This minute will remain draft until ratified by the UK NSC at its next meeting

UK National Screening Committee (UK NSC)

Note of the meeting held on the 28 June 2019

in

Cardiff, Wales

This meeting provided recommendation on the following;

Fetal Maternal and Child Health Conditions:

- Screening to prevent Stillbirth
- Screening for Cystic Fibrosis in pregnancy
- Screening for Parvovirus B19 infection in pregnancy
- Screening for LCHAD in newborns
- Screening for vision defects in children

Adult Conditions:

- Screening for Atrial Fibrillation

Members

Professor Bob Steele	Chair

Claire Bailey	Lead Clinical Nurse Specialist in breast screening, SW London
Professor Alan Cameron	Consultant Obstetrician at Southern General Hospital, Glasgow (Skype from 11:40-12:30)
Eleanor Cozens	Patient and Public Voice (PPV)
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 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 and Executive Medical Director, Cardiff and Vale University Health Board, University Hospital for Wales

Observers;

Natasha Alleyne	Department of Health and Social Science Screening Team, Emergency Preparedness and Health Protection Policy Global and Public Health Group
Dr Heather Payne	Senior Medical Officer for Maternal and Child Health, Welsh Government
Sarah Manson	Scottish Government
Dr Sue Payne	Scottish Government
Dr Carol Beattie	Northern Ireland

Invitees;

Dr David Elliman	Clinical lead for Newborn Infant Physical Examination and Newborn Blood Spot, PHE
Dr Ros Given – Wilson	Chair of the Adult Reference Group (ARG)
Ardiana Gjini	Public Health Wales
Dr Sharon Hillier	Chair of the Fetal Maternal and Child Health Group (FMCH)
Akhtar Nasim	Clinical Lead, National AAA Screening Programme'.
Dr Alan Smith	CMO, National Screening Service Republic of Ireland
Lisa Summers	AAA Screening, National Programme Manager
Deborah Tomlinson	NHS England
Caroline Vass	Registrar in Public Health

Secretariat

Professor Anne Mackie	Director of Programmes - UK National Screening Committee
John Marshall	UK NSC Evidence Lead
Dr Cristina Visintin	UK NSC Evidence Review Manager
Silvia Lombardo	UK NSC Evidence Review Manager
Paula Coles	UK NSC Senior Information Scientist
Zeenat Mauthoor	Secretariat
Kelly Waldron	Screening Administration Support Officer
Jo Harcombe	National Lead for Stakeholder Information and Professional Education and Training

Apologies

Members:

Professor Roger Brownsword	School of Law, Kings College London
Dr Louise Bryant	Associate Professor in Medical Psychology, University of Leeds
Dr Hilary Dobson	Consultant Radiologist and Deputy Director of the Innovative Healthcare Delivery Programme, University of Edinburgh
Dr Paul Cross	Consultant Cellular Pathologist, Queen Elizabeth Hospital Gateshead Health NHS Foundation Trust

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
Hilary Goodman	Operational Manager of Antenatal Services/Screening at Hampshire Hospitals Foundation Trust
Dr John Holden	Joint Head of Medical Division, Medical and Dental Defence Union of Scotland
Dr Anne- Marie Slowther	Reader in Ethics, University of Warwick

1. Welcome and Introductions

1.1. Professor Steele welcomed all to the meeting. A round of introductions was initiated for the benefit of the invitees to the Committee meeting.

1.2. Members were asked to provide an update on any new declarations of interest which may be relevant to this meeting. No new conflicts were raised. Existing declarations around NIPT had been expressed previously by Alan Cameron and Jane Fisher, however the Chair felt that this was not pertinent to the planned discussion.

1.3. Apologies were noted, and the Chair confirmed that the meeting was quorate with 11 members in attendance.

2. Minutes and Matters arising

2.1. An amendment was requested to be made on the February 2019 minutes:

- Under item 6 on the Pulse Oximetry report, the wording should be changed to state that the UK NSC was looking at the use of PO as an additional test in the Newborn and Infant Screening programme rather than a screen for PO.

2.2. Minutes were approved as a true and accurate record of the meeting held. It was agreed that minutes of the February 2019 meeting should be published as final.

2.3. 11 action points were identified from the February meeting of which five had been completed and would be discussed at the meeting. The remaining actions outcomes were as follows:

4a. Screening for Breast Cancer (additional screening with ultrasound after a negative mammography in women with dense breasts)

Zeenat to contact CRUK re its study on breast risk and to invite to a future meeting to present findings – In hand and discussions were taking place as to how soon this can be facilitated.

4b. Cervical Screening: Programme modifications

John Marshall to set up a consensus group to discuss the screening pathway for recurrent HPV positive and cytology negative women and women exiting the programme- In hand

5. FMCH report

Genomic sequencing to be added to a future UK NSC meeting- Zeenat to confirm arrangements- arranged for the November UK NSC meeting

6a. Pulse Oximetry

A three month public consultation should be opened on using Pulse Ox as an additional test in the Newborn and Infant Screening Programme - public consultation closes on 9 August

6b. Screening for Permanent Hearing loss is children at school entry

Prof Mackie to update the UK NSC on the work in England on school entry hearing screening- work to be presented at an upcoming FMCH reference group and updates shared with the UK NSC once developed.

