NHS
Antenatal and Newborn Screening Programmes

Regional Policy template for newborn screening for Inherited Metabolic Disease (IMD) in the South West (Bristol Newborn Screening Laboratory)

May 2018

Participating Trusts:

North Bristol NHS Trust

North Devon NHS Trust

Gloucestershire Hospitals NHS Foundation Trust

Plymouth Hospitals NHS Trust

Royal Cornwall Hospitals NHS Trust

Royal Devon and Exeter NHS Foundation Trust

Taunton and Somerset NHS Foundation Trust

Torbay and South Devon NHS Foundation Trust

University Hospitals Bristol NHS Foundation Trust

Weston Area Health NHS Trust

Yeovil District Hospital NHS Foundation Trust

Policy history

Version No.	Date	Author	Comments
1	20/11/2014	Helena Kemp	Distributed Dec 14
2	29/7/2015	Helena Kemp	Updated to reflect national guidelines and pathways ratified by IMD Screening Advisory Board April 28 2015
3	21/8/15	Helena Kemp	Links updated due to changes in screening websites and transfer of all screening information to Gov.UK website
4	21/12/15	Helena Kemp	Added names of participating Trusts
5	06/03/18	Helena Kemp	Updated to reflect: 1. April 2017 revised newborn blood spot screening performance standards 2. 2017 updated IMD clinical referral guidelines & pathways (all 6 IMD disorders) 3. Implementation of Saturday morning review of newborn screening results for MSUD, IVA & MCADD by newborn screening laboratories 4. Inclusion of guidance regarding the management of clinical incidents in screening programmes 5. Update contact details

Contents

Introduction

Screening for inherited metabolic disease has been in place in the UK since the 1960's when screening for Phenylketonuria (PKU) first began. More recently screening for Medium Chain Acyl CoA Dehydrogenase deficiency (MCADD) was introduced and in 2012/13 a study was undertaken to evaluate the utility for screening for other additional IMDs. In May 2014 the UK National Screening Committee announced its recommendation to include four additional inherited metabolic diseases as part of the national newborn screening blood spot programme, maple syrup urine disease (MSUD), isovaleric aciduria (IVA), glutaric aciduria type 1 (GA1) and homocystinuria (HCU). The national IMD screening programme now includes these six IMD conditions.

The early detection offered by newborn screening is a significant benefit for patients with all of the conditions included within the programme and in some cases can be lifesaving. The successful introduction of screening depends upon the cohesive management of testing as a programme of care from pre-screening information to screening results and in the case of positive cases enrolment into appropriate treatment. It is important that mothers are fully informed at each stage and that only clinically significant disease is detected with a minimum number of false positive cases. Once a screen positive patient is identified, the period of uncertainty required for any associated confirmatory testing must be kept to a minimum and parents supported during this trying time.

The South West Regional Policy (Bristol Newborn Screening Laboratory) was orginally produced by the SW Regional IMD Implementation Group as a guide for local implementation teams to inform the introduction of newborn screening for the four additional conditions throughout the region. At the same time the regional policies for PKU and MCADD were reviewed and, where possible, aligned to enable the production of a single unified policy for screening for IMD across the SW Region. The policy has now been updated and ratified by the South West Regional Newborn Screening Operational Group to reflect the 2017 updated IMD clinical referral guidelines, the 2017 Newborn Blood Spot Performance Standards and the introduction of Saturday morning reading and reporting of positive newborn screens for the IMD conditions IVA, MCADD & MSUD.

Further information regarding clinical referral pathways and management guidelines can be found on the British Inherited Metabolic Diseases Group (BIMDG) website (https://www.bimdg.org.uk). National Programme Policies, Standards and resources can be found on the website https://www.gov.uk/topic/population-screening-programmes

1 The conditions

Phenylketonuria

Phenylketonuria is one of the most common inherited metabolic disorders with an incidence across the UK of approximately 1 in 10 000 births. PKU is an autosomal recessively inherited disorder of amino acid metabolism caused by a deficiency of the enzyme phenylalanine hydroxylase (PAH). The enzyme is required to metabolise phenylalanine to tyrosine. A deficiency of the enzyme results in an accumulation of phenylalanine and associated metabolites in blood and tissues. The infant brain is sensitive to high phenylalanine levels and if left untreated, patients with PKU develop severe mental retardation, microcephaly and a proportion of patients develop epilepsy. Older patients have behavioural problems and some suffer from psychiatric illness.

Children with PKU requiring treatment are treated with a phenylalanine restricted diet to reduce the flux through the affected metabolic pathway thereby preventing the accumulation of toxic metabolites. Dietary therapy utilises a phenylalanine-free synthetic amino acid mixture as a substitute for natural protein and requires careful management to ensure appropriate vitamins and trace elements together with small amounts of natural protein are provided. Treatment should begin with minimum delay. Recommendations in the past have indicated that diet should be initiated by 20 days of age and continued throughout childhood.

An increased blood phenylalanine is not specific for PKU. In addition to disorders of phenylalanine hydroxylase deficiency, increased phenylalanine on newborn screening at 5-8 days may occur in several other situations. There are several rare disorders of pterin synthesis/recycling which may be associated with an isolated increase in phenylalanine at screening and therefore detected by the PKU programme. All babies with a PKU suspected screening result are tested for pterin disorders at follow up.

In some cases the phenylalanine increase is associated with an increase in tyrosine which is measured as part of the screening protocol. This situation can arise in conditions which cause liver disease in the neonate e.g. hepatitis, biliary atresia, CMV and some inherited disorders, in particular Galactosaemia and Tyrosinaemia type 1. There are also a number of other non-specific causes including prematurity, parenteral nutrition and transient illness. Babies with an associated increase in tyrosine require different investigation and management and urgent referral to an appropriate specialist clinician is essential.

Medium Chain Acyl CoA Dehydrogenase Deficiency

MCADD is an autosomal recessive condition that affects approximately 1 in 10,000 born in the United Kingdom. It is caused by a deficiency of an enzyme medium chain acyl CoA dehydrogenase. This enzyme is required to breakdown certain stored fats, medium chain length fatty acids, and is necessary to enable the body to use its own fat reserves to produce energy in periods of prolonged fasting or stress.

Complications of MCADD can arise during prolonged fasting but particularly occur during intercurrent illness when the body's demand for energy is high and Calorie

intake is often reduced. As fat fuels cannot be used these patients quickly use up glucose and can develop hypoglycaemia. Partially broken down fatty acids accumulate and this, along with low blood glucose concentrations, cause these patients to become drowsy, comatose and eventually to stop breathing. Without treatment this condition is associated with significant morbidity and mortality. Early identification by screening however results in early pre-symptomatic treatment reducing the risk of acute life-threatening episodes.

MCADD requires no special treatment when the child is well. Fasting should however be avoided. When illness occurs MCADD is easily treatable with an emergency feeding regime of high calorie drinks or, if unable to tolerate e.g. due to vomiting, urgent hospital admission for an intravenous 10% dextrose infusion. With early detection, monitoring and avoidance of fasts, children diagnosed with MCADD can lead normal lives particularly as 'safe' times between meals increase as they grow older.

