NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Centre for Clinical Practice – Surveillance Programme

Recommendation for Guidance Executive

Clinical guideline
CG71: Familial hypercholesterolaemia: the Identification and management of adults and children with familial hypercholesterolaemia

Publication date
August 2008

Previous review dates
August 2011
November 2014

Surveillance report for GE
June 2015

Surveillance recommendation
GE is asked to consider the proposal to update the following clinical questions in the guideline:

- In adults and children, what is the effectiveness of the following tests to diagnose familial hypercholesterolaemia (FH):
  - Biochemical assays?
  - Clinical signs and symptoms?
  - DNA testing?
  - Combinations and/or sequences of above?

  What is the effectiveness of DNA testing in all people (adults and children) who are suspected to have FH?

  What is the effectiveness of DNA testing for FH mutations among relatives of people with identified mutations for FH?

- What is the effectiveness (defined as case identification and cost-effectiveness secondarily) of the following strategies for identifying people with FH:
  - GP note searching using electronic data bases identifying patients with
    - i. history of early MI (<60 years) and Tcholesterol (TC) >7.5mmol/L
    - ii. family history of ischemic heart disease and hypercholesterolemia or;
  - Secondary care registers
    - iii. within coronary care units through identifying patients with history of early MI (<60 years) and Tcholesterol (TC) >7.5mmol/L or
    - iv. identification of patients through pathology registers with age <60 years and TC>9 mmol/L and LDL>5.5mmol/L or;
  - Cascade screening?

- What is the effectiveness in improving outcomes in individuals with FH of the following monotherapies:
  - Statins versus placebo

- Resins (bile acid sequestrants) versus placebo
- Niacin versus placebo
- Fibrates versus placebo
- Fish oils (omega 3 fatty oils) versus placebo
- Ezetimibe versus placebo)?

GE are asked to note that this 'yes to update' proposal will not be consulted on.

Key findings

			Potential impact on guidance	
			Yes	**No**
Evidence identified from literature search			✓	
Feedback from Guideline Development Group			✓	
Anti-discrimination and equalities considerations			✓	
Feedback from Triage Panel meeting			✓	
No update	**Partial update**	Standard update	Transfer to static list	Change review cycle
	✓			

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Surveillance review of CG71: Familial hypercholesterolaemia: the Identification and management of adults and children with familial hypercholesterolaemia

Recommendation for Guidance Executive

Background information

Guideline issue date: August 2008
3 year review: 2011 (no update)
6 year review: 2014 (no update)
Challenge to GE decision: 2015
NCC: National Clinical Guideline Centre

Outcome of three year surveillance review

1. CG71 previously underwent a surveillance review in 2011 when the review recommendation was that the guideline should not be considered for an update. Through the 2011 surveillance review new evidence was identified relating to diagnosis and identification strategies, pharmacological management and general treatment (diet). No new evidence was identified in these areas that would change the direction of current guideline recommendations.

Outcome of six year surveillance review

2. A literature search was conducted for systematic reviews published between 7th April 2011 (the end of the search period for the last surveillance review) and 9th October 2014 and relevant abstracts were assessed. Clinical feedback on the guideline was obtained from members of the GDG through a questionnaire.

3. A decision not to update the guideline was approved by GE in November 2014. However, in response to a challenge of the no to update decision by several GDG members in April 2015, a responsive review was undertaken to examine the new evidence and intelligence highlighted alongside the conclusions of the previous surveillance review conducted in 2014.

4. In June 2011, following a review of its policy on screening for adults with familial hypercholesterolaemia (FH), the UK National Screening Committee (NSC) determined that a systematic population screening programme for FH was not recommended. The NSC is currently in the process of reviewing this recommendation as part of the regular review cycle of all its policies. The review decision will be opened for consultation in July 2015 with the final publication date dependent on the outcome of the consultation.

5. New evidence that may impact on recommendations was identified relating to the following areas within the guideline:

Clinical area 1: Diagnosis – *recommendations 1.1.3, 1.1.12-1.1.15, 1.2.1-1.2.5*		
Q: In adults and children, what is the effectiveness of the following tests to diagnose familial hypercholesterolaemia (FH): • Biochemical assays? • Clinical signs and symptoms? • DNA testing? • Combinations and/or sequences of above? What is the effectiveness of DNA testing in all people (adults and children) who are suspected to have FH? What is the effectiveness of DNA testing for FH mutations among relatives of people with identified mutations for FH?		
Evidence summary	**GDG/clinical perspective**	**Impact**
Evidence identified from 3-year surveillance review Through a high-level search one systematic review[1] relevant to the clinical question was identified. The study concluded that in patients with genetically confirmed FH, xanthomas were associated with an increased risk of cardiovascular disease. It was considered that the evidence was consistent with the current guideline recommendations. Evidence identified from 6-year surveillance review A Health Technology Assessment[2] was identified which assessed the diagnostic accuracy and cost-effectiveness of Elucigene FH20	Feedback from the GDG indicated that DNA diagnosis methodology has changed greatly since the guideline was published, with increased availability of Next Generation Sequencing which has resulted in a cost reduction in the sequencing of FH genes. Four studies relating to NGS	The GDG highlighted that there are variations in the implementation of genetic testing which is consistent with feedback provided by the GDG at the previous surveillance review. In light of the feedback provided at the previous surveillance review, NICE produced the document 'Familial hypercholesterolaemia: implementation advice information - Genetic testing recommendations' which provides advice on how to implement the recommendations on genetic cascade testing

