how this should be commissioned into the pathway in an equitable way. This could be part of statement 5. Another consideration not currently covered is the fact that severe FH patients with HoFH and/or compound HeFH may have received maximally tolerated drug interventions with currently available drugs, and still fail to achieve target LDL-C reduction. Further interventions are required, and should be acknowledged in this Quality Standard. This could be via apheresis or could acknowledge the availability in future of pharmaceutical interventions targeted at this population. **Diagnosis** We are also concerned that the Quality Standard does not address the issue that patients are not being diagnosed early enough, and in sufficient numbers. We would welcome a statement on the need for more primary screening to identify patients not captured by the current practice of secondary screening from established cardiovascular (CV) registers and vascular checks, which are currently only offered to those over 40. Whilst improving diagnosis would increase the patient base, requiring a potential increase in service provision, and the subsequent costs associated with that, FH is based on a solid prevalence. This means that once the patient population has been identified and treated, it should not increase significantly. Diagnosing and treating FH earlier would, however, mean that treatment costs should stabilize and eventually reduce as improved management would lead to a reduction in elective and non-elective admissions for CV emergencies. Heart UK's FH report "Saving lives, saving families" highlights that "the greater the number of FH patients identified and treated, the greater the comparative and accrued health benefits and cost savings to the NHS". Improvements against such a	Thank you for your comment. The topic expert group prioritised the areas of care where practice is variable, or where implementation could have a significant impact on patient care and improved outcomes, and where there is potential to generate measurable indicators, based on the development sources listed. Following consultation an additional statement has been added to the quality standard on identification of people with FH based on raised cholesterol levels. Please see the final quality statement 1. The quality standard will be reviewed for the development of potential indicators for both the QOF and the CCGOIS. Please see the NICE quality standards library of topics which includes a standard planned for the transition between children and adult services.

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			statement could be measured using the Quality Outcomes Framework process to reward GPs who identify patients in line with expected population rates. **Identification of FH index cases** We are also concerned that the identification of FH index cases is not covered in this Quality Standard. Currently this has been limited to the identification of relatives of index cases and we believe there could be many people (potential index cases) who have undiagnosed FH which need to be identified. For example, patients who enter A&E with premature Myocardial Infarction (MI) are treated on high dose statins but there is currently no consideration as to whether the patient has FH, which may have been the cause of the MI. Audit data exists which identifies this as a specific issue. As we have stated previously in this response – a recent Heart UK report on FH found that increasing the number of patients identified and treated will positively impact the health benefits and cost savings for the NHS . **Transition to adult services** Also in there is no mention of the need to ensure transition arrangements are in place to manage the paediatric/adult interface required for FH children. We would call for a standard that focuses on managing the transition to an appropriate adult service to support their ongoing clinical needs.	
25	Heart UK	Question 2	Comment about General Question 2: The following important quality issues have not been covered Provision on professional nutritional advice should be an essential quality standard as covered in Section 1.3.2 of CG 71 “1.3.2.2 All people with FH should be offered individualised nutritional advice from a healthcare professional with specific expertise in nutrition”. Failure to include this standard could have a serious adverse effect on prioritisation of resources for nutritional support within specialist clinics Acute Cardiology - the identification of patients with FH among those admitted to hospital with acute coronary syndromes under the age of 60 years is a major area of weakness which should be addressed. All such patients should have a full non-fasting lipid profile at the time of hospital admission and if found to have hypercholesterolaemia >7.5 mmol/L should	Thank you for your comment. The topic expert group prioritised the areas of care where practice is variable, or where implementation could have a significant impact on patient care and improved outcomes, and where they represent key markers of clinical and cost effective care based on the development sources listed.

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			be examined for tendon xanthomas and have a family history taken. This could easily be incorporated into a quality standard. There should be a national register for confirmed homozygous and heterozygous FH, however the former numbers are small and the register should be easily established For patients with homozygous FH, lipoprotein apheresis should be considered after the age of 4 and before the age of 7 if optimal drug therapy has proved ineffective. Apheresis should be performed at weekly or bi-weekly intervals on a long-term basis and should be combined with maximum tolerated doses of atorvastatin or rosuvastatin plus ezetimibe 10mg daily. At least one volume of plasma or whole blood should be treated on each occasion, sufficient to acutely lower LDL by 60%.	
26	Heart UK	Question 2	Also consider this quality measure: Number of patients diagnosed with definite or possible FH have been offered written advice and given information about their genetic risk of inheritance and about patient support groups.	Thank you for your comment. The topic expert group considered all suggested measures and felt the measures chosen were most reflective of the statement.
27	Roche Products	Question 2	In the recently published *Cardiovascular Disease Outcomes Strategy* (Department of Health, 2013), the Government calls for action to ensure that cardiovascular disease (CVD) is managed as a single family of diseases. Of particular relevance to Familial Hypercholesterolaemia (FH) are actions to improve and enhance case finding in primary care and to improve care for patients living with CVD—both actions will empower patients to manage their own condition. At the time of this consultation, the scopes of a number of related quality standards referred to NICE by the Department of Health, are not yet available: acute coronary syndromes (including myocardial infarction); lipid modification; peripheral vascular disease; risk assessment of modifiable cardiovascular risk factors. Therefore, this consultation response is made in anticipation that, in the earliest possible timeframe: FH and related quality standards will be reviewed and aligned; and that NICE will review the work of NHS Improving Quality as it develops and evaluates new service models for CVD.	Thank you for your comment. When NICE quality standards are reviewed, we will make every effort to ensure that they are grouped and aligned with related topics in the library.
28	Sanofi	Question 2	Consideration for severe FH and/or compound HeFH patients We believe the most significant omission is that the Quality Standard does not make reference to the need to ensure those patients who remain at risk despite maximally tolerated treatment and those with severe disease,	Thank you for your comment. The topic expert group prioritised the areas of care where practice is variable, or where implementation could have a significant

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			(eg some HoFH), have access to mechanical interventions such as apheresis. We believe consideration should be given as to how this should be commissioned into the pathway in an equitable way. This could be part of statement 5. Another consideration not currently covered is the fact that many FH patients receiving the maximally tolerated doses of statins have uncontrolled LDL-C levels yet receive no further treatment intensification. The Quality Standard should look to ensure that, where possible, these patient receive the appropriate treatment intensification to control their LDL- C levels and reduce long term complications Diagnosis We are also concerned that the Quality Standard does not address the issue that patients are not being diagnosed early enough or in sufficient numbers. We would welcome a statement on the need for more primary screening to identify patients not captured by the current practice of secondary screening from established CV registers and vascular checks, which are currently only offered to those over 40. Whilst improving diagnosis would increase the patient base, requiring a potential increase in service provision, and the subsequent costs associated with that, FH is based on a solid prevalence. This means that once the patient population has been identified and treated, it should not increase significantly. Diagnosing and treating FH earlier would, however, mean that treatment costs should stabilize and eventually reduce as improved management would lead to a reduction in elective and non-elective admissions for CV emergencies. Heart UK's FH report "Saving lives, saving families" highlights that "the greater the number of FH patients identified and treated, the greater the comparative and accrued health benefits and cost savings to the NHS".2 Improvements against such a statement could be measured using the Quality Outcomes Framework process to reward GPs who identify patients in line with expected population rates. Identification of FH index cases We are also concerned that the identification of FH index cases is not covered in this Quality Standard. Currently this has been limited to the identification of relatives of index cases and we believe there could be many people (potential index cases) who have undiagnosed FH and need to be identified.	impact on patient care and improved outcomes, and where there is potential to generate measurable indicators, based on the development sources listed. An additional statement has been added to the final quality standard to address recognition and early diagnosis in primary care. Please see the final quality statement 1. The quality standard will be reviewed for the development of potential indicators for both the QOF and the CCGOIS. Please see the NICE quality standards library of topics which includes a standard planned for the transition between children and adult services.

