

# **Australasian consensus guidelines for the management of phenylketonuria (PKU) throughout the lifespan**

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## **ABSTRACT**

*Objective:* To provide strategy to metabolic clinics in Australia and New Zealand (Australasia) for the consistent management of phenylketonuria (PKU) throughout the lifespan.

*Methods:* In response to a request from the Metabolic Dietary Disorders of Australia (MDDA) to develop standardised guidelines for the management of PKU, a working party was formed by the Australasian Society of Inborn Errors of Metabolism (ASIAM) with membership from each centre that manages PKU within Australasia. The working party included consultant metabolic physicians, metabolic dietitians, a metabolic fellow in training, a metabolic nurse practitioner and a laboratory scientist. From January to March 2016, a non-systematic review of the literature was undertaken on the management and monitoring requirements of PKU. A summary of the literature including the recommendations was then circulated for comment from other Australasian health professionals working with individuals with PKU.

*Results:* Feedback was reviewed, collated and included in this guideline document for ASIAM endorsement and implementation across Australasian clinics. The detailed and specific management of maternal PKU was not addressed in this guideline as it was the basis of a separate Guideline (ASIAM 2015).

*Conclusion:* The need for consistent Australasian recommendations for the management of PKU is acknowledged. Despite the lack of high level evidence to inform clinical practice, best practice recommendations have been formulated based on the available published literature including international guidelines from Europe, Scotland (including the United Kingdom) and North America. Further and ongoing research is required to determine best management practices to promote optimal outcomes for individuals with PKU.

## **Key words**

phenylketonuria; PKU; phenylalanine; outcome; clinical practice guideline; L-amino acids; Phe-intake; blood-Phe; Phe-free formula

## **ABBREVIATIONS**

ACMG, American College of Medical Genetics

AI, Adequate Intake

ASIEM, Australasian Society of Inborn Errors of Metabolism

DQ, developmental quotient

DBS, dried blood spot

HPA, hyperphenylalaninaemia

IBW, Ideal Body Weight

IQ, intelligence quotient

LOE, level of evidence

MPKU, maternal phenylketonuria

MPKUCS, Maternal Phenylketonuria Collaborative Study

NBS, Newborn screening

NHMRC, Australian National Health and Medical Research Council

Phe, phenylalanine

PKU, phenylketonuria

RACP, Royal Australasian College of Physicians

RCPA, The Royal College of Pathologists of Australasia

RDI, Recommended Dietary Intake

SSIEM, Society for the Study of Inborn Errors of Metabolism

SIMD, Society for Inherited Metabolic Disorders

Tyr, tyrosine

WHO, World Health Organisation

## INTRODUCTION

Phenylketonuria (PKU); (OMIM 261600 and 261630) is an autosomal recessive inborn error of metabolism resulting from a deficiency of the enzyme, phenylalanine hydroxylase (PAH) and characterised by elevated blood phenylalanine (Phe) levels (Enns et al 2010). The overall incidence in Caucasian populations is approximately 1:10,000 (Scriver and Kaufman 2001).

The known neuropsychological complications of PKU include reduced executive function, attention deficit, decreased processing speed, cognitive impairment and disturbances in emotion and behaviour (Enns et al 2010; Vockley et al 2014; Singh et al 2014; Trefz et al 2011). These complications may still occur in children treated early and continuously even if they maintain acceptable Phe control, ie deficits have been documented in well controlled patients when compared with the general population and their siblings (Enns et al 2010; Vockley et al 2014; Singh et al 2014; Trefz et al 2011). However, these complications are more likely to be evident in children with sub-optimal Phe control. Mean Phe levels are inversely related with performance on neurocognitive tests at 12 years of age and IQ is negatively correlated with both age of initiation of diet and Phe levels between ages of 4 years to 10 years (Enns et al 2010). A recent meta-analysis demonstrated a 1.8 to 3.8 point reduction in IQ for each 100µmol/L increase in lifetime blood Phe level (Enns et al 2010). In addition, the stability of Phe levels over time is considered important for optimal executive functioning and intelligence, especially in children with classical PKU who are more prone to fluctuation in blood Phe level with changes in dietary Phe-intake (Enns et al 2010).

Combination therapy that includes a natural protein (Phe) restricted diet, supplemental phenylalanine-free amino acid formula (Phe-free formula), with or without co-factor therapy, (Sapropterin/BH<sub>4</sub>), for individuals with responsive forms of PKU, is required for adequate lifetime blood Phe control (Vockley et al 2014; Cunningham et al 2012) and increases the likelihood of best cognitive outcomes (Vockley et al 2014; Feillet et al 2010). High levels of Phe are harmful to the developing brain and there is conclusive evidence that well controlled blood Phe during the first 12 years of life significantly reduces severe intellectual impairment, seizures and behaviour disorders (Blau et al 2010; Vockley et al 2014). Evidence indicates that for best outcome, treatment should

be started by 10 days of age (van Spronsen et al 2017). Metabolic centres worldwide advocate for dietary interventions and associated monitoring for life to optimise intellectual function, mental health and executive function (Blau et al 2010; Vockley et al 2014).

Newborn screening for PKU has been available in Australasia since the mid to late 1960s. Infants with a confirmed diagnosis are managed by multidisciplinary teams in each of the Australasian specialist metabolic units with the philosophy of “diet for life”. The standard of care in Australasia promotes a co-ordinated, multi-disciplinary team approach with access to qualified physicians, dietitians, laboratory scientists, metabolic specialist nurses as well as psychosocial support.

## **GUIDELINE DEVELOPMENT**

At the request of the Metabolic Dietary Disorders of Australia (MDDA) which represents individuals with PKU, their parents, families and carers, the Australian Society of Inborn Errors of Metabolism (ASIM) called for expressions of interest from experienced members to form a working party to develop recommendations to guide the consistent management of PKU across Australasian clinics. The working party had multidisciplinary representation from all clinics and consisted of a metabolic nurse practitioner (AI), metabolic dietitians (ST, AM, CR, EM, EC, AS, ET, AE, CK, KH, CM, RA, TC), metabolic physicians (JF, SB), a metabolic fellow (KL) and a newborn screening scientist (VW).

