Management of PKU

February 2004

A consensus document for the diagnosis and management of children, adolescents and adults with phenylketonuria

NSPKU
The National Society for Phenylketonuria (United Kingdom) Limited

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Second edition April 1999
This edition Februaryy 2004 ISBN: 0 9535550 0 3

Published by The National Society for Phenylktonuria
P.O. Box 26642, London N14 4TD

The following comments have been received on the Management of PKU.

"I especially welcome its inclusion of the needs of adolescents and adults.

The publication of this document is most timely as it fits in well with work which the Department is carrying out in conjunction with the National Screening Committee for implementation of quality assurance management procedures for PKU screening. Your document provides a most valuable guideline which can be used as part of this process."

Professor Liam Donaldson
Chief Medical Officer

"The Paediatric Group of the British Dietetic Association support its production and distribution and are happy to endorse the contents without amendment."

Paediatric Group of the British Dietetic Association

"It is an impressively produced job and should help to raise the profile of the disease and its treatment."

R.J. Pollitt
Director of Neonatal Screening (Trent Region)

"I do like the document which has just the right amount of detail to appeal to colleagues and Trust Executives."

Dr. Godfrey Gillett
Consultant Chemical Pathologist

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2 Executive Summary

A CONSENSUS DOCUMENT FOR THE DIAGNOSIS AND MANAGEMENT OF CHILDREN, ADOLESCENTS AND ADULTS WITH PHENYLKETONURIA

The treatment of phenylketonuria (the most common inborn error of protein metabolism), an inherited metabolic disorder, is one of the great success stories of the last thirty years. Prior to the introduction of an effective national screening programme in 1969, most affected children sustained irreversible brain damage before diagnosis. Today, babies born with the disorder can expect to have the same career and social ambitions as normal unaffected people.

As knowledge about early treatment in phenylketonuria has grown, and the care of patients has improved, a national minimum standard of care should be provided. This document outlines the views of the Medical Advisory Panel of the NSPKU and provides a framework for the provision of this minimum standard.

The document firstly lists the aims of treatment. The screening, testing and reporting of results, followed by sensitive handling of positive results by a professional with current knowledge, is highlighted. The biochemical monitoring from first diagnosis to adulthood follows, with the acceptable phenylalanine concentrations for given ages.

The management of phenylketonuria in childhood requires a multidisciplinary approach across the hospital community interface.

The success of treatment means that there is now a generation of responsible young adults who have grown up largely unaffected by the disorder. We are just beginning to understand the later effects of phenylketonuria on the adult and adolescent brain, and, consequently, their continuing care is important and has to be provided within the adult service.

The needs of female patients are of particular importance because of the associated risks of pregnancy in the untreated mother with phenylketonuria. Untreated phenylketonuria will almost invariably lead to miscarriage or severe fetal damage should the pregnancy proceed. Strict control of the diet prior to conception is essential to prevent significant fetal damage and is essential if the benefits to one generation are not lost to the next.

Finally, the needs of handicapped phenylketonuric patients born before effective national screening was established provide a challenge. Evidence suggests that some of these patients may benefit from dietary intervention or treatment. Although the brain damage is irreversible, considerable improvements in behaviour have been observed, enabling these patients to lead a more fulfilling and happier life while easing the burden of carers.

3 Aims

This document has been compiled by the Medical Advisory Panel of the National Society for Phenylketonuria (NSPKU) and sets out the standards of practice and management which are considered to be reasonable and attainable in the management of phenylketonuria. A broad-based consensus approach has been taken as it is recognised that there is wide national variation in aspects of management. The Medical Advisory Panel recognises that there are constraints upon the resources of purchasers and providers, but, nonetheless, would wish to focus on ideal standards of care.

