BH4 IN THE MANAGEMENT OF PHENYLKETONURIA

ASIEM Clinical Guideline Document

Commissioned by the Australasian Society for Inborn Errors of Metabolism (ASIEM)

Index of Contents

Appendices

Background: Rationale

Phenylketonuria (PKU) is a treatable metabolic disorder that is routinely diagnosed through newborn screening in Australasia. The mainstay of treatment in PKU is dietary restriction of phenylalanine (Phe). It has been shown that oral supplementation of tetrahydrobiopterin (BH4) may improve blood Phe control and allow some relaxation of the dietary Phe restriction in responsive individuals with PKU. In Australia, Sapropterin, a synthetic form of BH4 (dispensed as 'Kuvan') is the only preparation currently registered for the use of Hyperphenylalaninaemia due to BH4 deficiency, and for PKU. A 5-year post marketing surveillance has been done in Australia with no adverse effects noted (a particular focus was renal function in patients from birth to 4 years of age). Although sapropterin is funded in Australia for the treatment of inherited BH4 deficiency, funding for BH4 treatment of PKU is not provided at this stage by the Pharmaceutical Benefit Scheme (PBS) (Australia) nor by Pharmac (New Zealand). In preparation for the possible future registration and funding of BH4 treatment by the above schemes, The Australasian Society for Inborn Errors of Metabolism (ASIEM) initiated and funded a large project canvassing experience and expectation, as well as identifying issues related to BH4 treatment. The aim of this project was to develop Australasian guidelines and education resources for metabolic healthcare teams on the use of BH4 for persons with PKU in Australasia.

Guidelines development group

The guidelines development group (GDG) consisted of seven Dietitians and one Consultant Physician with representation across all Australian states and New Zealand. The dietitians on the team have broad experience with paediatric, adult and pregnant patients with PKU. Two of the dietitians have personal experience with BH4 therapy. The medical clinician on the development team has been prescribing and using BH4 for patients in Victoria over the past 14 years.

Name	Role
Aoife Elliott (Project Officer)	Dietitian, Lady Cilento Children's Hospital, Brisbane, QLD
Prof Avihu Boneh (Medical Supervisor)	Consultant Metabolic Physician, Royal Children's Hospital, Melbourne, VIC
Barbara Dennison (Dietitian Supervisor until 2013)	Dietitian, The Children's Hospital at Westmead, Sydney, NSW
Annabel Sweeney (Dietitian Supervisor from 2013)	Dietitian, Women's and Children's Hospital, Adelaide, SA
Maureen Evans	Dietitian, Royal Children's Hospital, Melbourne, VIC
Rhonda Akroyd	Dietitian, Auckland City Hospital, Auckland, New Zealand
Mary Westbrook	Dietitian, Westmead Hospital, Sydney, NSW
Anne Rae	Dietitian, King Edward Memorial Hospital, Perth, WA
Christie Graham (from 2013)	Dietitian, The Children's Hospital at Westmead, Sydney, NSW

All members of the GDG are ASIEM members. The vast majority of the project work and write up was completed by the Project Officer Aoife Elliott with support and supervision provided by the Medical Supervisor, Prof Avihu Boneh, and the Dietitian supervisors Barbara Dennison (2012- 2013) and Annabel Sweeney (2013-2016).

Monthly teleconferences were held between the project officer and the medical and dietitian supervisors. Each meeting had an agenda and minutes were kept. Decisions regarding scope of the guidelines, stakeholder engagement, communication strategies and project planning were made at these meetings and recorded in the minutes to ensure that the project was kept on track. The minutes from each meeting were sent to all members of the GDG and comments were invited.

The GDG sought advice from the ASIEM BH4 Working Party as required throughout the project. The medical supervisor was the Chair of the ASIEM BH4 Working Party. The members of the ASIEM BH4 Working Party are listed below:

Name	Role
Prof Avihu Boneh (Chair ASIEM BH4 Working Party)	Consultant Metabolic Physician, Royal Children's Hospital, Melbourne, VIC
Dr Jim McGill	Consultant Metabolic Physician, Lady Cilento Children's Hospital, Brisbane, QLD
Prof John Christodoulou (Until December 2015) Dr Kaustuv Bhattacharya (from January 2016)	Consultant Metabolic Physician, The Children's Hospital at Westmead, Sydney, NSW
Dr Shanti Balasubramanian (Until December 2015)	Consultant Metabolic Physician, Princess Margaret Hospital for Children, Perth WA
Dr Drago Bratkovic	Consultant Metabolic Physician, Women's and Children's Hospital, Adelaide, SA

Guidelines Review Group

The Guidelines Review Panel is an independent panel that oversees the development of the guidelines and takes responsibility for monitoring its quality. The members of the Guidelines Review Panel were as follows:

Name	Role
Anita Inwood	Nurse Pracitioner, Lady Cilento Children's Hospital, Brisbane, QLD
Ashleigh Mitchell	Dietitian, The Children's Hospital at Westmead, Sydney, NSW
Emma Clover	Dietitian, Royal Adelaide Hospital, Adelaide, South Australia
Leah Queit	Dietitian, Princess Margaret Hospital, Perth, Western Australia
Erin Mullane	Dietitian, Melbourne, Victoria
Tracy Coote	Dietitian, Auckland City Hospital, New Zealand

Stakeholder Involvement:

Identified stakeholders included: children or adults with PKU, parents and carers of people with PKU, clinicians, dietitians, nurses, social workers and psychologists who regularly see patients with PKU across Australasia.

Conflict of Interests

All members of the Guidelines Development Group declared no conflict of interest that could interfere with their work on the guidelines.

This document refers to BH4 as a generic compound and is not referring to any currently available preparation of the compound for clinical use. It has been conceived, prepared and approved by health professionals who treat patients with PKU in Australia and New Zealand, based on professional considerations only.

Audience

The guidelines are intended for use by all healthcare professionals, particularly dietitians and clinicians, using BH4 therapy for individuals with PKU in Australasia. It is recognised that dietitians will be the health professionals most impacted by the guidelines in terms of time required to implement and manage patients on BH4 therapy.

Dissemination and Implementation strategy

As this was an ASIEM sponsored project the dissemination plan centred on dissemination initially through ASIEM and then through ASIEM members to other members of the clinical team looking after patients with PKU across Australasia. To ensure members were informed, project progress was presented to ASIEM members on two occasions at the HGSA Meeting in Queenstown in 2013 and the HGSA Meeting in Adelaide in 2014.

The guidelines will be supported with tools such as patient/carer information sheet and health professional algorithms for application in practice and will be disseminated through ASIEM. These have not been developed yet but once developed, all documents will be available for download on the ASIEM section of the HGSA Website.

Disclaimer

Australasian health professionals managing patients with PKU are advised to use clinical judgement, experience and expertise when deciding whether it is appropriate to apply guidelines. Recommendations in these guidelines are intended as a guide and may not be appropriate for use in every clinical situation.

The GDG recognises that recommendations that are to be implemented at a local level will be determined by the resources and structures within an individual service/department.

Funding

The Australasian Society for Inborn Errors of Metabolism (ASIEM) funded this project through a grant awarded to the GDG following a formal submission process.