3. Matters arising

***Director's* Update**

Prof Mackie gave an update on the following

Update on Screening for Severe Combined Immunodeficiency (SCID)

3.1. In 2017 the UK NSC recommended the delivery of screening for SCID should be evaluated in an NHS setting. However following discussions with Joint Committee on Vaccinations and Immunisation (JCVI) a call for further modelling was needed to evaluate the interaction between screening and offer of the BCG vaccine. There was concern that if a baby with SCID is given a live vaccine such as the BCG this could complicate their treatment. It is suggested that the vaccine should be delayed until the SCID status is known. Currently in the UK two live vaccines are given to children as part of the infant vaccination programme; BCG to protect against tuberculosis (TB) and rotavirus, a highly infectious stomach bug.

3.2. Further modelling was therefore undertaken to re-examine the SCID model to consider the implications of delivering the BCG vaccination at a later point. The report indicated that should BCG vaccines be offered at a later point, once the t-cell status of the baby is confirmed, there would be harm from missed BCG vaccinations consequent on a fall in babies vaccinated as high coverage programmes move to the community where coverage will almost certainly be lower. However, on balance the benefit to babies with SCID remained larger than the disbenefit from BCG.

3.3. Although there was some variability around the country as to how the BCG vaccine is being delivered, around 60% is given in England in community settings, rather than in

the maternity units, whilst in the devolved nations the delivery of neonatal BCG is mostly hospital based. With a move to delay the vaccination schedule, both Committees recognised that this would require a significant shift of the programmes delivery and that it would be important to monitor the uptake. It was agreed that the FMCH group would be tasked to develop evaluation questions to share with the JCVI when undertaking the evaluation.

3.4. Based on further modelling the UK NSC recommended that the BCG and rotavirus vaccinations should be delayed whilst SCID screening is offered.

Action 3a: FMCH to develop questions for the evaluation of SCID and to share with JCVI

Independent Breast Review and Statement on the Upper age limit in breast screening

3.5. The Independent Breast screening review (2018) set out its key findings and recommendations which looked at the missed screens for some 70 year old women in the English breast screening programme. A key task which arose from the review was for the UK NSC to see whether there was any evidence that could usefully inform a discussion about the upper age for breast screening. The UK NSC reviewed the evidence presented at its February meeting and unanimously agreed that based on the work undertaken so far, there was no direct evidence which could inform a discussion on a more specific stopping age for the final invitation in the breast screening programme and awaits the outcome of the Age X trial.

3.6. It was recognised by the Committee that there was an absence of evidence to change the current practice of the upper age being between 70-71. A pragmatic approach was adopted. In England, Scotland and Northern Ireland. The final screen should be offered within 36 months of the 68th birthday. Wales would aim to offer the last screen by the 70th birthday due to existing operational structures.

Sir Mike Richards Review

3.7. The interim report was published mid May and it is anticipated that the full report would be published in the Autumn. The scope of the review had expanded so the terms of reference were being revised and an updated version should be made available online in due course.

3.8. The UK NSC noted that interim report focussed on the following items:

i. Governance and accountability
ii. Uptake/ coverage and informed choice
iii. Delays in implementation
iv. IT
v. KPIs
vi. Population screening v targeted screening
vii. Healthcheck
viii. Workforce
ix. Research access

Genomics Report

3.9. Caroline Vass presented this item to the Committee.

3.10. In 2016 the Chief Medical Officer (CMO) in England, Professor Dame Sally Davies published her report on 'Generation genome' which outlined the current state of genomic offered in the NHS in England and made recommendations on how genomics could be explored further. A key recommendation directed to the UK NSC was how it should explore the opportunities offered by genomics in screening.

3.11. In response the Secretariat had worked with clinical, academic and patient reps on the screening programme Advisory committees to scan the horizon for potential uses of genomic technology.

3.12. The UK NSC acknowledged the potential use for genomics and were interested in the possibilities that the new advances in genomics would bring to population screening. Members were also keen to see a more technical document reviewing the

issues relating to whole genome sequencing in asymptomatic, average risk populations. The Secretariat agreed to scope such a review.

Action 3b: Caroline Vass to make amendments on the breast, SCID and polygenic section and to include a digital mammogram picture.

Action 3c: UK NSC to comment on confidential genomic report and to send comments to Caroline Vass by 16 July.

Action 3d: Final Genomic report to be shared with CMOs and then published.

Ethics Task Group Update: NIPT and Reflex testing

3.13. John Marshall presented the Committee with a confidential paper which explored the ethical considerations relating to reflex testing.

3.14. Over the last few years the UK NSC and its reference group FMCH have been considering the proposal to look at "reflex testing" as an alternative to the "recall" approach to deliver NIPT in the fetal anomaly screening programme. These two approaches reflex and recall share a contingent approach to offering NIPT, but with two major differences. Firstly, reflex testing aims to remove the break point, which is where women are recalled to discuss next steps following the results of the combined test if it shows that the fetus has a 1/150 or greater chance of having a trisomy, and secondly that the test is offered to women with a threshold of ≥1 in 800 rather than the ≥1 in 150 as currently offered in the recall approach. The UK NSC recognised that support to consider reflex testing was based on the ability to improve test accuracy, reduce anxiety and improve resource efficiency from a service delivery point of view.

3.15. The UK NSC recommended that reflex testing should not be offered for a number of reasons but that further work should be undertaken. The circulated paper shared, in

confidence, with the Committee aims to summarise the ethical issues raised by reflex testing.

3.16. Discussion on the paper was had in confidence and would be discussed further with the UK NSC's FMCH reference group.

