OREGON HEALTH AND SCIENCE UNIVERSITY
SCHOOL OF MEDICINE—GRADUATE STUDIES

DEVELOPMENT AND EVALUATION OF AN EDUCATIONAL TOOL TO COUNT PROTEIN FOR ADOLESCENTS AND YOUNG ADULTS WITH PKU

By

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A THESIS

Presented to the Graduate Programs in Human Nutrition
and the Oregon Health and Science University School of Medicine
in partial fulfillment of
the requirements for the degree of

Master of Science

December 2016

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ACKNOWLEDGEMENTS

Completing this thesis has been a period of immense learning for me, not only in the scientific arena, but on a personal and professional level as well. I would like to express my special appreciation and thanks to my advisor, Dr. Sandy Van Calcar. You have been a tremendous mentor and have taught me the value of hard work and dedication. I would also like to thank my committee members, Dr. Joyanna Hansen, Jeri Finn, and Maureen McCarthy, for your invaluable input and support. Thank you to Mike Lasarev for providing your vast knowledge of statistics to aide me in analyzing my data. This thesis would not have been possible without the help of you all.

A special thank you to my family and closest friends who have supported me wholeheartedly throughout my educational journey. Words cannot express how grateful I am to my mother and father for all the sacrifices you have made on my behalf to get me where I am today, and to my friends for keeping me sane!

LIST OF ABBREVIATIONS

CDRC	Child Development & Rehabilitation Center
DANEH	Developing & Assessing Nutrition Education Handouts
GMDI	Genetic Metabolic Dietitians International
GPHN	Graduate Programs in Human Nutrition
gm	Gram
IRB	Institutional Review Board
IQ	Intelligence Quotient
LNAA	Large Neutral Amino Acids
mg	Milligram
OHSU	Oregon Health & Science University
Phe	Phenylalanine
PAH	Phenylalanine Hydroxylase
PKU	Phenylketonuria
PI	Principal Investigator
QOL	Quality of Life
RD	Registered Dietitian
BH_4	Tetrahydrobiopterin
Tyr	Tyrosine
USDA	United States Department of Agriculture

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ABSTRACT

Background: Phenylketonuria (PKU) requires life-long dietary treatment to maintain optimum cognitive function. However, it is often difficult for adolescents and young adults to continue dietary treatment and maintain metabolic control. Counting protein is a new system for dietary management of PKU involving a simplified approach to the traditional diet of counting milligrams (mg) of phenylalanine (Phe). This simplified approach involves “free” consumption of most fruits and vegetables and counting protein content of all remaining foods containing higher amounts of Phe. Studies to date have shown that control of blood Phe concentrations can be just as effective with protein counting as with the traditional method, and protein counting may be an easier method to manage Phe intake. However, there are few educational resources for this dietary intervention. There is a need for age-appropriate materials that can be used to teach adolescents and young adults with PKU how to count and track their protein intake. This study aimed to develop an age-appropriate education tool and to evaluate its effectiveness by instructing a cohort of adolescents and young adults with PKU to count dietary protein to more effectively manage their metabolic disorder.

Methods: We developed an educational tool to teach adolescents and young adults with PKU a simplified approach to tracking Phe intake. The tool was evaluated by metabolic RDs (n=9) using the Developing and Assessing Nutrition

Education Handouts (DANEH) Checklist, developed by the Academy of Nutrition and Dietetics Foundation to assess its quality and usefulness, and a mean sum of scores >80% was considered high quality. After evaluation, the educational tool was used during an education session with adolescents and young adults (n=10, ages 15-25 years) followed by the Metabolic Clinic at Oregon Health and Science University (OHSU). Pre- and post-test questionnaires were developed to assess knowledge and motivation to count dietary protein. A two-sided binomial distribution test was performed on each question to determine any significant changes to participant responses between pre- and post-tests.

Results: The mean score from the DANEH checklist evaluations was 18 out of 20 (90%) indicating that the educational tool was of high quality. No significant differences were found in knowledge about protein counting or motivation to use this easier method to track dietary Phe intake. There was a trend towards improvement in knowledge about protein counting from pre- to post-test scores. There was a trend towards subjects indicating that they were “more unlikely” to track dietary protein on the post-test compared with pre-test. However, post-test qualitative answers suggested that these negative attitudes may be attributed to factors other than the effectiveness of the handout and tracking method.

Conclusions: These results suggest that protein counting could be an easier method for adolescents and young adults to understand than the traditional

method of counting Phe. Practitioners need to consider introducing simplified diet education at an earlier age to promote earlier transition to self-management, and encourage support from parents and peers when developing an education strategy for adolescents and young adults with PKU. Improved education tools and strategies can help improve treatment compliance and ultimately, overall quality of life (QOL).

CHAPTER 1: SIGNIFICANCE, SPECIFIC AIMS, AND HYPOTHESIS

PKU is an inherited metabolic disorder caused by a deficiency in phenylalanine hydroxylase (PAH), the enzyme responsible for the conversion of Phe to tyrosine (Tyr). Without this enzyme activity, Phe accumulates in the blood and brain and if untreated from birth, causes severe mental retardation. In individuals who were started on a therapeutic diet as neonates, life-long dietary restriction is required for optimum cognitive functioning. Current medical nutrition therapy for this disorder includes two major components: 1. a Phe-free medical food to meet total protein requirements and, 2. dietary protein restriction to reduce Phe intake to maintain blood Phe concentrations within the recommended range of 120 to 360 µmol/L (14,15).

For adolescents and young adults with PKU, this diet treatment can be difficult to understand and follow, and may be especially difficult for those with impaired executive functioning as a result of long-term elevations in plasma Phe. The dietitians in the OHSU Metabolic Clinic estimate that approximately 80% of adolescents and young adults with PKU who are followed by their clinic do not maintain blood Phe concentrations within the recommended treatment range. More effective nutrition education strategies are needed for adolescents and young adults to effectively manage their disorder over the long-term, with the overall goal of maintaining normal cognitive function.

Current dietary recommendations for this population involve a complicated system of counting total mg of Phe in natural protein sources. Emerging research

is showing that a more simplified approach to counting Phe in the diet could potentially be as effective as, if not more effective than, the current method (36). One such approach includes counting grams (gm) of protein rather than mg of Phe in high-Phe foods, but not counting “free” foods that include fruits, most vegetables, and low protein grain products containing <75 mg/100 gm serving. Counting gm of protein in food may be an easier method and concept for those with PKU to understand and, thus, may improve adherence.

In order to compare the effectiveness of counting protein with that of counting total Phe in the diet, patients need to be taught how to determine protein content of foods and to track their protein intake. Counting protein is a new system in dietary management of PKU, and there are few educational resources for this as an intervention to manage Phe intake. There is a need for age-appropriate educational materials that can be used to teach adolescents and young adults with PKU how to more effectively count and track their protein intake. In this study, we developed an educational tool specifically for adolescents and young adults with PKU and evaluated the effectiveness of this educational approach on patient knowledge and dietary adherence.

Hypothesis:

We hypothesized that with an age-appropriate and effective educational tool, adolescents and young adults with PKU will have a better understanding of how to count dietary protein to control their Phe intake and thus will improve their blood Phe concentrations.

Specific Aim 1:

To develop an age-appropriate educational tool that will instruct adolescents and young adults with PKU to count protein in their diet to more effectively manage their metabolic disorder, and to evaluate the quality and effectiveness of this educational tool by asking a group of metabolic dietitians to read and assess the tool by completing a standardized questionnaire.

Specific Aim 2:

To evaluate the effectiveness of the newly-developed educational tool by instructing a cohort of adolescents and young adults with PKU to count dietary protein using this tool and assessing their knowledge and clinical outcomes using a pre- and post-test format.

