UK National Screening Committee (UK NSC)

Note of the meeting held on the 26 February 2020

at

Park Plaza London Riverbank, 18 Albert Embankment, London, SE1 7TJ

This meeting provided recommendation on the following;

Fetal Maternal and Child Health Conditions:

- MPS I
- Familial Hypercholesterolaemia in children

Evidence Map outcomes on:

- 2018 Annual call submission for 22q11 Deletion Syndrome

Adult Conditions:

- Programme modification proposal in AAA- surveillance strategy

Members

Professor Bob Steele	Chair
Claire Bailey	Lead Clinical Nurse Specialist in breast screening, SW London
Professor Roger Brownsword	School of Law, Kings College London
Professor Louise Bryant	Associate Professor in Medical Psychology, University of Leeds
Eleanor Cozens	Patient and Public Voice (PPV)

Dr Paul Cross	Consultant Cellular Pathologist, Queen Elizabeth Hospital Gateshead Health NHS Foundation Trust
Professor Stephen Duffy	Director of the Policy Research Unit in Cancer Awareness, Screening and Early diagnosis and Professor of Cancer Screening, Centre for Cancer Prevention, Wolfson Institute of Preventive Medicine
Professor Gareth Evans	Consultant in Genetics Medicine, St Mary's Hospital, Manchester
Jane Fisher	Patient and Public Voice (PPV)
Professor Alastair Gray	Director at the Health Economics Research Centre, Nuffield Department of Population Health and Professor of Health Economics at the University of Oxford
Dr John Holden	Joint Head of Medical Division, Medical and Dental Defence Union of Scotland
Professor Chris Hyde	Public Health Specialist, University of Exeter
Dr Jim McMorran	GP, Coventry
Margaret Ann Powell	Patient and Public Voice
Dr Graham Shortland	Consultant Paediatrician, Cardiff and Vale University Health Board, Noah's Ark Children's Hospital for Wales (Vice-Chair)
Dr Anne- Marie Slowther	Reader in Ethics, University of Warwick

Observers;

Nimisha De Souza	Department of Health and Social Care, Screening Policy Team, Global and Public Health Group
Dr Heather Payne	Senior Medical Officer for Maternal and Child Health, Welsh Government
Dr Sue Payne	Scottish Government
Dr Carol Beattie	Northern Ireland

Professor Niall O'Higgins	Chair of the National Screening Advisory Committee, Ireland
Dr Alan Smith	Deputy CMO, Department of Health - Ireland

Invitees;

Mariejka Beauregard	Screening Fellowship
Dr David Elliman	Clinical lead for Newborn Infant Physical Examination and Newborn Blood Spot, PHE
Nick Hicks	National Co-ordinating Centre for HTA
Dr Ros Given – Wilson	Chair of the Adult Reference Group (ARG)
Dr Sharon Hillier	Chair of the Fetal Maternal and Child Health Group (FMCH)
Caroline Vass	PH Consultant
Akhtar Nasim	NHS AAA Screening Programme- Clinical lead

Secretariat

Professor Anne Mackie	Director of Programmes - UK National Screening Committee
John Marshall	UK NSC Evidence Lead
Dr Farah Seedat	UK NSC Evidence Review Manager
Silvia Lombardo	UK NSC Evidence Review Manager
Goda Kijauskaite	UK NSC Evidence Review Manager
Zeenat Mauthoor	Secretariat
Fabrice Lafronte	UK NSC Secretariat officer
Nick Johnstone- Waddell	Public and Professional Information lead

Apologies

Members:

Professor Alan Cameron	Consultant Obstetrician at Southern General Hospital, Glasgow
Dr Hilary Dobson	Consultant Radiologist and Deputy Director of the Innovative Healthcare Delivery Programme, University of Edinburgh
Hilary Goodman	Operational Manager of Antenatal Services/Screening at Hampshire Hospitals Foundation Trust

Apologies Observers:

Sam Cramond	NHS England and Improvement (NHSEI)

1. **Welcome and Introductions**

1.1. The Chair, Professor Steele, welcomed all to the meeting. An extended welcome was given to the standing observers from the Republic of Ireland, Prof Niall O'Higgins and Dr Alan Smith who joined the UK NSC. A round of introductions was initiated for the benefit of all invitees at the meeting.

