**UK National Screening Committee (UK NSC)**

**Note of the meeting held on the 15 June 2016**

**at**

**Health and Care Research Support Centre- Cardiff, Wales**

This meeting provided recommendation on the following conditions;

- Kernicterus
- Adolescent Idiopathic Scoliosis
- Toxoplasmosis

**Members**

| | |
|---|---|
| Professor Bob Steele (Chair) | Director of Centre for Research into Cancer Prevention and Screening, University of Dundee |
| Dr Sunil Bhanot | GP |
| 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 |
| Ms Jane Fisher | Patient and Public Voice (PPV) |
| Ms Hilary Goodman | Operational Manager of Antenatal Services/Screening at Hampshire Hospitals 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 |
| Dr John Holden | Joint Head of Medical Division, Medical and Dental Defence Union of Scotland |

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| Mrs 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;***

| | |
|---|---|
| Dr Hilary Angwin | Screening & Immunisation Lead, NHS England/PHE<br>Chair of FMCH |
| Dr Rosemary Fox | Director of Screening Division, Public Health Wales |
| Dr Margaret Boyle | Department of Health, Social Services and Public Safety<br>Northern Ireland |
| Dr David Elliman | Clinical lead for Newborn Infant Physical Examination and Newborn Blood Spot, PHE |
| Dr Dorian Kennedy | Deputy Director, Flu, Immunisation, Screening and Sexual Health, Department of Health |
| Dr Heather Payne | Senior Medical Officer for Maternal and Child Health, Welsh Government |
| Ms Sarah Manson | Scottish Government |
| Dr Sue Payne | Directors of Public Heath, NHS Scotland |
| Ms Nicole Redhead | Sexual Health, Screening and Sponsorship Branch Department of Health |
| Ms Jo Taylor | Sexual Health, Screening and Sponsorship Branch Department of Health |

**Secretariat**

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| Dr Anne Mackie | Director of Programmes - UK National Screening Committee |
| Mr John Marshall | Evidence Lead, PHE |

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| Miss Zeenat Mauthoor | Secretariat, PHE |
| Mr Nick Johnstone Waddell | National Information Lead |

**Apologies**

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|---|---|
| Professor Roger Brownsword | School of Law, Kings College London |
| Professor Alan Cameron | Consultant Obstetrician at Southern General Hospital, Glasgow |
| Ms Eleanor Cozens | Patient and Public Voice (PPV) |
| Dr Paul Cross | Consultant Cellular Pathologist, Queen Elizabeth Hospital Gateshead Health NHS Foundation Trust |
| Dr Hilary Dobson | Consultant Radiologist and Clinical Director of the West of Scotland Breast Screening Service and Honorary Senior lecturer, University of Glasgow |
| Professor Gareth Evans | Consultant in Genetics Medicine, St Mary's Hospital, Manchester |
| Professor Chris Hyde | Public Health Specialist, University of Exeter |
| Dr Greg Irving | GP |

**Presenters;**

| | |
|---|---|
| Dr Alice Bessey | School of Health and Related Research (ScHARR) |
| Professor Jim Chilcott | School of Health and Related Research (ScHARR) |
| Professor Andy Ewer | University of Birmingham, Neonatal medicine |
| Dr Benjamin Kearns | School of Health and Related Research (ScHARR) |

**Welcome and Introductions**

1. The new Chair of the Committee, Prof Bob Steele welcomed all to the meeting. As this was his first meeting, a brief summary of his work and interest in screening was provided. A round of introductions was initiated.

**New members**

The Committee was informed that three new members have since been appointed to the Committee fulfilling the role of a GP, Public Health Specialist and an additional PPV. The new members would attend the next meeting.

**Membership**

The Chair informed members that since the February meeting the following regular observers would no longer attend meetings: Ms Majella Byrne has moved department and her post is yet to be filled; it was also the last meeting for Dr Margaret Boyle who has been an observer on the UK NSC for over fifteen years and will soon be retiring, and Ms Nicola Redhead who was changing posts. The Committee thanked the observers for their hard work and support.

**Agenda Item Presenters**

The Chair welcomed Professor Jim Chilcott and Dr Alice Bessey from ScHARR to present the cost effectiveness of screening for Severe Combined Immunodeficiency (SCID) within the Newborn Blood spot screening programme.

Dr Benjamin Kearns, also from ScHARR to present the final results of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS).

Professor of neonatal medicine, Andy Ewer, to present the end project report on Newborn Pulse Oximetry Pilot

Apologies were noted.