CHAPTER 2: BACKGROUND

Introduction

PKU, also known as PAH deficiency, is an autosomal recessive inborn error of metabolism that is caused by the enzymatic deficiency of the hepatic PAH enzyme. This enzyme is required for the conversion of the essential amino acid Phe into Tyr. Affected individuals have a disruption in this metabolic pathway resulting in the accumulation of toxic concentrations of Phe in the blood and the brain as well as a deficiency in Tyr (1) **(Figure 1)**. Tyr becomes a conditionally essential amino acid and thus must be provided in the diet. Tyr is a precursor of dopamine as well as other catecholamine neurotransmitters such as epinephrine and norepinephrine.

In untreated PKU, the accumulation of high concentrations of Phe in the blood increases Phe in the brain leading to severe neurocognitive and neuro-motor impairment. One proposed mechanism of cognitive dysfunction is the competitive inhibition at the blood brain barrier of high levels of Phe with other large neutral amino acids (LNAAs), including Tyr, causing lower concentrations of neurotransmitters in the brain (2). The reduced cerebral protein synthesis from this inhibitory process is thought to be the main mechanism for cognitive dysfunction in this disorder (2,3). Poor myelination and reduced dendritic branching of neurons has been found in cerebral tissue of mice models and individuals with PKU collected post-mortem which is thought to be a consequence of the reduced cerebral protein synthesis (2,3).

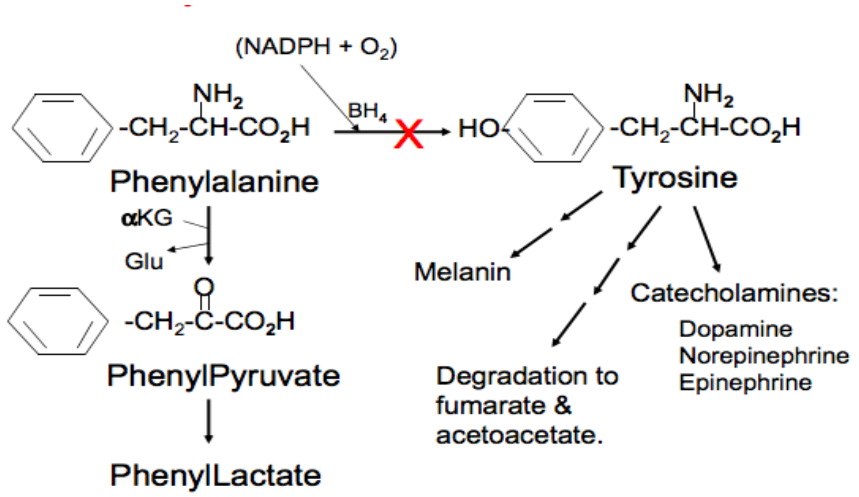


Figure 1. The block in the metabolic pathway of Phe to Tyr (adapted from University of Wisconsin-Madison Biomolecular Chemistry Lecture Slides)

In the United States, the incidence of PKU is approximately 1 in 12,000 births (4). In the 1960s PKU was the first metabolic disorder to be detected through population-based newborn screening and has continued to be effectively diagnosed by this method for over 50 years (4). Screening is completed on blood collected on filter paper spots from newborns within 24 to 48 hours of birth. Detection of an elevated concentration of Phe and an elevated Phe:Tyr ratio warrants further investigation to confirm the diagnosis of PKU (5). Newborn screening has significantly improved clinical outcomes in individuals diagnosed with PKU because it allows for early initiation of nutrition therapy, usually within the first week of life (4,15). In addition, the implementation of newborn screening has allowed for further research into the treatment of PKU including the question as to whether or not life-long treatment is necessary in this population (4). Moyle et al. (2007) found that early-treated adults with PKU (n=12) who were no longer

on-diet scored significantly poorer on perceptual organization and processing speed than a healthy, age and education-matched control group (n=12). The significant differences in neuropsychological test scores suggest that the poorer scores were related to the negative effects of high Phe concentrations on executive functioning in those who are off-diet (6). Ten Hoedt et al. (7) found that even adults who had a life-long history of good dietary adherence still experienced a temporary impairment in sustained attention and mood during short-term elevations of Phe. These results suggest that life-long treatment to maintain metabolic control is necessary for adults with PKU to achieve optimum cognitive functioning, thus increasing QOL.

Prior to newborn screening, individuals with PKU developed severe intellectual disability, seizures, and psychiatric disorders. Physical symptoms included a musty odor on breath, skin, or urine from excess Phe in blood, and the deficiency in Tyr caused lighter skin and hair color and skin disorders such as eczema (5). With dietary treatment initiated early in infancy, these clinical complications can be prevented (5). Even individuals with late-diagnosed PKU can still see potential cognitive improvements with initiation of nutrition therapy later in life. Lee et al. (8) assessed adults (n=34), ages 21 to 61 years, with late-diagnosed PKU who were born prior to the initiation of newborn screening. Participants were randomized into a placebo-controlled crossover study for initiation of a Phe-restricted diet for 60 weeks with assessment of various measures of behavior using a validated behavior checklist and behavior scale

(8). Only 17 of the 34 participants completed the study and no significant differences were found in standardized behavior measurements between the on-diet and off-diet period (8). However, 76% of caregivers rated participant's behavior more positively during the on-diet phase (8). Thus, there is a potential benefit of initiation of nutrition therapy, even with late-diagnosed PKU; however, there can be significant challenges in initiating and maintaining the diet for this late-diagnosed population. These challenges may also be similar in early treated individuals who are off-diet and trying to restart nutrition therapy (8).

Treatment

Nutrition therapy, the primary treatment for PKU for over 60 years, has been associated with decreased blood Phe concentrations resulting in improved clinical outcomes, including both physical and cognitive growth and development (12). A primary component of treatment includes maintaining an intake of Phe from dietary food sources to allow for sufficient Phe for growth and development, but preventing elevations in blood Phe concentrations. In the early 1950s, Bickel et al. (9,10) explored variations in diet treatment in a 2-year old girl diagnosed with PKU who displayed severe physical and cognitive deficits including the inability to crawl, stand, walk, or talk. The first 4-week phase provided a completely Phe-free diet resulting in normal blood and urine Phe-concentrations (9,10). However, continued use of a Phe-free diet caused weight loss followed by a return in elevated blood and urine Phe-concentrations and generalized amino-aciduria resulting from protein catabolism. When small amounts of Phe (0.3-0.5

gm/day) were provided in the form of whole milk, weight gain and biochemical abnormalities improved (9). With the continued Phe-restricted diet, there was a gradual improvement in the child's cognitive development including the ability to crawl, stand, and climb. However, when an additional 5 grams of Phe/day was added to the child's diet, an immediate deterioration in her condition was observed including the inability to crawl and stand. When the additional Phe was discontinued, recovery of these developmental deficits was observed within 3 weeks (9,10). Similarly, McBean et al. (11) reproduced these results after observing 31 children with PKU, under the age of 7 years, both on and off a low-Phe diet. The age of the child when dietary intervention was initiated was an important factor determining the extent of developmental deficits (11). Children who were started on diet within the first three months of life had higher IQ scores than those who were started on diet at a later age (11).

The other primary component of treatment of PKU includes amino acid-based medical foods that are Phe-free and supplemented with Tyr. Medical foods allow those with PKU to consume an appropriate amount of protein equivalents and other macro- and micronutrients in their diet to promote adequate growth and protein maintenance, yet prevent elevations in blood Phe (12). Prior to the introduction of medical food, physical growth was poor among children due to the restriction of total protein in a Phe-restricted diet (12). Acosta et al. (12) evaluated 67 children, ages 2 to 12 years, who had initiated diet treatment within the first month of life and who were consuming one of 3 different medical foods

(Phenex-2 Amino Acid-Modified Medical Food®, Phenyl-Free®, or Periflex®). Growth and nutrient intake was evaluated at baseline and every three months thereafter for 1 year. With all 3 formulas, mean nutrient intakes, except total energy, met or exceeded the recommended dietary intakes (RDI) and the formulas accounted for 76% to 80% of the participant's total daily protein intake (12). Medical formulas for PKU are not designed to meet total energy needs as some of an individual's daily energy requirement is met through food. Mean length or height z-scores indicated normal linear growth among the groups as compared to healthy children, and there were no significant differences in mean z-scores for weight or BMI at baseline and the end of the study (12). Thus, with the introduction of Phe-free medical foods, individuals with PKU are able to consume adequate protein to achieve normal growth and maintain adequate protein stores while still maintaining a low Phe intake to prevent elevated blood Phe and allow for normal cognitive functioning (13).