and LIPOchip compared to comprehensive genetic analysis (CGA) for the diagnosis of FH. The review found that CGA generated the greatest QALY gain compared to Elucigene and LIPOchip. The study reports the author's findings which were presented in the diagnostics assessment report and the diagnostics assessment report addendum used as the source of evidence for the NICE diagnostics guidance [DG2] Elucigene FH20 and LIPOchip for the diagnosis of familial hypercholesterolaemia. Both the index tests included in DG2 are no longer commercially available therefore this guidance has been withdrawn.	were highlighted by the GDG which suggested it is an effective method for diagnosis of FH[3-6]. Another study was highlighted by the GDG which indicated that there has been a reduction in the overall costs of providing a FH service, including DNA testing and cascade screening, compared to the original costs that were estimated in CG71[7]. The GDG also highlighted that there remain inequalities in the provision of FH services across UK. In particular, there is inadequate access to genetic testing in England compared to the rest of the United Kingdom, despite evidence of its cost-effectiveness. Clinical feedback from the GDG suggested that the cut-offs for Total and LDL-C for identifying FH patients as outlined in the guideline are too low to be feasible in General Practice and that the evidence needs to be re-examined as to the most appropriate cut-off.	for FH in practice. The clinical feedback and evidence provided by the GDG at the 6-year surveillance review indicates that there is now increased availability of Next Generation Sequencing which has resulted in a cost reduction in the sequencing of FH genes. This new intelligence has the potential to impact on the current guideline recommendations relating to DNA testing which state that a diagnosis of FH should be made using the Simon Broome criteria, which include DNA testing in combination with family history, clinical signs and cholesterol concentration. DNA testing is also recommended in combination with LDL-C concentration measurement as part of a cascade testing service to identify affected relatives of those individuals with a clinical diagnosis of FH.

Clinical area 2: Identification strategies – *recommendations 1.2.1-1.2.9*		
Q: What is the effectiveness (defined as case identification and cost-effectiveness secondarily) of the following strategies for identifying people with FH: • GP note searching using electronic data bases identifying patients with i. history of early MI (<60 years) and Tcholesterol (TC) >7.5mmol/L ii. family history of ischemic heart disease and hypercholesterolemia or; • Secondary care registers i. within coronary care units through identifying patients with history of early MI (<60 years) and Tcholesterol (TC) >7.5mmol/L or ii. identification of patients through pathology registers with age <60 years and TC>9 mmol/L and LDL>5.5mmol/L or; • Cascade screening?		
Evidence summary	**GDG/clinical perspective**	**Impact**
<u>Evidence identified from 3-year surveillance review</u> No evidence identified. <u>Evidence identified from 6-year surveillance review</u> A systematic review (including 6 studies) on the cost-effectiveness of FH screening was identified. The review found that compared to no screening, cascade screening for new cases of FH was cost-effective [8].	GDG feedback indicated that there is new evidence which impacts on the cost effectiveness of a cascade testing service. In particular: • One study was identified which demonstrated that the expiry of the patent for atorvastatin, reduced costs of DNA testing, and providing more FH care in general practice has the potential to decrease the costs of providing a FH service by over 50% of the costs estimated by CG71[7]. • Another study was identified which showed that the prevalence of FH appears to be higher than commonly	The new evidence identified through the literature search is consistent with the guideline recommendation which states that healthcare professionals should use systematic methods (that is, cascade testing) for the identification of people with FH. However, the feedback and new evidence identified by the GDG indicates that there have been changes relating to the cost effectiveness of cascade testing services which have the potential to impact on the economic model for cascade testing in the guideline and related guideline recommendations. Changes in the costs of delivering a cascade testing service may also impact on the implementation of recommendations which was raised as an issue by the GDG.

	perceived leading to underdiagnosis and undertreatment[9]; • A study was identified which showed that a high proportion of individuals with FH and no mutation are likely to have a polygenic rather than a monogenic cause, thus making cascade testing less effective in these families[10]. GDG feedback also highlighted a pilot study of child-parent screening for FH in children aged 1 or 2 years coming for immunisation. However, the abstract of the study reported no results[11]. Relating to this, an ongoing study was identified which will assess the concept of reverse cascade screening in infants at immunisation, with the parents of those with elevated LDL-C called in for testing. The study is likely to report in 2015. A study was identified by the GDG which suggested that a revised definition of severe FH is needed. The study adapted	

	the commonly used static LDL-C level of 8 mmol/L into an age and gender corrected percentile to identify patients with severe heterozygous FH[12]. Finally, a study was identified by the GDG evaluating a FH prediction model for detection of FH in primary care. The results of the study found that the model was effective in identifying individuals with greatest probability of having the condition[13].	
Clinical area 3: Management (pharmacological treatment) – *recommendations 1.3.1.1-1.3.1.32*		
Q. What is the effectiveness in improving outcomes in individuals with FH of the following monotherapies: • Statins versus placebo • Resins (bile acid sequestrants) versus placebo • Niacin versus placebo • Fibrates versus placebo • Fish oils (omega 3 fatty oils) versus placebo • Ezetimibe versus placebo)?		
Evidence summary	**GDG/clinical perspective**	**Impact**
Evidence identified from 3-year surveillance review Through a high-level search 21 studies relevant to the clinical question were identified. Adults Three studies[14-16] (a Health Technology Assessment and two systematic reviews) examined the use of ezetimibe for the	Clinical feedback was received regarding atorvastatin which has now come off patent, thereby reducing the cost of high intensity statin treatment. It was indicated that this reduction in price contributes to an overall	The evidence identified through the literature search at both the 3 year and 6 year surveillance reviews indicates that statin therapy is both safe and effective in improving outcomes in adults and children with FH. These findings are consistent with the current guideline recommendations relating to statin

