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Newborn Bloodspot Screening Wales
Sgrinio Smotyn Gwaed Newydd-anedig Cymru

Newborn Bloodspot Screening: Programme Handbook

A guide to newborn bloodspot screening (NBS) for health professionals in Wales

Details

This document brings together all the guidelines and publications that relate to the Newborn Bloodspot Screening Wales (NBSW) Programme.

To access information in this handbook click on the link to the section you require in the contents list. This will take you directly through to that part of the document. There are also links throughout the handbook to allow easier access to further information.

To return to the original section after using a link, press 'Alt' and left arrow.

If you choose to print this document, it is your responsibility to ensure you **always** refer to the most up to date version. Please be aware the electronic version will always be the most up to date.

February 2019

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1. Introduction and contacts

1.1 Introduction

This handbook informs and supports midwives, health visitors, neonatal nurses and other health professionals and staff who deliver the Newborn Bloodspot Screening (NBS) Programme in Wales.

The handbook provides a detailed outline of the NBS pathway and directs the user to other relevant publications. Health professionals can use it as a quick reference guide to answer specific questions.

1.1.1 Midwives

Useful information includes:

- Informed choice
- What to do if parents decline screening
- What to do if there is a family history of a condition
- Reasons for repeat bloodspot samples
- Explaining repeat samples to parents
- How parents receive results
- Guidelines for newborn bloodspot screening
- Sample taker registration

1.1.2 Health visitors

Useful information includes:

- What to do when a baby moves into area
- When to offer screening
- Which conditions screening covers
- Informed choice
- What to do if parents decline screening
- How parents receive results
- Guidelines for newborn bloodspot screening
- Sample taker registration

1.1.3 Neonatal nurses

Useful information includes:

- Informed choice
- What to do if there is a family history of a condition
- Pre and post transfusion bloodspot samples
- How prematurity affects screening
- Reasons for repeat bloodspots samples
- How parents receive results
- Guidelines for newborn bloodspot screening
- Sample taker registration

1.1.4 Other useful information

- NHS numbers
- Transporting samples
- Newborn Bloodspot Screening Wales System failsafe
- Quality assurance
- Programme policies and standards
- Screening pathways
- Incidence and positive predictive values

1.2 Contacting the Newborn Bloodspot Screening Wales (NBSW) programme

The NBSW programme is here to help. Feel free to contact us about any questions you have about newborn bloodspot screening via telephone or email.

Telephone – 029 2010 4427
Email – nbsw@wales.nhs.uk

Newborn Bloodspot Screening Wales
Floor 4
Number 2 Capital Quarter
Tyndall Street
Cardiff
CF10 4BZ

If parents have any concerns about their baby's screening, they should be advised to discuss them with their midwife, health visitor or GP.

NBSW Head of Programme, Programme Coordinators and Administration Support Team

Ruth Lawler, Head of Maternal and Child Screening:
Telephone – 029 2010 4432 Email - ruth.lawler@wales.nhs.uk

Catherine Boyce, NBSW Programme Coordinator:
Telephone – 029 2010 4399 Email - catherine.boyce2@wales.nhs.uk

Margaret Birch, NBSW Programme Coordinator:
Telephone – 029 2010 4634 Email – margaret.birch@wales.nhs.uk

Administration Support Team:
Telephone – 029 2010 4427 Email – nbsw@wales.nhs.uk

Newborn Screening Administration Failsafe Teams

The regional Newborn Screening Administration Failsafe teams can be contacted (office hours Monday - Friday) by health professionals who have queries about the follow up of babies identified by the Newborn Bloodspot Screening Wales System (NBSWS) failsafe. The teams can also be contacted to request the NHS number for a baby if it is not available prior to taking the sample.

South East Wales Team

Cardiff and Vale, Cwm Taf and Aneurin Bevan University Health Boards:
Telephone – 029 2074 3568

Mid and West Wales Team

Abertawe Bro Morgannwg and Hywel Dda University Health Boards and Powys Teaching Health Board:
Telephone – 01656 754085

North Wales Team

Betsi Cadwaladr University Health Board:
Telephone – 01978 727005

Email – PHW.NBSWFailsafe@wales.nhs.uk

The Wales Newborn Screening Laboratory

Health professionals should use the following telephone numbers to contact the laboratory:

- **To check that a sample has been received, or for any queries about demographic information on a bloodspot card:**
  Telephone – 029 2074 4032
  Laboratory fax number – 029 2074 4065

- **For all clinical enquiries (including interpretation of screening results) please contact:**

  Dr Fiona Stratford, Clinical Biochemist:
  Telephone – 029 2074 5448 Email – Fiona.stratford@wales.nhs.uk

  Professor Stuart Moat (Consultant Clinical Biochemist), Director of Wales Newborn Screening Laboratory:
  Telephone – 029 2074 3562 Email – stuart.moat@wales.nhs.uk

Newborn Screening Laboratory email: New.Screening.cav@wales.nhs.uk
Newborn Screening Laboratory
Department of Medical Biochemistry
University Hospital of Wales
Heath Park
Cardiff
CF14 4XW

1.3 Latest news

NBSW bulletins are produced regularly and provide information and updates on newborn bloodspot screening in Wales.

2. Screening pathway

Newborn bloodspot screening (NBS) enables early identification, referral and treatment of babies with 9 rare but serious conditions. The programme helps to improve their health and prevent severe disability or death.

Newborn bloodspot screening is when a small sample of blood is taken from the baby's heel on day five of life (counting day of birth as day 0). This blood sample is screened for rare but serious diseases that respond to early intervention to reduce mortality and/or morbidity. The screening test is part of routine postnatal care.

The offer of screening and collection of bloodspot samples is carried out by health professionals within the health boards in accordance with the NBSW guidance, standards and policies. The majority of samples are taken in the baby's home by the midwife. Neonatal or paediatric unit staff offer the screening and take samples for those babies who are inpatient in those areas at day five of life. Health visitors take responsibility for offering and arranging sample collection for eligible babies who have moved into Wales.

NBS samples are sent by prepaid envelopes (first class) to the Wales Newborn Screening Laboratory in Cardiff for testing. The laboratory accepts samples according to the UK bloodspot quality guidelines for screening laboratories. Babies suspected of having one of the conditions screened for are referred, according to the relevant clinical referral guidelines, to the appropriate specialist clinician for diagnostic tests and treatment. The results for each baby are sent to the local Child Health Department and are entered onto the Child Health System. The baby's health visitor discusses the results with the parents.

Pathways for newborn bloodspot screening in Wales, including guidance for the screening of older babies up to the age of 1 year, have been developed to clarify the process for health professionals.

2.1 Eligibility

All babies up to one year of age are eligible for NBS for all 9 conditions. This excludes the screening test for cystic fibrosis (CF), which is only offered for babies up to 8 weeks of age because the test is unreliable after this time.
In Wales, the eligible babies are:

- All newborn babies
- Any baby who is resident outside Wales but is receiving routine postnatal care in Wales
- Babies up to one year of age who are resident in Wales, or who move into Wales from elsewhere in the UK, if there is no evidence that:

    - they have an appropriate UK NBS result, or
    - that it has been declined in the UK
- All babies up to the age of one year who move into Wales from outside the UK (even if they have been screened outside the UK)

Babies who are eligible for screening are identified in each health board from midwife birth notifications. Eligible babies up to one year of age who move in to Wales are identified following registration on to the Welsh Child Health System.

The NBSW programme definition of eligible babies:

Eligible babies (newborn)

- A baby who is resident in Wales at day 5-8 of life
- A baby who is resident in Wales at day 5-8 of life, but is registered with an English GP
- A baby whose usual place of residence is outside Wales if they are under routine midwife care in Wales at day 5-8 of life

Babies who have been recorded as having died before the age of 5 days are not eligible.

Eligible babies (all)

- All babies up to one year of age who are resident in Wales
- A baby whose place of residence is outside Wales if they are under routine midwifery care in Wales at the time the newborn bloodspot test is due

Babies who have been recorded as having died before the age of 5 days are not eligible.

2.2 Conditions

In Wales all eligible babies are offered screening for the conditions below which are recommended by the UK National Screening Committee:

- Inherited metabolic disorders (IMDs):
    - Medium-chain acyl CoA dehydrogenase deficiency (MCADD)
    - Phenylketonuria (PKU)
    - Maple syrup urine disease (MSUD)
    - Isovaleric acidaemia (IVA)
    - Glutaric aciduria type 1 (GA1)
    - Homocystinuria (HCU)
- Congenital hypothyroidism (CHT)
- Cystic fibrosis (CF)
- Sickle cell disorders (SCD)

Babies suspected of having one of the conditions screened for will be referred for diagnostic tests and treatment to the appropriate specialist clinician. This is according to the relevant clinical referral guidelines.

MCADD, PKU, MSUD, IVA, GA1 and HCU are inherited metabolic diseases (IMDs) which can cause severe illness and/or developmental problems, including serious learning disability. MCADD, MSUD and IVA can be immediately life threatening in the newborn period.

If not identified early, CHT can cause permanent, serious physical problems and learning disabilities.

For CF and SCD, although screening cannot prevent periods of illness, early detection can improve health.

NBS results are reported as not suspected (screen negative), suspected (screen positive) or carrier (SCD only).

In any screening programme there are false positive results and false negative results. This means that a baby with a screen positive result may not have the condition. The likelihood that a baby with a screen positive result has the disorder varies with each condition.

2.3 Informed choice

Newborn bloodspot screening is recommended because it can improve health and prevent severe disability or even death.

Information is available to help parents make an informed choice about screening for their baby. A copy of the leaflet 'Newborn Bloodspot Screening – Information for parents' is made available for women in the antenatal period, and after the birth if required. The leaflet provides information on the conditions screened for, how the sample will be taken and how the parents will receive the results. It is bilingual (English and Welsh) and is available on the NBSW website in other formats including easy read, large print and mp3 audio version.

NBS is an invasive medical procedure and cannot be undertaken on babies without informed consent from a person with parental responsibility.

A person with parental responsibility must receive sufficient information and have opportunity to ask questions to enable them to give informed consent for NBS, and the opportunity to decline consent to be contacted for future research.

Parents must verbally agree to NBS. It is the health professional's responsibility to offer parents screening and record their decision in the baby's and mother's health records.

Parents must understand that they are agreeing to both testing and quality assurance processes that are an essential part of the screening programme. These include:

- completing the bloodspot card and taking the sample
- testing the bloodspot sample in the newborn screening laboratory
- additional testing of the same sample if the initial result is positive (may involve testing in another laboratory)
- contacting parents about the screening results - positive or negative, or carrier (only for SCD)
- referral to a specialist clinical team if the result is positive
- recording the screening results on laboratory and child health information systems, and the Newborn Bloodspot Screening Wales System (NBSWS)
- retention and storage of residual bloodspots for checking the screening results, monitoring and improving the screening programme

The UK National Screening Committee (UK NSC) has provided guidance on informed choice in screening.

Further information on offering NBS and recording the parents' decision is in the guidelines for newborn bloodspot screening.

2.4 Declined screening

Newborn bloodspot screening is strongly recommended but parents have the right to choose. The health professional should ensure that the parents have a good understanding of the benefits of screening.

Parents can decline screening for all or any of the conditions. They can decline screening for CHT, CF and SCD individually but can only decline the 6 IMDs as a group. This is because of the way that the laboratory tests for the IMDs.

If parents decline screening, the health professional must record their decision (and reason if stated) and notify the GP and health visitor.

The bloodspot card should be completed in full and sent to the Wales Newborn Screening Laboratory with 'Decline' for 'All' or specific test(s) recorded on the card.

Parents will be sent a letter from the programme that confirms their decision, together with information to let them know what to do if they change their mind. Further information about declined screening is in the guidelines for newborn bloodspot screening.

2.5 Day 5

The bloodspot sample is taken on day 5 (day of birth is day 0). Day 5 is a practical balance between not screening too early (which can affect the accuracy of the CHT screening test used in Wales) and not screening too late, to make sure there is early referral and treatment if needed.

Following the guidelines for newborn bloodspot screening helps the sample taker to take a good quality sample. The sample taker sends the sample on the same day to the screening laboratory for analysis. Parents will receive 'not suspected' results by 6 weeks after sample collection but suspected results as soon as they become available.

2.6 Residual bloodspots

Residual bloodspots are dried bloodspots that are 'left over' after the laboratory punches (removes) several small discs from the sample to complete screening.

After screening, the section of the card that has the written details of the baby is separated and destroyed. The remaining section containing the residual bloodspots is stored securely by the screening laboratory for at least 5 years. This part of the card is identified by a barcode number unique to both the card and the baby.

The laboratory uses residual bloodspots to check screening results, for testing equipment or methods, and for training and audit. It is a vital part of screening that helps to maintain high standards. If parents consent to screening, they cannot opt out of storage of their baby's residual bloodspots for these purposes.

2.6.1 Research uses

Residual bloodspots have other potential uses, including health research.
Some types of research are permitted without parents giving additional consent. This includes research that uses:

- anonymised samples (no details are linked to the bloodspots)
- 'de-identified' samples (some information is linked to the bloodspots but researchers are not able to identify the person that the sample comes from)

Sometimes researchers want to contact a child or family for research using the screening result or residual bloodspot card. In this case, the researchers must contact parents to ask permission. This might be years after screening. When parents consent to screening, they must also be asked if they consent to any future contact about this type of research.

If parents do not agree to future research contact, the 'No further research contact' box on the bloodspot card should be ticked at the time of sample collection.

2.6.2 Offering NBS screening

The healthcare professional who offers NBS must inform parents about the storage and potential uses of residual bloodspots. When offering NBS, make sure that parents understand:

- they are agreeing to processes that support the screening programme including storage of residual bloodspots for at least 5 years
- residual bloodspots can be used to check screening results, for testing equipment or methods, and for training and audit
- residual bloodspots can also be used for health research that does not identify their baby
- they must be asked if they consent to future contact about research that could identify their baby

The text in 'Newborn Bloodspot Screening – Information for parents' can be used to help discuss residual bloodspots with parents.

Further information can be found in the Code of Practice for the Retention and Storage of Residual Spots (2005) and the guidelines for newborn bloodspot screening.

2.7 Pre-transfusion / admission sample

Every baby admitted to a neonatal unit in Wales should have a single circle bloodspot sample taken on admission. This sample must be labelled *pre-transfusion sample,* kept, and then attached to the routine newborn bloodspot sample taken on day 5 of life (counting day of birth as day 0). Both samples should then be sent to the Newborn Screening Laboratory for analysis.

Transfused blood interferes with the interpretation of bloodspot screening results and may lead to a false negative screening result for SCD. The pre-transfusion is used to screen for SCD if the baby had a blood transfusion during the period between admission and day 5 of life, when the routine bloodspot sample is taken.

More information is available in the guidelines for newborn bloodspot screening and Appendix E which includes a flow chart, frequently asked questions and scenarios.

2.8 NHS number on the bloodspot card

The ability to correctly identify and track the progress of all babies through the screening process is vital. It is mandatory to record the baby's NHS number on the bloodspot card as it is the only unique identifier for the baby. A repeat sample is requested if the NHS number is not recorded on the card, or if it is invalid or illegible.

Care should be taken to ensure that the NHS number recorded on the card is correct and legible, particularly in the case of twin babies when mistakes are more likely to be made.

The NBS administration failsafe teams can be contacted to check or obtain an NHS number for a baby. They will be able check if the NHS number has been generated and if so, confirm the correct number for the sample taker.

Guidance for health visitors caring for babies who have moved into Wales from outside the UK is available in the guidelines for newborn bloodspot screening.

2.9 Transport

Completed bloodspot cards must be sent to the Wales Newborn Screening Laboratory on the same day (or, if not possible, within 24 hours of taking the sample). This is to make sure that the laboratory receives the sample in less than or equal to 4 working days and can process the sample as soon as possible.

The bloodspot cards should be sent in the NBSW first class prepaid envelopes and posted in a Royal Mail post box. It is important to make sure that the post box has a daily collection (Monday to Saturday).

If the NBSW prepaid envelope is not available, the sample should be sent by first class post to the laboratory.

There should be no delay in sending the bloodspot card to the laboratory. Cards should not be batched together for postage and there should be no additional checking that causes delay. Hospital or community internal mail systems should not be used because they can result in significant delays.

Health boards, in agreement with the laboratory and NBSW programme, should have contingency plans in place for any exceptional circumstances that may delay the samples reaching the laboratory (for example postal strikes, severe weather disruptions and at times of peak demand such as long bank holiday weekends).

2.10 Babies who have moved into Wales

Eligible babies up to one year of age who move into Wales should be offered bloodspot screening and have sample collection arranged at the earliest opportunity. This is to minimise the time before babies affected with any of the conditions can be referred into clinical care.

Screening for CF is only offered for babies up to 8 weeks of age because the test is unreliable after this time.

For babies approaching one year of age at the time of offer, it must be ensured that the sample is taken without delay so that it can be accepted for testing. The laboratory will only test samples taken from babies up to 13 months of age.

Parents will receive 'not suspected' results within 6 weeks of the sample being taken, and suspected results as soon as they become available.

The cut off at a year of age is a pragmatic decision, there are benefits of screening older infants and children, but these lessen with age.

More information is available in the guidelines for newborn bloodspot screening

2.11 The Newborn Bloodspot Screening Wales System (NBSWS) Failsafe

Babies can miss screening and bloodspot samples can sometimes fail to reach the screening laboratory or get delayed in transit. Babies affected by screened conditions can suffer serious harm by the time these failures are detected.

The impact on babies and parents, as well as the costs of treatment and care, is avoidable through the use of the Newborn Bloodspot Screening Wales System (NBSWS) failsafe which was introduced in February 2014. This information based failsafe system identifies babies in Wales who do not have a newborn bloodspot screening sample in the Newborn Screening Laboratory by day 14 of life (counting day of birth as day 0). NBSWS matches bloodspot test data from the Newborn Screening Laboratory system with the register of births on the Newborn Screening Database.

The day 14 lists are generated on every working day (Monday to Friday) and the relevant maternity units are contacted so that the babies can be followed up so that appropriate action can be taken. Other failsafe lists are also generated. For example, if the laboratory requests a repeat sample and it is not received within a specific time, the baby will be identified and followed up.

There are three Regional Newborn Screening Administration Failsafe Teams across Wales. The managers and their administration teams are responsible for contacting the health professionals in the health boards. Any queries relating to babies identified by the failsafe should be directed to these teams.

This system is not intended to replace any failsafe systems that are in place locally, or any other procedures for checking samples have been collected and despatched. It is very important that these remain in place.

How does the failsafe work?

On each working day (Monday to Friday) the Newborn Screening Administration Failsafe Teams generate the day 14 lists. They will then contact the maternity units (office hours) in the relevant health boards to follow up the babies on these lists. For each baby they find out if the sample has been taken and if so, when it was taken and sent to the laboratory.

The maternity staff are contacted initially, and if it is identified that a baby was an inpatient on a neonatal or paediatric unit at the time the NBS sample was due, the

health professionals in those areas will then be contacted. The relevant health visitor will be contacted for babies who have moved into Wales.

Every baby identified by the failsafe will be followed up. It is important that all staff know that they may be contacted, and that timely responses are essential to minimise any further delays in screening.

Action required

If the sample has been taken but was posted more than 5 working days ago, then the sample will need to be repeated within 48 hours.

If the sample had been sent within the last 5 working days, time will be allowed for this sample to arrive in the laboratory. The midwife will be asked to arrange a repeat sample to be taken once 5 working days has passed since sending the first sample.

Before taking the repeat sample, the sample taker should firstly contact the laboratory (Tel - 029 2074 4032) to check that the initial sample has not been received in the meantime.

If the sample has not been taken, and should have been, a request will be made to offer the screening and take the sample within 48 hours.

2.12 Obtaining NBS supplies

The NBSW programme sends out regular supplies of the parent information leaflets, bloodspot cards and prepaid envelopes to designated areas within each health board.

Queries about the location or distribution of supplies within the health boards should be directed to the relevant managers and/or the health board NBS governance lead.

For any additional assistance, or if you would like to request supplies please contact the NBSW programme.

2.13 Standards and data

The NBSW programme standards assess the newborn bloodspot screening process. The standards are a set of measures that have to be met to make sure screening is safe and effective.

All health professionals involved in the NBS pathway have a part to play in meeting these standards. For example, if the newborn bloodspot card is not accurately completed it can delay screen positive babies accessing treatment. This can result in permanent brain damage or even death if the baby has MCADD, MSUD or IVA.

The Newborn Bloodspot Screening Wales System (NBSWS) collects and collates information across the programme to monitor the quality of newborn bloodspot screening and provides quality assurance and management reports based on the policies and standards.

An annual statistical report is published by NBSW each year. The data from this report is presented at the NBSW annual general meetings which are held to enable a robust multidisciplinary review of the programme, to ensure that we are offering as high a quality programme as possible for our population.

2.14 Sample taker registration

The NBSW programme holds a database of the NBS sample takers in Wales as part of its quality assurance processes.

The database will be used as a mechanism to distribute information to sample takers and monitor the quality of the NBSW programme. Personal details are held securely and confidentially and will not be released outside the programme.

The Nursing and Midwifery Council have given their approval for health professionals to use their NMC number as a unique identifier and this should be recorded in the 'sample taker ID' field on the bloodspot card.

Sample takers who do not have an MNC number are issued with a unique identifier by NBSW after they have completed and returned the sample taker registration form.

Sample takers who have not yet registered are asked to complete and return the NBSW sample taker registration form.

3. Results and records

All parents should receive their baby's screening results within 6 to 8 weeks of completion of the bloodspot card.

3.1 Not suspected results

Parents must receive normal (not suspected) screening results within 6 to 8 weeks of the sample being taken. The agreed method for communicating these results is to send a letter directly to parents. This letter should be saved in the baby's personal child health record (PCHR).

The results letters are generated from the Newborn Bloodspot Screening Wales System (NBSWS) and sent by the NBS administration failsafe teams to parents within 6 weeks of the sample collection.

An information leaflet 'Newborn bloodspot screening – Your baby's results explained' is sent with the letter.

It is the health visitor's responsibility to make sure that parents have received the results by 6 weeks and that these have been recorded in the PCHR. The health visitor should discuss the results with the parents and answer any questions they may have.

The sample taker should tell parents to contact their health visitor if they do not receive the results by 6 weeks. It is very important that parents are not told that 'no news is good news'. It is also important that parents and health professionals understand that screening is not 100% accurate. If parents have any concerns about their baby's health they should see their GP or health visitor.

The NBS administration failsafe teams can be contacted by health professionals if there are any queries about the availability of results for parents.

3.2 Repeat samples

Parents may be anxious if their baby has had a repeat sample for clinical reasons as part of the screening pathway.

They can expect to receive the results as soon as they are available. The results letter will usually be received by the parents within 28 days of sample collection.

It is important that parents or families are reassured about normal results for the other screening tests as soon as possible.

3.3 Suspected results

Parents will be contacted as soon as possible if their baby has a screen positive result for a condition. This enables them to start treatment as soon as this can be arranged.

In all cases an appropriately trained healthcare professional must give the results to parents (verbally in most circumstances). They should give parents the national parent information leaflet for the particular condition.