Maple Syrup Urine disease

MSUD is an autosomal recessive caused by a deficiency of the branched chain alpha keto acid dehydrogenase complex. The condition occurs in approximately 1:200,000 live births. The resulting metabolic block leads to an increased concentration of the branched chain amino acids leucine, valine and isoleucine and their corresponding keto acids. These compounds accumulate in tissues resulting in a life threatening metabolic decompensation in some affected individuals and are elevated in the blood and urine. The name of the condition derives from the sweet smelling urine sometimes produced by affected individuals which some have likened to the smell of maple syrup.

The classic form of the disorder presents shortly after birth often in the first two weeks of life. Vomiting or difficulty feeding are often early symptoms accompanied by lethargy and progressive neurological deterioration. Intermediate and intermittent forms of the condition are also described. Patients with the intermediate form may present with developmental delay although the characteristic elevation of branched chain amino acids is still present. The intermittent form of the disease may only manifest at times of stress or infection and branched chain amino acids may not be continuously elevated. Rarer thiamine responsive disease has been described together with another variant which also affects the pyruvate dehydrogenase complex resulting in marked lactic acidosis.

It is likely that newborn screening will detect patients with the classic condition but may not detect individuals with intermediate or intermittent forms which have a spectrum of clinical and biochemical severity.

Isovaleric aciduria

Isovaleric acidaemia (IVA) is caused by a deficiency of isovaleryl-CoA dehydrogenase (IVD), an enzyme involved in the catabolism of the amino acid leucine. It is an autosomal recessive disease, with an estimated incidence of around 1 in 100,000 with a higher incidence in some locations and ethnic groups.

Loss of function of the enzyme leads to the toxic build-up of metabolites including isovaleric acid and its glycine and carnitine derivatives. The disease has a spectrum of clinical phenotypes which might include acute neonatal presentations, acute presentations at a later age and chronic intermittent presentations. The acute neonatal presentation is characteristically in the first two weeks after birth. Infants

are initially well, then develop vomiting and lethargy, progressing to coma. Patients may also present with similar symptoms at a later age, usually precipitated by an infection. Other patients present with chronic symptoms - failure to thrive and/or developmental delay, usually within the first year.

Over 25 mutations in the IVD gene have been associated with disease, a number of which lead to complete lack of the enzyme. Although a firm phenotype/genotype correlation has not been identified, recent research suggests that the 932C>T mutation in the IVD gene may be associated with a milder phenotype. Newborn screening has identified individuals with partial as well as complete IVD deficiency.

Glutaric aciduria type 1

Glutaric aciduria type 1 (GA1) is an autosomal recessive condition caused by a deficiency of the enzyme glutaryl-CoA dehydrogenase (GCDH). The estimated incidence in the UK is around 1 in 100,000 live births.

GCDH is involved in the metabolism of the amino acids lysine, hydroxylysine, and tryptophan. Defective catabolism causes the toxic accumulation of glutaric acid, 3-hydroxyglutaric acid, glutaconic acid, and glutaryl carnitine.

GA1 frequently presents with an encephalopathic crisis, which is most commonly between 9 months to 2 years. These are usually precipitated about 1-3 days after onset of a non-specific intercurrent illness, gastrointestinal infection or pneumonia and lead to dystonia and dyskinesia as permanent sequelae but with relative preservation of the intellect. There are also two other clinically recognised sub-groups of patients with GA1 who have an insidious or later onset form with non-specific symptoms including irritability and transient lactic acidosis. These infants go on to show delayed motor development. Very occasionally an individual might be asymptomatic.

Over 150 disease causing mutations have been identified; of these the R402W mutation is the most prevalent among Caucasians. Most mutations, including the R402W mutation, are associated with undetectable GCDH activity and excretion of high amounts of glutaric acid. However, mutations that lead to varying levels of residual GCDH activity and low excretion of glutaric acid have also been reported. Consequently, patients with GA1 can be divided into two biochemically defined subgroups based on the levels of glutaric acid present in the urine: low excretors and high excretors. Although these subgroups are clinically similar it is important to be aware as confirmatory testing in low excretors requires more complex follow-up, with either determination of GCDH enzyme activity or by mutation analysis of the GCDH gene.

Homocystinuria

The most common cause of homocystinuria is a defect in the enzyme cystathionine β-synthase (CBS); this is referred to as “classical” homocystinuria. The overall incidence in the UK is reported to be around 1 in 100,000 live births. The mode of inheritance of classical homocystinuria is autosomal recessive.

Classical homocystinuria is associated with a number of clinical and pathological abnormalities. Infants are usually normal at birth and without screening the diagnosis is not usually made until the first 2-3 years of life. Myopia followed by dislocation of the lens, osteoporosis, thinning and lengthening of the long bones,

mental retardation and thromboembolism affecting larger and small arteries and veins are the commonest clinical features. Without treatment, 25% of patients will die before the age of 30, usually as a result of arterial thromboembolism. There is a great deal of clinical heterogeneity, with some patients displaying all clinical symptoms whilst others display very few or none. The concentration of plasma total homocysteine can be measured to assess the clinical severity of disease and can be monitored to determine the response to treatment.

Homocystinuric patients can be sub-divided into two important biochemical phenotypes:

- Pyridoxine responsive (screen undetectable)
- Pyridoxine non-responsive (screen detectable)

In the UK approximately 50% of patients with classical homocystinuria are classified as pyridoxine responsive, these patients usually have milder symptoms and disease progression is slower and slowed further by oral pyridoxine (Vitamin B6) supplementation, they are very unlikely to be detected by newborn screening

2 Aims

1. To offer screening to all babies resident within the area covered by the Bristol Newborn Screening Laboratory

2. To inform parents of the IMD status of their newborn children.

3. To minimise morbidity and mortality from PKU, MCADD, MSUD, IVA, GA1 and HCU in infants born within the South West region.

3 Objectives

1. To identify and offer screening to all eligible infants.

2. To process tests for all those screened in a timely manner.

3. To ensure an appropriate level of understanding amongst professionals involved with the programme.

4. To appropriately follow up all infants identified as needing further investigative testing.

5. To accurately diagnose all infants born with PKU, MCADD, MSUD, IVA, GA1 and HCU

6. To ensure that information is provided to affected families in an acceptable and accessible manner and is appropriate to the needs of the relevant communities.

7. To ensure effective and acceptable follow up, care and support for infants with PKU, MCADD, MSUD, IVA, GA1 and HCU and their carers.

8. To audit the service on an ongoing basis and provide information on acceptability, effectiveness and resource implications.

9. To minimise the adverse effects of screening (anxiety, misunderstanding, inaccurate information, unnecessary investigation and follow-up, and inappropriate disclosure of patient-specific information).

4 The screening protocols

The newborn screening protocols have been agreed and endorsed by the IMD Scientific Advisory Board. The screening protocols are intended to:-

Maximise early detection of PKU, MCADD, MSUD, IVA, GA1 and HCU so that appropriate early pre-symptomatic treatment can be initiated and the risk of acute, life threatening episodes and/or the development of disease associated complications can be reduced.

Minimise the number of false positive results and the detection of unaffected carriers.