**Minutes and Matters arising**

2. Minutes were confirmed as a true and accurate record

Two action points were identified from the February meeting;

*Pulse Oximetry*

*For Pulse Oximetry to be added to the June agenda*- This has been completed and forms item 4.2 on the agenda

*UKCTOCS*

*Dr Sophie Whyte to provide Dr Mackie with a draft letter to write to UKCTOCS asking for data on prevalence- ScHARR have carried out the work without the data from UKCTOCS so this action is no longer required*

***Director's* Update**

3. Dr Mackie gave an update on the following

Update on combined testing in Fetal Anomaly Screening Programme (FASP)

3.1 Dr Mackie reminded the Committee that at its meeting on 9 November 2015 it recommended an evaluative roll out of an additional test (NIPT) to screen for Down's, Edwards' and Patau's syndromes as part of the NHS Fetal Anomaly Screening Programme. This approach was recommended because the evidence strongly suggests that NIPT test presents a more accurate screen for T21 and reduces the need for diagnostic invasive pre-natal testing (e.g. amniocentesis), which carries a risk of miscarriage. However there were some areas of uncertainty which could only be made less certain once a programme was in use. Evaluation would include choices that women make in usual maternity care (e.g. NIPT or invasive testing), accuracy for T13 and 18 and test "failure" rates.

3.2 Responders to the consultation had raised concerns about the ethical basis for screening for Down's syndrome as well as for the change in testing modalities. The Independent body, the Nuffield Council on Bioethics held a workshop in January to examine ethical issues relating to the use of NIPT. The Committee noted that the workshop had made no firm conclusions but recognised "that there were no clearly new ethical issues raised by using NIPT as a second test for aneuploidies as part of the NHS Fetal Anomaly Screening Programme".

3.3 The UK NSC noted that the workshop had also highlighted the need for balanced and accurate information to enable pregnant mothers and their partners to make informed choices at all steps along the screening pathway, including the offer of NIPT. Following a recommendation by the House of Commons Science and Technology Committee, work was in hand to develop a working definition of informed choice. In addition there was a clear commitment to ensure prospective parents get the right information and support throughout the screening process. If NIPT is introduced into the screening pathway for Down's syndrome, it would be supported by a programme of information and training for health professionals to enable them to facilitate the offer of screening and to explain the test and the possible results and options following the test.

3.4 The Committee discussed both the full report produced by Nuffield Council as well as noting the information provided from the Bioethics workshop. The Committee agreed

that on review, no new ethical issues about screening for T21, 18 &13 were raised by using NIPT and so agreed that the use of NIPT should be recommended as a contingent test in the antenatal screening programme for trisomy. The Committee agreed that an evaluative rollout would offer a framework to review the findings as they are generated whilst arrangements are in development. This will accommodate flexibility and allow the Committee to consider whether there is a need for any further recommendation relating to the antenatal screening programme.

Inequalities workshop feedback

3.5 Dr Mackie updated the Committee on a range of work Public Health England (PHE) was taking forward to identify and address inequalities in screening programmes in England following a workshop held last year. The work was grouped around several themes, including data, research and evaluation, sharing good practise, developing new evidence, implementing what works, public and screening information and providing guidance.

3.6 The Committee noted the actions and thanked Dr Mackie for the summary. Ms Sarah Manson also informed the Committee of work in hand in Scotland to reduce inequalities including work, like in England, to offer bowel screening, abdominal aortic aneurysm (AAA) screening and diabetic eye screening (DES) in prisons. Dr Margaret Boyle confirmed that similar work was being undertaken in Northern Ireland and it would be beneficial for the four countries to share strategies and good practice in this area.

Action: Ms Sarah Manson to share Scotland's strategy work on inequalities in screening with the four countries.

**Annual Stakeholder Event**

3.7 Mr Nick Johnstone-Waddell said that a second annual stakeholder event was scheduled for Wednesday 14th December 2016. The meeting would be in London but the venue is to be confirmed. The event will commemorate the UK NSC's 20th anniversary. Any members interested in presenting should contact the secretariat. Information and registration for the event will go live in the coming weeks.

3.8 Mr Johnstone-Waddell also informed the Committee that in response to recommendations made by the House of Commons Science and Technology Inquiry, a Task and Finish group has been set up to take forward the work on developing an agreed

definition of the term 'informed choice' for screening programmes to be measured and evaluated against, as well as developing and sharing best practice amongst the four countries.

Action: Committee members interested in participating in the annual stakeholder event to email Ms Zeenat Mauthoor

**Residual Blood spot Consultation**

4 Dr Elliman informed the Committee that this consultation on the storage and retention of residual bloodspots had been further delayed because of publishing restrictions around the EU referendum pre-election period.

**Presentation on the cost effectiveness of screening Severe Combined Immunodeficiency (SCID) in the Newborn Blood Spot screening programme**

5 Dr Jim Chilcott and Dr Alice Bessey presented their assessment of the incremental costs and health benefits and cost effectiveness of screening for SCID in the NHS Newborn Bloodspot Screening Programme. (Annex A)

5.1 The UK NSC reviewed the evidence for SCID in 2013 and recommended that screening should not be offered as there was insufficient information to address all the UK NSC's criteria. This included; uncertainty and lack of evidence about the epidemiology of the condition in the UK, the test performance and the clinical and cost effectiveness of offering screening compared to current practice.

5.2 Due to the potential benefits of early diagnosis there has been pressure amongst stakeholders for a screening programme for SCID to be introduced. ScHARR has developed a model to assess the cost effectiveness of universal screening for SCID.