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			For example, patients who enter A&E with premature Myocardial Infarction (MI) are treated on high dose statins but there is currently no consideration as to whether the patient has FH, even though this could be a cause of the MI. Audit data exists which identifies this as a specific issue. As we have stated previously in this response – a recent Heart UK report on FH found that increasing the number of patients identified and treated will positively impact the health benefits and cost savings for the NHS . Transition to adult services There is also no mention of the need to ensure transition arrangements are in place to manage the paediatric/adult interface required for FH children. We would call for a statement that focusses on managing the transition to an appropriate adult service to support young adult's ongoing clinical needs. 2 Heart UK, Saving lives, saving families' 2012, http://heartuk.org.uk/files/uploads/HUK_SavingLivesSavingFamilies_FHreport_Feb2012.pdf	
29	Sheffield Teaching Hospital NHS Trust	Question 2	NICE CG71: 1.3.2.2 Individualised nutritional advice from a HCP with specific expertise in nutrition. NICE CG71: 1.3.3 LDL-lowering apheresis NICE CG71: 1.5.2 Referral for evaluation of CHD	Thank you for your comment. The topic expert group prioritised the areas of care where practice is variable, or where implementation could have a significant impact on patient care and improved outcomes, and where they represent key markers of clinical and cost effective care based on the development sources listed.
30	ACB	Question 3	Comment about General Question 3: The most important statements are 2 and 3. DNA testing is essential for effective implementation of cascade testing which has not been undertaken widely, especially in England during the 5 years since the publication of CG71. Early diagnosis and effective prevention depends on cascade testing.	Thank you for your comment. The statements on DNA testing and cascade testing were progressed to the final quality standard.
31	Genzyme	Question 3	We believe the most important statements are 1, 4, 5 and 6. •As we have said in this document, the important factor is to have diagnosed adults and children referred to an expert in lipid management, and given the appropriate and effective treatment needed to reduce their LDL-C levels to 50% of baseline as defined in NICE guidelines. •It is also important that children are identified and treated as early as	Thank you for your comment. All draft statements were progressed to the final quality standard.

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			possible. •It is also important that relatives of those with FH are detected via cascade testing. This will improve patient outcomes and NHS resources in the long term. The implementation of NICE Guidelines on cascade screening has been poor and this standard could drive improvements in this areas. •If we were put the rest of the statements in order of importance we would suggest the following order: 3, 7, 2. •DNA testing is useful but not vital as FH can clearly be diagnosed and confirm via clinical factors, and the variation in the genetic presentation means that some patients will be FH positive even without a positive genetic confirmation.	
32	Heart UK	Question 3	Comment about General Question 3: The most important statements are 2 and 3. DNA testing is essential for effective implementation of cascade testing which has not been undertaken widely, especially in England during the 5 years since the publication of CG71. Early diagnosis and effective prevention depends on cascade testing.	Thank you for your comment. The statements on DNA testing and cascade testing were progressed to the final quality standard.
33	Roche Products	Question 3	Roche supports all seven proposed quality statements as they reflect critical stages in the patient pathway. The resulting quality improvements will facilitate the future use of novel drug treatments which have the potential to further improve patient outcomes (Alonso R *et al*., *Expert Rev. Cardiovasc. Ther.* (2013) **11**(3): 327–342).	Thank you for your comment. All statements were progressed to the final quality standard.
34	Sanofi	Question 3	We believe the most important statements are 1, 4, 5 and 6. As we have said in this document, the important factor is to have diagnosed adults and children referred to an expert in lipid management, and given the appropriate and effective treatment needed to reduce their LDL-C levels to 50% of baseline as defined in NICE guidelines. It is also important that children are identified and treated as early as possible and this can be detected via cascade testing. This will improve patient outcomes and NHS resources in the long term. The implementation of NICE Guidelines on cascade screening has been poor and this Quality Standard could drive improvements in this area. If we were put the rest of the statements in order of importance we would suggest the following order: 3, 7, 2. DNA testing is useful but not vital as FH can clearly be diagnosed and confirmed via clinical factors. Also, the variation in the genetic	Thank you for your comment. All statements were progressed to the final quality standard.

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			presentation means that some patients will be FH positive even without a positive genetic confirmation.	
35	Genzyme	Question 4	We agree with the proposed measures •In particular, we welcome the use of hard ratio based outcomes as a good, qualitative and quantitative way to measure success for identification, referral and treatment. • We believe the measures outlined in these statements are based on, and relate to, well established and accepted prevalence figures that will allow the monitoring of the referral path success. •The use of LDL-C reduction is accepted as a strong surrogate marker, and therefore is an appropriate measure. •However, we would add that the collection of CV event data could be gathered by the use of a register of FH patients – as the reduction in mortality and morbidity is the ultimate outcome. •This would deliver some "hard" data to support the investment in the management of FH patients nationally.	Thank you for your comments. It is not within the remit of the quality standard to suggest the use of a national register.
36	Heart UK	Question 4	Comment about General Question 4: The following measures appear to be in conflict with the original guidance appear inappropriate Standard 6 – the original guidance states "1.3.1.20 Lipid-modifying drug therapy for a child or young person with FH should USUALLY BE CONSIDERED by the age of 10 years." and "1.3.1.24 In EXCEPTIONAL INSTANCES, for example, when there is a family history of coronary heart disease in early adulthood, healthcare professionals with expertise in FH in children and young people SHOULD CONSIDER OFFERING……LIPID-MODIFYING DRUG THERAPY BEFORE THE AGE OF 10 YEARS." The statement appears to go beyond the original guidance and the current evidence base. Such decisions should be left with the specialist, however it may be appropriate that they should record the reasons chosen NOT to defer treatment until 16 -18 years, (e.g. LDL>6.0 and early mi in parent <40 years), as proceeding with treatment entails considerable investment of professional follow up time and anxiety for patients and their parents. Standard 4 – The original guidance recommends cascade testing from those with a clinical diagnosis of FH, made by the specialist, using the LDL-C charts if DNA diagnosis is not available. The standard as written implies that ONLY relatives of patients with Definite FH are offered cascade testing. As few patients are now identified with tendon	Thank you for your comment. The statement on lipid-modifying drug treatment for children has been changed and now refers to an assessment for drug treatment. The topic expert group agreed to limit the statement on cascade testing to a subset of the population where testing is most effective due to the lack of current services and the large resource implications. The topic expert group felt that once these services were available then it would be appropriate to extend the population to cover additional groups.

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			xanthomas this will restrict cascade testing almost exclusively to those families who are able to obtain a positive genetic diagnosis and will discriminate against the majority of those with a clinical diagnosis including the 10-15% of Definite FH with no mutation (DNA testing false negatives) but severely elevated LDL-C.	
37	Sanofi	Question 4	In particular, we welcome the use of hard ratio based outcomes as a good, qualitative and quantitative way to measure success for identification, referral and treatment. We believe the measures outlined in these statements are based on, and relate to, well established and accepted prevalence figures that will allow the monitoring of the referral path success. The use of LDL-C reduction is accepted as a strong surrogate marker, and therefore is an appropriate measure. However, we would add that the collection of CV event data could be gathered by the use of a register of FH patients – as the reduction in mortality and morbidity is the ultimate outcome. This would deliver some “hard” data to support the investment in the management of FH patients nationally.	Thank you for your comment. It is not within the remit of the quality standard to suggest the use of a national register.
38	ACB	QS 1	The numbers of patients meeting Simon Broome criteria for possible or definite FH is large and it will be difficult for providers to meet this standard. It would be helpful if those with the highest probability of having FH were accorded priority for referral e.g. 100% of those with LDL-C > 4.0 under 16 years, >5.0 under 60 years and >6.5 at any age,	Thank you for your comment. The topic expert group considered the resource implications for all statements and agreed referral to a specialist for confirmation of diagnosis and initiation of cascade testing was an important area of care for patients and would lead to improved outcomes.
39	BMA	QS 1	Subject to there being adequate specialist services commissioned, we are happy that this quality statement is appropriate.	Thank you for your comment.
40	British Heart Foundation	QS 1	The description of what the quality statement means for healthcare professionals does not explain what an FH specialist is, we would like this to be made clear.	Thank you for your comment. Further information on a specialist with expertise in FH is included in the definitions.
41	British Hypertension Society	QS 1	There is an assumption that primary care can recognise and make a possible diagnosis of FH. This would apply for both statements 1 & 2 – both are dependent on it being recognised. This element is probably outside the scope of the guideline - but a critical part of the pathway. If all patients are referred to a specialist and there are more than 110,000 patients in the UK, how many specialists do you require? Certainly many	Thank you for your comment. An additional statement has been added to the final quality standard to address recognition and early diagnosis in primary care. Please see final quality statement 1. The topic expert group considered the resource implications for all statements