Samples will be processed at a laboratory recognised as a newborn blood spot screening laboratory, adhering to the programme laboratory standards and using the recommended standard operating procedures:
https://www.gov.uk/topic/population-screening-programmes

Note screening for IMD will include all 6 conditions. Patients can only consent or decline all 6 conditions

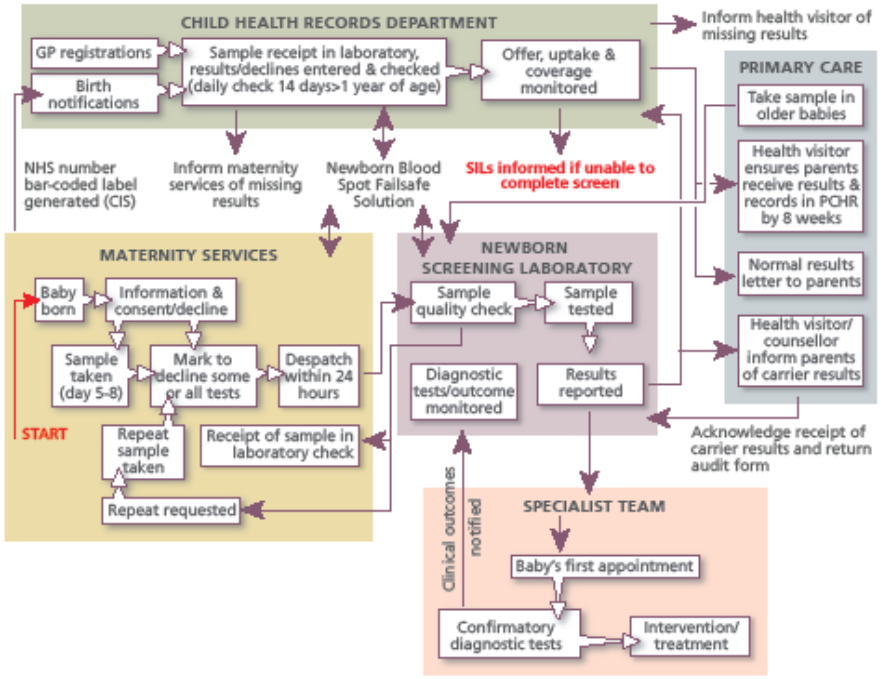
4a The screening process

Policy	Local arrangements	Professional responsible
1. Local policy and practice for service delivery for all aspects of the programme (including laboratory and diagnostic services) must adhere to national newborn blood spot screening standards and guidance, April 2017 https://www.gov.uk/topic/population-screening-programmes	*[insert local arrangements]*	
2. All women will be given a copy of the pre-screening information leaflet during the third trimester to enable parents to make an informed choice based on their individual values	*[insert local arrangements]*	**[e.g. community midwife].*
3. Screening should be preceded by the provision of written information, where possible in the parent's first language. There should be access to additional information and support if requested	*At least 24 hours before taking the heel prick, the midwife should ensure parents have a copy of the pre-screening information leaflet. This is available electronically via www.gov.uk/topic/population-screening-programmes and is included within 'Newborn Blood Spot Screening – Information and Support for Parents'.*	** [e.g. community midwife].*
4. Screening for IMD (includes PKU, MCADD, MSUD, IVA, GA1 & HCU) will be offered on a resident basis, at 5 days of age, as part of the Newborn Bloodspot Screening Programme. **Standard 4** **Acceptable Standard** >90% of first samples are taken on day 5 **Achievable Standard** ≥ 95% of first samples are taken on day 5.	*[insert local arrangements]*	** [e.g. community midwife].*
5. The offer of screening and the decision to accept or decline should be recorded. The blood spot card should be completed and clearly marked 'DECLINE' and sent to the	*[Insert detail of local arrangements and method of documentation e.g. recording in hand-held maternity notes and in the red book and blood spot card to be sent to screening laboratory for declines].*	** [e.g. community midwife].*

Policy	Local arrangements	Professional responsible
screening laboratory. **Note a decline for IMD screening includes all 6 conditions. It will not be possible to decline IMD screening for one or more of the 6 conditions.**		
6. Ensure the good quality blood spot is collected i.e. sample is taken at the right time, all data fields completed, contains sufficient blood for all tests, is not contaminated and reaches the lab in a timely manner. **Standard 6** **Acceptable standard** Avoidable repeat rate ≤ 2% **Achievable standard** Avoidable repeat rate ≤ 1%	*Insert local mechanisms to optimise and monitor avoidable repeat rate including KPI reporting and monitoring*	
7. The NHS number must be used on the blood spot card to identify the baby preferable provided on a bar-coded label **Standard 3** **Acceptable Standard** ≥ 90,0%of blood spot cards are received by the laboratory with the baby's NHS number on a barcoded label. **Achievable Standard** ≥ 95.0% of blood spot cards are received by the laboratory with the baby's NHS number on a barcoded label.	*[insert local arrangements]*	***[e.g. community midwife].*
8. Blood spot screening cards should be sent to the screening laboratory as soon as possible after the sample has been taken **Standard 5** **Acceptable Standard** ≥95.0% of all samples received by laboratory less than or equal to 3 working days of sample	*[insert local arrangements]* ***NB** Dispatch of blood spot screening cards should not be delayed in order to batch cards together in one envelope..*	** [e.g. community midwife].*

Policy	Local arrangements	Professional responsible
collection. **Achievable Standard** ≥99.0% of all samples received by laboratory less than or equal to 3 working days of sample collection.		
9. Professional responsibilities to support women and their partners throughout the screening process and manage adverse incidents to be identified in the local care pathway.	*See care pathway.*	*Professional responsibility is identified in the care pathway.*
10. There should be explicit governance arrangements to ensure all babies, including movers in, are offered screening including a documented failsafe policy **Standard 1a** **Acceptable** ≥ 95% of eligible babies have a result for each of the 9 conditions recorded on the CHIS at less than or equal to 17 days of age tested for all conditions **Achievable** ≥ 99% of eligible babies have a result for the IMDs recorded on the CHIS at less than or equal to 17 days of age. **Standard 1b (movers in)** **Acceptable** ≥ 95% of eligible babies have a result for each of the 9 conditions recorded on the CHIS at less than or equal to 21 days of notifying the CHRD of movement in **Achievable** ≥ 99% of eligible babies have a result for the IMDs recorded on the CHIS at less than or equal to 21 days of notifying the CHRD of movement in	*[insert local arrangements/local failsafe policy ref* *e.g.* *- arrangements for offering screening to babies in neonatal units or children' ward* *- Screening laboratory inform CHIS of status 01 codes* *- CHIS have mechanisms to notify midwifery service of babies who have not been screened by Day 17 (ideally Day 14) or within 21 days of moving into area* *- Use of the Northgate Failsafe system*	*Professional responsibility is identified in the care pathway.* *e.g.* *-Mother's named midwife is responsible for checking that appropriate arrangements have been made* *[lab to identify person with this responsibility]* *[CHIS to identify person with this responsibility]* *CHI to send written confirmation to GP/HV* *HCP performing 6–8 week infant physical examination to ensure result available and recorded*

4 b Process for offer and taking of test



4c Late testing

Babies who have not been screened during the newborn period should be screened up to 12 months of age in line with NHS Newborn Blood Spot Screening Programme guidance. After 12 months of age, if the family or GP have any clinical concerns a referral for paediatric assessment would be appropriate.