5.3 The Committee thanked both Prof Chilcott and Dr Bessey for the informative presentation. In discussion the Committee agreed that while screening for SCID could reduce mortality the model suggested that it is not possible to be certain that screening is cost effective. The Committee discussed the robustness of some of the assumptions in the model e.g. the discount rate used and costs of quality assurance. In addition, concerns were expressed about the large number of false positives and the potential this had for harm and how this might be measured.

5.4 There were also wider implications to be considered, for example the impact screening might have on the possible future introduction of a BCG immunisation programme for infants. As there were a few assumptions that had a large impact on the cost effectiveness the Committee agreed that the work should be subject to a technical appraisal through peer review to test the assumptions and methodological aspects of the study. In parallel a full review of SCID should be developed and consulted on so that the UK NSC can consider a full assessment of newborn screening for SCID.

Action: ScHARR to publish and peer- review SCID cost effectiveness document

Action: UK NSC secretariat to develop a document assessing SCID screening against screening criteria and consult on newborn screening for SCID

**Presentation on Ovarian Cancer Model using data from UK Collaborative Trial of Ovarian Cancer Screening Trial**

6 Mr Benjamin Kearns has been invited to the UK NSC meeting to present the final ScHARR model using the latest results from the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). (Annex B)

6.1. The Committee recognised that as UKCTOCS had not shown a reduction in mortality from ovarian cancer that screening for it should not be recommended at this time. The model developed by ScHARR would use data from UKCTOCS as longer term follow up data become available.

Action: UK NSC recommended that the committee await longer term outcomes from UKCTOCS

**Fetal Maternal and Child Health**

7. Dr Hilary Angwin, Chair of the FMCH, reported that the reference group had not met since June 2015. The future of the group had been discussed and it was agreed that the FMCH had an important function in quality assuring the evidence reviews and allowing more in depth discussion than is possible at UK NSC meetings. The Committee agreed that the FMCH played a vital role in supporting the UK NSC and in making recommendations and agreed the group should continue with a core group of members bringing in additional experts as appropriate. Terms of Reference should be revised. The Committee agreed with a proposal to establish an equivalent group for adult screening topics.

7.1. Dr Angwin provided the Committee with a summary of the Chair's Actions which related to items included on the main UK NSC agenda. In addition, the UK NSC was asked to provide direction on a review of the evidence for screening for tyrosinaemia type 1. This was reviewed as part of the regular cycle of reviews in March 2015 and was considered to be a potential candidate for screening. However due to several uncertainties regarding the epidemiology, test cut off and long term outcomes from early treatment a programme was not recommended. The public consultation suggested a number of issues which might be explored in more depth and an additional review of these had been completed. The UK NSC was invited to consider whether a stakeholder workshop would be of benefit to help feedback the findings from this extra piece of work. The Committee agreed that this would be a useful opportunity to explain the issues of the review in more detail during the consultation period

**Pilot results for Pulse Oximetry**

8. Professor Andy Ewer presented this item to the Committee.

8.1. Each year around 3,500 babies are born with some kind of heart defect. Severe heart problems are known as critical congenital heart disease (CCHD) and babies are at a significant risk of disability or death if they are not diagnosed and treated soon after birth. The use of Pulse Oximetry (PO) has shown to help detect CCHD before babies show any signs of any problems. In 2013 the UK NSC announced that it wished to further assess the use of PO as a means of detecting CCHD. The UK NSC agreed to run a pilot to help answer questions about the impact and implementation of such a test and to gauge whether such an offer was feasible within the Newborn and Infant Physical Examination screening programme (NIPE). The pilot completed in 2015 and Professor Ewer reported the findings of the pilot to the Committee.

8.2. Professor Ewer informed the Committee that 32,000 babies were screened using PO of which 239 were screen positive. 114 babies required neonatal care and 8 were identified as having CCHD. 2 were missed. The Pilot showed that the test performance of PO is consistent with research. However the overwhelming majority of babies with a positive screen do not have CCHD. Half were well and the rest had a variety of pulmonary, infective or neurological problems.

8.3. The Chair and the Committee thanked Professor Ewer for his presentation and the hard work and achievement in successfully screening over 32,000 babies using PO. The

Committee discussed the findings. They agreed that as the test has poor specificity for CCHD it was important to understand the effect on the screen positive babies. It was agreed that a modelling exercise should be undertaken as this would be the most efficient approach to gaining a better understanding of the costs and benefits to screen positive babies.

Action: The UK NSC requests that further work on the costs and benefits to screen positive/ CCHD negative babies be carried out and that the results of such an exercise be brought back to the Committee for consideration.

**Screening for Kernicterus**

9. Mr John Marshall presented this item to the Committee.

9.1. The evidence for screening for kernicterus was last reviewed in 2011. Kernicterus is a rare complication of neonatal jaundice which can be found in babies who have high levels of the substance called bilirubin. Bilirubin can cause jaundice which can be detected by the yellowing of the skin and the whites of the eyes. Higher levels of bilirubin circulating in the blood can travel to the brain and if not well treated can cause the condition which results in permanent brain damage.