1.2. Members were asked to provide an update on any new declarations of interest which may be relevant to this meeting. Now new conflicts were raised.

1.3. Apologies were noted from three members and the Chair confirmed that the meeting was quorate with 16 members in attendance.

2. **Minutes and Matters arising**

2.1 Carol Beattie requested for the wording under AOB to be revised and had since shared lines with Zeenat. The Committee approved the minutes from the 8 November meeting as being a true and accurate record of the meeting held. The minutes would now be published as final.

6 action points were identified from the November meeting with the following outcome

3a. Directors Update - Sir Mike Richard's Review

UK NSC to send comments/ observations on 'targeted screening' to Zeenat to collate- *this has now been superseded and no further action is needed*

3b. Directors Update- Genetic Alliance UK (GAUK) report on newborn blood spot conditions.

UK NSC secretariat to explore how better to explain population screening through a variety of channels- *the UK NSC has issued a response to the GAUK report*

3c. Directors Update- AAA Screening Intervals Strategy Update

A short public consultation to be opened to gather views on the proposal and cost effectiveness model which looks at altering the surveillance interval change in men from one to two years- *completed and this is on the agenda for a recommendation*

3d. Reflex DNA Testing Strategy for Trisomies- proposal

Prof Slowther to speak to UK NSC Secretariat about setting up an ethics workshop to discuss the areas of concern on reflex/ recall – *a workshop has been organised to take place in March*

4a. Adult Screening- Sudden Cardiac Death

Subsequent to ministerial decision on the recommendation for SCD, the UK NSC is to carefully communicate the outcome to stakeholders- *completed, a detailed 1 pager was issued and a meeting with the Charity is being set up.*

5a. Fetal Maternal and Child Health- Use of Pulse Ox

Subsequent to ministerial decision on the recommendation of Pulse Ox, UK NSC is to carefully communicate the outcome to stakeholders *in hand and a detailed 1 pager was issued and a meeting with the Charity is being set up.*

3. *Matters arising*

***Director's* Update**

Prof Mackie gave an update on the following

Genetic Alliance UK (GAUK) Report on newborn blood spot conditions

3.1 Following the publication of the GAUK Report, the UK NSC has since issued a response to DHSC to be shared with GAUK. Prof Mackie ran through the key areas addressed in the responding document and thanked those involved.

3.2 It was agreed that the response would be shared with the Committee.

3.3 Prof Mackie also informed the UK NSC that it was developing guidance in screening for blood spot conditions as a response to reoccurring queries. The aim of the guidance would be to outline what approaches may be taken to address common evidence gaps. This would then be shared with stakeholders once ready to get feedback.

Action 3a: Zeenat M to circulate the UK NSC's response to the GAUK report to the Committee

UK NSC Annual work plan for 2020/21

3.4 The Committee noted the proposed work due to be commissioned for 2020/21, as well as the ongoing work on evidence reviews for conditions from 2018/19 and 2019/20. The UK NSC would also be managing multiple programme modifications for the coming year. Key three yearly reviews to be covered but not limited to were: lung cancer, ovarian cancer, Cytomegalovirus(CMV), biliary atresia, iron deficiency in children, Human T-lymphotropic virus (HTLV), thrombophilia in all ages and vasa praevia. Additional workstreams which the UK NSC would be involved in also included but not limited to: pulse oximetry, screening for cardiac conditions associated with sudden cardiac death in the young, targeted screening, atrial fibrillation, bowel screening (FIT/bowelscope), cervical self-sampling, risk stratification, tyrosinaemia, ethics, genetic testing, artificial intelligence and asymptomatic bacteriuria.