- To specify the services required for the management of phenylketonuria from diagnosis by neonatal screening to adulthood including pregnancy;
- To outline the general rather than the specific principles of management;
- To provide evidence-based advice where possible while recognising that much of current treatment is based upon clinical experience;
- To clarify the disciplines and professions which care for patients with phenylketonuria and define their respective roles and responsibilities;
- To increase the awareness of purchasers and providers about phenylketonuria, and to produce guidelines to assist health authorities to define standards of care which the family and child can reasonably expect to receive;
- To ensure equity of access to services for phenylketonuria according to needs assessment;
- To ensure that specialist expertise is provided for adults and children and to recognise the multiple clinical interfaces, i.e. between general practitioner and paediatrician and adult physician;
- To reduce the risk of neurological damage by the effective control of plasma phenylalanine concentrations by dietary means and to ensure that children with phenylketonuria achieve maximal developmental potential;
- To encourage the maintenance of dietary and clinical supervision throughout life;
- To ensure that all girls and women with phenylketonuria are aware of the need for good dietary control preconceptually and throughout pregnancy;
- To ensure full recognition of the prescribing implications now that diet for life is encouraged;
- To ensure that parents are fully informed and have access throughout life to clearly written and regularly updated information on phenylketonuria, provided by health professionals, specialist centres and parent support groups.

4 What is PKU?

4.1 Background

Phenylketonuria is the most common inborn error of protein metabolism with an incidence of approximately 1 in 10,000 births (1 in 4,500 in Northern Ireland). If not correctly treated from soon after birth it results in severe mental handicap. Treatment by restricted dietary intake of phenylalanine (protein) has been shown to be effective. In the relatively short history of phenylketonuria, increasing knowledge, coupled with continual improvements in treatment, has resulted in the possibility of an excellent outcome for today's patient.

More recently, new problems have emerged, those of late neurological sequelae and fetal damage in mothers with phenylketonuria and, with these, the need to continue the multidisciplinary management approach into adult life.

In the UK, the provision of services for the treatment of phenylketonuria varies widely from centralised clinics and specialist teams to patient management by a local family practitioner working in isolation. Approximately 50% of phenylketonuric children are managed in non-specialist centres.

The Medical Advisory Panel believes that services should be provided or co-ordinated from a specialist multidisciplinary team based upon a regional centre, but recognise that geographical considerations may make it difficult for parents to attend specialist centres regularly.

4.2 Multi-Disciplinary Team

In the life-long management and supervision of phenylketonuria the following health care professionals make an important contribution. The responsibilities and roles of team members will inevitably overlap.

The specialist team should include:

- Paediatric dietitian/adult dietitian with experience of phenylketonuria and metabolic disease;
- Biochemist/chemical pathologist with responsibility for neonatal screening and biochemical monitoring;
- Clinical nurse specialist;
- Consultant paediatrician/adult physician with knowledge and experience in metabolic disease;
- Social worker;
- Clinical psychologist;
- Obstetrician/gynaecologist.

Specialist Teams based upon regional centres should be able to provide a multidisciplinary approach, ideally linked with screening centres, and should manage a minimum number of around 20 patients. A paediatric dietitian and a metabolic biochemical monitoring service are essential elements of the team approach offered by regional centres.

The team should work closely with local practitioners, general paediatricians and other agencies, and produce jointly protocols for collaborative management which should be regularly reviewed and updated according to audit principles.

5 Neonatal Screening

5.1 Requirements

The fundamental aim of screening is the early detection of phenylketonuria to allow the initiation of dietary treatment and the prevention of mental retardation and later morbidity.

The framework and guiding principles of the present neonatal screening programme for phenylketonuria were contained in the guidance note issued by the Department of Health in 1969 which specified that:

- Screening should be performed on a blood sample taken between the sixth and fourteenth days of life;
- Laboratory testing of blood specimens should be centralised and co-ordinated with facilities for confirmation of diagnosis and treatment;
- There should be a recording and tracing system to ensure that all babies are tested and results made known;

Although the organisation of the NHS has altered significantly since screening began, the basic principles of screening remain unchanged. However, there may, in the future, be a need for an earlier screening test to accommodate screening tests for other disorders.

A series of audit standards for the various steps in the process have been defined and should be ideally incorporated into service contracts for NHS providers.