9.2. The review in 2011 recommended that screening should not be offered as there were a number of uncertainties which related to the condition. The current review focused on these three areas of uncertainty; whether there was a clear bilirubin cut off level to identify which babies would develop kernicterus, what the effectiveness of existing and new treatments were and whether clinical management had since been optimised.

9.3. The conclusion of the review found that there was no evidence to suggest that a national screening programme would be able to detect and identify those babies would be at risk of developing kernicterus. Nevertheless the review did however identify that a significant improvement had since been made within the current clinical management practice. NICE has provided clear guidelines on the identification and management of neonatal jaundice and in May 2016 added a new recommendation on measuring and monitoring bilirubin levels in babies with prolonged jaundice.

9.4. The UK NSC recommended that a national screening programme for kernicterus should not be offered as;

- There is no evidence to suggest that screening could detect those babies who would be at risk of developing the condition

- There is no agreed threshold at which bilirubin is associated with the onset of kernicterus

| Criteria | | UK NSC Comments |
|---|---|---|
| **The Test** | | |
| 5 | There should be a simple, safe, precise and validated screening test. | There is no agreed cut off value for bilirubin |
| **The Treatment** | | |
| 10 | There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment. | A programme would be unable to correctly identify and detect babies earlier who may be at risk of developing kernicterus |
| **The Screening Programme** | | |
| 12 | Clinical management of the condition and patient outcomes should be optimised in all health care providers prior to participation in a screening programme. | NICE have produced guidelines for the management of neonatal janudice |

**Screening for Adolescent Idiopathic Scoliosis**

10. Mr John Marshall informed the Committee that adolescent idiopathic scoliosis (AIS) refers to the abnormal curvature of the spine which can develop during puberty. The condition means that the spine develops a side to side curvature usually resembling an "S" or "C" shape rather than the spine growing straight. A curvature in the spine is more than a 10̊. It is estimated that around 2-3% of people are believed to have scoliosis.

10.1. Mr Marshall highlighted to the Committee that in the 2012 review the Committee recommended not offering screening for AIS as there were a number of uncertainties which related to the condition which included the accuracy of the test in predicting which adolescents would have AIS and the evidence around the outcome of treatment for minor curvatures. An issue with scoliosis is that the curve in the spine can sometimes improve over time without the need for any treatment. There are many

factors that can influence whether the level of scoliosis improves, stays the same or in fact becomes more severe. Furthermore it is unknown whether early treatment can prevent severe scoliosis from developing.

10.2. The review focused on these key areas and explored whether there was any benefit from screening and treatment. The review concluded that the areas of concerns remain unanswered. Although there was a candidate screening test (Adams Forward Bend Test) there was no agreed age at which to offer the test and that an evidence based agreed cut off value for the test was absent. Furthermore the Committee agreed that as the prediction of scoliosis requiring treatment was poor further testing would be expected and this would involve exposure to radiation. Finally no studies of treatment of screen detected scoliosis were identified by the literature search. The Committee noted that no comments were received during the consultation.

The UK NSC recommended against a universal screening programme for AIS as;

- Although there is a candidate screening test for the condition there is no agreed age at which to offer screening and an evidence based cut off value is absent
- It is unclear whether there is any added benefit from screening compared to detection through clinical practice.

| | | |
|---|---|---|
| **The Test** | | |
| 6 | The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed. | There is no agreed cut off level nor is there an agreed age at which screening should be offered |
| **The Treatment** | | |
| 10 | There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment. | The progression of scoliosis is variable.<br><br>It is unknown whether treatment of screen detected scoliosis may be of benefit |
| 11 | There should be agreed evidence based policies covering which individuals should be offered treatment and the appropriate treatment to be offered. | |

**Screening for Toxoplasmosis**

11. This item was presented by Mr John Marshall.

11.1. Mr Marshall informed the Committee that toxoplasmosis is an infection caused by a parasite that can infect most warm blooded animals including humans. The infection is common but is rarely reported as there are often no symptoms. In a small number of people who do have symptoms many experience mild flu like symptoms. If a person has been infected with toxoplasmosis and has recovered they are usually protected from future infections. This also applies to pregnant women and to an unborn baby whose mother may have had the infection in the past. Mr Marshall informed the Committee that the concern arises in those women who have no history of the infection, acquire it for the first time in pregnancy, and can then pass on toxoplasmosis onto their unborn baby. Babies born with toxoplasmosis infection can have serious complications which could affect their nervous system, eyes heart and brain. The exact symptoms which a baby may experience and how serious those symptoms may be is unclear.

11.2. The UK NSC last considered screening for toxoplasmosis in the antenatal and newborn periods in 2011 and recommended that a screening programme for either period should not be offered due to the absence of randomised control trials (RCT) to evaluate the potential benefit and adverse effect from treatment, which would be a course of antibiotics.

11.3. Mr Marshall highlighted that screening for toxoplasmosis was offered in other countries however the effectiveness of the programme was questionable and that many were considering stopping screening.