4d Sibling testing

A new sibling born to the same parents when an index case with either PKU, MCADD, MSUD, IVA, GA1 or HCU has already been identified has a 1 in 4 risk of having the same disorder. In these circumstances it is recommended practice to test earlier than the 5-8 day time frame to avoid delays in diagnosis and parental anxiety. This does not remove the need to test at 5-8 days to screen for all other disorders tested as part of the blood spot screening programme.

The decision about when and how to test depends upon the disorder suspected. Note it is most important for disorders such as MSUD, MCADD and IVA which can potentially have an early neonatal presentation.

Older siblings of newly diagnosed screen detected cases, when born to the same parents, have a 1 in 4 chance of having the same disorder. Careful consideration should be given by the clinician investigating the baby referred via screening to the risks to other, older siblings in the family.

For guidance on testing of siblings contact the Regional Specialist Paediatric Metabolic Team and the Newborn Screening Laboratory

5 Newborn screening results

All screening results will be reported to Child Health Records departments in line with present policies for the Newborn Blood Spot Screening Programme with use of the appropriate status codes.
https://www.gov.uk/government/collections/newborn-blood-spot-screening-programme-standards-and-data

Written policies and mechanisms for relaying of results to parents must be developed locally to include professional responsibility for informing parents of the result, and clear process detail for follow-up of affected babies. Policies should be developed in line with national and regional guidance as detailed below.

5a. Condition 'not suspected'

Newborn screening results which are negative for all of the conditions are to be reported in a timely manner to parents.

Standard 12a – Timeliness of results to parents
Acceptable standard
100% of babies with a not suspected result for each of the conditions for whom a not suspected results letter was despatched directly to parents by the CHIS within 6 weeks of birth.
Standard 12b – Timeliness of results to parents (movers in)
Acceptable standard
100% of babies with a not suspected result for each of the conditions for whom a not suspected results letter was despatched directly to parents by the CHIS within 6 weeks of notification of movement in.

5b Condition 'suspected'

Babies identified as screen positive should have timely referral into clinical care in line with defined clinical referral pathway see below. Any repeat screening tests should be offered & collected in a timely manner in order that treatment and clinical referral targets are met.

Standard 7
Timely taking of a repeat blood spot sample
A repeat sample from the avoidable repeat category must be taken within 3 calendar days of the receipt of the request

Standard 11
Timely receipt into clinical care
A baby in whom an IMD (on first sample) is suspected should attend their first appointment by:
Acceptable 100% by 17 days of age
Achievable 100% by 14 days of age

5c Clinical referral and management guidelines

Guidelines for Clinical Referral for each of the 6 IMD conditions are outlined below and are in line with the guidance endorsed by the IMD Screening Advisory Board.

Notes

1. From May 2018 the Bristol Newborn Screening Laboratory, in line with 2017/18 Commissioning Intentions, will be reviewing screening results on a Saturday morning. Any positive screens for the three conditions IVA, MCADD & MSUD will be repeated and confirmed and referred to the SW Regional Paediatric Metabolic team on a Saturday.

   It will be the responsibility of the On-Call IMD Consultant to contact the family in the first instance. Contacting families at the weekend could be more problematic than during the week as the usual methods of communication may be unavailable. It is essential therefore that a local pathway to support the communication of positive screens arising on a Saturday morning is in place should there be any difficulties in contacting the family. This should include a local designated healthcare professional e.g. On-call midwife, who can be contacted by the IMD Consultant and who can provide local support. The local pathway should also describe an escalation process to be followed as outlined below. For the three conditions IVA, MCADD & MSUD, if the family cannot be contacted directly, the IMD Screening Programme Clinical Management guidelines advise the following:

   For the three conditions IVA, MCADD & MSUD, if the family cannot be contacted directly consider the following:

   - Leave a message on phone and ask to call back. Phone again after 2 & 4 hours if not contact
   - Ascertain if the baby is in hospital of birth & contact appropriate paediatric consultant/registrar
   - Contact midwife or community midwifery team for information via labour ward where baby born

- Home visit – if local designated contact (e.g. community midwife/nurse) available; if not at home leave note asking family to make contact

- Attempt contact/visit again following day.

2. The Newborn Screening Laboratory (NSL) will fulfil the role of the IMD screening clinical liaison service to co-ordinate the referral of all IMD positive screens.

3. A Specialist team should comprise:
    - A consultant Inherited Metabolic Disease (IMD) paediatrician with relevant expertise.
    - A paediatric dietitian with metabolic expertise
    - A clinical nurse specialist

   A designated team must include clinicians trained to receive IMD referrals and have a paediatric dietitian.

4. Protocols, guidelines and template letters for each IMD condition (PKU, MCADD, MSUD, IVA, GA1 & HCU) are available on the newborn bloodspot screening and BIMDG websites (links included within the following clinical referral pathways):

    a. Information leaflets for parents
    b. Technical resources
        i. Screening & diagnostic & sibling testing protocols
        ii. Clinical management guidelines
        iii. Dietetic management guidelines
        iv. Emergency regimens
        v. Template letters (GP letters, A&E letter)

PKU Clinical Management Guidelines*

** PKU Suspected

ON THE SAME DAY

1. Note parents should NOT be informed of a positive result if an appointment cannot be given for the same or next day e.g. parents should not be informed on a Friday unless an appointment is for that day or the Saturday. In this case contact should be deferred until after the weekend to the next working day
2. NSL informs the Specialist team who will inform the Designated team depending on baby's location. (to take place within 24hrs of informing the parents). Specialist/Designated team CONTACT FAMILY
3. Specialist or Designated team to:
   - Give the family an appointment time to attend the specialist (designated) centre the same or next day (including directions as required)
   - Arrange for the family to receive the 'PKU is suspected' leaflet (includes NHS Newborn Blood Spot Screening Programme website address and links to parent support group) (this can be via email, website address or face-to-face contact as per local protocol)
   - Give the family contact numbers for the PKU specialist
4. NSL informs GP, send PKU GP letter via fax / email copied to HV
5. NSL informs Local Screening Coordinator

FIRST REVIEW: FACE-TO-FACE - within 24 hours of informing family of screening result

Take diagnostic samples*** & send urgently to screening lab (courier). Inform lab
Dietetic review, commence dietary restriction if appropriate within 24 hours****
Clinician to ensure:

a. Family have received the 'PKU is suspected' leaflet, PKU specialist (designated) team contact details and appropriate dietary guidelines
b. Letters have been sent to the GP, local paediatrician and local dietitian as necessary

FIRST REVIEW &COMMUNICATION OF DIAGNOSTIC RESULTS - within 15 working days of the 1st face-to-face review

Clinical review and results: phenylalanine, tyrosine, pterins and dihydropteridine reductase (DHPR).
Arrange sibling screening if diagnosis confirmed*****
If diagnosis not confirmed see diagnostic protocol***

PKU CONFIRMED

Yes

Follow up visits for on-going management
Dietetic and clinical review

No

Follow diagnostic protocol***

* **PKU initial clinical management guidelines** www.bimdg.org.uk

** **PKU screening protocol** see Laboratory Guide for IMDs for details www.gov.uk/topic/population-screening-programmes/newborn-blood-spot

*** **PKU diagnostic protocol** for confirmatory tests see Laboratory Guide for IMDs https://www.gov.uk/topic/population-screening-

**** **PKU Dietetic Management Pathway** www.bimdg.org.uk/site/guidelines-enbs.asp

***** **PKU sibling testing** see Laboratory Guide for IMDs for details www.gov.uk/topic/population-screening-programmes/newborn-blood-spot

ii. PKU – 'Other Disorder Suspected'

1. For all 'Other disorder suspected' results the NSL will inform and discuss the result with the Specialist IMD team. The Specialist team will liaise with the relevant local paediatric team as required.