Lung cancer- publication of the NELSON trial

3.5 The Committee noted that results from the NELSON randomised control trial had been published in the last week. The Chair reminded the group that the aim of the trial was to determine whether low volume computed CT screening reduces lung cancer mortality in male former and current smokers. The Chair said that the findings of the publication suggested that a significant reduction could be attained in such high risk groups. The UK NSC would be looking at the evidence base for lung cancer as part of its 2020/21 workstream and would be commissioning supplementary work to support this. Members who would like to be involved were asked to express their interest via email to Zeenat

Action 3b: UK NSC members wishing to be involved in the lung cancer review and supplementary work to email Zeenat to express interest

HBV and HCV Screening

3.6 The Chair informed the Committee that in December the UK NSC had received a submission from the UK NSC's registered stakeholder, Hepatitis B Positive Trust to review the evidence to screen for Hep B &C in migrant populations. This is an existing condition on the UK NSC's regular review list, but was overdue. The Chair informed the Committee that screening for a select group with specific characteristics fell outside the UK NSC's remit however it would propose this as a candidate for targeted screening. The Committee concurred with this proposal and agreed for the condition to be removed from the UK NSC's regular review cycle.

Action 3c: Hepatitis B and C among ethnic minorities to be removed for the UK NSC's list and decision to be shared with submitter.

Action 3d: Hepatitis B and C among ethnic minorities to be added to a potential list of targeted screening candidates

UK National Screening Committee

CMO Single Body Advisory Committee

3.7 The first recommendation from the Professor Sir Mike Richard's Review on adult screening programmes, to set up a new advisory body for both targeted and population screening was in development.

3.8 A working group had been established and was starting work to scope and set the terms of reference for the new body to capture targeted and population screening. The Chair informed the Committee that the first meeting had been well attended with suitable representation from various screening bodies.

2019 Annual Call for Topic Submissions

3.9 The UK NSC ran its fourth annual call for topics submission from the 5 September to 4 December in 2019 and received a total of five submissions.

3.10 The call for topics allows members of the public and stakeholders the opportunity to put forward potential conditions for population screening which the Committee has not considered before. An evaluation group then meets in January to review the proposals to see whether they meet the UK NSC's initial triage step of being within the remit of the UK NSC, being a population screening programme, and not having been previously considered. The group then verifies that there is a test, treatment and references in peer reviewed published literature to support the call to screen.

3.11 The evaluation group met in January to review the five submissions and proposed next steps. These were then shared with both reference groups who agreed with the steps outlined below for each five proposals:

i. Liver cirrhosis

The proposal calls to screen high risk groups of the condition using transient elastography. Liver cirrhosis is scaring of the liver caused by long term liver damage which then prevents the liver from working properly.

This can then lead to liver failure. Although there is no cure for cirrhosis it is possible to manage symptoms through lifestyle changes.

The evaluation group agreed that this proposal fell outside the UK NSC's remit as it relates to high risk groups. It was proposed that no further work should be conducted. The Committee agreed.

ii. Fetal presentation

The proposal is to screen all pregnant women for fetal presentation using a handheld ultrasound device during routine antenatal appointments at around 36 weeks of gestation. The aim would be to detect the position of the baby to see if baby is head-down (cephalic) rather than bottom or feet first (breech position) or lying sideways (transverse position). The aim of the programme would to detect those babies who were not head-down and to offer options to help manipulate the baby's position to become head-down or offer a planned caesarean delivery to minimise harm to mother and baby.

The evaluation group agreed that this proposal had not been considered before and fell within a defined whole population group. It was agreed that an evidence map would be commissioned to scope the volume and type of published peer reviewed evidence there is available on this condition. The UK NSC agreed to this approach

iii. Dyslexia

The proposals suggest that children of school age are screened for dyslexia.