Action 3e: The ETG ethical consideration paper to be discussed at the September FMCH meeting

High Risk Screening

3.17. The Chair presented a confidential paper to the committee on population and high risk screening. Comments on the approach taken to screen for women at high risk of breast cancer were made and it was agreed that these would be incorporated into the paper.

3.18. Members of the Committee were asked to send comments on the internal paper to the Chair.

Action 3f: UK NSC members to send comments on the confidential high risk paper to the Chair by 16 July

4. **Adult Screening**

ARG Report

4.1 Dr Given-Wilson's, provided the Committee with a summary of developments following the ARG meeting held in May, which discussed key items such as the Sir Mike Richards Review, high risk screening and the AAA programme modification proposal.

4.2 One adult condition was out for public consultation

- Osteoporosis in post-menopausal women (due to close on the 2 August 2019)

Screening for Atrial Fibrillation (AF)

4.3 Atrial Fibrillation (AF) is a heart condition that causes an irregular and often a faster than normal heart rate. Typically, when the heart beats, its muscular walls contract to force blood out and around the body, they then relax so the heart can fill with blood again. This process is repeated every time the heart beats. However, in AF, the atria (heart's upper chambers) contract randomly and quickly so that the heart muscle does not get a chance to relax properly between contractions. This in turn reduces the heart's efficiency and performance. Atrial fibrillation can lead to an increased risk of stroke and death.

4.4 The UK NSC last looked at screening for AF in 2014 and recommended that screening should not be offered. This was because the review found that screening had the potential to do more good than harm. However, there was uncertainty around the risk of stroke in asymptomatic AF versus symptomatic AF. The review also raised as concerns that current clinical treatment pathways for AF had not been optimised and that, because of this, increasing the number of referrals through screening may be unethical.

4.5 The focus of the 2019 rapid review looked at six specific questions:

i. Is the risk of stroke similar between people with paroxysmal AF compared to people with persistent or permanent AF, or between people with asymptomatic compared to symptomatic AF?
ii. What is the benefit of treating screen-detected AF? Is there a benefit of formal screening programmes for AF over and above diagnosis of AF only through clinical practice?
iii. What is the reported accuracy of screening tests for all types of AF?
iv. Have randomised controlled trials (RCTs) demonstrated a benefit of screening for AF over and above diagnosis of AF only through clinical practice?
v. Is screening for AF in adults cost-effective?
vi. Is the current clinical pathway for AF optimised in terms of patient compliance and prescribing patterns for anticoagulants?

4.6 The criteria outcome for the 2019 review was a mixture of met, not met and uncertain. In particular, question 1 was found to be uncertain due to continuing inconsistencies and gaps in the evidence, particularly relating to paroxysmal and persistent AF. The review found that there was consistent evidence for both the number of stroke events and stroke risk being significantly higher in patients with permanent AF compared to paroxysmal AF. But, the evidence was less consistent between persistent and paroxysmal AF. A comment raised by Prof Hyde was that if the screening aim was to detect paroxysmal AF then this would not be practical because of its intermittent nature compared to persistent and permanent.

4.7 In regard to asymptomatic versus symptomatic AF the review found two studies reporting comparative data. One study demonstrated significantly more ischaemic stroke events in patients with asymptomatic AF compared to patients with symptomatic AF, but not for other types of stroke. Results for stroke risk were inconsistent, and both studies reported no significant differences for cardiovascular death. The Committee recognised that there was consistent evidence to suggest there were a range of options for a possible screening test but was concerned that with a lack of RCT evidence, the harms and benefits for the interventions had not been explored in a screen detected population and stated that this was vital when looking to introduce a national screening programme.

4.8 The Committee was made aware that the public consultation had closed the day before and had received over 450 comments. The majority of comments submitted expressed support to introduce population screening for AF outlining personal experiences and referring to the NHS long-term plan. The key points made about the evidence review was that there was a high rate of undiagnosed AF in the UK and that, as the cost effectiveness of screening was met in the 2019 review, this should lead to an offer of screening.

4.9 In contrast the Royal College of GPs and the Scottish National Advisory Committee on Heart Disease both agreed with the conclusion of the evidence review not to offer screening. Both organisations emphasised the lack of RCT evidence of benefit in a screened population and the RCGP drew attention to the uncertainty about the balance of benefit and harm in the absence of such trial evidence. This was also expressed in a few individual consultation comments.

4.10 One response received highlighted a possible missed paper from the review which would be looked at to see if it does meet the inclusion criteria. The Committee acknowledged the comments shared and were informed that a complete set would be circulated after the meeting.

4.11 Prof Hyde stated that there were two opposing statements. One that there was insufficient evidence to suggest the programme would be effective but another stating that it was likely to be cost effective. These differences sent contradictory messages. It was agreed that all comments on the evidence review would be fed back to the reviewers to consider and amend where appropriate.

4.12 The Committee agreed that the publication of the SAFER trial due in 2020/21 and work being done in Sweden would help provide essential RCT evidence needed to consider whether screen detection of asymptomatic AF and subsequent treatment is associated with more benefit that harm. This would then feed into the next review cycle for AF.

4.13 Based on the evidence and comments received so far, the UK NSC made a provisional recommendation that screening for AF should not be recommended. The final recommendation would be ratified through Chair's Action once the Committee had reviewed all comments.

Based upon the UK NSC criteria to recommend a population screening programme, screening for AF should not be introduced.