Audit standards may include those listed below:

5.1.1 Collection of specimen

Parents should be provided with written information about the nature of the test and offered a verbal explanation. All babies should be sampled within 6-14 days of birth. Blood samples must be dispatched promptly to the screening laboratory. There must be a process for the collection of repeat samples. A low proportion of babies may require a repeat sample because of insufficient blood on the first collection

5.1.2 Laboratory Testing

The screening laboratory should comply with national standards for analytical performance and be validated by external quality control schemes, and should hold or be working towards accreditation. Babies with abnormal results must be referred rapidly for further investigation and treatment.

5.1.3 Child Health Systems

There must be routine checking that all babies have been screened and coverage to be completed by twenty-eight days of age. Normal screening results should be reported to the parents through the health visitor or midwife. Abnormal results following confirmation should also be notified to the PKU Register.

5.2 Diagnosis of Phenylketonuria

All positive results should be communicated by face-to-face contact to the family from a designated health professional who must have current knowledge of phenylketonuria. This task may be undertaken by a clinical nurse specialist who has been trained and is part of the multidisciplinary team.

In the event of a positive test arrangements need to be made for immediate follow up within twenty-four hours. This should include referral to a consultant paediatrician in a specialist centre who has an expert knowledge of phenylketonuria and immediate access to supportive health professionals and laboratory services.

All positive screening tests must be confirmed with a quantitative measure of phenylalanine on a repeat specimen of blood and investigations undertaken to exclude the possibility of a defect in biopterin metabolism.

Dietary treatment should commence as soon as the diagnosis is confirmed

Following confirmation of the diagnosis of phenylketonuria, the extent of shared care should be agreed between the specialist centre, the district general hospital and the local family doctor.

Centres undertaking screening should ideally be responsible for the monitoring of phenylalanine during treatment. However, in all monitoring laboratories suitable analytical methods should be employed to ensure appropriate accuracy of testing and laboratories should participate in a national quality assurance control scheme. Results should be available in a timely fashion, i.e. within three working days of sample receipt in the laboratory. Reporting mechanisms should ensure that the results and copies be provided for the paediatrician, dietitian or a locally identified co-ordinator within each centre.

5.3 Biochemical Monitoring of Phenylketonuria in Childhood

The following recommendations are based upon the report of the MRC Working Party (1993) on Phenylketonuria. The MRC publication "Recommendation on Dietary Management of Phenylketonuria" is a valuable document which attempts to set out standards for the clinical management of phenylketonuria

5.3.1 Frequency of Monitoring

0 – 6 months, weekly
6 months - 4 years (school entry), fortnightly
thereafter monthly

More frequent blood samples may be sent in older children if the parents wish or if the phenylalanine concentrations are high or abnormally low.

5.3.2 Type of Specimen

Phenylalanine concentrations can be measured on liquid blood or dried blood spots. In order to make frequent monitoring practicable, carers should be trained to take blood samples at home which can then be posted to a laboratory with expertise in accurate micro-methods for phenylalanine measurement.

5.3.3 Desired Blood Phenylalanine Levels in Treated Phenylketonuric Patients

The acceptable range of phenylalanine is based upon the MRC report

0 – 5 years, 120 - 360 µmol/l
greater than 5 years, 120 - 480 µmol/l
greater than 10 years, 120 - 480 µmol/l

However, dietary compliance becomes more difficult in children over ten years and higher values up to 700 µmol/l can be accepted. Parents and adolescents should be aware that performance of specific tasks may be impaired at the higher phenylalanine concentrations.

5.3.4 Additional Biochemical Monitoring of Nutritional Status

This complements the clinical assessment of nutrition and anthropometry. Periodic testing is indicated if there are concerns about nutritional inadequacies. It may be appropriate to measure plasma vitamin and mineral concentrations. Vitamin B12 concentration should be measured annually in adolescents and adults on a diet in which protein intake is low, but who are not taking amino acid supplements.

6 Management of Phenylketonuria in Childhood (excluding adults and maternal PKU)

This requires a multidisciplinary approach across the hospital/community interface. Professional roles and responsibilities vary throughout the country and local practices have evolved according to the availability and expertise of health care professionals.

All those involved in the care and management of Phenylketonuria are expected to take part in research as necessary.