Currently, it is recommended that blood Phe concentrations be maintained between 120 and 360 μmol/L for optimum cognitive functioning in individuals with PKU (14,15). Phe is found in nearly all sources of natural protein, and because of the need for a tight restriction of Phe, even foods with a low protein content such as fruits and vegetables must be accounted for in the diet. For most patients, average intake of natural protein from all food ranges from 5 to 10 grams per day, equivalent to 250 to 500 mg Phe (1 gm protein provides approximately 50 mg Phe). Current methods to monitor Phe intake used in the United States

include counting mg of Phe or using a unit exchange system with 1 exchange equivalent to 15 mg of Phe (14). A patient's Phe tolerance is the amount of dietary Phe the individual can consume while maintaining blood Phe levels within an appropriate treatment range. Phe tolerance is influenced by numerous factors including age, degree of PAH deficiency, activity and growth rate (15).

A more recent addition (2007) to treatment for PKU is the use of sapropterin dihydrochloride (Kuvan®, Biomarin Pharmaceuticals), which is a synthetic form of tetrahydrobiopterin (BH_4) (16). BH_4 is the cofactor for PAH and when given in the synthetic form, can help lower blood Phe concentrations and increase dietary Phe tolerance in up to 50% of individuals with PKU (16). Douglas et al. (16) investigated the potential for an increase in long-term QOL in individuals with PKU (n=37), ages 10 to 49 years. After 1 year, QOL scores did not significantly change for the group as a whole, but there was a significant increase in reported QOL for individuals who responded to Kuvan® treatment (16). Responders had an increase in dietary Phe tolerance and required less medical food with reported improved overall QOL and satisfaction (16). Thus, sapropterin dihydrochloride may help improve long-term compliance to nutrition therapy for those who do respond to this medication.

Nutrition therapy remains the primary treatment for PKU and significantly improves clinical outcomes and QOL for affected individuals (9,10,12,14,15). However, the current methods of restricting and tracking Phe intake can be confusing and ineffective, and some clinicians have advocated for a more

simplified approach to track Phe intake by counting gm of protein rather than mg of Phe (36). It would be beneficial to evaluate different approaches to restricting intake of dietary Phe to help improve patient adherence while maintaining (or improving) control of blood Phe concentrations.

Poorly Controlled PKU and Executive Functions

In those with early-treated PKU, elevated blood Phe concentrations later in childhood or adolescence have been associated with a decline in executive functioning (1). Executive function comprises a set of mental skills that are coordinated in the frontal lobe of the brain and include higher-order cognitive processes related to organization and regulation that facilitate modifications in thought and behavior as a response to the environment (17). Some of these skills include reasoning, problem-solving, memory functions, managing time and attention, planning and implementing tasks, flexibility, and attention to detail (1,17). Deficits in executive functions in those with PKU appear to be related to the decrease in neurotransmitter production and increase in abnormalities in cerebral white matter that may disrupt the interconnectivity between different regions of the brain (17). Higher blood Phe concentrations are related to more serious deficits in executive functioning, and both historical Phe concentrations and Phe concentrations during developmentally critical periods of life appear to be more predictive of cognitive outcomes (1). Large fluctuations in blood Phe concentrations over the long-term can also have negative effects on IQ and cognition (18).

Thompson et al. (19) found a significant correlation between brain white matter changes found on MRI and blood Phe concentrations, suggesting that neurological deterioration persists throughout the lifespan in those with poor Phe control. Subjects with PKU (n=34), ages 8 to 33 years, were separated into groups based on their age at diagnosis (Group I were diagnosed <4 months of age and group II were diagnosed >4 months of age) (19). There were no significant differences between the two groups when comparing MRI grades and blood Phe concentrations (19). However, MRI analysis showed that the severity of changes in white matter were independently and positively correlated with higher mean blood Phe concentrations as well as the number of years that the subject was off-diet, regardless of the age of diagnosis and initiation of treatment, suggesting that life-long dietary adherence is important (19).

The concentration and variation of blood Phe appears to have a greater impact on verbal comprehension and perceptual reasoning skills during the first 12 years of life (20). Channon et al. (21) compared cognitive functioning of subjects with PKU (n=25), ages 18-38 years, who were diagnosed early and discontinued their diets in adolescence to subjects with PKU (n=25) who were also diagnosed early but remained on a continuous diet. The on-diet group performed significantly better than the off-diet group on accuracy and speed of performance, working memory tasks, and on speed of performance on inhibitory tasks (21). Moyle et al. (6) found similar results when comparing the neuropsychological test scores of early-treated adults with PKU (n=12) who were

off-diet at the time of testing to an age and education-matched control group. The subjects with PKU scored significantly poorer on perceptual organization and processing speed than the control group (6). However, even with life-long control of dietary Phe intake and maintenance of low blood Phe <400 μmol/L, subjects with PKU (≥8 years old) continue to show a mild impairment of executive functions during short-term elevations of Phe including temporary impairment in sustained attention and mood (7,22). Although early initiation and maintenance of nutrition therapy is incredibly important for optimum cognitive development in younger individuals, these results suggest that it is also important to continue nutrition therapy and metabolic control throughout adulthood for maintenance of cognitive function.

Despite early treatment, poor dietary adherence and long-term elevations in blood Phe can cause a significant decline in executive functioning skills as well as a negative effect on overall IQ. Waisbren et al. (23) found an inverse association between significant decreases in IQ scores with long-term increases in blood Phe concentrations. In addition, not only the mean Phe concentration, but also the variability of blood Phe control over a child's lifetime can influence IQ and executive functioning later in life suggesting that variability in blood Phe concentrations may be a better indicator of long-term cognitive performance than overall control of blood Phe concentrations (23). Children with PKU who have an average IQ (IQ score of 90-110) often do not exhibit executive functioning deficits, so overall IQ should not be the main indicator of blood Phe control (23).

Mild cognitive impairment has been demonstrated with temporary elevations in blood Phe concentrations and, thus, both variability of blood Phe and average blood Phe concentrations need to be monitored closely to maximize cognitive outcomes in individuals with PKU (24).

Results of these studies demonstrate that both early treatment and lifetime dietary adherence and control are essential for optimal cognitive and executive functioning outcomes. However, there are multiple factors that can become barriers to following a life-long diet and therefore negatively impact the QOL for individuals with PKU.

Factors Affecting Dietary Compliance and Quality of Life

Following a Phe-restricted diet can be difficult and many individuals with PKU have poor dietary compliance and struggle to maintain the diet long-term (25). Dietary compliance is assessed by monitoring blood Phe concentrations and current guidelines recommend maintenance of average Phe concentrations of 120 to 360 μmol/L for all age groups (15). Studies have shown that blood Phe concentrations among individuals with PKU increase with age, with a gradual decline in control beginning near adolescence and into adulthood (25,26). Guest et al. (27) found that 47% of patients discontinued their phenylalanine-restricted diet between 15 and 25 years of age.

Factors contributing to poor compliance include sociocultural barriers such as language, education level, food skills, and social activity (25). In adolescence, the power struggle between parent and child, peer pressure, trouble explaining

their condition to others, and the need to fit in with peers are common deterrents to dietary compliance (25,28,29). Thus there are numerous potential reasons for poor dietary compliance, both intentional and unintentional in nature (25,28,29). Some factors that have been found to encourage dietary adherence in adolescence include support from friends and family and maintenance of normal cognitive abilities (29). These potential encouraging factors could be used to help improve adherence among all age groups with PKU.