The working party was divided into two groups determined by professional stream. Group 1 (AI, KL, VW, SB, JF) consisted of medical, scientific and nursing health professionals who focused on biomarkers and monitoring. Group 2 (CK, ST, AM, CR, EM, EC, AS, ET, AE, KH, CM, RA, TC) consisted of dietitians. Each group identified key topics for inclusion including target blood Phe levels, monitoring requirements and dietary management. The working party completed a non-systematic review of the literature and drafted clinical guidelines for the management of PKU for the Australian and New Zealand population informed by these results. Working party meetings, discussion and collaboration were held by telephone, email and face-to-face meetings.

The draft guideline was released for consultation to all Australasian metabolic units and revisions were made based on these comments. The approved guideline was endorsed by ASIEM and included on the Human Genetics Society of Australasia (HGSA) website under *ASIEM Resources for Parents and Families*.

This document does not make reference to the special needs of individuals with maternal PKU as a separate guideline for the management of maternal PKU is available online from the ASIEM (ASIEM 2015).

## REVIEW OF LITERATURE

Recommendations are assigned a level of evidence (LOE) which were adapted from the Australian National Health and Medical Research Council (NHMRC 2014) evidence hierarchy.

Table 1. NHMRC levels of evidence

Level	Level of Evidence
1	Systematic review of evidence
2	Single experimental studies (e.g. randomised control trial)
3	Quasi-experimental studies (e.g. pseudorandomised trial, cohort study, single arm study)
4	Non-experimental studies (e.g. case report and case series)
5	Clinician Expert Opinion

## GUIDELINES

### **Blood Phenylalanine and Tyrosine Targets and Monitoring**

Dietary control has been recommended since the 1950s and levels were based on phenylalanine units of mg/dL (1mg/dL = 60umol/L). Most current recommendations are due to calculated SI unit equivalents of what was used as rounded mg/dL without any evidence base to determine an absolute best level in terms of umol/L. More recent literature is moving toward reassessment of levels of Phe in SI units. Considering the

measurement of uncertainty of all estimations of blood Phe levels, ASIEM recommends a more rounded value in  $\mu\text{mol/L}$  until further detailed evidence is obtained.

### **Initiation of Treatment:**

Given the inconsistency in reports of neurocognitive deficits in patients maintaining Phe levels between  $360\text{-}600\mu\text{mol/L}$  ( $6\text{-}10\text{mg/dL}$ ), expert opinion recommends initiation of dietary therapy at Phe levels  $>360\mu\text{mol/L}$  ( $6\text{mg/dL}$ ) (Weglage et al 1996; Vockley et al 2014). Infants with Phe levels  $<360\mu\text{mol/L}$ , who do not require dietary treatment, should be monitored regularly for the first 2 years of life. Ongoing annual or biannual monitoring appears to be sufficient, (Singh et al 2012; Vockley et al 2014) but there are no recommendations for the duration of this monitoring.

### **Recommendation 1**

***Patients with a blood Phe level above  $6\text{mg/dL}$  or  $360\mu\text{mol/L}$  should be treated as PKU. Treatment should start as soon as possible, ideally before 10 days of age (LOE 3)***

### **Recommendation 2**

***Infants with Phe levels between  $2\text{-}6\text{mg/dL}$  or  $120\text{-}360\mu\text{mol/L}$  without dietary restriction should be monitored at least until school age. (LOE 3)***

### **Blood Phenylalanine Targets:**

Blood-Phe levels of  $120\text{-}360\mu\text{mol/L}$  are the most widely recommended targets for children less than 12 years of age who required dietary therapy (Enns et al 2010; Vockley et al 2014; van Spronsen et al 2017; Ogier de Baulny et al 2007). Target Phe levels in adolescence and adulthood still vary by geographical location. While the clinical goal is still aimed at minimising the neurological sequelae of PKU, the variation in these target blood-Phe levels may reflect both the lack of a strong evidence base to inform them and the difficulty in maintaining long-term dietary compliance (Vockley et al 2014; van Spronsen et al 2017). Some metabolic centres accept phenylalanine levels up to  $600\mu\text{mol/L}$  after 12 years of age (van Spronsen et al 2017). Adolescents and adults with previously well controlled Phe levels have demonstrated increased anxiety and depression with Phe levels over  $700\mu\text{mol/L}$  and neuropsychological and cognitive deficits in Phe levels over  $1000\mu\text{mol/L}$  (Trefz et al 2011). Adults who choose to be 'off diet' and who consequently have poor blood Phe control, can experience neurological complications and vision loss and a return to dietary therapy with a reduction in blood

Phe levels may improve or reverse symptoms (van Spronsen et al 2017; Trefz et al 2011). Evidence is emerging for the improvement in behaviours, such as self-injury, tantrums and hyperactivity in previously untreated adults when Phe levels are maintained below 900 $\mu$ mol/L (Trefz et al 2011). Reports of more subtle neurocognitive changes including higher IQ, depression and anxiety are inconsistent in adult patients with Phe levels between 360 – 600 $\mu$ mol/L and more information is required on how best to assess neurocognitive outcomes when patients have maintained blood Phe levels within this treatment range (Vockley et al 2014). Recently published international guidelines are not consistent in target blood-Phe levels for individuals over 12 years of age. The US guideline recommends maintenance of target Phe of 120-360 $\mu$ mol/L throughout the lifespan (Vockley et al 2014), however the European guideline currently states acceptable blood-Phe levels between 120 – 600 $\mu$ mol/L after 12 years of age (van Spronsen et al 2017). Both guidelines do recommend decreased blood Phe-targets from previously accepted practice, and acknowledge that it will require a further dietary phenylalanine restriction for many individuals for these blood-Phe targets to be successfully implemented. It is acknowledged that ongoing studies and review will be required to provide further evidence to inform future recommendations.

### **Recommendation 3**

***Maintain blood Phe levels between 2-6mg/dL or 120-360 $\mu$ mol/L up to the age of 12 years old. (LOE 1)***

### **Recommendation 4**

***In patients over 12 years of age, an informed decision to accept phenylalanine levels above 360 $\mu$ mol/L may be appropriate in some cases. Individual blood Phe targets may be considered for some individuals, with consideration for the fact that both short and long term outcomes tend to be better with lower levels. (LOE4)***

### **Blood Tyrosine Targets:**

There is limited evidence to recommend target tyrosine (Tyr) levels and these are recommended to be maintained at 50-100 $\mu$ mol/L or within the normal laboratory range for each institution (Camp et al 2014). Monitoring of blood Phe:Tyr ratios may be important when assessing all patients with PKU, as well as those on sapropterin therapy (Camp et al 2014). They may also be of benefit as an index of dietary control (Trefz et al 2011). However, the recommended range for this ratio has not been determined and it is

not yet clear that monitoring this ratio conveys any additional advantage over blood Phe monitoring (van Spronsen et al 2017).