6.1 Role of Dietitian

- It is essential that a senior dietitian with experience in paediatrics and phenylketonuria cares for children with phenylketonuria and provides ongoing continuity of care. Ideally, the dietitian should care for a minimum of fifty patients.
- Initial teaching of parents in the dietary principles of the management of phenylketonuria – the parents need to be aware from an early stage that life long dietary treatment is probable.
- The dietitian has a key role in assuring nutritional adequacy of the diet, monitoring growth and supporting the family at key stages, e.g. early feeding, weaning and school entry.
- Education (family and school) and ultimately for the transfer of diet responsibility to the child. (This should include awareness of the need for preconceptual treatment in girls).
- Liaison with the family on results of biochemical monitoring, etc.
- Liaison with:
  the school on packed lunches, menu, etc;
  the general practitioner and community pharmacist on special products, food list and prescriptions;
  paediatrician with interest in metabolic disease and
  health visitor.
- Home visiting by dietitian should be encouraged. Although resource intensive, this enables a more accurate assessment of patients in their own environment.
- Regular adjustment of diet according to biochemical control and provision of advice on free food list, phenylalanine exchanges, amino acid supplements, etc.
- Development, revision and dissemination of written dietetic resources to families and relevant health professionals.
- Treatment during pregnancy may need to be provided by the paediatric dietitian in the absence of an effectively established adult antenatal service.

6.2 Role of Paediatrician

The fundamental and principal role of the paediatrician is to liaise and co-ordinate the activities of the other health care professionals. The paediatrician should have a specialist knowledge of metabolic disease in childhood, work in a specialist centre where there is expertise in paediatric dietetics and laboratory support for the monitoring of phenylalanine concentrations. In some areas of the country shared care with a local paediatrician would be appropriate.

- To organise regular clinical review and support. The outpatient schedule of attendance will vary, but the following option is considered to be a minimal requirement. More frequent review may be helpful during the early years;

  less than 2 years – 3 monthly review
  less than 5 years – 4 monthly review
  greater than 5 years – 6 monthly review

- To provide basic genetic counselling;
- To educate the parent and child by the provision (at relevant times) of written information and advice;
- To ensure that girls with phenylketonuria have an awareness from an early age of the need for preconceptual treatment;
- To monitor biochemical control by ensuring the regular measurement of phenylalanine concentrations at home or in the clinic;
- Many phenylketonuric patients and their carers collect samples at home. This requires the provision of sample cards, blood sampling equipment, initial training in the technique of sample collection and the establishment of a communications system in order that the results may reach the patient/carer in a timely manner;
- To ensure access to other specialist services according to need;
- To ensure that all patients are registered with the National PKU Register;
- To consider and advise on issues of education, careers and employment;
- To monitor growth and development;
- To liaise with the general practitioner on product prescription.

6.3 Role of Biochemist

- To organise biochemical testing as part of the definitive diagnosis of phenylketonuria, e.g. quantitative phenylalanine biopterins;
- To provide timely biochemical monitoring for clinical management and appropriate advice;
- To provide input into the multidisciplinary team providing patient management;
- To provide support for a home monitoring blood collection service;
- To ensure that patients are registered with the National PKU Register.

6.4 Role of Clinical Nurse Specialist

A specialist nurse (health visitor) with experience and knowledge of all aspects of phenylketonuria is available in certain centres. Such a post should be established in each specialist centre to provide an outreach service from the hospital to the community;

- To liaise with other health professionals about initial diagnosis and ongoing care;
- To provide initial contact with the parent (if possible by joint visit with GP) following the positive screening result;
- To teach the method of blood sampling for home monitoring;
- To provide a supportive role in early childhood;
- To provide sex education, family planning advice and preconceptual counselling in collaboration with others;
- To provide families with information regarding national and local support groups;
- To support patients not attending a specialist centre, in collaboration with their consultant and dietitian;
- To support pregnant females;
- To undertake relevant clinical research.