11.4. The review focused on three main areas; condition, test and treatment. It found that the burden of congenital toxoplasmosis and the proportion of women who are susceptible to the primary infection was unknown. Furthermore reports of antenatal screening suggested that the screening pathway was complicated and that there was poor compliance. There were no new studies of screening in the newborn period. In terms of treatment the review found no studies that had been published since the 2011 review to suggest that treatment in the antenatal period would reduce the risk of transmission from mother to unborn baby. A concern with the treatment, use of antibiotics, is the possible harms with it. It also remains unclear whether treatment in the

antenatal or neonatal period can reduce the severity of congenital infection. The Committee noted that no comments were received during the consultation period.

Based on the review the UK NSC recommended that a systematic population screening programme for toxoplasmosis is not recommended because;

- The incidence and prevalence of the condition remains unknown
- The test in antenatal period reports a high false positive rate and recent reports suggest poor compliance with the screening pathway
- There are no published studies to suggest that treatment in the antenatal period would reduce the risk of transmission to the fetus. There is also uncertainty about whether treat men tint he antenatal or neonatal periods can reduce the severity of the infection.

| Criteria | | Met / Not met |
|---|---|---|
| **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. | The incidence of the condition is unknown due the symptoms of those who present often experiencing mild flu like illness |
| **The Test** | | |
| 4 | There should be a simple, safe, precise and validated screening test. | The test in antenatal periods reports high false positives |
| **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 | It is unknown whether screening would be of benefit to the unborn if the mother was to be treated. |

| | | |
|---|---|---|
| | is no prospect of benefit for the individual screened then the screening programme shouldn't be further considered. | |

**Screening for Krabbe disease triage**

12. Mr John Marshall informed the Committee that a request to consider screening for Krabbe disease as a new topic was submitted to the UK NSC at the same point as the annual call for topics had been agreed, as the mechanism for receiving requests of this type. The circulated document sought to review the condition whilst developing an example of the type of document that might be used to evaluate submissions from the annual call for topics

12.1. Mr Marshall discussed the stages of the process to the Committee. Submissions were expected to provide information on the prevalence of the condition and, whether there is a test for it and if treatment is available which will benefit the individual. An evaluation of the submission's relevance to the UK NSC would be undertaken internally. Those which passed this stage would be evaluated to establish whether a more in depth review was justified. The Krabbe disease document was the first attempt to develop a format for evaluation at that stage. A proposal to review screening for adrenoleukodystrophy had been received from the charity ALD life. The charity had agreed to complete the submissions forms by way of a pilot for the annual call for topics and this experience would feed back into the planning work for the annual call.

12.2. In relation to Krabbe disease the Committee noted that two systematic reviews concluded that screening should not be recommended. Both reviews suggested that further work was required to measure the test performance as well as analyse the benefits and harms of early treatment. In additional, an evidence map indicates that the evidence base had not has not changed significantly since the publication of the systematic reviews.

The UK NSC recommended that based on a lack of peer reviewed evidence a systematic population screening programme for Krabbe disease should not be offered.

The Committee as agreed that the document was of a suitable level for the initial evaluation of topics and requested for Mr Marshall to confirm the outcome of the review for Krabbe disease to the submitter.

**Updates**

**NIHR NETSCC Update (for information)**

The Committee noted the updates

**SIGN Update (for information)**

The Committee noted the updates

**AOB**

None noted

**Date of the next meeting**

Wednesday 12 October- London

UK National Screening Committee

**Annex A**

# Economic impact of screening for SCID in the Newborn Bloodspot Screening Programme

## National Screening Committee

15 June 2016

Alice Bessey
Jim Chilcott
Jo Leavis
Ruth Wong

ScHARR
University of Sheffield

## Overview

**Methods**

- Model structure
- Epidemiology
- The TREC test
- Survival and Quality of Life outcomes
- Transplant, management & long term costs

**Results**

- Baseline
- Discounting & costs of test
- Analysis of impacts on people with non-SCID conditions

Questions and answers

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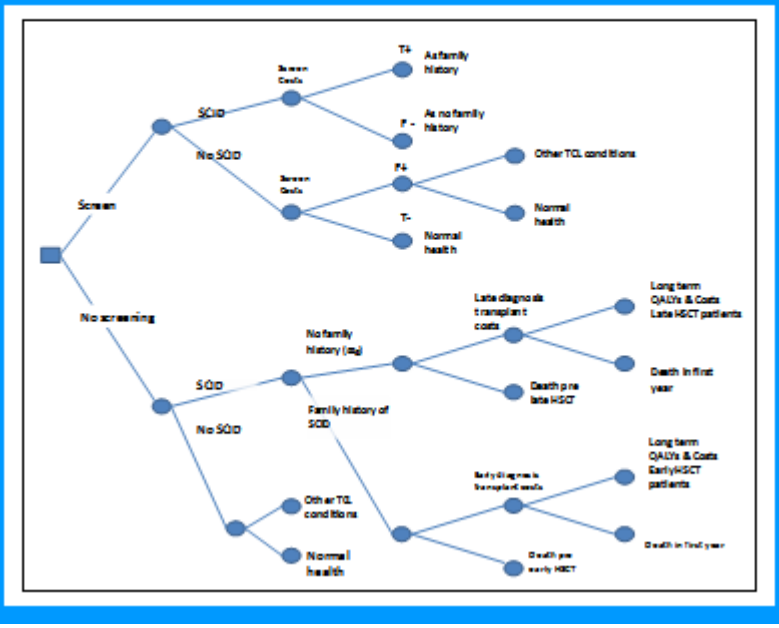
# Model Structure

