Public Health England

NHS

NHS Fetal Anomaly Screening Programme

Down's syndrome, Edwards' syndrome and Patau's syndrome screening Handbook for Laboratories

Valid from August 2018

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Public Health England (PHE) exists to protect and improve the nation's health and wellbeing, and reduce health inequalities. We do this through world-leading science, knowledge and intelligence, advocacy, partnerships and the delivery of specialist public health services. We are an executive agency of the Department of Health and Social Care, and a distinct delivery organisation with operational autonomy. We provide government, local government, the NHS, Parliament, industry and the public with evidence-based professional, scientific and delivery expertise and support.

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About PHE screening

Screening identifies apparently healthy people who may be at increased risk of a disease or condition, enabling earlier treatment or better informed decisions. National population screening programmes are implemented in the NHS on the advice of the UK National Screening Committee (UK NSC), which makes independent, evidence-based recommendations to ministers in the 4 UK countries. The Screening Quality Assurance Service ensures programmes are safe and effective by checking that national standards are met. PHE hosts the UK NSC secretariat.

www.gov.uk/topic/population-screening-programmes
Twitter: @PHE_Screening Blog: phescreening.blog.gov.uk
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Contents

Executive summary

The NHS Fetal Anomaly Screening Programme (FASP) has produced this handbook with support from the members of the programme advisory and task groups and in collaboration with health professionals from around England.

This practical guidance supports healthcare professionals and stakeholders in the operational delivery of the screening pathway. New screening coordinators, screening support sonographers and laboratory leads will find the handbook a source of information to support their induction and practice.

The handbook provides an update of recent changes to the programme. It refers to supporting documents and clinical guidance that providers should take into account to deliver a high quality screening programme.

Commissioners and screening and immunisation teams will find the handbook puts these documents into the context of the day to day work of the screening coordinators, screening support sonographers, screening laboratory teams and obstetricians and fetal medicine specialists who make up the FASP multi-disciplinary team (MDT).

The handbook provides:

- structure and governance of the NHS FASP programme
- a comprehensive outline of each of the conditions screened for
- clarity on the screening tests and terminology
- hyperlinks to information and supporting documents
- detail on the delivery of each step of the screening pathway
- key practice points to consider
- updates on current quality assurance, data collection and audit processes

The handbook will be updated regularly to ensure it continues to be a valid reference document.

Introduction

The purpose of this handbook is to bring together in one publication the NHS Fetal Anomaly Screening Programme's (FASP) policies, guidelines, recommendations, standards and specifications for Down's syndrome (T21), Edwards' syndrome (T18) and Patau's (T13) syndrome screening that relate to the work performed by screening laboratories.

Each NHS screening programme has a defined set of standards that providers have to meet to make sure that local programmes are safe and effective.

Quality assurance (QA) is the process of checking that these standards are met and encouraging continuous improvement and includes QA of Laboratories.

All NHS FASP screening laboratories must:

- be accredited by the UK Accreditation Service (UKAS) to ISO. 'Medical laboratories – Requirements for quality and competence (ISO 15189)' or be CPA accredited and actively transitioning towards ISO 15189
- participate in EQA schemes accredited to ISO. 'Conformity assessment. General requirements for proficiency testing schemes (ISO 17043)'
- meet the screening programme quality assurance requirements mapped to ISO 15189
- use ISO 15189 accredited reference laboratories

The UK Accreditation Service (UKAS) will look at both ISO 15189 and the screening requirements on behalf of PHE Screening Quality Assurance Services and the national screening programme.

Conventions
Throughout the document the following are used interchangeably:

- Down's syndrome is referred to as T21
- Edwards' syndrome as T18
- Patau's syndrome as T13

Related documents
This handbook is one part of a suite of five documents. The others are:

- Ultrasound Practitioner's Handbook: this sets out the requirements for ultrasound practitioners involved in the pathway for first trimester screening for Down's syndrome, Edwards' syndrome and Patau's syndrome.

- Screening programme handbook: this provides operational guidance and information for all practitioners involved in screening for Down's syndrome, Edwards' syndrome and Patau's syndrome and the 18^{+0} to 20^{+6} (18 weeks and 0 days to 20 weeks and 6 days) week fetal anomaly scan
- Service specification. Down's syndrome, Edwards' syndrome and Patau's syndrome screening (No.16) and 18^{+0} to 20^{+6} fetal anomaly scan (No.17). These documents outline the service and quality indicators expected by NHS England and the recommendations and standards of the UK NSC
- Screening standards: this document defines a set of standards relating to screening for Down's syndrome, Edwards' syndrome and Patau's syndrome screening and the 18^{+0} to 20^{+6} week fetal anomaly scan

The NHS Fetal Anomaly Screening Programme (FASP)

General principles of screening

Screening is a process of identifying apparently healthy people who may be at increased risk of a disease or condition. They can then be offered information, further tests and appropriate treatment to reduce their risk and/or any complications arising from the disease or condition. Further information regarding the general principles of screening can be found on GOV.UK

Background

NHS FASP, based in Public Health England, is an expert team that ensures national consistency and provides expertise. They support and manage on-going roll out, further technical and professional development of the programme and ensure quality and safety standards are maintained and continuously improved.

The screening programme has evolved from its establishment in 2001 when the majority of screening was performed using maternal biochemistry in the second trimester. The recommended method of screening is now first trimester screening, combining maternal age, biochemistry and ultrasound measurement of fetal nuchal translucency (NT) to provide a pregnant woman with her chance of having a baby with Down's syndrome, and/or Edwards' syndrome and Patau's syndrome. NHS FASP has established standardisation of the following to enable commissioners and quality assurance teams to assess the quality of the service provided:

- national standards, guidance and chance cut-off for Down's syndrome, Edwards' syndrome and Patau's syndrome screening programme in the light of emerging evidence
- a statistical service to ensure that laboratories have access to the best advice in maintaining their population medians
- specifications for chance calculation software to make sure that all laboratories calculate chance results in a uniform way

The policy

NHS FASP requires that there is equal access to uniform and quality-assured screening across England and women are provided with high quality information so they can make

an informed choice about their screening and pregnancy options. Education and training resources are available for staff covering all stages of the process, from informing women of test availability, through to understanding and supporting their decisions.

NHS FASP offers screening to all eligible pregnant women in England to assess the chance of the baby being born with Down's syndrome, and/or Edwards' syndrome or Patau's syndrome or a number of fetal anomalies (structural abnormalities of the developing fetus).

The screening policy is to offer screening to assess the chance of the baby being born with Down's syndrome, Edwards' syndrome or Patau's syndrome. The test of choice for both singleton and twin pregnancies is first trimester combined screening. Women can choose:

- not to have screening
- to have screening for T21 and T18 / T13
- to have screening for T21 only
- to have screening for T18 / T13 only.

More information on the conditions screened for can be found in the NHS FASP programme handbook.

Where the offer of screening is accepted, the first scan usually takes place between 11 to 14 weeks and includes a blood sample taken to test for Down's syndrome and/or Edwards' syndrome and Patau's syndrome, with a second scan for fetal anomalies between 18^{+0} to 20^{+6} weeks. The timing of the scans allows for further diagnostic tests if required and ensures women have time to consider decisions about continuing their pregnancy.

The second scan is designed to identify anomalies which indicate:

- conditions that may benefit from treatment before or after birth
- that the birth should be in an appropriate hospital/centre and/or to optimise treatment after the baby is born
- that the baby may die shortly after birth

Some women may choose not to be screened at all and it is important that this choice is respected.

Diagnostic testing can include chorionic villus sampling (CVS), which involves removing a small piece of tissue from the placenta, or amniocentesis, which involves removing a small amount of amniotic fluid (the fluid surrounding the baby in the uterus).