Maintaining a Phe-restricted diet is difficult, but non-compliance with the diet can negatively affect an individual's QOL. Bik-Multanowski et al. (30) compared the QOL of adults with PKU returning to a Phe-restricted diet to identify reasons for non-compliance. About 45% of subjects reported "severe" or "moderate distress" relating to their anxiety, depressiveness, and well-being when off-diet, but subsequently showed improvement in well-being after returning to the diet. However, of the initial 53 study participants, only 10 were able to complete the 9-month study, emphasizing the difficulty of resuming and maintaining such a restrictive diet. The most significant reasons for dietary non-compliance were the relatively high-cost of medical foods, poor knowledge of the PKU diet and problems consuming medical foods in social situations (30).

Enforcement of appropriate early treatment habits may be associated with improved dietary control. Crone et al. (31) analyzed parental behavioral factors of PKU patients (n=238), from age at birth to 22 years. Parents who believed that their child adhered well to the diet had a child with significantly lower Phe

concentrations compared to parents who believed that their children did not adhere well to the diet. Parents who reported that their child had difficulties consuming their medical food three times a day had children with higher Phe concentrations than those who did not report any difficulty (31). These results may indicate that parental attitudes are important for implementing the diet and promoting their child's adherence to the diet.

Thus, although there are many different factors that can contribute to poor dietary compliance, several potential factors have been identified that could help improve adherence to nutrition therapy.

Simplifying the Diet

A significant challenge for practitioners working with individuals with PKU is promoting sustained adherence for this difficult diet (25). Metabolic clinicians in Australia and Europe have taken a more simplified approach to counting Phe. In this approach, most fruits and certain vegetables do not need to be counted towards an individual's daily dietary Phe intake and are considered "free". Traditionally, all foods eaten would need to be counted towards an individual's daily Phe (mg) prescription in order to ensure maintenance of metabolic control. MacDonald et al. (32) evaluated free use of fruits and vegetables containing increasing increments of Phe intake from these foods over 15 weeks. Participants were instructed to freely eat fruits and vegetables containing <50 mg Phe/100 gm during part 1 of the study (weeks 1 to 3) and then were instructed to add at least one additional portion (20 gm) of fruits and vegetables containing 51-

75 mg Phe/100 gm during part 2 of the study (weeks 4 to 8). During part 3 of the study (weeks 9 to 15), participants were instructed to eat at least 3 portions (20 gm) of fruits and vegetables containing 76-100 mg Phe/100 gm weekly in addition to daily consumption of fruits and vegetables containing 51-75 mg Phe/100 gm. They found that addition of fruits and vegetables containing Phe up to 100 mg Phe/100 gm serving did not significantly increase blood Phe concentrations. Although median Phe intake did significantly increase overall (phase 2: 51 mg increase and phase 3: 39 mg increase in median Phe intake), it did not significantly or adversely affect metabolic control in the subjects (32).

In a similar study, Rohde et al. (33) found that participants consumed an average of 58 mg more Phe per day on a liberalized diet, but this increase in Phe intake did not have a negative effect on short-term metabolic control. Although a 58 mg increase in Phe per day (equivalent to approximately 1 gm of protein) is insignificant for the healthy population, this is a notable increase for someone living with PKU. At the 6- and 12-month follow-up, the average increase in Phe intake was 65 mg per day at 6 months and 70 mg per day at 12 months, yet blood Phe concentrations still remained stable (33,34). Zimmerman et al. (35) also investigated the effect of freely consuming fruits and vegetables containing less than 100 mg Phe/100 gm serving in 80 individuals with classic, moderate, and mild PKU, ages 2 years and older, compared to individuals with PKU on the traditional diet. Median blood Phe concentrations did not significantly differ between the simplified diet (classic= 355 µmol/L, moderate= 313 µmol/L, mild=

336 µmol/L) and the traditional diet (classic= 275 µmol/L, moderate= 200 µmol/L, mild= 300 µmol/L) (35). Interestingly, there were more individuals in the group of subjects >16 years of age with Phe concentrations within the recommended reference range (100-600 µmol/L for individuals >10 years) when they used the simplified diet compared to the traditional diet suggesting that the simplified diet could be an easier and more effective method of tracking Phe intake for individuals in this age group (35).

An additional approach to the simplified diet is to count protein rather than Phe in the diet. Sweeney et al. (36) compared an exchange system based on counting gm of protein (1 gm protein= 50 mg Phe) to the traditional exchange system based on counting mg of Phe (1 unit= 15 mg Phe) and found that there was no significant difference in blood Phe control of study participants between the two diet approaches and all participants preferred the simplified protein exchange system (36).

These studies have shown that a less strict approach to dietary treatment is not only a more favorable method to individuals with PKU, but also does not significantly increase their blood Phe concentrations. However, the current literature has not looked at how this simplified diet can be taught to patients with PKU to help improve metabolic control and better understand dietary treatment.

Education Material

Educational tools currently used in the management of PKU have limited effectiveness to promote dietary compliance and control of blood Phe

concentrations, and more effective approaches of nutrition education to promote dietary compliance are needed for these patients. Current tools include one-on-one counseling, handouts, support groups, classes, parents as role models, and computer-based dietary software (37). An international study compared the views of practitioners to parents and patients regarding PKU education and found a discrepancy in views between the groups. Practitioners regularly utilized a combination of one-on-one counseling with educational handouts and perceived this as the most effective approach to nutrition education. However, while parents of patients found one-on-one counseling to be most effective, patients considered their families the most effective education tool. This suggests that practitioners need to focus more on overall family dynamics and education rather than one-on-one counseling with patients. In addition, 78% of patients found handouts to be the least effective education tool (37). This finding could potentially be related to the complexity of specific handouts. Certainly it is beneficial to take an individualized approach to dietary education and consider the patient's age and literacy level.

Adolescents and young adults that are transitioning to manage their own treatment face numerous challenges that affect maintenance of their diet, and the role of healthcare providers is to help their patients overcome barriers and provide ongoing support and resources. Current resources include specialty clinics, summer camps, and written educational resources. Durham-Shearer et al. (38) aimed to investigate the effect of different forms of patient-focused

educational resources on knowledge, dietary compliance, and serum Phe concentrations in 71 adolescents and adults with PKU. Although most participant's self-reported awareness of dietary recommendations improved, this awareness did not result in improved compliance to the diet even when the educational resource format most preferred by the subjects was utilized (38).

Effective Education Materials

Development of effective educational material has been extensively studied in those with diabetes mellitus (39,41,42,43,45). When developing educational materials, characteristics of the target audience, such as age and literacy level, and social trends must be considered to help avoid potential barriers to treatment compliance. Especially among today's adolescent population, technology plays a large role in everyday life and needs to be considered in development of educational materials. Although studies investigating diabetes self-management and technological support did not find significant differences in the ability to manage disease between those using technology and those using standard management tools, there was a significant increase in self-efficacy in those using technology for management (39,40,41). The use of technological support in education and management of disease may be beneficial; however, more research is needed to evaluate the long-term effects and efficacy of incorporating technology in disease self-management.

The use of visual aids has also been studied in adolescents with diabetes. A randomized, controlled study comparing the use of food photographs to written

food lists to assess changes in knowledge about carbohydrate counting found that both groups improved knowledge of carbohydrate counting, but the group using the photographic material had a more significant improvement from pre- to post-test scores (42). Additionally, 77% of participants in the group using the photographic material rated the material as “excellent” compared to only 43% of participants using the written food list group (42). Thus, for those with PKU, the addition of visual aids to educational tools could help engage adolescents and improve their knowledge and self-efficacy of treatment.

When developing educational materials, literacy level is an important consideration in assessing an individual’s understanding of presented material (43). Mikhail et al. (44) found that regardless of literacy level, participants receiving educational pamphlets written at the 5th grade level or below had significantly higher comprehension of the material than the participants receiving pamphlets written at the 10th grade level. In addition to considering the reading grade level of educational handouts, the teach-back method has also been shown to improve understanding. Using this method, educators are able to have patients or clients restate what was presented to assess comprehension of the material. Negarandeh et al. (43) explored the impact of different educational strategies on knowledge and self-management of patients with type 2 diabetes and found that the use of the teach-back method and pictorial images both significantly improved knowledge and adherence to medication and diet compared to the control group. Thus, the use of visual aids in addition to utilizing

the teach-back method could help improve understanding and dietary self-management for adolescents and young adults with PKU.