2. Same day review is recommended for this category of screening result as the findings may be indicative of a condition requiring prompt investigation and management. Review of these cases as part of the national review of PKU Screening Programme indicated that the majority of these cases were inpatients at the time of the screening result (PKU Expert Group Report http://www.newbornscreening-bloodspot.org.uk).

3. Further testing for disorders that may be associated with elevated phenylalanine and tyrosine levels should be undertaken. This will include at least full blood count, clotting, urea and electrolytes, bicarbonate, calcium, phosphate, split bilirubin, AST/ALT, alkaline phosphatase, gamma GT, albumin, cholesterol, triglycerides, urine organic acids (in particular succinyl acetone), galactose-1-phosphate uridyl transferase and plasma amino acids. If there is significant liver dysfunction advice should be sought from a liver unit.

MCADD Clinical Management guidelines*

** MCADD Suspected

ON THE SAME DAY

1. NSL informs the Specialist team who will inform the Designated team depending on baby's location. First review appointment arranged (to take place within 24hrs). NSL must provide the following:
   a. Hospital of birth
   b. Parent telephone number
   c. Telephone number of midwifery contact (Saturdays)
2. Specialist/designated team to CONTACT FAMILY (if family CANNOT BE CONTACTED see Note 1 page 17.)
   a. If infant well and feeding regularly:
   i. Advise parents about regular feeding & emergency management if the infant becomes unwell including assessment at the local hospital as per b. below. Arrange face to face hospital review same or next working day
   ii. Arrange for the family to receive the 'MCADD is suspected' leaflet and MCADD A&E letter and contact details of the Specialist team.
   iii. Contact the paediatric team at the local or specialist hospital to inform them of the patient & make arrangements for assessment & management if the patient becomes unwell.
   b. If infant unwell/feeding poorly/doubts about clinical situation
   i. Specialist team instruct parents to go to local hospital or specialist hospital A&E
   ii. Specialist team to liaise with the hospital on call paediatric consultant (or Registrar) for assessment and initial management
   iii. Fax/email information to the hospital for clinicians & parents 'MCADD is suspected' leaflet and MCADD A&E letter and contact details of the Specialist team.
3. NSL informs Local Screening Coordinator

FIRST REVIEW: FACE-TO-FACE - within 24 hours of screening result

a. Well baby
i. Obtain diagnostic samples*** including DNA & send urgently to screening lab (courier). Inform lab.
ii. Ensure adequate feeding & dietetic review**** (emergency regimen & feeding review, advice on safe fasting times).
Iii. Ensure family have specialist/designated team contact details.
iv. Discharge home with A&E letter, appropriate leaflet ('MCADD is suspected'/confirmed), emergency regimen, BIMDG emergency guidelines & glucose polymer. Instruct to take to hospital if unwell.

b. Unwell baby
i. Obtain diagnostic samples*** including DNA & send urgently to screening lab (courier). Inform lab.
ii. Follow BIMDG emergency guidelines
iii. Before discharge ensure adequate feeding & dietetic review**** (emergency regimen & feeding review, advice on safe fasting times).
Iii. Ensure family have specialist/designated team contact details.
iv. Discharge home with A&E letter, appropriate leaflet ('MCADD is suspected'/confirmed), emergency regimen, BIMDG emergency guidelines & glucose polymer. Instruct to take to hospital if unwell.

Follow up to be arranged at specialist/designated centre within 5 working days, inform GP & send MCADD GP letter via fax/e-mail

* **MCADD initial clinical management guidelines** www.bimdg.org.uk

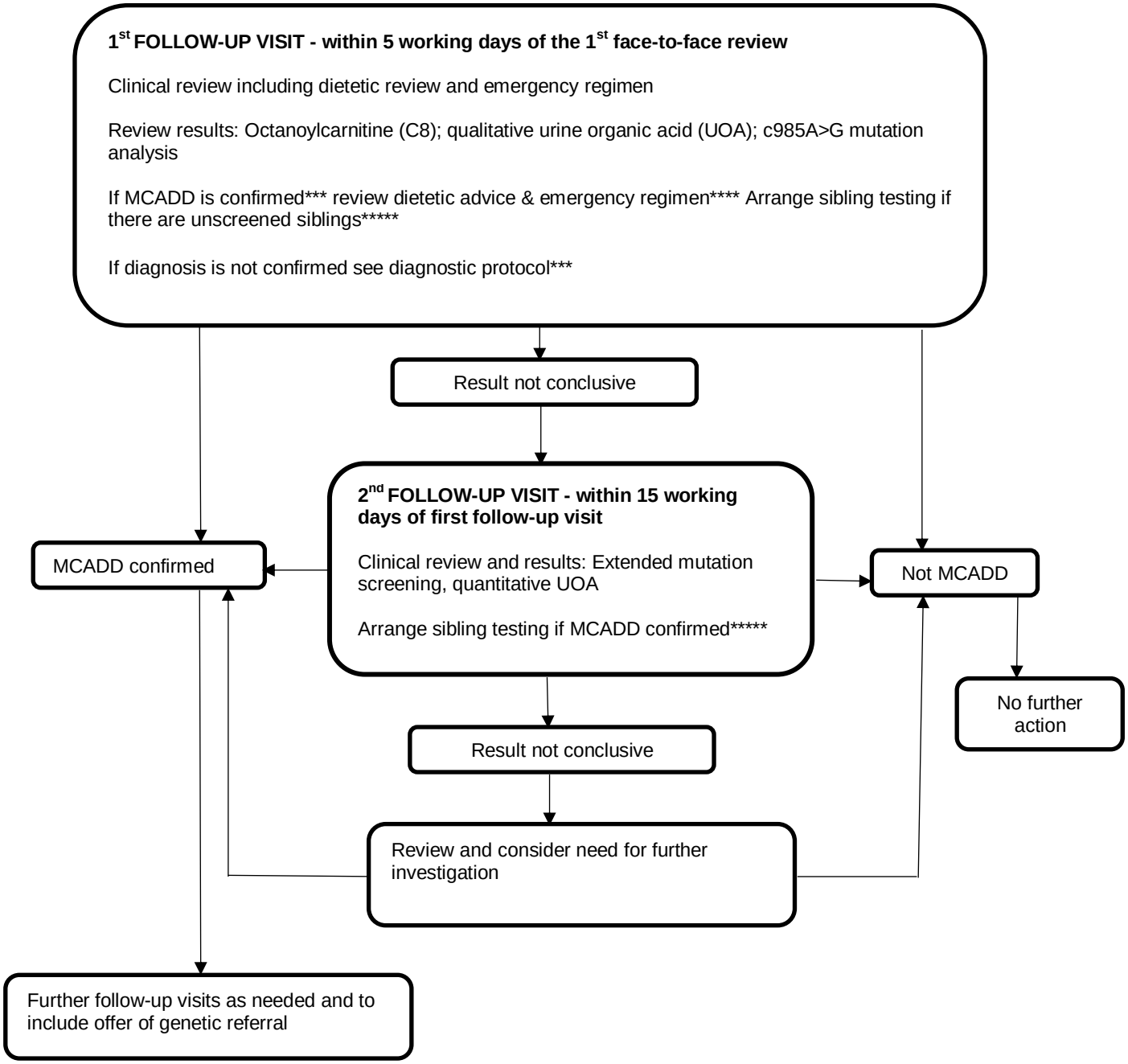
** **MCADD screening protocol** see Laboratory Guide for IMDs for details www.gov.uk/topic/population-screening-programmes/newborn-blood-spot