Screening tests

First trimester combined test

The combined test uses maternal age, the nuchal translucency measurement (NT) and two biochemical tests, free beta hCG and PAPP-A, together with the gestational age calculated from the crown rump length (CRL) measurement, to calculate the chance of the pregnancy being affected by T21 or T18/T13. The combined test can be performed when the CRL is between 45.0mm to 84.0mm which corresponds to 11^{+2} to 14^{+1} weeks of gestation. If the ultrasound measurement shows that the CRL is less than 45.0mm, the woman should be recalled for a further scan to measure the NT. If the CRL is greater than 84.0mm, the second trimester quadruple test should be offered.

The first trimester combined test allows earlier decision making for women. In practice, two models are available for performing the combined test:

1. a maternal blood specimen may be taken (from 10 weeks onwards) prior to the ultrasound scan. The biochemistry results can then be made available at the time of the NT scan and the combined test result can be calculated at the time of the appointment. Although the result may be calculated by the sonographer, the laboratory remains responsible for the software that calculates the screening result. Midwifery and/or ultrasound departments must have a process in place to share ultrasound measurements and final screening results with the laboratory to enable timely audit of all results.

2. a maternal blood specimen may be taken at the time of the ultrasound scan and the combined test result made available within a few days of the biochemistry results being authorised by the laboratory.

The gestational age, for the purposes of standardising marker values, should be calculated by use of crown rump length (CRL) obtained by ultrasound measurement. Combined screening can be offered (including IVF pregnancies) where the crown rump length (CRL) measurement of the baby is between 45.0mm and 84.0mm Where the CRL is above 84.0mm then gestational age should be calculated using the head circumference (HC) (Loughna et al, 2009).

Maternal age in in-vitro fertilisation (IVF) pregnancies using donor eggs should be derived from the date of birth or age of the donor at the time of egg collection as this is required for calculation of prior chance. (Risk Calculation Software Requirements for Down's syndrome Screening 2013).

NHS FASP recommends that the Down's syndrome and Edwards' syndrome and Patau's syndrome screening chance result generated from first trimester combined screening must not to be recalculated up or down following the initial screening test or at the 18^{+0} to 20^{+6} fetal anomaly ultrasound scan due to the presence or absence of a single ultrasound marker of less predictive power than increased nuchal fold (Smith-Bindman et al, 2001).

Second trimester quadruple test

There will always be a need for a screening test in the second trimester for those women who book too late for first trimester testing or when an NT measurement cannot be obtained in the first trimester.

The quadruple test uses maternal age and four biochemical markers measured from 14^{+2} weeks until 20^{+0} weeks: - AFP, hCG (total, intact or free beta subunit), uE3 and Inhibin-A. Although this combination of markers has a lower detection and a higher screen positive rate than the combined test, it is the nationally recommended screening strategy for the second trimester.

An ultrasound scan will be required to date the pregnancy and a fetal head circumference (HC) is the recommended measurement for women presenting in the second trimester. If the HC is ≥ 101.0mm then the blood sample for the quadruple test may be taken. If the CRL is > 84.0mm but the HC is < 101.0mm there are two options; to assess the gestational age of the pregnancy using the HC and, to calculate from that, the date the woman will be between 14^{+2} to 20^{+0} weeks of pregnancy and offer an appointment for blood sampling or to rebook the woman for a further scan at 15 weeks of pregnancy (calculated from the HC) where the HC can be re-measured and bloods taken.
For more information regarding the practicalities of a solution to combining dating and screening requirements at the first pregnancy scan see Chudleigh et al 2011.

National standards

The national standards seen in Table 1 state the threshold for the national programme and will be reported on each year by the Down's syndrome Quality Assurance Screening Service (DQASS) and the National Congenital Anomaly and Rare Diseases Registration Service (NCARDRS).

Table 1. National standards – thresholds for performance

Screening strategy	Thresholds	
	Acceptable	**Achievable**
T21	Standardised DR 85%	
	Standardised SPR 1.8-2.5%	Standardised SPR 1.9-2.4%
T18/T13	Standardised DR 80%	
	Standardised SPR 0.1-0.2%	Standardised SPR 0.13-0.17%
T21/T18/T13	Standardised DR 80%	
	Standardised SPR 1.8-2.5%	Standardised SPR 1.9-2.4%
Quadruple (T21)	Standardised DR 80%	
	Standardised SPR 2.5-3.5%	Standardised SPR 2.7-3.3%

*The DR and SPR for the quadruple test relate to singleton pregnancies only.

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Markers used in screening tests

Maternal age

All women have a chance of having a baby with Down's syndrome, Edwards' syndrome or Patau's syndrome and this chance increases with age. The older a mother, the more chance she has of having a baby with one of these conditions.

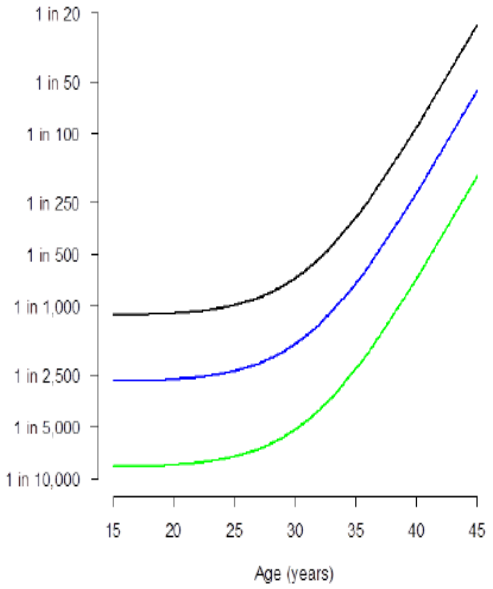

Table 2 - example for a woman who is 16 weeks pregnant

Maternal age	Chances of having a pregnancy affected by Down's syndrome	Probability
20 years	1 in 1500	0.07%
30 years	1 in 900	0.1%
40 years	1 in 100	1%

Figure 1: Graph to illustrate the likelihood of a pregnancy affected by Down's syndrome, Edwards' syndrome or Patau's syndrome according to maternal age showing T21 (black line), T18 (blue line), T13 (green line). The chance is at the time of the 12 weeks scan.

Biochemical markers

There are five analytes (commonly referred to as markers) measured by the laboratory that are used to calculate the likelihood of a pregnancy being affected by Down's syndrome, Edwards' syndrome or Patau's syndrome – six if human chorionic gonadotropin (hCG) and its free beta subunit are considered as two separate analytes.

Screening laboratories must use the recommended combination of biochemical markers for both the first and second trimester screening tests.

Alpha fetoprotein (AFP)
AFP is a glycoprotein of 591 amino acids produced by the yolk sac and the fetal liver. Its level in fetal serum increases until the end of the first trimester and then gradually decreases. Concentrations are much lower in maternal serum but they continue to rise until about week 32. An increased level in maternal serum is associated with a possible open neural tube defect such as spina bifida, although ultrasound scanning is the recommended screening test for neural tube defects. Decreased levels in the second trimester are associated with Down's syndrome.

Human chorionic gonadotropin (hCG)
hCG is a glycoprotein of 244 amino acids produced by the developing embryo and later by the placenta. It is a dimeric molecule composed of an alpha and a beta subunit. The alpha subunit is common to several other hormones [luteinising hormone (LH), follicle stimulating hormone (FSH) and thyroid stimulating hormone (TSH)]. The beta subunit is unique to hCG. Concentrations of hCG rise exponentially after conception reaching a peak at about 9-12 weeks, then falling to reach a plateau at about 20 weeks. Some of the beta subunit (less than 1% of the intact dimeric hCG) is free in the blood and this molecule can be measured by the laboratory as a distinct entity. A raised level of hCG and/or the free beta subunit in the first and second trimester is associated with an increased chance of a Down's syndrome affected pregnancy. A decreased level is associated with both Edwards' syndrome and Patau's syndrome.

Unconjugated oestriol (uE3)
Oestriol is one of the three main steroid hormones produced by the feto-placental unit during pregnancy. It is made in the placenta from the 16-hydroxydehydroepiandrosterone produced by the fetal liver. Once in the maternal circulation most of the oestriol undergoes conjugation with glucuronides or sulphate but about 10% remains as the unconjugated form. Low levels of uE3 in the maternal circulation in the second trimester are associated with Down's syndrome.