Acknowledgements

The development of these guidelines was greatly assisted by the following people: Members of the ASIEM BH4 Delphi Panel, respondents to the international BH4 'experts' e-mail survey, patients and parents who responded to the questionnaires, and Anita Inwood (Recruitment in QLD).

Updating the guidelines

The usual shelf life for a clinical guideline is approximately 3 years. At the time of finalisation of these guidelines BH4 therapy has not yet been approved as a subsidised treatment for PKU in Australasia. Therefore the monitoring and auditing of the use of these guidelines cannot be standardised across all sites at this time. It is recommended that those sites who are currently using BH4 therapy or who plan to use BH4 therapy with their patient group should use these guidelines (and the education resources, once developed), to be used in conjunction with the guidelines. Feedback on these guidelines will therefore come from these sites and it is recommended that this feedback is incorporated into future updates of these guidelines and education tools, and is included as an agenda item for discussion at the ASIEM AGM in 2019. An updated evidence search with papers published after those included in this review will also be required.

1.0 INTRODUCTION

Phenylketonuria (PKU) results from deficiency in the activity of the enzyme phenylalanine hydroxylase (PAH). The cofactor for this enzyme is Tetrahydrobiopterin (BH4) [1]. It has been demonstrated through several placebo-controlled, double blind studies that approximately 20% to 50% of all patients with PKU respond to orally administered pharmacological doses of BH4 with significantly lower blood phenylalanine (Phe) concentrations, which are sustained, and thus increased dietary Phe tolerance allowing significant relaxation or even discontinuation of dietary Phe restriction [2-8]. Improved bone mass and significant improvements in white matter integrity have also been found [9, 10]. BH4 has been shown to be safe and well tolerated with only few adverse events reported [11]. BH4 may therefore provide an alternative to traditional diet therapy for some patients with PKU.

In Australia, two centres (RCH Melbourne and Westmead Children's Hospital, Sydney) have been assessing new patients with PKU for responsiveness to BH4 through a loading test, done shortly after the results of newborn screening are available. Both sites perform a loading test using 20mg/kg BH4 with monitoring over 24 hours to assess responsiveness. Westmead Children's Hospital currently offers the test only to newborns. RCH-Melbourne has offered the test to a few older children with PKU, adding a pre-test Phe load of 100mg/kg when the test was done on a child who had been already on the PKU diet, to avoid ceasing the diet [33, 49]. A longer trial using 20mg/kg/day of BH4 over one week in patients aged 2-18 years with a 25mg/kg/day Phe load for a lead-in period of two days and throughout the trial has also been reported by the Westmead group [34].

BH4 is an expensive treatment option but the cost of its use has not been formally assessed against the cost-saving of special PKU formulae, which are subsidised in Australia and New Zealand. BH4 is Therapeutic Goods Administration- (TGA) approved in Australia but it is not listed on the Pharmaceutical Benefits Scheme (PBS) for the treatment of patients with PKU. Some families have chosen to pay for the medication themselves. Currently there is only a small number of patients with PKU on BH4 in Australia, mainly in Victoria. All other states and territories, as well as New Zealand, are not offering BH4 therapy as an option due the financial burden it would place on families.

The introduction of BH4 as a treatment option for PKU has yielded many new challenges. Yet despite the fact that there are many papers published on BH4 loading protocols and BH4 therapy in the introductory phases, information on the long-term management of patients including national guidelines is lacking. Several centres have concluded that clinical protocols are required for correctly and efficiently establishing whether a patient will respond to BH4, which patient groups to test, and how to manage long-term dietary change while maintaining control of blood Phe, ensuring adequate nutrition and preventing excess weight gain [36, 37]. More specifically, protocols are needed for managing specific patient populations: infants, young children, adolescents, pregnant women, and previously untreated adults. Consideration must also be given to minimising the overall cost of treatment, avoidance of false expectations regarding responsiveness to treatment by patients and carers as well as the implications of this treatment in responsive patients in the long-term [20].

There are no studies to date that report patient/carer consultation or engagement in the development of guidelines or education resources for BH4 therapy. There is also little published data on national guidelines for BH4 therapy or detailed roles and responsibilities of individual multidisciplinary team members during the introduction and ongoing management of BH4 therapy [36, 37]. References to

aspects of the role of the dietitian and the implied role of the medical team and the social worker are reported in a few studies [36, 37]. However, individual team members' roles are not fully described in the literature.

If BH4 is eventually listed for use in the treatment of PKU in Australasia through the PBS and Pharmac, changes may need to be undertaken in the ongoing management of these patients and the resulting impact on the multidisciplinary teams (MDT) who manage them may be significant. Due to the relatively small size but wide geographical spread of the Australasian population, the frequent interstate movement of patients and the limited resources available to metabolic services, and considering consistency, continuity and equity, the development of guidelines and education resources for BH4 therapy for Australasian patients is essential and will benefit all patients and metabolic centres.

1.1 Aim/Remit of the project

To develop Australasian guidelines and education resources for the healthcare teams on the use of tetrahydrobiopterin (BH4) for persons with PKU in Australasia.

1.2 Scope

In preparation of this document, the GDG needed to take into account different patient settings and allow for varying healthcare structures including different multidisciplinary teams who care for patients with PKU across Australia and New Zealand to achieve the best clinical objectives for this patient group. Therefore, recommendations had to be applicable across the whole health service regardless of the age of the patient and his/her location of residency. This document includes BH4-treatment recommendations for patients with PKU of all ages.

It should be noted that this document does not deal with the type of loading test(s) and/or other methods of identifying responsive patients that should be done; this has been be left for the clinicians to agree upon separately.

Key Clinical Questions covered by the Guidelines:

1: What is a clinically significant response to BH4 therapy for the Australasian population?

2: Who should be offered a trial of treatment with BH4 therapy?

3: Should pre-trial Phe tolerance be assessed using a Phe load?

4: What assessment criteria should be used for the pre-trial work up of patients?

5: How should responders be managed during the initial dietary challenge phase?

6: How should patients on long term BH4 treatment be managed?

7: What is the role of the multidisciplinary team in BH4 therapy?

8: For patients/carers, what is the preferred method(s) of receiving information about treatment or management changes related to PKU?

2.0 METHODOLOGY

2.1 Ethics and Governance Approval

Ethics approval was obtained from the National Health and Medical Research Council (NHMRC) for Queensland, New South Wales and Victoria through the National Ethics Application Form (NEAF) version 2.1. Site specific approvals were sought and granted for Mater Health Services Brisbane, Royal Children's Hospital Brisbane, The Children's Hospital at Westmead, Westmead Hospital and the Royal Children's Hospital in Melbourne.

2.2 Literature Review

An extensive literature search was performed with the assistance of a clinical librarian in July 2013 and re-performed in January 2016 to capture any additional literature published while the guidelines were being completed. Pubmed, Scopus, Web of Knowledge and Embase were searched along with other sources such as Google Scholar. Papers that were published or accepted for publication in peer-reviewed journals were considered as evidence by the GDG. Conference paper abstracts were also reviewed. The search also included any monitoring, management or treatment guidelines or protocols. "Grey literature", available via websites such as AHRQ, NHMRC, NHS and other organisational websites were also reviewed. Key words for the search were identified by the GDG as shown in the table below. Non-English language papers were excluded from the search. The project officer critically appraised all full papers for accuracy and completeness. A summary of the results is presented in Appendix II.