*** **MCADD diagnostic protocol** for confirmatory tests see Laboratory Guide for IMDs https://www.gov.uk/topic/population-screening-programmes/newborn-blood-spot

****MCADD Dietetic & Emergency Management guidelines www.bimdg.org.uk/guidelines/guidelines-child.asp

***** **MCADD sibling testing** see Laboratory Guide for IMDs for details www.gov.uk/topic/population-screening-programmes/newborn-blood-spot

MCADD Clinical referral pathway (continued)



MSUD Clinical Management Guidelines*

** MSUD 'Suspected'

ON THE SAME DAY

1. NSL informs Specialist team who will inform Designated team if required (depends on baby's address) to arrange urgent hospital admission
2. Specialist team to CONTACT FAMILY (if family CANNOT BE CONTACTED see Note 1 page 17.)
3. Specialist team to instruct family to go to appropriate hospital with 24 hr paediatric cover. Offer to arrange an ambulance.
4. If initial review not at Specialist Centre, Specialist team to liaise with the hospital (Designated or on call Paediatric Consultant)
   a. Fax/email information to the hospital for clinicians and parents, BIMDG MSUD guidelines, 'MSUD is suspected' leaflet contact numbers for the MSUD specialist team.
   b. Clinical assessment & admission to hospital **regardless of clinical status**
   Obtain blood gases, U&E, LFT, FBC, cultures, urine ketones dipstick, site IV cannula
   c. Hospital to liaise with clinical centre regarding clinical state
   d. Commence clinical management** (Specialist or Designated team)
      i. IV 10% dextrose/0.45% saline + added potassium infusion
      ii. Transfer to specialist centre. If GCS <8 intubate, ventilate & organise PICU retrieval
      iii. If transfer not possible same day, obtain diagnostic samples*** and send urgently to screening laboratory (courier) & inform lab
      iv. If transfer not possible same day, specialist team to organise supplies of MSUD Anamix Infant formula, isoleucine & valine sachets and feeding plan****
   e. Continue liaison between specialist & local hospital until transferred
5. NSL & Specialist team inform GP (as soon as is practicable), send MSUD GP letter via fax / email & copy to HV
6. NSL Informs Local Screening Midwife by phone

FIRST REVIEW within 24 hours of screening result
Ideally face to face, in exceptional circumstances via telephone/video conference/skype
Review diagnostic test results
(If at DGH do not discharge until review by specialist centre)

Alloisoleucine Positive?

Original NBS card Alloisoleucine Positive?

Yes

Yes

No

MSUD UNLIKELY
Presumptive false positive.
Investigate and treat
Exclude liver disease including galactosaemia.

Possible intermittent MSUD
Send for genetics/enzymology.
Manage as MSUD until result known.

MSUD CONFIRMED
Clinical management via specialist centre
Arrange sibling screening*****

* **MSUD initial clinical management guidelines**
www.bimdg.org.uk

** **MSUD screening protocol** see Laboratory Guide for IMDs for details www.gov.uk/topic/population-screening-programmes/newborn-blood-spot

*** **MSUD diagnostic protocol** for confirmatory tests see Laboratory Guide for IMDs
https://www.gov.uk/topic/population-screening-programmes/newborn-blood-spot

****MSUD Dietetic Management Pathway
www.bimdg.org.uk/site/guidelines-enbs.asp

***** **MSUD sibling testing** see Laboratory Guide for IMDs for details www.gov.uk/topic/population-screening-programmes/newborn-blood-spot

**IVA Suspected

ON THE SAME DAY

1. NSL informs Specialist team who will inform Designated team, depending on baby's location, to arrange urgent hospital admission.
2. Specialist team to CONTACT FAMILY (if family CANNOT BE CONTACTED see Note 1 page 17.)
3. Specialist team to instruct family to go to specialist centre – if not possible to go to appropriate hospital with 24 hr paediatric cover. Offer to arrange an ambulance
4. If initial review not at Specialist Centre, Specialist team to liaise with the hospital (Designated or on call Paediatric Consultant/Registrar) for assessment.
   a. Fax/email information to the hospital for clinicians and parents, IVA A&E letter, 'IVA is suspected' leaflet contact numbers for the IMD specialist team.
   b. Commence clinical management:

A. Well baby

   i. Obtain diagnostic samples*** and send urgently to screening laboratory (by courier) inform lab
   ii. Ensure adequate feeding & obtain history of maternal antibiotics, nipple cream use & full drug history (cause of false positive)
   iii. Discharge home with BIMDG emergency guidelines & glucose polymer. Instruct to take to hospital if unwell

B. Unwell baby

   i. Clinical assessment & admission to hospital **regardless of clinical status**
   ii. Obtain history of maternal antibiotics, nipple cream use & full drug history (cause of false positive)
   iii. Obtain blood gases, ammonia, U&E, LFT, FBC, cultures, urine ketones dipstick. Site IV cannula.
   iv. Hospital to liaise with specialist team regarding clinical status
   v. Obtain diagnostic samples*** and send urgently to screening laboratory (by courier) inform lab
   vi. IV 10% dextrose/0.45% saline infusion
   vii. Carnitine - specialist centre to organise supply and send to local hospital if necessary.
   viii. Reintroduce natural protein within 24-48 hours (refer to **IVA dietetic management pathway******)
   ix. Transfer to specialist centre as soon as appropriate
5. Hospital to feedback to specialist team with a review within 2 hours of admission if not already transferred
6. NSL inform GP, send IVA GP letter via fax / email copy to HV
7. NSL inform Local Screening Midwife by phone

FIRST REVIEW with parents within 24 hours of screening result
If not already seen in specialist centre, speak directly via telephone or other communication
Review available test results.
Re-introduce natural protein within 24-48 hours, refer to dietetic management pathway ****
(If inpatient at DGH do not discharge until agreed by specialist centre)

WELL BABY
Specialist team to review face to face within 5 working days of diagnostic sampling with the results.