Criteria (only include criteria included in the review)	**Met/Not Met/uncertain**
The Condition	
1. The condition should be an important health problem as judged by its frequency and/or severity. The epidemiology, incidence, prevalence and natural history of the condition should be understood, including *development from latent to declared disease and/or there should be robust evidence about the association between the risk or disease marker and serious or treatable disease.*	**Uncertain**

The Intervention	
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**
The Test	
4. There should be a simple, safe, precise and validated screening test.	**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**
14. The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (value for money). Assessment against this criteria should have regard to evidence from cost benefit and/or cost effectiveness analyses and have regard to the effective use of available resource	**Met**
Implementation Criteria	
15. Clinical management of the condition and patient outcomes should be optimised in all health care providers prior to participation in a screening programme.	**Uncertain**

Action 4a: Complete set of consultation comments for AF to be shared with the Committee. Members to raise any objection to the recommendation to the Secretaria

Action 4b: Comments on the AF evidence summary to be sent to the reviewers to consider

Action 4c: Chair to take Chair's Action on AF to make a final recommendation

AAA Surveillance – programme modification

4.14 The UK NSC examined the programme modification proposal seeking to extend the surveillance intervals from one to two years in men with small abdominal aortic aneurysms (measuring 3.0cm- 3.9cm). The UK NSC were given a presentation on the proposal by Akhtar Nasim and Lisa Summers. It was noted that extension of the surveillance intervals was an area of active interest internationally.

4.15 The proposal suggests that evidence taken from a systematic review along with meta analysis and published programme data, indicates that such a change would reduce the surveillance burden in men who are at low risk of rupture without negatively impacting on outcomes. Extension of the intervals would also reduce costs.

4.16 The UK NSC supported the proposal in principle as being a pragmatic approach to an evolving programme. It was agreed that an update of an existing HTA model of surveillance intervals would help quantify key outcomes of the proposed strategy and explore its cost effectiveness. The updated model would compare the two surveillance strategies (programme proposal and European Society of Vascular Surgery guidance) against those included in the earlier iteration of the HTA model.

4.17 It was noted that NICE was currently developing guidance on the diagnosis and management of AAA and that this introduced some time pressure on the modelling exercise. The HTA team had been contacted and estimated that the exercise could be completed in the early Autumn. Once completed the proposal, would then be publicly consulted on and brought back to the UK NSC for a final recommendation. The Committee granted that a shorter public consultation could be carried out in order to limit the possibility of discordance

with forthcoming NICE guideline. It was agreed that a truncated consultation, of six weeks based on current timescales, would enable the results of the process to reach the November meeting. It was also agreed that, in the meantime, the NAAASP should prepare to implement the modification.

Action 4d: John Marshall to share the proposal with HTA to review

Action 4e: Truncated public consultation on the programme modification for the modification of the AAA surveillance intervals to be opened

5. Fetal Maternal and Child Health

FMCH Report

5.1 The Chair provided the Committee with a verbal summary of developments and discussions from the FMCH meeting in May. Two conditions post consultation were discussed by FMCH at its May meeting and are on the agenda for a final recommendation:

- Screening to prevent stillbirth
- Screening for LCHAD

The following 3 conditions were currently out for public consultation:

- Use of PO as an additional test in the Newborn and Infant Screening Programme (close 9 August)
- Screening for dental disease (close 9 September)
- Screening for Varicella susceptibility (close 24 September)

Screening for the prevention of Stillbirth

5.2 The Chair informed the Committee that this was the first time the UK NSC had looked at the evidence to screen for the prevention of stillbirth. The request had been made by the then Secretary of Health in relation to its national maternity safety strategy as well as NHS England's Saving Babies' Lives; care bundle, both aiming to reduce the number of neonatal deaths and stillbirths in the UK. The UK NSC evidence review focused on low risk singleton pregnancies and concentrated on placental problems only.

5.3 Stillbirth is defined as when a baby is born dead after 24 or more weeks of pregnancy. Many stillbirths are linked to complications related to of the placenta, the vital organ that links the baby's blood supply to the mother and helps nourish the baby whilst in the womb.

5.4 As this was the first time the UK NSC was looking at the evidence to prevent stillbirth four key questions were highlighted focussing on the tests and treatments:

i. The effectiveness of tests to predict the risk of stillbirth.
ii. The appropriate monitoring regime for pregnancies that have been identified by screening to be at risk of stillbirth.
iii. The effectiveness of interventions to prevent stillbirth in women identified as high risk through screening that is not elective birth.
iv. The effectiveness of elective caesarean section (CS) or induction of labour to prevent stillbirth in pregnancies at risk.

5.5 The Committee were informed by Cristina Visintin, that the review focused on stillbirths caused by placental dysfunction, distinguishing between early pregnancy (or preterm stillbirth— stillbirth occurring before 37 weeks gestation) and late (term stillbirth — stillbirth occurring after 37 weeks gestation) stillbirths where possible.

5.6 The review found that a large volume of evidence was identified in relation to screening tests using ultrasound and/ or biochemistry; . however, no tests were found to be appropriate for use in a screening programme aimed at identifying pregnancies at risk of pre-term or term stillbirth due to placental dysfunction in clinical practice.

5.7 Only 3 studies were found that assessed monitoring regimes for pregnancies at high risk of stillbirth. Although one study in the preterm period presented a possible monitoring regime, the evidence around this was limited and did not allow for any conclusions to be drawn on the optimal monitoring strategy for pregnancies identified as high risk in a screening programme.