Personalizing the method of delivery can help enhance the primary messages of the education being given and received (45). Koonce et al. (45) assessed the effects of educational material targeted at specific health literacy level and learning styles of adults with diabetes (n=81) and found that participants in the intervention group performed significantly better on knowledge questions at both 2 and 6-weeks compared to the control group. The reading grade level of educational material as well as the learning style preferences of patients are important factors to consider when delivering health-based education.

Although this has been extensively studied with other health conditions, there is limited evidence to suggest that these factors can help improve health maintenance of individuals with PKU. The proposed study aimed to utilize these principles and methods to provide effective education to adolescents and young adults with PKU with the long-term goal of improving life-long dietary compliance.

CHAPTER 3: METHODS

Methods

This pilot study was completed at the Child Development and Rehabilitation Center (CDRC) Metabolic Clinic at OHSU Doernbecher Children's Hospital. The two main goals of the study were 1. to develop an age-appropriate educational tool, reviewed and approved by metabolic dietitians, that allows adolescents and young adults with PKU to count total protein to manage their metabolic disorder and, 2. to evaluate the effectiveness of the newly-developed educational tool by instructing a cohort of 10 adolescents and young adults with PKU to count protein using this tool and subsequently assessing their knowledge. Subjects between the ages of 13 and 25 years who were diagnosed with classical PKU by newborn screening were recruited from patients routinely followed by the CDRC Metabolic Clinic. Each subject participated in one 20-minute educational session completed during a routine clinic visit at OHSU Doernbecher Children's Hospital or at an out-of-clinic visit scheduled at a designated destination near the subject's residence. This study was approved by the OHSU Institutional Review Board (IRB#15229).

Educational Resource Development

Publisher Lite version 1.6.0 was used to develop the educational tool. The reading level of the material was assessed using the Flesh-Kincaid scale available on Microsoft Word with a target reading level of 5th grade. The education material utilized information from the online database,

HowmuchPhe.org (National PKU News, Seattle, WA), for conversion of gm of dietary protein and mg of Phe per 100 gm serving size. HowmuchPhe.org includes a comprehensive list of foods with mg Phe, number of exchanges (1 exchange = 15 mg Phe), and protein content per a given serving size in a standard household unit and gm weight. This program was developed using ingredient-based amino acid food analysis. It is accessible to the public with a yearly subscription. Access to HowmuchPhe.org was obtained through a renewable subscription by OHSU's CDRC Metabolic Clinic.

The educational tool **(Appendix E)** includes lists of foods separated according to the type of food and then further separated into categories based on protein content. The separate food lists include “free foods” (foods with < 75 mg Phe/100 gm serving), vegetables and dried fruits, dairy alternatives, and starches/grains/cereals/breads. The categories in each of these food groups include low protein (1 gm/serving), moderate protein (2 gm/serving), and high protein (3 gm/serving). Included foods were chosen based on popularity of consumption in the adolescent PKU population based on the CDRC metabolic dietitians’ experience, and included snack foods like potato chips, French fries, and cookies. Using HowmuchPhe.org, specific foods were assessed based on the amount of Phe per 100 gm serving. Foods containing ≥75 mg Phe/100 gm were categorized based on the protein content of a standard serving size of food (½ cup) unless otherwise noted in the food list. All foods were moved up to the next protein category if their protein content surpassed the preceding protein

category (i.e. foods with 2.1 gm protein per ½ cup serving were placed in the 3 gm category). This was an important precautionary measure to consider because we wanted to ensure that if participants were using the tool, they would not be consuming more than their prescribed Phe intake because of the tool itself. A list of “Foods to Avoid” was also included which contains foods with a protein content >3 gm/100 gm serving, too high to include in the PKU diet. The educational tool incorporates photo images of foods and their protein content to provide a visualization of serving sizes. For all photos, foods were placed on a white plate with a red-striped background for uniformity, and a standard-sized, optic yellow, tennis ball was included in all the photos to help the reader visualize actual serving sizes relative to a tangible object. The final portion of the tool includes information about reading food labels and additional resources to assist in utilizing protein counting as a method to track dietary protein intake. A Nutrition Facts label is presented with key portions of the label highlighted, including the serving size and protein content. The additional resources include downloadable mobile phone applications and internet resources to aid in tracking protein consumption and/or aid in searching protein content in specific foods.

Educational Resource Evaluation

Metabolic dietitians who are members of Genetic Metabolic Dietitians International (GMDI) were recruited via email to evaluate the completed educational tool. A select group of these dietitians was identified and recruited by the principal investigator (PI). The dietitians agreeing to participate were emailed

a PDF version of the tool and a SurveyMonkey link that contained the Developing and Assessing Nutrition Education Handouts (DANEH) Checklist developed by the Academy of Nutrition and Dietetics Foundation. Using the DANEH checklist, the metabolic dietitians objectively evaluated the quality of the education tool and offered subjective feedback about the material. The RDs were also given an option to provide additional comments at the end of the survey. Using these evaluations, the PI and study coordinator modified the educational tool, as deemed appropriate, based on trending comments from the metabolic RDs **(Appendix D)**.

The DANEH checklist was developed by the Academy Foundation as part of the Healthy Food Bank Resource Hub's Future of Food project **(Appendix G)**. The checklist incorporates 22 constructs that were identified by a literature review as quality indicators to be included in nutrition education handouts. These constructs were separated into five main topic areas, including content, behavior focus, cultural sensitivity, written word, and organization and readability. The Academy Foundation recommends that a score of 16 out of 21 (76%) or higher be considered high quality material. For the purposes of this project, one question (“Current, accurate, and consistent with USDA Dietary Guidelines and MyPlate”) was removed from the checklist because the recommended medical nutrition therapy for PKU is not consistent with the USDA Dietary Guidelines and is not relevant to this educational tool. Therefore, for this project, a score of 16 out of 20 (80%) or higher was considered high quality.

Clinical Assessment of the Educational Resource

Study Participants

Study subjects included males and females between the ages of 13 and 25 years who were diagnosed with classical PKU by newborn screening and started on diet in early infancy. All were established patients in the CDRC Metabolic Clinic and had a routine follow-up clinic appointment scheduled during the months of April through August 2016 or had been seen in clinic within the previous 6 months. Informed consent and signatures from both parents and/or guardians and subjects under the age of 18 years was obtained. For those over age 18, parental or guardian consent was not required. Inclusion and exclusion criteria are shown in **Table 1**.

Adolescents and young adults between the ages of 13 and 25 years were selected because they are a key group of individuals with PKU followed by the CDRC Metabolic Clinic who are beginning to, or already are, managing their diet on their own.

Screening

Potential study participants were identified by a review of the Metabolic Clinic schedule listed in the OHSU electronic health record. Prior to a scheduled appointment, potential participants were mailed a recruitment letter and consent form for the study **(Appendix A and C)**. One week prior to the appointment, potential subjects were given a follow-up phone call to answer any questions and gauge their interest in participating **(Appendix B)**. Prior to the clinic appointment,

the medical chart of all potential participants was reviewed and discussed with the clinic RD to determine individual dietary Phe and protein needs. Typically, the simplified diet prescribes 70% of an individual's Phe needs as foods that need to be measured and counted; this allows for the remaining 30% of Phe needs to account for the Phe content of foods that are considered "free" using this method. However, since the target population included individuals with typical blood Phe concentrations above the recommended range (120 to 360 µmol/L), an estimate of 70-100% of each subject's Phe needs was prescribed. This prescribed amount of Phe was converted to gm of protein (50 mg Phe = 1 gm protein) and this was used as each subject's protein allowance for the study. On the day of the clinic appointment, the study coordinator met with potential subjects (and their legal parent or guardian for those under age 18 years) to complete the informed consent process. The study was reviewed with the subjects and their parents or guardians, all questions were answered, and all consent forms were signed prior to initiating study activities. Study data was also collected from each subject's OHSU electronic medical record during the clinic appointment and during a follow-up assessment that was conducted via telephone or email one month after the appointment.