6.5 Role of Psychologist

Children with classical PKU represent a high risk group for impairment of intellectual function. As the ultimate goal of treatment is the prevention of mental deterioration, it is essential that the developmental course of the child is closely monitored. Children with PKU should be studied individually by means of serial psychometric assessments and evidence sought for results that might be attributable to fluctuating phenylalanine levels. Treatment by dietary restriction involves considerable modification of normal eating behaviour by the child and cooking behaviour by the carer. Motivation to comply with diet depends on psychological factors such as knowledge of the condition, understanding of the treatment goal, reassurance that the diet is working successfully and resistance to peer and other pressures to deviate from the strict regimen. There are thus psychological aspects to both measurement and maintenance of treatment, the clinical psychologist's role being primarily:

- To provide serial developmental assessments from infancy to adolescence;
- To determine the extent to which indices of development reflect phenylalanine control as opposed to psychosocial or other factors;
- To assist patient and parent understanding of the need for dietary treatment;
- To foster patient and parent motivation to comply with treatment;
- To liaise with educational psychology services over matters of scholastic learning and behaviour that might be related to phenylketonuria or its treatment.

6.6 Role of Social Worker

- To inform families of national and local support groups;
- To review benefits to which the family may be entitled.

Other Professional Roles (those not part of the team)

6.7 Role of General Practitioner

The family doctor is responsible for the co-ordination of care within the community and the overall management of the child and family;

- To ensure the prescription of special products, protein substitutes and low protein foods in sufficient quantities to obviate the need for frequent attendances and repeat prescriptions;
- To ensure effective liaison with all health care professionals;
- To ensure that adolescents and adults with phenylketonuria have access to specialist services;
- To advise on family planning and refer for preconceptual management.

6.8 Role of Health Visitor and Midwife

- The responsibility of health visitors and midwives for screening is subject to regional variation;
- To undertake the collection of initial and/or repeat blood samples for neonatal screening and to despatch these expeditiously;
- To provide information to mother and family at the time of initial sample collection as to the nature of the test (leaflets are available);
- To confirm that all babies have had a neonatal screening test and that the negative result is recorded within the child's health record according to locally agreed procedures;
- To act as liaison between the hospital and community.

6.9 Genetics

PKU is inherited as an autosomal recessive disorder. Couples who have an affected child have a one in four recurrance risk for each further pregnancy. Some families may want formal genetic counseling and should be referred to a clinical geneticist.

More than 400 mutations have been reported in the phenylalanine hydroxylase gene. Some mutations are known to be associated with a severe phenotype and others with milder disease.

Prenatal diagnosis is usually possible in pregnancies at risk of PKU. Genetic analysis must already have been undertaken on the affected child and both parents. Ideally, both mutations should have been identified. If this is not possible, polymorphic markers within the gene usually allow gene tracking of the high risk allele. Genetic analysis should be undertaken prior to pregnancy in families who think they might want prenatal diagnosis. The results of prenatal tests can then be available within about 48 hours.

6.10 Role of Support Groups

These groups provide an opportunity for families to meet others with phenylketonuria. They offer social and practical support through the exchange of ideas and information on diet, etc., via newsletters, conferences. They provide a forum to lobby nationally on behalf of patients for an equitable share of health care resources for the management of phenylketonuria.

7 Adults & Adolescents

Special Considerations

7.1 Clinics for adults and adolescents

These exist in only a few centres in the UK and provide for the transfer of care of children with phenylketonuria to the adult sector. An adult/adolescent clinic is the ideal. This should be run jointly by a paediatrician and an adult physician both with an interest in metabolic disease, within an adult hospital and with a dedicated dietitian in attendance. Access to biochemical monitoring is required. Paediatric specialist centres should consider, in collaboration with purchasers, a strategy for the provision of long term services for patients with phenylketonuria. Where it is current practice to care for adults and adolescents in paediatric centres this should continue until effective alternatives have been established.

7.2 Frequency of attendance at adult clinics

This will depend upon the degree of dietary restriction. Patients on diet should be reviewed every six months. Patients not on diet still require clinical review and should be seen annually, in view of reports of neurological impairment in a minority of patients. Vitamin B12 concentrations should be measured annually in adolescents on a protein restricted diet without amino acid supplements.