### **Recommendation 5**

***Plasma Tyr levels should be maintained between 50-100 $\mu$ mol/L and supplementation considered if repeatedly low e.g. <30 $\mu$ mol/L. (LOE 3).***

#### **Monitoring Blood Levels:**

Monitoring of blood-Phe levels using dried blood spot (DBS) sampling has been demonstrated to be effective as it is minimally invasive, requires only a small sample of blood and can be transported and stored at room temperature while maintaining sample stability (Pecce et al 2013). It also reliably correlates with plasma Phe levels (Ney et al 2014). Timing of samples is recommended to be at a consistent time of day, either in the morning following an overnight fast when blood Phe levels are generally highest or 3-4 hours following a usual low protein meal and Phe-free formula (Camp et al 2014; Ahring et al 2011). Frequency of monitoring should be twice weekly for newly diagnosed babies until levels are stable, weekly until 1 year of age, at least fortnightly for 1-12 years of age, up to monthly in adolescence and adulthood (Vockley et al 2014; van Spronsen et al 2017). Blood Phe monitoring frequency may be increased as clinically indicated. It is recommended that a health professional report results of pathology tests to parents/carers/patients within a timely manner (Camp et al 2014). Infants should ideally have results reported directly to caregivers as soon as possible, which will allow the impact of dietary changes between blood tests to be measured.

### **Recommendation 6**

***Monitoring should be performed with either dried blood spot (DBS) or plasma amino acids, at a consistent time of day, either in the morning following an overnight fast or 3-4 hours following a usual low protein meal and Phe-free formula (LOE 3)***

### **Recommendation 7**

***Phe and Tyr should be monitored:***

- 1. In infancy: twice per week until stable and within the target range, weekly until one year of age (at the discretion of the treating metabolic team)***
- 2. Childhood: at least fortnightly to monthly throughout childhood***
- 3. Adolescence and Adulthood: a minimum of monthly***

### **Recommendation 8**

***Results from monitoring samples should be reported as soon as practicable and within the turnaround time targets of the testing laboratory. Follow up contact from the metabolic team should occur as soon as possible after this. (LOE 5)***

### **NUTRITIONAL MANAGEMENT**

The goal of nutritional management for individuals with PKU is to achieve and maintain Phe concentrations in the target treatment range, while supporting optimal growth, development and mental functioning (Camp et al 2014; MacLeod and Ney 2010). There is a wealth of evidence to show that a diet restricted in Phe from natural protein improves neurocognitive outcomes for individuals with PKU (Singh et al 2014; Ahring et al 2011; Dokoupil et al 2012; Burrage et al 2012). Dietary phenylalanine restriction is therefore the cornerstone of therapy (van Spronsen et al 2017).

Dietary therapy consists of:

1. Natural protein restriction using individual Phe tolerance;
2. Phe-free formula required to meet total protein and micronutrient requirements;
3. Low protein foods to meet appetite and energy requirements (van Spronsen et al 2017; MacLeod 2009).

When energy and total protein intake (natural protein + Phe-free formula) is inadequate, there will be insufficient amino acids for protein synthesis and resultant catabolism will cause PHE to be released from body cells, increasing blood Phe concentrations (van Spronsen et al 2017). Consequently, it is essential to ensure adequate intake of all amino acids and energy (van Spronsen et al 2017; Gizewska et al 2015).

The restrictive and complex nature of the PKU diet creates challenges in achieving nutritional adequacy and long term compliance and may negatively affect quality of life in some individuals (Enns et al 2010; Dokoupil et al 2012; Hafid and Christodoulou 2015; Poustie and Wildgoose 2010). The following summary of recommendations, dietary intake and monitoring highlights this in more detail and makes recommendations for both paediatric and adult population groups.

### **Growth and Body Weight:**

Reports of growth outcomes in early and continuously treated individuals with PKU are inconsistent (Dokoupil et al 2012). Growth and nutritional deficits in individuals with PKU may be related to both the degree of dietary restriction or unidentified intrinsic features specific to PKU itself (Enns et al 2010; Trefz et al 2011). These may include faltering growth particularly in the first years of life (Schaefer et al 1994; Verkerk et al 1994; Weglage et al 1994), a reduced final adult height, decreased peak bone mass in young adults, increased incidence of overweight and micronutrient deficiencies (Enns et al 2010; Vockley et al 2014; van Spronsen et al 2017; Trefz et al 2011; Camp et al 2014; Lohner et al 2013). Normal linear growth has been reported in a retrospective longitudinal study (Belanger-Quintana and Martinez-Pardo 2011) and reaching full growth potential should be the expected outcome in children who are now diagnosed with PKU.

There is emerging evidence to suggest that the PKU population may be at a higher risk of overweight and obesity due to the restrictive nature of the diet, and reliance on high carbohydrate, high fat food options (Enns et al 2010; Camp et al 2014; Pecce et al 2013; Rocha et al 2015). Improved Phe tolerance has been associated with higher fat free mass (MacLeod 2009) confirming recommendations to maintain an optimal body composition through a healthy diet and lifestyle.

### **Recommendation 9**

***The aim of PKU treatment is for all affected people to achieve and maintain a healthy weight and reach their full adult height potential. (LOE 3)***

#### **Growth Monitoring:**

It is important to regularly monitor individuals with PKU to ensure appropriate weight and height gain during childhood and adolescence and that a healthy weight is maintained in adulthood. Monitoring of weight and anthropometric data should occur at every clinic visit (Vockley et al 2014; van Spronsen et al 2017; Camp et al 2014; Singh et al 2016).

In infants and children, growth should track appropriately along standardised weight and height percentiles, with serial measurements regularly plotted on the recommended growth charts used in Australian and New Zealand (NHMRC 2006). Weight for length in children >2 years of age should also be plotted on age appropriate growth charts. The

NHMRC guidelines recommend that all adults 18 years or older should maintain a healthy weight for height in the BMI range 18-25kg/m<sup>2</sup> (NHMRC 2006). This should also apply to the PKU population (NHMRC 2006).