Resource	Search strategy and search success
Pubmed	#1 (("Phenylketonurias"[Mesh] OR "Phenylketonuria, Maternal"[Mesh])) AND (tetrahydrobiopterin OR BH4 OR sapropterin OR Kuvan) Filters: published in the last 10 years AND #2 Search protocol* #3 Search (monitor* OR guideline* OR manag* OR treat*)
Scopus	(TITLE-ABS-KEY(hyperphenylalanimemia OR hyperphenylalanaemia OR phenylketonuria OR pku) AND TITLE-ABS-KEY(sapropterin OR tetrahydrobiopterin OR bh4 OR kuvan))
Web of Knowledge	Topic=(hyperphenylalanimemia OR hyperphenylalanaemia OR phenylketonuria OR pku) AND Topic=(sapropterin OR tetrahydrobiopterin OR bh4 OR kuvan)
Embase	(hyperphenylalanimemia OR hyperphenylalanaemia OR phenylketonuria/exp OR pku/exp) AND (sapropterin/exp OR tetrahydrobiopterin/exp OR bh4 OR kuvan/exp) AND [english]/lim AND [2003-2014]/py
Other sources	Google Scholar Grey Literature via websites such as AHRQ , NHMRC, NHS, and other organizational websites

2.3 Development & delivery of an "International PKU Experts" e-mail survey

In order to ensure the ASIEM Guidelines would be as practical as possible, an international e-mail survey to 11 'BH4 experts' (identified through their publications or conference presentations) was developed to capture hands-on, day- to-day experience not reported in the literature. A total of 10 questions were formulated by the GDG for the international e-mail survey. The process was as follows:

(1) Personalised e-mail sent to the main contributors to research, which included reference to protocols and longer term management of patients in the clinical setting.
(2) Questions were based around areas where there is no agreement in the literature and around practical management issues of patients, with any reference to what may not have been included in their published research i.e., lessons learned.
(3) After two weeks, a reminder e-mail was sent to those who had not responded, asking them to nominate another member of their team to respond to if they were not available for response.
(4) Results were incorporated into the guidelines document as 'international expert opinion'.

The survey was distributed in October 2013 and a total of 7 responses were received. A summary of the results from the international expert e-mail survey is shown in Appendix III.

2.4 Development & delivery of a postal 2-round Delphi Survey of "Australasian PKU Experts"

Australasian expert opinion was sought through a Consensus-Based Approach (using the Delphi technique) to address clinically relevant questions that were not adequately addressed in the literature or where there was conflicting reports or opinions. Australasian health professionals who regularly care for people with PKU, including clinicians, dietitians, nurses, social workers and psychologists across all Australian states and New Zealand were invited to participate in the process (a total of 51 available professionals). This was done in order to ensure that all opinions have been recorded and considered before the recommendations are finalised and to reduce the chance of postcode lottery of patient care across geographical borders.

Potential resource implications of applying the Guidelines were considered and explored through specific questions formulated in a Delphi Survey of Australasian health professionals dealing with PKU. Two rounds of postal Delphi surveys were performed (see Appendices IV and V for surveys)

Prior to commencing the process, consensus cutoff was set at 75%; i.e., consensus would be obtained only when 75% or more of participants agreed with a statement. A 5-point Likert scale was used to assess agreement to each statement. Outliers, i.e. those who expressed an extreme view were not excluded prior to reporting the percentage agreement. Quantitative and qualitative feedback was provided to panellists between rounds. Statements that achieved consensus in round 1 were excluded from round 2. Statements that achieved 'near' consensus were left unchanged and were included in round 2, with 'clarification points' to ensure that each statement was unambiguous and to demonstrate relevance. Statements where consensus was not achieved due to a true difference in opinion and where it was unlikely that agreement would be reached were excluded from round 2.

Of the invited Delphi panellists, 45 responded, representing a **90%** response rate. In round 2 of the Delphi survey (sent out in July 2014) 44 panellists were invited to participate (one panel member had retired), and 39 responded, representing **89%** response rate.

2.5 Development and Delivery of a Patient/Carer Phone Survey

A patient/carer telephone survey (see appendix I), was used to investigate areas of patient/carer concern around BH4 therapy and to assist in the development of the patient/carer education materials. As the majority of patients with PKU in Australasia are Caucasian and English speaking and the phone survey required a good level of spoken English, non-English speaking participants were excluded from the study. The incidence of PKU in Indigenous and Torres Strait Islander populations is extremely low. While these populations were not excluded from the study the nature and format of the survey and the rarity of PKU in this population no special considerations were made to include these participants. All participants were over the age of 18 years and either they or their child were currently attending the local metabolic clinic and were approached to consider consenting to participate in the study by their local metabolic dietitian (associate investigator)/metabolic nurse.

There were eight participant groups, with the aim of recruiting at least 6 participants in each of the groups. However, recruitment rate was lower than hoped for. Details of the eight groups were as follows:

Group	Perspective	No. of recruited individuals
1: Parents of Infants (<12 months) with PKU	Education requirements for parents who have only recently learned about PKU and its treatment. It ensured that infant specific issues were addressed	5
2: Parents of children with PKU aged 1-4 years	Education requirements related specifically to the toddler/young child developmental stage.	2
3: Parents of children with PKU aged 5-12 years	Education requirements related specifically to the primary school child developmental stage	3
4: Parents of children/ adolescents aged 13-17 years	Education requirements related specifically to the secondary school child developmental stage and the issues associated with this age group	2
5: Male adult patients with PKU	Personal perspective on education requirements related to BH4 therapy in adulthood	3
6: Female non-pregnant adult patients with PKU	Personal perspective on education requirements related to BH4 therapy in adulthood	3
7: Female patients with PKU currently or previously pregnant	Personal perspective on education requirements related to BH4 therapy in adulthood and during pregnancy	3
8: Parents of children who are treated with BH4 (all ages)	Parental perspective on personal experience and education requirements related to children (age 0-18 years) on BH4 treatment	7 (representing 9 children)

A specifically formulated questionnaire was developed by the GDG using open questions that sought to engage patients and carers in discussion around current knowledge and expectations of BH4 therapy, any potential barriers to BH4 therapy and how patients/carers prefer to receive information regarding management of PKU. Representation was sought from all patient age groups included patients with and without previous experience with BH4. Ethics approval was obtained prior to contacting any patients/carers.

2.6 Formation of Recommendations

The results of a comprehensive literature review on BH4 therapy in PKU, of the international e-mail survey of BH4 'experts' and of the two-round Australasian Delphi Surveys responses, with input from patients/carer were used for the construction of guidelines for Australasia. It should be acknowledged that the level of evidence for each of the conclusions is low because large double blind studies have not been published. Nevertheless, the guidelines are largely based on current experience and understanding.

Based on panellist feedback from the Delphi Survey, a summary of the Guidelines has to compliment the full guidelines document.