treatment of adults with FH and found some evidence of its effectiveness at reducing low-density lipoprotein cholesterol (LDL-C) levels in patients. A further 5 studies[17-21] (3 RCTs, a systematic review and a pooled analysis) indicated that different types of statins were effective in improving outcomes in adults with FH. In addition, a cost effectiveness study[22] indicated that high-intensity statins are cost-effective for patients with FH between 20 and 59 years. Overall, it was considered that the identified evidence supported the existing guideline recommendations relating to the use of statins and ezetimibe monotherapy for the treatment of adults with FH. <u>Children</u> Twelve studies[23-34] (7 systematic reviews, 4 RCTs and 1 meta-analysis) were identified relating to the efficacy of different types of monotherapy for the treatment of paediatric patients with FH. In particular, the identified evidence indicated that statins and bile acid sequestrants were effective in reducing LDL-C levels. It was concluded that the new evidence was consistent with the current guideline recommendations relating to statin monotherapy for children and adolescents with FH and offering other lipid-modifying drug therapies to children and young people intolerant of statins. <u>Evidence identified from 6-year surveillance review</u> An updated systematic review and meta-analysis was identified which indicated that statin therapy leads to a greater decrease in common carotid artery intima-media thickness compared to placebo or usual care. Sub-group analysis showed significant effects of lovastatin and simvastatin, followed by pravastatin and rosuvastatin[35].	reduction in providing a cascade testing service for FH. GDG feedback also indicated that there is new evidence suggesting that there are no serious safety issues relating to statin therapy in children, and that earlier initiation of statins may be needed to prevent cardiovascular events later in life. The GDG highlighted that there will be a reduction in the price of ezetimibe to that of generic drugs in 2016. In addition, the results of the IMPROVE-IT CVD outcomes study with ezetimibe were due to be published in November 2014. However, these will be considered as part of the update to TA132, due for publication in 2016. The GDG highlighted 3 studies[37-39] relating to Evolocumab (an anti-PCSK-9 antibody therapy) for the treatment of FH. Evolocumab does not currently have marketing authorisation in the	treatment, in particular: • Statins should be the initial treatment for all adults with FH. • Lipid-modifying drug therapy for a child or young person with FH should usually be considered by the age of 10 years. • When the decision to initiate lipid-modifying drug therapy has been made in children and young people, statins should be the initial treatment. GDG feedback highlighted that the patent for atorvastatin has now expired and that atorvastatin has consequently reduced in price. The economic model developed for the guideline concluded that high intensity statins were cost-effective for all age groups if the cost of atorvastatin 80mg was assumed to be the same as that of generic simvastatin 80mg. Given that the price of atorvastatin has now reduced in price, this may impact on the current guideline recommendation which states: healthcare professionals should consider prescribing a high-intensity statin to achieve a recommended reduction in LDL-C concentration of greater than 50% from baseline. It was also highlighted that the cost of ezetimibe will reduce to that of generic drugs in 2016. However, this is covered by TA132 which is currently being reviewed to take

An update to a systematic review[36] which was considered at the previous surveillance review was identified. The findings of the review suggested that in the short term statins were effective in reducing LDL cholesterol concentration in children with FH and that there were no safety concerns.	UK but has been referred to NICE for a Technology Appraisal which is scheduled to be published in April 2016. In addition, the GDG highlighted that there is new evidence relating to the drug Lomitapide for the treatment of homozygous FH. However, the study did not meet the study type inclusion criteria for this clinical question which included RCTs only. Lomitapide is licensed as an adjunct to a low-fat diet and other lipid-lowering medicinal products with or without low density lipoprotein (LDL) apheresis in adult patients with homozygous FH and was included in scoping discussions as part of a MTA on 'Evolocumab, ezetimibe and lomitapide for treating homozygous familial hypercholesterolaemia'. However, following the consultation exercise and scoping workshop, it was decided that an appraisal of evolocumab, ezetimibe and lomitipide for treating	account of the recent findings of the IMPROVE-IT CVD outcomes study and is due for publication in 2016. A number of studies relating to Evolocumab were identified by the GDG. However, Evolocumab has been referred to NICE for a Technology Appraisal which is scheduled to be published in April 2016. Clinical feedback indicated that there are new treatment options available for homozygous FH, in particular Lomitapide which is licensed for use in this group. However, no studies which met the inclusion criteria for the clinical question were identified.

	homozygous FH is not appropriate and therefore a formal referral from the Department of Health was not sought. The GDG indicated that other new treatment options are available for homozygous FH, including apolipoprotein B synthesis inhibitors, although no further details were provided. Clinical feedback was received highlighting that ciprofibrates are no longer available. However, this should not impact on the guideline recommendations which do not specify the type of fibrates to be used. Feedback from one GDG member indicated that recommendations presented in the European Atherosclerosis Society consensus guideline suggest that the target LDL-C value in FH patients following treatment should be 2.5mmol/l, and in those with CHD 2mmol/l. These are lower than the 50% baseline reduction in LDL-C as recommended in CG71.	