5.8 Six studies (in 7 articles) reported on possible interventions for high-risk pregnancies. Even among pregnancies at risk, stillbirth was a considerably rare event, which increased the uncertainty around the outcome. Based on the evidence found by this review, it is not possible to ascertain the effectiveness of interventions to prevent pre-term or term stillbirths or stillbirth overall. Without further studies, no intervention can be recommended as effective or preferable to elective birth.

5.9 This review also found limited volume of evidence on the risk of stillbirth upon induction of labour compared with expectant management. However, only one study reported stillbirths. From this study it appears that induction of labour may be beneficial for preventing preterm but not term stillbirths. However, the poor quality of that study precludes drawing any definite conclusions. Due to the poor quality and targeted scope of the evidence considered in this review, the effectiveness and safety of induced delivery for the prevention of preterm or term stillbirth in screen-detected high-risk pregnancies cannot currently be ascertained.

5.10 Following a three month public consultation four sets of comments were received, all which supported the conclusions of the review to not offer

population screening. One of the responses suggested that a paper had been missed. On review, the paper had been incorrectly excluded and had since been included. The paper did not however change the outcome of the review.

The UK NSC recommended that a population screening programme to prevent stillbirth should not be introduced in the UK.

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**
7. There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals.	**Not Met**
The Intervention	
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 shouldn't be further considered.	**Not Met**
10. There should be agreed evidence based policies covering which individuals should be offered interventions and the appropriate	**Not Met**

intervention to be offered.	

Screening for Cystic Fibrosis in pregnancy

5.11 John Marshall presented this item to the Committee.

5.12 Cystic Fibrosis (CF) is an inherited chronic health condition whereby thick and sticky mucus builds up in the body around the lungs and digestive system. This then causes problems with breathing and digestion.

5.13 There are two ways in which CF can be picked up currently in the UK:

i. Newborn screening

In 2006 the UK NSC recommended newborn screening for CF. Most cases are picked up by this national programme.

ii. Carrier testing

If someone has a history of CF in their family then carrier/ cascade testing is offered.

5.14 Pregnancy screening for CF involves testing both parents to see if they are carriers of a faulty CFTR gene. If both parents are found to be carriers then further testing is offered to see if the baby will inherit the faulty gene. As there is no cure for CF the aim of screening is to provide parents to make a fully informed decision about their pregnancy.

5.15 The UK NSC last considered the need for a review of screening for CF in pregnancy in 2006. At this time screening for CF in newborns was introduced and a review was not commissioned. The potential focus of a review of antenatal screening has since been considered intermittently within the FMCH.

5.16 The 2019 evidence review summary focussed on four key questions with the following outcomes

i. Incidence and prevalence of CF and carrier status – Met (incidence around 3.19 per 10,000 births per year and prevalence around 1.59 per 10,000)

ii. Relationship between genotype and phenotype - Not met (phenotype could not be reliably predicted from genotype)

iii. Mutations covered by the test and its accuracy – Not met (No UK studies were identified since those undertaken in the 1990's)

iv. Acceptability of CF screening in the UK – Not met (no studies in the UK were identified)

5.17 Overall the evidence review found no new UK published studies since the 1999 HTA which looked at screening or the acceptability to screen. The Committee recognised that a reason for the lack of evidence in this area could be due to the shift in focus from antenatal to newborn screening.

5.18 Only one set of comments was received from the Royal College of Midwives who supported the conclusion to not offer antenatal screening for CF.

The UK NSC recommended that a population screening programme for Cystic Fibrosis in pregnancy should not be offered.

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 Condition	
2. The condition should be an important health problem as judged by its frequency and/or severity. The epidemiology, incidence, prevalence and natural history of the condition should be understood, including	**Prevalence and incidence – met** **Genotype-phenotype association – not met**

development from latent to declared disease and/or there should be robust evidence about the association between the risk or disease marker and serious or treatable disease.	
The test	
4. There should be a simple, safe, precise and validated screening test.	**Not Met**
8. If the test is for a particular mutation or set of genetic variants the method for their selection and the means through which these will be kept under review in the programme should be clearly set out.	**Not Met**
The screening programme	
12. There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/ intervention) is clinically, socially and ethically acceptable to health professionals and the public.	**Not Met**

Screening for Parvovirus B19 infection in pregnancy

5.19 It was indicated to the Committee that the work undertaken to look at Parvovirus B19 was carried out using the piloted approach of evidence mapping, which the UK NSC had blogged about and discussed at its February meeting. The consultation for this condition had closed two days prior and that a full set of comments would be circulated to the UK NSC after the meeting.

5.20 The process of evidence mapping allows the UK NSC to scan for published literature and look at the volume and type of evidence that is available on the certain condition in order for the Committee to consider whether there is sufficient evidence to commission a more in-depth review of the topic.

5.21 Parvovirus B19 is a common infection, usually presenting as a rash in school age children. It is an airborne virus usually transmitted through respiratory droplets.

The infection usually manifests as a flu-like illness and is often characterised by a rash of the cheeks which can spread. The infection usually lasts a few weeks. However, in both adults and children about 20-30% of cases do not cause any symptoms.