2.7 Reviewing the guidelines

A draft version of the guidelines document was sent to the clinical stakeholders that had been involved in the development phase. Comments on the draft document were invited from these stakeholders. The guidelines development group was advised of these comments and discussion occurred regarding any decision to incorporate these comments into the final version without compromising the evidence-based nature of the recommendations or to amend the wording in the document to ensure the reasoning behind a recommendation was more apparent.

The guidelines review group of experts (listed on page 5) reviewed the Guidelines document before its final acceptance.

3.0 ASIEM BH4 GUIDELINES SUMMARY

3.1 Who should be offered a trial of treatment with BH4 therapy?

Patient groups who are offered a trial of BH4 vary across the world. Blau et al recommend that the treatment is offered to all patients for the purpose of equality [15]. Other centres also offer the treatment to all patients (personal e-mail communication with Hilary Vernon, Johns Hopkins, 2013; Amy Cunningham, New Hayward Genetics Centre, New Orleans, 2013). While others offer to all with caveats for example at Boston Children's Hospital children are established on diet first but BH4 is offered to patients under 1 year especially for mild or moderate PKU however they have found that often for children < 4 years parents like to wait until the child is old enough to communicate regarding adverse events and MPKU patients are informed of the lack of data regarding outcomes in pregnancy before offering BH4, (personal e-mail communication with Fran Rohr on behalf of Harvey Levy, Boston Children's Hospital, 2013).

Others conclude due to the high cost of BH4 therapy that a trial should be offered to patients of highest priority and greatest clinical need. The neonatal BH4 loading test is currently reported as being routinely performed in neonates diagnosed with PKU in most of Europe (excluding the UK and Sweden), Western Canada [20] and in two states in Australia [33, 34]. BH4 is not listed for therapeutic use in Europe for children with PKU under the age of 4 years. Therefore centres in Europe wait until after the child's first birthday (personal e-mail communication with Skadi Beblo, University Children's Hospital, Leipzig, Germany, 2013). During pregnancy BH4 is classified a pregnancy class C drug due to lack of well-controlled studies [13] and therefore is not routinely offered as a treatment option in many countries. However, some centres will offer BH4 therapy as an option in pregnancy such as in Europe where the guidelines stipulate BH4 may be used if there is clear and proven danger to the developing foetus and where strict dietary therapy has not resulted in adequate Phe control [12]. Many centres in America also use BH4 in pregnancy with one of the large centres reporting that they would not choose pregnancy as the ideal time to start BH4, they would continue with BH4 for women already on it and would not hesitate to commence BH4 if necessary (personal e-mail communication with Barbara Burton, Chicago Children's Hospital, 2013).

Sufficient evidence regarding efficacy in the late diagnosed and untreated adult population is also lacking [13]. Nevertheless, some centres are beginning to treat this population group with good outcomes including overall health, and improvement of difficult behaviours (personal e-mail communication with Hilary Vernon, Johns Hopkins, 2013).

To gain consensus for who should be offered a trial in Australasia this question was posed to the Delphi panel. Consensus was obtained for only one group of patients, those with moderate PKU.

Who should be offered a trial of BH4 therapy?	Percent agreement of those who answered	Number of individuals who responded	Yes	No	Don't know/ unsure	Did not answer
Patients with **moderate** PKU (Phe levels >600-	92%	n= 37	n=34	n=0	n=3	n=2

1200µmol/L at diagnosis)						

There was a 72% agreement regarding the option to offer a BH4 therapy trial for patients with mild PKU (Phe levels <600µmol/L at diagnosis), just below the cut off for consensus. Panel members were also asked which patient age ranges/categories Australasia should include for consideration of BH4 therapy. The categories that gained consensus are listed below:

Patient age range/category to be considered for BH4 therapy	Percent agreement of those who answered	Total who answered this statement	Yes	No	Don't know/ unsure	Did not answer
newborns- 1 year	75%	n= 35 (90%)	n=29	n=1	n=5	n=4 (10%)
1-4 years	87%	n=38 (97%)	n=34	n=1	n=3	n=1 (3%)
4-8 years	87%	n=38 (97%)	n=34	n=1	n=3	n=1(3%)
18 years plus	77%	n=30 (92%)	n=30	n=2	n=4	n=3 (8%)

The remaining two categories late diagnosed/treated and maternal PKU did not gain support. Due to the lack of consensus in the literature, the GDG therefore based their recommendation on the results of the Australasian Delphi Survey.

Recommendation 1: Patients of any age with "mild PKU" (Phe levels >600-1200µmol/L at diagnosis) should be offered a trial of BH4 therapy.

3.2 What is a clinically significant response to BH4 therapy for the Australasian population?

A clinically significant response to BH4 therapy is usually defined using an arbitrary ≥30% reduction in blood Phe levels following treatment. This reduction in blood Phe appears to offer an adequate compromise between specificity and sensitivity during the loading test [14] however, some centres will accept lower response thresholds [15], [16] (personal e-mail communication with Barbara Burton, Children's Memorial Hospital, Chicago, 2013). Some centres accept a decline greater than the individual circadian Phe level variation [17] or recommend the consideration of other indicators of responsiveness including increase in tolerance of dietary Phe of up to 2-3 times baseline tolerance [18], [19], [20], [21], improvement in behaviour [13], or improved quality of life (QoL) measures [21]. Successful treatment with BH4 can lead to relaxation and in some cases cessation of the low Phe diet [18], [19], [22] however, continued blood Phe monitoring is recommended [23] as BH4 is proposed as an adjuvant therapy rather than an absolute replacement for the diet [24].

Since there are variable reports in the literature regarding how a clinically significant response to BH4 therapy is demonstrated, this question was posed in the ASIEM Delphi Survey and the results were:

Criterion	Percent Agreement
≥30% reduction in blood Phe concentrations (n=38)	95%
An increase in dietary Phe tolerance by ≥50% (n= 39)	89%
A decrease in Phe free formula prescription by at least 25% while maintaining adequate blood Phe control (n= 39)	77%

Recommendation 2: In Australasia a clinically significant response to BH4 therapy will be considered if it fulfils any of the three criteria:

(a) A ≥30% reduction in blood Phe concentrations following a BH4 loading test
(b) An increase in dietary Phe tolerance by ≥50% of that at baseline (i.e. without BH4)
(c) A decrease in Phe free formula prescription by at least 25% of that at baseline (i.e. without BH4) while maintaining adequate blood Phe control as per the accepted guidelines for PKU treatment

(Note: in Victoria, three patients have been diagnosed with hyperphenylalaninaemia and not treated with diet but noted to have gradually increased blood phe levels. BH4 was introduced at a low dose and blood Phe normalised. No formal loading test was done).

3.3 Should pre-trial Phe tolerance be assessed using a Phe load?

At present, there are two PKU population groups in Australasia: those who had a BH4 loading test or other means of determination of BH4 responsiveness, and those who did not. The following relates to the latter group.

Assessment of maximal Phe tolerance prior to a BH4 treatment is controversial. Some centres elect to assess tolerance pre-load [35] [20] while others do not [36], (personal e-mail communication with Barbara Burton, Chicago Children's Hospital, 2013 and Amy Cunningham, New Hayward Genetics Centre, New Orleans, 2013). The majority of centres recommend that dietary Phe supplementation may be given prior to commencing the BH4 trial in a patient who had been on a diet with blood Phe levels within the optimal range (per the PKU treatment guidelines) [36], (personal e-mail communication with Skadi Beblo, University Children's Hospital, Leipzig, Germany, 2013).