If a baby has a screen positive result for one of the conditions, the parents will usually be contacted within the following timeframes:

- Congenital hypothyroidism (CHT) or an inherited metabolic disorder (IMD) – before 3 weeks of age
- Cystic fibrosis (CF) - before 4 weeks of age
- Sickle cell disorder (SCD) - before 6 weeks of age

The timing for receiving the screening results given above relies on the NBS tests being carried out between 5 and 8 days after birth, ideally on day 5.

The initial clinical referral guidelines for each condition set out the agreed methods and timeframes for contacting parents.

All results letters for babies with screen positive results are sent to the baby's health visitor, and not directly to the parents. This will happen once it is confirmed that the baby has been received into clinical care, and the parents have had the opportunity to discuss the results with a clinician. The health visitor will be contacted by an NBSW coordinator who will discuss the results and provide appropriate information. The results are sent to the health visitor in a pack containing:

- Cover letter for health visitor
- Letter for parents containing all bloodspot screening results
- Parent information leaflet - 'Newborn bloodspot screening – Your baby's results explained'
- Leaflet for the health visitor providing information about the condition

The health visitor will then arrange to discuss the results with the parents at a face to face visit.

3.4 Sickle cell disorder carrier results

The aim of newborn bloodspot screening for sickle cell disorders (SCD) in Wales is to identify babies who have a SCD, and not to identify babies who are carriers of a SCD.

However, as a by-product of the screening test protocol, very occasionally babies will be identified as being a healthy carrier of a SCD or other haemoglobin variant (approximately 3 or 4 per year). When a baby is identified as a carrier, this

information needs to be communicated to the parents of the baby. The pathway for undertaking this communication is via the health visitor so that parents are informed by a professional with whom they are in routine contact.

The NBSW programme will identify the baby's health visitor and contact them to discuss the SCD carrier result and provide additional information to support their discussion with the parents. The results are sent to the health visitor in a pack containing:

- Cover letter for health visitor
- Information leaflet for health visitor
- Letter for parents containing all bloodspot screening results
- Parent information leaflet - 'Newborn bloodspot screening – Your baby's results explained'
- SCD carrier or other haemoglobin variant carrier information leaflet

Information for the parents

The parents need to be informed that the results of the NBS test identify that their baby is a carrier of a SCD. The main message for the parents is that this result does not mean that their child will be unwell, and that their baby will not develop a SCD.

The main implication of the SCD carrier result is that it provides genetic information that is important in the future, when that child becomes an adult and is considering having children. It is important because if two carriers of a SCD have children together, there is a one in four (25%) chance, for every child conceived, that the child will be affected by a SCD.

The health visitor should discuss and offer the parents a referral to the All-Wales Medical Genetic Service (AWMGS). The parents can be referred to this service if they would like further advice and information.

3.5 Babies who have not been screened

A 'not screened' letter will be sent to parents of babies who have not been screened despite attempts by health professionals to offer and arrange sample collection.

The letter which is sent to the parents from the NBSW programme, recommends screening and provides information about what to do if they want their baby screened. The guidelines for newborn bloodspot screening provide more information.

3.6 Laboratory system

NBS results are recorded on the bloodspot screening Laboratory Information Management System (LIMS) as part of the testing process. If the sample has been sent to another laboratory to complete the screening test, the result will be recorded on their system.

3.7 Newborn Bloodspot Screening Wales System (NBSWS)

NBS results are recorded on the Newborn Bloodspot Screening Wales System (NBSWS). This makes sure that every baby is offered screening and minimises the chance of a baby missing screening.

3.8 Child Health Information Systems

Child Health Information Systems are child administration systems used by community Child Health Departments (CHDs). They provide a clinical record for individual children, including NBS results.

4. Repeat bloodspot samples

The Newborn Screening Laboratory requests repeat bloodspot samples for a variety of reasons. A repeat sample must be taken as advised by the laboratory. There are two 2 types of repeat samples. These are 'avoidable repeat' and 'unavoidable repeat' samples.

4.1 Avoidable repeat samples

Avoidable repeat samples are repeat samples that can be avoided. This could be due to:

- insufficient blood
- inappropriate application of blood
- incomplete or inaccurate data on the card
- a delay in the laboratory receiving the sample
- contamination of the sample
- a pre-transfusion/admission sample and day 5 sample on the same card
- damage to the sample in transit
- use of an expired card
- a sample taken when the baby was too young

Take an avoidable repeat sample within 72 hours of receipt of the request unless the baby is undergoing blood transfusions.

4.1.1 Harms caused by avoidable repeat samples

Avoidable repeat samples can cause anxiety for parents, distress to babies and delays in the screening process. This could lead to delayed identification and treatment of an affected baby. Avoidable repeats also waste healthcare resources (each repeat costs the NHS around £100). In some cases parents may refuse to consent to a repeat, which means that the baby will have incomplete screening.

4.1.2 Bloodspot quality

A good quality bloodspot sample is:

- taken at the right time
- has accurate and complete data
- contains enough blood to perform all tests
- is sent to the newborn screening laboratory in a timely manner
- is not contaminated
- is not compressed

In the laboratory, several small discs are 'punched' (removed) from the bloodspots to be used in the screening process. The sample needs to be sufficient to screen for all of the conditions and for further testing if required, for example, to check a screen positive result.

Evidence shows that poor quality samples could lead to a baby with a condition being missed (false negative result) or referral of a baby without a condition for further tests (false positive result).

The Wales Newborn Screening Laboratory follows a national, evidence based procedure on bloodspot quality, with standardised consensus agreed acceptance and rejection criteria. To make sure the laboratory does not request an avoidable repeat, sample takers must obtain 4 good quality bloodspots and complete all fields on the bloodspot card accurately. The guidelines for newborn bloodspot screening provide more information.

4.1.3 Insufficient blood

If the circles contain a small bloodspot or blood has not soaked through to the back of the card, there will be insufficient blood to complete screening accurately. This can give a false negative result.

4.1.4 Inappropriate application of blood

Do not:

- apply several small spots of blood to the circle (multi spotted sample) because this can give a false negative result
- apply pressure to the spot to spread the blood out to fill the circle (compressed sample); compressed blood spots have a significantly higher risk of a false negative result
- layer one spot of blood directly on top of another or apply blood to the front and back of the bloodspot card because this can give a false positive result

4.1.5 Incomplete or inaccurate data on the card

Incomplete or inaccurate data on the bloodspot card, for example, no/inaccurate NHS number, will result in a repeat request because the baby cannot be accurately identified. This will delay treatment if the baby's screening result is positive.

The NBS administration failsafe teams can be contacted to check or obtain the NHS number for a baby.

4.1.6 Delay in laboratory receiving the sample

It is important that the laboratory receives the bloodspot card promptly so that they can refer screen positive babies quickly. Timeliness of despatch enables early analysis and subsequent treatment.

Send the bloodspot sample to the Newborn Screening Laboratory on the same day. If this is not possible, send within 24 hours of taking the sample. Do not delay sending samples in order to batch bloodspot cards together for postage.

The bloodspot cards should be sent in the NBSW first class prepaid envelopes and posted in a Royal Mail post box. It is important to make sure that the post box has a daily collection (Monday to Saturday). If the NBSW prepaid envelope is not available, the sample should be sent by first class post to the laboratory.

The laboratory will reject samples received more than 14 days after the sample was taken, due to the risk of an inaccurate result.

4.1.7 Contamination

Contamination of the sample, for example if the card gets wet, will give an inaccurate result.

4.1.8 Pre-transfusion/admission and day 5 sample on the same card

This can cause confusion and lead to inaccurate results.

4.1.9 Damaged in transit

Samples damaged in transit can give inaccurate results.

4.1.10 Expired card

The expiry date is for quality control. After this date, the quality of the filter paper and therefore the results cannot be guaranteed.

The expiry date on the card should be checked before sample collection.

4.1.11 Taken when the baby was too young

This is when a sample is taken before day 5 (excluding pre transfusion samples). This may give rise to a false positive result for congenital hypothyroidism (CHT). It is important to calculate day 5 using day of birth as day 0. Sample takers should

be aware that some IT systems record day of birth as day 1, and this may result in taking the sample too early.

4.2 Unavoidable repeat samples

Unavoidable repeats are repeat samples that are required for clinical reasons, such as:

- prematurity
- borderline thyroid stimulating hormone (TSH) results
- blood transfusions

4.2.1 Prematurity

Prematurity can mask CHT. Babies born at less than 32 completed weeks gestation (less than or equal to 31 weeks + 6 days) need a second bloodspot sample taken, in addition to the day 5 sample, to screen for this condition. The second sample is taken when the baby reaches 28 days of age (day of birth is day 0) or on the day of discharge home from hospital, whichever is sooner.

The health professional should follow the steps below to take the second sample.

1. Explain to parents that a repeat sample is recommended as the routine day 5 test may not pick up CHT in babies born at less than 32 completed weeks gestation.
2. Take the repeat sample at either 28 days of age or immediately before the baby is discharged home (whichever comes first).
3. Fill 2 circles on the card with blood and write 'CHT preterm' in the card's comments box. If the baby is being discharged home before 28 days of age, write 'discharged home' on the card.

Further information and scenarios relating to the CHT Preterm policy can be found in Appendix F.

4.2.2 Borderline TSH results

This is when the result is borderline for CHT. Another sample is required to confirm the result. The repeat sample must be taken 7 to 10 days after the initial borderline sample to detect any meaningful change in TSH levels.

Fill 4 circles on the card with blood and mark the card 'CHT borderline'.

Make parents aware of the 2 possible outcomes from this repeat test.

1. CHT not suspected. The health professional should inform the baby's parents directly and as soon as possible to relieve anxiety (this can be by telephone).

2. CHT suspected. The newborn screening laboratory refers the baby directly to a paediatrician. If the result is another 'borderline' then the baby will also be referred.

4.2.3 Blood transfusions

When a baby has had a blood transfusion before the day 5 sample, another sample (4 bloodspots) is needed at least 3 clear days after the last transfusion for CF, CHT and inherited metabolic disease (IMD) screening. This allows time for metabolite concentrations to return to pre transfusion levels.

You must record the date of the last blood transfusion on the bloodspot card and on discharge or transfer notifications.

4.3 Explaining repeat samples to parents

It is important to inform parents why their baby needs a repeat sample. Parents are more likely to feel satisfied with the screening process if the reasons for a repeat sample are clearly explained.

The sample taker should explain:

- why a second bloodspot sample is needed to complete screening
- when the parents can expect to receive the result
- whom to contact if they do not receive the result
- if their baby has a positive screening result they will be contacted as soon as the result is available

If the family no longer lives in the original area of birth this request should be passed on to the responsible health professional according to local procedures. Copies of any 'request for repeat sample' documentation from the laboratory should be included. It is also essential to inform the screening laboratory that it has not been possible to take the sample and provide contact information. This must be done immediately.

4.4 Taking a repeat sample

When taking a repeat sample, the guidelines for newborn bloodspot screening should be followed.

When completing the bloodspot card, make sure that the:

- 'repeat sample' box is ticked
- reason for the repeat is given in the comments box

4.5 Results

Parents may be anxious if their baby has had a repeat sample. They can expect to receive the results as soon as they are available. The results letter will usually be received by the parents within 28 days of sample collection.

It is important that parents/families are reassured about normal results for the other screening tests as soon as possible.

4.6 Monitoring avoidable repeats

The NBSW programme monitors avoidable repeat rates and performance data is reported periodically to each health board.

The acceptable avoidable repeat rate is less than or equal to 2% (that is, 1 in 50 samples).

5. Family history

Taking a family history during pregnancy is important for establishing:

- if there is a family history of any of the conditions screened for during newborn bloodspot screening (NBS)
- the need to refer parents for an obstetrician appointment
- the need to refer parents for genetic counselling
- an appropriate birth plan that is written in the mother's notes
- a referral and care plan for the baby following birth (this is extremely important for a baby at risk of having an inherited metabolic disease (IMD)
- correct interpretation of NBS results

If there is a known family history (on either parent's side) of one of the conditions screened for, then the sample taker must note the condition in the comments box on the bloodspot card.

For example, write 'family history of phenylketonuria (PKU)'. This is so that the laboratory knows why the sample has been taken early.

5.1 When to take the sample

If there is a family history, early NBS samples are recommended for some conditions.

The Wales Newborn Screening Laboratory and paediatrician should be contacted to discuss and arrange any early testing required. The laboratory will advise what tests are needed, when they should be carried out, and how the sample(s) should be transported to the laboratory.

In all cases, early samples should be followed by the routine day 5 sample for the other conditions. When taking the day 5 sample, write on the bloodspot card that it is a second sample and the reason for the early sample.

The table below summarises when to take NBS samples:

Condition	Early sample	Routine sample	Comment for NBS card
Sickle cell disorders (SCD)	N/A For babies who have been identified during the pregnancy as having a high chance of inheriting a sickle cell or other significant haemoglobin disorder, please refer to the Antenatal Screening Wales standards - *6.7.2 Postnatal Care* for action required.	Day 5	Results of both parents
Cystic fibrosis (CF)	N/A	Day 5	Family history of CF
Congenital hypothyroidism (CHT)	N/A	Day 5	Family history of CHT
Phenylketonuria (PKU)	Newborn Screening card (4 spots) **48 hours** after birth	Day 5	Family history of PKU
Medium-chain acyl-CoA dehydrogenase deficiency (MCADD)	Newborn screening card (4 spots) and urine sample **24 to 48 hours** after birth. Take samples as close to 24 hours of life as possible due to risk of metabolic decompensation.	Day 5	Family history of MCADD
Maple syrup urine disease (MSUD)	An early newborn screening card is **not** required. Plasma sample and urine sample **12 to 24 hours** after birth. Send the samples **urgently**, **via the local laboratory**, to the Newborn Screening Laboratory.	Day 5	Family history of MSUD

Isovaleric acidaemia (IVA)	Newborn Screening card (4 spots) and urine sample **24 to 48 hours** after birth Take samples as close to 24 hours of life as possible due to risk of metabolic decompensation.	Day 5	Family history of IVA
Glutaric aciduria type 1 (GA1)	Newborn Screening card (4 spots) and urine sample **24 to 48 hours** after birth Take samples as close to 24 hours of life as possible due to risk of metabolic decompensation.	Day 5	Family history of GA1
Homocystinuria (HCU)	N/A	Day 5	Family history of HCU

Family history of an inherited metabolic disorder that is not screened for

Please contact Professor Stuart Moat to discuss whether diagnostic testing is required. This includes family history of galactosaemia and tyrosinaemia, conditions which can occasionally be identified as a by-product of newborn screening but are not routinely screened for.

5.2 Family history of IMDs

It is important to test babies with a family history of an inherited metabolic disease (IMD) at the earliest opportunity (this applies to all the IMDs except HCU where there is not a need for urgent treatment). The tests required depend on the specific IMD and may include early bloodspot samples, urine samples and plasma samples.

Failure to diagnose and treat an IMD early can lead to serious illness and possible death. Fortunately, early diagnosis and treatment minimises the complications and most children, once diagnosed, lead healthy normal lives.

Action during pregnancy

The midwife should discuss the pregnancy at an early stage with the local specialist metabolic team, genetic service and obstetric team. Careful management of the birth will be planned to minimise the risk of a metabolic

decompensation. The management of care should be led by the obstetric team and specialist metabolic team.

The Newborn Screening Laboratory should also be informed of the family history by telephone and in writing. Advice will be given regarding any action required.

The health board governance lead should be informed so that they are aware and can provide guidance and support as required in the management of care during pregnancy and after the birth.

Sample collection

It is the responsibility of the local paediatrician at the hospital in which the baby was born to organise a newborn bloodspot sample to be collected for early screening, before the baby is discharged from hospital.

Transport of samples to the Wales Newborn Screening Laboratory

For PKU, an early bloodspot card is the only sample required. This can be sent directly to the Newborn Screening Laboratory in the NBSW prepaid envelope in which the routine screening cards are normally sent.

For family history of the other conditions, send all of the required samples to the local biochemistry laboratory.

All these early samples should be **sent urgently** to the Wales Newborn Screening Laboratory. To do this, the sample should be sent to the laboratory of the hospital in which the baby was born. The local laboratory will then arrange transport to ensure the sample reaches the Wales Newborn Screening Laboratory within the specified time. **Both laboratories should be contacted** to confirm the arrangements so they know when to expect the sample.

The samples should be sent in an **envelope clearly marked as 'URGENT for Newborn Screening (FAO Stuart Moat)'.** It should be ensured that bloodspots are not put in a plastic bag.

Samples should arrive at the Wales Newborn Screening Laboratory at the University Hospital of Wales (UHW), Cardiff within 1 working day of collection.

- Samples can be analysed on the day of sample collection if the sample is received by 12pm lunchtime Monday – Friday
- Samples are not analysed at the weekend, therefore samples collected on a Thursday or on a Friday morning should arrive in the laboratory by 12pm on Friday so the sample can be analysed before the weekend
- Occasionally, it is not possible for samples collected on a Friday to get to UHW by 12pm. In these circumstances, samples should arrive at UHW by 12pm on Monday, as should samples collected at the weekend.

The Newborn Screening Laboratory **must be informed** that they are expecting the sample(s) so that arrangements can be made for testing them at the earliest opportunity after receipt.

Sending samples by taxi

All samples from babies with a family history of MSUD must be sent by taxi. It may also be necessary to send samples from babies with a family history of the other conditions so the samples can be analysed within the timeframes outlined above. The local laboratory will liaise with the Newborn Screening Laboratory at UHW to arrange this.

If a sample is sent to the laboratory by taxi, the driver should go to:
Pathology Reception (Medical Biochemistry and Immunology), Upper ground floor, B Block, University Hospital of Wales, CF14 4XW.

Contacts

For any queries regarding this protocol, or to inform the Newborn Screening Laboratory of babies with a family history of the IMDs and to discuss appropriate action please contact:

Dr Fiona Stratford, Clinical Biochemist:
Telephone – 029 2074 5448 Email – Fiona.stratford@wales.nhs.uk

Professor Stuart Moat (Consultant Clinical Biochemist), Director of Wales Newborn Screening Laboratory:
Telephone – 029 2074 3562 Email – stuart.moat@wales.nhs.uk

5.2.1 Management of conditions

If the results indicate that the baby might have one of the conditions, the specialist metabolic team will advise the family how to manage their baby's condition.

If an affected child has older siblings, the metabolic clinician will offer, if appropriate for the disorder, testing of those children if they have not had newborn screening for that disorder.

PKU

Before results: the baby should be established on a normal milk intake (bottle or breast milk) until the results become available.

MSUD

Before results: guidelines for the prospective management of a baby at risk of MSUD at birth are available from BIMDG. Consider transferring the baby to a specialist metabolic centre as soon as possible.

IVA

Before results: guidelines on 'Management of a baby at risk of an organic acidaemia at birth' are available from BIMDG. Consider transferring the baby to a specialist metabolic centre as soon as possible.

HCU (pyridoxine unresponsive)

Before results: no special management of the baby is required.

MCADD and GA1

Before results: it is essential that the baby maintains a good milk intake. A full term baby should be fed every 4 hours and a preterm baby every 3 hours.

Babies are particularly at risk in the first 72 hours after birth when feeding is being established. Top up feeds of expressed breast or formula milk may be necessary in the first 48 to 72 hours until feeding is established. If oral feeds are not tolerated, or if the baby is unwell in any way, make an urgent referral to a metabolic paediatrician for review. The paediatrician will review the baby and consider nasogastric tube feeds or starting intravenous glucose.

Guidelines for the prospective management of a baby at risk of MCADD at birth are available from the BIMDG.

5.3 Family history of CF

We do not recommend early screening for babies with a family history of CF. Take the routine NBS sample on day 5 as normal.

5.4 Family history of CHT

We do not recommend early screening for babies with a family history of CHT as there is no benefit to the baby. This is because there is a surge in thyroid stimulating hormone (TSH) in the first few hours of life. Screening using this protocol is only accurate after the TSH level has decreased, usually after a few days. Take the routine NBS sample on day 5 as normal.

5.5 Family history of SCD

An early newborn bloodspot screening sample is not required.

For babies who have been identified during the pregnancy as having a high chance of inheriting a sickle cell or other significant haemoglobin disorder, please refer to the Antenatal Screening Wales standards - *6.7.2 Postnatal Care* for action required.

6. Education and training

Education and training resources are available for health professionals who are involved in newborn bloodspot screening (NBS) in Wales. They are available from the NBSW website.

Health professionals can use these resources to keep their knowledge up to date or to cascade training in the health boards.

6.1 Films

The films provide guidance on taking good quality bloodspot samples. The films include:

Good quality newborn bloodspot screening samples – understanding laboratory requirements and processes - shows the process of testing an NBS sample in the laboratory and highlights why good quality samples are important.

Newborn bloodspot screening in neonatal units – covers aspects of NBS for babies who are being cared for in neonatal units, and the additional requirements needed for screening these babies.

6.2 PowerPoint presentations

PowerPoint presentations have been produced for the training of health professionals in the health boards. They include:

Newborn bloodspot screening training – covers all aspects of NBS for health professionals.

Newborn bloodspot screening training for health visitors – provides guidance specifically for health visitors and includes the reporting of results to parents.

The NBSW programme can be contacted if any support is required with training.

6.3 Guidance for sample takers

The Guidance for sample takers - Quick reference guide can be printed out to be used as a prompt card for students and new sample takers.

It provides guidance for taking good quality bloodspot screening samples and includes the actions required when parents decline screening.

7. Conditions

7.1 Inherited metabolic disorders (IMDs)

Inherited metabolic diseases (IMDs) are rare but serious inherited conditions. Babies with these conditions may have problems processing amino acids (the building blocks of proteins) or breaking down fats quickly enough to produce energy.

IMDs are autosomal recessive conditions. This means that babies are only born with an IMD if they inherit 2 faulty copies of the gene involved, one from each parent.

Babies with IMDs cannot usually produce a particular enzyme needed for metabolism. Enzymes help to convert one type of molecule into another. Enzyme deficiency may cause a build-up of some molecules that are harmful.

Without treatment babies with some of these conditions can become suddenly and seriously ill, while others develop irreversible problems more slowly. The symptoms of the conditions are different; some may be life threatening or lead to severe developmental problems.

NBS in Wales tests for 6 IMDs. These are:

- Medium-chain acyl CoA dehydrogenase deficiency (MCADD)
- Phenylketonuria (PKU)
- Maple syrup urine disease (MSUD)
- Isovaleric acidaemia (IVA)
- Glutaric aciduria type 1 (GA1)
- Homocystinuria (HCU)

A table providing key facts about MSUD, IVA, GA1 and HCU can be found in Appendix D.

7.1.1 Medium-chain acyl-CoA dehydrogenase deficiency (MCADD)

What is MCADD?

MCADD is a rare inherited condition in which there is a deficiency in the enzyme medium-chain acyl-CoA dehydrogenase which is needed for the breakdown of certain stored fats (medium-chain fatty acids).

Fatty acids are an important energy reserve during periods of poor calorie intake, prolonged periods between meals or during infections and sickness. In these situations people with MCADD have high levels of partially broken down fatty acids and low blood glucose concentrations which can result in a metabolic crisis.

What causes MCADD?

MCADD is an inherited disorder. MCADD occurs when a baby is born with neither copy of their MCADD gene functioning correctly because both genes have an alteration (also known as gene mutation). For this reason MCADD is called an autosomal recessive disorder.