Although body mass index (BMI) is commonly used to assess overweight in population groups, the value of body composition monitoring to determine to what extent being overweight is in fact due to increased fat mass has been suggested for PKU (Rocha et al 2015). Bedside methods to assess body composition such as the use of skin fold callipers or bioelectrical impedance analysis (BIA) are not yet widely used as a part of routine clinical care in Australasian clinics.

#### **Recommendation 10**

***Anthropometric data (weight, length/height, head circumference, BMI or BMI percentiles in paediatrics) should be collected at each clinic visit or phone contact and plotted on appropriate growth charts or converted to Z-scores to enable monitoring of growth:***

**1. For children:**

- 1. (0-1yo) at each clinic appointment, including head circumference**
- 2. (1-7yo) at least 6 monthly. Including head circumference up to 36 months.**
- 3. (8-18yo) a minimum of 6 monthly**

**2. For adults: (>18yo) at least every annually (LOE 3)**

#### **Bone Health:**

Reduced bone mineral density has been reported in PKU patients across all age groups (Dixon et al 2014; MacDonald et al 2011). The cause of reduced bone density could be multifactorial and not necessarily due to inadequate dietary intake of calcium and vitamin D (Dixon et al 2014; MacDonald et al 2011). While decreased bone density is a known complication of PKU, the utility of routine screening has not been established (Vockley et al 2014). The assessment of bone health should be regularly conducted by the dietitian as part of routine dietetic consultation and review of usual diet histories for patients with PKU.

### **Recommendation 11**

***Bone mineral densitometry measurement should only be considered when specific clinical reasons exist or when patients are known to be at particular risk of metabolic bone disease.***

## **DIETARY REQUIREMENTS**

Energy and protein requirements are based on actual weight for individuals within the healthy weight range, but need to be adjusted using Ideal Body Weight (IBW) or matched weight for height for overweight or obese paediatric and adults patients respectively. This is because requirements relate directly to the metabolically active, fat-free mass rather than actual body weight (MacLeod and Ney 2010; NHMRC 2006). Regular review of individualised treatment plans by experienced metabolic dietitians and physicians is critical to this process (Hagedorn et al 2013).

### **Recommendation 12**

***Diet history should be assessed regularly, including feeding/eating patterns, PKU supplement compliance, intake of fruit and vegetables and intake of high fat and high sugar foods and drinks. Anthropometric measurements should also inform dietary energy intake. Review of diet intake via telephone or face-to-face consultation should occur as part of routine follow up, at a minimum frequency of:***

<b><i>For Children: (0-1yo)</i></b>	<b><i>Monthly</i></b>
<b><i>(1-7yo)</i></b>	<b><i>1-6 months</i></b>
<b><i>(8-18yo)</i></b>	<b><i>6-12 months</i></b>
<b><i>For Adults: (&gt;18yo)</i></b>	<b><i>6-12 months (LOE 5)</i></b>

**Additional clinical review may be indicated**

## **Energy**

Adequate energy intake is required for metabolic processes, physiological function, activity, growth and synthesis of new tissues (NHMRC 2006). Energy is derived from ingested foods and fluids via the breakdown of carbohydrates, fats and protein. In PKU, the composition of the diet differs from that of the non-PKU population due to the restriction of natural protein. To adjust for this, adequate protein and energy for growth and repair is obtained from Phe-free formula and specialised low protein foods. This is in addition to an allowance from foods naturally low in phenylalanine such as fruits, vegetables, cereals and grains.

Recent evidence confirms that the total energy requirements for individuals with PKU does not differ from gender- and age-matched controls (Vockley et al 2014; van

Spronsen et al 2017; Singh et al 2014; Ney et al 2014). As energy requirements are influenced by factors such as age, gender, body composition, protein intake, health status and activity (NHMRC 2006; Aguiar 2015), it is recommended that energy requirements for PKU be individually assessed by an experienced dietitian using established principles (Singh et al 2014; Ney et al 2014 (NHMRC 2006; Aguiar 2015). In general, energy intake in children and adults with PKU should reflect the Estimated Energy Requirement (EER) as per the Nutrient Reference Values (NRVs) for Australia and New Zealand (NHMRC 2006). However, it is important to recognise that energy requirements obtained by predictive equations are only approximate, as large variations in energy needs between individual do exist (NHMRC 2006).

Very active sports people, athletes and those persons in physically demanding employment have a higher energy requirement than the general population and this should be individualised to need. When growth faltering or excessive weight gain are evident, dietary counselling must be individualised to ensure appropriate energy intake is achieved. Early prevention of inappropriate weight gain and identification of potentially detrimental eating/feeding behaviours is important to avoid the complications associated with reduced Phe tolerance with excess fat mass (Rocha et al 2012) and catabolism in those not meeting total energy or protein intakes.

### **Recommendation 13**

***Energy requirements should be calculated on an individual basis, based on the following:***

- 1. Overweight or obese:**
  - 1. Children: use ideal weight for height**
  - 2. Adults: use adjusted ideal body weight**
- 2. Underweight and healthy weight patients:**
  - 1. Children & Adults: use actual body weight (LOE 5)**

### **Protein**

Protein provides an essential structural and functional role in the body (NHMRC 2006; MacDonald et al 2011). The primary function of dietary protein is to provide amino acids which serve as building blocks of all vital organs, muscle, hormones and biological fluids such as blood (MacDonald et al 2011). The human body requires a constant supply of high quality protein to maintain growth and other physiological functions (MacDonald et al 2011).

### **Total Protein:**

The amount of total protein required for an individual will depend on age, PKU severity, body weight, natural protein intake, and the protein utilisation from the protein substitute. Protein intake may also be determined or modified based on blood phenylalanine levels and growth or weight changes. Recently released guidelines (van Spronsen et al 2017; Singh et al 2016) from Europe and the USA recommend that total protein intake should be at least 140-150% of the RDI to account for the reduced availability of amino acids compared to whole proteins, and to optimise blood-Phe levels.

**Table 1** shows the recommended protein intake for individuals with PKU based on age ranges. These recommendations are a considered a guide only and dietitians will consider an individual's circumstances in prescribing an appropriate level of protein. It should be noted that some infants, including those born pre-term, may require a higher protein intake to promote adequate growth and blood Phe control (Dixon et al 2014).

There is no evidence for a variation in protein requirement for adults with PKU as they age. This may be a consequence of there being few adults on diet at an advanced age. Australian and New Zealand Nutrient Reference Values recommend an increase in protein intake for those over 70 years of age. These protein values should be extrapolated to 140% of requirements for PKU elderly adults until there are further studies investigating the ideal protein requirement for adults with PKU.