The evaluation group agreed that it falls within the UK NSC's remit and had not been considered before. The group agreed that from a screening point of view the submission shows uncertainty as to whether a validated and reliable screening tool was available. The UK NSC noted the concerns raised and agreed that the secretariat would commission an evidence map on the test accuracy for a screening programme, before commissioning the evidence map to perform a scoping search on the question to see the appropriate age of testing.

In the final document it is important to have a narrative review on the condition (definition etc), the burden of the condition, possible (if there is evidence) connection between dyslexia and metal health and negative outcomes of screening/testing.

iv. <u>Pressure reducing carotid stenosis; vascular dementia; regional cerebral hypotension</u>

The proposal submitted looks to screen all seniors over the age of 50 using an adapted mobile phone which would measure and take specialised photographs of the face to identify low blood pressure in a portion of their brain.

The evaluation group agreed that this proposal meets the initial two-point criteria and that an evidence map should be commissioned. The UK NSC agreed with this approach

v. <u>5q spinal muscular atrophy</u>

The proposal calls for newborn screening for 5q spinal muscular atrophy (SMA).

The evaluation group agreed that the proposal did not meet the inclusion criteria for the annual call for new topics, as SMA screening in newborns is included in the list of condition that the UK NSC regularly reviews and it was part of the latest UK NSC review. However, it was agreed to consider this submission as an early update given the new evidence submitted by the stakeholder may have an impact on the UK NSC's 2018 recommendation to not offer antenatal or newborn screening for SMA.

The UK NSC evidence team assessed whether the new evidence would have an impact on the conclusions of the 2018 UK NSC evidence review and presented these conclusion to this meeting.
The proposal drew attention to developments relating to the treatment. The evidence presented by the NURTURE study showed promising results in relation to the efficacy of the drug nusinersen in asymptomatic individuals with SMA type I to II. However, it is important to note that these are preliminary results and the study is due to report its conclusion in 2025. The recent change in the NICE guidance on the use of nusinersen as a treatment option in 5q SMA in individuals with pre-symptomatic SMA, or SMA types 1, 2 or 3 is also a significant development and focuses attention on screening. However, the information provided in the proposal does not include new evidence in relation to other criteria that were not met in the 2018 review such as the screening test. Moreover, there are concerns on the cost-effectiveness of the treatment, for which an estimate is currently difficult because of the lack of evidence on the long-term benefits and the possibility of regression. Therefore, an early update would be unlikely to change the conclusion of the review overall.

3.12 It was agreed that the outcome of each proposal would be communicated to the submitter.

Action 3g: UK NSC secretariat to issue outcome letter on the five annual call for topic proposals and to commission evidence maps for the three agree conditions (fetal presentation, dyslexia and Pressure reducing carotid stenosis; vascular dementia; regional cerebral hypotension

3.3 Targeted Screening- Lynch Syndrome

3.13 NHSEI colleague, Dan Cariad presented the UK NSC with a confidential presentation on targeted screening for Lynch syndrome.

4. Adult Screening

ARG Report

4.1 Dr Given-Wilson provided the Committee with a summary of developments following the ARG meeting held in January. Two adult conditions were open for public consultation which included Bladder cancer (closes on 6 April) and Depression (closes on 24 May)

Human Papillomavirus (HPV) Modelling

4.2 The UK NSC plans to commission a mathematical model to see what screening strategies would be clinically and cost effective to offer populations who are vaccinated or in the vaccinated age groups. Dr Seedat shared a scoping review which was commissioned last year to help inform the scope and decision problem for the upcoming model.

4.3 Whilst this work is in development, the UK NSC upheld its recommendation that all women and people with a cervix aged 25 to 64 should be invited for screening every five years, even if they have been vaccinated.

Abdominal Aortic Aneurysm (AAA) Screening Interval Strategy- programme modification proposal

4.4 The Committee welcomed Mr. Akhtar Nasim, NHS AAA screening programme clinical lead to the meeting to discuss the post consultation comments received on the proposed modification to the current AAA screening surveillance intervals.