The enzyme medium-chain acyl-CoA dehydrogenase enables the body to use fat reserves to produce energy. Deficiency of medium-chain acyl-CoA dehydrogenase causes a block in the medium-chain length step of fat breakdown. This leads to a build-up of medium-chain fatty acids, in particular octanoyl carnitine (C8) and its metabolites, and results in inefficient breakdown of fat.

What are the clinical effects?

As a result of not being able to use their fat reserves, children with MCADD quickly use up glucose and may develop hypoglycaemia. The high levels of partially broken down fatty acids and low blood glucose concentrations can result in metabolic crisis, with serious life threatening symptoms including drowsiness, seizures, brain damage and even death. MCADD can cause death at the first episode of metabolic crisis experienced.

Affected children are usually well until potentially life threatening symptoms become apparent. Metabolic crises can arise during periods of stress caused by an illness, fasting or vomiting, when the child need to break down fat quickly.

How common is MCADD?

MCADD is an autosomal recessive inherited condition which affects about 1 in 10,000 babies born in the UK. It is estimated that three or four babies in Wales are born with this condition each year. Screening for MCADD started in Wales in June 2012.

What are the benefits of screening for MCADD?

Newborn bloodspot screening means that babies who have MCADD can be identified early. This allows special attention to be given to the baby's diet, including making sure they feed regularly. This care can prevent serious illness and allow babies with MCADD to develop normally. If babies are not screened for MCADD and they do have the condition, the diagnosis may only be made when they become suddenly and seriously unwell.

What is the treatment for MCADD?

The management of babies with MCADD focuses on avoiding metabolic crises by the adherence to a regular 'safe' feeding schedule, and the active management of febrile illnesses or vomiting. Babies with MCADD will receive care from a specialist metabolic team.

Babies with MCADD who are well, can be fed normally: either breast feeding or formula feeding every three to four hours. However, it is important that babies do not fast for longer than six hours (day or night).

Older babies may be able to fast for a longer time if it has been established that the 'safe' interval between feeds can be lengthened (on metabolic team advice).

Children with MCADD can be on a normal, healthy diet. When the child is well, there is no specific dietary management apart from avoiding long periods without food.

If a baby or child is unwell and/or is not feeding well, very frequent feeds or drinks of glucose polymer need to be given. This is called the 'Emergency Regimen'. Glucose polymer will provide energy and help prevent the body fat stores being used for energy. If the emergency regimen is not tolerated by the baby or child, they will need urgent treatment including IV dextrose in hospital. If there is any doubt at all, a child with MCADD must be taken to hospital.

How effective is the treatment?

With early detection and monitoring and avoidance of fasts, children diagnosed with MCADD can lead normal lives particularly as the 'safe' time between meals expands as they grow older. They are expected to have a normal life span.

What are the implications for other members of the family?

If parents have a child with MCADD, the risk of them having another affected child is 1 in 4 (25%). If the affected child has older siblings, the parents will be offered testing of those children for MCADD. If the parents have other children in the future, the babies should be offered MCADD screening earlier than routine screening. This should be undertaken between one and two days after birth. As MCADD is an inherited condition, parents can be offered and referred to specialist genetic services for further information and advice.

Other family members may have concerns about the implications for them. Family members can be referred to specialist genetic services for advice and information.

Following a screen positive result for MCADD, babies are referred to an appropriate clinician in accordance with the clinical referral guidelines.

Further information: https://www.metabolicsupportuk.org/

7.1.2 Phenylketonuria (PKU)

What is phenylketonuria?

Phenylketonuria (PKU) is a rare inherited condition in which there is a build-up of phenylalanine in the body. Phenylalanine is an amino acid and is present in many

foods. The build-up of phenylalanine is neurotoxic and harmful to the brain. Without treatment, PKU can cause severe, irreversible mental disability.

What causes PKU?

PKU occurs when a baby is born with neither copy of their PKU gene functioning correctly because both genes have an alteration (also known as a gene mutation). For this reason PKU is called an autosomal recessive disorder.

Usually people consume more amino acids (proteins) than they need and the extra amino acids are broken down. The enzyme that breaks down phenylalanine is called phenylalanine hydroxylase (PAH) and this converts phenylalanine to tyrosine. Tyrosine is used to make a number of important chemicals for the body such as dopamine and melanin.

Classic PKU is the most severe form of a high phenylalanine and is caused by a deficiency of the enzyme phenylalanine hydroxylase (PAH). This enzyme deficiency will cause a raised phenylalanine but a low tyrosine concentration.

There is also a milder form of the condition, so called hyperphenylalaninaemia. This condition may not require treatment as phenylalanine concentrations are not as high as in the classical condition. Approximately 1 in 5 babies with high phenylalanine on newborn bloodspot screening will have hyperphenylalaninaemia. High phenylalanine concentrations can also be caused by defects in biopterin, the co-factor for phenylalanine hydroxylase. Biopterin defects are also diagnosed via newborn bloodspot screening but treatment differs from that for classical PKU.

What are the clinical effects?

Babies with PKU have high concentrations of circulating phenylalanine and lower concentrations of tyrosine. Phenylalanine is neurotoxic and tyrosine is required for normal brain development. Clinical features in children with PKU worsen over time due to increased build-up of phenylalanine and untreated children with PKU develop brain damage. At 6-12 months developmental delay is observed followed by severe, irreversible mental retardation, microcephaly and seizures around the age of two years.[1]

How common is PKU?

PKU affects approximately 1 in 10,000 babies in the UK. This means that approximately four babies are born with PKU in Wales each year.

Galactosaemia which is a by-product of screening for PKU, is a rare genetic disorder in which the person is unable to break down galactose to glucose. This results in the build-up of galactose which can cause serious complications and has a high mortality rate. Treatment is the exclusion of lactose and galactose from the diet.

What are the benefits of screening for PKU?

Screening is beneficial as the adverse effects of PKU can be prevented if treatment for the condition is started early. It is recommended that treatment should begin by 14 days of age to minimise adverse effects.

What is the treatment for PKU?

Babies are started on a phenylalanine restricted diet in order to ensure that circulating phenylalanine concentrations are kept as low as possible. PKU patients therefore have lower protein intake and so require supplements containing vitamins, minerals and all essential amino acids (excluding phenylalanine).

Phenylalanine levels are measured on a regular basis to ensure that the level is within the target range, and this is by either heel prick for babies or finger prick for older children. Phenylalanine concentrations in children with PKU are monitored by testing weekly bloodspot samples between 0-6 months of life, fortnightly from 6 months to 4 years and then monthly thereafter.[2]

How effective is the treatment?

Treatment is extremely effective if started early and if the diet is strictly followed. Later start of treatment is associated with lower IQ, whereas babies with PKU in which treatment is started in the first few weeks have near normal IQ.[1]

What are the implications for other members of the family?

If parents have a child with PKU the risk of them having another affected child is 1 in 4 (25%). If the parents have other children in the future they should be offered PKU screening earlier the routine screening. This should be undertaken between one and two days after birth.

As PKU is an inherited condition, parents can be offered and referred to specialist genetic services for further information and advice. Other family members may have concerns about the implications for them and can also be referred to specialist genetic services for advice and information.

Following a screen positive result for PKU, babies are referred to an appropriate clinician in accordance with clinical referral guidelines.

References

1. Pollitt RJ, Green A, McCabe A et al. Neonatal screening for inborn errors of metabolism: cost, yield and outcome. Health Technol Assess 1997;1:1-203.
2. National Society for Phenylketonuria (NSPKU). Management of PKU. February 2004. Further information: http://www.nspku.org

7.1.3 Maple Syrup Urine Disease (MSUD)

What is maple syrup urine disease?

Maple syrup urine disease (MSUD) is a rare inherited disorder that prevents the breakdown of some of the building blocks of protein, the amino acids leucine, isoleucine and valine in the blood. Without treatment, MSUD can lead to serious problems including coma and permanent brain damage.
The condition is named maple syrup urine disease because high levels of these amino acids can cause an unusual sweet smell in the urine and sweat.

What causes MSUD?

MSUD occurs when a baby is born with neither copy of their gene to break down the amino acids leucine, isoleucine and valine functioning correctly. MSUD is an autosomal recessive disorder because both genes have an alteration (also known as a gene mutation).

Usually people eat more amino acids (building blocks of protein) than they need and the extra amino acids are broken down and removed from the body. People with MSUD are unable to break down the amino acids leucine, isoleucine and valine (these are also known as the branched chain amino acids). When the levels of these amino acids get very high, they are harmful.

There are three forms of MSUD: the classical (severe form of the disease), the intermediate form and the intermittent (mild form of the disease). Most patients have the classical form of the disease.

What are the clinical effects?

People with MSUD are at risk of developing a metabolic crisis. This typically occurs in the first days or weeks of life but can occur later on in the first year of life or even later during childhood.

The symptoms that can develop in the newborn period include poor feeding, irritability, sleepiness, vomiting, breathing difficulties and fast breathing and coldness. If the baby is not treated they may deteriorate, have fits, go into a coma and are at risk of dying.

Sometimes a baby may not develop symptoms of a metabolic crisis until later during childhood, and in these cases a crisis may be caused by having an illness such as an infection or upset stomach.

How common is MSUD?

MSUD is a rare disease and affects about 1 in 116,000 babies born in the UK. It is estimated that in Wales one baby will be born every three to four years with MSUD.

What are the benefits of screening for MSUD?

Newborn bloodspot screening means that babies who have MSUD can be identified early and be given treatment, and parents can be made aware of the management of their baby if they become unwell. If babies are not screened for MSUD and they have the condition, the diagnosis may only be made if the baby or child develops symptoms including a metabolic crisis.

What is the treatment for MSUD?

Treatment aims to reduce the build-up of the harmful amino acids which can cause a metabolic crisis and learning difficulties. This is mainly dietary management and needs to be undertaken with the advice of a specialist metabolic team including a specialist dietitian. The patient has a low protein diet with regular blood monitoring and supplementation of essential amino acids.

All baby milks (including breast milk) contain more protein than can be tolerated by babies with MSUD. Breast feeding is encouraged but the amount of milk a baby with MSUD is given needs to be measured and controlled. A special baby milk which does not contain leucine, valine and isoleucine is given to meet dietary requirements.

Babies and children with MSUD are at risk of having metabolic crisis when they have infections or an illness such as diarrhoea or vomiting. The risk of a crisis can be reduced by starting a special feed called the emergency regimen, which is a glucose polymer, and stopping protein-containing milk and food. It is also important to give a special amino acid formula with supplements to help control the levels of harmful amino acids in the blood. The specialist metabolic dietitian advises the parents on how to give the emergency regimen. Parents are also advised of when they need to seek urgent medical care.

How effective is the treatment?

With early diagnosis and treatment, most children with MSUD develop normally. However, patients need to stay on their low protein diet with supplements throughout life and will need to use their emergency regimen during illness.

Patients with the milder form of the disease, under specialist advice, can have a less restricted diet and may only need to avoid high protein foods and use their emergency regimen during illness.

What are the implications for other members of the family?

If parents have a child with MSUD, the risk of them having another affected child is 1 in 4 (25%). If the affected child has older siblings, the parents will be offered testing of those children for MSUD. If parents have other children in the future, the babies should be offered screening earlier than routine screening. This should be undertaken 12 to 24 hours after birth.

As MSUD is an inherited condition, parents can be offered and referred to specialist genetic services for further information and advice. Other family members may have concerns about the implications for them and can also be referred to specialist genetic services for advice and information.

Following a screen positive result for MSUD, babies are referred to an appropriate clinician in accordance with the clinical referral guidelines.

Information adapted from the information resource for parents and professionals on the Expanded Newborn Screening Programme and Rare Conditions websites.

Further information: https://www.metabolicsupportuk.org/

7.1.4 Isovaleric Acidaemia (IVA)

What is isovaleric acidaemia?

Isovaleric acidaemia (IVA) is a rare inherited disorder that prevents the breakdown of a building block of protein, the amino acid leucine. This then causes a harmful build-up of a substance called isovaleric acid in the blood. Without treatment, IVA can lead to serious problems including coma and permanent brain damage.

What causes IVA?

IVA occurs when a baby is born with neither copy of their gene to break down the amino acid leucine functioning correctly. IVA is an autosomal recessive disorder because both genes have an alteration (also known as a gene mutation).

Usually people eat more amino acids (building blocks of protein) than they need and the extra amino acids are broken down. People with IVA have a problem breaking down an amino acid called leucine. Leucine is broken down to isovaleric acid which is normally further broken down to make energy. People with IVA are unable to break down isovaleric acid. This acid builds up in the body and causes harmful effects.

IVA can vary in severity and in some mild forms of IVA the risk of problems is lower.

What are the clinical effects?

IVA can affect babies in different ways. Some babies start to develop symptoms of a metabolic crisis in the first days or weeks of life. These symptoms can include poor feeding, irritability, sleepiness, vomiting, breathing difficulties and fast breathing and coldness. If the baby is not treated they may deteriorate, have fits, become unconscious and are at risk of dying.

Sometimes a baby may not develop symptoms of a metabolic crisis until later in the first year of life or later during childhood. In these cases a metabolic crisis may be caused by having an illness such as an infection or stomach upset. Other children with IVA may not develop a metabolic crisis but may have learning difficulties.

How common is IVA?

IVA is a rare disease and affects about 1 in 155,000 babies born in the UK. It is estimated that in Wales one baby will be born every four to five years with IVA.

What are the benefits of screening for IVA?

Newborn bloodspot screening means that babies who have IVA can be identified early and be given treatment, and parents can be made aware of the management of their baby if they become unwell. If babies are not screened for IVA and they have the disorder, the diagnosis may only be made if the baby or child develops symptoms including metabolic crisis.

What is the treatment for IVA?

Treatment aims to reduce the build-up of toxins which can cause metabolic crisis and learning difficulties. This is dietary management and medication and needs to be undertaken with advice from a specialist metabolic team including a specialist dietitian. The patient has a low protein diet with the aim to reduce the amount of leucine. Foods are measured to ensure that the right amount of protein is eaten each day with sufficient for normal growth and development.

All baby milks (including breast milk) contain more protein than can be tolerated by babies with IVA. Breast feeding is still encouraged but the amount of milk a baby with IVA is given needs to be measured and controlled. A special baby milk is sometimes given to meet dietary requirement but this depends on how much protein the child is allowed.

Medications called L-carnitine and/or glycine are used to help clear some of the toxins that develop.

Babies and children with IVA are at risk of having a metabolic crisis when they have infections or illnesses such as diarrhoea or vomiting. The risk of a crisis can be reduced by starting a special feed called the emergency regimen, which is a glucose polymer, and stopping protein-containing milk and food. Medications should also continue whilst the emergency regimen is being given. The specialist metabolic dietitian advises parents on how to give the emergency regimen. Parents are also advised of when they need to seek urgent medical care.

How effective is the treatment?

With early diagnosis and treatment, babies with IVA can have a low protein diet and medication to improve their long term outlook and prevent metabolic crises. Patients will need to use their emergency regimen during illness. This will help to reduce the risk of long term brain damage.

What are the implications for other members of the family?

If parents have a child with IVA, the risk of them having another affected child is 1 in 4 (25%). If the affected child has older siblings, the parents will be offered testing of those children for IVA. If parents have other children in the future, the babies should be offered screening earlier than routine screening. This should be undertaken between one and two days after birth.

As IVA is an inherited condition, parents can be offered and referred to specialist genetic services for further information and advice. Other family members may have concerns about the implications for them and can also be referred to specialist genetic services for advice and information.

Following a screen positive result for IVA, babies are referred to an appropriate clinician in accordance with the clinical referral guidelines.

Information adapted from the information resource for parents and professionals on the Expanded Newborn Screening Programme and Rare Conditions websites.

Further information: https://www.metabolicsupportuk.org/

7.1.5 Glutaric Aciduria Type 1 (GA1)

What is glutaric aciduria type 1?

Glutaric aciduria type 1 (GA1) is a rare inherited disorder that prevents the breakdown of certain building blocks of protein, in particular the amino acids lysine and tryptophan, and can cause a harmful build-up of a substance called glutaric acid in the blood. Without treatment, GA1 can lead to serious problems including coma and permanent brain damage.

What causes GA1?

GA1 occurs when a baby is born with neither copy of their gene for breaking down the amino acids lysine and tryptophan functioning correctly. GA1 is an autosomal recessive disorder because both genes have an alteration (also known as a gene mutation).

Usually people eat more amino acids (building blocks of protein) than they need and the extra amino acids are broken down and removed from the body. People

with GA1 are unable to break down the amino acids lysine and tryptophan and so harmful substances build up.

What are the clinical effects?

GA1 can affect babies in different ways. Babies usually have no symptoms in the first days or weeks of life. In the first year of life some children can develop symptoms of floppiness or weakness, delay in reaching some of their developmental milestones and have a relatively large head.

Babies with GA1 are at risk of developing a metabolic crisis when they have an illness (such as an infection or vomiting), and these symptoms can include poor feeding, floppiness and sleepiness. If the baby is not treated they may deteriorate, become unconscious and go in to a coma. Unfortunately, after a coma most patients have permanent brain damage. The brain damage causes problems with muscle control which can cause difficulties relating to movement (abnormal posture and involuntary jerky movements), feeding and breathing.

How common is GA1?

GA1 is a rare disease and affects about 1 in 109,000 babies born in the UK. It is estimated that in Wales one baby will be born every three to four years with GA1.

What are the benefits of screening for GA1?

Newborn bloodspot screening means that babies who have GA1 can be identified early and given treatment, and parents can be made aware of the management of their baby if they become unwell. If babies are not screened for GA1 and they have the disorder, the diagnosis may only be made if the baby or child develops symptoms including potentially a metabolic crisis. Treatment before symptoms are detected can usually prevent brain damage in GA1, but if brain damage has occurred this cannot be reversed.

What is the treatment for GA1?

Treatment aims to reduce the build-up of toxins which can cause metabolic crisis and brain damage. This is mainly dietary management and needs to be undertaken with the advice of a specialist metabolic team including a specialist dietitian. The patient has a low protein diet to reduce the amount of the amino acids lysine and tryptophan in the diet.

All baby milks (including breast milk) contain more protein than can be tolerated by babies with GA1. Breast feeding is encouraged but the amount of milk a baby with GA1 is given needs to be measured and controlled. A special baby milk without the amino acids lysine and tryptophan is given to meet dietary requirements.

A medication called L-carnitine is given to help clear some of the toxins that develop. Babies and children with GA1 are at risk of having a metabolic crisis when they have infections or have illness such as diarrhoea or vomiting. The risk of a crisis can be reduced by starting a special feed called the emergency regimen, which is glucose polymer, and stopping protein-containing milk and food. The specialist metabolic dietitian advises parents on the emergency regimen. Parents are also advised of when they need to seek urgent medical care.

How effective is the treatment?

With early diagnosis, treatment and appropriate management if the child becomes unwell, metabolic crises may be prevented. Regular treatment with a low protein/low lysine diet and medication can reduce the risk of long term brain damage. Patients will need to use their emergency regimen during illness.

What are the implications for other members of the family?

If parents have a child with GA1, the risk of them having another affected child is 1 in 4 (25%). If the affected child has older siblings, the parents will be offered testing of those children for GA1. If parents have other children in the future, the babies should be offered screening earlier than routine screening. This should be undertaken between one and two days after birth.

As GA1 is an inherited disorder, parents can be offered and referred to specialist genetic services for further information and advice. Other family members may have concerns about the implications for them and can also be referred to specialist genetic services for advice and information.

Following a screen positive result for GA1, babies are referred to an appropriate clinician in accordance with the clinical referral guidelines.

Information adapted from the information resource for parents and professionals on the Expanded Newborn Screening Programme and Rare Conditions websites.

Further information: https://www.metabolicsupportuk.org/

7.1.6 Homocystinuria (HCU)

What is homocystinuria?

Homocystinuria (HCU) is a rare inherited disorder that prevents the breakdown of a building block of protein, the amino acid homocysteine. This then causes a harmful build-up of homocysteine in the blood. Without early treatment, this can lead to long term health problems including learning difficulties, eye problems, osteoporosis and blood clots or strokes.

What causes HCU?

HCU occurs when a baby is born with neither copy of their gene to break down homocysteine functioning correctly. HCU is an autosomal recessive disorder because both genes have an alteration (also known as a gene mutation).

What are the clinical effects?

HCU can affect babies in different ways. Babies with HCU are usually well in early life, although symptoms may develop later if untreated. Some children develop problems with their eyes, including severe short sightedness and dislocation of the lens.

Without early diagnosis and early start of treatment, children can develop damage to the brain, including learning difficulties. Children may also have thin bones (osteoporosis), bone and joint problems and may develop blood clots or strokes.

How common is HCU?

HCU is a rare disease and affects about 1 in 144,000 babies born in the UK. It is estimated that in Wales one baby will be born every four to five years with HCU.

What are the benefits of screening for HCU?

Newborn bloodspot screening means that babies who have HCU can be identified early and given treatment to prevent the build-up of homocysteine, and the child is expected to grow and develop normally and have a normal life expectancy. If babies are not screened for HCU and they have the disorder, the diagnosis may only be made if the baby or child develops symptoms.

What is the treatment for HCU?

Treatment is given to prevent the build-up of homocysteine. In some babies with HCU the level of homocysteine can be controlled by giving vitamin B6 (pyridoxine). If this is not effective then HCU can be treated with a special low protein diet and extra supplements and medications. This is undertaken with advice from a specialist metabolic team including a specialist dietitian.

All baby milks (including breast milk) contain protein. Breast feeding is encouraged for babies with HCU but the amount of milk may need to be limited. A special baby milk can be given to meet dietary requirements. Supplements and medicine that can be given include folic acid, vitamin B12 and betaine.

Patients with HCU need to have regular blood tests to monitor the level of homocysteine in their blood.

How effective is the treatment?

Early diagnosis and treatment with a low protein diet will help improve the long term outlook and prevent problems from developing. Without treatment, around a quarter of patients are at risk of having a life threatening blood clot before the age of 30 years.

What are the implications for other members of the family?

If parents have a child with HCU the risk of them having another affected child is 1 in 4 (25%). If the affected child has older siblings, the parents will be offered testing of those children for HCU.

As HCU is an inherited disorder, parents can be offered and referred to specialist genetic services for further information and advice. Other family members may have concerns about the implications for them and can also be referred to specialist genetic services for advice and information.

Following a screen positive result for HCU, babies are referred to an appropriate clinician in accordance with the clinical referral guidelines.

Information adapted from the information resource for parents and professionals on the Expanded Newborn Screening Programme and Rare Conditions websites.

Further information: https://www.metabolicsupportuk.org/

7.2 Congenital Hypothyroidism (CHT)

What is congenital hypothyroidism?

Congenital hypothyroidism (CHT) is a condition where the baby's thyroid gland fails to develop or work properly and fails to make the thyroid hormone called thyroxine. Thyroxine is needed for normal growth and development.

What causes CHT?

If the problem is with the gland itself this is called primary congenital hypothyroidism. This can be caused by the thyroid gland being absent (agenesis), being positioned in the wrong place (ectopic thyroid) or severely reduced in size (hypoplastic). Another cause of primary hypothyroidism is when the gland is normal or enlarged in size and in the correct position, but there is a problem with the production of thyroxine (dyshormonogenesis).

Alternatively, hypothyroidism can be caused by defects earlier in the chemical pathway that regulates the production of thyroxine. The thyroid gland doesn't work in people who have very low levels of thyroid stimulating hormone (also called thyrotropin), produced by the pituitary gland. This is called secondary

hypothyroidism. Not all cases of secondary hypothyroidism are detected by newborn screening.