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			more than currently available. Certainly there will be very few paediatricians with specialist knowledge. None of this will be possible without new money or a major defunding of other services.	and agreed referral to a specialist for confirmation of diagnosis and initiation of cascade testing was an important area of care for patients and would lead to improved outcomes.
42	Genzyme	QS 1	We fully support the inclusion of this statement. The important factor in the treatment of FH is to have diagnosed adults and children referred to an expert in lipid management and given the appropriate and effective treatment needed to reduce their LDL-C levels to 50% of baseline, as defined in NICE guidelines. Increased levels of patient referrals and subsequent numbers, will require a close examination of capacity to manage the increased demand from lipid clinics and specialists.	Thank you for your comment. The topic expert group considered the resource implications for all statements and agreed referral to a specialist for confirmation of diagnosis and initiation of cascade testing was an important area of care for patients and would lead to improved outcomes.
43	Heart UK	QS 1	The numbers of patients meeting Simon Broome criteria for possible or definite FH is large and it will be difficult for providers to meet this standard. It would be helpful if those with the highest probability of having FH were accorded priority for referral e.g. 100% of those with LDL-C > 4.0 under 16 years, >5.0 under 60 years and >6.5 at any age,	Thank you for your comment. The topic expert group considered the resource implications for all statements and agreed referral to a specialist for confirmation of diagnosis and initiation of cascade testing was an important area of care for patients and would lead to improved outcomes.
44	NHS South Central Cardiovascular Network	QS 1	“People with a clinical diagnosis of familial hypercholesterolaemia (FH) are referred to a specialist with expertise in FH. “ The SCCVN suggest that this statement is reworded to read: People with a clinical diagnosis of familial hypercholesterolemia (FH) are managed by a general practitioner with appropriate advice and guidance (and referral if required) from a specialist with expertise in FH. Rationale: Based on our discussions with commissioners within the NHS South Central area we anticipate that most GPs have the skills to offer first line lipid management to patients with FH supported by appropriate advice and guidance from secondary care specialists underpinned by a robust education programme. There is a concern that a quality standard that is seen to drive increased secondary care activity is likely to be a barrier to commissioning an FH cascade testing service.	Thank you for your comment. The topic expert group considered the resource implications for all statements and agreed referral to a specialist for confirmation of diagnosis and initiation of cascade testing was an important area of care for patients and would lead to improved outcomes.
45	North Trent Network of Cardiac Care	QS 1	Members expressed concern that the 1 statement started too far down the care pathway. They expressed a lack of surety that GPs would be able to recognise signs and identify possible FH and investigate accordingly.	Thank you for your comment. An additional statement has been added to the final quality standard to address

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			Meaningful acceptable lower cholesterol limit is also needed. Suggested statement 1 - people having visible signs and symptoms or are suspected of having FH (family history) are investigated thoroughly and in a timely manner in order to confirm a suspected clinical diagnosis of FH	recognition and early diagnosis in primary care. Please see final quality statement 1.
46	RCPCH	QS 1	Data source – Local data collection. How will this data be captured – via GPs or via specialists? Are there mechanisms in place to do this?	Thank you for your comment. It is expected that local data sources and audits where appropriate will be considered in order to measure the quality statements in full.
47	Roche Products	QS 1	Roche welcomes this quality statement as it is aspirational and reflects ESC/EAS Guidelines for the management of dyslipidaemias which state that management should ideally involve a lipid clinic (Reiner Z et al., European Heart Journal (2011) 32: 1769–1818). To support the aims of early diagnosis and initiating treatment as early as possible the statement should clearly indicate the need for prompt referral and include when subsequent specialist referral is appropriate (as previously recommended by NICE clinical guideline 71, 2008: when a reduction in LDL-C concentration of greater than 50% from baseline is not achieved; intolerance or contraindications to statins or ezetimibe). Proposed statement: People ~~with a clinical diagnosis of familial hypercholesterolaemia (FH) are referred to a specialist with expertise in FH~~ are referred to a specialist with expertise in familial hypercholesterolaemia (FH) as soon as a clinical diagnosis of FH is made and, for those receiving lipid lowering therapy, when subsequent treatment review is necessary.	Thank you for your comment. Each quality statement focusses on one key concept making the statements clear, concise and more easily measureable. The topic expert group felt the quality improvement area was on specialist referral for confirmation of diagnosis and initiation of cascade testing.
48	Roche Products	QS 1	To reflect the quality statement proposed above, the following modifications are suggested: Structure: Evidence of local arrangements to ensure people with <u>an initial</u> clinical diagnosis of FH <u>or when subsequent treatment review is necessary</u> are referred <u>promptly</u> to a specialist with expertise in FH. Process: <u>c) The proportion of adults not achieving a maximal reduction of LDL-C concentration who are referred to a specialist with expertise in FH.</u> <u>Numerator – The number of people in the denominator referred to a</u>	Thank you for your comment. Please see response to comment 47.

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			specialist with expertise in FH. Denominator – The number of adults with FH not achieving a maximal reduction in LDL-C concentration d) The proportion of adults with FH and intolerance or contraindications to statins or ezetimibe who are referred to a specialist with expertise in FH. Numerator – The number of people in the denominator referred to a specialist with expertise in FH. Denominator – The number of adults with FH and intolerance or contraindications to statins or ezetimibe	
49	Roche Products	QS 1	To reflect the quality statement proposed above, the following modifications are suggested: **Service providers** ensure systems are in place for people with an initial clinical diagnosis of FH or when a subsequent treatment review is necessary to be referred promptly to a specialist with expertise in FH. **Healthcare professionals** promptly refer people with an initial clinical diagnosis of FH or when a subsequent treatment review is necessary to a specialist with expertise in FH. **Commissioners** ensure they commission services that promptly refer people with an initial clinical diagnosis of FH or when a subsequent treatment review is necessary to a specialist with expertise in FH. **People** who are given an initial clinical diagnosis of FH because they have high cholesterol and other signs or when subsequent treatment review is necessary are promptly referred to a specialist with expertise in FH.	Thank you for your comment. Please see response to comment 47.
50	Sanofi	QS 1	We fully support the inclusion of this statement. The important factor in the treatment of FH is to have diagnosed adults and children referred to an expert in lipid management and given the appropriate and effective treatment needed to reduce their LDL-C levels to 50% of baseline, as defined in NICE guidelines.	Thank you for your comment. The statements on referral to a specialist and treatment for adults and children were progressed to the final quality standard.
51	Sheffield Teaching Hospital NHS Trust	QS 1	Do you need a definition here of a “specialist” Should it be – 2 measurements of fasting LDL-C concentration. If the 2nd is non-fasting it may drop below the SB cut-off and a clinical diagnosis missed.	Thank you for your comment. Further information on a specialist with expertise in FH is included in the statement definitions.

