

## NHS Fetal Anomaly Screening Programme

### Review of the Model of Best Practice 2008: Down's syndrome screening for England

Gateway Number 9674

#### Background

The UK National Screening Committee (UK NSC) was given responsibility by the Department of Health (DH) to oversee the implementation of a national strategy for Down's syndrome screening which would improve the standard of local services and provide uniformity. Two Health Technology Appraisal (HTA) reports were pivotal in shaping future policy for Down's syndrome screening, and provided the base evidence for the first national Down's syndrome screening policy called a 'Model of Best Practice' in 2003.(1;2) All Trusts were expected to provide a universal screening programme which met a 60% detection rate (DR) for a 5% or less false positive rate (FPR) during 2004 to 2005.(3) Additionally, Trusts were also expected to work towards improving their baseline programmes by improving the DR to 'greater than 75% with a FPR of less than 3%' by April 2007. The next iteration of the national Down's syndrome screening policy was published in 2008(4) and set out that Trusts would be expected to improve on their programme standards. It stipulated a 'DR of equal to or greater than 90% of affected pregnancies with a SPR equal to or less than 2%' by April 2010 which required the introduction of more sophisticated technologies to be employed in order to reach the standard.

In line with the triennial policy review processes set out by the UK NSC this policy has been reviewed during 2010 to ascertain if any changes are needed. Policies (and standards) must conform to the best current evidence available from the research and clinical setting and for these reasons a formal UK NSC established review process is undertaken by all screening programmes. (5)

Presently, 89% of Trusts are on target to meet the previous Model of Best Practice policy and extensive work is being undertaken to support 100% implementation.

## **UK NSC review process adopted to review the Down's syndrome screening policy**

As with previous editions of the Model of Best Practice, the established review process laid down by the UK NSC was undertaken for this policy (Appendix 1). The timescale for the review of this policy was set out over 12 months (Appendix 2). The first step was to review the available evidence in preparation for step two, the external review. The Socio-economic Research and Intelligence Observatory (SERIO) in Plymouth University was commissioned by the Programme Centre to undertake a survey to *'search relevant, recent research literature in order to inform the policy review of Down's syndrome screening...'* (6) (Appendix 3). The report generated, was a comprehensive review of publications concerned with first and second trimester screening strategies (including ultrasound) covering Trisomy 13, 18 and 21.

An external review was undertaken in London on Tuesday 8 June. An invited audience attended the first aspect of the 'external review' which comprised of current and emerging evidence for Down's syndrome screening, presented by a number of well known experts in the field. Holding this event meant that key individuals had the opportunity to review the SERIO evidence, hear about current strategies and newer developments in the scientific field. The meeting effectively was a 'think tank', and an opportunity to appraise the current policy and look at what had been achieved since April 2007.

A national consultation event generated 27 responses (ranging from local Trust staff, biochemists and the RCOG and RCR) which were critiqued by the National Down's Syndrome Core Reference Group (DoSyCoRG) (Appendix 4). Governmental pressures, society/community concerns, media, maternal/parental experience and economic issues were also debated.

This current policy is supported by the NHS Constitution, (7)NICE guidelines, (8;9) RCOG Standards for Maternity Care(10) and the recent NHS White Paper.(11)

## Topics outside of the scope of this policy

### Trisomy 13 and Trisomy 18

There is evidence to support first and second trimester maternal serum screening for Trisomy 13 (Patau’s syndrome) and Trisomy 18 (Edward’s syndrome), although it is not sufficiently robust to introduce it into the NHS FASP at present. The expert policy group has decided to look at the evidence through the UK NSC review process as a separate item.

### The rationale for not recommending Integrated and Serum Integrated Tests

Screening within the NHS, must be cost effective, easy to deliver and achieve the agreed targets. There are a number of considerations given to recommending a screening test which is simple, practical to implement, workable in the NHS, has less service delivery risks, acceptable to women, achieves the agreed standard and is also cost effective compared to others. The *Integrated and Serum Integrated Test* require women to have two serum tests on different appointments for the risk result to be generated. Failing to attend the second appointment renders the test invalid and so there is a responsibility for busy healthcare professionals (usually a midwife) to trace defaulters and ensure they complete the screening cycle. There is a risk that the completion of the test will not occur, data cannot be correlated from one attendance to another, a greater chance that results will be not be accurate because of the differing variables involved and that screening follow up and closure of the screening on those women who change post codes during the two appointments may not be achieved. The result of the test is provided later in the pregnancy limiting the timeframe for decision making. Equally, the more complex the process the more likely are clinical errors to occur. Costs incurred from all strategies have been assessed which provides evidence that the combined screening test is more cost effective whilst still delivering to the set standard.