Ongoing research

6. The following ongoing research was highlighted by the GDG:
    - IMPROVE-IT CVD outcomes study with Ezetimibe is due in 11/2014 [being considered as part of the update to TA132].
    - Ongoing trials relating to anti-PCSK-9 antibody therapies for FH which are due for release in 2016 although it is unlikely that there will be any evidence supporting their use as safe and effective drugs until 2017 [no details provided].
    - Two large studies on the utility of carrying out FH case finding in general practice will be published shortly [no details provided].
    - A study funded by the MRC on Child-parent Cascade Testing is likely to report in 2015 [no details provided].
    - A Health Technology Assessment has been proposed to examine total cholesterol cut-offs for FH using The Health Survey for England Time Series Dataset and the QRESEARCH large consolidated database [no further details provided].

Anti-discrimination and equalities considerations

7. The GDG highlighted that there are inequalities in terms of access to FH services, particularly relating to the provision of genetic testing which is considered to be poor in England compared to the rest of the United Kingdom. This issue was also highlighted by the GDG at the previous surveillance review. In light of this feedback, NICE produced the document 'Familial hypercholesterolaemia: implementation advice information - Genetic testing recommendations' which provides advice on how to implement the recommendations on genetic cascade testing for FH in practice.

Implications for other NICE programmes

8. This guideline relates to a published quality standard for Familial hypercholesterolaemia (QS41, published August 2013).

9. None of the quality statements are likely to be affected by the proposed areas for update.

Triage panel recommendation

10. The new evidence that may potentially impact on guideline recommendations was considered by the Triage Panel.

    i. ***In adults and children, what is the effectiveness of the following tests to diagnose FH:***
        - ***Biochemical assays?***
        - ***Clinical signs and symptoms?***
        - ***DNA testing?***
        - ***Combinations and/or sequences of above?***

What is the effectiveness of DNA testing in all people (adults and children) who are suspected to have FH?
What is the effectiveness of DNA testing for FH mutations among relatives of people with identified mutations for FH?

The Triage Panel discussed DNA testing and the increased availability of next generation DNA sequencing which can be done more quickly and effectively. However, the Panel were not sure whether the recommendations would change as a result of the new technology and therefore whether an update in this area was needed. The Panel also agreed that there are inequalities in terms of provision of DNA testing although felt that this was more of an implementation issue. It was agreed that further work was needed to re-examine the cut-off levels for Total and LDL-C for diagnosis of FH recommended in the guideline. Updating this question was not considered to be urgent.

a. **Decision:** NICE to update this clinical question.

ii. ***What is the effectiveness (defined as case identification and cost-effectiveness secondarily) of the following strategies for identifying people with FH:***
- ***GP note searching using electronic data bases identifying patients with***
  - ***i. history of early MI (<60 years) and Tcholesterol (TC) >7.5mmol/L***
  - ***ii. family history of ischemic heart disease and hypercholesterolemia or;***
- ***Secondary care registers***
  - ***iii. within coronary care units through identifying patients with history of early MI (<60 years) and Tcholesterol (TC) >7.5mmol/L or***
  - ***iv. identification of patients through pathology registers with age <60 years and TC>9 mmol/L and LDL>5.5mmol/L or;***
- ***Cascade screening?***

The Triage Panel agreed that this question needs to be updated to reflect new evidence which shows only do cascade testing where there is an identified mutation, changes in prevalence and atorvastatin now being off patent. It was felt that this question should be updated with more urgency than the other questions under consideration.

b. **Decision:** NICE to update this clinical question.

iii. ***What is the effectiveness in improving outcomes in individuals with FH of the following monotherapies:***
- ***Statins versus placebo***
- ***Resins (bile acid sequestrants) versus placebo***

- ***Niacin versus placebo***
- ***Fibrates versus placebo***
- ***Fish oils (omega 3 fatty oils) versus placebo***
- ***Ezetimibe versus placebo)?***

The Triage Panel agreed that the 50% LDL-C target reduction from treatment needs to be reviewed as well as individualised risk assessment in accordance with national guidelines. However, in light of the ongoing development of new drug treatments and forthcoming Technology Appraisals, it was agreed that updating this question was not as urgent as the question on identification strategies and that the timing of the update would require consideration and coordination in line with the timetable for the relevant technology appraisals.

c. **Decision:** NICE to update this clinical question.

Conclusion

11. Through the surveillance review of CG71 new evidence which may potentially impact guideline recommendations was identified in the following areas:
    a. Diagnosis
    b. Identification strategies
    c. Management (pharmacological treatment)

12. All these areas were considered by the Triage Panel where it was decided that 3 questions require an update at this time.

13. The question relating to identification strategies was considered by the Triage Panel to need to be updated with more urgency than the other questions under consideration.

14. For all other areas of the guideline no evidence was identified that would impact on recommendations.

15. The UK National Screening Committee is currently in the process of reviewing its recommendation on screening for FH in adults as part of the regular review cycle of all its policies.

Mark Baker – Centre Director

Sarah Willett – Associate Director
Philip Alderson – Consultant Clinical Adviser
Emma McFarlane – Technical Advisor
Diana O'Rourke – Technical Analyst

Centre for Clinical Practice
June 2015

Appendix 1 Decision matrix

Surveillance and identification of triggers for updating CG71. The table below provides summaries of the evidence for key questions for which studies were identified.