**Table 1: Guidelines for total protein requirements for PKU across the lifespan (protein equivalent from protein substitute and natural protein exchanges)**

Age	PKU Recommended Protein Intake grams/kg*/day (Dixon et al 2014)
Birth -12 months	2.0 -3.0 (see note a)**
1-3 years	2.0 - 2.5
4-10 years	1.5 - 2.0
10-18 years	1.0 - 1.5
19-70 years	140% of RDI (van Spronsen et al 2017;
>70 years	
Pregnant or Lactating	

	Dixon et al 2014) for age/gender or if pregnant or lactating
Athletes	see note <u>b</u>

\* Ideal body weight for height age/ Adjusted IBW (half way ideal may be used) as per dietetic assessment.

\*\* Meeting the above recommendations for some breast-fed infants may prove difficult when the child is allowed to feed to appetite.

a Infants are fed either breast milk or standard infant formula together with a Phe-free infant formula at amounts to maintain blood-Phe levels within the recommended treatment range for age

b Increased protein may be required for active sports people, athletes and those persons in physically demanding employment and should be individualized to need.

### **Recommendation 14**

***Established predictive equations should be used by the dietitian to estimate energy requirements. These can be tracked overtime via growth in children, or stable weight in adults, and adjusted to achieve ideal growth or a healthy weight range. (LOE 5)***

#### **NOTE 1**

***The total protein requirement for individuals with PKU is greater than the normal population requirements for age/gender. (LOE 3)***

#### **Natural Protein (Phe-intake)**

Phe is an essential amino acid and adequate amounts must be consumed to prevent deficiency and to support tissue repair, growth, and protein turnover. Increased amounts will be required during periods of accelerated growth or during pregnancy and lactation (MacLeod and Ney 2010). Phe requirements are considered the same for those with PKU as for individuals with normal PAH activity (Singh et al 2014; Harnett et al 2013; Aldamiz-Echeramia et al 2014). Although exact Phe requirements are not well defined, there may be appreciable sparing of Phe with the increased intake of Tyr (WHO 2007).

Natural protein tolerance in PKU has been defined as the Phe intake that maintains the blood Phe level within the prescribed target treatment range (Dixon et al 2014). The amount of Phe tolerated depends on several factors including the degree of PAH impairment, net protein catabolism, other Phe disposal pathways, non-protein: energy ratio, growth rate, age, gender, adherence to low protein diet and adequate Phe-free formula intake (Dixon et al 2014). Natural protein (Phe intake) is determined by blood Phe levels and considers this in combination with the reported dietary intake (Vockley et al 2014; Ogier de Baulny et al 2007; Aldamiz-Echeramia et al 2014). Allowing natural

protein intake to Phe tolerance may help to promote optimal long term growth (Macdonald and Asplin 2006).

For optimal phenylalanine control, natural protein (Phe intake) should be evenly distributed over the day and consumed with the Phe-free formula (Dixon et al 2014). No more than half of the natural protein prescription should be consumed at any one time (Dixon et al 2014). Except for many fruits and vegetables, one gram of protein in food is estimated to be equivalent to 50mg of Phe (Poustie and Wildgoose 2010).

Phe deficiency is rarely reported, however it is crucial to recognise the signs and symptoms and treat promptly. These include generalised amino aciduria, alopecia, (perineal) rash and poor or variable growth in preschool children. Symptoms may also include anorexia and listlessness (MacDonald et al 2011).

### **Breastfeeding**

Consistent with recommendations for healthy infants, breast feeding is encouraged for infants with PKU (NHMRC 2012; Ministry of New Zealand 2012). Consultation with midwives or lactation consultants may be of benefit for some mothers who experience breastfeeding problems.

Breast milk is naturally lower in Phe than standard infant formula (Dixon et al 2014). Good blood Phe control is documented in infants fed either expressed breast milk by feeding bottle or direct feeding at the breast (Rocha et al 2012). Several methods of breast milk delivery have been shown to be successful, including alternate feeding of a Phe-free formula by bottle and feeding at the breast; mixing a measured quantity of expressed breast milk and Phe-free formula together in a bottle at each feed; or feeding a measured quantity of Phe-free protein substitute prior to breastfeeding to appetite at each feed. Recent evidence suggests that mothers of babies diagnosed with PKU value being able to normalise this aspect of their child's diagnosis by successfully breastfeeding (Banta-Wright et al 2015). When breast-feeding is not possible or preferred, infants with PKU can be successfully managed with use of regular infant formula.

### **Recommendation 15**

***Individual protein requirements should be calculated based on the following:***

- 1. Overweight or obese:***
  - 2. Children: use ideal weight for height***
  - 3. Adults: use adjusted ideal body weight***
- 2. Underweight and healthy weight patients:***
  - 4. Children & Adults: use actual body weight***

### **Recommendation 16**

***Sufficient natural protein should be provided to ensure that minimum Phe requirements are met, as reflected by Phe levels within the target treatment range for age. (LOE 3)***

### **Note 2**

***Phe deficiency is rare but possible due to over-restriction of natural protein. Side effects of deficiency should be recognised and treated immediately. (LOE 3)***

### **Synthetic protein: (Phe-free formula and glycomacropeptide)**

Synthetic protein (Phe-free formula) is necessary to provide adequate protein requirements, essential amino acids, micronutrients and energy and will also improve satiety (Dokoupil et al 2012; NHMRC 2006). In more severe forms of PKU, a suitable Phe-free formula is critical for prevention of protein and micronutrient deficiency and to achieve and maintain optimal metabolic control (Dixon et al 2014). Evidence indicates that provision of other L-amino acids will reduce absorption of phenylalanine from the gut and passage of Phe into the brain via competition for transport (van Spronsen et al 2017). Synthetic amino acids in Phe-free formula are absorbed and oxidised more rapidly than intact protein (Ney et al 2014; Hartnett 2013; Aldamiz-Echeramia et al 2014), resulting in reduced utilisation for protein synthesis. This is reflected in increased total protein intake recommendations for individuals with PKU compared to healthy populations (Singh et al 2014; Hartnett 2013; Burrage et al 2012; NHMRC 2006; Aldamiz-Echeramia et al 2014; Acosta 2010).