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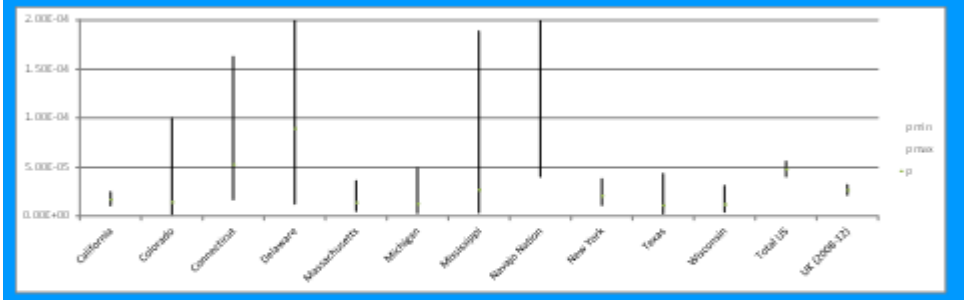
# Incidence of SCID in the UK




SCID in the UK: 2012-2015 82 cases
Expect 12.8-19.6 cases annually
Ascertainment bias: 0.1-4.5 cases missed
Total 13-24 cases

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# The TREC test

TREC screening a two stage test

Current US programmes threshold 20-40 TREC copies/µl

Planned UK threshold 20 copies/µl

Adams[1] found presumptive positive rate of 0.04%

Model assumes

- Sensitivity: 99% (98.5%, 99.5%)
- Specificity: 100%

Basecase cost £3.50 for both stages (£2.50-£4.00 investigated)

1. Adams SP et al. Screening of neonatal UK dried blood spots using a duplex TREC screening assay. Journal of Clinical Immunology. 2014;34(3):323-30.

# Survival outcomes

## Mortality pre and post transplant (after Brown[2])

| | | Total | Survival | Deaths | Mortality |
|---|---|---|---|---|---|
| Early diagnosis | Before HSCT | 60 | 59 | 1 | 1.7% |
| | After HSCT | 59 | 54 | 5 | 8.5% |
| | Overall mortality | 60 | 54 | 6 | 10.0% |
| Later diagnosis | Before HSCT | 48 | 31 | 17 | 35.4% |
| | After HSCT | 31 | 19 | 12 | 38.7% |
| | Overall mortality | 48 | 19 | 29 | 60.4% |

Mortality assumed to occur in the year of transplantation / diagnosis and subsequent mortality as per general population.

2. Brown L et al. Obstetrical and Gynecological Survey. 2011;66(7):398-9.

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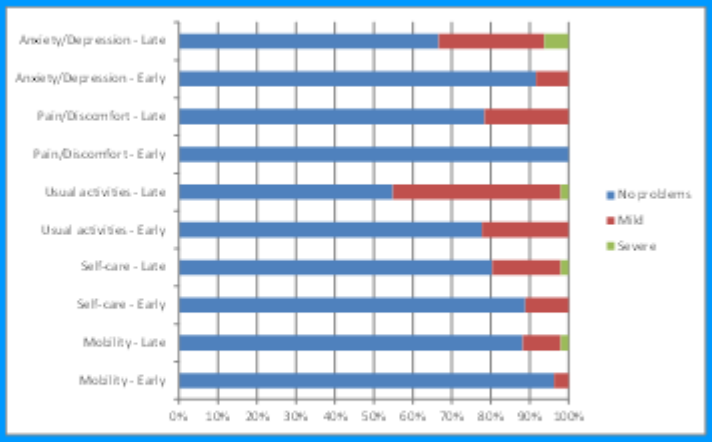
# Quality of life outcomes

Random sample of UK SCID patients with early and late HSCT. Records mapped to EQ5D 3 level health state descriptions




EQ5D TTO
(Adult)

Early HSCT: 0.95 (se 0.02)
Late HSCT: 0.82 (se 0.04)

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# Costs

## Screening costs

- £3.5 per baby
- £182,000 additional staff costs
- £35,000 UV/PCR cabinets
- £276 confirmation costs (Flow cytometry & immunology appointment)

## Non-SCID incremental costs

- £553 pre-terms and secondary to other conditions
- Variant SCID 5 year follow-up- £22,000 per year (includes treatment with IG and antibiotics and appointments)
- Other syndromes - £2035 per year

## HSCT

- Early diagnosed £128,000 (85.6 days total – 2.6 critical care)
- Late diagnosed £231,000 (152 days total – 8 days critical care)
- Death before HSCT £43,000 (25 days total – 12.5 days critical care)