Conclusion from previous surveillance	Summary of new evidence/intelligence	Clinical feedback from the GDG	Impact
71-01: In adults and children, what is the effectiveness of the following tests to diagnose FH: • **Biochemical assays?** • **Clinical signs and symptoms?** • **DNA testing?** • **Combinations and/or sequences of above?** **What is the effectiveness of DNA testing in all people (adults and children) who are suspected to have FH?** **What is the effectiveness of DNA testing for FH mutations among relatives of people with identified mutations for FH?**			
Through a high-level search one systematic review[1] relevant to the clinical question was identified. The study concluded that in patients with genetically confirmed FH, xanthomas were associated with an increased risk of cardiovascular disease. It was considered that the evidence was consistent with the current guideline recommendations.	A Health Technology Assessment[2] was identified which assessed the diagnostic accuracy and cost-effectiveness of Elucigene FH20 and LIPOchip compared to comprehensive genetic analysis (CGA) for the diagnosis of FH. The review found that CGA generated the greatest QALY gain compared to Elucigene and LIPOchip. The study reports the author's findings which were presented in the diagnostics assessment report and the diagnostics assessment report addendum used as the source of evidence for the NICE diagnostics guidance [DG2] Elucigene FH20 and LIPOchip for the diagnosis of familial hypercholesterolaemia.	Feedback from the GDG indicated that DNA diagnosis methodology has changed greatly since the guideline was published, with increased availability of Next Generation Sequencing (NGS) which has resulted in a cost reduction in the sequencing of FH genes. Four studies relating to NGS were highlighted by the GDG which suggested it is an effective method for diagnosis of FH[3-6]. Another study was highlighted by the GDG which indicated that there has been a reduction in the overall costs of providing a FH service, including	The GDG highlighted that there are variations in the implementation of genetic testing which is consistent with feedback provided by the GDG at the previous surveillance review. In light of the feedback provided at the previous surveillance review, NICE produced the document 'Familial hypercholesterolaemia: implementation advice information - Genetic testing recommendations' which provides advice on how to implement the recommendations on genetic cascade testing for FH in practice. The clinical feedback and evidence provided by the GDG at the 6-year surveillance review indicates that there is now increased availability of Next

Conclusion from previous surveillance	Summary of new evidence/intelligence	Clinical feedback from the GDG	Impact
	Both the index tests included in DG2 are no longer commercially available therefore this guidance has been withdrawn.	DNA testing and cascade screening, compared to the original costs that were estimated in CG71[7]. The GDG also highlighted that there remain inequalities in the provision of FH services across UK. In particular, there is inadequate access to genetic testing in England compared to the rest of the United Kingdom, despite evidence of its cost-effectiveness. Clinical feedback from the GDG suggested that the cut-offs for Total and LDL-C for identifying FH patients as outlined in the guideline are too low to be feasible in General Practice and that the evidence needs to be re-examined as to the most appropriate cut-off.	Generation Sequencing which has resulted in a cost reduction in the sequencing of FH genes. This new intelligence has the potential to impact on the current guideline recommendations relating to DNA testing which state that a diagnosis of FH should be made using the Simon Broome criteria, which include DNA testing in combination with family history, clinical signs cholesterol concentration. DNA testing is also recommended in combination with LDL-C concentration measurement as part of a cascade testing service to identify affected relatives of those individuals with a clinical diagnosis of FH.
71-02: What is the coronary heart disease (CHD) risk of people with suspected FH: • **who have a confirmed DNA mutation or** • **who do not have a confirmed DNA mutation?**			
No evidence identified.	No evidence identified.	A study was highlighted by the GDG[40] which found that the mean carotid IMT of individuals with a molecular diagnosis of FH and low LDL-C levels was	No impact. The new evidence highlighted by the GDG suggests an increased risk of CHD is linked to LDL-levels and not specifically to

Conclusion from previous surveillance	Summary of new evidence/intelligence	Clinical feedback from the GDG	Impact
		smaller than those with a molecular diagnosis of FH and high LDL-C levels, but not significantly different to those without FH.	the presence of a DNA mutation. This evidence is consistent with the current guideline which state that although DNA testing has a role in increasing the certainty of diagnosis, FH can be managed without the knowledge of DNA mutation; and the lack of an identified mutation does not mean that the individual is not at high risk. Therefore the decision to offer treatment should be informed by clinical assessment.
71-03: What is effectiveness (defined as case identification and cost-effectiveness secondarily) of the following strategies for identifying people with FH: • **GP note searching using electronic data bases identifying patients with** **i. history of early MI (<60 years) and Tcholesterol (TC) >7.5mmol/L** **ii. family history of ischemic heart disease and hypercholesterolemia or;** • **Secondary care registers** **i. within coronary care units through identifying patients with history of early MI (<60 years) and Tcholesterol (TC) >7.5mmol/L or** **ii. identification of patients through pathology registers with age <60 years and TC>9 mmol/L and LDL>5.5mmol/L or;** • **Cascade screening?**			
No evidence identified.	A systematic review (including 6 studies) on the cost-effectiveness of FH screening was identified. The review found that compared to no screening, cascade screening for new cases of FH was cost-effective[8].	GDG feedback indicated that there is new evidence which impacts on the cost effectiveness of a cascade testing service. In particular: • One study was identified which demonstrated that the expiry of the patent for atorvastatin, reduced costs of DNA testing, and providing more FH care in general practice has the	The new evidence identified through the literature search is consistent with the guideline recommendation which states that healthcare professionals should use systematic methods (that is, cascade testing) for the identification of people with FH. However, the feedback and new evidence identified by the GDG indicates that there have been changes relating to the cost effectiveness of cascade testing services

Conclusion from previous surveillance	Summary of new evidence/intelligence	Clinical feedback from the GDG	Impact
		potential to decrease the costs of providing a FH service by over 50% of the costs estimated by CG71[7]. • Another study was identified which showed that the prevalence of FH appears to be higher than commonly perceived leading to underdiagnosis and undertreatment[9]; • A study was identified which showed that a high proportion of individuals with FH and no mutation are likely to have a polygenic rather than a monogenic cause, thus making cascade testing less effective in these families[10]. GDG feedback also highlighted a pilot study of child-parent screening for FH in children aged 1 or 2 years coming for immunisation. However, the abstract of the study reported no results[11]. Relating to this, an ongoing study was identified which will assess the concept of reverse cascade screening in infants at immunisation, with the	which have the potential to impact on the economic model for cascade testing in the guideline and related guideline recommendations. Changes in the costs of delivering a cascade testing service may also impact on the implementation of recommendations which was raised as an issue by the GDG.