An example of this is given below in Table 1. for 5000 screening tests.

This strategy includes the complete screening pathway,	Cost in £s for a population of 5000 women who all accept	
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invasive procedure and diagnosis by the appropriate method for the gestation.	screening including 15% of those presenting late and will undergo quadruple testing.	
Quadruple screening	<b>215,493.84</b>	100% of women undergoing this strategy
Combined	<b>180,218.20</b>	85% of women undergoing Combined and 15% accepting Quadruple
Integrated	<b>202,641.98</b>	85% of women undergoing Integrated testing and 15% accepting Quadruple
Serum Integrated	<b>184,016.01</b>	85% of women undergoing Serum Integrated testing and 15% accepting Quadruple

*Table 1. The costs of different screening strategies for 5000 screening tests. NHS FASP, PentAG and KTP. 2010. Decision Planning Tool. NHS Fetal Anomaly Screening Programme: Exeter, UK. Unpublished.*

Additionally, prospective data from the national *Down's syndrome Screening Quality Assurance Support Service* (DQASS) has reported marked improvements in the DR and SPR for Combined testing which is currently reported at 2.2%.

Because of the above considerations '*Integrated*' and '*Serum Integrated Tests*' are not recommended for use within NHS Trusts.

### **Policy recommendations**

The policy recommendations are that the policy remains mainly the same until the next review in 2013. The main recommendation from both the expert group and the consultation is that time should be given to consolidate and embed present changes before any more are introduced.

The only change being implemented in this model of best practice is that the cut off/threshold for the second trimester test is reduced from 1 in 200 to 1 in 150 and so is in line with the first trimester cut off. This will improve (reduce) the screen positive rate (SPR) for the second trimester test with little detriment to the detection rate (DR). It has to be acknowledged that the second trimester test recommended will not meet the 90% DR for 2% SPR. Therefore women should be encouraged to present early and be made aware of the benefits of doing so if they want screening.

The overall timeline for pregnancy chromosomal screening (test) and the laboratory risk calculation is from 10 weeks and 0 days to 20 weeks and 0 days of pregnancy.

The gestational age window for *Combined Test* starts from 10 weeks and 0 days to 14 weeks, 1 day in pregnancy. The *Quadruple Test* window starts from 14 weeks and 2 days to 20 weeks and 0 days. A maternal blood sample is required for the analysis of hCG, alfa-fetoprotein ( $\alpha$ FP), unconjugated oestriol ( $uE^3$ ) and Inhibin-A. This test has been retained in this policy because there will always be women who book too late in pregnancy for combined testing (about 15% of the pregnant population) and wish to have screening. Although the quadruple test only just meets the 2010 standard there is presently no other screening strategy that is available for women presenting beyond 14 weeks and 2 days in pregnancy. It is therefore important that women are made aware of the lesser performance of the quadruple test and that commissioners have in place the offer of Combined testing for those who book in the recommended time window.

## SCREENING POLICY FOR DOWNS'S SYNDROME: PROGRAMME OUTCOMES

Service providers and commissioners are expected to implement and meet the following programme requirements within their local hospital Trust.

A ministerial statement referred to by the Chief Medical Officer in 2001, informed the NHS that a Down's syndrome screening test must be offered to all pregnant women regardless of age.(12) This should be accomplished adhering to and using the strategies and timeframes set out:

### Overall timeline for undertaking Down's syndrome screening: timeframe from 1 April 2011

The screening (test) will be undertaken from 10 weeks, 0 days to 20 weeks, 0 days of pregnancy.

- a) From 10 weeks, 0 days the 'Combined Test' (maternal serum and nuchal translucency scan). The recommended strategy.
- b) From 14 weeks, 2 days to 20 weeks, 0 days, the 'Quadruple Test' (maternal serum) for those presenting later.