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52	ACB	QS 2	Patients will have a clinical diagnosis of possible or definite FH made in primary care before referral. The role of the specialist is to confirm the FH phenotype, in which case DNA testing may be appropriate. It may not be appropriate to offer DNA testing to all such patients e.g. those with weak/no family history or clinical signs, those with no potentially affected relatives or phenotype consistent with an alternative diagnosis.	Thank you for your comment. The topic expert group felt it was important to offer DNA testing to all people with FH to confirm the diagnosis. It will be for the person with FH and the clinician to decide jointly if it is appropriate.
53	ACP	QS 2	The practicality of this depends on the interpretation of 'a clinical diagnosis' – we would suggest that this should be limited to those diagnosed as 'definite FH' at least initially.	Thank you for your comment. A definition of a clinical diagnosis has been added to the definitions.
54	BMA	QS 2	We agree that people with a clinical diagnosis of familial hypercholesterolaemia should be offered DNA testing, but the statement should specify that this referral should come from the specialist to whom the patient has been referred.	Thank you for your comment. The statement has been revised to say the DNA testing should be part of a specialist assessment. The audience descriptors and definitions have been updated accordingly to indicate the DNA testing would be offered by a specialist.
55	British Hypertension Society	QS 2	Genetic testing for all very desirable and currently the availability is nearer to zero.	Thank you for your comment. The topic expert group recognised the lack of available services and therefore felt it was an area for quality improvement.
56	Genzyme	QS 2	While we welcome the focus on the early diagnosis of FH and treatment of children in the Quality Standard, we believe that DNA testing is not vital as FH can clearly be diagnosed and confirmed via clinical factors. Evidence shows that variation in the genetic presentation means that some patients will be FH positive even without a positive genetic confirmation. We would also recommend the inclusion of a requirement to ensure that children have a managed transition to an appropriate adult service to support their on-going clinical needs.	Thank you for your comment. The topic expert group felt it was important to offer DNA testing to all people with FH to confirm the diagnosis where possible but recognised some people with FH may not have a DNA mutation and to initiate cascade testing. Please see the NICE quality standards library of topics which includes a standard planned for the transition between children and adult services.
57	Heart UK	QS 2	Patients will have a clinical diagnosis of possible or definite FH made in primary care before referral. The role of the specialist is to confirm the FH phenotype, in which case DNA testing may be appropriate. It may not be appropriate to offer DNA testing to all such patients e.g. those with weak/no family history or clinical signs, those with no potentially affected relatives or phenotype consistent with an alternative diagnosis.	Thank you for your comment. The topic expert group felt it was important to offer DNA testing to all people with FH to confirm the diagnosis. It will be for the person with FH and the clinician to decide jointly if it is appropriate.

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58	North Trent Network of Cardiac Care	QS 2	Concern was expressed about the lack of specific mention or focus on counselling or joint decision making and patient choice. It was felt that DNA testing has significant implications for the patient and the family. Positive results have an impact in relation to getting insurance, mortgages, life / critical illness insurance etc. etc. People need to understand the full implications of going down that road. Needs to be included in the definition.	Thank you for your comment. Quality statements focus on one concept only and the topic expert group felt it was important to ensure DNA testing was offered. The topic expert group recognised the importance of shared decision making and informed consent and decided to add an additional measure and refer to the UK genetic testing network standard to address this area.
59	RCN	QS 2	DNA testing should be offered to those who fit Simon Broome (SB) criteria of Familial Hypercholesterolaemia (FH). Currently this does not routinely happen, (within Wales) based on SB clinical criteria but using a modified Dutch genotyping scoring system with a much higher LDL concentration required for those without premature CVD, to access genetic testing.	Thank you for your comment. The expectation is that quality statements and measures will be used and adapted locally.
60	Sanofi	QS 2	While we welcome the focus on the early diagnosis of FH and treatment of children in the Quality Standard, we believe that DNA testing is not vital, as FH can be diagnosed and confirmed via clinical factors. Evidence shows that variation in the genetic presentation means that some patients will be FH positive even without a positive genetic confirmation. We would also recommend the inclusion of a requirement to ensure that children have a managed transition to an appropriate adult service to support their ongoing clinical needs.	Thank you for your comment. The topic expert group felt it was important to offer DNA testing to all people with FH to confirm the diagnosis where possible and recognised some people with FH may not have a DNA mutation. Please see the NICE quality standards library of topics which includes a standard planned for the transition between children and adult services.
61	Sheffield Teaching Hospital NHS Trust	QS 2	People with a clinical diagnosis of familial hypercholesterolaemia (FH) are offered DNA testing by a specialist with expertise in FH. I think this should be made clear to avoid inappropriate referral for DNA testing by non-specialists.	Thank you for your comment. The statement has been revised to say the DNA testing should be part of a specialist assessment. The audience descriptors and definitions have been updated accordingly to indicate the DNA testing would be offered by a specialist.
62	Sheffield Teaching Hospital NHS Trust	QS 2	Number of those with a clinical diagnosis of FH who are offered DNA testing. Number with definite FH who have a DNA mutation identified. Number with possible FH who have a DNA mutation identified.	Thank you for your comment. The topic expert group felt the measures chosen were most reflective of the statement.
63	Sheffield Teaching	QS 2	**Commissioners** ensure they commission services that offer DNA testing	Thank you for your comment. Quality

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	Hospital NHS Trust		to people with a clinical diagnosis of FH and services that offer genetic counselling to people who are undergoing DNA testing for FH.	statements focus on one concept only and the topic expert group felt it was important to ensure DNA testing was offered. The topic expert group recognised the importance of counselling and informed consent and decided to add additional measure and refer to the UK genetic testing network standards to address this area.
64	ACB	QS 3	Lipid diagnostic tests should be avoided before 1 year of age, it would be reasonable to offer DNA testing from 2 to 10 years.	Thank you for your comment. The topic expert group agreed the development sources to be used and the guidance states that children at risk of FH should have diagnostic tests carried out by the age of 10 years or at the earliest opportunity with no lower age limit. It is not within the remit of the quality standard to review the guideline recommendations.
65	ACP	QS 3	The recommendation to test by 10 years, taken from CG71, may be out of date – there is much international debate regarding the age for testing, partly because lifestyle factors, especially smoking advice, have been found to be considerably more effective if changes are adopted *before* the age of 7 (Albert Weigman, personal communication), and as such 10 would be too late. If genetic cascading is available, many advocate testing as early as possible, eg with a buccal swab in infancy.	Thank you for your comment. The topic expert group agreed the development sources to be used and the guidance states that children at risk of FH should have diagnostic tests carried out by the age of 10 years or at the earliest opportunity with no lower age limit. It is not within the remit of the quality standard to review the guideline recommendations.
66	ACP	QS 3	See comments above; There is debate about the optimum age for lipid diagnostic tests, it is reasonable to offer DNA testing from birth.	Thank you for your comment. The topic expert group agreed the development sources to be used and the guidance states that children at risk of FH should have diagnostic tests carried out by the age of 10 years or at the earliest opportunity with no lower age limit. It is not within the remit of the quality standard to review the guideline recommendations.
67	BMA	QS 3	We agree that children at risk of familial hypercholesterolaemia should be	Thank you for your comment. A specialist