Conclusion from previous surveillance	Summary of new evidence/intelligence	Clinical feedback from the GDG	Impact
		parents of those with elevated LDL-C called in for testing. The study is likely to report in 2015. A study was identified by the GDG which suggested that a revised definition of severe FH is needed. The study adapted the commonly used static LDL-C level of 8 mmol/L into an age and gender corrected percentile to identify patients with severe heterozygous FH[12]. Finally, a study was identified by the GDG evaluating a FH prediction model for detection of FH in primary care. The results of the study found that the model was effective in identifying individuals with greatest probability of having the condition[13].	
71-04: What is the effectiveness in improving outcomes in individuals with FH of the following monotherapies: • **Statins versus placebo** • **Resins (bile acid sequestrants) versus placebo** • **Niacin versus placebo** • **Fibrates versus placebo** • **Fish oils (omega 3 fatty oils) versus placebo** • **Ezetimibe versus placebo)?**			
Through a high-level search 21 studies	An updated systematic review and	Clinical feedback was received	The evidence identified through the

Conclusion from previous surveillance	Summary of new evidence/intelligence	Clinical feedback from the GDG	Impact
relevant to the clinical question were identified. Adults Three studies[14-16] (a Health Technology Assessment and two systematic reviews) examined the use of ezetimibe for the treatment of adults with FH and found some evidence of its effectiveness at reducing low-density lipoprotein cholesterol (LDL-C) levels in patients. A further 5 studies[17-21] (3 RCTs, a systematic review and a pooled analysis) indicated that different types of statins were effective in improving outcomes in adults with FH. In addition, a cost effectiveness study[22] indicated that high-intensity statins are cost-effective for patients with FH between 20 and 59 years. Overall, it was considered that the identified evidence supported the existing guideline recommendations relating to the use of statins and ezetimibe monotherapy for the treatment of adults with FH. Children Twelve studies[23-34] (7 systematic reviews, 4 RCTs and 1 meta-analysis) were identified relating to the efficacy of different types of monotherapy for	meta-analysis was identified which indicated that statin therapy leads to a greater decrease in common carotid artery intima-media thickness compared to placebo or usual care. Sub-group analysis showed significant effects of lovastatin and simvastatin, followed by pravastatin and rosuvastatin[35]. An update to a systematic review[36] which was considered at the previous surveillance review was identified. The findings of the review suggested that in the short term statins were effective in reducing LDL cholesterol concentration in children with FH and that there were no safety concerns.	regarding atorvastatin which has now come off patent, thereby reducing the cost of high intensity statin treatment. It was indicated that this reduction in price contributes to an overall reduction in providing a cascade testing service for FH. GDG feedback also indicated that there is new evidence suggesting that there are no serious safety issues relating to statin therapy in children, and that earlier initiation of statins may be needed to prevent cardiovascular events later in life. The GDG highlighted that there will be a reduction in the price of ezetimibe to that of generic drugs in 2016. In addition, the results of the IMPROVE-IT CVD outcomes study with ezetimibe were due to be published in November 2014. However, these will be considered as part of the update to TA132, due for publication in 2016. The GDG highlighted 3	literature search at both the 3 year and 6 year surveillance reviews indicates that statin therapy is both safe and effective in improving outcomes in adults and children with FH. These findings are consistent with the current guideline recommendations relating to statin treatment, in particular: • Statins should be the initial treatment for all adults with FH. • Lipid-modifying drug therapy for a child or young person with FH should usually be considered by the age of 10 years. • When the decision to initiate lipid-modifying drug therapy has been made in children and young people, statins should be the initial treatment. GDG feedback highlighted that the patent for atorvastatin has now expired and that atorvastatin has consequently reduced in price. The economic model developed for the guideline concluded that high intensity statins were cost-effective for all age groups if the cost of atorvastatin 80mg was assumed to be the same as that of generic simvastatin 80mg. Given that the price of atorvastatin has now reduced in price, this may impact on the current guideline recommendation which states: healthcare professionals should consider