7.3 Prescription Charges of Adults and Adolescents

These become payable after the sixteenth birthday with exemptions for those unemployed, in higher education or pregnant. Prescription charges create difficulties for many families particularly for preconceptual treatment. Adults will require advice about the most cost effective way to meet prescription charges.

7.4 Diet for Life

The need for lifelong dietary treatment is a difficult issue and there is no clear evidence which provides overwhelming support for this suggestion. Nevertheless, certain experts maintain that phenylalanine restriction should be lifelong whereas others advocate that after a full and informed discussion the patient needs to decide. This approach demands that the doctor or counsellor has current and expert knowledge. No matter whether the patient decides to continue or terminate the diet, regular annual clinical review is essential.

7.5 Preconceptual Counselling

Counselling of mothers before pregnancy on fetal risks associated with a high plasma phenylalanine concentration is essential. Ideally, preconception treatment and family planning advice should be given by the paediatrician and clinical nurse specialist before transfer to an adult clinic. Reinforcement of this advice and the provision of written information is necessary throughout adolescence. Later, at the adult clinic, specific risks of congenital malformation and intellectual impairment in the offspring should be fully explained.

7.6 Maternity Care

Phenylketonuric women and partners wishing to start a family should be seen by clinical and dietetic experts at a specialist centre or adult clinic. Reintroduction of diet or the re-establishment of strict dietary control is essential before conception. The aim of dietary treatment is to keep the mother's blood phenylalanine concentration between 60 and 240 µmol/l, prior to conception and throughout the pregnancy. The dietitian will require to teach the principles of dietary protein restriction and provide practical advice on diet preparation and the use of food lists, particularly if mother has not recently had a protein restricted diet. Arrangements will require to be made for regular blood testing. Ideally, blood phenylalanine should be measured at least weekly during the pregnancy. Full amino acid profile, vitamins, minerals, trace elements and full blood count should be measured monthly. Antenatal admission may be necessary for dietary stabilisation. Fetal ultrasound and scanning should be scheduled as per routine unless there are clinical concerns about intrauterine growth retardation.

7.7 Offspring of Mother with Phenylketonuria

Offspring of mothers with phenylketonuria should be assessed for phenylketonuria as per the routine neonatal screening programme at six to fourteen days. Initial examination of the infant should be by a neonatologist aware of the clinical features of infants born to mothers with phenylketonuria. Psychologists should conduct assessments at one, four and eight years, and results should be notified to the PKU Register. Clinical follow up should be by a paediatrician with an interest in phenylketonuria and metabolic disease.

7.8 Dietary Treatment of the Untreated Adult with Phenylketonuria

Older patients who may never have had dietary protein restriction or have only been treated for a brief period, create special practical problems of management as many have learning difficulties and behavioural problems. The role of dietary protein restriction and treatment in these patients is uncertain. There appears to be no clear data as to who will benefit from diet. Starting restrictive diet after brain damage will not reverse damage, but current research indicates that the diet may be beneficial in other ways. Case studies have shown that there may be improvement in observed behaviour with reduced aggression, self injurious behaviour and hyperactivity, with more positive moods and increased social awareness, together with an increased attention span. Current research also suggests that approximately half of untreated adult patients may show clinical benefit. However, untreated adults who have previously been on a normal or free diet may find the restrictive nature of the diet difficult to accept, and staff and carers will need to be trained to cope with the preparation of the diet and subsequent monitoring to ensure compliance. Therefore, the diet should only be given to patients under close medical supervision (dietetic involvement is essential). Prior to implementation a base-line for behaviour, mental functioning, nutritional intake and phenylalanine concentrations should be established. Establishing a low phenylalanine diet in the untreated adult phenylketonuria is difficult, but may be worthwhile. However, the full implications of cost, monitoring and dietary compliance need to be fully considered.

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Appendix

1 The PKU Register:

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Produced by the National Society for Phenylketonuria
and its Medical Advisory Panel.

NSPKU

The National Society for Phenylketonuria (United Kingdom) Ltd.

The Society is a registered charity.
It offers support to PKUs and their families by producing various publications including a quarterly newsletter, organising formal and informal meeting and conferences.

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http://web.ukonline.co.uk/nspku April 1999/3k