5.22 The Committee last looked at the evidence to screen for Parvovirus B19 in 2014 and concluded that population screening should not be recommended. This was because there was a lack of evidence around the testing process. Screening would identify large numbers of women who were susceptible to the infection but offer no prevention strategy to avoid reinfection. There was also no information around intervention to prevent the transmission of the infection from mother to fetus as well as how you would treat the fetus if it contracted the infection. Based on the evidence gaps the 2019 evidence mapping exercise looked at two key areas from the 2014 review to see if:

i. Whether there was a vaccination for Parvovirus B19 and
ii. Whether there was now an intervention to prevent the transmission of the infection from mother to fetus

5.23 The 2019 evidence map found that had been no published evidence on either of the key areas to develop a vaccine or on preventing transmission of the infection to fetus.

5.24 Only two early consultation comments had been shared with the Committee, both of which supported the conclusion of the evidence map to not undertake further work on this. Cristina Visintin informed the UK NSC at the meeting that a total of three comments had been received. All of which supported the outcome of the evidence map. It was recognised by the Committee that there was still significant knowledge gaps and research needs which needed to be addressed before screening could be considered.

5.25 The UK NSC agreed to make a provisional recommendation, in advance of receiving the full set of consultation comments, that based on the outcome of the evidence map for screening for Parvovirus B19 that further work should not be commissioned at this present time and that population screening should not be recommended.

Screening for LCHAD in newborns

5.26 The UK NSC was reminded that at the February meeting, it had been agreed that a final recommendation would be deferred until further input had been sought from the Inherited Metabolic Disease Screening Advisory Board (IMD) which had now been received.

5.27 Long-chain 3-hydroxyacyl dehydrogenase (LCHAD) deficiency and Mitochondrial Trifunctional Protein (MTP) are autosomal recessive disorders which prevent the body from breaking down certain types of fats and changing them into energy which the body needs to function. The condition can lead to complications with the liver, heart and muscles and can cause brain damage. Special dietary management is needed to help manage the condition as well as ongoing support from clinical experts.

5.28 The Committee last looked at the evidence to screen for LCHAD in 2014 as part of the newborn blood spot expansion. The Committee agreed that screening for LCHAD should not be offered as no cases of asymptomatic LCHAD were identified by screening during the expanded newborn screening study of 2012/13.

5.29 The 2019 evidence review looked at the four key areas:

i. The frequency of the condition in the UK
ii. The links between the genes and symptoms for people with LCHAD/MTP deficiency
iii. How good the test is at finding people with the condition
iv. The advantages of early treatment following screening versus later treatment following the onset of the illness.

5.30 The 2019 evidence review found that there were no studies from the UK on the number of babies born with LCHAD, although two European studies were identified and supported the prevalence outcome as being consistent with the with the results

from the last systematic review on the birth prevalence of five inherited metabolic diseases including LCHAD, which estimated approximately 0.67 per 100,000 births.

5.31 The review found no evidence to indicate whether the screening test could distinguish between milder and more severe types of the condition. Additional concerns raised by the review, which were echoed by the Committee, were the number of false positives that the test might generate and a lack of follow up on outcomes for babies who had a negative test to ensure that the test result was correct.

5.32 A complete set of comments following the consultation was recirculated to the Committee, six stakeholders participated. Five stakeholders favoured screening. A point raised was that the incidence of LCHAD during the 2012/13 expanded newborn screening study was unusually low and a longer pilot period would have been likely to demonstrate a higher incidence. However, the review found that the rate of identification was in line with expectations. Five cases were identified in the screening area during the pilot period; 1 was clinically detected and already being treated at the point of testing and before return of the test result, 1 was identified through cascade testing, 1 received a false negative result and two cases died before screening would have been offered. The issue may rather be the testing time or test cut off, early presentation or detection via other available routes (i.e. cascade testing). The Committee noted that, even if the two deceased cases were excluded, then the rate of three screen positive cases would still be in keeping with the incidence expected for LCHAD.

5.33 Another point made by the stakeholders was that the pilot study did not demonstrate any dis-benefit in terms of any unacceptable false positive rates. A comment made about the 2019 evidence review was that the conclusion of there being a high false positive rate was not applicable to the UK setting. This was because the studies referred to in the evidence review used cut off values that were considered low and offered testing which occurred before day 5. However, the Committee noted that the evidence review had taken into consideration the point expressed and the reviewers had updated the report to

clarify that even when removing the non-comparable studies, there were still inconsistencies with marker type and thresholds used across studies and that even the UK study had limitations, with the single true positive case having already been detected clinically.

5.34 With regards to treatment, the Committee noted there were some studies although small and at high risk of bias, that did signal possible benefit from early treatment. Stakeholders felt that this is should be a sufficient reason to offer screening adding that the inclusion of LCHAD to the newborn bloodspot programme would not increase costs for laboratories and that it would align the UK with other countries that do offer screening for LCHAD. The Committee accepted that generating evidence on treatment outcomes was challenging in rare diseases. However, the Committee was not confident that screening was the answer, as the benefit of pre-symptomatic treatment may not be entirely dependent on screen detection for a large proportion of cases, given early presentation of some cases (i.e. before day 5) and sibling detection of others.

5.35 The Committee recognised that the economic evaluation did suggest that a screening scenario could be potentially cost saving when compared to no screening. However, as highlighted by the authors, the model had significant uncertainties. This was particularly the case in relation to the the test's inability to distinguish between LCHAD and generic MTP deficiency and uncertainties relating to differences between treatment outcomes in LCHAD and generic MTP.