What are the clinical effects?

The thyroid gland usually starts working in the unborn fetus from about 20 weeks gestation. The mother's own thyroid doesn't provide enough thyroxine to maintain sufficiently high levels in the fetus.

In very severe cases of CHT babies may be born with, or quickly develop, some of the signs and symptoms of CHT. These may include feeding difficulties, sleepiness, constipation and jaundice. However, CHT is rarely diagnosed by clinical means in the newborn period.

If babies with CHT are not treated, they fail to grow properly and will have 'mild to severe' mental disability. In the most severe cases children also have a lack of co-ordination, jerky movements and tremors. In general, patients with complete absence of the thyroid gland (called thyroid agenesis) are the most severely affected.

Babies with secondary hypothyroidism often have additional health problems. These can include facial features, low blood sugar, jaundice and small genitals. Some children with secondary hypothyroidism don't develop the condition until they are older, and present in later childhood with reduced physical growth from associated pituitary insufficiency. These children will not be identified by newborn bloodspot screening.

How common is CHT?

CHT affects about 1:3,000 babies born in the UK. Approximately 18 babies are born with CHT in Wales each year.

Why does a baby have CHT?

Congenital hypothyroidism is not usually an inherited condition. In the rare cases it is inherited, it is usually the condition where the thyroid gland is in the right place but it cannot produce thyroxine (dyshormonogenesis).

What are the benefits of screening for CHT?

The aim of screening is to identify as soon as possible which newborns are more likely to have CHT so that a diagnosis can be made and treatment can be started. Treatment is very effective at preventing physical and mental disability. Treatment should start by 14 days of age.

What is the treatment for CHT?

Babies with primary hypothyroidism are treated by replacing the thyroxine that the body cannot produce. This is levothyroxine (thyroxine), given once a day, in the form of crushed tablets by mouth. Regular blood tests are needed to check the thyroxine levels and make sure the dose is correct. The later the treatment is started, the more the baby's development is affected by the condition.

How effective is the treatment?

Experience with screening for congenital hypothyroidism in the UK has found that almost all children who are diagnosed and treated from an early age will grow and develop normally.

However, a small proportion of children who have had severe hypothyroidism in the womb may have some difficulties such as poor hearing, clumsiness or trouble with learning. These problems can be reduced if hypothyroidism is picked up early and treated as described above.

Following a screen positive result for CHT, babies are referred to an appropriate clinician in accordance with the clinical referral guidelines.

Further information:

http://btf-thyroid.org/

http://www.gosh.nhs.uk/medical-conditions/search-for-medical-conditions/congenital-hypothyroidism

7.3 Cystic Fibrosis (CF)

What is cystic fibrosis?

Cystic Fibrosis (CF) is one of the UK's most common inherited life-threatening diseases. CF is a disease in which abnormal movement of salt and water into and out of cells causes a build-up of thick, sticky mucous. This occurs particularly in the lungs and digestive system.

What causes CF?

CF is an inherited condition. CF occurs when a baby is born with neither copy of their CF gene functioning correctly, as both genes have an alteration (also known as a gene mutation). For this reason, CF is called an autosomal recessive disorder. The effects of the gene mutations can be variable depending on the exact gene mutations present in an individual.

Mutations in the cystic fibrosis transmembrane conductance regulator gene (CFTR) lead to too much salt and water building up in cells. The CFTR gene codes for the CFTR protein which functions as an ion channel to control water, sodium and chloride movement across the cell membrane. 70% of CF patients have the most common mutation of the gene (p.Phe508del).

What are the clinical effects?

There are a range of different gene mutations which result in different clinical presentations. A spectrum of disease exists with some patients having only lung dysfunction, some only digestive symptoms and others having a combination of both. In the respiratory system the mucous prevents bacterial clearance, therefore, making patients prone to chest infections.

In many people with CF, the small channels that carry the digestive juices become clogged with sticky mucus. The enzymes can build up in the pancreas which becomes inflamed and damaged over time. Digestive tract abnormalities include pancreatic insufficiency, which leads to malabsorption, steatorrhoea and poor growth, and intestinal obstruction, meconium ileus and gastro-oesphageal reflux.[1]

How common is CF?

CF affects approximately 1 in 2,500 babies in the UK meaning that approximately 12 to 14 babies are born with CF in Wales each year.

What are the benefits of screening for CF?

There is a debate on whether screening for CF significantly improves outcome, as results from studies differ and many studies have not found an improvement in lung function. Despite this, nutrition and therefore cognitive function have been found to be greatly improved in the screened population. Although debate exists regarding clinical outcome, quality of life is improved as a result of screening as hospital stays are fewer and shorter in duration than in children who are not screened.[2]

What is the treatment for CF?

CF is treated using a combination of therapies:

- Physiotherapy – used to physically clear mucus from the lungs
- Medication – Bronchodilators to open the airways, antibiotics to treat infection, steroids to reduce inflammation
- Nutrition – Pancreatic enzymes are given to aid digestion, high calorie diet is recommended and vitamin A, D and E supplements are given as these fat soluble vitamins are lost in the stools

How effective is the treatment?

Current treatment can improve quality of life but there is currently no cure for CF. Work is currently underway into the use of gene therapy in CF.

What are the implications for other members of the family?

If parents have a child with CF the risk of them having another affected child is 1 in 4 (25%). As CF is an inherited condition, the parents can be offered and referred to genetic services for further information and advice. Other family members may have concerns about the implications of CF for them and can also be referred to specialist genetic services for advice and information.

Following a screen positive result for CF, babies are referred to an appropriate clinician in accordance with clinical referral guidelines.

References

1. Davies JC, Alton EWFW, Bush A. Cystic Fibrosis. BMJ. 2007;335:1255-59.
2. Balfour-Lynn IM. Newborn screening for cystic fibrosis: evidence for benefit. Arch Dis Child. 2008;93 (1):7-10.

Further Information: https://www.cysticfibrosis.org.uk/

7.4 Sickle Cell Disorders (SCD)

What are sickle cell disorders?

Sickle cell disorders (SCD) is a term that describes a group of conditions in which haemoglobin in red blood cells is abnormal in structure. This causes red blood cells to take up a shape like a crescent moon or farmer's sickle when de-oxygenated. Sickled red blood cells are not as flexible as normal red blood cells and can cause blockages within small blood vessels. Sickled red blood cells do not last as long as normal red blood cells and therefore their rate of production is increased.

What causes sickle cell disorders?

Sickle cell disorders are autosomal recessive inherited conditions. A SCD occurs when a baby is born with neither copy of their haemoglobin gene functioning correctly because both genes have an alteration (also known as 'gene mutations'). The gene mutation affects the structure of haemoglobin.

In areas of the world where malaria was common, people who had one copy of the gene mutation (sickle cell carriers) were more likely to survive malaria than those who had the usual haemoglobin. This is why sickle cell haemoglobin is found in people whose ancestors come from Africa, Asia, Middle and Far East and the Mediterranean.

There are many different haemoglobin gene mutations. The ones commonly seen in the UK population are Haemoglobin S (HbS), Haemoglobin C (HbC), Haemoglobin E (HbE), Haemoglobin D (HbD^{Punjab}), beta thalassaemia and alpha thalassaemia. A sickle cell disorder occurs if HbS is inherited from one parent and either HbS or another mutation is inherited from the other parent.

What are the clinical effects?

Clinical effects arise from tissue and organ damage caused by blockages of blood vessels and from the increased red blood cell production. The effects of SCD can include pain, anaemia, jaundice, enlarged spleen and infections. Sickle cell disorders are of variable severity, and there is currently no way of accurately predicting the clinical course for an individual patient. Exacerbations of the condition known as 'sickle cell crises' can be life-threatening.

How common are Sickle Cell Disorders?

The prevalence of sickle cell disorders varies according to ancestral origins with the highest prevalence in populations whose ancestors lived in malaria endemic areas. In the UK, the condition affects approximately 1 in every 2000 live births. Wales is a low prevalence area for sickle cell disorders and approximately three or four babies are born with SCD in Wales each year.

What are the benefits of screening for SCD?

Screening for SCD allows the start of early treatment to prevent infections and to start health monitoring and parental education. It has been shown that newborn bloodspot screening when linked to timely diagnostic testing, parental education and clinical monitoring, reduces morbidity and mortality for sickle cell disorders in infancy and childhood.[1,2]

The aim of newborn bloodspot screening for SCD in Wales is to identify babies who have a SCD and not to identify babies who are carriers of an SCD.

What is the treatment for SCD?

Patients are given prophylactic antibiotics to prevent infection, folic acid to maintain the increased rate of red cell production and medication for painful crisis. Parents are given education and support to deal with the episodes of pain and to recognise the signs of a sickle cell crisis to help prevent serious complications. Enrolment into the care of a specialist medical team ensures that care provided meets nationally agreed standards.

There are specific treatments under the care of the specialist team that include hydroxycarbamide (also known as hydroxyurea) which acts to reduce the tendency of red blood cells to sickle. Regular blood transfusions can be used to

prevent stroke and reduce complications of SCD but this has long term adverse effects of iron accumulation in the heart and liver.

How effective is the treatment?

The treatment can improve quality of life, reduce life threatening complications, prolong life and reduce hospital admissions but may not be effective in a small minority of patients, for whom bone marrow transplant is an option.

Sickle cell disorders can be cured by allogeneic (sibling or matched unrelated donor) bone marrow transplant. This is reserved for very severe cases in which other treatment has not been effective.

What are the implications for other members of the family?

If parents have a child with SCD, the risk of them together having another affected child is 1 in 4 (25%). As SCD is an inherited condition, parents can be offered and referred to genetic services for further information and advice. Other family members may have concerns about the implications of SCD for them and can also be referred to specialist genetic services for advice and information.

Following a screen positive result for SCD, babies are referred to an appropriate clinician in accordance with the clinical referral guidelines.

References

1. Berg AO. Sickle cell disease, diagnosis, management and counselling in newborns and infants. The agency for Health Care Policy and Research. J Am Board Fam Pract 1994;7:134-140
2. Vichinsky E, Hurst D, Earles A, Kleman K, Lubin B. Newborn screening for sickle cell disease: effect on mortality. Pediatrics 1988;81:749-755

Further information: http://sct.screening.nhs.uk

8. Programme overview

Programme Aim

The aim of the Newborn Bloodspot Screening (NBS) programme in Wales is to offer all eligible babies, at day 5 of life, quality assured screening for rare but serious diseases that could benefit from early intervention and reduce mortality and or morbidity from the disease.

Programme delivery

The Screening Division of Public Health Wales is responsible for the planning, preparation and delivery of the Newborn Bloodspot Screening Wales (NBSW) programme. NBSW is one of three programmes within Maternal and Child (MAC) Screening, which has an overall Programme Lead. There are NBSW programme co-ordinators, and administration support across the MAC programmes. The other two programmes are Antenatal Screening Wales (ASW) and Newborn Hearing Screening Wales (NBHSW).

Offer of screening and sample collection

The offer of newborn bloodspot screening to eligible babies and the collection of bloodspot samples is undertaken by health professionals within the seven health boards in Wales.

The programme offers bloodspot screening to every newborn baby who is resident in Wales at day 5 of life and to every infant who becomes resident in Wales, up to one year of age.

Testing of samples and referral of screen positive babies

The Wales Newborn Screening Laboratory in Cardiff is responsible for testing the screening samples taken in Wales and for the referral of babies suspected of having conditions. Babies are referred to a network of clinicians and designated medical leads in the health boards. The programme has external Quality Assurance Advisors which include some of the medical leads.

The Newborn Bloodspot Screening Wales System (NBSWS)

The Newborn Bloodspot Screening Wales System (NBSWS) has been developed to support the management of a safe and sustainable programme across Wales. This system collects and collates information across the programme to monitor the quality of newborn bloodspot screening and provides quality assurance and management reports based on the policies and standards.

NBSWS also identifies babies for whom the programme expects to receive either a bloodspot card or decline for the test(s), and initiates failsafe procedures for possible 'missed' babies. This failsafe system identifies babies in Wales who do not have a newborn bloodspot screening sample in the Newborn Screening Laboratory by day 14 of life. Every baby identified by the failsafe is followed up by the administration failsafe teams. The three regional teams across Wales are staffed by newborn screening managers and administrative staff who work across both the NBSW and Newborn Hearing Screening Wales (NBHSW) programmes.

Governance Leads

In each health board there is a Governance Lead for Antenatal and Newborn Screening. This role, funded by Screening Division, Public Health Wales, is to act as liaison between the health board and NBSW, and to lead the provision of newborn bloodspot screening in the health board to ensure the provision of an effective and efficient service.

Policies and Standards

The policies and standards outline what needs to be achieved in all aspects of the programme.

The scope

NBSW is responsible for the baby up to the point of the issue of normal results or the onward referral following a screen positive test result to an appropriate clinician (in accordance with the clinical referral guidelines for each condition).

NBSW is responsible for:

- Identifying eligible babies to be offered screening
- Providing supporting information
- Providing results
- Identifying babies suspected of having one of the conditions screened for
- Referring babies suspected of having one of the conditions screened for to an appropriate clinician
- Working with the service to ensure the quality of the bloodspot sample taken meets the national laboratory standards
- Providing quality standards and protocols, and managing a quality system
- Raising public and professional awareness of the screening programme
- Evaluating the programme in Wales and contributing to UK wide evaluation
- Ensuring staff working within the programme are appropriately trained
- Developing training materials to support staff working within the programme

9. Guidelines

Guidelines for Newborn Bloodspot Screening

These guidelines are written for the screening programme in Wales.

Health boards are encouraged to develop local processes in line with these guidelines.

The guidelines aim to:

- provide a consistent and clear approach to newborn bloodspot sampling
- support healthcare workers in promoting newborn bloodspot screening
- support parents in making an informed choice about newborn bloodspot screening for their baby
- support sample takers in obtaining good quality samples to prevent the need for avoidable repeats
- reduce pain and discomfort during the heel puncture

1. Preparation for taking the bloodspot sample

It is important to offer parents an informed choice about screening for their baby, to gain consent and to prepare them for the blood sampling procedure. Babies that move into an area and are eligible for screening should be offered screening as soon as possible.

Section	Action	Reasoning
Antenatal period – provide information and take family history		
1.1	A copy of the leaflet 'Newborn Bloodspot Screening – Information for parents' is made available for women in the antenatal period.	To enable parents to make an informed choice about screening for their baby. [1-6] Providing information about the screening during pregnancy allows time for parents to process this information and gives them more opportunity to discuss this.

	Requests for the leaflets can be made via nbsw@wales.nhs.uk The leaflet is bilingual (Welsh and English) and is available in other formats on the NBSW website: www.newbornbloodspotscreening.wales.nhs.uk For other languages, arrangements should be made with local interpreter services.	The leaflet provides information on the conditions screened for, how the sample will be taken and how parents will receive results. It also advises parents on how to prepare for the bloodspot sample (warmth, comfort and feeding of baby).
1.2	Parents should be asked if they have a family history of any of the inherited metabolic diseases.	To ensure a plan is put in place for early testing if appropriate.
Postnatal period – offer screening and record parent's decision		
1.3	Ensure parents still have access to the pre-screening leaflet at least 24 hours before taking the sample. If not, ensure a copy of the leaflet is given to the parents. Where 'parent' is stated it also refers to the person with parental responsibility in cases where this is not the parent.	
1.4	A health professional should offer screening and record the parent's decision [7]. The benefits of screening should be clearly explained. They should explain the procedure to the parents and provide the opportunity for them to ask questions. The health professional should record in the maternity/professional record that newborn bloodspot screening has been	Good record keeping is an integral part of nursing and midwifery practice. [8] Newborn bloodspot screening is an invasive medical procedure and cannot be undertaken on babies without informed consent from a person with parental responsibility.

	discussed and recommended, the leaflet given and verbal consent sought.	
1.5	Parents should be asked if they wish to be contacted about research linked to the screening programme. If a parent does not wish to be contacted about future research on their baby's newborn bloodspot screening sample, the **'No research contact'** box on the bloodspot card should be ticked at the time of sample collection.	Stored bloodspot cards can be used to monitor and improve the newborn screening programme. In accordance with the Code of Practice for the Retention and Storage of Residual Spots. [9] Permission is necessary to involve participants in research, and this is an opportunity for the person with parental responsibility to decline to be contacted for research in the future.
1.6	**If there is parental consent to screening:** Record the parent's screening decision as 'consent' in the Personal Child Health Record (PCHR) and maternity/professional record. If the baby is in hospital, record the parent's consent decision in the baby's hospital records.	By recording information in the PCHR, parents and other health professionals will have information about the status of the baby in relation to the screening test. This also allows staff delegated to take the sample (a maternity support worker, for example), to check the maternity/professional record to confirm that the parents have given informed consent before taking the sample.

1.7	The bloodspot sample should be taken on day 5* for all babies regardless of medical condition, medication, milk feeding and prematurity. **For the purpose of screening, day of birth is day 0** (note that some information systems record day of birth as day 1, which could cause the sample to be taken on the incorrect day). Arrange a convenient time to take the bloodspot sample on this day. *In exceptional circumstances the sample can be taken between day 5 and day 8.	To enable timely detection of abnormal results and referral to specialist care. To ensure parents are aware of when the newborn bloodspot screening test will happen. For example, if the baby has had a blood transfusion (see section 5.5).
1.8	Parents can decline screening for CHT, CF and SCD individually but the six IMDs can only be declined as a group.	The screening laboratory tests for all of the IMDs using one punched disc (see section 3.7).
1.9	**If the parents decline screening:** The health professional responsible for ensuring that screening has been offered should: • record each condition declined and the reason (if stated) in the PCHR and maternity/professional record (and baby's hospital records if applicable) • if screening is declined for all conditions, complete the information on the bloodspot card as described in section 2 (add the reason	To monitor declines, to send timely notification of a decline of one, some or all conditions to the screening laboratory, NBSWS failsafe and child health department (CHD), and to prevent unnecessary follow up.

	for the decline if stated) and send marked **'Decline – all conditions'** to the laboratory • ask the parent to sign the bloodspot card. If it is not possible to obtain a signature, this should be recorded on the card before sending it to the laboratory • record their name and enter their NMC number in the 'sample taker ID' box on the bloodspot card • if screening is declined for only one or some of the conditions (see section 1.8), arrange for the bloodspot sample to be taken. The bloodspot card should be completed and marked **'Decline – XX'** (where XX is the condition(s) declined – add the reason for the decline if stated) • inform the GP and health visitor of the conditions declined in writing	To confirm their decision to decline screening. To provide a record on the bloodspot card of the health professional responsible for offering screening and completing information on the card. Notifying the family's GP ensures that the GP does not assume testing has been completed and thereby, should symptoms arise, rule out the possibility of an affected child.
1.10	Inform parents whom to contact if they change their mind or would like further information. Record this information in the PCHR. Inform the parents that NBS can be offered up to one year of age and that CF screening is only offered up to 8	To ensure parents know how to have their baby screened if they wish.

	weeks of age because the test becomes unreliable after this time. Inform parents that a letter confirming the conditions declined will be sent to them, together with an information leaflet ('Newborn bloodspot screening – Your baby's results explained') which provides information about declined screening and what to do if they change their mind and want their baby screened in the future.	To provide parents with written confirmation of their decision and information on the possible consequences of their baby not being screened.

2. Entering the details on the bloodspot card

Recording the baby's NHS number on the bloodspot card is mandatory. It should be ensured that the NHS number is available prior to taking the sample.

Do not delay screening for babies who have moved into Wales from outside the UK and do not have an NHS number. For these babies, the sample should be taken in accordance with the guidance below.

Section	Action	Reasoning
2.1	Check expiry date on the front of the bloodspot card.	The laboratory will be unable to process the sample if the bloodspot card is out of date, and a repeat sample will be required, resulting in a possible delay in treatment.
2.2	When completing the bloodspot card, care must be taken to place the card on a clean surface.	To avoid contaminating the bloodspot sample.
2.3	Complete the details on the bloodspot card **at the time of sampling.** **When completing the information fields it is important that the information is accurate, legible and complete:** • check with the parents that all details on the bloodspot card are correct and make any necessary changes	Mistakes and omissions can occur if information is written on the card before the visit/appointment. If the laboratory is unable to read the information on the bloodspot card or the card is not fully/accurately completed, the sample will not be processed and the baby will require a repeat sample. Repeat samples lead to delays in the referral of

		babies for diagnostic tests and treatment, and can cause anxiety and distress to families.
	• **use block capital letters to complete <u>all</u> fields on the bloodspot card**	All information on the bloodspot card is required by the laboratory.
	• check with parents to ensure **current** parent contact telephone number (preferably mobile) is recorded on the card	To enable **prompt referral** of babies who are suspected of having any of the conditions screened for. The parents will need to be contacted by phone to arrange for the baby to be seen by a clinician. Babies suspected of having an inherited metabolic disorder (IMD) such as MCADD, MSUD or IVA should be referred to be seen by a clinician within 24 hours of the result.
	If a baby who has moved in from outside the UK does not have an NHS number:	
	• ensure taking the sample is **not delayed** because of this	To enable babies with conditions to be identified and referred into clinical care at the earliest opportunity.
	• contact the regional Newborn Screening Administration Failsafe team	The team will be able to check if an NHS number has been generated. If so, they can provide the correct number so that it can be recorded on the bloodspot card.

	• if an NHS number has not been generated, record clearly in the comments box on the card '**Baby moved in from outside the UK – no NHS number'** • inform the Wales Newborn Screening Laboratory that the sample is being sent to them. This should be in writing (email) within 24 hours of taking the sample, and include the following information: ○ baby moved in from outside the UK – no NHS number ○ baby's name ○ date of birth ○ address ○ date of sample ○ date sample is posted in Royal Mail box ○ sample taker's contact number The email should be sent to the: Wales Newborn Screening Laboratory generic email (New.Screening.cav@wales.nhs.uk)	This informs the laboratory so that they will test the sample and issue results. If this is not recorded, the laboratory will request a repeat sample. The laboratory will then know to expect the sample for this baby and will follow up with the sample taker if it is not received within a specified time. This will also act as a failsafe for babies who are not yet registered on the Child Health System, as they will not be identified by the Newborn Bloodspot Screening Wales System (NBSWS) failsafe.
2.4	Record any of the following in the 'comments' box on the bloodspot card: • baby's known medical condition • family history relevant to the conditions screened for: ○ medium-chain acyl-CoA dehydrogenase deficiency (MCADD) ○ phenylketonuria (PKU) ○ maple syrup urine disease (MSUD) ○ isovaleric acidaemia (IVA) ○ glutaric aciduria type 1 (GA1) ○ homocystinuria (HCU) ○ congenital hypothyroidism (CHT)	To make the Newborn Screening Laboratory aware so that appropriate protocols can be followed.