4.5 Mr Marshall provided a summary to the Committee which charted the development of the work thus far. In June 2019, the UK NSC received a proposal from the NHS AAA screening programme which sought to extend the screening intervals from 1 to 2 years in men with aneurysms measuring 3.0-3.9cms.

4.6 The UK NSC agreed that a HTA cost effectiveness model should be used to explore this proposal and found that such a move would accrue a saving of £300,000 over a 30 year cohort with a small life year loss of 1.2 years and 0.9 QALY loss. The Committee expressed concern at its meeting in November 2019 and noted that the current programme being highly cost effective was an important factor in the debate. A shortened consultation was opened to gain wider input whilst being mindful that NICE had delayed publication of its guidance on AAA. It was agreed that additional questions should be asked on the: model, opinions on the proposed extension of the surveillance intervals and any further comments.

4.7 After a 6-week consultation Mr Marshall informed the Committee that 11 stakeholders responded to the AAA consultation. Four agreed with the move to extend the screening interval whilst seven preferred the status quo, citing that there would be small monetary gain yet a small increase risk of rupture. The responses also acknowledged that the current programme was highly cost effective and highlighted uncertainty about the psychological impact of the modification on the men in the surveillance programme. The UK NSC reviewed the comments and given its uncertainty agreed that it would not recommend the programme modification to extend surveillance intervals in men with aneurysms measuring 3.0 to 3.9cms. Mr Marshall said that this would be fed back to NICE who had agreed to link into the final UK NSC recommendation. The Chair asked Mr Nasim if he had any comments.

Mr Nasim expressed his disappointment with the outcome and discussed the quality of the modelling and the accuracy of the cost inputs. It was noted that the underlying model used in the evaluation had been developed for an earlier HTA project and adapted for this project. It was accepted that more up to date costings might change the absolute value of the cost savings arising from the modification. But the time pressure on the project meant that it was not possible to up date these. Importantly, the pattern of the outcomes was logical and was consistent with the outcomes of an earlier model used by NICE. Both models suggested that the potential for efficiency gains from changes to the surveillance intervals were very limited. Research on the improvement of cardiovascular outcomes, the psychological impact of diagnosis and surveillance and on the natural history of AAA was starting up. The Committee agreed that this may provide a context for reconsideration of the surveillance intervals and thanked Mr Nasim for his understanding.

The UK NSC agreed that it would not recommend the programme modification to extend surveillance intervals in men with aneurysms measuring 3.0 to 3.9cms.

5 Fetal Maternal and Child Health

FMCH report

5.1 Dr Sharon Hillier provided the Committee with a brief summary of developments following the FMCH meeting in January. Only one FMCH condition was out for public consultation which was repeat screening for syphilis in pregnancy and is due to close on the 11 May. The UK NSC was also informed of ongoing work that was in development which included; programme modification proposal of newborn screening for beta-thalassaemia and cystic fibrosis new generation sequencing. The UK NSC noted that the 2018 annual call submission for carbon monoxide screening which led to an evidence map being commissioned did not justify further work and so would not be pursued.

Screening for Mucopolysaccharidosis type I (MPS I)

5.2 Silvia Lombardo presented this item to the Committee which was the second time the UK NSC had looked at it.

5.3 Mucopolysaccharidosis type I (MPS I) is a rare genetic disorder. People with MPS I have a faulty version of an enzyme called alpha-L-iduronidase. This enzyme breaks down certain sugars in the body. When the enzyme does not work as it should (like in people with MPS I), these sugars can build up, causing problems with children's physical and mental development. Hurler syndrome is the most severe form of MPS I whereas Hurler-Scheie and Scheie syndromes are the less severe forms of the condition.