Table 1. Inclusion and Exclusion Criteria

Inclusion	Exclusion
Adolescents and young adults age 13 to 25 years	Pregnant or lactating females
Diagnosis of classical PKU	Diagnosis of concurrent illness
Receive treatment at OHSU/CDRC Metabolic Clinic	English as a second language

Education Session

One pre-test and one post-test evaluation was developed based on the educational tool. The pre-test consisted of seven questions and the post-test consisted of 6 questions including short answer, fill-in the blank, multiple choice, and basic computational questions to assess patient knowledge, and one Likert-scale question to assess motivation to change dietary behavior and utilize protein counting as a method of tracking dietary Phe **(Figure 2)**. Subjects were administered the pre-test after agreeing to participate in the study and signing all consent forms. The pre-test included a final question regarding the preferred method for future contact (mail, email, or both) for the post-test evaluation. After completion of the pre-test, the education session lasted approximately 20 minutes. Participants were reminded of their individual protein prescriptions based on meeting 70-100% of their estimated Phe prescription. The first 10 minutes of the session was dedicated to explaining how to use the education tool and answering any questions. During the remainder of the session, the teach-back method was utilized to help ensure understanding of the material and enhance participant knowledge through practice. A brief 24-hour recall was collected and the participant used this information to practice using the protein counting method using the educational tool. Once the education session was complete and all questions were answered, the participants were reminded that the post-test would be sent to them in one month.

Follow-up Assessment

One month after participating in the education session, subjects were mailed or emailed the post-test based on their preferred method of contact indicated on their pre-test evaluation. The post-test was similar to the pre-test consisting of 6 questions that included short answer, fill-in the blank, multiple choice, and basic computational questions to assess patient knowledge, and one Likert-scale question to assess motivation to change dietary behavior and utilize protein counting as a method of tracking dietary Phe (Figure 2). Participants received a follow-up telephone call one week after distribution of the post-test to answer any questions and remind the participant to complete the evaluation.

Figure 2. Pre- and Post-test Questionnaires*

Pre-test Evaluation

Age: _____ **Participant Identifier:** _____

1. Do you currently keep track of your dietary Phe intake?

   Yes No Sometimes

   a) If yes, what method do you use (such as counting exchanges or counting milligrams of Phe)? _____

   b) If you don't usually keep track of your Phe intake, why not?

   _____

2. Have you heard of counting protein as a method to track dietary Phe intake?

   Yes No

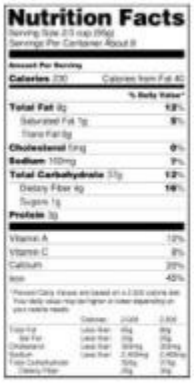
3. Approximately how many milligrams (mg) of Phe are in one gram of protein?

   a) 15 mg
   b) 25 mg
   c) 50 mg
   d) 75 mg

4. Using the Nutrition Facts label below, how much is one serving of this food? **2/3 cup**

   a) How much protein is in one serving of this food? **3 gm**

   b) How much protein will be in two servings of this food? **6 gm**



5. From the list of foods below, which do not need to be counted as part of your daily protein intake (circle all that apply).

Soy Milk French Fries Green Beans Orange Juice

Bell peppers Graham Crackers

6. On a scale of 1 to 5, with 1 being extremely likely and 5 being extremely unlikely, how likely are you to track dietary Phe if there was an easier method of tracking?

1 2 3 4 5

Very likely *Maybe* *Very Unlikely*

7. What is the best method of contact to send a post-test evaluation (mail/email/telephone)? Please list best method and contact information below.

_____

Post-test Evaluation

Age: _____ **Participant Identifier:** _____

1. After learning to use the educational tool for protein counting, do you keep track of your dietary protein intake?

   Yes **No** **Sometimes**

   a) If yes, do you use the protein counting method? _____

   b) If you do not use the protein counting method, why not? _____

2. Please list what you like/do not like about counting protein as a method to track dietary Phe intake.

   _____

   _____

3. Approximately how many milligrams (mg) of Phe are in one gram of protein?

   a) 15 mg
   b) 25 mg
   c) 50 mg
   d) 75 mg

4. Using the Nutrition Facts label below, how much is one serving of this food? **2/3 cup**

   a) How much protein will be in one serving of this food? **3 gm**

   b) How much protein will be in two servings of this food? **6 gm**

5. From the list of foods below, which do not need to be counted as part of your daily protein intake (circle all that apply).

Soy Milk French Fries **Green Beans** **Orange Juice**

Bell peppers Graham Crackers

6. On a scale of 1 to 5, with 1 being extremely likely and 5 being extremely unlikely, how likely are you to use protein counting as a method to track dietary Phe intake?

1 2 3 4 5

Very likely *Maybe* *Very Unlikely*

*Answers to the questions are indicated in bold

Outcome Variables

Outcome variables were measures of quality and effectiveness of the developed educational resource. Overall quality of the educational tool was assessed using the DANEH checklist by 9 practicing metabolic dietitians in the United States. An overall score of 80% or higher on the checklist was considered a high quality rating.

Effectiveness of the educational tool was measured by a pre- and post-session questionnaire administered to the subjects. The questionnaire consisted of 6 questions relating to knowledge of protein counting and motivation to change behavior. The question types included short answers, fill-in the blank, multiple choice, and basic computational questions.

Statistical Analysis

Statistical analysis was completed on all participant responses to the DANEH checklist evaluation. All responses to each question were combined into one group. For the subjects participating in the education session, statistical analysis was run separately on each question based on participant responses to pre- and post-tests. Descriptive statistics were expressed as the mean $\pm$ SD. STATA version 14.2 was used for all statistical analyses. Microsoft Excel was used to produce data tables and figures.

Educational Tool Evaluation

A two-sided binomial distribution test was used to determine the best estimate of the possible number of successful outcomes for questions that would

be marked “met” vs “unmet” by the metabolic dietitians (n=9) on the DANEH checklist. Confidence intervals (95%) were calculated using Wilson’s score interval to determine a 95% level of certainty of the true proportion of questions that would be answered “met” in the future. The educational tool was considered high quality with a mean total sum of scores of 16 out of 20 (80%) or higher. A p-value ≤ 0.05 was considered statistically significant.

Pre- and Post-test Evaluation

Two-sided binomial distribution tests were performed individually on all quantitative questions (Pre- and post-test questions # 1, 3, 4, 5, 6) to determine the best estimate of the possible number of successful outcomes that indicate “improved” vs “worse” between pre- and post-test answers. Confidence intervals (90%) were calculated using Wilson’s score interval to determine a 90% level of certainty of the true proportion of questions that would be “improved” or have “no change” between pre- and post-test answers in the future. The questions containing three parts (questions #4 and #5) were grouped into one score and graded on a scale from 0 to 3 points. Participants received one point for each question answered correctly to add to a maximum score of 3 out of 3 points. Participants whose scores increased were considered to have an improved score. Participants who did not exhibit any change from pre- to post-test were excluded from analysis. The Wilcoxon Signed-Rank test could attempt to make a correction for these participants with no change, but was not used since the attempt to correct this would skew the results in such a small sample size. Also,

this test uses a z-statistic, which would assume that the population is a larger sample. Therefore, these participants were excluded and a binomial distribution was used to analyze results. A p-value ≤ 0.05 was considered statistically significant. Each participant's response to qualitative questions is displayed in tables and any trends in responses to specific questions are identified.

CHAPTER 4: RESULTS

Checklist Evaluation Scores

Twelve registered dietitians who were members of GMDI were contacted and agreed to participate in evaluating the educational resource. Of these 12 dietitians, 9 responses (75%) were received after the allotted 2-week period for response. The mean total of all scores from the RDs was 18 out of 20 (90.6%), ($p<0.000$), 95% CI [0.85, 0.94], showing the educational tool is of high quality, as indicated by a score ≥80% for all questions **(Table 2)**. Some criteria of greatest concern (marked unmet on DANEH checklist) with the educational tool included criteria in the behavior focus, organization and readability, and cultural sensitivity topic areas of the DANEH checklist. Based on participant responses, the specific constructs that were most commonly unmet included, a) “give specific examples of desired behavior” (n=3), b) “have culturally appropriate images” (n=3), and c) “use left-justified text blocks” (n=5). Additional comments from participants are shown in **Appendix D**.