Due to the controversy in the literature the Australasian Delphi panellists were asked whether a pre-trial Phe load should be used if the patient is compliant with the PKU diet and current blood Phe levels are within the therapeutic range. There was no consensus to this question with 33% of respondents indicating 'don't know/unsure' and only 49% supportive of a pre-trial Phe load.

No recommendation can be made regarding whether pre-trial Phe tolerance should be assessed using a Phe load at this point.

3.4 What assessment criteria should be used for the pre-trial work up of patients?

A number of authors have recommended that an assessment should be made of the patient/carer willingness and ability to comply with the protocol including ongoing monitoring requirements, compliance with medications and ability to adhere to recommended dietary adjustments [12, 13]. An adequate level of discipline and organisational skills are essential for families with an older child or adult undergoing a trial and an ongoing high level of commitment to the therapy if it is successful ideally should be assessed pre-trial [12]. Furthermore, management of patient/carer expectations should be an essential ongoing process (personal e-mail communication with Hilary Vernon, Johns Hopkins 2013) [12]. Preparation of a patient/carer contract may also be considered with conditions for withdrawal of BH4 as a therapy option [12].

In order to determine what assessment criteria would be reasonable to include in the pre-trial work up of Australasian patients, Delphi panellists were asked to rate the importance of the assessment of certain criteria prior to offering a trial of BH4. The list of possible criteria was compiled from any recommendations reported in the literature. The criteria which gained consensus were:

Assessment criteria for pre-trial work up of patients	Agreement
Patient/carer's ability to comply with the BH4 protocol including medications, dietary advice and ongoing monitoring requirements (n=39)	95%
Patient's actual current dietary Phe tolerance (n=40)	83%
Patient/carer's expectations of BH4 therapy (n=41)	88%
Patient/carer's ability to comply with current prescribed PKU diet (n=39)	90%
Patient's current nutritional status including height, weight, BMI, current dietary intake (n= 40)	80%
Patient's recent clinic visit history (n= 40)	95%
Patient's baseline blood Phe levels (n= 40)	85%
Patient's current actual daily Phe-free formula intake (n= 39)	87%
Imminent life changes that may affect the trial e.g., new job/school, travel, new exercise regimen (n = 36)	80%
Whether the patient is currently catabolic (is unwell/has inadequate energy intake) (n = 36)	87%
Preparation of a patient/carer contract with conditions for withdrawal of BH4 as a therapy option should be considered prior to offering a trial of BH4 (n = 37)	90%

The recommendation for the assessment criteria to include for pre-trial work up of patients was derived from the results of the Australasian Delphi Survey.

Recommendation 3: Assessment criteria for pre-trial work up of patients should include:

(a) Patient/carer's ability to comply with the BH4 protocol
(b) Patient/carer's expectations of BH4 therapy
(c) Patient's recent clinic visit history
(d) Patient's actual current dietary Phe tolerance
(e) Patient/carer's ability to comply with current prescribed PKU diet
(f) Patient's current nutritional status including height, weight, BMI, current dietary intake
(g) Patient's baseline blood Phe levels
(h) Patient's current actual daily Phe-free formula intake
(i) Whether the patient is currently catabolic (is unwell/has inadequate energy intake)
(j) Imminent life changes that may affect the trial e.g., new job/school, travel, new exercise regimen
(k) Preparation of a patient/carer contract with conditions for withdrawal of BH4 as a therapy option should be considered prior to offering a trial of BH4

3.5 How should responders be managed during the dietary transition phase after starting BH4?

During the dietary transition phase, the time to reach final dietary Phe tolerance varies from a few weeks to several months [20]. Establishment of new Phe tolerance should be conducted under stable conditions when the patient is not pregnant, is not undergoing significant life changes and is not catabolic [8], [12], [13], [21]. It is important to confirm that the prescribed dietary Phe adjustments are both understood and adhered to thus preventing excessive or inadequate dietary Phe intake. This will ensure accurate interpretation of response during the introduction and adjustment phase [12]. A small number of authors have reported various step-wise approaches to the dietary transition [13], [20], [21]. The source of additional Phe used varies between centres as does the rate of introduction of dietary Phe and the concurrent monitoring requirements.

A number of authors have outlined protocols for the dietary transition and ongoing management of responders [13, 37-40]. These protocols vary with respect to blood Phe monitoring requirements, the rate, and quantity of the introduction of dietary Phe as well as the source of dietary Phe [37] [40]. Some centres introduce dietary Phe using commonplace whole foods [20] (personal e-mail communication with Hilary Vernon, Johns Hopkins 2013; Skadi Beblo, Leipzig, Germany, 2013; Smadar Abraham, Israel, 2013), while others use milk or egg powder initially switching to whole foods once tolerance is established [16], [31], [37], [41] (personal e-mail communication with Kathleen Huntington Portland, 2013 and Amy Cunningham, New Hayward Genetics Centre, New Orleans, 2013). It may be assumed that patients would rather consume additional protein as whole foods during the challenge period however reticence to eat certain high protein foods has been reported [16], [20] and this may affect the patient's ability to meet their dietary Phe goals. Conversely, others have reported that using whole foods is more natural for families and compliance is better although it can be more difficult to quantify and adjust protein intake (personal e-mail communication with Hilary Vernon, Johns Hopkins, 2013).

In view of the lack of consensus in the literature, the merits of each approach for the initial management of responders were considered by the Australasian experts. The Delphi Survey was used to determine how we should proceed with patient management once a clinically meaningful response to BH4 has been confirmed (i.e., the initial management of responders while the new Phe tolerance is being established). Statements that gained consensus were:

Initial management of responders/Dietary Transition phase	Agreement
The increase in Phe tolerance should be assessed using regular foods rather than Phe supplements (n = 35)	82%
Dietary Phe increases will be in 10-20% increments (n = 35)	85%
Total energy intake should be controlled for during the dietary transition phase (n= 40)	77%
While the new Phe tolerance is being assessed blood monitoring and dietary changes will be done weekly (n= 40)	93%
Patient/carer should be asked to keep a food record throughout the dietary transition phase (n= 40)	88%
Patients will require more frequent outpatient clinic follow up with the MDT during the dietary transition phase (n= 40)	78%
The dietitian will be responsible for making dietary modifications during the dietary transition phase (n= 40)	93%
Phe free formula should continue unchanged until the new Phe tolerance is established (n = 35)	85%
If using regular foods to assess increase in Phe tolerance this would be done by switching to regular versions of the low protein (LP) foods usually consumed in the diet e.g., bread, pasta. If tolerated, other high protein foods would then be introduced such as dairy products, meat, eggs and fish (n= 40)	78%

Recommendation 4: Initial management of responders should include the following:

(a) The increase in Phe tolerance should be assessed using regular foods rather than Phe supplements
(b) This would be done by switching to regular versions of the low protein (LP) foods usually consumed in the diet e.g., bread, pasta. If tolerated, other high protein foods would then be introduced such as dairy products, meat, eggs and fish
(c) Dietary Phe increases will be in 10-20% increments
(d) Total energy intake should be adequate to ensure there is appropriate weight gain or stability, i.e. no weight loss which can have negative impact on phe levels
(e) Phe free formula should continue unchanged until the new Phe tolerance is established
(f) While the new Phe tolerance is being assessed blood monitoring and dietary changes will be done weekly
(g) The dietitian will be responsible for making the dietary changes during the dietary challenge phase
(h) Patient/carer should be asked to keep a food record and will require more frequent outpatient clinic follow up with the MDT during the dietary challenge phase

3.6 How should patients on long term BH4 treatment be managed?

The decision to continue BH4 treatment after the initial assessment period is not always straightforward. The BH4 challenge may be viewed as a screening test with long-term supplementation and ongoing evaluation required to demonstrate true responsiveness [11]. Therefore, a decision to offer a patient ongoing BH4 therapy following the loading test and dietary modification may need to be made on a case by case basis, assessing the available evidence in the context of each patient [21] [15].