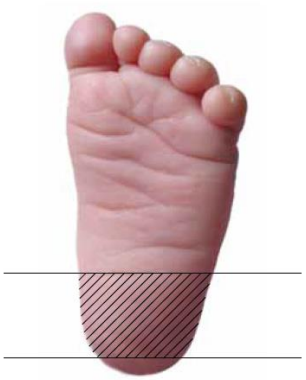
	○ cystic fibrosis (CF) ○ sickle cell disorders (SCD) The family history guidance provides more information. • reason for sample if not routine sample taken on day 5 (for example, pre-transfusion, preterm CHT) • reason for any repeat or second samples • name of person applying blood to card if not recorded as sample taker • any screening tests declined, plus a parent's signature and date of decline • baby has moved in from outside the UK – no NHS number	To ensure the result is interpreted correctly. To confirm to the laboratory the reason for repeat. To ensure that the person applying blood to the card can be identified to receive sample quality feedback if required. To confirm the parental decision to decline screening. Informs the laboratory so that they will test the sample, and not request a repeat sample as no NHS number recorded.
2.5	Check the completed bloodspot card with the parents and make any necessary changes. The guidance for completing the bloodspot card provides more information.	To ensure that the baby's and mother's details are accurate before collecting the bloodspot sample.

3. Collecting the bloodspot sample

Section	Action	Reasoning
3.1	Sample takers should check that consent for screening has been obtained from the parent or other person with parental responsibility, and that this is recorded.	To ensure that consent has been obtained for the procedure.
3.2	Recommend comfort measures for the baby. Ensure the baby is cuddled and in a secure position for taking the sample – swaddling the baby may reduce pain/discomfort. [10,11] Engaging the baby through face-to-face contact, voice and touch may be beneficial. Suggest the baby is breast feeding during the heel prick as an analgesic. [12-15] An alternative to breast feeding is to offer expressed breast milk or non-nutritive sucking (for example a pacifier). [13-15] Whilst there is no evidence that formula feed has analgesic properties, parents may comfort formula-fed babies with a feed during the procedure.	To make it easier for the baby to regain his or her calm and cope with the procedure. To reduce the pain/discomfort of the procedure. Painful procedures are a medical indication for use of pacifiers. This does not undermine Unicef UK's *Baby Friendly Initiative standards.* [16]
3.3	Clean the heel by washing thoroughly with plain water using cotton wool/gauze. The water should not be heated and the baby's foot should not be immersed.	Contamination of the sample may affect the test results. The NHS Newborn Blood Spot Screening Programme has received reports of babies being scalded/burned during

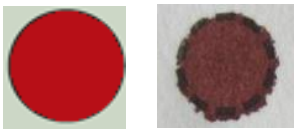
		warming of the heel in preparation for bloodspot sampling. [17,18]
	If faecal matter cannot be removed from the foot with water, use a mild, unperfumed soap to clean away the faecal matter and then rinse the foot thoroughly.	Soap or detergent can irritate infantile skin. Faeces contain very high concentrations of immunoreactive trypsinogen (IRT) (IRT is measured during screening for CF). Faecal contamination may lead to a false-positive result.
	Do not use alcohol or alcohol wipes.	The use of alcohol for skin preparation in neonates and premature infants can cause burns and blisters. [19]
	The heel should be completely dry before taking the sample. Soft paraffin solutions such as Vaseline® should not be used for heel punctures.	To comply with infection control guidelines. [20] Paraffin solutions can alter the results of the bloodspot test and can clog the equipment used.
3.4	Wash hands and apply gloves.	Universal precaution before taking a blood sample. [20,21]
3.5	Ensure the baby is warm and comfortable. **Warming of the foot is not required.** Obtain the sample using an age-appropriate automated incision device (different lancets are available for different ages). [22-24]	There is no evidence that warming aids blood flow. [22, 23, 25, 26] Automated incision devices reduce pain and bruising, allow users to obtain the sample more quickly and reduce the risk of accidental

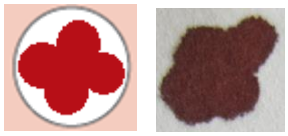
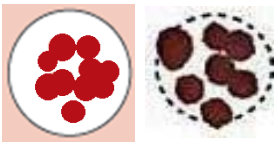
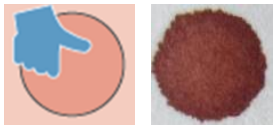
	There is some evidence that an arch-shaped incision device is more effective in providing a good quality sample, reducing the number of heel punctures per sample, the time taken to complete the sample, bruising, the time the baby cried, and the need to repeat the sample. [22,23]	injury from manual lancets. [22-24]
	Manual lancets **must not** be used.	
	For full-term and preterm infants, the external and internal limits of the calcaneus are the preferred puncture site. This is marked by the shaded areas in Figure 1. Skin puncture must be no deeper than 2mm.	The skin to calcaneus depth is greater in these areas.
	For infants who have had repeated heel punctures, the areas marked in Figure 2 may also be used. When using the whole plantar surface, an automated incision device with a penetrative depth of no more than 1mm is recommended. [27]	To minimise the risk of calcaneal puncture that may lead to calcaneal osteomyelitis (inflammation or infection of the heel bone). [27, 28]
	Avoid posterior curvature of the heel.	This reduces the soft tissue damage and pain from repeated heel puncture in the same area.
	Allow the heel to hang down to assist blood flow.	
	Before activation place the automated incision device against the heel in accordance with manufacturer's instructions.	This is to ensure the correct depth of incision is achieved – not too deep to cause harm to the baby, and not too shallow to prevent adequate blood flow.

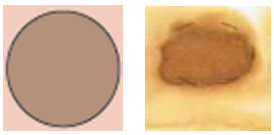
3.6	Adapted from Jain & Rutter [29] **Figure 1** For full-term and preterm infants  **Figure 2** For infants who have had **repeated** heel punctures  These sites are also suitable for infants up to a year of age.	
3.7	**Good quality bloodspots are vital to ensure that babies with rare but serious conditions are identified and treated early.** The aim is to fill each circle on the bloodspot card, using a **single** drop of blood for each circle (see Figure 3). **Wait** for the blood to flow and a hanging drop to form. Allow one spot of blood to **drop** onto each of the circles on the bloodspot card. Do not allow the heel to make contact with the card as this can prevent blood from soaking through to the back of the card. There is no need to discard the first drop.	Evidence shows that poor quality samples could lead to a baby with a condition being missed (false-negative result) or a baby without a condition being referred for further tests unnecessarily (false-positive result). [30] The laboratory punches out several small discs from the bloodspots to complete screening. The sample needs to be sufficient to screen for all of the conditions and to be used for further testing if required, for example to check a screen-positive result. The first drop of blood can be

		used if the baby's heel has been cleaned thoroughly.
	Do not squeeze the foot in an attempt to increase blood flow.	This can cause pain and bruising to the baby. [11, 22, 23]
	Allow the blood to fill the circle by natural flow, and seep through from front to back of the bloodspot card. Fill each of the four circles completely. Always ensure that the sample is applied to the front of the card and not the back. Spots that exceed the dotted lines on the filter paper are acceptable provided that a single drop of blood has been used.	This gives the optimum amount of blood for the laboratory to use.
	Do not compress or apply pressure to the bloodspots (for example when sealing the postage envelope).	Applying pressure reduces the density of blood on the sample – there is **significant risk** that this could lead to a **'suspected'** result being **missed** (see Figure 3).

3.8 **Figure 3**

	Correct	Reasoning
	A single, evenly saturated drop of blood that fills the circle completely and soaks through to the back of the bloodspot card	Good quality bloodspots are essential to obtain accurate screening results – **this prevents babies with a condition being missed (false-negative result) or babies without a condition being referred for further tests unnecessarily (false-positive result)**

	Incorrect	Reasoning
	Insufficient sample: small volume spots (that is, underfilled circles)	Risk of false-negative result
 front of card  back of card	Insufficient sample: blood not soaked through to the back of the bloodspot card	Risk of false-negative result
 	Inappropriate application of blood: multispotted (that is, several small spots of blood)	Risk of false-negative result
  (can be identified through staining of the envelope)	Compressed sample	Significant risk of false-negative result

	Inappropriate application of blood: layered sample (for example one spot of blood is layered directly on top of another) or blood applied to the front and the back of the bloodspot card	Risk of false-positive result
	Contaminated sample	Risk of inaccurate result

(Images of real samples courtesy of Wyn Griffiths, South East Thames Screening Laboratory and Roanna George, Wales Newborn Screening Laboratory).

3.9	**If the blood flow ceases:** The congealed blood should be wiped away firmly with cotton wool or gauze. Gently 'massage' the foot, avoid squeezing, and drop the blood onto the bloodspot card.	 To disturb the clot and encourage blood flow. To reduce the amount of discomfort caused by the procedure.
3.10	**If the baby is not bleeding, a second puncture is necessary:** The second puncture should be performed on a different part of the same foot or on the other foot, as marked by the shaded areas in Figures 1 and 2 (section 3.6).	 The original site is avoided to prevent the sample from containing excessive tissue fluid and to reduce pain.
3.11	When sample collection is complete, wipe excess blood from the heel and apply	To prevent excessive bleeding and bruising and to protect the wound.

	gentle pressure to the wound with cotton wool or gauze.	
3.12	Apply a hypoallergenic spot plaster if required and remind the parent to remove the plaster in a few hours.	

4. After taking the bloodspot sample

It is important that the laboratory receives the blood sample promptly to ensure that screen positive babies are seen quickly. Parents also need to know when to expect the results. This will help to reduce their concerns about the results.

Section	Action	Reasoning
4.1	Allow bloodspots to air-dry away from direct sunlight or heat before placing in the glassine envelope – take care to avoid contamination.	Wet samples can stick to the envelope and a repeat sample will be required. Glassine envelopes provide additional protection from external damage.
	There is currently no evidence to support a minimal drying time but taking the sample at the beginning of the visit will allow for a longer drying time.	
	Send the bloodspot card in the NBSW prepaid/stamped addressed envelope (first class) on the same day. If not possible, send within 24 hours of taking the sample. Sending the sample should not be delayed in order to batch bloodspot cards together for postage. Samples should be posted into a Royal Mail post box. Ensure that the post box used is one that is emptied daily (Monday to Saturday).	Ensures that the bloodspot card is received in the laboratory within four working days of the sample being taken. Timeliness of despatch enables early analysis and subsequent treatment.
	Hospital or community internal mail systems should **not** be used to send samples. If the NBSW prepaid envelope is not available, the sample should be sent by first class post to: Professor Stuart Moat, Newborn Screening Laboratory, Department of Medical Biochemistry, University Hospital	Using internal mail systems can result in significant delays in the receipt of samples in the laboratory.

	Of Wales, Heath Park, Cardiff, CF14 4XW. Requests for further supplies of NBSW prepaid envelopes can be made via nbsw@wales.nhs.uk Before sending the sample to the laboratory there should be no additional checking that would cause delay. Health boards, in agreement with the Wales Newborn Screening Laboratory and the NBSW programme, should have contingency plans in place for any possible exceptional circumstances that may delay samples reaching the laboratory in time, for example postal strikes, severe weather disruptions. Record date, method, bloodspot card serial number and location of sample despatch, as per local protocol.	This can cause delayed despatch. The laboratory rejects samples if received more than 14 days after the sample was taken, and a repeat will be required. For internal audit purposes, and to provide a cross-check between sample taker and laboratory.
4.2	Record that the sample has been taken in the PCHR and maternity/professional record, complying with local protocols. Record and notify the baby's screening status on discharge / transfer notifications.	Good record keeping is an integral part of nursing and midwifery practice. Also ensures that further samples are not taken unnecessarily. [8] To ensure that screening status is known and to transfer responsibility for obtaining any outstanding tests (in accordance with local pathway).
4.3	Inform parents that they will receive the results within six weeks [31]. If the baby screens positive for a condition the	To ensure all parents receive results of screening.

	parents will be contacted sooner (please see 'Newborn Bloodspot Screening – Information for parents' for further details). Inform parents how they will receive the results. Ensure that parents know to contact their health visitor if results are not received within six weeks.	The health visitor will be able to follow up to obtain the results for the parents.

5. Special circumstances: babies born preterm or cared for in hospital specialist units

Some babies will be in hospital when their bloodspot sample is due to be taken. This section highlights the needs of babies who are cared for in neonatal units (this includes paediatric intensive care units, neonatal intensive care units, special care baby units, cardiac units, surgical units, transition wards, etc.), preterm babies born at less than 32 weeks (less than or equal to 31 weeks + 6 days) and those who experience multiple bloodspot samples taken from the heel.

Section	Action	Reasoning
5.1	Babies admitted to neonatal units are likely to have multiple blood samples taken.	
	Bloodspot screening should be coordinated with other tests when possible.	To minimise the number of invasive procedures.
	Venepuncture or venous / arterial sampling from an existing line can be used to collect the bloodspot sample onto the card. This is providing the sample is not contaminated with EDTA/heparin and the line is cleared of infusate.	Contamination with EDTA can affect newborn screening results.
	Do not use heparinised capillary tubes.	Lithium heparin can affect DNA testing. This could affect the protocol used to detect CF and SCD.
5.2	Every baby admitted to a neonatal unit at less than five days of age (counting day of birth as day 0), should have a **single** circle bloodspot sample taken on admission (to ensure a sample is taken prior to any blood transfusion). This	The routine screening test for SCD cannot be performed on the routine day 5 sample if the baby has received a blood transfusion before the sample has been taken.

	should be on a separate bloodspot card marked **'Pre-transfusion'.** Complete **all** the details on the bloodspot card as described in section 2. Tape or a sticky label can be placed over the three unused circles. The pre-transfusion/admission sample guidance provides more information.	If the baby had received a blood transfusion before day 5 when the routine sample is due, the pre-transfusion sample will be used to screen for SCD. See the glossary for a definition of 'blood transfusion'. To avoid the day 5 sample being added to the pre-transfusion bloodspot card.
5.3	The pre-transfusion bloodspot card should be stored with the baby's medical records in line with local protocols and sent to the newborn screening laboratory together with the routine day 5 sample (stapled together). The pre-transfusion sample must not be stored in a plastic bag/poly pocket. If the baby is transferred to another unit before the day 5 sample has been taken, ensure the pre-transfusion bloodspot card is sent separately to the Newborn Screening Laboratory at the time of transfer.	To prevent the need for DNA analysis to complete SCD screening (see section 5.6). Sending the cards together helps the screening laboratory to match them. Storage of the sample in a plastic bag or poly pocket prevents further drying of bloodspot making it more vulnerable to compression.

	Details of newborn sampling should be documented and included in transfer information.	To ensure new unit is aware that the pre-transfusion sample has been taken.
5.4	The routine bloodspot sample (four filled circles) should be taken on day 5* for all babies regardless of medical condition, medication, milk feeding and prematurity. **For the purpose of screening, day of birth is day 0** (some information systems record day of birth as day 1, which could cause the sample to be taken on the incorrect day). *In exceptional circumstances such as when the baby has had a blood transfusion, the sample can be taken between day 5 and day 8. Complete the details on bloodspot card as described in section 2.	To enable timely detection of abnormal results and initiation of appropriate treatment.
5.5	When a baby has had a blood transfusion, either intrauterine or in the newborn period, an interval of at least three clear days is required between the transfusion and the routine bloodspot sample for CF, CHT and the IMDs. (For intrauterine transfusion count day of birth as date of transfusion). However, in the event of multiple blood transfusions, even if it has not been at least three clear days since the last transfusion, a routine bloodspot sample should be sent by day 8 at the latest regardless. In this scenario, a repeat sample will be needed at least three clear days after the last transfusion.	To enable metabolite concentrations to return to pre-transfusion levels. To ensure all babies are screened by day 8 regardless of blood transfusion status and to reduce the chance of missing a baby with one of the conditions.

	See Appendix E for further information including a flowchart and scenarios. The date of the last blood transfusion before the bloodspot sample must be recorded on the bloodspot card and on discharge / transfer notifications. The type of transfusion(s) should also be recorded on the bloodspot card.	To aid interpretation of the guidelines. To permit appropriate interpretation of results. This is important information which is required for the screening of sickle cell disorders.
5.6	If a baby who has been transfused has not had a pre-transfusion sample taken, the laboratory will forward the routine day 5 sample to the DNA laboratory for analysis as a failsafe.	To ensure all babies are screened for SCD.
5.7	An assessment of the baby's level of distress and ability to tolerate handling must be made before initiating comfort measures. [32] Where appropriate for the baby's condition, analgesia and comfort measures may be used as described in section 3.2. An alternative to breastfeeding is to offer expressed breast milk, non-nutritive sucking (for example a pacifier) or a sucrose or glucose solution (if available). [13,14,15,33,34] If a sucrose or glucose solution is given, this must be documented on the bloodspot card.	To reduce the pain/discomfort of the procedure. Painful procedures are a medical indication for use of pacifiers or sweet solutions. This does not undermine Unicef UK's *Baby Friendly Initiative standards.* [16] The laboratory will take this into consideration when analysing the results.
5.8	Inform parents of any outstanding screening tests, and record this in the PCHR if available, and	To ensure that all babies are screened.

	maternity/professional record. Advise parents which health professional will be responsible for completing the bloodspot screening for their baby and approximately when it will occur. When the care of babies is transferred, it should be ensured that there is a robust process for notifying the screening status. This includes a clear record of the screening status in the discharge/transfer documentation.	
CHT screening for preterm infants		
5.9	Babies born at less than 32 weeks (less than or equal to 31 weeks + 6 days) require a second bloodspot sample to be taken in addition to the day 5 sample (counting day of birth as day 0). These babies are to be tested when they reach 28 days of age (counting day of birth as day 0) or on day of discharge home, whichever is the sooner. Babies discharged home prior to 28 days of age should have the second CHT sample taken on the day of discharge, before they go home.	To ensure a valid sample for CHT screening as immaturity can mask this condition.
	See Appendix F for further information and a list of possible scenarios (including when a baby has had a blood transfusion).	To enable interpretation of the policy.
	Complete the details on the bloodspot card as described in section 2, recording **'CHT preterm'** on the bloodspot card. Write the gestational age on the card.	To ensure laboratory is aware of reason for second sample.
	If the baby is being discharged home before 28 days of age, write **'discharged home'** on bloodspot card.	To ensure laboratory knows why the CHT preterm sample was taken before day 28. If it

		is not recorded on the card that the baby has been discharged home, the laboratory will request a repeat sample.
	Two circles on the bloodspot card should be filled with blood.	
	The responsibility for taking each sample lies with the healthcare professional that is responsible for clinical care at the time the bloodspot sample is due.	To ensure babies who are transferred at less than 28 days of age have all newborn bloodspot tests completed.
	For babies who are transferred before they reach 28 days of age, the responsibility for completing screening is transferred to healthcare professionals in the receiving unit.	To ensure screening will be completed by receiving unit.
	Record all bloodspot samples taken in baby's hospital records, on transfer documentation, PCHR and on an auditable IT system.	To ensure all babies born at less than 32 weeks (less than or equal to 31 weeks + 6 days) are screened.

6. Ensuring completeness of coverage of newborn screening

Section	Action	Reasoning
Older babies		
6.1	Babies up to one year of age who become the responsibility of the health board, should be offered screening by a health professional for all nine conditions if there are no documented UK bloodspot screening results (or declines) for MCADD, PKU, CHT, CF and SCD.	To identify any affected baby and ensure treatment commences as soon as possible.
	This offer of screening should be for all conditions except CF if the baby is over 56 days of age.	The routine screening test for CF (IRT) is no longer reliable after 56 days of age.
	If there are documented results for these five conditions no further offer of screening is required.	Until all UK countries are screening for the nine conditions recommended by the UK NSC, routine screening will be considered complete if results are available for the five conditions screened for prior to expansion of the programme.
	If there are no documented results of UK newborn bloodspot screening, contact the Regional Newborn Screening Administration Failsafe Team.	The team can check on the Newborn Bloodspot Screening Wales System (NBSWS) to confirm if screening has been completed (or declined). If the baby has moved in from elsewhere in the UK, checks can be made to confirm the sample has been received and tested in a UK Newborn Screening laboratory.

	If the conclusive results cannot be found, parents should be given information and offered screening (see section 1).	
	GP to be informed according to local processes if baby is too old to be screened for CF.	To ensure the family's GP does not assume testing for CF has been completed.
	All babies who become the responsibility of the health board after moving in to Wales from outside the UK, should be offered screening even if they have had screening completed outside the UK.	To enable all babies up to one year of age who are resident in Wales to be offered UK quality assured newborn bloodspot screening.
	If the parents consent to screening:	
	Health boards should ensure that they have access to staff that are trained and responsible for taking bloodspot samples from infants when they are no longer the responsibility of the midwifery unit.	
	Take a sample using the bloodspot card (completed as described in section 2) and send to the screening laboratory.	
	Either a capillary or venous sample can be spotted onto the bloodspot card. If an automated incision device is used, ensure it is age-appropriate (different lancets are available for different ages).	Venepuncture, when taken by a skilled phlebotomist, is less painful than heel prick; however this may be technically difficult in babies. [35, 36]
	If a venous sample is obtained, it should be ensured that only one drop of blood is applied to each of the four circles on the card.	To obtain a good quality sample and accurate results, only one drop of blood should be applied to each circle.
	Record the method of sample taking clearly on the bloodspot card.	This will help the laboratory with the interpretation or erroneous results.

	Inform parents that they will receive the results within six weeks [31]. If the baby screens positive for a condition the parents will be contacted sooner. The screening status for the baby will be recorded as 'not screened' on the NBSWS failsafe system if the health professional has made at least two attempts to contact the family to offer and complete screening. The health professional should ensure that the regional administration failsafe team is informed promptly of progress to enable them to update the system and record screening status. The healthcare professional responsible for ensuring that screening has been offered should inform the CHD, GP and health visitor if the baby is not screened. **If the baby is approaching one year of age when they are identified as eligible for screening:** Babies should be offered the screening as soon as possible, before 12 months of age. If the parents consent to the screening, the sample should be taken at the earliest opportunity. If the sample cannot be taken before 12 months of age, it must be taken before the baby is 13 months old. The following action should be taken: • Record the baby's age on the bloodspot card • Inform the Newborn Screening Laboratory:	This allows the parents to be sent a letter confirming the 'not screened' status without delay. The letter provides information about the benefits of screening and what they need to do to arrange screening up to one year of age. To minimise the time before babies affected by any of the conditions can be referred into clinical care, and to ensure that screening can be completed within the specified timeframe. The Newborn Screening Laboratory will only test samples taken from babies up to 13 months of age. The laboratory will take the baby's age into consideration when analysing the results.

	Dr Fiona Stratford, Tel – 029 2074 5448 Email: Fiona.stratford@wales.nhs.uk or Professor Stuart Moat Tel – 029 2074 3562 Email: stuart.moat@wales.nhs.uk Laboratory email: New.Screening.cav@wales.nhs.uk The Newborn Bloodspot Screening Pathways A and B provide more information. **If the parents decline screening:** See sections 1.9 and 1.10 for actions to complete**.**	
Repeat samples		
6.2	Informed consent must be taken for all repeat samples (see section 1). Parents should be informed of the reason for the repeat. Unavoidable repeat samples may be required from a few babies due to prematurity, borderline thyroid stimulating hormone (TSH) results or having received a blood transfusion. These samples should be taken as soon as possible or at the age directed by the screening laboratory. Ensure that the 'repeat sample' box is ticked on the bloodspot card. Record the reason for repeat in the comments box on the card A one week interval between samples is recommended for borderline TSH	To enable parents to make an informed choice about screening for their baby [1-6]. To ensure screened babies receive a valid result. To confirm to the laboratory the reason for repeat. An interval of one week is required to detect any

	results. Take a bloodspot sample with four circles filled and mark the bloodspot card **'CHT borderline'**. The laboratory may also request a repeat sample due to any of the following (avoidable repeat samples):	meaningful change in TSH levels.
	• too young for reliable screening (sample taken on day 4 of life or earlier)	May give rise to a false-positive result for CHT.
	• too soon after transfusion (less than 72 hours)	Metabolite concentrations may not have returned to pre-transfusion levels.
	• insufficient sample	Risk of false-negative result (a baby with a condition could be missed). [30]
	• inappropriate application of blood	Risk of false-negative or false-positive result. [30]
	• compressed, damaged or contaminated sample	Significant risk of false-negative result / risk of inaccurate result. [30]
	• day 0 (pre-transfusion sample) and day 5 sample on same bloodspot card	Unable to confirm baby's age at time of sample collection.
	• possible faecal contamination	Risk of inaccurate CF result.
	• incomplete or inaccurate data on the bloodspot card, for example no/inaccurate NHS number	Unable to confirm identity of baby.
	• expired bloodspot card used	Risk of inaccurate result.
	• more than 14 days in transit, too old for analysis	Risk of inaccurate result.
	• damaged in transit	Risk of inaccurate result.