5.36 The suggestion that the requirement to have high quality published evidence should not be applicable to rare diseases was discussed. The Committee recognised that this point had been raised in consultation comments on other reviews. The Committee noted that it does not apply the screening criteria uniformly across the many disease areas it works on. For example, it does not rigorously impose the criterion that RCT evidence is necessary, sibling cases are accepted as a proxy for a screened population and international evidence was accepted more readily than in common conditions. Furthermore, the recent addition of four conditions to the bloodspot screening programme was accepted with very limited evidence on treatment

outcomes. However, this introduces a great deal of uncertainty regarding the balance of benefits and harms relating to screening for a particular condition. In relation to this, it was noted that a mechanism for post implementation evaluation of bloodspot screening had still not been identified. Because of this it was difficult to be confident that evidence would be generated following a decision to implement based on formally weak evidence. In the case of LCHAD /MTP deficiency, a key limitation was an understanding of whether affected babies presented at a point where screening would enable pre-symptomatic treatment and whether the test was able to detect them if they did. This was considered quite basic information which might be collected retrospectively.

5.37 Dr Shortland asked if he could raise a few points which had been expressed to him from the IMD community and this was welcomed. The first point was that clinicians recognised that the evidence review undertaken was thorough. But they felt that if a more appropriate cut off had been applied, not necessarily those values stated in the studies, then the sensitivity and specificity of the test would be acceptable. Secondly, that there is data on LCHAD in the UK, though it was not published, that might help the Committee understand whether the babies present at a point that could enable pre-symptomatic treatment. Dr Shortland said that the IMD community, overall, felt that the evidence presented on treatment was clinically as strong as the evidence presented for the other four blood spots conditions which was approved in 2014 and so screening for LCHAD should be introduced.

5.38 The Chair thanked Dr Shortland for sharing these comments. The Chair reiterated the necessity of having good data available (preferably published) to allow the UK NSC to take this into consideration when looking at the evidence to introduce screening. It was not enough to suggest that there was supportive, but not shared, unpublished data. The Committee expressed its frustration at this and urged clinicians who held the data to make it available (preferably through publication) so that the UK NSC could formally consider it. This could be taken forward through the early update process if new data became available before the next programmed review.

The UK NSC recommended that a population screening programme for LCHAD/MTP should not be offered.

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 Condition	
1. The condition should be an important health problem as judged by its frequency and/or severity. The epidemiology, incidence, prevalence and natural history of the condition should be understood, including development from latent to declared disease and/or there should be robust evidence about the association between the risk or disease marker and serious or treatable disease	**Met for Question 1 and not met for Question 2**
The Test	
4. There should be a simple, safe, precise and validated screening test.	**Not Met**
The Intervention	
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 shouldn't be further considered.	**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**

Screening for Vision Defects in Children

5.39 The UK NSC last looked at this in 2012 and recommended that vision screening for children aged 4 to 5 years should continue to be offered in an orthoptic led screening service. The aim of screening is to detect any vision defects early, mainly amblyopia (lazy eye) in order to refer to a specialist and offer interventions before reduced vision becomes permanent. The review found that there was only limited evidence of clinical effectiveness and cost effectiveness was uncertain. However, there was also an absence of evidence of harms from screening warrant its cessation.

5.40 Cristina Visintin informed the Committee that the 2012 review had found that the implementation screening for vision defects was varied across the country, as Local Authorities were responsible for the commissioning of the screening service. To address this variability Public Health England had published guidance to reinforce and raise awareness of these responsibilities and have worked closely with health professionalsand the British and Irish Orthoptic society to develop such materials.

5.41 As screening for vision defects is offered the aim of the 2019 review was to conduct a triage review which sought to identify any evidence which may indicate a “red flag” suggesting that further exploration of programme cessation may be necessary. Triage reviews have a surveillance function and are not intended as comprehensive reviews of the programme. Therefore, the first question evaluated by this review was in relation to the possible harms experienced by individuals after participating in a childhood vision screening programme for vision defects. No red flags were identified. There remained an absence of evidence to suggest that there were harms associated with the offer to screen for vision defects in children aged 4-5 years.

5.42 The second part of this review aimed to address important evidence gaps found by the previous UK NSC evidence review for the childhood screening programme. The following three key questions were evaluated:

i. What is the long-term adverse impact of amblyopia with and without treatment?
ii. What is the clinical effectiveness of vision screening in children aged 4 to 5 years?
iii. What is the cost-effectiveness of vision screening in children aged 4 to 5 years?

5.43 When looking at the effect of treated and untreated amblyopia, it was found that although amblyopia can impact reading speed in individuals with amblyopia because it has an influence on the type of eye movements which are used to track words across a page, reading comprehension is unchanged, and the 'real-life' consequences of this remain unclear. Also, the evidence suggested that amblyopia had no impact on educational outcomes and self-esteem; however, this was limited to one study. The evidence summary did not identify any evidence of the impact of amblyopia on patient perceived disutility, general health, quality of life, adverse health events, or specific occupational restrictions. No studies were identified looking explicitly at untreated amblyopia. Thus, this evidence summary is unable to comment on the impact of untreated amblyopia.

5.44 The review found an absence of direct evidence on the clinical effectiveness of screening. It reported weak but consistent evidence suggesting that populations which undergo childhood vision screening have statistically lower prevalence of amblyopia in adulthood compared to historical controls. However, causal relationships between the two are not proven. Furthermore, there was no evidence on the effect of screening on quality of life, socioeconomic outcomes, behavioural and functional outcomes, or patient-perceived disutility of amblyopia or of bilaterally poor vision due to loss of vision in the better eye of an amblyopic individual later in life. The Committee acknowledged that was some weak evidence that suggested that there was impact of amblyopia on outcomes; however, it was limited to one study.