Table 2. DANEH Checklist Evaluation Scores

Variable	Mean (%)±SD	95% CI	p-value
Educational Tool Evaluation (n=9)	90.6±6.3	[0.85, 0.94]	0.000

Description of Study Participants

Of the 24 eligible participants that were sent recruitment letters in the mail, 4 females and 8 males consented to participate in the study. Two participants did not complete the post-test questionnaire within the 1-month follow-up period and were considered lost to follow-up, thus results from 10 participants were included in analysis. Participant characteristics are shown in **Table 3**. The average age of the participants was 18.6 (±3.7) years. The average blood Phe and Tyr concentrations over the previous 3 years was calculated for each participant based on values from their electronic medical record. The average blood Phe concentration of all participants was 750.4 (±296.1) µmol/L and the average blood Tyr concentration was 84.0 (±24.1) µmol/L. Only two of the 10 participants (20%) reported counting dietary Phe intake at the start of the study, and one of the 10 participants (10%) reported that he had never heard of protein counting as a method to track dietary Phe intake. Three out of 10 of participants (30%) were prescribed Kuvan®, as documented in their medical record. The number of filter papers sent in to measure Phe/Tyr was recorded from January 2013 through September 2016 as a measure of health care compliance (Table 3). In general, participants with mean blood Phe concentrations within the recommended treatment range (120-360 µmol/L) completed more blood filter paper tests during the 3-year period than those who did not.

Table 3. Participant Characteristics

Subjects (n=10)	Age (yrs)	Sex (M/F)	[1]Counts Phe?	[2]Mean Phe level (SD) µmol/L	[2]Mean Tyr level (SD) µmol/L	[3]# of Filter Papers	[3]Uses Kuvan?
1	23	M	No	972 (237.6) *range: 804-1140*	135.5 (10.6) *range: 128-143*	0	No
2	25	F	No	1103.4 (292.8) *range: 550-1615*	64.8 (34.5) *range: 26-156*	18	No
3	24	M	Sometimes	1210.2 (298.8) *range: 668-1886*	77.3 (52.9) *range: 30-182*	18	No
4	16	F	Sometimes	720.7 (211.6) *range: 241-1441*	110.5 (103.3) *range: 38-1221*	127	Yes
5	16	M	Sometimes	465.5 (198.1) *range: 62-862*	66.4 (21.8) *range: 35-137*	74	No
6	17	M	No	828.7 (495.7) *range: 11-1824*	80.6 (46.8) *range: 27-230*	35	No
7	15	M	Yes	339 (225.8) *range: 15-1341*	75.7 (30.5) *range: 25-211*	148	No
8	17	F	Yes	833.1 (137.7) *range: 593-1021*	98 (49.5) *range: 55-195*	7	No
9	15	M	No	394.5 (221.4) *range: 38-1002*	75.7 (28) *range: 26-179*	69	Yes
10	18	F	Sometimes	636.5 (317) *range: 100-1201*	55.4 (23) *range: 29-159*	68	Yes

[1] Based on pre-test evaluation responses (pre-test question #2)

[2] Phe and Tyr levels are average values from blood filter paper tests charted in the patient's electronic medical record within the prior 3-year period (2013-2016). Recommended treatment ranges: Phe 120-360 µmol/L; Tyr 45-89 µmol/L

[3] As charted in patient's electronic medical record

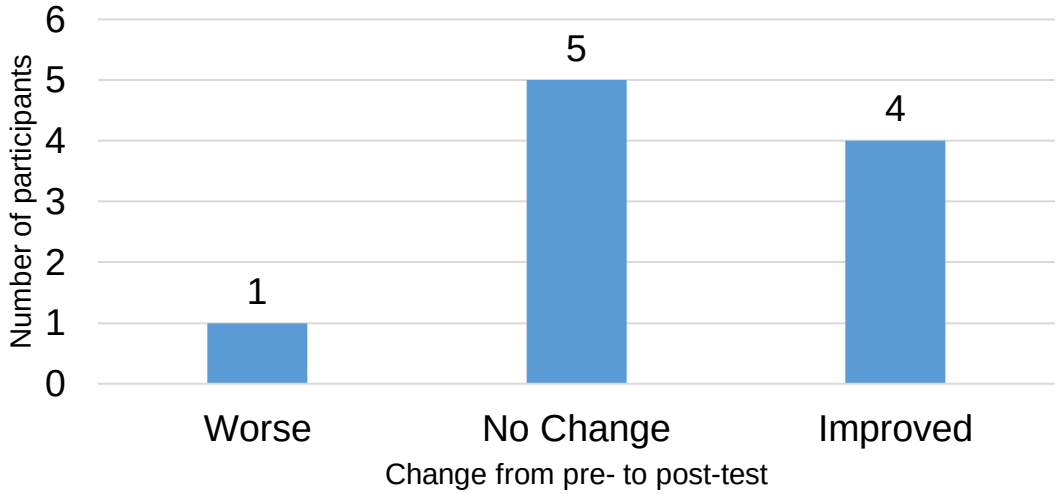
Questionnaire Scores

All participant responses to qualitative questions (Pre-test question # 1b & Post-test question # 1b & 2) are summarized below and shown in **Table 4**. Changes in participant responses to quantitative questions (Pre- and post-test question # 1, 3, 4, 5, 6) are summarized below.

Question 1: Do you keep track of your dietary Phe/protein intake?

Comparing pre- and post-test answers, responses from 4 of 10 participants (40%) changed from “no” to “yes or sometimes” and 1 participant’s (10%) response changed from “yes” to “sometimes” **(Figure 3, 4, and 5)**. Although not statistically significant (p=0.375), there was a trend towards improvement in participant report to keep track of dietary Phe/protein intake. No participants reported “no” to keeping track of their protein intake on the post-test. Based on the sample data, 90% of responders (9/10) reported a response that indicated “no change” (n=5) or “improved” (n=4) in their ability to keep track of protein, suggesting that the participant’s abilities did not decline during the month after the education session. In the future, we estimate that an actual proportion between 65 and 98% of subjects would be a reasonable value for those who would indicate “no change” or “improved” after answering this question if this study was to be conducted again, 90% CI [0.65, 0.98].

Figure 3. Distribution of Responses
Question #1 (n=10): Do you keep track of your dietary Phe/protein intake?



Worse: Participant response changed from “yes” on pre-test to “sometimes or no” on post-test
No change: Participant reported the same response on both pre- and post-test
Improved: Participant response changed from “no or sometimes” on pre-test to “sometimes or yes” on post-test

Figure 4. Pre-test Question 1: Do you keep track of your dietary Phe intake? (n=10)

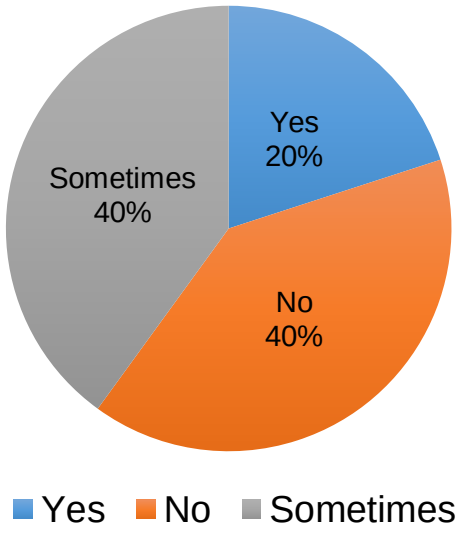
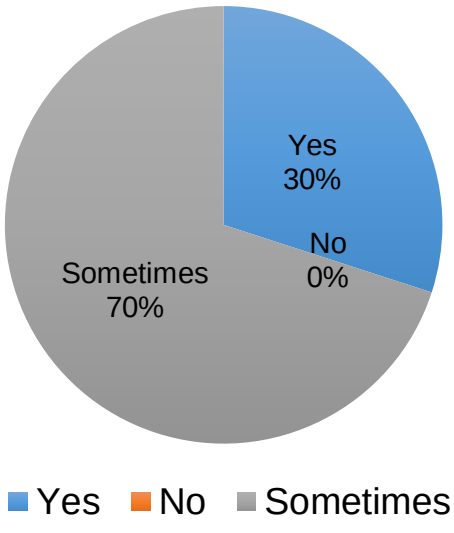


Figure 5: Post-test Question 1: Do you keep track of your dietary Protein Intake? (n=10)



Question 1b: Why don't you keep track of your Phe/protein intake?