	• sickle – too premature for testing When a repeat sample is requested for any of the above reasons, the sample should be taken within 72 hours of the receipt of the request (unless ongoing transfusions).	Risk of inaccurate result.
Failsafe processes		
6.3	Health boards should ensure failsafe arrangements are in place for notifying screening status when the care of a baby is transferred. This includes babies who are transferred in the neonatal period or discharged home before screening for all tests is complete. Health boards should have robust processes in place to ensure that: • all eligible babies are identified • all identified babies are offered screening • all babies, whose parents accept the offer of screening, are screened • all samples are received in the screening laboratory • all positive babies receive treatment within national standards • parents receive the results within six weeks	To ensure all babies eligible for screening are screened, all positive babies receive timely treatment and parents receive their results within six weeks. [31] To prevent irreversible harm that can be caused to babies affected by the screened conditions when samples are delayed or are not received by the laboratory.

	The Newborn Bloodspot Screening Wales System (NBSWS) failsafe is checked daily (Monday to Friday) to identify babies that might have missed NBS screening or have incomplete screening. Health boards should have robust processes in place to manage the follow up of babies identified by the NBSWS failsafe. The screening status of all eligible babies should be recorded on an auditable child health IT system. Local failsafe systems or procedures for checking samples have been collected and despatched should remain in place. It is important that any checking procedures do not delay the despatch of samples to the laboratory.	To ensure all eligible babies are offered screening and are screened. Local processes may sometimes identify missed screening earlier than if identified by the NBSWS failsafe.

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Appendix A: Glossary and Abbreviations

Glossary

affected	When someone has a condition, it is said they are affected. In screening terms, a child who is affected with cystic fibrosis is a child who has the genetic make up for cystic fibrosis, whether or not they have signs or symptoms.
amino acid	Our bodies break down protein foods like meat and fish into amino acids (the building blocks of protein). Any amino acids that aren't needed are usually broken down and removed from the body. Babies with some of the inherited metabolic diseases that are screened for are unable to break down one or more amino acids. When levels of these amino acids get very high, they are harmful.
antenatal screening	Antenatal screening is screening which is carried out before a baby is born. This can include carrying out tests on the pregnant mother and/or the biological father of the baby or the unborn baby. Antenatal screening includes tests for a wide range of conditions.
audit	A systematic comparison of screening, treatment and other management procedures with an agreed set of standards.
blood sampling	This refers to the collecting of blood to undertake tests. In the case of newborn screening it refers to the collection of small amounts of blood from the baby's heel. This is done by pricking the heel.
bloodspot	When newborn babies are five to eight days old a sample of blood is taken from their heel and spotted onto a special type of filter paper. A number of tests are then carried out on these bloodspots. This is called newborn bloodspot screening.
blood transfusion	In the context of newborn screening, the transfusion of whole blood or any blood product that will affect the circulating concentration of the measured metabolite. The overall effect of any such transfusion will depend on a number of variables:

	• circulating blood volume • circulating concentration of metabolites • distribution of metabolite between intracellular and extracellular compartments • volume and rate of transfusion • concentrations of metabolite in transfused fluid • time since transfusion In practice, this refers to blood transfusions, exchange transfusions, platelets and fresh frozen plasma. An interval of at least three clear days is required between a transfusion of any of these and a bloodspot sample. If a bloodspot sample has been taken within at least three clear days of a transfusion, a repeat sample should be taken at least three clear days after the last transfusion. We recommend that albumin transfusions should **not** be included in the definition and that this should not delay the taking of the samples.
calcaneus	The bone of the heel.
calendar days	Calendar days are all days in a month including weekends and holidays. For some of the NBSW standards the timelines refer to calendar days because there is a clinical need for a definitive time in which an action should be taken. For example, an avoidable repeat sample should be taken within three calendar days.
Child Health Records Department (often referred to as 'Child Health')	The Child Health Department holds records for each child who is born. When a mother gives birth the child health department is notified of the birth. The results of newborn screening tests are also reported to child health.
circle	A circle, measuring 10.5mm in diameter, marked on the bloodspot card. There are four circles on the card which provide a guide to the volume of blood required for bloodspot screening. The circles should each be filled completely by a single drop of blood.
clinician	A healthcare practitioner who specialises in seeing, diagnosing and/or treating patients.

conclusive result	A conclusive result is any of the following; not suspected, suspected, not suspected other disorder or carrier. This includes any results that were tested by DNA for sickle cell disorders. For babies greater than 8 weeks of age, not tested for CF is also a conclusive result.
condition	There are lots of different words used to describe illnesses. They are sometimes called diseases, or disorders, or conditions.
congenital hypothyroidism (CHT)	Congenital hypothyroidism (CHT) is a condition where the baby's thyroid gland fails to develop or work properly and fails to make the thyroid hormone called thyroxine. Thyroxine is needed for normal growth and development. Without thyroxine, babies do not grow properly and can develop permanent, serious physical problems and learning disabilities. Babies with CHT can be treated early with thyroxine tablets and this will allow them to develop normally. CHT has been screened for in Wales since 1981.
consent	Agreement to a test, plan of action or particular treatment having received full information about the risks and benefits ('informed consent'), and having had the opportunity to ask questions.
coverage	When talking about screening programmes, people often talk about coverage. This is the proportion of people actually screened. This is usually measured as a percentage. The success of screening programmes is sometimes measured by the coverage achieved.
cystic fibrosis (CF)	Cystic fibrosis (CF) is one of the UK's most common inherited life-limiting diseases. CF is a disease in which abnormal movement of salt and water into and out of cells causes a build-up of thick, sticky mucous. This occurs particularly in the lungs and digestive system. Babies with CF may not gain weight well, have frequent chest infections and a limited life span. If babies with CF are treated early with a high-energy diet, medicines and physiotherapy, they may live longer, healthier lives. CF has been screened for in Wales since December 1996.

diagnosis / diagnostic test	A diagnostic test is one which tests for a specific condition, and allows doctors to confirm whether or not someone has a condition. Diagnostic tests often follow screening tests. For example, a newborn baby might be screened for cystic fibrosis. The screening result shows that the baby probably has the condition. Further diagnostic tests will then be carried out to find out whether the child definitely has cystic fibrosis. This is then considered the confirmed result.
disease	There are lots of different words used to describe illnesses. They are sometimes called diseases, or disorders, or conditions.
disorder	There are lots of different words used to describe illnesses. They are sometimes called diseases, or disorders, or conditions.
eligible babies (newborn)	In Wales, eligible babies (newborn) are defined as: • A baby who is resident in Wales at day 5-8 of life • A baby who is resident in Wales at day 5-8 of life, but is registered with an English GP • A baby whose usual place of residence is outside Wales if they are under routine midwife care in Wales at day 5-8 of life Babies who have been recorded as having died before the age of 5 days are not eligible.
eligible babies (all)	In Wales, eligible babies (all) are defined as: • All babies up to one year of age who are resident in Wales • A baby whose place of residence is outside Wales if they are under routine midwifery care in Wales at the time the newborn bloodspot test is due Babies who have been recorded as having died before the age of 5 days are not eligible.
false-negative result	A false-negative result is one where the person is thought not to have the condition, but then turns out to have the condition. For example, when a child who has a negative screening result for cystic fibrosis (and is therefore thought not to have the condition) turns out to have cystic fibrosis.
false-positive result	A false-positive result is one where the screening result is positive, but the person turns out not to have the condition as determined by diagnostic tests. For example,

	when a child who has a positive screening result for CHT (and is therefore thought to be affected on the basis of the screening result) turns out not to have CHT. For parents, receiving a false-positive result can mean that they think that their child is sick, when actually they are healthy.
glassine envelope	Glassine is a light-weight, semi-transparent material that contains no chemicals which can harm the sample and is fairly resistant to moisture.
glutaric aciduria type 1 (GA1)	Glutaric aciduria type 1 (GA1) is a rare inherited disorder that prevents the breakdown of certain building blocks of protein, in particular the amino acids lysine and tryptophan. For people with GA1, eating normal amounts of protein can cause harmful substances to build up in the blood and urine. In children with GA1, a minor illness, such as a chest infection or a tummy upset, can lead to serious problems. Without treatment, the child can go into a coma. Though most children come out of the coma, they usually have brain damage that affects their ability to control their muscles and movements. This means that they may be unable to sit, walk, talk or swallow. GA1 can be treated with a protein-restricted diet and carnitine. A different regimen is required when the child is ill, and they may need to be hospitalised. GA1 has been screened for in Wales since January 2015.
homocystinuria (HCU)	Homocystinuria (HCU) is a rare inherited disorder that prevents the breakdown of a building block of protein, the amino acid homocysteine. This then causes a harmful build-up of homocysteine in the blood. Without early treatment this can lead to long term health problems including learning difficulties and eye problems, osteoporosis and blood clots or strokes. HCU can be treated with a protein-restricted diet and extra supplements and medicines. HCU has been screened for in Wales since January 2015.
inherited metabolic disease (IMD)	A genetic disease that affects the metabolism. Babies with inherited metabolic conditions cannot process certain substances in their food.

	Without treatment, babies with some of these conditions can become suddenly and seriously ill. The symptoms of the conditions are different; some may be life threatening or lead to severe developmental problems. They can all be treated by a carefully managed diet, which is different for each condition and may include additional medicines.
isovaleric acidaemia (IVA)	Isovaleric acidaemia (IVA) is a rare inherited disorder that prevents the breakdown of a building block of protein, the amino acid leucine. This then causes a harmful build-up of a substance called isovaleric acid in the blood. Children with IVA can become severely unwell. Without treatment, this can lead to a coma and permanent brain damage. Some babies with IVA have problems within a few days of birth; other children become unwell at a few months or years of age, maybe during a minor illness, such as a chest infection or a tummy upset. IVA can be treated with a protein-restricted diet and carnitine and glycine. A different regimen is required when the child is ill, and they may need to be hospitalised. IVA has been screened for in Wales since January 2015.
incidence	The number of new cases of a disease within a defined group of people over a period of time.
manual lancet	A lancet that is pushed into the tissues by hand. It does not allow for accurate control of the depth of the puncture.
maple syrup urine disease (MSUD)	Maple syrup urine disease (MSUD) is a rare inherited disorder that prevents the breakdown of some of the building blocks of protein, the amino acids leucine, isoleucine and valine in the blood. For people with MSUD, eating normal amounts of protein can cause a harmful build-up of these amino acids in the blood. Many babies with MSUD become unwell when they are a few days old. Without treatment, this leads to a coma and permanent brain damage. In older children a minor illness, such as a chest infection or a tummy upset, can lead to serious problems. As in babies, this can lead to a coma unless treated correctly. MSUD can be treated with a protein-restricted diet. A different regime is required when the child is ill, and they may need to be hospitalised.

	The condition is named maple syrup urine disease because high levels of these amino acids can cause an unusual sweet smell in the urine and sweat. MSUD has been screened for in Wales since January 2015.
medium-chain Acyl-CoA dehydrogenase deficiency (MCADD)	MCADD is a rare inherited condition in which there is a deficiency in the enzyme medium-chain acyl-CoA dehydrogenase which is needed for the breakdown of certain stored fats (medium-chain fatty acids). This makes it difficult for the body to break down fatty acids and produce energy, and can cause sudden death in infants. Fatty acids are an important energy reserve during periods of poor calorie intake, prolonged periods between meals or during infections and sickness. In these situations people with MCADD have high levels of partially broken down fatty acids and low blood glucose concentrations which can result in a metabolic crisis. Most of the time children are well, but an infection or relatively long period without food upsets their metabolism causing coma and sometimes death. Treatment involves ensuring that children do not go for long periods without food and special management if they do get an infection. Periods of not eating can safely get longer as the child grows. MCADD has been screened for in Wales since June 2012.
newborn screening	All screening on a newborn baby is called newborn (or neonatal) screening. Current newborn screening includes hearing screening, screening for abnormal hips and other physical problems, and bloodspot screening.
normal (result)	Sometimes when the result of the test shows that the child is unlikely to have the condition tested for, people say the result is normal. In general it is best to avoid using this term, as it is not always clear what normal is meant to be. Its meaning may be unclear to both parents and health professionals.
NHS Newborn Blood Spot Screening Programme	This refers to the national programme in England that works in partnership with those organising newborn blood spot screening locally to support a high quality service responsive to the needs of families. The English programme also works in partnership with the blood spot screening programmes in Scotland, Wales and

	Northern Ireland to deliver a high quality service across the UK.
personal child health record (PCHR)	This is the child health record which is held by the parent, also called the 'red book'. It is normally issued by the midwife or health visitor.
phenylketonuria (PKU)	Phenylketonuria (PKU) is a rare inherited condition that prevents the breakdown of a building block of protein, the amino acid phenylalanine. For people with PKU, eating normal amounts of protein can cause a harmful build-up of phenylalanine in the blood. The build-up of phenylalanine is neurotoxic and harmful to the brain. Without treatment PKU can cause severe, irreversible mental disability. If identified early, the child can be put on a restricted-protein diet with supplements and the brain can develop normally. PKU has been screened for in Wales since 1970.
quality assurance (QA)	Improving performance and preventing problems through planned and systematic activities including documentation, training and review.
referral	The process by which a patient is transferred from one professional to another, usually for specialist advice and/or treatment.
screen negative result	Screening results are not 100% conclusive. Instead they provide presumptive results. A screen negative result is a result which suggests that the child does not have the condition for which they are being screened. Sometimes people will say that the result is 'normal'. For example, a screen negative result for cystic fibrosis (CF) means that it is highly likely that the child does NOT have CF. This screen negative result is NOT usually confirmed using further tests, but it is assumed the child is not affected. A screen negative result will be reported as 'not suspected'.
screen positive result	Screening results are not 100% conclusive. Instead they provide presumptive results. A screen positive result is a result which shows that the child is likely to have the condition for which they are screened.

	Sometimes people will say that the child is affected. Positive screening results are then confirmed using diagnostic tests. For example, a screen positive result for congenital hypothyroidism (CHT) means that it is highly likely that the child has CHT, but this must be confirmed by further tests. A screen positive result will be reported as 'suspected'.
screening	Screening is when healthy children and adults are tested to see if they are likely to develop a condition. Screening tests don't generally confirm that a person has a disease. Usually they will not feel ill from these conditions in any way at the time when they're screened. Screening allows diseases to be identified early, before any signs of illness. This means people can be treated quickly and hopefully avoid getting seriously ill. Screening happens at different ages, and for different conditions. Newborn bloodspot screening in Wales includes tests for congenital hypothyroidism (CHT), cystic fibrosis (CF), sickle cell disease (SCD) and six inherited metabolic diseases (IMDs): phenylketonuria (PKU),medium-chain acyl-CoA dehydrogenase deficiency (MCADD), maple syrup urine disease (MSUD), isovaleric acidaemia (IVA), glutaric aciduria type 1 (GA1) and homocystinuria (pyridoxine unresponsive)(HCU).
sickle cell disorders (SCD)	Sickle cell disorders (SCD) is a term that describes a group of conditions in which haemoglobin in red blood cells is abnormal in structure. This causes red blood cells to take up a shape like a crescent moon or farmer's sickle when de-oxygenated. Sickled red blood cells are not as flexible as normal red blood cells and can cause blockages within small blood vessels. Babies who have these conditions will need specialist care throughout their lives. People with SCD can have attacks of severe pain, get serious, life threatening infections and are usually anaemic (their bodies have difficulty carrying oxygen). Babies with SCD can receive early treatment, including immunisations and antibiotics, which, along with support from their parents, will help reduce the chance of serious illness and allow the child to live a healthier life. SCD has been screened for in Wales since 2013.

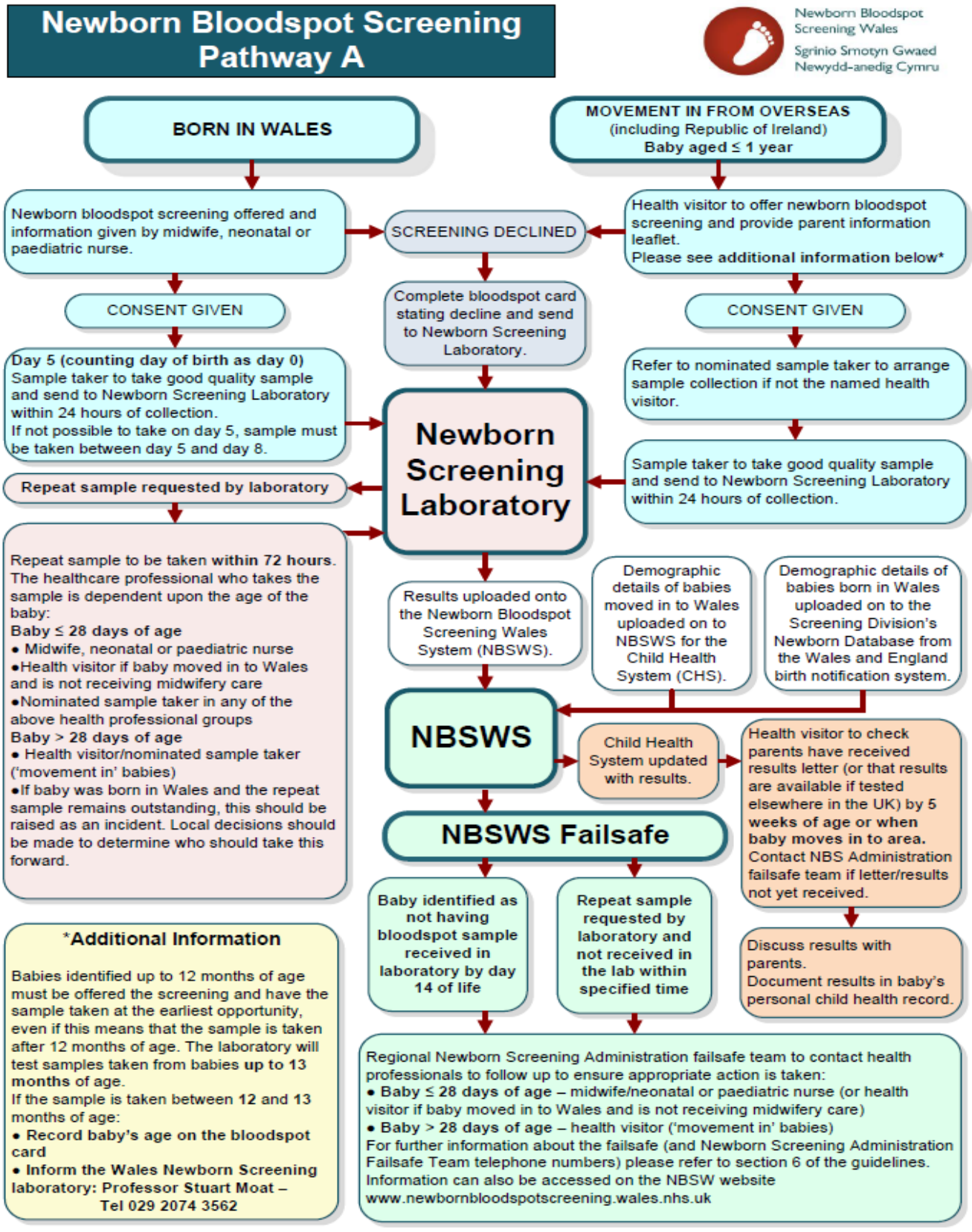
UK National Screening Committee (UKNSC)	This is a national advisory body which makes recommendations about screening to the UK Departments of Health.
working days	For the purpose of newborn bloodspot screening working days are currently Monday to Friday with the exception of bank holidays. Working days are referred to in the standards to take into account the normal working days for the Newborn Screening Laboratory and Royal Mail.

Abbreviations

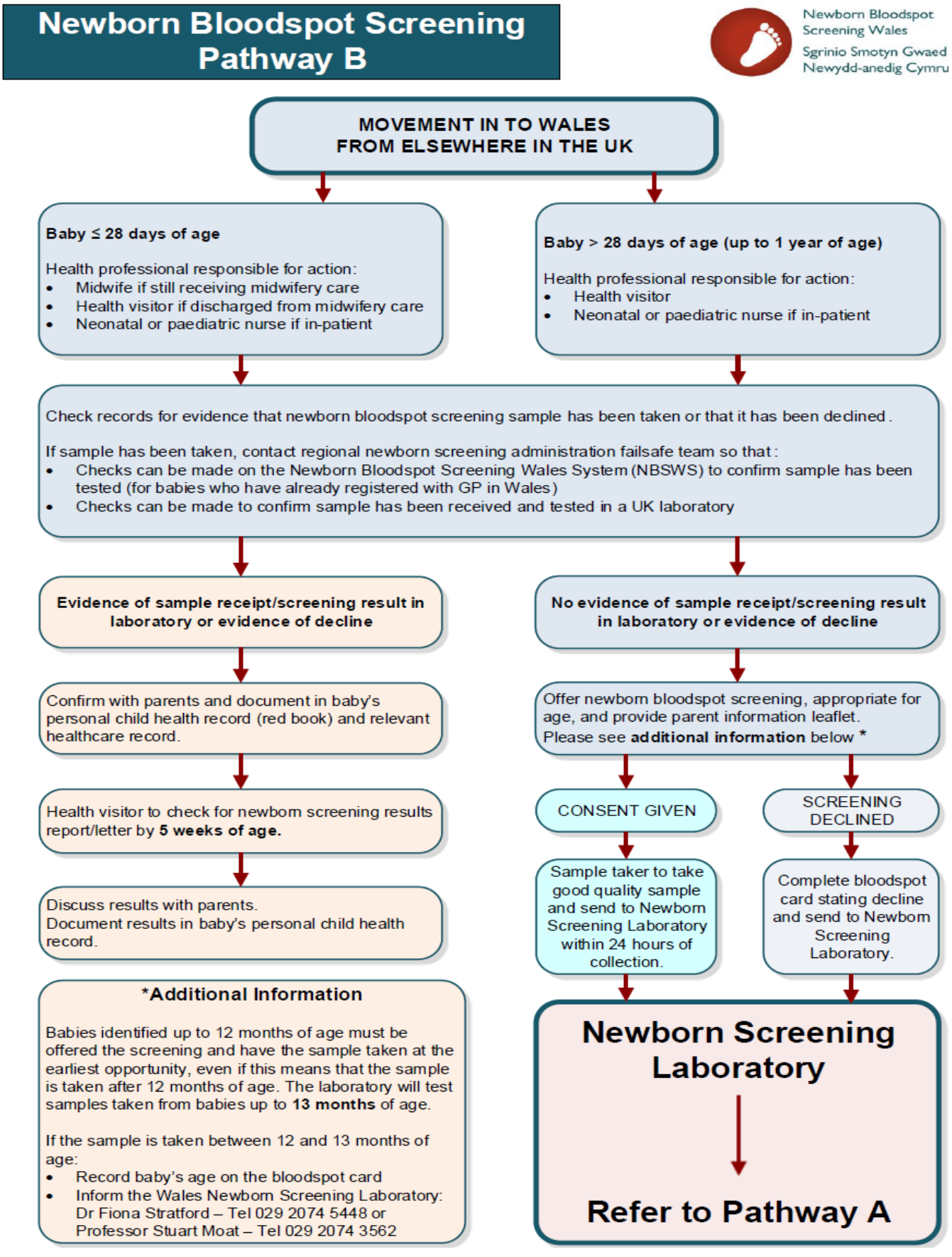
ASW	Antenatal Screening Wales
AWMGS	All-Wales Medical Genetic Service
BIMDG	British Inherited Metabolic Disease Group
CF	cystic fibrosis
CFTR	cystic fibrosis transmembrane conductance regulator
CHD	Child Health Department
CHT	congenital hypothyroidism
DNA	deoxyribonucleic acid
EDTA	ethylenediaminetetraacetic acid
GA1	glutaric aciduria type 1
HCU	homocystinuria
IMD	inherited metabolic disorder
IQ	intelligence quotient
IRT	immunoreactive trypsinogen
IVA	isovaleric acidaemia
LIMS	Laboratory Information Management System
MAC	Maternal and Child
MCADD	medium-chain acyl-CoA dehydrogenase deficiency
MSUD	maple syrup urine disease
NBHSW	Newborn Hearing Screening Wales
NBS	newborn bloodspot screening
NBSW	Newborn Bloodspot Screening Wales
NBSWS	Newborn Bloodspot Screening Wales System
NMC	Nursing and Midwifery Council
PCHR	personal child health record (“red book”)
PKU	phenylketonuria
PPV	positive predictive value
SCD	sickle cell disorders
TSH	thyroid stimulating hormone
UHW	University Hospital of Wales
UK NSC	UK National Screening Committee

Appendix B: Newborn bloodspot screening pathways

Pathway A relates to babies born in Wales and those who have moved in from outside the UK. All babies in pathway A are to be offered screening.