## Long term outcomes

- Enteral feeding for low weight (2% vs 17%)
- Developmental delay (5% vs 19%)
- Booster transplants (6%)
- IG replacement therapy (25%)
- ADHD (21%)
- Prophylactic antibiotics (24% vs 29%)
- Immunosuppressive treatment with steroids (6%)

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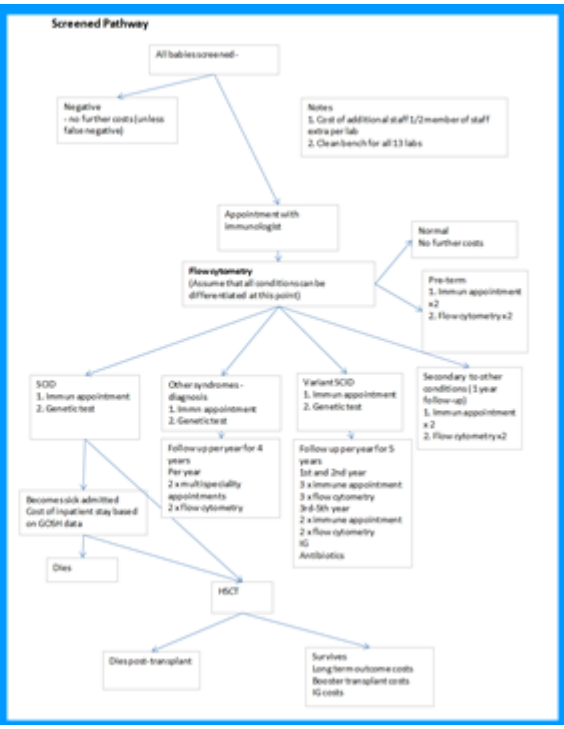
# Screening Pathway



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# RESULTS
## Newborns identified

| | | Mean | 95% CI | |
|---|---|---|---|---|
| No screening | Newborns with SCID detected family history | 4.9 | 3.1 | 6.9 |
| | Newborns with SCID detected symptomatically | 11.1 | 8.4 | 14.1 |
| | Newborns with SCID not diagnosed | 1.5 | 0.1 | 4.5 |
| Screening | Newborns with SCID | 17.3 | 13.5 | 21.7 |
| | Newborns with Variant SCID | 4.4 | 0.1 | 16.1 |
| | Number of Syndromes | 15.2 | 3.6 | 35.0 |
| | Number of secondary to other conditions | 5.9 | 0.3 | 19.1 |
| | Number of Pre-terms | 6.6 | 0.4 | 20.7 |
| | Total presumptive positives | 311.5 | 37.8 | 858.3 |

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## Survival and QoL

| | Mean | 95% CI | |
|---|---|---|---|
| Total QALYs screening | 1208 | 926 | 1543 |
| Total QALYs no screening | 633 | 458 | 837 |
| Incremental | 575 | | |
| Total discounted QALYs screening | 408 | 313 | 521 |
| Total discounted QALYs no screening | 214 | 155 | 283 |
| Incremental | 194 | | |
| Total life years screening | 1267 | 972 | 1610 |
| Total life years no screening | 712 | 518 | 936 |
| Incremental | 555 | | |
| Total discounted life years screening | 428 | 328 | 544 |
| Total discounted life years no screening | 240 | 175 | 316 |
| Incremental | 187 | | |

## Conclusions

- Screening results in an increase in total costs, decrease in early mortality and increased QALYs.
- At a threshold of £20,000 per QALY there is uncertainty in the cost-effectiveness results
- The uncertainty is reduced at a threshold of £30,000 per QALY, using a discount rate of 1.5%, or a lower screening test cost
- High degree of uncertainty on the impact of the non-SCID TCL cases identified

Annex B

# An economic evaluation of the cost-effectiveness of screening for ovarian cancer amongst post-menopausal women who are not at high risk of ovarian cancer

Benjamin Kearns,
The University of Sheffield

## Study aims

- Assess the cost-effectiveness of the three screening strategies evaluated in UKCTOCS:
  - No screening,
  - Multimodal screening (MMS),
  - Ultrasound screening (USS).

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# Methods

Model-based economic evaluation

- Three systematic reviews
  - Ovarian cancer screening trials,
  - Ovarian cancer economic, and
  - Ovarian cancer utility studies.
- Supplemented by evidence from clinical advisors, national reference source, cancer registry data.





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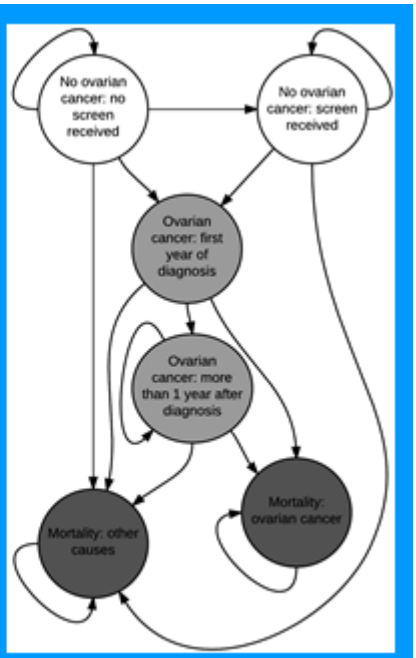
# Simplified schematic of Markov model

- Detailed evidence not available from UKCTOS.
- Estimates of effectiveness estimated from UKCTOCS mortality publication.
- Outcomes: healthcare costs (£ 2013/14) and quality-adjusted life years (QALYs).