3.6.1 Removal of low protein foods and Phe-free formula

The introduction of BH4 alongside the usual dietary management of PKU is a complex issue [39]. Following a decision to continue BH4 therapy consideration must be given to the titration of BH4 dosage, the removal of special low protein (LP) or low-Phe food products (including any LP food allowances) and the reduction or removal of Phe-free formula. Most studies conclude that BH4 responsive patients no longer require special LP products in their diet [42]. As these products are mainly used to provide adequate energy and variety in the protein restricted diet they rarely provide a significant supply of micronutrients. Therefore, if adequate variety and energy can be derived from the diet with the new natural protein allowance on BH4 therapy, LP products and the accompanying low protein food grant could be ceased to minimise the cost of treatment. This question was posed to Delphi panellists to determine a consensus approach for Australasia (see table below).

Reduction of Phe-free formula is recommended when total protein requirements can be met through diet. Singh et al have adopted a stepwise approach to the removal of formula which occurs in 25% reductions after Phe tolerance has been established [21]. MacDonald et al recommend that formula is not reduced

unless all vitamin and mineral requirements are also able to be met through diet however, they do not specify exactly how this is to occur practically [12]. This group and others recommend that it is essential for patients to remain familiar with and accepting of the taste of Phe-free formula in case it needs to be reintroduced in illness, pregnancy or if BH4 therapy is discontinued [39]. Other centres have reported a complete or near complete cessation of Phe-free formula [42] without reintroduction during illness [42](personal e-mail communication with Barbara Burton, Children's Memorial Hospital, Chicago, 2013). Careful consideration of dietary adequacy should be undertaken when Phe-free formula intake is being reduced.

These questions were presented to the Delphi participants. The responses are shown below:

Statement	Agreement
Low protein products and the accompanying low protein food grant should be ceased if adequate energy and variety can be derived from the diet with the new dietary protein allowance(as assessed by the dietitian) (n= 39)	87%
Once the new dietary Phe tolerance and optimal BH4 dosage have been established the next step is to assess if Phe-free formula can be reduced (n= 40)	85%
Reduction of Phe-free formula is recommended when estimated total protein requirements can be met through diet and blood Phe is stable (n= 40)	80%
Once estimated total protein requirements can be met through diet and blood Phe is stable, Phe-free formula should be reduced in quantities of 25% per stage (n= 39	77%

Based on the above, the following recommendation is made:

Recommendation 5: Removal of special low protein / low Phe foods and Phe-free formula

(a) The special low protein/low phenylalanine food products and the food grant should be ceased if adequate energy and variety can be derived from the diet with the new dietary protein allowance (as assessed by the dietitian).
(b) Once the new dietary Phe tolerance and optimal BH4 dosage have been established Phe-free formula can be reduced
(c) Reduction of Phe-free formula in quantities of 25% per stage is recommended when estimated total protein requirements can be met through diet and blood Phe is stable.

3.6.2 Dietary adequacy on BH4

Reports on overall dietary adequacy while on long-term BH4 therapy vary. Some authors report improved growth parameters such as height z score [31] whereas others conclude that no improvement has been observed in anthropometric variables [39, 44]. Singh et. al. reported a significant decrease in energy per kilogram body weight over a 24 month period associated with a decrease in prescribed quantity of Phe-free amino acid formula [31]. On the other hand, others report no difference on energy intake [20], [42]. Singh et. al. also reported that plasma albumin and total protein remained stable within the reference

range during treatment while plasma transthyretin concentrations were at the minimum reference range at baseline (19.8+/ 3.3mg/dl) but increased during the first 12 months of follow-up ($p<0.001$) and then stabilized. In this study haemoglobin and haematocrit concentrations started improving significantly ($p<0.001$) 9 months into BH4 therapy and then stabilised after 12 months [31]. Hennermann et al report intakes below daily recommendations for calcium in 8 patients, vitamin B12 in 5 patients and iron in 2 patients out of a cohort of 18 patients on a liberalised diet without additional Phe-free formula [20].

Recent studies have highlighted the potential micronutrient deficits that may occur on a relaxed diet without Phe-free formula; or on a protein intake of <0.5g/kg from Phe-free formula; or on a protein intake <120% of the current recommendations [43]. Thiele et. al. assessed the quality of diet post BH4 implementation in eight BH4-responsive children and found dietary consumption of vitamin D, iron, calcium, iodine and zinc were significantly decreased during BH4 treatment with no significant difference in macronutrient or energy intake [42]. In this study the dietary intake of almost all micronutrients was considerably lower in the BH4 treated children compared to healthy children in the population. The decreased micronutrient consumption in this population was mainly due to a decrease or cessation of the Phe-free amino acid supplement and a reduction in fruit intake on BH4 therapy. By contrast, Lambruschini et. al. reported no differences in nutritional markers even when Phe-free formula was ceased, yet they report that plasma selenium levels increased without significant changes to dietary intake [40]. It is recommended that certain patients on a liberalized diet without additional intake of Phe-free formula may require additional supplementation of vitamins and micronutrients [13], [20], [43].

Although there are no consistent findings regarding overall dietary adequacy while on long-term BH4 therapy it is important that dietary adequacy continues to be assessed when non-dietary treatments are used as either an adjunct or replacement to traditional diet therapy for PKU [45]. A number of centres have recommended regular assessment of nutritional status while on BH4 therapy using biochemical markers [12]. Acosta et. al. suggest a list of measurements including plasma albumin, transthyretin, ferritin, iron, haemoglobin, selenium, zinc, calcium and fatty acids which should be completed once pre-BH4 therapy, 6 monthly post BH4 introduction and during the Phe introduction phase and then annually post stabilisation in line with patients not on BH4 therapy.