5.4 The UK NSC first looked at screening for MPS I in 2014/15 and recommended that population screening for the condition should not be introduced because:

- there was not enough evidence that current tests are sufficiently reliable for use in screening
- there was not enough evidence that early treatments for MPS I would lead to better outcomes compared to current practice
- parents of MPS I babies had different views on whether screening should be introduced with some being concerned about the loss of a 'carefree' period in which they could bond with the child and in which a gradual awareness of the condition might facilitate acceptance of the diagnosis.

5.5 Based on these areas of uncertainty the 2019 evidence review focussed on two key questions:

i. What is the accuracy of commercially available screening tests in dried blood spots (DBS) to detect MPS I? (criterion 4)

ii. Does early initiation of treatment with haematopoietic stem cell transplantation (HSCT) and/ or enzyme replacement therapy (ERT) following screening provide better outcomes compared to usual clinical care? (criterion 9)

5.6 The Committee noted the findings of the evidence review which were that there is still not enough evidence to recommend population screening for MPS I. This is because there is insufficient evidence to support that newborn screening tests for MPS I in dried blood spots (DBS) using tandem mass spectrometry or fluorometric assays are sufficiently accurate to identify all babies with MPS I. Only four studies were identified but there was a lot of variation in regards to the screening test method used. This in turn increased the risk of bias and limited the reporting of test accuracy parameters. In addition, as stated in the evidence review, the UK NSC recognised that assessment of test accuracy parameters, such as sensitivity and specificity, is difficult to achieve in studies of screening for rare diseases and that additional studies with improved methodological consistency (in terms of index test cut-offs, repeat testing and the reference standard used) may be achievable and would allow for an informative evaluation of a putative test to be used in screening for MPS I in newborn babies.

5.7 Thirteen studies evaluated the relationship between age at initiation of haematopoietic stem cell transplantation (HSCT) or enzyme replacement therapy (ERT) and clinical outcomes for MPS I patients. The quality of the included studies was generally low, and the risk of bias was high. Although some studies indicated a statistically significant association, the effect was small. It is therefore unclear whether early diagnosis of MPS I would lead to a clinically significant improvement in patients' symptoms. Other studies did not demonstrate any effect of age of treatment initiation on clinical outcomes. Overall, there is insufficient evidence to determine whether early initiation of HSCT or ERT improves clinical outcomes for MPS I patients compared to current practice.

5.8 Following the UK NSC's 3-month public consultation two comments were received having directly contacted 21 stakeholders. Comments from the consultation supported the findings of the review. Dr Shortland expressed support with the recommendation and stated that he was aware that following the UK NSC's review that the clinical community was already working to collect better quality data.

The UK NSC agreed with the recommendation that, based on the evidence presented, the introduction of population screening for MPS I should not be recommended

Criteria (only include criteria included in the review)	Met/Not Met
Section 1 - Criteria for appraising the viability, effectiveness and appropriateness of a screening programme	
The Test	
4. There should be a simple, safe, precise and validated screening test.	**Not Met**
The Screening Programme	
9. There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care. Evidence relating to wider benefits of screening, for example those relating to family members, should be taken into account where available. However, where there is no prospect of benefit for the individual screened then the screening programme should not be further considered.	**Not Met**

Screening for Familial Hypercholesterolaemia in Children

5.9 The Chair introduced this item to the Committee and invited Dr Seedat to present the findings.

5.10 Familial hypercholesterolaemia (FH) is a hereditary condition that causes a person to have very high cholesterol (fat) in the blood. Bad cholesterol known as (low density lipoprotein (LDL)) then builds up in the blood vessels putting the person at risk of developing heart disease in their early adult life. The cholesterol build-up usually starts from childhood.

5.11 The aim of offering a population screening programme would be to offer children a blood test to see if they have inherited FH. This would lead to early diagnosis and early treatment to prevent the development of heart disease later in life. Treatment would

consist of a healthy diet combined with medication to help reduce cholesterol. The usual medications are called statins which are recommended to children with FH from 10 years of age.