### Core Screening standard: Timeframe 1 April 2011

A detection rate (DR) of more than 90%, for a screen positive rate (SPR) of less than 2% (of affected pregnancies) for England for those undergoing Combined screening.

A detection rate (DR) of more than 75%, for a screen positive rate (SPR) of less than 3% (of affected pregnancies) for England for those undergoing Quadruple screening.

### Screening threshold: Timeframe 1 April 2011

All recommended screening strategies are set at a 1 in 150 'cut-off' at term (higher risk)

### Confirmatory testing for higher risk results

Chorionic villus sampling (CVS) or amniocentesis under direct ultrasound guidance for a 'higher risk' result

### Confirmatory analysis

Confirmatory analysis for diagnostic purposes is by QF-PCR.(13)

## Supporting information

### Key components and practicalities of the Combined Test

Key requisites for the Combined Test are the linear fetal measurement of the crown rump length (CRL) to estimate fetal gestational age (dating scan), measurement of the nuchal translucency (NT) space at the back of the fetal neck and maternal blood to measure the serum markers of Pregnancy Associated Plasma Protein A (PAPP-A) and human chorionic gonadotrophic hormone (hCG). An appointment slot of 20 minutes is recommended for both the CRL and NT measurement.

The sonographic measurements of CRL and NT require the skills of a trained ultrasound practitioner (sonographer or clinician) who has the minimal qualifications to undertake ultrasound and specialist training in NT scanning. Without these credentials the potential to either under or over-estimate the NT can happen and generate unnecessary maternal anxiety due because of an inaccurate risk result.

In the late first trimester of pregnancy (about 11 ½ weeks onwards) the fetus begins to stretch and uncurl from its flexed position, which makes CRL and NT measuring somewhat easier. From a laboratory perspective, PAPP-A performs better within early first trimester (from 10 weeks). Thus, in striking a balance between the benefits of all the markers, Trusts should consider screening women around 11 weeks, 2 days of pregnancy. There is evidence for PAPP-A being undertaken from 9 weeks gestation and the Programme Centre is mindful of this and will continue to review this area.

Further information about the Combined Test and NT scanning can be found in the '*Online Nuchal Translucency Training Resource*' and the '*Condensed Education and Training Module for Trisomy 21 (CEM 21)*'. <http://fetalanomaly.screening.nhs.uk/NTResource/>

### **NT measurement and capacity**

All Trusts presently provide dating scans and the ability to measure NT is increasing. By the end of 2010 89% of Trusts are expected to have this in place. The development of capacity to undertake NT measurement and provide education, training and support for professionals is a key priority for the period 2010 to 2013.

### **Rationale for changing the CRL measuring window**

The British Medical Ultrasound Society (BMUS) introduced a new formula for estimating gestational age from CRL measurements. A CRL of 45.0 mm, used to equate to 11 weeks, 0 days. Now it equates to 11 weeks, 2 days. Similarly, the upper window CRL measurement of 84.0 mm, which used to equate to 14 weeks, 0 days, now equates to 14 weeks, 1 day. (14) The new CRL ranges are supported by published evidence.

For the purposes of risk calculation, practitioners must ensure that all fields on the laboratory form are completed and that the CRL and NT measurement are provided in millimeters and not fetal gestational age weeks.

### **Rational for changing the threshold (screening 'cut-off') levels for risk measurements**

The 'cut-off' is an arbitrary distinction between high risk (screen positive) and low risk (screen negative) results. To ensure that the measurement of performance, quality assurance and decision-making are nationally consistent, individual results should be categorized as higher and lower risk. Between 2007 to 2010 the Programme Centre set the cut-off for second trimester at 1 in 200 at term, and for first trimester screening, 1 in 150 at term. Because screening performance has significantly improved, the cut off for both can be set at 1 in 150 at term without any substantial loss in detection rate.

## **Confirmatory testing**

A confirmatory diagnostic service will be offered for all screen positive results. The main services in place at present are amniocentesis and chorionic villus sampling (CVS), both of which have a 1% associated risk of miscarriage.

Clinicians providing either a CVS or amniocentesis service should be trained to the competencies expected of subspecialty training in maternal and fetal medicine, the RCOG Fetal Medicine Advanced Training Skills Module (ATSM) or other international equivalent. Where clinicians are providing amniocentesis and/or CVS outside of a tertiary centre (fetal medicine unit), then referrals should be 'pooled' so that clinical expertise and competency is maintained by undertaking an adequate number of procedures.