In most individuals with classical PKU, the Phe-free formula will provide ~75- 85% of the daily protein intake (Dixon et al 2014). In a randomised controlled trial a higher dose of protein substitute was shown to contribute to lower blood-Phe levels (Aldamiz-Echeramia

et al 2014). Despite this, the total amount of protein substitute recommended must be considered within the context of the whole diet and should not contribute to excessive protein or energy intakes or reduce appetite for food.

The ingestion of a large single dose of amino acids has shown to result in a rapid absorption and oxidation of the amino acids, consequently the Phe-free formula should be consumed in small, frequent doses, three to four times per day, spread as evenly as possible over the day, to allow the most effective use of the ingested amino acids (MacDonald et al 2011; Aldamiz-Echeramia et al 2014; Macdonald and Asplin 2006).

Phe-free formulas come in a wide variety of forms and flavours including: powders, ready to drink liquids, paste/gel, pudding, bar and tablets. Most supplements have added vitamins, minerals, trace elements and DHA. Phe-free formulas are the primary source of tyrosine and are conditionally essential in PKU (Macdonald and Asplin 2006).

#### **Glycomacropeptide:**

Historically, Phe-free formulas have contained L-amino acids. New supplements for use in PKU and based on a protein known commercially as glycomacropeptide (GMP) have recently become available in Australia. GMP is a very low phenylalanine containing intact protein that has been supplemented with arginine, histidine, leucine, tyrosine and tryptophan improving the amino acid content to make it suitable for the treatment of PKU (MacLeod and Ney 2010; Ney et al 2014). Initial studies indicate the potential for GMP protein to provide benefits to bone health, promotion of satiety, and may contribute to dietary compliance due to the improved palatability (Hafid and Christodoulou 2015; Van Calcar et al 2009). Although results appear promising, further research is needed to identify any potential risk and/or beneficial outcomes from long-term use.

Large neutral amino acid supplements, which are used in some countries, are not currently subsidised under the Australian or New Zealand prescription systems and their use will not be detailed in this document.

### **Recommendation 17**

***Sufficient Phe-free amino acid supplements should be prescribed to provide the additional protein needed to meet total protein requirements for adequate growth and Phe control in patients with PKU. (LOE 3)***

#### **Tyrosine:**

Tyrosine is conditionally essential in PKU as it is not supplied endogenously by phenylalanine hydroxylation. Tyr is important for synthesis of cerebral neurotransmitters (epinephrine, norepinephrine and dopamine), thyroxine and melanin. Supplementation is recommended by the Medical Research Council Working Party in the UK to be given at a dose of 100-120 mg/kg/d, which is five times that recommended for the non-PKU population (MacDonald et al 2011). A Cochrane review of Tyr supplementation in PKU concluded that there is insufficient evidence currently available for recommendations to be made on the appropriate level of supplementation (Webster and Wildgoose 2013). Although tyrosine is available from natural protein, in PKU the majority of the tyrosine intake comes from the synthetic formulas. In general, if adequate Phe-free formula is administered, Tyr should be provided in sufficient quantities. However, Tyr is the least soluble of the amino acids and may form sediment in Phe-free formulas. Individuals with PKU should be recommended to shake or stir all premade drinks and be encouraged to consume the entire contents of their supplement (Dixon et al 2014).

#### **Note 3.**

***Tyrosine is conditionally essential in PKU and requirements in PKU are higher than the general population. (LOE 3)***

### **Recommendation 18**

***Natural and synthetic protein intakes should be spread out as evenly as possible over the day: at least 3 – 4 times per day (LOE 3)***

### **Recommendation 19**

***Sufficient Phe-free amino acid supplements should be prescribed to provide the additional protein needed to meet total protein requirements for adequate growth and Phe control in patients with PKU. (LOE 3)***

## **Nutrient Intake**

Non-compliance with prescribed PKU supplements increases the risk of low intake of micronutrients particularly vitamin B<sub>12</sub>, vitamin B<sub>6</sub>, folic acid, copper, selenium, zinc and iron (Dixon et al 2014; MacDonald et al 2011). Most Phe-free formulas are fortified with vitamins and minerals at the level determined by the Australian and New Zealand Nutrient Reference Values (Enns et al 2010). Vitamin B<sub>12</sub> deficiency has been reported in adolescents and adults with PKU who are off diet or on a less restricted diet. In particular, those who have continued a low protein diet because of distaste for meat and animal products, but discontinued Phe-free formula (Singh et al 2014; Ney et al 2014). There are also reports of low levels of folate, calcium, iron, vitamin A, vitamin D, zinc, copper, selenium and essential fatty acids, however the clinical significance of low blood levels of some nutrients has not been well established (Enns et al 2010; van Spronsen et al 2017; Trefz et al 2011; Camp et al 2014; Lohner et al 2013; Walter 2011). Persistently low levels of some nutrients could contribute to neurocognitive and visual impairment, as well as the specific symptoms of the nutritional deficiencies (Enns et al 2010; Trefz et al 2011).

Recommendations support the regular assessment of plasma (blood) concentrations of nutrients including plasma amino acids, liver function tests, full blood count, vitamin B<sub>12</sub>, folate, calcium, iron studies, vitamin A, vitamin D, essential fatty acids, and trace minerals (zinc, copper, selenium) (Ogier de Baulny et al 2007). However, there is little evidence to support such comprehensive assessment for those with good metabolic control and compliance with diet and protein supplement recommendations. It is not clear what the optimal frequency of this monitoring should be; although yearly is suggested (van Spronsen et al 2017; Cunningham et al 2012; Singh et al 2016).

### **Recommendation 20**

***Consider nutritional investigation and vitamin and mineral supplements if inadequate intake including from fortified Phe-free formula to meet the Australian and New Zealand nutrient reference values. (LOE 5)***

### **Recommendation 21**

***Fortified phe-free formula should not be prescribed in quantities that provide amounts of micronutrients, particularly fat-soluble vitamins, higher than the Australian and New Zealand nutrient reference values. (LOE5)***

### **Essential Fatty Acids:**

The intake of long chain polyunsaturated fatty acids (LCPUFA), particularly the omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are critical for neurological and retinal development (Infante and Huszagh 2001; Bazan 2007). Depletion of EPA and DHA has been detected in patients with PKU (Lohner et al 2013). This reduction is thought to be a consequence of the inherently low fat content of a protein restricted diet and possibly due to inhibitory effects of Phe metabolites on the endogenous synthesis of DHA (Infante and Huszagh 2001). Studies exploring omega-3 LCPUFA status and supplementation are predominantly in children with PKU (Lohner et al 2013).