5.45 When looking at cost effectiveness, no new studies were identified from the previous reviews.

5.46 The consultation closed on the day of the UK NSC meeting. A total of four comments were received, two of which had been circulated to the Committee. The four comments were discussed at the meeting and it was agreed that these would be circulated to the Committee after the meeting. A comment from The College of Optometrists stated that the evidence review was entitled screening for vision defects; however, it focused primarily on amblyopia which in their view was too narrow and should be broadened to include other vision defects such as refractive error and strabismus (squint). The Committee acknowledged the comment that vision defect is a broad and encompassing term; however, the most commonly detected vison defect in children of this age where treatment is offered to prevent permanent blindness is amblyopia. The Committee recognised that through this screening other vision defects may also be detected. Several comments raised possible missed papers which Cristina said would be reviewed, to see if they had been missed or excluded for specific reasons. Another comment raised which would be fed back to the reviewers was around the discussion of harms. It was suggested that harms should not only be looked at from those arising from the screening programme but should also include harms from interventions too. One stakeholder also suggested that the recommendation should be rephrased to reflect a competence-based service rather than one based on professional boundaries. The Committee discussed this and agreed that the recommendation reflects the screening pathway and agreed that no changes were necessary at this stage

5.47 Prof Hyde expressed his discomfort with the proposed recommendation where it was felt that screening was being endorsed where multiple reviews had found little, if any, evidence of benefit. To say there was ‘no evidence of harms’ would not be accurate but rather there was an absence of evidence on harms being more appropriate. The Committee agreed with these points but noted that screening for vision defects was a longstanding intervention and that the natural history of amblyopia meant that early intervention was needed if its clinical course was to be modified.

5.48 The Committee discussed the difficult position it faced when looking at areas of historical screening practice which pre-dated the UK NSC and were introduced based on criteria which were different to those which were currently used. The evidence relating to these established programmes is generally insufficient to be confident about removing or endorsing the programme.

5.49 Prof Mackie informed the Committee, that the issues raised by Prof Hyde was something that the UK NSC was starting to look at and as a first step had requested that a mechanism to collect data on child hearing screening programme was being taken forward. The UK NSC also said that it would see if the HTA would be able to develop a methodology to test decommissioning existing programmes. The Committee were supportive of this and it was agreed that further discussion of this was required. In relation to vision screening it was noted that the possibility of comparative research may not have been precluded as substantial areas of the country did not offer screening. In these areas it may be possible to ensure that a high quality service is implemented to manage clinically presenting cases and that outcome data from the two approaches could be collected and compared. If this approach was taken there may be less pressure on Local Authorities to implement screening on the basis of poor evidence.

The UK NSC recommended that there should be no change to the current guidance on screening for vision defects in children aged 4- 5 years and that this should remain under review.

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 Condition	
3. The condition should be an important health problem as judged by its	**Not Met**

frequency and/or severity. The epidemiology, incidence, prevalence and natural history of the condition should be understood, including development from latent to declared disease and/or there should be robust evidence about the association between the risk or disease marker and serious or treatable disease.	
The screening programme	
12. 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 overdiagnosis, overtreatment, false positives, false reassurance, uncertain findings and complications	**Not Met**
14. The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (value for money). Assessment against this criteria should have regard to evidence from cost benefit and/or cost effectiveness analyses and have regard to the effective use of	**Not Met**

available resource	

Updates

NIHR NETSCC Update (for information)

The Committee noted the updates

SIGN Update (for information)

The Committee noted the updates

AOB

None

UK National Screening Committee

This minute will remain draft until ratified by the UK NSC at its next meeting

UK National Screening Committee (UK NSC)

Chair's Action

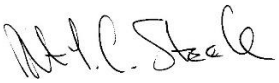
Following the 28 June 2019 meeting

NOTIFICATION OF CHAIR'S ACTION ON BEHALF OF THE COMMITTEE

Action Number	Item to be addressed	Initial status	Reason for Chair's Action	Decision
1.	Screening for AF	A sub set of comments received from the three month public consultation to screen for AF was shared with the Committee alongside the consultation evidence summary for screening for AF. The Committee noted the comments received so far and the evidence presented and provisionally recommended that population screening for AF should not be introduced.	As the consultation closed the day prior to the UK NSC meeting and had over 450 responses submitted, the Committee had not reviewed all comments. It was agreed that the Committee would receive the complete set of consultation responses after the meeting and any member would raise any objection to the provisional recommendation. No comments were received from members.	Based on the evidence provided the UK NSC recommends that a population screening programme for AF should not be introduced.

2.	Screening for Parvovirus B19 Infection	A sub set of comments received from the three month public consultation on the evidence map to screen for Parvovirus B19 was shared with the Committee. The Committee noted the two comments received so far and the evidence presented and provisionally recommended that further work need not be commissioned at the current time and so population screening for Parvovirus B19 Infection should not be recommended.	The consultation closed two days prior to the UK NSC meeting. The complete set of comments were sent to the Committee to review in its entirety and forward any comments or objections to the provisional recommendation. No comments were received from members.	Following an evidence mapping exercise on screening for Parvovirus B19, the UK NSC agrees that no further work be commissioned at this time and uphold the recommendation that population screening programme for Parvovirus B18 should not be introduced.

I confirm that I have taken Chair's action in relation to the decisions recorded above.

Signed: 
Date: 02 August 2019