Pathway B relates to babies who have moved in to Wales from elsewhere in the UK. Babies in this pathway would need to be assessed to see if they are eligible.



Appendix C: Guidance for completing the bloodspot screening card

NHS Number is the only unique identifier for a baby. It is essential – a repeat will be requested without it. 1

Surname by which the baby will be known. 2

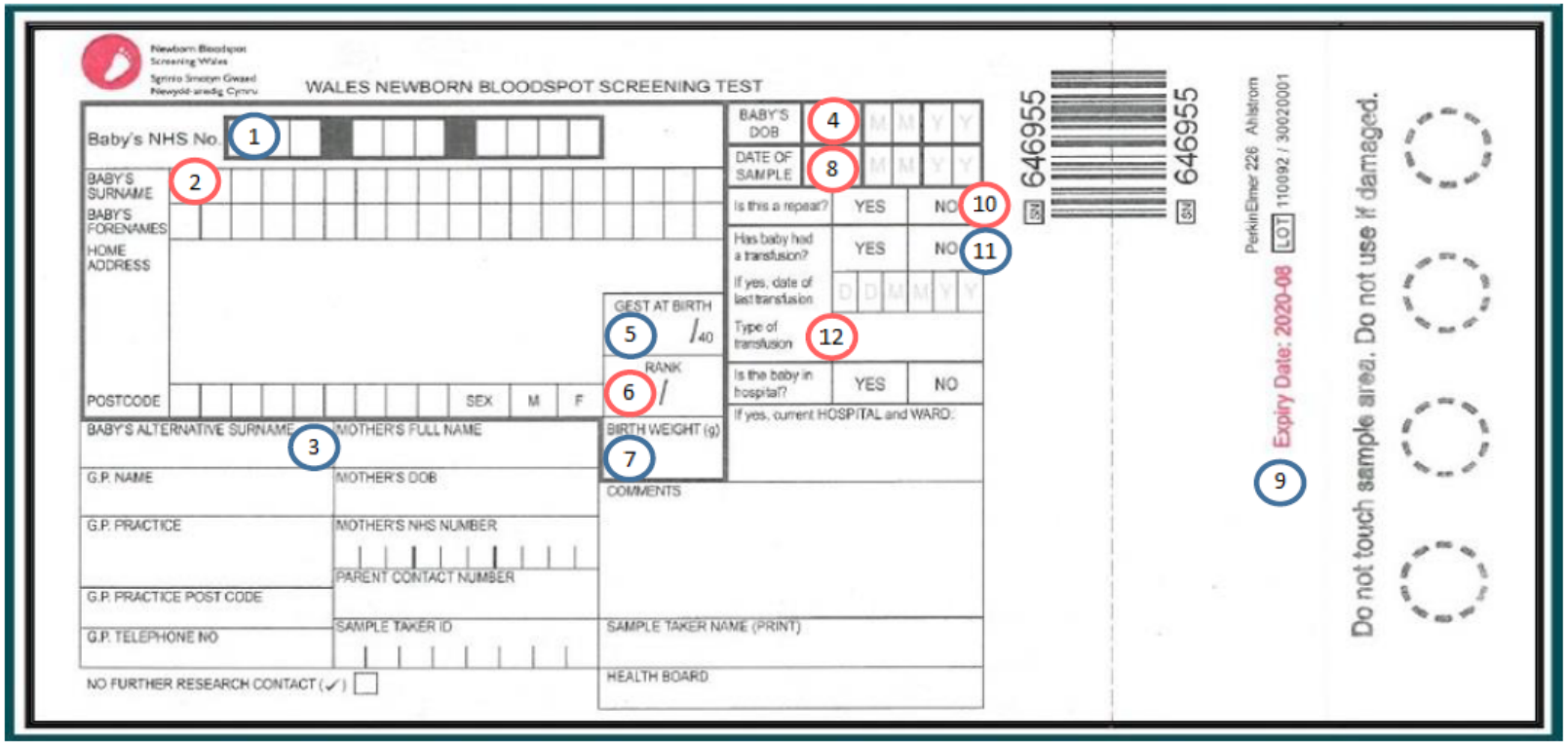
Baby's alternative surname Record surname by which the baby will be known if local policy requires mother's surname in box 2. 3

DOB is essential for the card to be processed. 4

Gestational age of baby at birth is essential for a valid CHT result. 5

Rank identifies birth order. Refer to back of card. 6

Birth weight is important – can aid interpretation of results. 7



Date of sample is essential for the card to be processed. 8

Expiry date must be checked before sample collection. A repeat sample will be requested if the card has expired. 9

Is this a repeat? Record reason in the comments box. 10

Record if a **blood transfusion** has been given to baby either intrauterine or after birth. **Record date of last (most recent) transfusion.** If intrauterine, count day of birth as date of last transfusion. 11

Type of transfusion is important information required for the screening of sickle cell disorders. 12

If **baby is in hospital** at time of sample, record which hospital and ward. 13

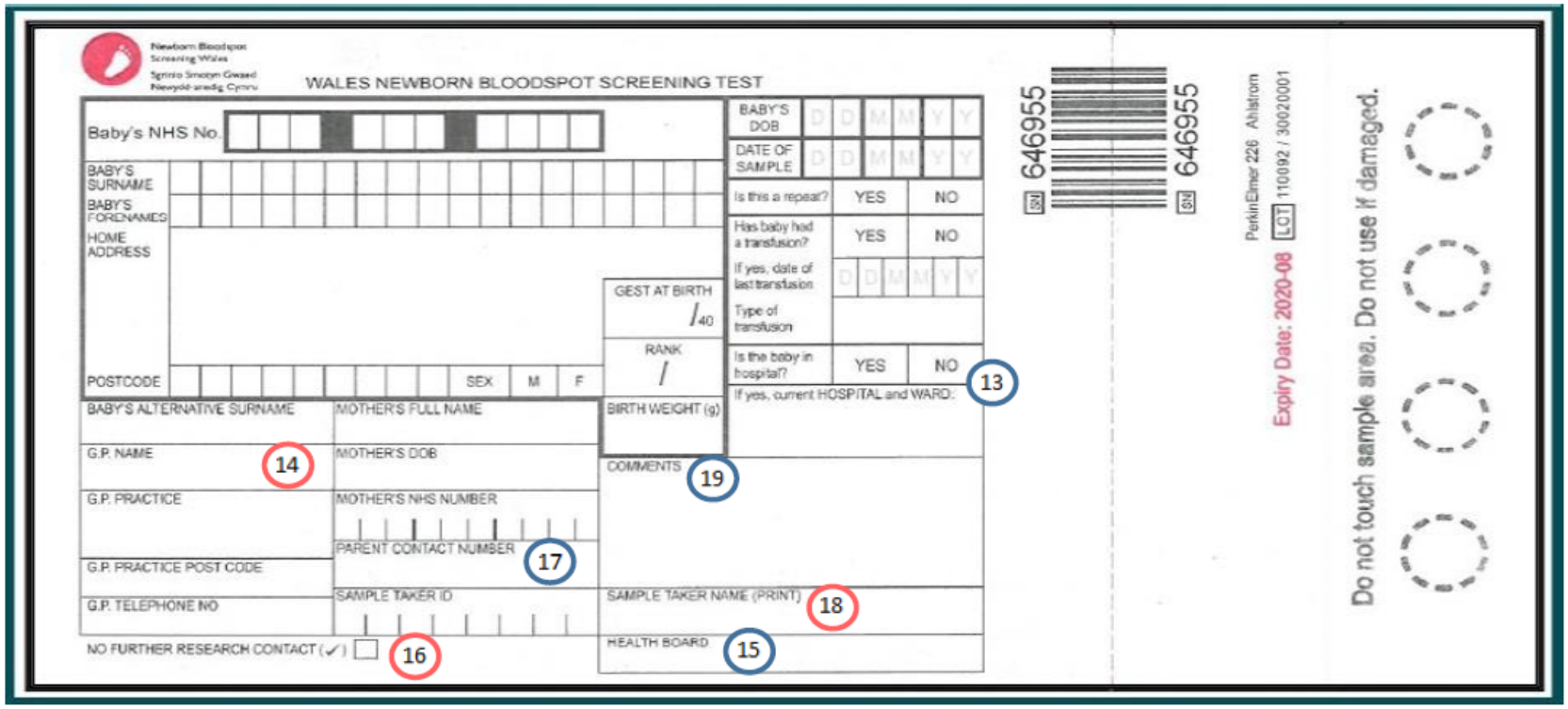
GP practice name, telephone number, address and postcode are essential to enable follow up of baby. 14

Refers to **Health Board** providing care at the time of the test. 15

Parents should be asked if they consent to future **contact about research** linked to NBSW. Tick the box if they do not wish to be contacted. 16

Current **contact number for parents** is essential to enable follow up of baby. 17

Sample taker ID is their NMC number, or a number issued by NBSW. 18



Record in **Comments box:**

- Any screening tests declined, plus a parent's signature
- Any known medical condition in baby, or any relevant family history e.g. CF, inherited metabolic disorder (state disorder). Is the mother a carrier of an abnormal Hb or thalassaemia?
- Reason for any repeat or second samples
- Reason for sample being taken at a different time from routine day 5 test e.g. pre transfusion, preterm CHT, family history of an inherited metabolic disorder (state disorder)
- Any complications in pregnancy or labour that may have affected the baby
- Name of person applying blood to card if not recorded as sample taker

19

Appendix D: Inherited metabolic disorders (IMDs) - Key facts

Disorder	**Glutaric aciduria type 1 (GA1)**	**Homocystinuria (HCU)**	**Isovaleric acidaemia (IVA)**	**Maple syrup urine disease (MSUD)**
Problem breaking down	Amino acids: • Lysine • Tryptophan	Amino acid: • Homocysteine	Amino acid: • Leucine	Amino acids: • Leucine • Isoleucine • Valine
Incidence in Wales (estimated number of affected babies born)	One every 3-4 years	One every 4-5 years	One every 4-5 years	One every 3-4 years
	Estimated that two babies will be born with one of these conditions each year.			
Early effects	Usually no symptoms in first weeks of life. In first year of life some children develop: • floppiness/ weakness • delays in reaching developmental milestones • relatively large head Risk of **metabolic crisis** during illness (eg infection or vomiting). Signs may include: • poor feeding • floppiness • sleepiness • abnormal movements	Babies usually well in early life	Risk of **metabolic crisis** in **first days** or **weeks** of life. Symptoms include: • poor feeding • irritability • sleepiness • vomiting • breathing difficulties Others develop metabolic crisis later in first year of life or later in childhood - **during** illness.	Risk of **metabolic crisis, typically** in **first days** or **weeks** of life. Symptoms include: • poor feeding • vomiting • irritability • sleepiness • breathing difficulties Symptoms can present ***before bloodspot screening results are known.***

<table>
<tr><th>Disorder</th><th>GA1</th><th>HCU</th><th>IVA</th><th>MSUD</th></tr>
<tr><td>Untreated</td><td>Untreated metabolic crisis can lead to:
• coma
• permanent brain damage
• lasting abnormal muscle control</td><td>Young children can develop:
• brain damage and learning difficulties
• eye problems

Can also develop:
• osteoporosis
• other bone or joint problems
• blood clots or strokes</td><td>Untreated metabolic crisis can lead to:
• coma
• permanent brain damage
• death

Some children may not develop metabolic crisis - may have learning difficulties.</td><td>Untreated metabolic crisis can lead to:
• coma
• permanent brain damage
• death

Some children first develop metabolic crisis later in childhood – during illness (eg infection or gastric upset).</td></tr>
<tr><td rowspan="3">Treatment</td><td colspan="4">Low protein diet – with advice from specialist metabolic team.</td></tr>
<tr><td>Medication

• L-carnitine</td><td>Medication and Supplements
• Vitamin B6 (pyridoxine)
• Folic acid
• Vitamin B12
• Betaine</td><td>Medication

• L-carnitine and/or
• Glycine</td><td>Supplements

• Essential amino acids</td></tr>
<tr><td>Emergency Regimen during illness -
• Giving glucose polymer
• Stopping protein-containing milk/food
• May need to be hospitalised</td><td></td><td colspan="2">Emergency Regimen during illness -
• Giving glucose polymer
• Stopping protein-containing milk/food
• May need to be hospitalised

Babies can become suddenly and seriously ill requiring urgent medical attention.</td></tr>
</table>

Appendix E: Sickle cell disorders (SCD) screening pathway for neonatal units

Every baby admitted to a neonatal unit in Wales should have a single bloodspot sample taken on admission. This sample must be labelled *pre-transfusion sample,* kept and then attached to the routine newborn bloodspot sample taken on day 5 of life (counting day of birth as day 0). Both samples should then be sent to the Newborn Screening Laboratory for analysis.

Transfused blood interferes with the interpretation of bloodspot screening results and may lead to a false negative screening result for sickle cell disorders (SCD). The pre-transfusion is used to screen for SCD if the baby had a blood transfusion during the period between admission and day 5 of life, when the routine bloodspot sample is taken.

Questions and answers about the pathway

1. What are the implications of this pathway for neonatal unit staff?

Neonatal unit staff who have responsibility for taking NBS samples must ensure that a pre-transfusion sample (one spot) is taken for every baby admitted to the neonatal unit, as part of the admission process. Parents will need to be given information about NBS, and their informed consent for this screening should be obtained.

The routine NBS sample taken at day 5 is **not a repeat sample** and should not be recorded as such on the bloodspot card.

2. How should the pre-transfusion be stored and where?

The pre-transfusion sample should be stored as per local policy. It should be ensured that the relevant staff know where the sample is stored so that it is sent to the laboratory with the routine NBS sample. A recommended way of storing this sample would be to put it in the NBSW prepaid envelope or other non-plastic envelope, and to securely attach it to the baby's notes/file.

3. If the baby doesn't have a blood transfusion, does the pre-transfusion sample still need to be sent to the laboratory with the routine sample?

All pre-transfusion samples should be sent to the laboratory, attached to the routine sample, even if the baby has not had a blood transfusion.

4. What happens if the baby is discharged from the neonatal unit before the routine sample is due or has been taken (ie baby is day 0-4 of life, counting day of birth as day 0)?

If the baby is discharged home or is transferred to a postnatal ward, paediatric ward or to another neonatal unit before the routine sample has been taken, the pre-transfusion sample should be sent separately from the neonatal unit to the Newborn Screening Laboratory, at the time of discharge or transfer.

It should be clearly documented in the baby's notes and on the discharge/ transfer summary, that a pre-transfusion sample has been taken and that a routine sample is due on day 5. This is so that the health professional who takes the routine sample knows to record in the comments box on the bloodspot card that the baby has been an inpatient on a neonatal unit, and that a pre-transfusion sample has been taken.

This information on the card will alert the laboratory so that the two samples can be matched together.

5. If a baby is admitted to the neonatal unit specifically for a septic screen, and is expected to be transferred out of the unit following this care, should a pre-transfusion sample be taken?

Pre-transfusion samples should be taken for **all** babies admitted to the neonatal unit who are day 0-4 (counting day of birth as day 0), regardless of the expected length of stay on the unit, or of the reason for their admission.

6. What if the pre-transfusion sample is not taken on admission?

The pre-transfusion sample should be taken **as soon as possible** if the baby has not had a blood transfusion. If the baby has had a blood transfusion, the pre-transfusion sample is not then possible.

When the routine NBS sample is taken, the sample taker should record on the bloodspot card that the baby has had a blood transfusion, and the date of the last transfusion. It should also be recorded in the comments box that a pre-transfusion sample has not been taken.

The screening for sickle cell disorders will then have to be tested using a different protocol at increased cost and will result in a delay in diagnosing a baby with a sickle cell disorder.

7. What if the baby is due to have, or already has had a routine bloodspot screening sample taken?

If the baby is admitted to the unit and is either due to have the routine bloodspot screening sample (ie baby is day 5 of life), or has already had this sample taken (ie older than day 5 of life), then there is no need to take the pre-transfusion sample.

It is important to ensure that if the routine sample is due, that it is carried out **before** any blood transfusions are given. The bloodspot card should be completed in full, and should include the information that the baby has not had a blood transfusion and that the pre-transfusion sample has not been taken.

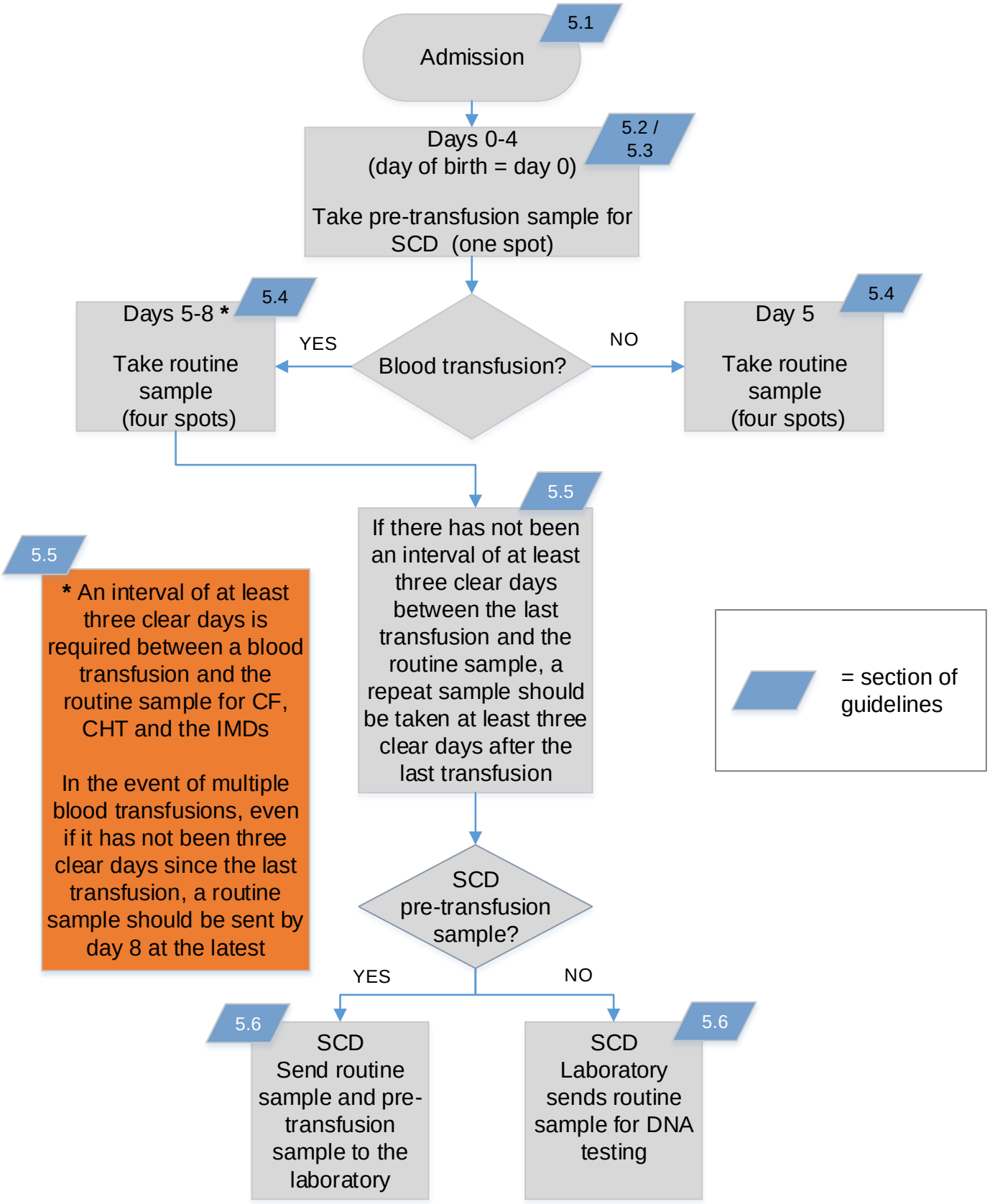
8. Can a bloodspot sample be obtained from an arterial line?

Venous or arterial sampling from an existing line is an alternative for babies in special circumstances, providing the sample is not contaminated with heparin or EDTA and the line is cleared of infusate.

9. If the baby has had platelets or fresh frozen plasma, is this regarded as a blood transfusion?

If the baby has received platelets or fresh frozen plasma only then this does not affect the screening analysis for sickle cell disorder, as the analysis is on the red blood cells only. The type of transfusion should be recorded on the bloodspot card as this is important information required for the screening of sickle cell disorders.

Blood transfusions – flowchart and scenarios



Scenarios

Scenario 1

A baby has a blood transfusion on day 4 and no further transfusions. When should the routine sample be taken?

Solution

The routine sample should be taken on day 8. In this scenario there is no need for a repeat as there are at least three clear days between the transfusion and the routine sample.

Scenario 2

A baby has a blood transfusion on day 5, 6 or 7. When should the routine sample be taken?

Solution

The routine sample should ideally be taken on day 5 before the transfusion. If it is not taken on day 5, the routine sample should be taken by day 8 at the latest. A repeat is then required 3 clear days after the baby is given the transfusion.