Inhibin-A
Inhibin-A is a dimeric molecule comprised of an alpha and a beta polypeptide chain linked by a disulphide bridge. (A similar molecule called Inhibin-B has the same alpha chain but a different beta chain). It is produced by the corpus luteum and the placenta during pregnancy with levels increasing during the first trimester, then declining to reach a plateau in the second trimester before increasing again in the third trimester. Elevated levels in the second trimester are associated with pregnancies affected by Down's syndrome.

Pregnancy associated plasma protein - A (PAPP-A)
PAPP-A is a large zinc glycoprotein produced by the placenta where it is thought to regulate the activity of factors responsible for the growth of the placenta. Low levels in maternal blood in the first trimester are associated with pregnancies affected by Down's syndrome, Edwards' syndrome and Patau's syndrome.

Effect of vaginal bleeding on biochemical markers used in screening for Down's syndrome, Edwards' syndrome and Patau's syndrome

There are concerns that a history of significant maternal vaginal bleeding might change the levels of biochemical markers used in the combined and quadruple tests. NHS FASP recommends women are offered the screening tests in the normal way (calculating the chance based on maternal age, NT, free beta hCG and PAPP-A levels or the chance based on AFP, free beta hCG, Inhibin and UE3), as current evidence suggests that the biochemical marker levels are not significantly different in women with this history.

Effect of 'vanished twin' on biochemical markers used in screening for Down's syndrome, Edwards' syndrome and Patau's syndrome

Combined screening
When ultrasound shows there is an empty second pregnancy sac, the biochemical markers appear no different to those in a singleton pregnancy and the combined test of NT, PAPP-A and free beta hCG can be used to calculate the chance result.

When ultrasound shows that there is a second sac containing a non-viable fetus (sometimes called 'vanished' twin), it is possible there could be a contribution to the maternal biochemical markers for many weeks. It is recommended that in this event, where a woman has accepted screening, the CRL and NT measurements should be undertaken and a local policy be in place to provide referral to a health professional with the relevant skills and knowledge to discuss the options available for testing which fall outside the remit of the NHS screening programme.

Quadruple screening
When ultrasound shows there is an empty second pregnancy sac or there is a second sac containing a non-viable fetus (sometimes called "vanished" twin), the biochemical markers appear no different to those in a singleton pregnancy and the Quadruple test can be used.

Ultrasound markers

Nuchal translucency (NT)
Nuchal translucency is the ultrasound appearance of a collection of fluid under the skin behind the neck of the fetus in the first trimester of pregnancy. The thickness of the nuchal translucency is measured by the sonographer and used in calculating the chance of the pregnancy being affected by Down's syndrome, or Edwards' syndrome and Patau's syndrome. An increased NT measurement is associated with an increased chance of these autosomal trisomies as well as other fetal anomalies such as cardiac defects, but as with all screening tests, a pregnancy with an increased NT may also have a normal outcome.

Where screening in the first trimester using the combined screening strategy is accepted, the biochemical component of the test must be completed. Therefore, where an NT measurement of ≥3.5 mm is recorded, a blood sample must be taken but referral should not be delayed to await the biochemistry marker levels and results should be forwarded to the clinician as soon as they are available to support discussion of further investigative options with the woman.

Crown rump length (CRL)
The gestational age of the fetus is calculated from the ultrasound measurement between the top of the head (crown) to the bottom of the buttocks (rump) known as the crown rump length (CRL). The gestational age in days can be calculated by the use of tables or an equation from the CRL measurement. Whilst it is acknowledged that the description of the first trimester screening test is primarily described within a gestational age timeframe (10^{+0} weeks to 14^{+1} weeks), entry into the screening programme within the laboratory should be based on CRL measurements of 45.0mm to 84.0mm rather than gestational age of weeks and days. Because the concentration of the biochemistry markers is dependent on the gestational age of the fetus, it is important that the CRL is measured accurately.

Head circumference (HC)
If the CRL is greater than 84.0mm, it is recommended that the gestational age of the fetus is calculated using the fetal head circumference (HC). Ultrasound measurements of the biparietal diameter (BPD using 'outer to outer' calliper placement) and the occipital- frontal diameter (OFD using 'outer to outer' calliper placement) are used to

calculate the head circumference which can then be used to date the pregnancy, Loughna et al (2009).

Information about NHS training for competency in the measurement of nuchal translucency (NT) and crown-rump length (CRL) and the recommended measurements charts can be found in the ultrasound practitioner's handbook.

Singleton pregnancies

Combined test chance results

For women screened using the combined test, dependent of their screening choice, the following chance results will be reported:

- a term chance of T21 and a term chance of T18/T13
- a term chance of T21 only
- a term chance of T18/T13 only

Quadruple test chance results

Quadruple screening can be offered between 14^{+2} and 20^{+0} weeks.

For women screened using the quadruple test a single term chance of T21 will be reported.

Twin pregnancies

Having more than one baby in a pregnancy complicates screening. Each feto-placental unit will contribute to the concentrations of the biochemical markers used in the chance calculation. In the first trimester there is an NT measurement for each fetus.

Combined screening in twin pregnancies

The test of choice for twin pregnancies is first trimester combined screening. Every opportunity must be made to maximise the offer of first trimester combined screening. Chance results to be reported are:

- a term chance of T21 and a term chance of T18/T13
- a term chance of T21 only
- a term chance of T18/T13 only

For women screened using the combined test, where a dichorionic twin pregnancy is identified the chances will be reported for each fetus. In a monochorionic twin pregnancy both fetuses are either affected or unaffected so the chance will be the same and a single “pregnancy” chance will be reported.

Quadruple screening in twin pregnancies

For the small number of women who have a twin pregnancy and miss the opportunity of having first trimester screening, we can offer the choice of a second trimester quadruple test for Down's syndrome only.

This means the decision making process is more difficult for women as this test is less sensitive than first trimester combined screening and any subsequent decisions about invasive diagnostic testing and selective reduction will have to be made later in the pregnancy.

The policy takes into account the following facts:

- chorionicity is likely to be difficult to ascertain in the second trimester and therefore unknown
- the chance of a T21 birth from a dizygotic twin pregnancy is higher than that from a singleton pregnancy

This is as an interim policy to provide equity of choice for women whilst further evidence and other strategies become available.

Quadruple screening in twin pregnancies can be offered to women:

- who present for the first time in the second trimester or
- where the Nuchal Translucency (NT) could not be measured in the first trimester

For this reason women considering screening should have a discussion with a healthcare professional with an interest in multiple pregnancies to assist in facilitating an informed choice.

There are likely to be between 500-1600 women with twin pregnancies in the eligible population each year who fall outside of the combined testing programme who may be offered second trimester quadruple testing. Pregnancies in this group are likely to be of uncertain chorionicity compared to the general population of twin pregnancies. Amongst these, fewer than four affected pregnancies would be expected.

Monochorionic twins

- the chance of a T21 birth from a monochorionic pregnancy is lower than that from a singleton pregnancy due to a higher fetal loss rate amongst affected pregnancies

- the performance of screening in monochorionic twins is comparable to that of singletons: a detection rate is 80% for a standardised screen positive rate of 3%

Dichorionic twins

- the chance of a T21 birth of at least one baby from a dichorionic twin pregnancy is higher than that from a singleton pregnancy
- in dichorionic twins, where one is affected and the other unaffected, the performance is poorer due to the markers being less discriminatory but is better than using maternal age only, where the detection rate is only 30% for a 5% screen positive rate
- in dichorionic twins the detection rate is 40-50% for a standardised screen positive rate of 3%

It should be noted that the approach used in calculating a quadruple twin pregnancy chance results is referred to as ‘pseudo’ risk/chance in the literature. This is the established methodology currently available and simply means that the chance would be accurate in predicting a false-positive rate (which relates only to the marker distributions in unaffected twin pregnancies). The chance is a pregnancy related chance, that is, not fetal specific.