In order to gain consensus for an Australasian approach to the assessment of nutritional adequacy a number of measures were presented to the Delphi Panel to rate. The measures/statements that gained consensus are listed here:

Measure/Statement	Agreement
Weight (n= 40)	100%
Height/Length (n= 40)	100%
BMI or BMI percentile (n= 40)	98%
Patient's current actual daily Phe free formula intake (if relevant) (n= 40)	95%
Patient/carer's ability to comply with current prescribed/recommended diet (n= 40)	100%
Diet history or diet diary including assessment of core food groups, overall energy intake and vitamin and mineral adequacy (n= 40)	98%
Plasma amino acids (n= 40)	78%
Iron studies (n= 40)	90%
Vitamin B12 (n= 40	95%
Vitamin D (n= 40)	93%
Zinc (n= 40)	83%
Nutritional biochemical markers should be completed on an **annual basis** after the first 12 months post BH4 introduction (n= 40	88%

3.6.3 Ongoing monitoring

Unchanged tyrosine (Tyr) levels have been reported while on BH4 therapy [18, 49]. Humphrey et al also reported reduced variability in Phe: Tyr ratio in BH4 responsive patients compared to age matched controls who were not responsive to BH4 [49]. Transiently low Phe levels (<26 µmol/L) have been reported on BH4 therapy when insufficient dietary Phe is consumed [8]. Therefore, frequent monitoring of Phe and Tyr (daily to weekly depending on the centre) is recommended during the dietary transition phase with reversion to usual local monitoring guidelines once stabilised [12]. More frequent clinic visits may also be required during the initial phases of treatment on BH4 [12] particularly for children during phases of rapid growth (personal communication with Hilary Vernon, Johns Hopkins, 2013).

Although detailed guidelines outlining the long-term management of responsive patients are crucial [15] they are only beginning to emerge [20], [12], [13]. There are no widely accepted guidelines for the long term management of patients on BH4 treatment. Therefore key recommendations from any published guidelines were included in the Australasian Delphi Survey to attempt to gain consensus for an Australasian approach to long term management. Panellists were asked to rate statements according to what they thought clinics in Australasia should assess/monitor/consider and what steps would be taken during long term management of patients on BH4. Statements which received consensus were:

Statement	Agreement
Compliance & cooperation of the patient/carer with BH4 therapy including ability to adhere to ongoing monitoring requirements and dietary recommendations should be assessed/considered (n= 40)	98%
Patient's overall longer term response to BH4 therapy at the end of the dietary transition phase should be assessed (n= 40)	98%
Once established on BH4 therapy and the diet is stabilised**, blood monitoring and clinic visits** will occur at the **same frequency** as for patients with PKU who are not on BH4 treatment (n= 41)	81%
The ongoing **prescription for BH4 should be reassessed** and adjusted as appropriate **at each clinic visit** (n= 41)	83%
Vitamin and mineral supplements may be required if dietary assessment or patient's nutritional biomarkers indicate they are necessary (n= 41)	98%
Patients/carers should be **educated** about achieving a **healthy diet with increased Phe tolerance** (n= 41)	100%
Assessment of patient's current **nutritional status** including height, weight, BMI, current dietary intake should be completed regularly for patients on BH4 therapy (n= 41)	95%
Assessment of patient's current **nutritional biomarkers** such as iron studies, pre-albumin, Vitamin B12 should be completed regularly for patients on BH4 therapy)n= 41)	88%
Where **possible**, **neuropsychiatric and/or educational assessments** should be completed regularly on patients to **assess outcome** on BH4 therapy (n= 41)	85%

Based on the above, the following recommendation is made with regards to dietary adequacy and long term management:

Recommendation 6: Long term management and monitoring of responders: Assessment and schedule:

(a) Patients will be assessed with regards to their compliance & cooperation of the patient/carer with BH4 therapy including ability to adhere to ongoing monitoring requirements and dietary recommendations
(b) At the end of the dietary transition phase, patients will be assessed with regards to their overall longer term response to BH4 therapy
(c) Once established on BH4 therapy and the diet is stabilised, clinic visits and blood monitoring will occur at the same frequency as for other patients with PKU who are not on BH4 treatment
(d) The ongoing prescription for BH4 should be reassessed and adjusted as appropriate at each clinic visit. Once the new dietary Phe tolerance is established and blood Phe is stable BH4 should be titrated to the minimum quantity per kg required to maintain adequate blood Phe control
(e) Patients/carers should be educated about achieving a healthy diet with increased Phe tolerance
(f) Vitamin and mineral supplements may be required if dietary assessment or patient's nutritional biomarkers indicate they are necessary
(g) Assessment of patient's nutritional status including height/length, weight, BMI or BMI percentile, recent diet history or diet diary including assessment of core food groups, current actual daily Phe free formula intake (if relevant), overall energy intake and vitamin and mineral adequacy should be completed regularly for patients on BH4 therapy
(h) Assessment of patient's nutritional biochemical markers such as plasma amino acids, iron studies, zinc, Vitamin B12 and Vitamin D should be completed regularly for patients on BH4 therapy and on an annual basis after the first 12 months post BH4 introduction
(i) Where possible, neuropsychiatric and/or educational assessments should be completed

3.6.4 Sick day management while on BH4 therapy

There are no clear guidelines covering BH4 therapy during illness. Some centres have reported that it may be necessary to reintroduce or increase previously decreased volumes of Phe-free formula during times of catabolic stress such as trauma or febrile illness [12, 18, 46-48]. Others such as Johns Hopkins do not adjust diet or medications unless there is a prolonged illness (personal communication with Hilary Vernon, Johns Hopkins, 2013) or not at all (personal communications with Barbara Burton, Children's Memorial Hospital, Chicago, 2013; Fran Rohr, Boston Children's Hospital, 2013; Amy Cunningham, New Hayward Genetics Centre, New Orleans, 2014). Sick day management while on BH4 therapy was also examined in the Delphi Survey however there was no consensus on the approach that should be taken.

With no clear guidelines in the literature and no consensus from the panel of Australasian experts there is no recommendation for sick day management at this stage

3.7 THE ROLE OF THE MULTIDISCIPLINARY TEAM IN BH4 THERAPY

There are no published reports describing in detail the role and responsibilities of individual multidisciplinary team (MDT) members during the introduction and ongoing management of BH4 therapy [12, 13]. References to aspects of the role of the dietitian and the implied role of the medical team and the social worker are reported in a few studies [12, 13]. When this question was posed in the international e-mail survey of BH4 experts in October 2013 most centres reported that they have defined roles, namely: Physician: initiates the discussion about BH4 treatment with patients and prescribes it (Fran Rohr on behalf of Harvey Levy, Boston Children's Hospital), checks general health, calculates BH4, Phe and amino acid mixtures (Skadi Beblo, University Children's Hospital, Leipzig, Germany); Dietitian: follows up blood Phe levels and manages dietary changes (Fran Rohr on behalf of Harvey Levy, Boston Children's Hospital; Kathleen Huntington, Portland), and "hands on management" (Amy Cunningham, New Hayward Genetics Centre, New Orleans). At Chicago Children's Hospital the clinic coordinator (genetic counsellor) describes the treatment trial, obtains the consent and the dietitian reports the Phe results and consults with the physician regarding determination of responsiveness and continuation of treatment, however it was noted that there can be some 'blurring of roles' (Barbara Burton, Chicago Children's Hospital).