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			offered diagnostic testing, but the statement should specify that this should be done in a child focused/friendly service and that a specialist in treating children with familial hypercholesterolaemia must be commissioned.	with expertise in FH in children and young people and child focussed settings are included in the definitions.
68	Genzyme	QS 3	We welcome the focus on the early identification and treatment of children and the detection of relatives via cascade testing. We believe the identification of relatives with FH through cascade screening is important as this will improve patient outcomes and save NHS resources in the long term. Cascade screening was recommended in the 2008 NICE Guidelines but has been poorly implemented.	Thank you for your comment. The statements on identification and treatment of children and cascade testing have been progressed to the final quality standard.
69	Heart UK	QS 3	Lipid diagnostic tests should be avoided before 1 year of age, it would be reasonable to offer DNA testing from 2 to 10 years.	Thank you for your comment. The topic expert group agreed the development sources to be used and the guidance states that children at risk of FH should have diagnostic tests carried out by the age of 10 years or at the earliest opportunity with no lower age limit. It is not within the remit of the quality standard to review the guideline recommendations
70	Sanofi	QS 3	We welcome the focus on the early identification and treatment of children and the detection of relatives via cascade testing. We believe identification by cascade testing will improve patient outcomes and save NHS resources in the long term by improving the management of FH from an earlier age. Diagnosing and treating FH earlier would mean that treatment costs should stabilize and eventually reduce as improved management would lead to a reduction in elective and non-elective admissions for CV emergencies. Heart UK's FH report "Saving lives, saving families" highlights that "the greater the number of FH patients identified and treated, the greater the comparative and accrued health benefits and cost savings to the NHS".1 Cascade screening was recommended in the 2008 NICE Guidelines but has been poorly implemented.	Thank you for your comment. The statements on identification and treatment of children and cascade testing have been progressed to the final quality standard.
71	AstraZeneca UK Limited	QS 4	We would suggest including 'and genetic counselling' at the end of the proposed quality statement on cascade testing. To help identify the	Thank you for your comment. Quality statements focus on one concept only and

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			denominator ie the number of relatives of person with FH we would align our recommendation to that of the Heart UK's 'Saving Lives, Saving Families' report presented at the Parliamentary debate in February 2012 which recommended that a national patient register and database should be established to enable better cascade screening across the UK. This register should also include IT capacity to conduct the screening process. PASS Clinical is a clinical database with features which make it particularly useful for FH cascade testing programmes and has been adapted for use in Wales. PASS features the ability to help co-ordinate cascade testing at a national level. Families who are spread out over large geographical areas provide a challenge to health professionals carrying out FH cascade testing. Therefore the TEG may wish to provide further information regarding this software in the Quality Standard.	the topic expert group felt it was important to ensure cascade testing was offered. The topic expert group recognised the importance of counselling but felt that this would be addressed by the specialist services providing the testing.
72	BMA	QS 4	We agree that relatives of those with familial hypercholesterolaemia should be offered testing, but there is little information in the statement about how this should be organised, with no information about how to trace relatives. The statement should offer some suggestion of process and should make it clear that the process of tracing and testing should be organised by the specialist in secondary care.	Thank you for your comment. The topic expert group did not feel it was in the remit of the quality standard to be too prescriptive on how the service should be configured. Please see the support for commissioners document published alongside the quality standard for further information. The audience descriptors and definitions now make reference to specialists with expertise in FH offering cascade testing.
73	British Heart Foundation	QS 4	Our work, funded in conjunction with the Welsh Government, is a real life exemplar of the implementation of FH screening in practice. The BHF introduced a cascade screening programme in Wales. We are pleased to see the implementation of a nationwide cascade screening system and encourage NICE to continue to engage with our organisation on this.	Thank you for your comment.
74	British Hypertension Society	QS 4	Cascade testing for relatives, would be great, though there needs to be a big investment to make that happen too. There are a limited number of FH nurses in the country and they certainly couldn't cope with rolling this out.	Thank you for your comment. The topic expert group recognised the lack of available services and therefore felt it was an area for quality improvement.
75	Genzyme	QS 4	We welcome the focus on the early identification and treatment of children and the detection of relatives via cascade testing. We believe the identification of relatives with FH through cascade screening is important as this will improve patient outcomes and save	Thank you for your comment.

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			NHS resources in the long term. Cascade screening was recommended in the 2008 NICE Guidelines but has been poorly implemented.	
76	North Trent Network of Cardiac Care	QS 4	Concern was expressed that currently the system seemingly relies on the patient making contact with family members. It was strongly felt health professional should have a joint responsibly for contacting the family as well and that this should be included within the definition/statement.	Thank you for your comment. Each quality statement focusses on one key concept making the statements clear, concise and more easily measureable. The topic expert group felt the quality improvement area was to ensure relatives were offered cascade testing but did not feel it was in the remit to be too prescriptive on how this service should be configured. Please see the support for commissioners document published alongside the quality standard for further information.
77	RCN	QS 4	This draft standard states that relatives of people with a confirmed diagnosis of FH are offered cascade testing. Previously this was assessed on clinical grounds based on Simon Broome criteria for possible or definite FH. Within this statement access to cascade testing for family members would only include those with a definite Simon Broome diagnosis. Given the current low identification rates of genetic mutations in those tested with FH, including those with a definite diagnosis for cascade testing only, could invariably miss a high proportion of relatives who may well fit the Simon Broome criteria themselves and thus be at risk.	Thank you for your comment. The topic expert group agreed to limit the statement on cascade testing to a subset of the population where testing is most effective due to the lack of current services and the large resource implications. The topic expert group felt that once these services were available then it would be appropriate to extend the population to cover additional groups.
78	Roche Products	QS 4	Roche are highly supportive of this quality statement. As highlighted in the recently published Cardiovascular Disease Outcomes Strategy (DH, 2013) the processes for identifying inherited cardiac conditions need to improve. This statement and the proposed quality measures will ensure baseline data is available to assess the impact of future proposals.	Thank you for your comment.
79	Sanofi	QS 4	We welcome the focus on the early identification and treatment of children and the detection of relatives via cascade testing. We believe the identification of relatives with FH through cascade screening is important as this will improve patient outcomes and save NHS resources in the long term, as set out above. Cascade screening was recommended in the 2008 NICE Guidelines but has been poorly implemented.	Thank you for your comment.

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80	Sheffield Teaching Hospital NHS Trust	QS 4	Do you need a definition of “nationwide, systematic cascade process” i.e. should this include access to pedigree software?	Thank you for your comment. The topic expert group did not feel it was in the remit of the quality standard to be too prescriptive on how the service should be configured. Please see the support for commissioners document published alongside the quality standard for further information.
81	ACB	QS 5	Drug treatment in adults should be based on High intensity lipid lowering therapy. For the convenience of patients, >50 % reduction of non-HDL-cholesterol should be accepted as equivalent. Pre-treatment baseline LDL-C may not be available in a substantial proportion of previously diagnosed cases and the calculation will not be made and the cases discounted. Absolute LDL-C values <2.5 mmol/L (non-HDL-C <3.0) for primary prevention and 2.0 mmol/L (non-HDL-C <2.5) should be the targets for secondary prevention in patients with no baseline values. Those failing to achieve the targets should be referred/re-referred to a specialist.	Thank you for your comment. Quality standards are not expected to be used retrospectively therefore it is important that for people newly identified with FH baseline LDL-C concentration is recorded. The topic expert group agreed the development sources to be used and it is not within the scope of the QS to revisit these recommendations.
82	ACP	QS 5	There is now good evidence that established plaque will only regress when LDL –C concentrations of around 1.7 are achieved. There may be a case for advocating this where there is evidence of established CVD?	Thank you for your comment. The topic expert group agreed the development sources to be used and it is not within the scope of the QS to revisit these recommendations.
83	ACP	QS 5	See comments above; target LDL cholesterols for secondary prevention may need to be lower. Also complicated by the definition of ‘baseline levels’ – these are often ill-defined; but difficult to come up with an alternative.	Thank you for your comment. The topic expert group agreed the development sources to be used and it is not within the scope of the QS to revisit these recommendations.
84	Aegerion Pharmaceuticals Limited	QS 5	The draft quality statement 5 sets a standard of reducing LDL-C by 50%. Current guidelines stipulate that the mean LDL-C of patients with HoFH should be reduced to <6.5 mmol/l or by >65% from baseline,18 which nearly always necessitates the use of apheresis. Reducing LDL-C by 50% is an inappropriate standard for HoFH where the baseline levels are so high that even a 50% reduction leaves LDL-C levels post treatment that are associated with CVD progression and early death. A more appropriate target in this high risk group is <2.5mmol/l for high risk patients and <1.8mmol/l in very high risk patients. This is the target set	Thank you for your comment. The topic expert group recognised people with homozygous were a specific group who required special consideration however because of the low incidence of homozygous FH and the need for specialist care, the group agreed to exclude people with homozygous FH with the understanding that this group was still