The term chance cut-off of 1 in 150 is applied to the pseudo risk/chance.

Because the calculation of chance results in twin pregnancies relies on limited evidence and assumptions, the chance estimate should be interpreted by suitably experienced practitioners.

The risks of miscarriage and other procedure related complications are higher in twin pregnancies, usually quoted as 1 in 50. If one fetus is affected selective reduction may be an option.

Please refer to NICE for guidance on screening for Down’s syndrome, Edwards’ syndrome and Patau’s syndrome in higher multiple pregnancies (triplets and more).

Chance cut-off

NHS FASP defines the national cut off and this is currently set at 1 in 150 at term for both first and second trimester screening tests. A woman with a chance of 1 in 150, or greater (1 in 2 to 1 in 150), of having a pregnancy affected by Down's syndrome or Edwards' syndrome and Patau's syndrome in the first trimester or Down's syndrome only in the second trimester is considered to be in the 'higher chance' group. Women in this group are offered diagnostic test such as chorionic villus sampling (CVS) or amniocentesis to directly investigate the fetal chromosomes.

Women having screening using the combined test, dependant of their screening choice, up to two chance results are reported:

- a chance for T21 and a chance for T18/T13
- a chance for T21 only or T18/T13 only

The cut-off is based on a chance at term rather than a chance at the time of the screening test. The main reason for this is that the original studies on the likelihood of having a Down's syndrome affected pregnancy is based on the birth prevalence of the condition before screening was implemented.

There is a significant fetal loss rate between the time of screening and birth but the loss rate is not exactly known. A chance at the time of screening would need to make assumptions about the fetal loss rate during the various stages of pregnancy. This will be kept under review.

Chance calculation software

The software used to calculate the Down's syndrome, and Edwards' syndrome or Patau's syndrome, chance result from the biochemical and ultrasound markers is complex and best provided and supported by commercial suppliers. The screening programme developed a specification for the chance result calculation software for laboratories in England. Software in use in screening laboratories must meet the requirements of this specification.

This specifies in detail all the aspects that need to be incorporated into the software package to provide consistent chance results across the country. Some variables that need to be entered into the software are defined by the local user to take account of the reagents used for screening and the characteristics of the local population they are screening. These would normally be decided by the laboratory in collaboration with DQASS – the statistical support service provided by PHE.

Request form and data fields

The table below includes the data fields that need to be included when designing a laboratory screening request form for Down's syndrome, Edwards' syndrome and Patau's syndrome. Supplier software and data entry methods may vary. To maximise the potential for supporting screening laboratories effectively and driving quality improvement in the programme's performance, all data items specified below would be helpful to the DQASS service, and NHS FASP recommends as request forms and electronic data fields are developed, these are included. Fields highlighted in bold text below must be provided to DQASS.

Table 3 – Request form and data fields required when screening for Down's syndrome, Edwards' syndrome and Patau's syndrome

Patient ID: (can affix label)	Surname Forename(s) NHS No (or equivalent in Scotland, if they utilise this form) Hospital number. Date of birth Address Postcode
Requesting details:	**Hospital name/code** Consultant name/code Midwife name/code Hospital/clinic contact no.
Sample details:	**Collection date and time Taken by (initials)** Combined/ Quad test (tick boxes) **Down's syndrome chance required [Yes] [No]** **Edwards' syndrome/Patau's syndrome chance required [Yes] [No]**
Pregnancy details:	LMP date **Date of ultrasound** **Sonographer initials/DQASS ID Code (1st trimester screening) HC/CRL/NT measurements (enough space for twins)** **Twin chorionicity – unknown/monochorionic/dichorionic** Gestation in weeks and days at scan **Smoking – none/stopped in pregnancy/number of cigarettes per day** Nicotine replacement – e-cigarettes/patches/other **Diabetes – No/Type 1/Type 2 -**on insulin /Type 2 – not on insulin **Maternal weight at sampling (in kg)** **Previous T21 Previous T18/T13** **IVF pregnancy Donor egg** **Date of birth or age of donor at time of egg collection** Date of egg harvest Assisted pregnancy by induction of ovulation **Family origins of pregnant women:**

	UK White N European White S or other European White Other non-European White Black African or Caribbean S Asian S.E Asian Mixed races: White and black (African or Caribbean) White and Asian Black and other

Report formats

The chance result report may contain a number of information fields, for example, biochemistry marker values, the NT measurement, the Down's syndrome chance, the Edwards' syndrome and Patau's syndrome combined chance, as well as the necessary demographics of the mother, date of the specimen, destination of the report.

Achieving the right balance is important to ensure adequate information is given to understand the chance assessment report versus too much information that has the potential to cause confusion. Only results and comments relating to the conditions screened for as part of the NHS screening pathway for Down's syndrome, Edwards' syndrome and Patau's syndrome in this pregnancy should be included on the laboratory report.

In addition to the data given on the screening request form (as listed in table 3) the following data items must be included in the results report:

- analytical results for each biochemistry marker and the NT measurement for the first trimester combined test, with units of measurement and corrected MoM value
- all the relevant information used for calculating the screening result, for example: date of birth, maternal weight, smoking history, ethnicity, scan measurement data and, where appropriate, IVF, diabetes, previously affected pregnancy and twins
- the factors for which the markers were corrected, i.e. weight, smoking, ethnicity and where appropriate, IVF, diabetes, previously affected pregnancy and twins
- the Down's syndrome prior chance and adjusted chance
- the Edwards' syndrome and Patau's syndrome combined prior chance and adjusted chance
- for women screened using the combined test, where a dichorionic twin pregnancy is identified the chances will be reported for each fetus. In a monochorionic twin pregnancy both fetuses are either affected or unaffected so the chance will be the same and a single chance will be reported. For the quadruple test a pregnancy risk will be reported
- the classification of the chance into the higher and lower chance category with an indication of the chance cut-off used

Examples of letters for use in informing women of their screening chance results can be found in the appendix 1.

Specimen transport and storage

Blood taken for Down's syndrome, Edwards' syndrome and Patau's syndrome screening should be collected into a plain or serum gel (SST) tube. It is important that the correct order of draw is followed and that a screening sample should always be taken first if a full blood count sample is being taken at the same time.
Tubes containing ethylene-diamine-tetra-acetic acid (EDTA) must be avoided due to significant interference of EDTA in the immunoassays used to measure the serum markers for screening.

Blood samples taken for Down's syndrome, Edwards' syndrome and Patau's syndrome screening should be processed as soon as possible. This is because free beta hCG is likely to increase in concentration over time due to the dissociation of the intact hCG molecule. This effect is temperature dependant and the rate of deterioration of the sample increases with increasing temperature. The guidance below is for samples transported and stored at room temperature as this is most likely to be the conditions in clinics and during transport to laboratories. However, during periods of increased temperatures providers should consider both storing and transporting samples in cool bags to reduce the effects on the markers, particularly free beta hCG.

It is good practice for the sample to be centrifuged and separated from the clot, if a gel separator tube is not used, within 24 hours of collection. If this is not possible, samples may remain as whole blood at room temperature for up to 48 hours. Samples received as whole blood after 48 hours from sample collection should be rejected.

Table 4 - Screening sample stability acceptance criteria

Sample Type	**Room temperature (20°C)**	**4°C**
Whole blood (unseparated)	48 hours	5 days
Serum (separated)	72 hours	14 days

Serum samples are stable up to 72 hours at room temperature.
All samples that have been transported or stored at room temperature for longer than 72 hours should be rejected.

The stability of the samples is significantly improved by refrigeration at 4°C, with whole blood samples and serum stable for several days. High temperatures (in excess of 30°C) should be avoided as deterioration of free beta hCG occurs within 4 hours following sample collection.

Analysers and kits

There are several suppliers in the UK providing assays and analysers that are Conformité Européene (CE) marked for use in Down’s syndrome, Edwards’ syndrome and Patau’s syndrome screening.

NHS FASP does not have a preferred supplier and laboratories must decide which analyser best suits their purpose.