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# Key assumptions

- ROCA does not contribute to screen costs.
- Health-related quality of life (HRQoL):
  - Association between stage at diagnosis and HRQoL.
  - No impact of screening *per se*.
  - Treatment (including false positives) reduces HRQoL for one year.
  - After treatment HRQoL same as general population.
- Diagnosis of ovarian cancer outside of screening not associated with false positives.



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# Key inputs

- Cost of MMS: £60.81 (CA-125 cost from ECDC)
- Cost of USS: £61.09 (Ultrasound from reference costs)

| Stage at diagnosis | Treatment costs | Utility values | No screen % diagnosed | MMS % diagnosed | USS % diagnosed |
|---|---|---|---|---|---|
| Stage I | £7,077 | 0.700 | 16% | 27% | 16% |
| Stage II | £7,451 | 0.575 | 8% | 11% | 8% |
| Stage III | £9,142 | 0.487 | 56% | 50% | 57% |
| Stage IV | £6,004 | 0.445 | 19% | 12% | 20% |



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# Modelling long-term effectiveness

Three possible approaches:

1) Use time-series models to extrapolate hazard (no screening) and hazard ratios (MMS, USS).
2) As 1), but treatment effects (hazard ratios) shrunk in the long-term.
3) Fit separate survival models to each trial arm.
4) Fit the same survival model to each trial arm.





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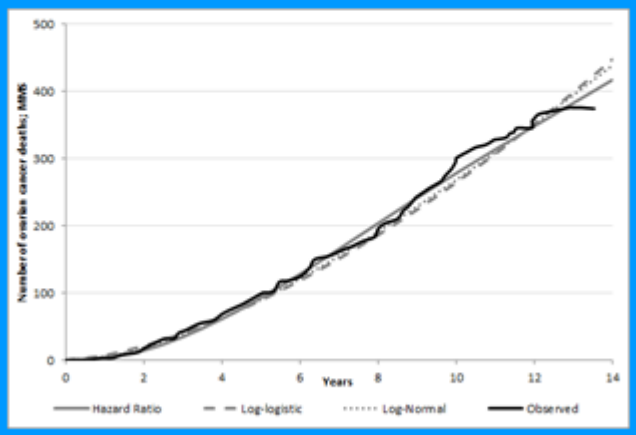
# Fit to observed data…



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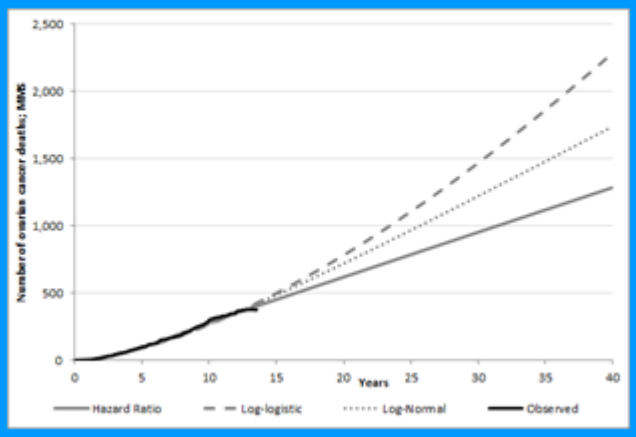
## …And long-term estimates



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## Cost-effectiveness results

| Probabilistic results | No screening | Multimodal screening | Ultrasound screening |
|---|---|---|---|
| Costs | £179 | £598 | £824 |
| QALYs | 14.290 | 14.357 | 14.297 |
| Life Years | 24.660 | 24.803 | 24.729 |
| Ovarian cancer deaths % | 3.19% | 1.41% | 2.35% |

- MSS more effective and less expensive than USS
- MMS more effective and more expensive than no screening. Incremental cost per QALY: £8,864



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# Key sensitivity analyses

| Sensitivity analyses | ICER MMS vs USS |
|---|---|
| Base-case | £8,459 |
| Use separate survival models for extrapolation | £18,372 |
| Use the same survival models for extrapolation | £36,769 |
| Shrink extrapolated effects 1% per year | £9,257 |
| Shrink extrapolated effects 5% per year | £12,643 |
| Diagnosis outside screening; same false positives as MMS | £6,691 |
| Cost of MMS reduced from £60.81 to £35.34 | £5,071 |
| Cost of MMS increased from £60.81 to £75.35 | £10,394 |



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# Conclusions

- MMS and USS both result in health benefits than no screening, but at increased costs.
- MMS is more effective and cheaper than USS.
- The base-case ICER for MMS vs no screening was £8,864 per QALY (95% confidence interval £2,600 to £51,576).
- A key uncertainty is the long-term effectiveness of MMS.



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