Women should be offered the choice of either CVS in the first instance if they have a high risk Combined Test result. The alternative is amniocentesis after 15 weeks. Improved screening has and will continue to reduce the overall number of high risk (SPR) results. This in turn will reduce the demand on clinicians providing a diagnostic service.

The type of laboratory sample analysis provided will depend on the indication for referral. QF-PCR will be undertaken to provide a confirmatory result.

## **Quality assurance**

Audit and monitoring are central functions of the UK NSC National Screening Programmes and these help to continually improve the quality of screening and ensure women receive the best available risk evaluation. It is recommended therefore that all screening strategies, including those using NT, are part of external quality assessment and assurance schemes. This includes participation in DQASS. Anonymised biochemistry and ultrasound NT patient data are sent to

DQASS where the median values and performance of the screening test are assessed against the recommended programme outcomes.

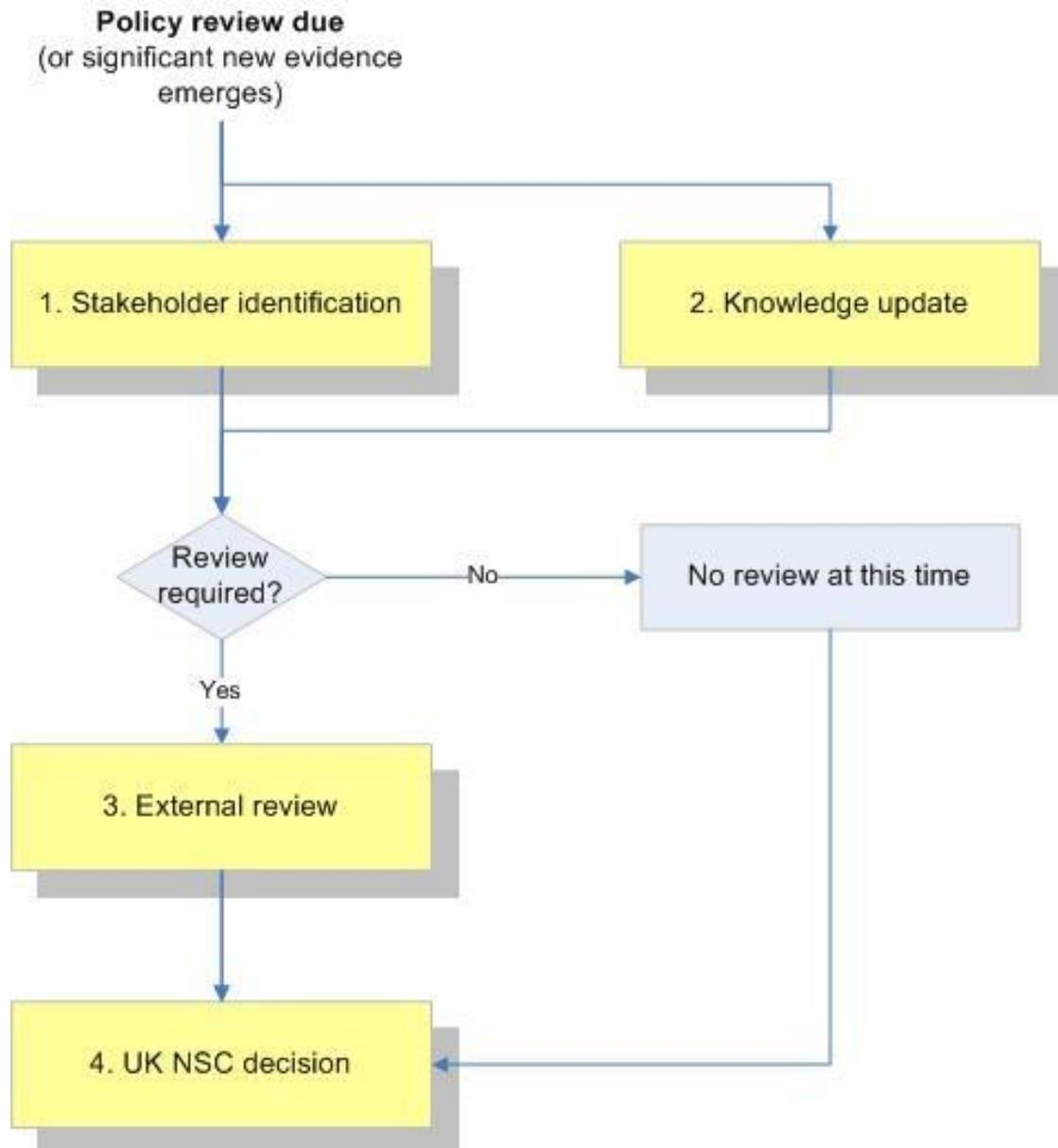
DQASS issues a full report, with a summary report and letter to the Chief Executive of the Trust, and the relevant stakeholders sitting within the current Public Health departments (including public health directors, screening leads and commissioners). It is recommended that all laboratories should undertake Clinical Pathology Accreditation (CPA) and be part of the National External Quality Assurance Scheme (UK NEQAS)