Some assays are available on random access analysers which overcome the need to batch specimens. All assays should be verified and used according to the manufacturer’s instructions and any deviations must be fully validated in compliance with Medical laboratories — Requirements for quality and competence (ISO 15189:2012).

Analysers must be maintained according to the manufacturer’s instructions and a comprehensive maintenance record log compiled, preferably in an electronic format. Standard operating procedures that would pass a UKAS assessment must be in place in the laboratory for each assay and all procedures relating to the screening work of the laboratory.

Laboratory throughput

NHS FASP specifies the following throughput criteria for laboratories (or laboratory network) undertaking screening for Down's syndrome, Edwards' syndrome and Patau's syndrome:

- a standalone screening laboratory must have a workload of at least 8000 specimens per annum for each of the first and/or second trimester screening tests that are offered
- all laboratories with a workload of less than 8000 specimens per annum for a specific screening test must be part of a network screening service for that test
- each laboratory in a network screening service must have a minimum throughput of 2000 specimens per screening test per annum
- in a network screening service the total aggregated specimens must be no less than 8000 specimens per annum

A laboratory network screening service must meet the following criteria:

- the network screening service must be directed by a person who has executive accountability and the competence as assessed by UKAS to assume governance responsibility for the service. A clear governance structure that integrates with Trust governance and quality structures must be outlined
- there must be an agreed contractual arrangement between all laboratories in the network screening service and the commissioners of the service
- the network screening service lead will receive one six monthly combined DQASS report
- each laboratory in the network screening service must have identical screening policies
- each laboratory in the network screening service must have identical analytical procedures (analysers, kit lots etc.)
- each laboratory in the network screening service must have chance calculation software with an identical chance calculation algorithm and population parameters

It is envisaged that the above criteria will improve the quality of the screening programme by:

Achieving precision in the DQASS assessment of laboratory performance
To achieve effectiveness and statistical precision in the DQASS assessment of laboratory performance and to sufficiently make accurate estimates of standardised screen positive rates an annual throughput of 8000 is required.

In cases where laboratory throughput is small, DQASS is unable to measure performance with reliability. For example in a recent DQASS report based on a sample size of less than 700 records over a six month period the feedback to the laboratory was as follows:
“There is insufficient data to assess whether or not there are substantial deviations from target. Overall the estimated median MoM shows a small positive bias, but is within 5% of target. Given the small sample size, any flag assigned to this marker should be interpreted with caution. The flag allocated may not be a reliable measure of performance due to low throughput.”

An annual throughput of 8000 enables the monthly mean log10 MoM within each cycle to be estimated to within ±0.1 standard deviations with 95% confidence.

Achieving sufficiently precise estimates of standardised screen positive rates
An annual throughput of 8000 enables the SPR for each cycle to be estimated within ± 0.5% with 95% confidence.

Enabling proportionate quality improvements whilst sustaining and developing expertise
T21/T18/T13 screening is a specialist, complex and continually evolving area of work. A minimum laboratory throughput will enable this expertise to be concentrated and developed. It will also enable DQASS to give additional focused support where it is required.

The principle of a network screening service with a minimum of 2000 samples per test per year enables laboratories with a smaller throughput to maintain the ability to monitor performance whilst working in a consistent way to a set of common standards. It also allows capacity and capability building to develop proficiency and technical expertise in a safe and efficient way.

Promoting efficiency
A high throughput, particularly where technology in use requires batching of samples, means that laboratories will be able to meet recommended turnaround times for results; poor turnaround times could delay diagnosis and on-going management options.

The workload required to effectively and efficiently run a small throughput laboratory is about the same as, if not more, than a laboratory with a larger throughout. It could be argued that the effort and resources needed for internal and external QA are greater and therefore less cost effective.

Enabling laboratories internal quality control (IQC) to detect biases in MoM values in a timely way

Although DQASS provides a highly beneficial external QA service, it should be remembered that this is a retrospective analysis on the whole. In addition to the retrospective audit feedback that DQASS provides, laboratories must also have IQC processes that are performed frequently enough to enable timely changes where required.

This enables laboratories to be responsive to changes in real time. To detect changes in biases in a timely manner a high throughput is required.

Internal quality control (IQC)

Because the chance calculation involves the results of several markers, it is vital that each measurement is as accurate as possible to minimise the inaccuracy of the final chance reported.

The quality control procedures employed by the laboratory must be sufficiently rigorous to detect problems with the assays, not only on a day-to- day basis but also to check problems like a gradual drift of results with time and changes that may occur when a new batch of reagents is brought into use.

Manufacturer’s recommendations for internal quality control (IQC) must be strictly adhered to, but regarded as the minimum requirements, and additional controls included especially if an assay is particularly troublesome.

It is good practice to include validated IQC material from another supplier rather than rely solely on the controls provided by the manufacturer of the assay kit. Senior staff should examine long term trends in IQC data to detect assay drift and particular attention should be paid to comparing patient and IQC results when a new batch of reagents is introduced.

Significant shifts in population medians have been observed on occasions with the introduction of a new reagent batch, which can then impact on the risks reported if it is not anticipated and allowed for. Similar effects have been seen after analyser maintenance and vigilance is required at all times.

Quality assurance

Quality assurance of screening programmes

Each NHS screening programme has a defined set of standards that providers have to meet to ensure that local programmes are safe and effective.

All commissioners and service providers must refer to the public health functions agreement (Section 7A) NHS FASP service specification (No 16), and supporting standards and laboratory handbook to ensure a programme is set up correctly and is meeting the standards and guidance set by NHS FASP.

Quality assurance (QA) is the process of checking that these standards are met and encouraging continuous improvement and includes:

- advice on the development of national quality standards
- monitoring of how services meet (or fail to meet) standards
- providing expert screening advice for incident management
- facilitating quality review of services, including peer advice
- supporting on a day-to-day basis, those involved in commissioning or providing screening services

QA covers the entire screening pathway; from identifying who is eligible to be invited to screening, through to referral and treatment where required/appropriate.

The aim of QA is to maintain minimum standards and drive continuous improvement in the performance of all aspects of screening and to ensure that all women and their babies have access to high quality screening wherever they live. QA is essential in order to minimise harm and maximise benefits of screening.

Formal QA visits to local screening programmes provide the forum for a peer review of the whole multidisciplinary screening pathway - an assessment of the effectiveness of team working within the local screening programme and associated referral sites.

Regional QA teams:

- advise providers and commissioners about reducing risks in local screening programmes
- assess the robustness of local arrangements through audit, as part of peer review and in the investigation of any incidents as they occur

- act as a conduit for information and dialogue at national, regional and local levels, additionally sharing learning
- participate in a formal process of QA, which is the responsibility of each local screening programme
- monitor the performance of the local programmes in a variety of ways such as review of statistics, regional meetings or informal visits, all of which offer a valuable insight into the activity of a local programme

Regional QA Teams will review reports of assessments and surveillance of screening laboratories by UKAS.

Quality assurance of NHS FASP laboratories

Laboratories undertaking Down's syndrome, Edwards' syndrome and Patau's syndromes screening must:

- be accredited by the UKAS to ISO. 'Medical laboratories – Requirements for quality and competence (ISO 15189) or be CPA accredited and actively transitioning towards ISO 15189
- participate in EQA schemes accredited to ISO. 'Conformity assessment. General requirements for proficiency testing schemes (ISO 17043)' (e.g. National External Quality Assessment Service (NEQAS) scheme for peptide hormones)
- submit data to the DQASS as specified in sections 8 and 15 of this handbook
- meet the screening programme quality assurance requirements mapped to ISO 15189
- and use ISO 15189 accredited reference laboratories

UKAS will look at both ISO 15189 and the screening requirements on behalf of PHE Screening Quality Assurance Services and the national screening programme.