Scenario 3

A baby is given red blood cells on day 4 and platelets on day 6. When should the routine sample be taken and is a repeat needed?

Solution

In the event of multiple blood transfusions, even if it has not been at least three clear days since the last transfusion, a routine blood spot sample should be sent by day 8 at the latest. In this scenario, the routine sample should be taken on day 8 and a repeat sample taken at least three clear days after the baby is given the last transfusion (on day 10, with days 7, 8 and 9 being the three clear days). See the calendar below for illustration.

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
			Day 0: Day of birth Take pre-transfusion bloodspot	Day 1	Day 2	Day 3
Day 4 Baby given red cells	Day 5	Day 6 Baby given platelets	Day 7	Day 8 Take 4 spot sample as ALL babies must have a sample sent by day 8	Day 8	Day 10 Take a repeat 4 spot sample as baby is now 3 clear days post transfusion
Day 11	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17

Appendix F: Congenital hypothyroidism (CHT) newborn bloodspot screening policy for preterm babies

Preterm babies require a second test for congenital hypothyroidism (CHT) as the routine bloodspot screening test result can be incorrectly negative because of the baby's prematurity.

CHT Preterm Policy

All babies born at less than 32 weeks gestation (less than or equal to 31 weeks+6 days) should be offered a second preterm CHT test at 28 days of age (counting day of birth as day 0) or on day of discharge home whichever is the sooner.

Additional information can be found in the guidelines for newborn bloodspot screening.

The consultant neonatologist or general paediatrician is professionally responsible for ensuring that the second CHT sample is offered, and that the sample is obtained whilst the baby is an in-patient in neonatal or paediatric services. If a baby is moved to another hospital, responsibility for taking the second CHT sample is transferred to the receiving hospital.

To enable the Newborn Screening Laboratory to report a valid CHT result, it is essential that the gestational age at birth is recorded accurately on the bloodspot card.

The babies will still be on the neonatal or paediatric units when the second sample is required, and therefore responsibility for taking the sample is clearly defined.

Background

Screening for CHT aims to detect babies who do not produce adequate thyroxine from birth. Babies may not produce adequate thyroxine because their thyroid gland has not developed, or has failed to develop properly, or they cannot produce active thyroid hormone due to an inherited deficiency.

If babies with CHT are not treated they can develop a serious and permanent physical and mental disability. Babies who are identified as having CHT are treated with thyroxine tablets.

Screening for CHT is based on thyroid stimulating hormone (TSH) levels measured in the bloodspot sample taken 5 days after birth (counting day of birth as day 0). Babies whose screening results show raised TSH levels are referred promptly to an endocrinologist for specialist care.

Preterm infants, especially those born between 23 and 27 weeks gestation, are more likely to have low TSH levels at the time of the first routine newborn bloodspot screening test. This may be due to a number of factors including immaturity of thyroid function, the effects of acute illness and/or the use of iodine containing compounds in imaging and surgery. It is these preterm infants who show a delayed rise in TSH levels after birth who are the target population for the preterm second CHT screening test.

An expert sub-group comprising representatives from the British Society of Paediatric Endocrinology (BSPED), the British Association of Perinatal Medicine (BAPM) and the UK Newborn Screening Laboratory Network (UKNSLN) reviewed the evidence and consulted on the policy prior to its implementation across the UK in April 2012. They concluded that the optimal gestational age threshold for second testing is 32 weeks gestation (testing required when babies are born at a gestation less than or equal to 31 weeks + 6 days).

Routine newborn bloodspot screening

The preterm CHT sample for babies born at less than 32 weeks gestation is taken in addition to the routine bloodspot screening sample. The newborn bloodspot screening sample should be taken on day 5 of life (counting day of birth as day 0). All babies (irrespective of gestational age) are offered this screening.

The conditions currently screened for in Wales are:

- Congenital hypothyroidism (CHT)
- Cystic fibrosis (CF)
- Inherited metabolic disorders (IMDs):
    - Medium-chain acyl-CoA dehydrogenase deficiency (MCADD)
    - Phenylketonuria (PKU)
    - Maple syrup urine disease (MSUD)
    - Isovaleric acidaemia (IVA)
    - Glutaric aciduria type 1 (GA1)
    - Homocystinuria (HCU)
- Sickle cell disorders (SCD)

Questions and Answers about the CHT preterm policy

1. What are the implications of this policy for neonatal unit staff?

The CHT preterm policy applies to babies born under 32 weeks gestational age. These babies will be under the care of the in-patient neonatal or paediatric services when the second CHT sample is due at 28 days of age. If babies are discharged home prior to 28 days of age they should have the second CHT sample taken on the day of discharge, before they go home.

The consultant neonatologist or general paediatrician is professionally responsible for ensuring that the second CHT sample is offered, and that the sample is obtained whilst the baby is an in-patient in neonatal or paediatric services. The bloodspot samples will be taken by appropriate health professionals providing care on the neonatal or paediatric units.

If a baby is moved to another hospital, responsibility for taking the second CHT sample is transferred to the receiving hospital.

2. What are the implications of this policy for midwives?

All second CHT preterm samples should be taken whilst the babies are in-patients in neonatal or paediatric services. It is therefore unlikely that midwives will be required to take these second samples.

3. How many bloodspots need to be collected for the second preterm CHT sample?

Two bloodspots (two circles filled and evenly saturated) are required on the screening card for the second preterm CHT sample.

CHT preterm policy – scenarios

Scenario 1

A baby is born at 32+0 weeks gestation. Is a CHT preterm repeat needed?

Solution

No – only babies born at less than 32 weeks (less than or equal to 31+6 weeks) should be offered a CHT preterm repeat.

Scenario 2

A baby is due to be discharged on day 27 and has a CHT preterm repeat taken. The baby then stays in hospital another night. The laboratory asks for a repeat sample as the sample wasn't taken on the correct day.

Solution

If the baby is due to be discharged home before day 28, write '**discharged home'** on the bloodspot card to ensure the laboratory knows why the repeat sample was taken before day 28. This is an exceptional circumstance but by informing the laboratory the baby was due to be discharged home the sample will not generate a repeat request.

Scenario 3

A baby did not have a CHT preterm repeat taken on day 28 because he/she was given a blood transfusion on day 27 and was discharged home soon afterwards. The responsibility for taking the CHT preterm repeat was transferred to the community. The reason for this was to avoid the baby having a heel prick in hospital and a second heel prick at least three clear days after the blood transfusion.

Solution

This scenario will occur infrequently. If a baby is fit for discharge but requires a top-up blood transfusion, treat as day of discharge and take the CHT preterm repeat sample pre-transfusion. Write '**discharged home'** on the card.

Scenario 4

A baby did not have a CHT preterm repeat screen at day 28 because he/she was given a blood transfusion on day 27 and then transferred to another neonatal unit.

Solution

Record clearly on the transfer documentation and IT system that screening is incomplete and transfer responsibility to complete screening to the receiving unit. Take the CHT repeat sample at least three clear days after the last transfusion.

Scenario 5

A baby is having multiple blood transfusions around day 28. Should a repeat be taken at least three clear days after each transfusion?

Solution

No – only one repeat is needed, as soon as there is a window of at least three clear days. Ideally this should be as close to day 28 as possible.

Appendix G: Sickle cell disorder (SCD) carrier information for health visitors

Newborn Bloodspot Screening Wales
Sgrinio Smotyn Gwaed Newydd-anedig Cymru

Information for health visitors to support discussions with parents whose baby is identified as a carrier of a sickle cell disorder.

Newborn Bloodspot Screening in Wales

In Wales all eligible babies are offered screening for the conditions below which are recommended by the UK National Screening Committee:

- Inherited metabolic disorders (IMDs)
  - Medium-chain acyl CoA dehydrogenase deficiency (MCADD)
  - Phenylketonuria (PKU)
  - Maple syrup urine disease (MSUD)
  - Isovaleric acidaemia (IVA)
  - Glutaric aciduria type 1 (GA1)
  - Homocystinuria (HCU)
- Congenital hypothyroidism (CHT)
- Cystic fibrosis (CF)
- Sickle cell disorders (SCD)

Newborn bloodspot screening for sickle cell disorders was implemented in Wales on 1 June 2013.

What are sickle cell disorders?

Please note this information relates to people who have a sickle cell disorder. People who are identified as a carrier do not have a sickle cell disorder and therefore will not develop symptoms.

Sickle cell disorders are a group of conditions in which haemoglobin in red blood cells is abnormal in structure. This causes red cells to become sickle-shaped ('sickled') when de-oxygenated. Sickled red blood cells are not as flexible as normal red blood cells, causing blockages of small blood vessels. Also, they do not

last as long in the blood stream so they are produced at an increased rate by the body.

The blood vessel blockages and the increased production can cause medical problems for the affected individual. The symptoms can include pain, anaemia, jaundice, enlarged spleen and infections. Exacerbations of the condition, known as 'sickle cell crises', can be life-threatening.

How is the baby a carrier of a sickle cell disorder?

The baby has one copy of a haemoglobin gene that does not function correctly because the gene has an alteration (also known as a gene mutation). The baby is likely to have inherited this altered gene from one parent.

In areas of the world where malaria was common, people who had one copy of the haemoglobin gene mutation (sickle cell carriers) were more likely to survive malaria than those who had the usual haemoglobin. That is why sickle cell haemoglobin is found in people whose ancestors come from Africa, Asia, Middle and Far East and the Mediterranean.

Why are babies identified as carriers of a sickle cell disorder as part of the newborn screening programme?

The aim of newborn bloodspot screening for sickle cell disorders in Wales is to identify babies who have a sickle cell disorder, and not to identify babies who are carriers of a sickle cell disorder.

However, as a by-product of the screening test protocol, very occasionally babies will be identified as being a healthy carrier of a sickle cell disorder. When a baby is identified as a carrier, this information needs to be communicated to the parents of the baby.

How is this information communicated to the parents?

The pathway for undertaking this communication is via the health visitor so that parents are informed by a professional with whom they are in routine contact. The NBSW programme will identify the baby's health visitor and contact them to discuss the SCD carrier result and provide additional information to support their discussion with the parents.

What information does the health visitor need to give the parents?

The parents need to be informed that the results of the NBS test identify that their baby is a carrier of a sickle cell disorder.

The main message for the parents is that this result does not mean that their child will be unwell, and that their baby will not develop a sickle cell disorder.

The main implication of the SCD carrier result is that it provides genetic information that is important in the future, when that child becomes an adult and is considering having children. It is important because if two carriers of a SCD have children together, there is a 1 in 4 (25%) chance, for every child conceived, that the child will be affected by a SCD.

The health visitor should discuss and offer the parents a referral to the All-Wales Medical Genetic Service (AWMGS). The parents can be referred to this service if they would like further advice and information.

Implications for other family members

For a child to be a carrier of a SCD, one of the parents is likely also to be a carrier of a SCD. If the parents want to discuss the implications of this for other members of the family and for future pregnancies, they can be referred to the AWMGS for advice.

Referral to the All-Wales Medical Genetic Service

If the parents would like to be referred to the AWMGS, the health visitor should contact the service on (029) 20742577 explaining that the parents have a baby who has been identified as being a carrier for a SCD by newborn bloodspot screening. The health visitor will then be sent a referral form which should be completed by the health visitor and returned to AWMGS. The genetic service will follow up the referral, contact the parents and an appointment will be offered in a local genetics clinic.

Appendix H: Incidence and positive predictive values

The table below shows the approximate UK incidence and positive predictive value of each condition.

The positive predictive value (PPV) is the likelihood that a baby with a screen positive result will have the condition. This varies with each condition.

Condition	UK incidence	PPV%	Without early treatment, the condition can result in
MCADD	1 in 10 000	80-90%	serious illness and possible death
PKU	1 in 10 000	80-90%	permanent brain damage and serious learning disabilities
MSUD	1 in 150 000	50%	coma, permanent brain damage and possible death
IVA	1 in 150 000	50%	coma, permanent brain damage and possible death
GA1	1 in 300 000	50%	coma and neurological damage
HCU	1 in 300 000	50%	learning difficulties, eye problems, osteoporosis, blood clots or strokes
CHT	1 in 2000	70%	permanent, serious physical problems and learning disabilities
CF	1 in 2500	70%	poor weight gain, frequent chest infections and reduced life expectancy (symptoms can be present even with treatment)
SCD	1 in 2800	95%	severe pain, life threatening infections and anaemia (symptoms can be present even with treatment)

Appendix I: When screening started

The table below shows the year that screening for each condition was fully implemented in Wales and England.

Condition	Screening implemented in Wales:
MCADD	2012
PKU	1970
MSUD	2015
IVA	2015
GA1	2015
HCU	2015
CHT	1981
CF	1996
SCD	2013

Appendix J: Results letter – parents

GIG CYMRU NHS WALES | Iechyd Cyhoeddus Cymru Public Health Wales

Newborn Bloodspot Screening Wales
Sgrinio Smotyn Gwaed Newydd-anedig Cymru

00 January 2016

Newborn Bloodspot Screening Wales
No 2 Capital Quarter, Tyndall Street
Cardiff
CF10 4BZ

Parent or carer name
The Old House
Somewhere
West Wales
ZX00 0XZ

Dear (parent or carer name)

Your baby had a sample of blood taken from their heel for newborn bloodspot screening and the results of the tests are below.

Baby's name: Forename and surname
Date of birth: 00.00.00 **NHS No:** 000 000 0000

Medium chain acyl-CoA dehydrogenase deficiency (MCADD)	Not suspected
Phenylketonuria (PKU)	Not suspected
Maple syrup urine disease (MSUD)	Not suspected
Isovaleric acidaemia (IVA)	Not suspected
Glutaric aciduria type 1 (GA1)	Not suspected
Homocystinuria (pyridoxine unresponsive) (HCU)	Not suspected
Congenital hypothyroidism (CHT)	Not suspected
Cystic fibrosis (CF)	Not suspected
Sickle cell disorders (SCD)	Not suspected

Please note that the purpose of screening is to identify babies more likely to have these conditions and screening is not 100% accurate.

The leaflet included with this letter explains the newborn bloodspot screening results and lets you know if you need to do anything. If you have any questions about your baby's screening, please discuss them with your health visitor or your GP.

Please keep this letter with your baby's personal child health record (their 'red book').

Yours sincerely

Ruth Lawler
Head of Maternal and Child Screening

Crystal Mark 22059
Clarity approved by Plain English Campaign

Appendix K: Parent leaflet explaining result

Newborn Bloodspot Screening Wales
Sgrinio Smotyn Gwaed Newydd-anedig Cymru

GIG CYMRU NHS WALES
Iechyd Cyhoeddus Cymru
Public Health Wales

Newborn bloodspot screening – Your baby's results explained

Newborn bloodspot screening is offered to all newborn babies and is usually carried out five to eight days after their birth. We test the blood sample for rare but serious diseases that respond to early specialist care and treatment. **Newborn bloodspot screening is offered to all babies up to one year of age.**

The letter we have sent you with this leaflet gives you the results of your baby's bloodspot screening tests. This leaflet explains the results and lets you know if you need to do anything.

Not suspected

A 'not suspected' result for any of the conditions your baby has been screened for means that your baby probably does not have the condition.

Suspected

A 'suspected' result means that your baby may have the condition they were screened for and they will need more tests to confirm if they have the condition. If we suspect your baby has one of the conditions, we will have referred them to an appropriate clinical team. If you have any questions about your baby's care, please contact your baby's specialist doctor or GP.

Screening incomplete

This means that we have not been able to complete the screening process for some or all of the conditions using the sample provided, and will need another sample. **Please contact your midwife or health visitor to arrange for another sample to be taken so that the screening tests can be completed.**

Declined

Our records show that you did not want your baby to have newborn bloodspot screening for one or more of the conditions, or that you have decided you do not want a repeat sample taken. **Newborn bloodspot screening for all of the conditions is recommended by the UK National Screening Committee**. Most babies screened will not have any

of the conditions. However, for the small number that do, newborn bloodspot screening means that these babies can receive early specialist care and treatment. Early treatment can improve their health and prevent severe disability or even death.

If you change your mind and want your baby to have the screening tests, please contact your midwife or health visitor. Newborn bloodspot screening is offered to all babies up to one year of age. However, screening for cystic fibrosis is only offered up to eight weeks of age because the test is unreliable after this time.

Not tested for cystic fibrosis

Your baby has not been tested for cystic fibrosis because they were older than eight weeks when the sample was taken. Screening for cystic fibrosis is only offered up to eight weeks of age because the test becomes unreliable after this age.

Too old for screening

We have not been able to test the blood sample taken from your baby's heel. This is because your baby was older than one year and was above the age that the screening tests can be carried out. If you have any concerns about your baby's health please contact your GP.

Sickle cell disorder carrier

Occasionally, the screening process may identify a sickle cell disorder carrier. If your baby was found to be a sickle cell disorder carrier your health visitor will already have told you this.

Sickle cell disorders screening is for sickle cell disorders only and not for other haemoglobin variants or thalassaemia.

Please note that the purpose of screening is to identify babies more likely to have these conditions, and screening is not 100% accurate.

If you have any questions about your baby's screening, please discuss them with your health visitor or your GP.

You can find more information about newborn bloodspot screening on the website:
www.newbornbloodspotscreening.wales.nhs.uk

Version 1 March 2016

Appendix L: Declined screening letter

GIG CYMRU NHS WALES | Iechyd Cyhoeddus Cymru Public Health Wales

Newborn Bloodspot Screening Wales
Sgrinio Smotyn Gwaed Newydd-anedig Cymru

00 January 2016

Newborn Bloodspot Screening Wales
No 2 Capital Quarter, Tyndall Street
Cardiff
CF10 4BZ

Parent or carer name
The Old House
Somewhere
West Wales
ZX00 0XZ

Dear (parent or carer name)

You were offered newborn bloodspot screening for your baby. Our records show that you did not want your baby to have this screening for the conditions shown in the table below.

Baby's name: Forename and surname
Date of birth: 00.00.00 **NHS No:** 000 000 0000

Medium-chain acyl-CoA dehydrogenase deficiency (MCADD)	Declined
Phenylketonuria (PKU)	Declined
Maple syrup urine disease (MSUD)	Declined
Isovaleric acidaemia (IVA)	Declined
Glutaric aciduria type 1 (GA1)	Declined
Homocystinuria (pyridoxine unresponsive) (HCU)	Declined
Congenital hypothyroidism (CHT)	Declined
Cystic fibrosis (CF)	Declined
Sickle cell disorders (SCD)	Declined

The leaflet included with this letter gives you more information and explains what you need to do if you change your mind and want your baby to have the screening tests.

If you have any questions about newborn bloodspot screening, please speak to your health visitor or GP.

Please keep this letter with your baby's personal child health record (their 'red book').

Yours sincerely

Ruth Lawler
Head of Maternal and Child Screening

Crystal Mark 21131
Clarity approved by Plain English Campaign

Appendix M: Not screened letter

GIG CYMRU NHS WALES | Iechyd Cyhoeddus Cymru Public Health Wales

Newborn Bloodspot Screening Wales
Sgrinio Smotyn Gwaed Newydd-anedig Cymru

00 January 2016

Newborn Bloodspot Screening Wales
No 2 Capital Quarter, Tyndall Street
Cardiff
CF10 4BZ

Parent or carer name
The Old House
Somewhere
West Wales
ZX00 0XZ

Dear (parent or carer name)

Baby's name: Forename and surname
Date of birth: 00.00.00 **NHS No:** 000 000 0000

Newborn bloodspot screening is offered to all newborn babies and is usually carried out five to eight days after their birth. The blood sample is screened for rare but serious diseases that respond to early specialist care and treatment.

Our records show that your baby has not had this screening.

Newborn bloodspot screening for all of the conditions is recommended by the UK National Screening Committee. Most babies screened will not have any of the conditions. However, for the small number that do, newborn bloodspot screening means that these babies can receive early specialist care and treatment. Early treatment can improve their health and prevent severe disability or even death.

If you would like to have your baby screened please contact your midwife or health visitor as soon as possible. They will be able to discuss the newborn bloodspot screening with you and make arrangements for it to be carried out.

Newborn bloodspot screening is offered to all babies up to one year of age. However, screening for cystic fibrosis is only offered up to eight weeks of age because the test becomes unreliable after this time. Please note that the purpose of screening is to identify babies more likely to have these conditions and screening is not 100% accurate.

Please keep this letter with your baby's personal child health record (their 'red book').
Further information can be found in the 'Newborn Bloodspot Screening – Information for parents' leaflet which is available from your midwife or health visitor, or on the website: www.newbornbloodspotscreening.wales.nhs.uk.

Yours sincerely

Ruth Lawler
Head of Maternal and Child Screening

Crystal Mark 22059 Clarity approved by Plain English Campaign

Appendix N: Health visitor cover letter – suspected result

GIG CYMRU NHS WALES | Iechyd Cyhoeddus Cymru Public Health Wales

Newborn Bloodspot Screening Wales
Sgrinio Smotyn Gwaed Newydd-anedig Cymru

00 May 2018

Newborn Bloodspot Screening Wales
No 2 Capital Quarter, Tyndall Street
Cardiff
CF10 4BZ
Tel: 029 2010 4427
Email: nbsw@wales.nhs.uk

Dear Health Visitor

As discussed, the newborn bloodspot screening results for a baby on your case load have been reported as 'Suspected' for one of the nine conditions.

The parents have been informed of this result and the baby has now been received into clinical care.

The enclosed letter for the parents provides all the newborn bloodspot screening results for their baby. Please give this letter to the parents, together with the information leaflet which explains the results.

For your information, a leaflet about the suspected condition is also enclosed.

Please contact the Newborn Bloodspot Screening Programme Co-ordinators on the telephone number above if you have any queries or require further support.

Yours sincerely

Ruth Lawler
Head of Maternal and Child Screening

Appendix O: Health visitor cover letter – Sickle cell disorder carrier

GIG CYMRU NHS WALES | Iechyd Cyhoeddus Cymru Public Health Wales

Newborn Bloodspot Screening Wales
Sgrinio Smotyn Gwaed Newydd-anedig Cymru

00 May 2018

Newborn Bloodspot Screening Wales
No 2 Capital Quarter, Tyndall Street
Cardiff
CF10 4BZ
Tel: 029 2010 4427
Email: nbsw@wales.nhs.uk

Dear Health Visitor

As discussed, the results for the routine newborn bloodspot screening for sickle cell disorders for a baby on your case load have been reported as **probable sickle cell disorder carrier** or other **haemoglobin variant carrier**. This genetic information is not clinically significant.

The parents need to be informed of the results of the sickle cell disorder screening, and that they can be referred to the All Wales Medical Genetic Service if they would like further advice and information. An information leaflet to support your discussion with the parents is enclosed, and this explains how to refer parents to the All Wales Medical Genetic Service.

The enclosed letter for the parents provides all the newborn bloodspot screening results for their baby. **Please inform the parents of these results within 14 days of the date of this notification.**

Please give the results letter to the parents, together with the information leaflets which explain the newborn bloodspot screening results.

Please could you contact us to let us know when you have informed the parents of the results, as this information is required for auditing this part of the screening programme.

If you have any queries or require further support, please contact the Newborn Bloodspot Screening Programme Co-ordinators on the telephone number above.

Yours sincerely

Ruth Lawler
Head of Maternal and Child Screening