Review and report undertaken and compiled by Mrs. Donna Kirwan National Projects Officer to NHS FASP and Mrs.Pat Ward, National Programme Director.

Chair of the expert review group – Professor Peter Soothill.

## Appendix 1

### UK NSC Policy Review Process



## Appendix 2

### NHS Fetal Anomaly Screening Programme (NHS FASP)

#### Review of Down's syndrome screening policy 2010. – review scope and process

##### Background.

Screening for Down's syndrome has been implemented as a Ministerial commitment since 2001 with the first policy being published in 2003, Model of Best Practice. Following a further review a revised policy was set out in 2008 which takes the service up until 2010. The main drive of the most recent policy is to implement combined screening in England by 2010 with a core standard of a detection rate of greater than 75% for a less than 3% screen positive rate. We are presently on target to meet that standard. The developmental standard is set at 90% detection rate for a 2% screen positive rate for 2011.

The policy is reviewed every three years in line with the UKNSC process.

##### Aim

During 2010 the policy review will take place in line with set UKNSC process. This is to determine if there are any changes required to the present strategy and assess any new technologies which may improve the screening test outputs.

##### Areas for assessment

1. New strategies or evidence which may improve the sensitivity and specificity, including nasal bones and ductus venosus.
2. Reviewing the present cut offs
3. Reviewing the present overall standard of sensitivity and specificity.
4. Assessing whether T13 and T18 screening can be incorporated into the earlier combined screening rather than the later US scan at 18 weeks.

- The possibility of screening before 10 weeks of pregnancy

### Approach.

The review will include a wide systematic review of present world evidence and incorporate expert views from the field as well as collaborative working with the professional colleges.

### Time frame

It is expected that this will take 12 months to complete. More detailed timescales are set out below.

### Overall Plan

- Perform initial systematic review of evidence, commission from the Social Research & Regeneration Unit, (SRRU) Plymouth.
- Convene small expert group to review the evidence and suggest basic recommendations.
- Convene a larger meeting of wider stakeholders for their comments on the initial recommendations
- Produce a consultation document and undertake a formal wide consultation
- Ratify comments from the consultation using small expert group
- Completion and agreement from the FMCH and UKNSC prior to the gateway review.
- Final agreement from the Gateway process.

	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan
<b>1.Initial review</b>													
<b>2. Small group</b>													
<b>3.Larger meeting</b>													
<b>4.Consultation doc</b>													
<b>5.Ratify comments</b>													
<b>6.FMCH and UKNSC</b>													
<b>7.Gateway process</b>													

The initial review (1) should clearly set out the requirements of what should be reviewed and the time periods those publications cover. This will be an independent review of evidence with

no person having a vested interest. It is suggested that it will be undertaken by the Social Research & Regeneration Unit, A University of Plymouth Centre of Expertise who have performed reviews for us previously.

A small Expert Group (2) to provide expert knowledge, agree comments and provide final recommendations will be convened.

It is envisaged that the larger group meeting (3) will include all areas for assessment so that agreement can be reached on a base policy at this meeting. 70 will be included to obtain the service level views on how implementation may take place. This should also include commissioners as well as public health representatives.