The laboratory must be able to demonstrate robust oversight and leadership for screening, including:

- senior leadership for screening in the laboratory
- contingency plans for screening
- participation in cross-organisational and multidisciplinary arrangements
- management review and annual screening report

The laboratory must be able to demonstrate good communication and collaboration with other services in the screening pathway, including:

- documented procedures for communication with other services
- formal agreements with referral laboratories
- incorporation of screening into the laboratory quality management system

- standard operating procedures to track samples from point of receipt to authorisation and reporting of screen positive results to clinical services
- inclusion of users in assessment and review

The laboratory must have effective procedures to assess and manage safety and performance including:

- documented risk management policy for the laboratory as part of the overall risk management arrangements for the screening pathway
- audit schedule in line with screening risks and performance requirements
- procedures to audit and ensure screening is completed, from point of receipt of to communicating screen positive results to clinicians
- compliance with the NHS Screening Programmes guidance for managing safety incidents
- provision of standards and Key Performance Indicators (KPIs) and other data and screening activity data to NHS Screening programmes

Down’s syndrome screening Quality Assurance Support Service (DQASS)

DQASS is a service commissioned by Public Health England to support NHS FASP.

Aims of DQASS

The main aim of DQASS is to monitor and support the quality and effectiveness of prenatal screening in England. DQASS provides feedback and support to laboratories, sonographers and to NHS FASP.

The analyses provided by DQASS are used to improve the performance of the screening through feedback on all aspects of the test to laboratories, ultrasound departments and commercial suppliers.

DQASS works on a rolling audit of screening test data on a six monthly cycle. The statistical analysis monitors the screening process at various levels: from the overall standardised screen positive rate at the top level to specific adjustments for ethnicity, smoking and other factors applied to individual biomarkers. Through meta-analyses DQASS provides information on effects of factors such a smoking that can be used to improve screening performance.

All NHS FASP screening laboratories must be part of DQASS and submit their data according to the schedule provided by DQASS.

Information DQASS needs from laboratories

A designated person in each laboratory must provide the data specified below for a six-month period in Excel format with anonymised individual patient data contained in separate rows. Data provided should only include screening performed as part of NHS FASP using either combined screening or quadruple screening testing strategies. Data related to other testing strategies such as the integrated test or private screening arrangements should be removed by the laboratory prior to the data being submitted to DQASS.

Each column should correspond to a specific data field. The first row should contain the variable label. For the combined test, each row should correspond to a fetus. For the quadruple test each row should correspond to a pregnancy.

Items in bold should be included in data returns to DQASS if available and added where request card and software updates are made.

Table 5 – Data required by DQASS

Pseudo ID	
Maternal/Pregnancy Characteristics	Maternal date of birth Maternal age at Expected Date of Delivery LMP date Maternal weight at test date in kg (One decimal place) Smoking (Stopped before pregnancy/ Stopped during pregnancy/Smoker) Smoking number per day (*Nicotine replacement – e-cigarettes/patches/other if included on request and available*) Ethnicity Diabetes – No/Type 1/Type 2 Insulin (Yes/No) Previous Trisomies (T21, T18, T13) Twin/Singleton Fetus number (1, 2) Chorionicity (MC, DC) Date of sample
Biochemical Markers	Blood sample date Gestational age (in days) at blood sample date AFPconcentration[1] uE3 concentration[1] Total hCG concentration[1] Free Beta hCG concentration[1] PAPPAconcentration[1] Inhibin concentration[1] AFP MoM[2] uE3 MoM[2] ThCG MoM[2] Free Beta hCG MoM[2] PAPPA MoM[2] Inhibin MoM[2]
Ultrasound Scan	Scan date CRL mm (one decimal place) HC mm (one decimal place) NT mm (one decimal place) DQASS Identity code of sonographer and USS department
Chance results	Prior chance for T21 Prior chance for T18/T13 Chance for T21 Chance for T18/13

[1] In cases where biochemical measurements of a particular marker are produced from different instruments, the instrument used should be given in a separate field.

[2] MoM values should be provided after all corrections for gestation, weight, ethnicity, twins, have been applied

The laboratory should liaise with the screening support sonographer (SSS) to ensure that the DQASS ID codes for the sonographers are up to date and that the codes can be matched to an ultrasound department to enable feedback to be given.

If some of the above data is not recorded then a blank column, or a column with NA in each cell, should be reported. Although it is not used for the statistical analysis, the following information should be provided for comparison purposes:

- current medians by day, or regression equation used, indicating both the gestational age and weight adjustment equations used
- current algorithm parameters, means, standard deviations, correlation coefficients for both the unaffected and affected outcomes
- dates of lot and median changes and corresponding lot numbers
- analyser and software used
- any specific queries should be attached

DQASS reports

DQASS undertakes a range of statistical analysis on the data provided and produces reports summarising activity and performance.

Laboratories receive detailed information on serum analyte performance and a summary ultrasound report of the departments they support.

Ultrasound practitioners receive information on their paired NT and CRL distributions in relation to the Fetal Medicine Foundation (FMF) reference curve and a summary laboratory report will be sent to the SSS.

Table 6: DQASS Report dissemination

Report	Recipient	Information included
Individual practitioner report	Practitioner via SSS NHS FASP (only red flags National QA team (only red flags)	Practitioner ID Number of measurements Flag status Bias relative to FMF reference curve
Ultrasound department summary report	SSS Laboratory NHS NHS FASP National QA team Regional QA team SILs via Regional QA team	Screening laboratory and time period covered by report For each practitioner - ID number, number of scans, median NT, median CRL, median bias and flag status 95% confidence intervals for estimated bias for each practitioner Previous cycle flag status
Laboratory summary report	Laboratory SSS NHS trust chief executives - all trusts using the laboratory NHS FASP National QA Team Regional QA Team SILs via Regional QA team	Number of pregnancies covered in the data set and the number with a risk given DQASS modelled screening performance (DR, FPR, SPR) Data collected, ultrasound measurements and algorithm parameters used First trimester marker performance with reference to the NT comparison to the FMF reference curve NT MoM diagnostics Biochemistry estimated median values Sonographer ID compliance Recommendations and actions

Contacting DQASS

DQASS
ITTC Building,
Room 303 Tamar Science Park
1 Davy Road
Derriford
Plymouth
Devon, PL6 8BX

Email: dqass@plymouth.ac.uk
Telephone: 01752 764437
Fax: 01752 762114

Education and training

e-learning resources

Providers are responsible for funding minimum training requirements to maintain an effective screening workforce including Continuous Professional Development (CPD). NHS FASP and UK NSC provide on-line educational resources to support CPD.

Those specific to laboratory based staff include:

- Screening for Down's syndrome, Edwards' syndrome and Patau's syndrome screening e-learning resource
- Antenatal and Newborn screening resource

It is the responsibility of providers to ensure that training is completed satisfactorily and recorded and that there is a system in place to assess on-going competency.

The provider should also ensure that there are adequate numbers of appropriately trained staff in place to deliver the screening programme in line with best practice guidelines.

NHS FASP holds annual meetings for biochemistry staff involved in the screening pathway to discuss programme developments and offer support to the laboratories in driving quality improvement. DQASS also hold regular workshops and information updates. Attendance by a representative of all laboratories is recommended and encouraged.

Sign up to the PHE Screening blog

Signing up to the PHE Screening blog is the best way to keep in touch with news, views and updates relating to all the work of PHE screening and the FASP programme.

Visit www.phescreening.blog.gov.uk to sign up for email alerts.
You can also join the screening conversation at Twitter by visiting @PHE_Screening

Information for the public

Screening tests for you and your baby booklet
‘Screening tests for you and your baby’ is the recommended information booklet covering both antenatal and newborn screening.

Each screening programme is described in a standard format. This makes it easier for the public to compare the various tests and, crucially, to understand that some decisions are more complex than others.

Screening standards and key performance indicators (KPIs)

Screening standards

Screening standards were introduced to provide a way of measuring how well the screening programmes are doing in important areas. Key performance indicators (KPIs) are a subset of the screening standards for the NHS screening programmes

These contribute to the quality assurances of screening programmes but are not, in themselves, sufficient to quality assure or performance manage screening services. They help local screening services to identify potential problems so they can be put right and have led to changes in practice and implementation of measures to prevent errors occurring in the screening pathway.

