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# UK National Screening Committee

Is there evidence to alter the current UKNSC recommendation to offer a national screening programme for phenylketonuria in newborn babies ? A pilot of the triage approach

## Screening Topic: Newborn screening for phenylketonuria (PKU)

Delivery date: December 2015

### Contents

## 1. Background to the triage reports

This report is a rapid triage assessment of whether the existing national screening programme (NSP) for phenylketonuria in newborns should be continued.

For conditions for which population screening programmes are recommended by the National Screening Committee (NSC) the triage process focuses on whether there is new evidence suggesting that the NSP should be stopped.

It consists of an externally produced report on a literature search undertaken to identify whether any papers have been published:

- addressing screening programme cessation
- reporting harms from screening
- reporting balance of harms and benefits from screening

The aim of these reports is to identify any "red flags" that suggest that an NSP needs to be reviewed in greater detail. They do not aim to identify all new literature relating to screening for the condition; instead they focus specifically on evidence relating to the three areas specified above.

If no papers are identified on the above topics, a recommendation to continue the programme is made. If papers on programme cessation or harms from screening are identified, the UK NSC will consider whether further work is necessary before making a recommendation on the topic.

Stakeholders will be contacted for comments on the recommendation and a three month consultation will be hosted on the UK NSC website.

Based on the triage report and stakeholder comments the Committee decides whether to recommend that the issue is considered in more depth. Where further evaluation is considered appropriate, the options may include an evidence summary, primary research, systematic review, cost effectiveness assessment, modelling. .

## 2. Executive summary

This triage assessment identified one study with potential relevance to the possible harms of PKU screening.

This mixed-methods study included a systematic review to identify reports of adverse outcomes from PKU screening in the pre-1980s United States (Brosco et al. 2008). It identified reports of 2 children identified as false positives, 4 children given "inappropriate treatment" (though not specified whether due to screening, or with adverse outcome), and 4 reports of screen-detected children with moderately raised phenylalanine having adverse outcome.

This was the only potentially relevant study identified. This suggests that there have been some reports of harms of PKU screening (false positives or adverse effects), at least pre-1980s. Overall, the authors of this review concluded that there was minimal evidence of harms. It was unclear what proportion these false positives and adverse outcomes represent of the total number of studies and population size identified, but as screening is of all newborns the proportions are likely to be small. The adverse outcomes experienced by the children were not described in detail in the abstract. This is also an historical review of the US screening programme that may not have a high level of relevance to the current UK programme. PKU remains one of the core conditions in the recommended uniform newborn screening panel from the US Department of Health and Human Services' Advisory Committee on Heritable Disorders in Newborns and Children.

Recommendation: This study alone does not provide sufficient evidence that the evidence supporting the national PKU screening programme needs to be reviewed in more depth or that the programme should be stopped.

## 3. Introduction to the condition

The current NSP being assessed is newborn bloodspot screening for phenylketonuria (PKU). PKU is an inherited metabolic condition where there is a defect in the enzyme phenylalanine hydroxylase which converts phenylalanine in the body into tyrosine. The defect leads to an accumulation of phenylalanine in the body tissues which affects the normal development of the brain causing learning difficulties. Phenylalanine is an amino acid present in many foods, and the management approach is dietary. People affected need to follow a strictly controlled low protein diet from birth, with care coordinated through dieticians and other healthcare professionals. This is usually continued throughout life. Early treatment from birth should allow for normal brain development.

PKU is one of the conditions currently screened for as part of the NHS newborn blood spot (NBS) screening programme. This is offered for all newborn babies, with the blood sample usually taken 5 days after birth (sometimes to Day 8). The screening test examines level of phenylalanine in the blood.

This external review has searched the literature published between 2004 up to December 2015, and reviewed the results at title and abstract level to establish whether there is evidence:

- Indicating that other countries have terminated PKU screening
- reporting harms from PKU screening
- reporting balance of harms and benefits from PKU screening

## 4. Description of the evidence

Forty one publications were selected at the first pass sift as being potentially relevant to these three questions based on title and abstract. These were reviewed more closely at abstract level at a second pass appraisal.

One of these 41 publications met inclusion criteria as having some relevance to these questions. Details of this study are extracted in Table 1. The remaining studies were excluded as they did not appear at abstract level to contain information relevant to harms of or cessation of PKU screening. The excluded studies predominantly included surveys of screening practice, disease incidence and treatment in European countries (either specific to PKU or to rare metabolic diseases in general); economic analyses (indicating that PKU screening was cost effective); and non-systematic reviews/editorials discussing treatment options, response and outcomes in people with PKU (including need for treatment optimisation).