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			within the ESC/EAS Guidelines for the management of dyslipidaemias produced by The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). 19 These targets are those recommended for the management of patients with HeFH. As the majority of HoFH patients have already had one CV event, most will fall into the latter category with a target LDL-C of <1.8mmol/l. The recent publication by Graesdal et al 20, in a cohort of 7 Norwegian patients, reported a LDL –C level at the time of diagnosis (untreated) of 18.2 [15.3–32.8] mmol/L. Patients were treated with regular once-weekly apheresis combined with the maximum-tolerable doses of a statin and ezetimibe which resulted in a substantially reduced LDL cholesterol to 5.1 [4.5–7.3] mmol/L pre-apheresis and 2.2 [1.3–2.8] mmol/L post-apheresis with a calculated interval mean LDL cholesterol was 4.2 [3.5–5.7] mmol/L. Hence a reduction of LDL-C from 18.2mmol/L to 4.2mmol/L or 77% was achieved. Despite this substantial achievement, 6 of the 7 patients had evidence of progression of their CVD whilst on therapy. This demonstrates the need for stricter targets in the management of patients with HoFH. Draft recommendations for the management of HoFH are currently being developed by the Task Force of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). We therefore recommend a more appropriate quality measurement in the standard for HoFH patients is the proportion of HoFH patients with LDL-C levels below 1.8mmol/l. This measure becomes more relevant with the introduction of medications which, when used in combination with other lipid lowering approaches, have the potential to reduce LDL-C levels below 1.8mmol/l.	covered by the guideline recommendations.
85	Aegerion Pharmaceuticals Limited	QS 5	Apheresis As statins have lower efficacy in HoFH, there is a need to manage the condition with additional therapies. The current standard of care includes apheresis as discussed in CG71 - Identification and management of familial hypercholesterolaemia. This quality standard does not include recommendations on apheresis. Apheresis is an extracorporeal process for removal of atherogenic LDL-C	Thank you for your comment. The topic expert group recognised people with homozygous were a specific group who required special consideration however because of the low incidence of homozygous FH and the need for specialist care, this area was not

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			and lipoprotein (a) (Lp(a)) particles from whole blood or plasma at weekly or bi-weekly intervals by adsorption, precipitation or differential filtration. The procedure commonly takes 3-4 hours per session. LDL-C levels rapidly rebound after an apheresis procedure and as such best criterion of long-term efficacy is the interval mean concentration between consecutive procedures.18 Current guidelines stipulate that the mean LDL-C of patients with HoFH should be reduced to <6.5 mmol/l or by >65% from baseline,18 which nearly always necessitates the use of apheresis. This is at odds with quality statement 5 which is therefore not relevant to HoFH. Currently, there are three main indications for undertaking long-term Lipoprotein apheresis: (1) Patients with homozygous familial hypercholesterolaemia (FH) whose serum cholesterol remains >9 mmol/l or decreases by < 50% despite treatment with high dose statin, plus ezetimibe and/or bile acid sequestrants and/or nicotinic acid-containing compounds.16 (2) Patients with heterozygous FH or other forms of severe hypercholesterolaemia and with progressive coronary heart disease (CHD) whose LDL cholesterol remains > 5 mmol/l or decreases by < 40% on maximally tolerable doses of combined drug therapy. (3) Patients with a raised level of Lp(a) (> 600 mg/l, measured with a Kringle IV- independent assay) (HyperLp(a)) and with progressive CHD despite treatment with maximally tolerable combined drug therapy.	progressed for statement development. The group agreed to exclude people with homozygous FH with the understanding that this group was still covered by the guideline recommendations.
86	AstraZeneca UK Limited	QS 5	High intensity statin is included in the guideline recommendations and the draft quality measure. We therefore request that low dose, high intensity statin be included in the proposed quality statement in line with CG71 recommendation and to ensure an appropriate tolerability profile and use of statins as the first choice lipid lowering agents.	Thank you for your comment. The aim of the statement is to focus on the outcome of treatment therefore the recommended lipid-modifying drug treatments have been included in the definitions.
87	AstraZeneca UK Limited	QS 5	We would recommend clarifying the proposed quality statement to read 'People above the age of ten years of age...' or there seems to be a gap for children aged above 10 years and below 18 years within the Quality Standard set.	Thank you for your comment. The aim of the statement is to focus on the outcome of treatment. The evidence from the guideline is for adults only and therefore cannot be extended to include children.
88	AstraZeneca UK Limited	QS 5	The statement supporting the use of nicotinic acid should be revisited especially in light of the recent HPS2-THRIVE and AIM-HIGH study and the withdraw of niacin/laropiprant across the EU.	Thank you for your comment. It is not within the remit of the quality standard to revisit the guideline recommendations.
89	Genzyme	QS 5	We fully support the inclusion of this statement.	Thank you for your comment. The topic

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			The important factor in the treatment of FH is to have diagnosed adults and children referred to an expert in lipid management and given the appropriate and effective treatment needed to reduce their LDL-C levels to 50% of baseline, as defined in NICE guidelines. However, we believe the most significant omission is that the Quality Standard does not make reference to the need to ensure those patients who remain at risk despite maximally tolerated treatment, and those with severe disease, (eg some HoFH), have access to mechanical interventions such as apheresis. We believe consideration should be given, within this statement, as to how this should be commissioned into the pathway in an equitable way as access to LDL-Apheresis services is currently fragmented. Appropriately aggressive management of LDL-C in primary care due to concerns with prescribing responsibility and costs associated with high cost more specialised treatments is a potential barrier to effective management.	expert group recognised people with homozygous were a specific group who required special consideration however because of the low incidence of homozygous FH and the need for specialist care, this area was not progressed for statement development. The group agreed to exclude people with homozygous FH with the understanding that this group was still covered by the guideline recommendations.
90	Heart UK	QS 5	Drug treatment in adults should be based on High intensity lipid lowering therapy. For the convenience of patients, >50 % reduction of non-HDL-cholesterol should be accepted as equivalent. Pre-treatment baseline LDL-C may not be available in a substantial proportion of previously diagnosed cases and the calculation will not be made and the cases discounted. Absolute LDL-C values <2.5 mmol/L (non-HDL-C <3.0) for primary prevention and 2.0 mmol/L (non-HDL-C <2.5) should be the targets for secondary prevention in patients with no baseline values. Those failing to achieve the targets should be referred/re-referred to a specialist.	Thank you for your comment. The topic expert group agreed the intent of the statement was to achieve the recommended reduction and additional information on the use of high-intensity statins has been added to the definitions as the means of reaching this target. Quality standards are not expected to be used retrospectively therefore it is important that for people newly identified with FH baseline LDL-C concentration is recorded. The topic expert group agreed the development sources to be used and it is not within the scope of the QS to revisit these recommendations.
91	MSD	QS 5	Draft quality statement 5: Drug treatment in adults: We agree with the importance and relevance of draft quality standard #5, which encourages the appropriate treatment of adults with FH, in order to achieve a recommended reduction in LDL-C concentration of greater than 50% from baseline.	Thank you for your comment. The 1-year timeframe has been retained in the final quality standard.