NHS FASP screening standards that are relevant for the Down's syndrome, Edwards' syndrome and Patau's syndrome biochemical screening laboratories are:

Standard	Laboratory responsibility
Standard 1: Coverage and identifying population (T21/T18/T13 screening)	Data source
Standard 3a: The test performance - screen positive rate (SPR) (T21/T18/T13)	Data source
Standard 3b: The test performance - Detection rate (DR) (T21/T18/T13 screening)	Data source & responsible for submission of monthly report of higher chance results to NCARDRS
Standard 5: The test turnaround time (T21/T18/T13 screening)	Data source & responsible for submission to NHS FASP programme as part of annual standards data reporting process

The KPI (FA1) for the Down's syndrome, Edwards' syndrome and Patau's syndrome screening programme that has relevance to the laboratory is:
'The proportion of laboratory request forms providing complete data prior to screening analysis and submitted to the laboratory within the recommended timeframe of 10^{+0} to 20^{+0} weeks' gestation'.

Although this KPI is not a reflection of the performance of the laboratory, the laboratory provides the data for completion of the statistics.

NHS FASP screening standards that are relevant for the Down's syndrome, Edwards' syndrome and Patau's syndrome diagnostic (genomic) laboratories are:

Standard	Laboratory responsibility
Standard 9a,b,c,d: Diagnose (T21/T18/T13 screening and 18^{+0} to 20^{+6} fetal anomaly ultrasound)	Data source (submitted annually via Association for Clinical Genomic Science – ACGS)

Reports to National Congenital and Rare Diseases Registration Service (NCARDRS)

All biochemical screening laboratories are required to provide a monthly report of all higher chance results from the NHS FASP Down's syndrome, Edwards' syndrome and Patau's syndrome screening pathway using either the combined or quadruple test, using the dataset requirements provided by the NCARDRS team for antenatal screening.

Screening safety incidents

A screening safety incident is any unintended or unexpected incident(s) that could have or did lead to harm to one or more persons who are eligible for NHS screening; or to staff working in the screening programme.

A screening safety incident can affect populations as well as individuals. It is an actual or possible failure in the screening pathway and at the interface between screening and the next stage of care.

Although the level of risk to an individual in an incident may be low, because of the large numbers of people offered screening, this may equate to a high corporate risk. It is important to ensure that there is a proportionate response based on an accurate investigation and assessment of the risk of harm. Due to the public interest in screening, the likelihood of adverse media coverage with resulting public concern is high even if no harm occurs.

A screening laboratory must have an incident management policy in line with the screening managing safety incidents guidance. This guidance outlines how screening incidents should be reported and investigated. The escalation procedure within the host trust should be described and an up-to-date list of incidents and their associated investigation reports maintained.

Local risk management policies require staff to assess the risk associated with laboratory processes and how they can be improved within the laboratory. One way is to prepare a risk assessment of the screening pathway in the laboratory to identify risks and review how they could be mitigated.

An online resource for managing screening safety incidents is also available.

Lessons to be learnt from screening incidents are shared via the screening blogs.

The laboratories are also be expected to inform the Medicines and Healthcare Products Regulatory Agency (MHRA) of any adverse incidents that causes, or has the potential to cause, unexpected or unwanted effects involving the safety of patients or other persons.

Glossary

Amniocentesis

An invasive procedure undertaken from about 15 completed weeks (15^{+0}) onwards to obtain a sample of amniotic fluid (liquor) surrounding the fetus. Using an aseptic technique whilst under continuous ultrasound guidance, a sterile needle is passed through the mother's abdomen, uterus and amniotic sac. A sample of amniotic fluid is aspirated with a syringe and sent for analysis to test for a range of chromosomal and inherited disorders. Up to 1 out of every 100 women who have an amniocentesis will miscarry.

Amniotic fluid

Also known as 'liquor', this is the fluid surrounding the fetus during pregnancy. It contains substances and cells from the fetus, which can be removed by amniocentesis and examined.

Biochemical markers

Analytes (commonly referred to as markers) measured by the laboratory that are used to calculate the likelihood of a pregnancy being affected by a condition or syndrome.

Chance

The likelihood that an event will occur.

Chance cut-off

Determines those women who are in the 'higher chance` group and considered to screen positive.

Chorionic villus sampling (CVS)

An abdominal or cervical procedure performed under continuous ultrasound guidance after 10 completed weeks in pregnancy to obtain a sample of placental tissue for chromosomal or genetic analysis. The range of chromosomal and genetic conditions that can be detected is similar to those for amniocentesis. Up to 1 out of every 100 women who have a CVS will miscarry.

Chromosome

Structures found in the nucleus of cells, composed of DNA and proteins. Normally humans have 46 chromosomes in each cell, 23 from each parent. Of these, 22 are autosomes and one is a sex chromosome.

Combined test

Between 11^{+2} and 14^{+1} weeks of pregnancy, a combination of the nuchal scan measurement and a blood sample from the mother which measures the concentration of pregnancy associated plasma protein-A (PAPP-A), and free beta human chorionic gonadotrophin (Free beta hCG). Together with the mother's age and the gestation of the pregnancy, these are used to estimate the chance that the fetus is affected with Down's syndrome.

Crown rump length (CRL)

Ultrasound measurement between the top of the head (crown) to the bottom of the buttocks (rump). To be eligible for first trimester combined screening as part of the NHS screening programme the CRL should measure between 45.0mm and 84.0mm.

Cut-off level

Screening tests divide people into a group at lower risk of the condition being screened for, and a group at higher risk who are then offered further investigations. The cut off level is a point defined by the programme and used to distinguish higher and lower chance.

Detection rate

The proportion of affected individuals with a positive screening result.

Diagnostic test

Refers to the process involved in obtaining a definite diagnosis. For example the diagnostic test on an amniocentesis sample (invasive procedure) is the full karyotype or QF-PCR.

Down's syndrome (trisomy 21)

Down's syndrome is caused by an extra copy of chromosome 21 in all or some cells of the body.

A person with Down's syndrome will have some level of learning disability. This means they will find it harder than most people to understand and to learn new things. They may have communication challenges and difficulty managing some everyday tasks. People with Down's syndrome have distinctive facial features but they do not all look the same.
Some health problems are more common in people with Down's syndrome. These include heart conditions and problems with hearing and vision. Many health problems can be treated but unfortunately around 5% of babies will not live past their first birthday.

Edwards' Syndrome (trisomy 18)

Babies with Edwards' syndrome have an extra copy of chromosome 18 in all or some cells.
Sadly the survival rates are low and of those babies born alive only around 10% live past their first birthday. Some babies may survive to adulthood but this is rare. All babies born with Edwards' syndrome will have a learning disability and a wide range of physical challenges, which can be extremely serious. They may have problems with their heart, respiratory system, kidneys and digestive system.
Babies with Edwards' syndrome may have a low birthweight.

Eligible population

Target group for offer of screening.

Embryo

A fertilised ovum (egg) in the early stage of development. In humans the term is reserved for the first eight weeks of development.

False-negative result
Screening tests divide people into lower and higher risk groups. Some people with a negative screening test result do actually have the condition being screened for. These people are said to have a 'false-negative' result.

False-positive result

Screening tests divide people into lower and higher risk groups. Some people with a positive screening test result do not actually have the condition being screened for. These people are said to have a 'false-positive' result.

Fetal anomaly

Structural abnormalities with how the fetus has developed.

Fetal anomaly ultrasound scan

A detailed ultrasound scan, sometimes called the mid-pregnancy or 20-week scan. It is a screening test offered to all pregnant women and is usually carried out between 18 and 21 weeks of pregnancy. It produces a 2-dimensional black and white image that gives only a side view of the baby and it checks for major physical abnormalities in the baby; although it can't pick up every abnormality.

Fetus

In humans, the unborn child after the end of the eighth week of pregnancy to the 24th week of pregnancy.