Conclusion from previous surveillance	Summary of new evidence/intelligence	Clinical feedback from the GDG	Impact
the treatment of paediatric patients with FH. In particular, the identified evidence indicated that statins and bile acid sequestrants were effective in reducing LDL-C levels. It was concluded that the new evidence was consistent with the current guideline recommendations relating to statin monotherapy for children and adolescents with FH and offering other lipid-modifying drug therapies to children and young people intolerant of statins.		studies[37-39] relating to Evolocumab (an anti-PCSK-9 antibody therapy) for the treatment of FH. Evolocumab does not currently have marketing authorisation in the UK but has been referred to NICE for a Technology Appraisal which is scheduled to be published in April 2016. In addition, the GDG highlighted that there is new evidence relating to the drug Lomitapide for the treatment of homozygous FH. However, the study did not meet the study type inclusion criteria for this clinical question which included RCTs only. Lomitapide is licensed as an adjunct to a low-fat diet and other lipid-lowering medicinal products with or without low density lipoprotein (LDL) apheresis in adult patients with homozygous FH and was included in scoping discussions as part of a MTA on 'Evolocumab, ezetimibe and lomitapide for treating homozygous familial hypercholesterolaemia'.	prescribing a high-intensity statin to achieve a recommended reduction in LDL-C concentration of greater than 50% from baseline. It was also highlighted that the cost of ezetimibe will reduce to that of generic drugs in 2016. However, this is covered by TA132 which is currently being reviewed to take account of the recent findings of the IMPROVE-IT CVD outcomes study and is due for publication in 2016. A number of studies relating to Evolocumab were identified by the GDG. However, Evolocumab has been referred to NICE for a Technology Appraisal which is scheduled to be published in April 2016. Clinical feedback indicated that there are new treatment options available for homozygous FH, in particular Lomitapide which is licensed for use in this group. However, no studies which met the inclusion criteria for the clinical question were identified.

Conclusion from previous surveillance	Summary of new evidence/intelligence	Clinical feedback from the GDG	Impact
		However, following the consultation exercise and scoping workshop, it was decided that an appraisal of evolocumab, ezetimibe and lomitipide for treating homozygous FH is not appropriate and therefore a formal referral from the Department of Health was not sought. The GDG indicated that other new treatment options are available for homozygous FH, including apolipoprotein B synthesis inhibitors, although no further details were provided. Clinical feedback was received highlighting that ciprofibrates are no longer available. However, this should not impact on the guideline recommendations which do not specify the type of fibrates to be used. Feedback from one GDG member indicated that recommendations presented in the European Atherosclerosis Society consensus guideline suggest that the target LDL-C value in FH patients following	

Conclusion from previous surveillance	Summary of new evidence/intelligence	Clinical feedback from the GDG	Impact
		treatment should be 2.5mmol/l, and in those with CHD 2mmol/l. These are lower than the 50% baseline reduction in LDL-C as recommended in CG71.	
71-05: What is the effectiveness of adjunctive pharmacotherapy with statins in individuals with FH: • **Statins and resins** • **Statins and niacin** • **Statins and fibrates** • **Statins and fish oils** • **Statins and resins with nicotinic acid** • **Statins and ezetimibe?**			
Through a high-level search 4 studies relevant to the clinical question were identified. <u>Adults</u> Three RCTs[41-43] were identified which focused on the effectiveness of statin therapy in combination with bile acid sequestrant plus ezetimibe, ezetimbine plus niacin and ezetimbine alone. All the studies found that the treatments were effective in reducing LDL-C levels in adults with FH. <u>Children</u> The results of one RCT[44] indicated that in adolescents with heterozygous FH co-administration of ezetimibe with simvastatin provided higher LDL-C	No evidence identified.	None identified through GDG questionnaire	It was considered that the evidence identified at the 3 year surveillance review supported the evidence presented in the guideline which concluded that combination therapy in adults is superior to monotherapy in the treatment of FH individuals to lower LDL-C. In relation to combination therapy in children, it was considered that further evidence was required before this area could be considered for inclusion in the guideline. No new evidence was identified at the 6 year surveillance review.

Conclusion from previous surveillance	Summary of new evidence/intelligence	Clinical feedback from the GDG	Impact
reductions compared with simvastatin alone.			
71-06: What is the effectiveness of aggressive (maximal) cholesterol lowering in individuals with FH using pharmacological therapy?			
No evidence identified.	No evidence identified.	None identified through GDG questionnaire	No relevant evidence identified.
71-07: What information and support is required for: • **adults** • **children and young people** **being considered for diagnosis of FH?**			
No evidence identified.	No evidence identified.	None identified through GDG questionnaire	No relevant evidence identified.
71-08: What is the effectiveness of dietary interventions to improve outcome in: • **adults and children and young people with heterozygous or homozygous FH?** **What is the effectiveness of dietary interventions to improve outcome in the general population?**			
Through a high-level search two studies relevant to the clinical question were identified. One systematic review[45] was unable to make any conclusions about the effectiveness of a cholesterol-lowering diet or any of the other dietary interventions suggested for FH due to a lack of available evidence. The results of another study[46] (a randomised dietary intervention study) indicated that plasma sitosterol/cholesterol ratio was higher during plant sterol-rich dietary intervention periods than during the low plant sterols periods. However, it was considered that there was	An update to a systematic review[47] which was considered at the previous surveillance review was identified. The review reported that plant sterols are more effective than a cholesterol-lowering diet in terms of reducing total cholesterol levels and serum LDL cholesterol. However, due to a lack of data relating to the primary outcomes of incidence of heart disease, number of deaths and age at death, the authors concluded that there was no evidence for the effectiveness of a cholesterol-lowering diet for FH.	None identified through GDG questionnaire	Due to the limited evidence available about the effectiveness of cholesterol lowering diets in the FH population in the development of the guideline, evidence from the general population was used to derive recommendations. Evidence on the longer term use of stanols and sterols was also insufficient to enable the GDG to draw definitive conclusions regarding their effectiveness. The evidence identified at both the 3 year and 6 year reviews was consistent with the findings in the guideline, and is therefore unlikely to impact on the current recommendation which states: Healthcare