5.12 The UK NSC noted that in Netherlands and Norway both countries offer cascade testing whilst Slovenia is the only country in Europe to have implemented universal childhood screening since 1995.

5.13 The UK NSC last looked at screening for FH in children in 2015/16 and recommended that screening should not be offered because:

- there were no studies that examined how well a population-wide screening test for children performed in practice
- there were no studies that assessed whether child screening reduces morbidity and mortality from FH
- there was little relevant evidence on the ethical issues and acceptability of universal child screening, including the management of the condition in screen-detected children.

5.14 As part of the UK NSC's three yearly review, the 2019 review focussed on the following three key questions:

- what are the optimum age and test cut-off values (total cholesterol [TC] and/or low-density lipoprotein cholesterol (LDL-C) concentration [mmol/l]) for screening children for FH? – addressing Criterion 5 (there should be a simple, safe and precise screening test)
- does universal screening for FH in children reduce FH-related morbidity and mortality in the screened individual? – addressing Criterion 11 (there should be evidence from high quality randomised controlled trials that the programme is effective in reducing morbidity and mortality)
- are there harms from universally screening children for FH? – addressing Criterion 13 (the benefit gained by individuals from the screening programme should outweigh any harms)

5.15 Dr Seedat informed the Committee that the 2019 evidence summary found that there was still not enough evidence to recommend population screening for FH in children as the criteria were not met. This is because;

- there is still uncertainty as to what the optimal screening age should be (1–2 years or 9–10 years). Two UK studies met inclusion criteria for this question. One large prospective screening pilot of children aged 1–2 years (10,000 in children) and one smaller retrospective study evaluating the test performance of the total cholesterol (TC) and LDL-C thresholds in children 9 years of age. The large prospective screening pilot found that half of the children with FH variants had a TC level below the cut off meaning that they would not be detected by this test, whilst almost a third that did not have the FH gene variants had 2 sequential cholesterol samples above the threshold (multifactorial/polygenic FH). There is some uncertainty over the natural history of multifactorial/polygenic FH and whether it is distinct from FH. Therefore, there is a need to understand how FH would be diagnosed in the context of a universal screening programme, whether the current diagnostic criteria of carriage of gene variants and/or positive family history indicative of FH is necessary or whether raised cholesterol alone is sufficient, given that the latter is the mediator of cardiovascular risk. In the retrospective study the best combination found for both sensitivity and specificity was when using the LDL-C cut-off (1.84 MoM) at 9 years. Screening at age 9–10 years could potentially give a better indication of whether FH variants are going to raise cholesterol/cardiovascular risk. This could also have the benefit of placing diagnosis at the time when treatment can be started. However, this was a very small study with only six cases, therefore it might not be generalisable to a large population and larger studies are required to confirm the findings.
- no evidence was found to inform whether universal screening affects FH-related morbidity or mortality compared with no screening. There was adequate evidence that statin treatment reduces LDL-C and TC levels at up to one year in children meeting diagnostic criteria for FH from age 9 – 10 years and that statin treatment is safe in this population in the short to medium term, up to 2.5 years. Despite the lack of direct

evidence that statins reduce FH-related morbidity in the longer term, they are expected to be beneficial for this group. By contrast, there is no evidence to inform whether starting lifelong statins is beneficial for children with multifactorial/polygenic FH identified by screening.

- there is no evidence to inform whether a universal screening programme may be associated with harms.

5.16 Only four comments were received following the UK NSC's three-month public consultation. Two comments from the consultation were supportive of the findings of the review whilst the other two raised concerns, suggesting that the Wald et al prospective study could address some of the uncertainties that review identified.