Gestational age

The duration of an ongoing or completed pregnancy, measured from the first day of the last menstrual period (usually about two weeks longer than that measured from conception). Gestational age is usually measured in weeks and days.

Invasive diagnostic test

A method used to obtain a sample, to aid diagnosis e.g. amniocentesis and chronic villi sampling are invasive diagnostic tests.

Laboratory throughput

Number of samples analysed per cycle.

Marker

An identifiable physical location on a chromosome whose inheritance can be monitored. Markers can be expressed regions of DNA (genes) or some segment of DNA with no known coding function but whose pattern of inheritance can be determined.

Miscarriage

Loss of a fetus before the 24th week of pregnancy.

Nuchal translucency scan (NT)

Between 11^{+2} and 14^{+1}, the thickness of fluid in the tissue space within the nape of the fetal neck, the nuchal translucency, can be measured. An increased amount of fluid may indicate that the fetus has Down's syndrome, structural or genetic anomaly. By combining the mother's age and the gestation of the pregnancy with information from the scan an individual statistical chance of an anomaly can be given for that particular pregnancy. If the chance is one in 150 or higher a diagnostic test, such as CVS, will be offered.

Patau's Syndrome (trisomy 13)

Babies with Patau's syndrome have an extra copy of chromosome 13 in all or some cells.
Sadly the survival rates are low and of those babies born alive only around 10% live past their first birthday. Some babies may survive to adulthood but this is rare.
All babies born with Patau's syndrome will have a learning disability and a wide range of physical challenges, which can be extremely serious. They may have problems with their heart, respiratory system, kidneys and digestive system. Around half of babies with Patau's syndrome will have a cleft lip and palate. Babies with Patau's syndrome may have a low birthweight.

Placenta

The structure that provides the fetus with nourishment during development. It is attached to the wall of the uterus and connects to the fetus through the umbilical cord.

Prevalence

The proportion of people in a population who have a given disease or attribute.

Quadruple test

Second trimester test to calculate the risk of Down's syndrome, usually based on the measurement of AFP, uE3, free b-hCG (or total hCG), and inhibin-A together with the woman's age.

Quality assurance (QA)

A system for monitoring and maintaining high standards in every aspect of a screening programme.

Screening

Testing people who do not have or have not recognised the signs or symptoms of the condition being tested for, either with the aim of reducing risk of an adverse outcome, or with the aim of giving information about risk.

Screening pathway

The whole system of activities needed to deliver high quality screening. It ranges from identifying and informing those to be offered screening through to the treatment and follow up of those found to have abnormality, and support for those who develop disease despite screening.

Screening safety incident

An unintended or unexpected incident(s) that could have or did lead to harm to one or more persons who are eligible for NHS screening; or to staff working in the screening programme.

Screening test

A test or inquiry used on people who do not have or have not recognised the signs or symptoms of the condition being tested for. It divides people into lower and higher chance groups.

Syndrome

Combination of symptoms and signs grouped together to form a disorder.

Trisomy

Three copies of a particular chromosome rather than two.

Twins

May be genetically identical (monozygous) when they arise from a single fertilised egg or non- identical (dizygous) when they arise from two separate eggs.

Ultrasound scan

An ultrasound scan is a safe and painless test that uses sound waves to make images. It is like radar.

Appendix 1

Template A. Lower chance result letter – Down's syndrome screening only

Dear <name>,

Re: Your first trimester screening result

You recently had the 'combined test' to screen for Down's syndrome. This has shown that your baby has a **lower chance** of having this condition.

For this pregnancy, you have 1 chance in <number> of having a baby with Down's syndrome.

To understand what '1 chance in <number>' means, imagine you have a bag of <number> apples, of which 1 is red and the rest are green. If you pick an apple at random, you have '1 chance in <number>' of picking a red one.

We do not offer further testing at this level of chance.

It is important to understand that there is still a small chance of giving birth to a baby with Down's syndrome because the screening tests do not detect some babies with this condition. A lower chance result does not mean that there is no chance at all that the baby has Down's syndrome, just that it is unlikely.

If you have any questions about your result, you can contact me using the details below.

You can find more information about antenatal screening for this condition, including details of parent support groups, at www.nhs.uk/depscreening.

Yours faithfully,

<co-ordinator name>

Antenatal Screening Co-ordinator

Office: <phone number>

Mobile: <phone number>

Email: <email address>

Template B. Lower chance result letter – screening for all 3 conditions

Dear <name>,

Re: Your first trimester screening results

You recently had the 'combined test' to screen for Down's syndrome, Edwards' syndrome and Patau's syndrome. This has shown that your baby has a **lower chance** of having these conditions. Your individual chances for this pregnancy are as follows:

- Down's syndrome 1 chance in <number>
- Edwards' syndrome and Patau's syndrome 1 chance in <number>

To understand what, for example, '1 chance in <number>' means, imagine you have a bag of <number> apples, of which 1 is red and the rest are green. If you pick an apple at random, you have '1 chance in <number>' of picking a red one.

We do not offer further testing at this level of chance.

It is important to understand that there is still a small chance of giving birth to a baby with Down's syndrome, Edwards' syndrome or Patau's syndrome because the screening tests do not detect some babies with these conditions. A lower chance result does not mean that there is no chance at all that the baby has Down's syndrome, Edwards' syndrome or Patau's syndrome, just that it is unlikely.

If you have any questions about your results, you can contact me using the details below.

You can find more information about antenatal screening for these conditions, including details of parent support groups, at www.nhs.uk/depscreening.

Yours faithfully,

<co-ordinator name>

Antenatal Screening Co-ordinator

Office: <phone number>

Mobile: <phone number>

Email: <email address>

Template C. Lower chance result letter – Edwards' syndrome and Patau's syndrome screening only

Dear <name>,

Re: Your first trimester screening result

You recently had the 'combined test' to screen for Edwards' syndrome and Patau's syndrome. This has shown that your baby has a **lower chance** of having these conditions.

For this pregnancy, you have 1 chance in <number> of having a baby with Edwards' syndrome or Patau's syndrome.

To understand what '1 chance in <number>' means, imagine you have a bag of <number> apples, of which 1 is red and the rest are green. If you pick an apple at random, you have '1 chance in <number>' of picking a red one.

We do not offer further testing at this level of chance.

It is important to understand that there is still a small chance of giving birth to a baby with Edwards' syndrome or Patau's syndrome because the screening tests do not detect some babies with these conditions. A lower chance result does not mean that there is no chance at all that the baby has Edwards' syndrome or Patau's syndrome, just that it is unlikely.

If you have any questions about your result, you can contact me using the details below.

You can find more information about antenatal screening for these conditions, including details of parent support groups, at www.nhs.uk/depscreening.

Yours faithfully,

<co-ordinator name>

Antenatal Screening Co-ordinator

Office: <phone number>

Mobile: <phone number>

Email: <email address>

Template D. Lower chance result letter quadruple test – Down's syndrome screening only

Dear <name>,

Re: Your second trimester screening result

You recently had the 'quadruple test' to screen for Down's syndrome. This has shown that your baby has a **lower chance** of having this condition.

For this pregnancy, you have 1 chance in <number> of having a baby with Down's syndrome.

To understand what '1 chance in <number>' means, imagine you have a bag of <number> apples, of which 1 is red and the rest are green. If you pick an apple at random, you have '1 chance in <number>' of picking a red one.

We do not offer further testing at this level of chance.

It is important to understand that there is still a small chance of giving birth to a baby with Down's syndrome because the screening tests do not detect some babies with this condition. A lower chance result does not mean that there is no chance at all that the baby has Down's syndrome, just that it is unlikely.

If you have any questions about your result, you can contact me using the details below.

You can find more information about antenatal screening for this condition, including details of parent support groups, at www.nhs.uk/depscreening.

Yours faithfully,

<co-ordinator name>

Antenatal Screening Co-ordinator

Office: <phone number>

Mobile: <phone number>

Email: <email address>