Conclusion from previous surveillance	Summary of new evidence/intelligence	Clinical feedback from the GDG	Impact
insufficient consistent evidence on the effectiveness of dietary interventions in improving outcomes in people with FH to recommend an update of the guideline at that the 3 year surveillance review.			professionals should advise people with FH that if they wish to consume food products containing stanols and sterols these need to be taken consistently to be effective.
71-09: What are the key components of assessment and review for: • **adults** • **children and young people** **with homozygous or heterozygous FH including the information and support required for individuals (adults and children) with FH regarding** **i. diet** **ii. exercise and/or regular physical activity** **iii. smoking cessation?**			
No evidence identified.	No evidence identified.	None identified through GDG questionnaire.	No relevant evidence identified.
71-10: What is the effectiveness of investigations to assess the degree of atherosclerosis to improve outcome in individuals with heterozygous FH? **i. Exercise ECG** **ii. Carotid IMT** **iii. Coronary calcium** **iv. Cardiac catheterisation** **v. Echocardiography** **vi. MRI** **vii. Electron beam CT** **viii. Coronary angiography** **ix. MR angiography** **x. Carotid Doppler** **xi. Doppler ultrasound** **xii. IVUS (intra-vascular ultrasound)** **xiii. Thallium scan** **xiv. Stress echocardiography**			
No evidence identified.	No evidence identified.	The GDG highlighted 4	The studies identified by the GDG related

Conclusion from previous surveillance	Summary of new evidence/intelligence	Clinical feedback from the GDG	Impact
		studies[48-51] relating to the role of imaging in the identification, screening and risk stratification of patients with FH e.g. computed tomography coronary angiography, CT calcium scoring, carotid ultrasound and magnetic resonance imaging. A cross-sectional analysis of an observational cohort study on the role of Lipoprotein(a) was also highlighted by the GDG. The findings suggested that high levels of Lipoprotein(a) are associated with increased risk of cardiovascular disease[52].	to different investigations for the assessment and monitoring of patients with FH. Further consistent evidence is needed before this area can be considered for an update.
71-11: What is the clinical and cost effectiveness of the following interventions to reduce LDL cholesterol and improve outcome in individuals with either heterozygous FH or homozygous FH: • **Apheresis alone versus no intervention/usual care** • **Apheresis and drug therapy versus drug therapy alone** • **Plasmapheresis & drug therapy versus drug therapy alone** • **Ileal bypass versus no intervention (heterozygote)** • **Apheresis versus plasmapheresis**			
No evidence identified.	No evidence identified.	None identified through GDG questionnaire	No relevant evidence identified.
71-12: What are the appropriate indications for: **i. Combined heart and liver transplantation or** **ii. Liver transplantation alone in homozygous FH?**			
No evidence identified.	No evidence identified.	None identified through GDG questionnaire	No relevant evidence identified.

Conclusion from previous surveillance	Summary of new evidence/intelligence	Clinical feedback from the GDG	Impact
71-13: What information/counselling should be provided to girls/women of child bearing potential with FH with respect to hormonal and other contraceptive methods?			
No evidence identified.	No evidence identified.	None identified through GDG questionnaire	No relevant evidence identified.
71-14: What information or care should be provided to: • **pregnant women or women considering pregnancy with FH with respect to:** **i. lipid modifying treatment use or** **ii. FH related complications around pregnancy/labour/delivery?** • **lactating women with FH with respect to:** **i. lipid modifying treatment use?**			
No evidence identified.	No evidence identified.	None identified through GDG questionnaire	No relevant evidence identified.
Research recommendations			
71RR-01: What is the clinical and cost effectiveness of identifying a person with FH (defined by DNA testing) from GP registers and from secondary care registers?			
Through a focused search two observational studies[53,54] relevant to the clinical question were identified. The studies focused on the identification of new cases of FH through computer and note-based searching in primary care and through national registers. However, it was considered that there was insufficient evidence to answer this research recommendation at this time.	No evidence identified.	GDG feedback indicated that two large studies on the utility of carrying out FH case finding in general practice will be published shortly although no further details were provided.	The evidence identified at the 3 year surveillance review was considered insufficient to answer the research recommendation. No new evidence was identified at the 6 year surveillance review, however, clinical feedback indicated that there is ongoing research in this area. This area will be evaluated again at the next surveillance review of the guideline.
71RR-02: What is the clinical effectiveness and safety of differing doses of lipid-modifying therapy in children with FH?			
Through a focused search one RCT[55] relevant to the clinical question was identified. The results of the study indicated that early initiation of statin	No evidence identified.	None identified through GDG questionnaire	The evidence identified at the 3 year surveillance review was considered insufficient to warrant an update of the guideline relating to the area suggested by

Conclusion from previous surveillance	Summary of new evidence/intelligence	Clinical feedback from the GDG	Impact
treatment in adolescents and young adults with FH delays the progression of carotid IMT.			the research recommendation. No new evidence was identified at the 6 year review which would impact on the research recommendation.
71RR-03: What are the appropriate indications, effectiveness and safety of LDL apheresis in people with heterozygous FH?			
No evidence identified.	No evidence identified.	None identified through GDG questionnaire	No relevant evidence identified.
71RR-04: What are the implications of FH for the safety of a mother during pregnancy and what are the risks of fetal malformations attributable to pharmacological therapies?			
No evidence identified.	No evidence identified.	None identified through GDG questionnaire	No relevant evidence identified.
71RR-05: What is the utility of routine cardiovascular evaluation for asymptomatic people with FH?			
No evidence identified.	No evidence identified.	None identified through GDG questionnaire	No relevant evidence identified.

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