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			We notice that the draft quality statement will provide a structure for measuring the number of adults with FH achieving an LDL-C reduction of >50% from baseline within 1-year (as specified by the 'outcome' within the Draft quality measure). MSD agree with the setting of a 1-year timeframe for the outcome measure in this quality statement, as this should serve to drive a more rapid reduction in patients' LDL-C levels.	
92	MSD	QS 5	In this section, eight recommendations from CG71 (Ref 1) are listed as the source clinical guideline references upon which draft quality statement #5 is based. Of these, recommendation 1.3.1.3 is specifically highlighted as a "key priority for implementation". This recommendation states that health care professionals (HCPs) should consider prescribing a high-intensity statin to achieve a recommended reduction in LDL-C concentration of greater than 50% from baseline. Whilst statins are recognised as the appropriate first line option for most patients, there are some for whom statin therapy is neither an appropriate nor adequate option to control serum total or LDL cholesterol concentrations. CG71 (Ref 1) provides recommendations on the appropriate use of ezetimibe (as monotherapy, or co-administered with initial statin) for such patients, based on the recommendations of NICE TA132 (Ref 2). The appropriate treatment option will be dependent on each individual patient's profile. MSD believes that all recommendations from CG71 should be treated with equal importance, and considers it inappropriate for the quality statement to list one specific recommendation as a "key priority for implementation" above other recommendations. We therefore suggest this text should be removed. Ref 1: NICE Clinical guideline 71 "Identification and management of familial hypercholesterolaemia" - August 2008. Available at: http://www.nice.org.uk/nicemedia/live/12048/41697/41697.pdf (accessed 25/03/13) Ref 2: NICE Technology Appraisal guidance 132: "Ezetimibe for the treatment of primary (heterozygous–familial and non-familial) hypercholesterolaemia"– November 2007. Available at	Thank you for your comment. The source guidance references the guideline recommendations and highlights those which were identified as a key priority for implementation (KPI) during guideline development. It is not within the remit of the quality standard to revisit the KPIs in the guidance.

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			http://www.nice.org.uk/nicemedia/live/11886/38799/38799.pdf (accessed 25/03/13)	
93	North Trent Network of Cardiac Care	QS 5	Concern was expressed that GPs would attempt to treat/manage raised cholesterol themselves without specialist input /support. Whilst this wasn't viewed as a particular negative it was felt that frequent reviews and the need for aggressive reduction of cholesterol was critical. Again a lack of confidence was expressed about a GPs ability to do this in a timely way and a collective opinion expressed that GPs tended to adopt a wait and see approach that would be particularly unhelpful with this cohort of people. The group felt that clear guidelines around acceptable wait and see timelines and acceptable cholesterol reduction was needed to be written into the statement/definitions along with meaningful acceptable lower cholesterol limit. It was felt that an automatic referral should be triggered for people with cholesterol that is resisting reduction and falling outside of an acceptable wait and see period.	Thank you for your comment. The topic expert group recognised the importance of treatment being delivered by an appropriately trained healthcare professional and have updated the definitions to indicate this statement should be provided by either a specialist with expertise in FH or a GP through a shared care arrangement.
94	RCN	QS 5	There needs to be some reference to lipoprotein apheresis in the standards as it is included in the Familial Hypercholesterolaemia NICE guideline and is very under used in the UK. Perhaps it could be added into Statement 5 under what to do if it is not possible to reduce the LDL by >50% from baseline.	Thank you for your comment. The topic expert group recognised people with homozygous were a specific group who required special consideration however because of the low incidence of homozygous FH and the need for specialist care, this area was not progressed for statement development. The group agreed to exclude people with homozygous FH with the understanding that this group was still covered by the guideline recommendations.
95	Roche Products	QS 5	Roche welcomes the inclusion of this quality statement as international and NICE guidelines recognise the importance of treating to an agreed target in patients with FH. Mirroring NICE guidance, the National Lipid Association highlights that long-term reduction in LDL cholesterol of >50% essentially normalises the adverse consequences of FH to the level of the general population and therefore should be the initial goal of therapy in all adult FH patients. However, the general population still has significant cardiovascular risk and intensification of therapy in FH may be justified	Thank you for your comment. Each quality statement focusses on one key concept making the statements clear, concise and more easily measurable. The topic expert group felt the quality improvement area was on the outcome of treatment.

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			(Robinson JG and Goldberg AC. Journal of Clinical Lipidology (2011) 5, S18-29). As such, the proposed statement would be aspirational if it reflected current ESC/EAS Guidelines for the management of dyslipidaemias (Reiner Z et al., European Heart Journal (2011) 32: 1769–1818): "the recommended treatment is aimed at reaching the LDL-C goals for high risk subjects (<2.5 mmol/L, less than ~ 100 mg/dL) or in the presence of CVD of very high risk subjects (<1.8 mmol/L, less than ~ 70 mg/dL); if targets cannot be reached, maximal reduction of LDL-C should be considered using appropriate drug combinations in tolerated doses." We recognise the difficulty in achieving such levels in individual patients but believe that the addition of novel approaches, if shown to have a favourable efficacy and safety profile with long-term use, will significantly improve the achievement of LDL-C goals in most high risk patients (Alonso et al., Expert Rev. Cardiovasc. Ther. (2013) 11(3), 327–342). In addition, the statement does not include an indication of when or how often response should be assessed. ESC/EAS guidelines suggest 8 (+/- 4) weeks after starting drug treatment and 8 (+/- 4) after adjustments to treatment until within the target range. Recommended modification: Adults with familial hypercholesterolaemia (FH) receive lipid-modifying drug treatment to ~~reduce~~ achieve a maximal reduction of LDL-C but at least a 50% reduction from baseline LDL-C using appropriate drug combinations in tolerated doses reviewed at no less than 12 weekly intervals after treatment modification ~~LDL-C concentration by more than 50% from baseline~~.	
96	Roche Products	QS 5	To reflect the newly proposed quality statement, the following modifications are suggested: **Structure**: Evidence of local arrangements to ensure adults with FH receive lipid-modifying drug treatment to ~~reduce LDL-C concentration by more than 50% from baseline~~ achieve a maximal reduction of LDL-C but at least a 50% reduction from baseline LDL-C using appropriate drug combinations in tolerated doses reviewed at no less than 12 weekly intervals after treatment modification **Process:** The proportion of adults with FH receiving lipid-modifying drug	Thank you for your comment. Please see response to comment 95.

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			treatment reviewed by a specialist with expertise in FH at less than a 12 week interval after treatment modification **Numerator** – the number of people in the denominator reviewed by a specialist with expertise in FH less than 12 weeks after treatment initiation or modification **Denominator** – the number of adults with FH receiving lipid-modifying drug treatment **Outcome:** Number of adults with FH whose LDL-C concentration is reduced by more than 50% from baseline from baseline within 1 year Number of high-risk adults with FH whose LDL-C concentration is reduced to <2.5 mmol/L (less than ~ 100 mg/dL) within 1 year. Number of very high-risk adults with FH (in the presence of CVD) whose LDL-C concentration is reduced ~~by more than 50% from baseline~~ to <1.8 mmol/L (less than ~ 70 mg/dL) within 1 year.	
97	Sanofi	QS 5	We fully support the inclusion of this statement. The important factor in the treatment of FH is to have diagnosed adults and children referred to an expert in lipid management and given the appropriate and effective treatment needed to reduce their LDL-C levels to 50% of baseline, as defined in NICE guidelines. However, we believe the most significant omission is that the Quality Standard does not make reference to the need to ensure those patients who remain at risk despite maximally tolerated treatment and those with severe disease, (eg some HoFH), have access to mechanical interventions such as apheresis. Access to LDL-Apheresis services is currently fragmented. As part of this statement, we believe consideration should be given to how this should be commissioned into the pathway in an equitable way. 1 Heart UK, Saving lives, saving families' 2012, http://heartuk.org.uk/files/uploads/HUK_SavingLivesSavingFamilies_FHreport_Feb2012.pdf We also believe that concerns in primary care around prescribing	Thank you for your comment. The topic expert group recognised people with homozygous were a specific group who required special consideration however because of the low incidence of homozygous FH and the need for specialist care, this area was not progressed for statement development. The group agreed to exclude people with homozygous FH with the understanding that this group was still covered by the guideline recommendations.