It is suggested that there may be a neuro protective benefit of the omega-6 LCPUFA, arachidonic acid (AA), and DHA in particular (Bazan 2007) as elevated Phe levels leave patients with PKU susceptible to neurological damage. A study of neurocognitive outcomes and DHA status in PKU patients found better verbal ability in those with higher DHA concentrations (Yi Shi and Singh 2015). In addition to neurological benefits, DHA status has also been positively associated with bone mineral density in groups of PKU patients (Lage et al 2010).

Improvements in other parameters of neurological development including fine motor skills and visual responses have also been observed in studies of DHA supplementation in children with PKU (Feillet and Agostoni 2010). The longer-term effects of short term supplementation are unknown.

Data from adult studies indicate reductions in LCPUFA may be less severe in adults than those reported in children (Moseley et al 2002). High levels of the omega-3 essential fatty acid, alpha-linolenic acid (ALA), can be associated with low DHA levels, suggesting supplementation should be performed with DHA rather than its precursors (Bosdet et al 2014) although supplementary ALA may be better tolerated due to the strong taste and smell associated with preformed AA and DHA (Rose et al 2005).

Optimal LCPUFA supplementation dosage remains unclear as there is lack of research into the effectiveness of supplementing essential fatty acids in the diet of individuals with PKU (Lohner et al 2013). It would, however, be prudent to suggest that all patients

with PKU work with their dietitian to meet adequate intakes for healthy populations as outlined in the Nutrient Reference Values for Australia and New Zealand.

### **Recommendation 22**

***The dietitian should ensure adequate intake of LCPUFA as per the Australian and New Zealand Nutrient Reference Values. If monitored, LCPUFA levels are low, a fortified Phe-free formula or a fish-oil supplement should be prescribed (LOE 5)***

#### **Artificial Sweeteners:**

Aspartame and Acesulphame-Aspartame (additive numbers 951 and 962) are artificial sweeteners that are composed of 50% phenylalanine and need to be avoided in patients with PKU (van Spronsen 2017). These are often labelled in Australasia as NutraSweet, Equal and Canderel. Other artificial sweeteners commercially available are safe as they do not contain aspartame. Some medications such as antibiotics contain aspartame and short treatment courses might need to be given if no alternatives are readily available (van Spronsen 2017)

## **OTHER TREATMENTS**

#### **Tetrahydrobiopterin (BH<sub>4</sub>):**

Tetrahydrobiopterin (BH<sub>4</sub>) is the co-factor for PAH. It is well established that some patients with PKU, in particular those with higher residual PAH activity, may respond to cofactor therapy (BH<sub>4</sub>). The use of this therapy results in a significant increase in Phe tolerance and/or a decrease in blood Phe concentrations (van Spronsen et al 2017), generally resulting in a less restricted diet. In Australia and New Zealand, BH<sub>4</sub> is currently used in only a few centres as the government only subsidises the cost for BH<sub>4</sub> deficiency disorders. Applications for subsidised approval of this drug for PKU are in process.

### **Recommendation 23**

***No recommendation is made here as there is a separate guideline addressing PKU managed with tetrahydrobiopterin and can be found on the ASIEM Resources Page (ASIEM 2017)***

### **Sick Day Management:**

During illness, adequate energy intake will limit catabolism and the resulting elevated blood-Phe levels (van Spronsen et al 2017; Camp et al 2014). Some centres advocate a reduction of natural protein and an increase in the supplemental protein and total energy intake to assist with limiting catabolism. This requires more research to elucidate the most beneficial treatment in times of illness.

### **CLINIC FREQUENCY**

There are no studies to inform the ideal frequency of clinic review or type of clinic follow up that could include phone, teleconference or face-to-face consultation. Current best practice is to review children in a multidisciplinary clinic which includes a physician, clinic nurse, dietitian, psychologist and social worker. This should be conducted at least 3 monthly until 1 year of age and at least 6 monthly throughout childhood (van Spronsen 2017; Hartnett 2013; Bannick et al 2015). To date no adult studies have addressed this aspect of care.

#### ***Recommendation 24***

***Patients should be reviewed within a specialist metabolic clinic. In paediatric settings, this should include a physician, dietitian, nurse, psychologist and psychosocial support worker with expertise in inborn errors of metabolism and particularly in PKU. (LOE 5)***

#### ***Recommendation 25***

***Patients should be reviewed in a multi-disciplinary clinic via face-to-face or teleconference consultation at least 3 monthly for the first year of life, and at least 6 monthly throughout childhood, and at least yearly throughout adulthood. (LOE 5)***

### **PSYCHOSOCIAL SUPPORT**

There are significant neuropsychological sequelae because of poorly controlled PKU, including reduced executive function, attention deficit, decreased processing speed, cognitive impairment, emotional/mood disturbances and behaviour problems (Enns et al 2010; Blau et al 2010; Vockley et al 2014; van Spronsen et al 2017; Feillet et al 2010; Trefz et al 2011). These can occur in childhood, adolescence or adulthood. Attention difficulties may have a negative impact on academic progress, self-esteem and emotional development of children and adolescents with PKU. This can result in persistent difficulties in school with an increased need for tutoring or to repeat a

class/year level and discontinuation of studies (Enns et al 2010; Trefz et al 2015; Mütze 2011). These neuropsychological manifestations may complicate dietary adherence exhibited through difficulties with protein counting, problems with recording dietary intake and making impulsive food choices (Enns et al 2010).

Current recommendations from the USA include regular formal psychological assessment in the domains of intellectual functioning, executive functioning, behavioural and emotional functioning and adaptive skills. These should be repeated every 2-3 years or as clinically indicated throughout childhood and adolescence (with ongoing 2-3 yearly behavioural and emotional psychological testing throughout adulthood) (Vockley et al 2014). It is unclear if this can or should be provided in the Australian and New Zealand healthcare frameworks in those with good compliance with therapy. Other groups have identified parent or self-administered screening tools that could be used to determine the need for more formal evaluation (Camp et al 2014). International guidelines also identify the importance of including a psychologist as part of the multidisciplinary team for PKU management and emphasis good communication with schools and other care providers (Hagedorn et al 2013).