A wide consultation(4) will take place with all areas for a period of no less than 6 weeks. This will include the professional colleges, public health leads, Heads of Midwifery, sonography departments, laboratories, cytogenetics and the regional teams. (This is presently not an exhaustive list)

The small Expert group (5) will ratify the comments and produce a final document.

(6) This will be forwarded to the FMCH and UKNSC for agreement.

(7). It will be submitted to the Gateway process for final DH agreement before publication

### **Appendix 3**

#### **Literature Survey for the Review of Down's Syndrome Screening Policy 2010**

##### **1. Introduction**

The Socio-economic Research and Intelligence Observatory (SERIO) at the University of Plymouth was commissioned by the Fetal Anomaly Screening Programme Steering Group (FASPSG) to undertake a literature survey. The survey was required to search relevant, recent research literature in order to inform the policy review of Down's syndrome screening taking place, in line with UKNSC process, in 2010.

The survey of the literature was to focus upon research publications concerned with:

1. Screening strategies, including combined, integrated, quadruple, contingency and repeated screening.
2. Specific markers: nuchal translucency as part of the combined screening strategy, absent nasal bone, and ductus venosus flow.

3. Specific serum markers, including Pregnancy Associated Placental Protein A (PAPP-A), A Disintegrin and Metalloprotease 12 (ADAM 12), Free Beta Human Chorionic Gonadotropin (HCG), total HCG, AlphaFeto Protein (AFP), Unconjugated Estriol (uE3) and Inhibin-A, as part of screening strategies.

4. Screening between 8 and 10 weeks of gestation, to follow on from the literature search carried out by SERIO in 2008.

5. Screening for trisomy 13 and trisomy 18 prior to 14 weeks of gestation.

6. Detection and screen positive rates of screening for T13 and T18 by the 18 – 21 weeks scan as a comparator to above (5).

### 1.1 Protocols

It was agreed that:

The literature search was to focus upon publications dating from 2000 onward and 2003 in the case of nuchal translucency; Upon research conducted in the UK, USA, Western Europe and Australia; and, The report on the literature search would include annotated bibliographies related to each section of the report.

### 1.2 Procedures

#### 1.2.1 Locating References Relating to Specific Markers

Keyword searches were carried out using Pub Med and COPAC.1 Apparently relevant titles were followed up by accessing abstracts. Articles were accessed/ordered where the abstract suggested relevance. The search of sites was undertaken between 1st January 2010 and 1st March 2010.

Search terms related to the specific markers and ultrasound features were combined with terms relating to 'Down' or 'Down's syndrome', 'trisomy 21', 'trisomy 18' and 'trisomy 13' and 'prenatal detection'. Searches were limited to English language research papers and reports.

Initial searches were undertaken using combinations of the following terms:

The specific marker or ultrasound feature;

Down/Down's/ syndrome/trisomy 21/ trisomy 18/ trisomy 13 prenatal detection;

Down/Down's syndrome /trisomy 21/trisomy 18/trisomy 13 prenatal detection/diagnosis first/second/ trimester;

Down/Down's syndrome/ trisomy 21 prenatal detection/diagnosis first trimester screening; and,

Down/Down's syndrome/trisomy 21 early 1st trimester detection/ detection pre-/prior to 10 weeks of gestation.

This strategy was underpinned by a search and re-search technique, in order to try to ensure that the location of relevant research documents by the research team was as comprehensive as possible.

## Appendix 4

### Membership of Down's Syndrome screening Core Reference Group (DoSyCoRG)

Mrs. Pat Ward	National Programme Director NHS FASP
Mrs. Donna Kirwan	National Projects Officer NHS FASP
Professor Peter Soothill	Chair of NHS FASP Steering Group Professor of Fetal Medicine, University of Bristol
Professor Dave Wright	Professor of Computing and Mathematics, University of Plymouth
Mr. Pran Pandya	Director of Fetal Medicine, University College of London Hospitals.
Mrs. Jane Mc Farlane	Antenatal and Newborn Screening Coordinator/Supervisor of Midwives Hull and East Yorkshire Hospitals NHS Trust
Dr. Rowena Clayton	Director of Public Health, West Midlands SHA
Mr. Aris Papageorghiou	Consultant in Fetal Medicine, St Georges Hospital, University of London
Professor. Kevin Spencer	Consultant Biochemist & Clinical Lead Barking, Havering & Redbridge University Hospitals NHS Trust

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