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			responsibility and costs associated with more specialised treatments may prevent appropriately aggressive management of LDL-C. We believe this is a potential barrier to effective management and must be overcome.	
98	Sheffield Teaching Hospital NHS Trust	QS 5	Add: Women with FH should be advised that lipid-modifying drug treatment should not be taken during breastfeeding.	Thank you for your comment. The equality and diversity considerations have been updated to include women who are breastfeeding.
99	BMA	QS 6	We agree with this statement, but in addition to the setting being child focused, the treatment should be carried out by an expert in treating children with familial hypercholesterolemia.	Thank you for your comment. The quality statement states the assessment should be carried out by a specialist with expertise in FH in children and young people.
100	Genzyme	QS 6	We fully support the inclusion of this statement. The important factor in the treatment of FH is to have diagnosed adults and children referred to an expert in lipid management and given the appropriate and effective treatment needed to reduce their LDL-C levels to 50% of baseline, as defined in NICE guidelines.	Thank you for your comment. Statements on the treatment of adults and children were both progressed to the final quality standard.
101	RCPCH	QS 6	Draft quality measure b), is this really necessary? The decision to commence statins in children depends on many factors (such as family history and children's views on taking the medicine – many choose to wait until adulthood) and does not necessarily reflect quality of care. It is very important to discuss treatment with the families as reflected in measure a) and this should be the only quality measure.	Thank you for your comment. The quality statement has been updated and now refers to an assessment for lipid-modifying drug treatment. The measures have been amended accordingly.
102	Sanofi	QS 6	We fully support the inclusion of this statement. The important factor in the treatment of FH is to have diagnosed adults and children referred to an expert in lipid management and given the appropriate and effective treatment needed to reduce their LDL-C levels to 50% of baseline, as defined in NICE guidelines.	Thank you for your comment. Statements on the treatment of adults and children were both progressed to the final quality standard.
103	ACB	QS 7	Non-fasting lipid profile should be acceptable and non-HDL-C targets used instead. Weight and blood pressure should be measured in adults.	Thank you for your comment. The topic exert group agreed the development sources to be used and could therefore only include those components within the guideline.
104	ACP	QS 7	Non-fasting lipid profile should be acceptable, but it should also be stressed that the patients should be otherwise well, so that the measured lipid values are not influenced by any infection / inflammation within the previous 3 months. (alternatively a C-RP measurement could be	Thank you for your comment. The topic exert group agreed the development sources to be used and could therefore only include those components within the

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			undertaken)	guideline.
105	Aegerion Pharmaceuticals Limited	QS 7	Specialist Care Draft quality statement 7 states that people with FH are offered a structured review at least annually. We believe that this annual review should be conducted by a specialist with expertise in FH, as covered by draft quality statement 1. This is even more important for patients with HoFH, given the severity of the disease and the incidence of major cardiovascular events. We therefore propose that draft quality statement 7 should we revised to "People with familial hypercholesterolemia (FH) are offered a structured review, at least annually, by a specialist with expertise in FH".	Thank you for your comment. The topic expert group felt the review could be carried out by either a specialist or in primary care where this was appropriate and therefore did not feel they could stipulate who conducted the review in the quality statement.
106	AstraZeneca UK Limited	QS 7	We would recommend the withdrawing of quality standard 7 as advice on the risks of smoking should be covered under quality standard 8 as part of the annual review.	Thank you for your comment. Assessing smoking status, and offering advice and information on smoking cessation services is included as a component of the annual review.
107	BMA	QS 7	It must be made clear in the statement that it should be the specialist who carries out the annual review.	Thank you for your comment. The topic expert group felt the review could be carried out by either a specialist or in primary care where this was appropriate and therefore did not feel they could stipulate who conducted the review in the quality statement.
108	Genzyme	QS 7	We fully support this statement. We believe an annual review of progress toward target LDL-C level reduction is necessary to ensure effectiveness of intervention being used. In the absence of cardiovascular (CV) event reduction data, this is the surrogate marker of success. We would also recommend the introduction of a national register to record the incidence of CV events in patients with FH to help quantify the impact of the standard on CV outcomes.	Thank you for your comment. It is not within the remit of the quality standard to suggest the use of a national register.
109	Heart UK	QS 7	Non-fasting lipid profile should be acceptable and non-HDL-C targets used instead. Weight and blood pressure should be measured in adults.	Thank you for your comment. The topic exert group agreed the development sources to be used and could therefore only include those components within the guideline.

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110	North Trent Network of Cardiac Care	QS 7	The inclusion of the lifestyle elements as part of the review was particularly welcomed by the group but it was felt strongly that all of the ones included in the NICE guidance should be included in the definitions and not just be limited to mentioning smoking status. The particular lifestyle factors that impact on lipid levels should all be mentioned separately.	Thank you for your comment. The topic exert group agreed the development sources to be used and could therefore only include those components within the guideline.
111	RCN	QS 7	We welcome the recommended annual review. Further to quality statement 1 that recommends individuals with FH are referred to a specialist, this would usually be in lipid clinics in secondary care. Due to capacity issues of those with many differing dyslipidaemias attending lipid clinics, many FH patients are being discharged. If the follow up care of those with FH may potentially occur in primary care, should this not be reflected more specifically in the standard and qualify for specialist review if required and if so to be given by whom?	Thank you for your comment. The topic expert group felt the review could be carried out by either a specialist or in primary care where this was appropriate and therefore did not feel they could stipulate who conducted the review in the quality statement.
112	RCPCH	QS 7	Definition of structured review: "…..should include all of the following components" – this should be changed to "should include ~~all of~~ the following components as appropriate". E.g. contraceptive advice may not be appropriate for younger children.	Thank you for your comment. The definition wording has been updated to include 'where appropriate'.
113	Roche Products	QS 7	The quality statement would be clarified if it was consistent with QS 1 and 6. *People with familial hypercholesterolaemia (FH) are offered a structured review, with a healthcare professional with expertise in FH, at least annually.*	Thank you for your comment. The topic expert group felt the review could be carried out by either a specialist or in primary care where this was appropriate and therefore did not feel they could stipulate who conducted the review in the quality statement.
114	Roche Products	QS 7	The definition would be clearer if it included a statement to the effect that the annual review quality statement would be clarified if it was consistent with QS 1 and 6. *People with familial hypercholesterolaemia (FH) are offered a structured review, with a healthcare professional with expertise in FH, at least annually.*	Thank you for your comment. The topic expert group felt the review could be carried out by either a specialist or in primary care where this was appropriate and therefore did not feel they could stipulate who conducted the review in the quality statement.
115	Sanofi	QS 7	We fully support this statement. We believe an annual review of progress toward target LDL-C level reduction is necessary to ensure the patient is getting the optimum outcome possible and that the current intervention is the most appropriate choice for that patient.	Thank you for your comment. It is not within the remit of the quality standard to suggest the use of a national register.

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			In the absence of CV event reduction data, this is the surrogate marker of success. We would also recommend the introduction of a national register to record the incidence of CV events in patients with FH to help quantify the impact of the standard on CV outcomes.	
116	Sheffield Teaching Hospital NHS Trust	QS 7	Does this refer to patients with a clinical diagnosis of possible FH or just those with definite?	Thank you for your comment. The statement refers to anyone with a diagnosis of FH both possible and definite.
117	Sheffield Teaching Hospital NHS Trust	QS 7	People with familial hypercholesterolaemia (FH) are offered a structured review at least annually by a specialist with expertise in FH.	Thank you for your comment. The topic expert group felt the review could be carried out by either a specialist or in primary care where this was appropriate and therefore did not feel they could stipulate who conducted the review in the quality statement.
118	Sheffield Teaching Hospital NHS Trust	QS 7	Should also include: •Measurement of weight/BMI in adults •Assessment for any other CV risk factors e.g. hypertension, diabetes, rheumatoid arthritis •Measure fasting lipid profile, fasting glucose and ALT. (glucose 2 fold – 1. As additional CV risk 2. Association between long term use of statins and T2DM. ALT because normally on high dose statin and trials such as PROVE-IT have shown increased risk of raised ALT/hepatitis.)	Thank you for your comment. The topic expert group agreed the development sources to be used and could therefore only include those components within the guideline.

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