Delphi panellists were asked which health professional is most suitable to complete certain key tasks with respect to BH4 management. The results are outlined below:

Task	Health Professional	Agreement
Initial discussion with patient/carer about potential trial of BH4 (n= 45)	Clinician	100%
Detailed discussion about what would be involved in the BH4 trial (n= 45)	Clinician Dietitian	78% 73%*
Assessment of patient/carer's **ability to comply** with BH4 protocol including medications, dietary advice and ongoing monitoring requirements (n= 45)	Dietitian Clinician	93% 73%*
Assessment of patient/carer's **expectations of BH4 therapy** (n= 45)	Clinician Dietitian	73%* 73%*
Assessment of whether the patient is currently catabolic (is unwell or has an inadequate energy intake) (n= 45)	Dietitian Clinician	78% 76%
Assessment of patient's current nutritional biomarkers such as iron studies, pre-albumin, Vitamin B12 (n= 45)	Clinician Dietitian	82% 76%
Patient's baseline blood Phe levels (n= 45)	Clinician	84%
Requesting of blood tests during assessment of new Phe tolerance (n= 45)	Clinician	87%
Reporting of blood test results during assessment of new Phe tolerance (n = 45)	Dietitian	76%
Decision on whether the patient will continue on BH4 therapy long term (n= 45)	Clinician	100%

Decision on cessation of low protein food allowance (n= 45)	Clinician	89%
Decision on reduction of Phe-free formula (n= 45)	Dietitian	96%
Decision on sick day management while on BH4 therapy (n= 45)	Clinician	82%
Ordering of biochemical nutritional markers while on BH4 (n= 45)	Clinician	93%

∗Did not reach consensus of 75% however may be included as recommendations for potential roles of these staff members.

Note: There was no consensus regarding the following:

Assessment of patient's recent clinic visit history. If has not recently attended, decision on whether patient/carer will need to attend ≥1 clinic prior to being offered a trial (n= 45)	Clinician	62%∗

This may be interpreted as a preference for a collective responsibility of the team. In that respect, the nurse and social worked may provide background information and assessment.

Recommendation 7: In BH4 Management:

(a) The Clinician will have primary responsibility for:

I. **Initial discussion with patient/carer about potential trial of BH4**
II. **Detailed discussion about what would be involved in the BH4 trial**
III. **Assessment of patient's baseline blood Phe levels**
IV. **Requesting of bloods during assessment of new Phe tolerance**
V. **Decision on whether patient will continue on BH4 therapy long term**
VI. **Decision on cessation of low protein food allowance (if applicable)**
VII. **Decision on sick day management while on BH4 therapy**
VIII. **Ordering of biochemical nutritional markers while on BH4 (if applicable)**

(b) The Clinician and the dietitian will be responsible for:

I. **Assessment of patient/carer's ability to comply with BH4 protocol including medications, dietary advice and ongoing monitoring requirements**
II. **Assessment of patient/carer's expectations of BH4 therapy**
III. **Assessment of whether the patient is currently catabolic (is unwell or has an inadequate energy intake)**

(c) The Dietitian will be responsible for:

I. **Assessment of patient/carer's ability to comply with BH4 protocol including medications, dietary advice and ongoing monitoring requirements**
II. **Reporting of bloods during assessment of new Phe tolerance**
III. **Decision on reduction of Phe-free formula**

(d) All members of the treating team will be responsible for:

I. **Assessment of the patient's recent clinic visit history. If has not recently attended, decision on whether patient/carer will need to attend ≥1 clinic prior to being offered a trial**
II. **Assessment of any imminent life changes that may affect the treatment e.g., new job/school, travel, new exercise regimen etc.**

3.8 COMMUNICATION WITH PATIENTS/PARENTS

There are no studies to date that report patient/carer consultation or engagement in the development of protocols or education resources for BH4 therapy. There are also no published data on the availability of specifically developed patient or clinician education resources for BH4 therapy. The GDG decided to develop these guidelines for BH4 therapy using patient/carer engagement through the patient/carer phone survey and the results of the clinician Delphi survey. A full presentation of parents' and patients' perspective is provided in Appendix IX.

3.8.1 Patients'/Carers' preferred presentation of guidelines

We surveyed 21 (including one parent of two patients) participants from Queensland and New South Wales across all major patient groups to investigate areas of patient/carer concern around BH4 therapy and to assist in the development of the patient/carer education materials. In addition, we surveyed 7 parents from Victoria (representing 9 patients) whose children are on BH4 treatment.

Using a scale of 1-10 with 1 being the lowest score and 10 being the highest score patients/carers were asked what their preferred method(s) of receiving information about treatment or management changes was. The results of this survey are shown below:

Method of receiving Information	Mean / 10*	Range*	Median /10*
Face to face in clinic as a one on one appointment (n=27)	**8.17**	1-10	**9**
Face to face in clinic in a group with other people with PKU/caring for people with PKU (n=27)	**6.28**	1-10	**7**
Written information in a booklet/information sheet (n=27)	**7.44**	4-10	**7.5**
Insert for the PKU handbook (n=25, n/a=2)	**6.78**	1-10	**7**
Online on a website as written information (n=27)	**7.54**	2-10	**7.5**
Online on a website as a voice over power point presentation (n=207	**6.59**	2-10	**7**
Over the phone (n=27)	**7.87**	1-10	**9**
Other: post - 4 participants nominated this method (n=4)	**9.25**	7.5-9.5	**8.88**
Other: email- 5 participants nominated this method (n=10)	**9.75**	7-10	**9.35**
Other: texting of blood results to phone with return phone number if wished to discuss results- 1 participant nominated this method (n=1)	**8**	8	

The preferred format of the written information was:

Preferred method of written information	Yes	No
Short and succinct with key points only (e.g., up to 2 pages long)	3	0
Longer with more detail to refer to (e.g., 3 pages plus long	3	2
A combination of both i.e., a summary page with more detail provided for you to refer to as required, or at a later date	18	0

As there are no published data on specifically developed patient education resources for patients on BH4 therapy that used patient/carer consultation the GDG based their recommendation solely on the results of the Patient/Carer Phone Survey:

Recommendation 8: Presentation of guidelines to parents/guardians

(a) Information to parents should be provided face to face individually or in a group in clinic or by phone
(b) Written Information to patients/carers about treatment or management changes should be delivered by email or post in the format of a combination of a summary page with more detail also provided to refer to as required or at a later date.
(c) Information to parents should include available data on side effects and long term outcome, as well as practical information regarding the preparation, delivery and stability of BH4 or sapropterin.

It should be noted that no distinction was made in the questionnaires to parents between initial information and follow up information. It is acknowledged that this may have caused some confusion. We assume that that communication by phone and/or email are suitable for follow-up but not for initial discussion.

3.8.2 Health Professionals preferred presentation of guidelines

The preferred mode of presentation of the clinical guidelines to health professionals is a combination of summary pages with more detail provided that they can refer to at a later date (82% of Delphi panellists; n= 45).

3.9 CONCLUSIONS

Detailed guidelines for long-term management of patients with PKU on BH4 therapy including information on dealing with the day-to-day practical management of patients are scarce. There are no reported national guidelines for the implementation and ongoing management of patients on BH4 therapy, no agreed strategies for the use of BH4 in conjunction with diet, no definitions of roles and responsibilities of the multi-disciplinary team during BH4 therapy and no reports of patient/carer education materials developed through patient/carer engagement. This document represents an effort to fill in these gaps and will serve as a platform for metabolic centres in Australasia for a streamlined approach to treatment of patients with PKU who are BH4 responsive.

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