There was one additional abstract reported as a “historical overview” with a focus on identifying harms of six NBS programmes in the US one of which was PKU. This abstract did not provide data and concluded that no problems were identified where children were treated due to false positive results. It was unclear from the abstract whether this was a systematic review, but as this was by the same authors of the included PKU-specific systematic review (Table 1), this was excluded.

Table 1

| Publication details | Study details | Population | Intervention/test and comparator | Main findings | Comments |
|---|---|---|---|---|---|
| Screening programme cessation | | | | | |
| No studies identified | | | | | |
| Harms from screening | | | | | |
| Brosco et al. 2008.<br><br>Brosco JP, Sanders LM, Seider MI, et al. Adverse medical outcomes of early newborn screening programs for phenylketonuria. Pediatrics. 2008;122(1):192-7 | Mixed methods study, US<br><br>Systematic review for adverse outcomes, and interview of key participants of screening programs (all pre-1980s in US) | Reports no population-based studies of early PKU screening programs identified; otherwise number of relevant studies and population not reported | PKU screening pre-1980s but not otherwise specified. | States to have identified:<br>One report of "2 infants treated after false positive results who were developmentally delayed".<br>Unpublished evidence of 4 cases of inappropriate treatment (though adverse outcomes are not reported).<br>Four published reports of adverse outcomes from treating screen-detected children who had only moderate or transitory raised phenylalanine.<br>Concludes: "little evidence of death or disability from the inappropriate treatment of well children who were falsely identified" | Specific to US and to pre-1980s PKU screening.<br><br>May not be relevant to current UK screening programme.<br><br>Study methods, inclusion/exclusion criteria, and total body of evidence retrieved were not reported in the abstract. |
| Balance of harms and benefits from screening | | | | | |
| No studies identified | | | | | |

## 5. Methodology

It is intended that the triage process for each NSP will be performed every three years. This review is the first triage review for PKU and includes literature published in the past 10 years.

Sifting has been carried out in two stages. The first pass sift was conducted by an information specialist at title and abstract level, to remove clearly non-relevant material e.g. animal studies, or studies of different screening programmes. The second pass sift was performed by a health research analyst and this sift examined the results more closely at title and abstract level to remove those studies clearly not relevant, and select those meeting inclusion criteria for summary.

The reports focus on high quality studies, i.e. systematic reviews, randomised controlled trials, non-randomised controlled trials, cohort studies or screening programme evaluations that appear at abstract level to have covered potential harms of the NSP, the balance of harms and benefits, or screening programme cessation. Lower level evidence such as case series and case reports, non-systematic reviews, editorials or opinion pieces are not included unless they clearly highlight potential harms of the NSP indicating the need for further evaluation.

Studies on any issues other than the three questions of interest are not included. For example, studies examining cost effectiveness (unless relevant to the UK and highlighting the balance of benefits and harms), or studies assessing modifications to an existing screening programme (e.g. changing age at screening, screening test used, screening interval etc.) would be excluded. Studies evaluating management of the condition are also excluded unless they indicate that the existing treatment is ineffective or harmful, which may suggest that harms of screening outweigh outweigh any benefits.

These triage reports are rapid assessments to identify any “red flags” which indicate the need for further assessment of the NSP. They are complemented by consultation with stakeholders to identify any additional issues which may not be represented in the literature identified.

## 6. Search strategy

We searched the following bibliographic databases:

- Medline (via Embase.com)
- Embase
- The Cochrane Library: including the Cochrane Database of Systematic reviews; Cochrane Central Register of Controlled Trials (CENTRAL); Database of Abstracts of Reviews of Effects (DARE); Health Technology Assessment Database (HTA); NHS Economic Evaluation Database (EED)

The searches were limited by date to include studies published since 2004. No language limits were used. Methodological filters were not used as they would not have been appropriate given the focus of the research questions.

The search strategy was developed through testing to identify the best balance between sensitivity and specificity that was fit for purpose. The search strategy used both indexing terms and text words as relevant records could have been indexed in different ways (or not indexed at all). The Embase search strategy was translated for the other databases and adapted to take into account the databases size, coverage and available indexing terms.

The search strategy was based on the PICO framework and combined three major concepts: the population (condition), neonatal screening, and harms from screening or screening programme cessation. (See table below)