UNWELL BABY
Specialist team to review face to face as soon as is practicable with the available results. Arrange to feedback remaining results by 5 working days of diagnostic

Plasma C5 ≥ cut off
Urine IVG normal
Urine MBG normal

Uncertain

Repeat investigation

Effect of antibiotics (Pivalate)

Check pivalate result from initial screening result

Plasma C5 ≤ cut off
Urine IVG normal
Urine MBG normal

Screen false positive

IVA UNLIKELY
No treatment needed - discharge

Plasma C5 ≥ cut off
Urine IVG normal
Urine MB increased

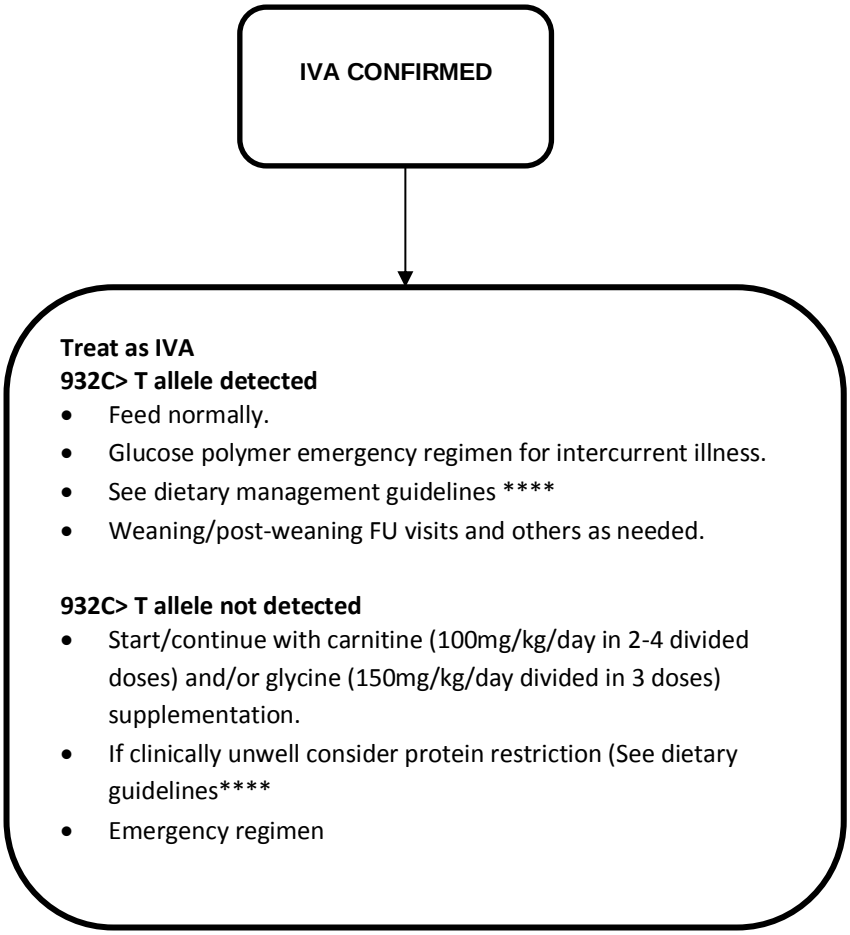
Short/branched chain acyl-CoA dehydrogenase deficiency (SBCAD).

Long term FU. No ER

Plasma C5 ≥ cut off
Urine IVG increased
Urine MBG normal

IVA CONFIRMED
Treat as IVA (refer to dietetic & clinical management guidelines)
Arrange sibling screening*****
if IVA confirmed **PTO**

IVA Clinical Management guidelines* (continued)



* **IVA initial clinical referral guidelines and standards** www.bimdg.org.uk

** **IVA screening protocol** see Laboratory Guide for IMDs for details www.gov.uk/topic/population-screening-programmes/newborn-blood-spot

*** **IVA diagnostic protocol** for confirmatory tests (Laboratory Guides for IMDs) https://www.gov.uk/topic/population-screening-programmes/newborn-blood-spot

**** **IVA dietetic management pathway** for details see www.bimdg.org.uk/site/guidelines-snbs.asp

***** See **IVA sibling testing -** Laboratory Guide for IMDs for details www.gov.uk/topic/population-screening-programmes/newborn-blood-spot

GA1 Clinical Management Guidelines*

****GA1 Suspected**

ON THE SAME DAY

1. NSL informs Specialist team who will inform Designated team if required (depends on baby's address).
2. Specialist/Designated team CONTACT FAMILY. Note parents should NOT be informed of a positive result if an appointment cannot be given for the same or next day e.g. parents should not be informed on a Friday unless an appointment is for that day or the Saturday. In this case contact should be deferred until after the weekend to the next working day.
3. Specialist team to organise review at specialist centre same day/next day.
4. If unwell, liaise with local hospital for review & management
5. NSL & Specialist team inform GP (as soon as is practicable), send MSUD GP letter via fax / email & copy to HV
6. NSL Informs Local Screening Midwife by phone

FIRST REVIEW: FACE-TO-FACE - within 24 hours of family contact

1. Consent for DNA testing to be obtained
2. Take diagnostic samples*** and send to screening lab by courier. Inform Lab.
3. Ensure adequate feeding
4. Provide BIMDG emergency guidelines & glucose polymer. Instruct to take to hospital if unwell

Within 5 working days of diagnostic samples
Review available results and communicate with family

Biochemisty abnormal

Yes

No

Arrange 1st FOLLOW-UP VISIT - within 5 working days of the 1st face-to-face review

Arrange 1st FOLLOW-UP VISIT – with DNA results within 15 working days of the 1st face-to-face review

GA1 CONFIRMED

Yes

No

Treat as GA1 (refer to dietetic and clinical management guidelines)
Arrange sibling screening if GA1 confirmed*****

Follow diagnostic protocol***

* **GA1 initial clinical management guidelines** www.bimdg.org.uk

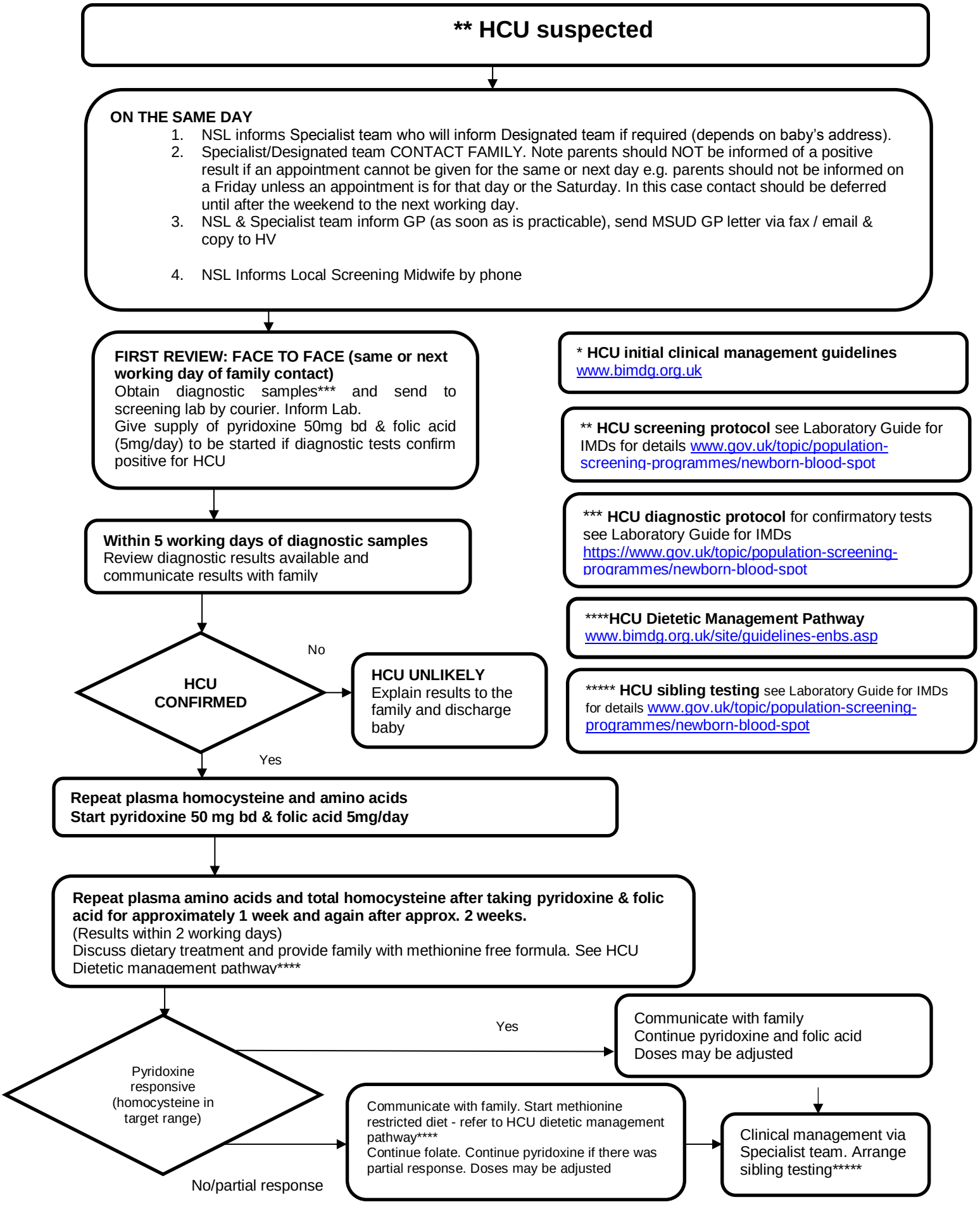
****GA1 screening protocol** see Laboratory Guide for IMDs for details www.gov.uk/topic/population-screening-programmes/newborn-blood-spot