5.17 There were four main issues raised. The stakeholders disagreed with the evidence review conclusions that '*There is a remaining uncertainty in the evidence regarding consensus on the diagnostic criteria that should be used to definitively diagnose FH in children identified through universal screening*'. They suggest that cut-offs and screening policy are based on evidence, such as the Wald et al prospective screening cohort study, would identify children with the higher cholesterol levels who would be at risk of future cardiovascular disease, and therefore, would benefit from statin treatment. Such children would be eligible for treatment in accordance to the NICE clinical guideline (CG) 71 on the identification and management of FH.

5.18 Dr Seedat informed the Committee that the two included UK studies found that the TC cut-off had poor sensitivity for identifying children with FH as defined by carriage of an FH gene variant. Furthermore, the small retrospective study showing a promising LDL-C cut-off required further evaluation of its findings before this could be applied to a national population screening programme.

5.19 Secondly, the consultation responses give considerable emphasis to the fact that high cholesterol increases risk of atherosclerosis. Therefore, screening would identify children with the highest cholesterol levels who would be at future cardiovascular risk and would benefit from statin treatment, which have been demonstrated to be an effective and safe treatment. Dr Seedat clarified that the review did not dispute that

there was an association or that children who are diagnosed with FH should not have statin treatment (according with NICE guidance); however, uncertainty remains around the optimum age of screening, the test and cut offs.

5.20 The third point raised by stakeholders was that an RCT for the effectiveness of a screening programme for FH in children would be unethical and that statin use long term beyond two years had been already been proven at reducing risk of future morbidity/mortality in children with FH. The review found that the evidence to demonstrate this was limited and of a low quality. The review accepts that long-term RCTs of treatment vs no treatment in diagnosed FH would not be ethical. However, it may not rule out all RCTs. For example, evidence might be obtained by RCTs of screening (and treatment) vs no screening (and treatment). It also did not seem unreasonable to consider that follow-up of non-randomised comparative populations (for example in the FH register) might continue in the longer term.

5.21 The fourth contested point was around the statement that future studies were needed to ascertain public and professional views of FH screening. Stakeholders stated that the prospective Wald et al study covered this and found that the public and professional were accepting of this. For completeness, the review searched all included studies for information on the views of the public and healthcare professionals in relation to universal screening for FH in young children. However, only two studied were identified by the search that provided sufficient information for inclusion. These studies were small, gave inconclusive results particularly because the views on the care and potential treatment of their child were not explored, and it was unclear whether these views relate to child screening or parents' carriers screening. Stakeholders also suggested that a publication looking at perceptions and preferences of the general population concerning universal screening of FH in children had been missed by the review. Dr Seedat said that the publication fell outside the search date hence why it had not been included but the reviewers assessed this study and concluded that even if it had it been included it would not change the outcome and

recommendations of the review. This paper will be considered for inclusion in the next review.

5.21 The Committee queried the unethical point of an RCT, agreeing that treatment versus no treatment for diagnosed FH patients would be unethical, but that an RCT to explore a screening programme would not. Dr McMorran stated that in his experience using LDL-C, he has come to see that the test is given as an estimate rather than being measured which therefore makes it more difficult to identify people with high cholesterol as that method does not always work. In his experience of genetic testing in adults, Dr McMorran said that current tests do not include all potential gene variants, therefore, only a proportion of adults with FH (who have the included gene variants) are identified.

5.22 The Chair thanked the Committee for comments and agreed with the recommendation that;

The UK NSC does not recommend population screening for FH in children.

Criteria (only include criteria included in the review)	Met/Not Met
Section 1 - Criteria for appraising the viability, effectiveness and appropriateness of a screening programme	
The Test	
5. The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed	**Not Met**
The Screening Programme	

11. There should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an "informed choice" (such as Down's syndrome or cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.	**Not Met**
13. The benefit gained by individuals from the screening programme should outweigh any harms for example from over-diagnosis, overtreatment, false positives, false reassurance, uncertain findings and complications	**Not Met**

Updates

NIHR NETSCC Update (for information)

The Committee noted the updates

AOB

None noted