**Search strategy (Embase.com)**

| Concept | Search strategy |
|---|---|
| Population | 1. 'phenylketonuria'/de<br>2. 'hyperphenylalaninemia'/de<br>3. phenylketonuria:ab,ti OR pku:ab,ti<br>4. phenylalaninemia:ab,ti OR hyperphenylalaninemia:ab,ti OR hyperphenylalaninaemia:ab,ti OR hyperphenylalanaemia:ab,ti OR hyperphenylalanemia:ab,ti<br>5. 'phenylalanine hydroxylase deficiency':ab,ti<br>6. 'dihydropteridine reductase deficiency':ab,ti<br>7. 1 or 2 or 3 or 4 or 5 or 6 |
| Screening | 1. 'newborn screening'/de<br>2. ((neonat* OR newborn*) NEAR/2 screen*):ab,ti<br>3. 'mass screening'/de<br>4. 'newborn'/de<br>5. 3 and 4<br>6. 1 or 2 or 5 |
| Programme cessation or harms | 1. ceas*:ab,ti OR cessation:ab,ti OR stop:ab,ti OR stopped:ab,ti OR continu*:ab,ti OR discontinu*:ab,ti<br>2. appropriate*:ab,ti OR inappropriate*:ab,ti OR unnecessary:ab,ti OR question*:ab,ti<br>3. harmful:ab,ti OR harm*:ab,ti OR adverse:ab,ti<br>4. benefit*:ab,ti AND (risk*:ab,ti OR harm*:ab,ti)<br>5. 'side effect'/exp)<br>6. (side NEAR/1 effect*):ab,ti<br>7. overdiagnosis:ab,ti OR 'over diagnosis':ab,ti<br>8. 'patient safety'/exp<br>9. 'risk assessment'/de<br>10. 'risk benefit analysis'/exp<br>11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 |

## Search results

| Databases searched | Dates searched | Number of hits |
|---|---|---|
| Medline and Embase (Embase.com) | 2004-07/12/2015 | 222 |
| CENTRAL (Cochrane Library) | 2004-07/12/2015 | 7 |
| NHS EED (Cochrane Library) | 2004-07/12/2015 | 3 |
| HTA (Cochrane Library) | 2004-07/12/2015 | 3 |
| **Total number of hits** | | **235** |
| **Total number after de-duplication** | | **231** |
| **Total number after first appraisal** | | **41** |

**Embase.com search strategy**

#1 'newborn screening'/de 13746
#2 ((neonat* OR newborn*) NEAR/2 screen*):ab,ti 12206
#3 'mass screening'/de 49630
#4 'newborn'/de 498406
#5 #3 AND #4 2463
#6 #1 OR #2 OR #5 19026
#7 'phenylketonuria'/de 8803
#8 'hyperphenylalaninemia'/de 1422

#9 phenylketonuria:ab,ti OR pku:ab,ti 7181
#10 phenylalaninemia:ab,ti OR hyperphenylalaninemia:ab,ti OR hyperphenylalaninaemia:ab,ti OR hyperphenylalanaemia:ab,ti OR hyperphenylalanemia:ab,ti 1510
#11 'phenylalanine hydroxylase deficiency':ab,ti 142
#12 'dihydropteridine reductase deficiency':ab,ti 122
#13 #7 OR #8 OR #9 OR #10 OR #11 OR #12 10345
#14 #6 AND #13 1832
#15 ceas*:ab,ti OR cessation:ab,ti OR stop:ab,ti OR stopped:ab,ti OR continu*:ab,ti OR discontinu*:ab,ti 1265546
#16 appropriate*:ab,ti OR inappropriate*:ab,ti OR unnecessary:ab,ti OR question*:ab,ti 1495204
#17 harmful:ab,ti OR harm*:ab,ti OR adverse:ab,ti 609591
#18 benefit*:ab,ti AND (risk*:ab,ti OR harm*:ab,ti) 166742
#19 'side effect'/exp 398996
#20 (side NEAR/1 effect*):ab,ti 268067
#21 overdiagnosis:ab,ti OR 'over diagnosis':ab,ti 3449
#22 'patient safety'/exp 68643
#23 'risk assessment'/de 369811
#24 'risk benefit analysis'/exp 43498
#25 #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 3897895
#26 #14 AND #25 356
#27 #14 AND #25 AND [2004-2016]/py 222

**Cochrane Library search strategy**

#1 MeSH descriptor: [Neonatal Screening] this term only 281
#2 (neonat* or newborn*) near/2 screen*:ti,ab,kw 562
#3 MeSH descriptor: [Mass Screening] this term only 4456
#4 MeSH descriptor: [Infant, Newborn] explode all trees 13439
#5 #3 and #4 120
#6 #1 or #2 or #5 604
#7 (phenylketonuria or pku):ti,ab,kw 227
#8 MeSH descriptor: [Phenylketonurias] explode all trees 104
#9 (phenylalaninemia or hyperphenylalaninemia or hyperphenylalaninaemia or hyperphenylalanaemia or hyperphenylalanemia):ti,ab,kw 24
#10 'phenylalanine hydroxylase deficiency':ti,ab,kw 9
#11 'dihydropteridine reductase deficiency':ti,ab,kw 1
#12 #7 or #8 or #9 or #10 or #11 247
#13 #6 and #12 Publication Year from 2004 to 2015 13

## 7. References

### Included after second pass sift

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