*** **GA1 diagnostic protocol** for confirmatory tests see Laboratory Guide for IMDs https://www.gov.uk/topic/population-screening-programmes/newborn-blood-spot

******GA1** Dietetic Management Pathway www.bimdg.org.uk/site/guidelines-enbs.asp

***** **GA1 sibling testing** see Laboratory Guide for IMDs for details www.gov.uk/topic/population-screening-programmes/newborn-blood-spot

HCU Clinical Management Guidelines*



6 Training and education

Training resources for the screening programme can be accessed via the following links:

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https://www.gov.uk/guidance/nhs-population-screening-education-and-training

https://portal.e-lfh.org.uk/

Other useful resources can be found on the NHS Screening Programmes Website www.gov.uk/topic/population-screening-programmes/newborn-blood-spot

A local policy for education and training reflects National Guidance and should include the following:

Policy	**Local arrangements**	**Professional responsible**
1. Provision of an education and training programme for all healthcare professionals involved in the screening process, where appropriate utilizing tools and media provided by the PHE screening.	*All newly employed healthcare professionals involved in the screening process will have training in the Trust's newborn blood spot screening programme as part of their induction programme.* *All healthcare professionals involved in the screening process will undertake an annual update session.*	** [e.g. Local screening coordinator /practice development midwife, HV, lead paediatrician, dietitian].* *Update training sessions to be organized by *.* *All healthcare professionals responsible for ensuring annual update undertaken.*
2. All education and training provided should be evaluated and audited, where appropriate utilising tools and media provided by the PHE screening.	*A record of attendance of training will be maintained.*	**[e.g. Local screening coordinator /practice development midwife, HV, lead paediatrician, dietitian].*
3. Annual review of	*Review of training needs will be undertaken.*	** [e.g. Local screening coordinator /practice development midwife, HV,*

Policy	**Local arrangements**	**Professional responsible**
training needs.		*lead paediatrician, dietitian].*

7. Quality Management and Clinical Governance

Policy	Rationale	Local arrangements	Professional responsible
1. The clinical governance group [*insert local name*] is responsible for arranging release of audit data to identified regional and national screening teams in line with Caldicott and Governance arrangements.	To monitor compliance and adherence to national standards and assist in future strategic planning and commissioning of screening services.	*[insert local arrangements].*	*Local Clinical Steering Group.*
2. Policies and procedures for the management and reporting of incidents arising from the screening programme should be in place and be consistent with NHS England guidance: Managing Safety Incidents in NHS Screening Programmes https://www.gov.uk/government/publications/managing-safety-incidents-in-nhs-screening-programmes	To ensure safe and coherent screening for the population in accordance with the national service specification.	*[insert local arrangements].*	*Local Clinical Steering Group.*
3. Provision of appropriate information for inclusion in national or local registers/audits must be provided.	To assist in the monitoring of the outcomes of screening and incidence of IMD.	*[insert local arrangements].*	*[*name of identified lead*].*
3. The clinical steering group [*insert local name*] is responsible for ensuring appropriate links are in place with the Regional Newborn Blood spot Screening	To enable effective performance management and	*[Insert names of groups and links and attendance requirements*].	*

Policy	**Rationale**	**Local arrangements**	**Professional responsible**
Operational Management Group and input to/review the output from the Annual Regional Newborn Screening Governance Group	quality assurance of locally delivered screening programmes.		
4. All stakeholders (Acute Trust, CCG, CHRD, PHE) must contribute to the newborn screening annual audit pertaining to the previous fiscal year	All stakeholders have access to information regarding the screening programme.	*[insert local arrangements for production of report].*	*

8 Regional contacts

Team	Name	Email
Screening and Immunisation Lead, Public Health England,	Dr Alison MacKenzie	alison.mackenzie6@nhs.net
Screening and Immunisation Managers, Public Health England	Mr Matthew Dominey Mr Daniel Messom	matthew.dominey@nhs.net daniel.messom@nhs.net
Director of Bristol Newborn Screening Laboratory	Dr Helena Kemp	Helena.Kemp@nbt.nhs.uk
Principal Clinical Scientist Newborn Screening Laboratory	Leila Cornes	Leila.Cornes@nbt.nhs.uk
IMD Specialist Team:		
Consultant Metabolic Paediatricians	Dr Germaine Pierre Dr Effie Chronopoulou	Germaine.Pierre@UHBristol.nhs.uk Efstathia.Chronopoulou@UHBristol.nhs.uk
Regional Metabolic Dietitian	Camille Newby	Camille.Newby@UHBristol.nhs.uk
Regional Metabolic Specialist Nurse	Katie Smith	Katie.Smith5@UHBristol.nhs.uk
Regional Quality Assurance Team ANNB (South West) Public Health England		
Senior Quality Assurance Advisor	Siobhan O'Callaghan	so'callaghan@nhs.net
Quality Assurance Advisors	Maggie Denholm	maggie.denholm@nhs.net
	Sharon Evans	Sharonevans1@nhs.net
Regional Biochemical Genetics Diagnostic Laboratory	Dr Helena Kemp	Helena.Kemp@nbt.nhs.uk
CLIMB		www.climb.org.uk

9 Local contacts [*insert local team]*

Team	Name	Email
Local Public Health Lead		
Local Screening Coordinator		
Local designated MCADD Specialist Team: Lead Paediatrician Lead Dietitian		
Local HV Lead Local Biochemistry Laboratory Lead Local Child Health Records Department contact		