Increased psychosocial support is advised when poor compliance is observed in children and/or their caregivers. Health care workers are duty-bound to protect the health and safety of each child under their care. It is suggested that when > 50% of Phe concentrations are out of target range during a period of 6 months, metabolic teams should consider increased frequency of blood-Phe monitoring and outpatient visits, and provide re-education on disorder management. Social work should be involvement at this time (van Spronsen et al 2017). When ~100% of blood PHE concentrations are out of target range during a period of ~6 months, and other signs of non-adherence or patient safety issues are apparent, healthcare workers should consider consultation with child protection services (van Spronsen et al 2017).

Compliance with both dietary therapy and monitoring requirements by adolescents and young adults particularly during the period of transition to adult services may cause increased concerns for the treating clinics (Vockley et al 2014; Trefz et al 2011; Trefz et al 2015; Mütze 2011; Hagedorn et al 2013; NHMRC 2006). Moreover, there is a paucity of adult treatment centres and maintaining adult care within a paediatric treatment centre

may not adequately foster individual independence (Vockley et al 2014; van Spronsen 2017; Trefz et al 2015; Mütze 2011). A structured, gradual, and deliberate transition process to commence in late childhood/early adolescence, including discussion of pregnancy-related issues in young women is now recommended (Camp et al 2014; Bannick et al 2015; Trefz et al 2015; Trefz et al 2015; Mütze 2011). Poor compliance may be reflected in sub-optimal metabolic control during this time, thus input from a psychologist and/or social worker is increasingly recognised as important in both paediatric and adult services (Vockley et al 2014; van Spronsen et al 2017; Bannick et al 2015; Trefz et al 2015).

#### **Recommendation 26**

***Complete assessment of development and intellectual functioning, executive functioning, behavioural and emotional functioning and adaptive skills should be performed prior to commencement of primary school (or earlier if developmental problems identified) and, if clinically indicated, upon commencement of high school. (LOE 5)***

#### **Recommendation 27**

**Where specialist adult services exist, discussion of transition of care to such services should commence at high school entry and the process reviewed yearly. Where such services do not exist, a suitable adult service should be identified by the treating physician as a minimum prior to completion of high school. (LOE 5)**

### **Education Tools and Strategies**

As PKU is primarily managed by diet alone, the role of the dietitian is to equip the patients and their family with the knowledge and skills required to follow a low protein diet as part of their daily life. The National PKU protein counting guidelines (Sweeney et al 2012) endorsed by ASIEM in 2015 are used throughout Australasia as the recommended protein-counting tool to allow consistency in practice. Many other tools are now available especially with the emergence of smart device applications and web based protein counting tools.

Anecdotally, most Australasian clinics where PKU is treated predominantly use one-on-one counselling with written information/handouts for education. A recent study found similar strategies used predominantly in clinicians surveyed in the US, with other techniques being cooking demonstrations, peer to peer counselling and parent and/or

patient centred group education (Bernstein et al 2014). In this study, clinicians identified written handouts as being least effective for education across all age groups, yet it was the second most utilised method (Bernstein et al 2014). A large proportion of patients surveyed also selected handouts to be least effective and majority of patients reported that their families were considered to be the most effective education tool. Use of computer-based tools were more popular amongst patients who were more compliant with their dietary regimen. Studies of children and adolescents with other chronic diseases have suggested a preference for one-on-one education, and that adolescents with PKU preferred a parent present during education sessions (Szybowska 2007). There is limited evidence available regarding group education approaches for PKU management. Short term reduction in blood Phe levels and perceived isolation have been observed in adolescent girls who attended a PKU camp. However, these benefits were not sustained past 12 months post camp (Singh et al 2014). Further studies comparing group and individual approaches to PKU management may be of benefit. However, small patient numbers and insufficient facilities are perceived barriers to facilitation of group sessions (Bernstein et al 2014). Whilst increasing knowledge about the condition and diet is important to a point, knowledge alone does not result in better compliance to dietary regimens and improved metabolic control (Durham-Shearer 2008). Current recommendations suggest the education method must be suitable for the individuals learning style, dietary acceptance and readiness for change (Singh et al 2014). More research is needed to identify more successful methods in engaging behaviour change and improving dietary compliance in patients with PKU, especially in adolescent and adult patients.

The ASIEM PKU Handbook used in conjunction with the National PKU protein counting guidelines (Sweeney et al 2012) and the New Zealand Phe-exchange booklet ensures consistent education across PKU clinics in Australia and New Zealand. These tools have been developed after review of the literature and clinician consensus within Australia and New Zealand. They are therefore most relevant to our patient population. Patients and families must be given guidance on selecting appropriate resources available online. Dietitians can assist in directing patients to tools that suit their individual learning style, level of education and lifestyle. Web based protein-counting tools that use databases of Australian and New Zealand foods should be used for families wishing to utilise electronic resources.

**Recommendation 28**

***PKU associated community activities outside of clinic such as cooking demonstrations, camps, peer to peer counselling and group education sessions should be supported and encouraged.  
(LOE 5)***

**Recommendation 29**

***The Women's and Children's Hospital Low Protein Diet for phenylketonuria PKU has been endorsed by ASIEM and should be used as the low protein counting tool for individuals with PKU. (LOE 3)***

**CONCLUSION**

Continuous monitoring throughout the lifespan for individuals with PKU is required to ensure optimal long term neurocognitive and growth outcomes. Best outcomes occur within a multi-disciplinary team environment which includes experienced representatives from medicine, nursing, dietetics, scientists, social workers and psychologists.

These recommendations should be considered as a guide only. Long term outcomes can be achieved by a tailored program that may be at variance with the general recommendations.

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- The PKU Handbook (HGSA 2005)

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AI – Has received honoraria and travel grants to educational meetings from BioMarin Inc

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VW - Nil

JF - Nil

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CM – Has received sponsorship from Nutricia and Vitaflo to attend IEM dietitians meetings

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## **Contributions**

AI – Working party lead, literature search, medical management write-up, amalgamation of the dietetic and medical document, final edit

KL– Literature search, clinical lead medical management write-up, amalgamation of the dietetic and medical document, final edit

SB - Literature search, clinical lead medical management write-up, amalgamation of the dietetic and medical document, final edit

VW - Literature search, final edit ST - Dietetic write-up and final editor

JF - Literature search, final edit

CK - Literature search, clinical lead dietetic management write-up, amalgamation of the dietetic document

AM – Literature search, dietetic write-up and final editor

EM – Literature search, dietetic write-up and final editor

EC – Literature search, dietetic write-up and final editor

KH – Literature search, dietetic write-up and final editor

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CM – final editor

RA – final editor

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