Question 2 Pre-test: Have you heard of counting protein as a method to track dietary Phe intake?

Question 2 Post-test: What do you like/not like about counting protein as a method to track dietary Phe intake?

Only one out of 10 participants (10%) reported that they had never heard of counting protein as a method to track dietary Phe intake on the pre-test. All participant responses to qualitative questions (Pre-test question # 1b & Post-test question # 1b & 2) are shown in **Table 4**. Common trends in participant responses on the pre-test included that they were "too busy", "too lazy", or "don't know how to" keep track of their dietary Phe. Some participants also reported tracking dietary Phe based on their mood. Similar trends in these responses were noted in the post-test as well. Three participants reported using the protein counting method as a method to track their Phe intake on their post-test evaluations. Of these 3 participants, one participant's answer stayed the same from pre- to post-test and 2 participants initially reported "sometimes" tracking dietary Phe.

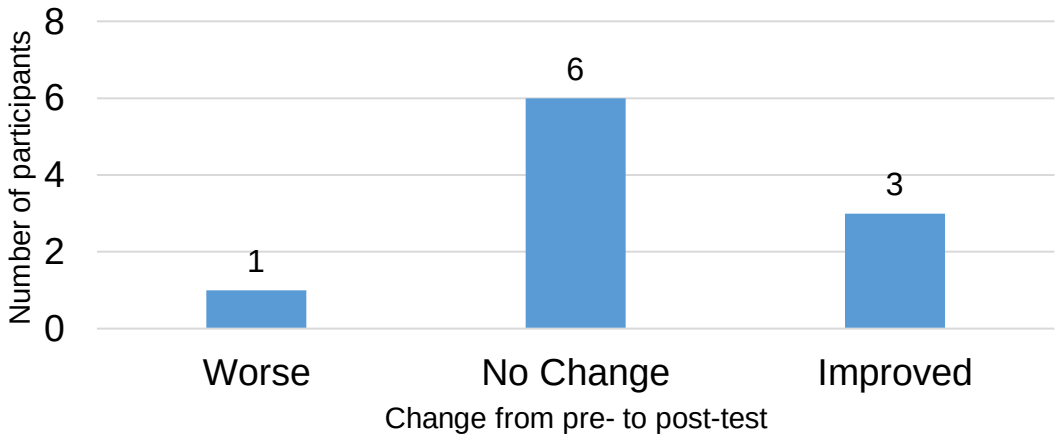
Table 4. Qualitative Pre- & Post-test Answers

Subject (n=10)	Pre-test Question #1b: Why don't you keep track of your Phe intake?	Post-test Question #1b &/or 2: If you do not use the protein counting method, why not? What do you like/not like about counting protein as a method to track dietary Phe intake?
1	"I'm pretty confident in knowing what would be too high in Phe or not, and make the choice to be more liberal"	"It is hard to gauge what PKU is significantly effecting in my brain at this stage in life since I don't believe I am at high risk any longer"
2	"Insurance barriers to diet education"	"Don't like keeping track because it's hard, but a lot easier to use handout (using pictures) and gives more freedom to eat"
3	No response	"Too lazy to count"
4	No response	"Makes me feel different"
5	"I base it much more off my mood"	"It takes time to measure all food out"
6	"Not really in the habit, don't know how to"	"It's very easy to count the protein"
7	No response	"It lets me eat more cantaloupe and vegetables and breads and pastas"
8	"Because it is more difficult"	"I use the protein counting method and have for years"
9	"Because I'm too lazy and I have an idea about how much I eat everyday"	"I don't like not knowing how much protein is in some stuff"
10	"Busy"	"I don't like the time commitment"

Question 3: Approximately how many milligrams (mg) of Phe are in one gram of protein?

Of the 10 participant responses, four subjects answered this question correctly on the pre-test and an additional three participants answered this correctly on the post-test. One participant that answered correctly on the pre-test answered incorrectly on the post-test **(Figure 6)**. The reported change was not statistically significant (p=0.625). Based on the sample data, 90% of responders (9/10) indicated “no change” (n=6) or “improved” (n=3) responses to this question suggesting that participant’s knowledge did not decline during the month after the education session. In the future, we estimate that an actual proportion between 65 and 98% of subjects would be a reasonable value for those who would indicate “no change” or “improved” after answering this question if this study was to be conducted again, 90% CI [0.65, 0.98].

Figure 6. Distribution of Reponses
Question #3 (n=10): How many milligrams of Phe are in one gram of protein?

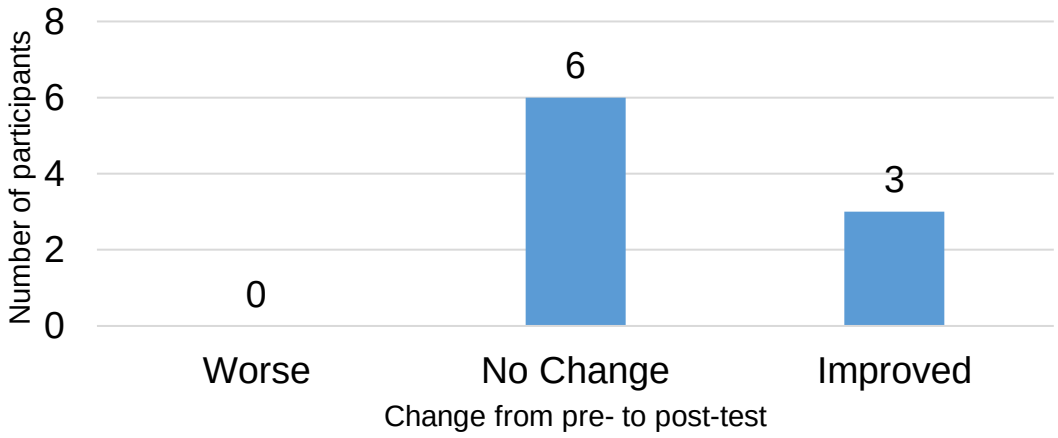


Worse: Participant response changed from correct on pre-test to incorrect on post-test
No change: Participant reported the same response on both pre- and post-test
Improved: Participant response changed from incorrect on pre-test to correct on post-test

Question 4: Using the Nutrition Facts label below, how much of the food is in one serving of this food? a) How much protein is in one serving of this food? b) How much protein will be in two servings of this food?

Of the 9 participant responses, no participants who answered this question correctly (n=5) on the pre-test got it wrong on the post-test (p=0.250). The three parts of this question were grouped into one score and graded on a scale from 0 to 3 points. Participants received one point for each question answered correctly to add to a maximum score of 3 out of 3 points. Participants whose scores increased were considered to have an improved score. In this case, all participants who improved from pre- to post-test had a score of 3 out of 3. Based on the sample data, 100% of responders (9/9) reported a response that indicated "no change" (n=6) or "improved" (n=3) suggesting that participant's knowledge did not decline during the month after the education session **(Figure 7)**. In the future, we estimate that an actual proportion between 77 and 100% of subjects would be a reasonable value for those who would indicate "no change" or "improved" after answering this question if this study was to be conducted again, 90% CI [0.77, 1].

Figure 7. Distribution of Reponses
Question #4 (n=9): Using the nutrition facts label, how much is one serving of this food? How much protein is in one serving? In two servings?

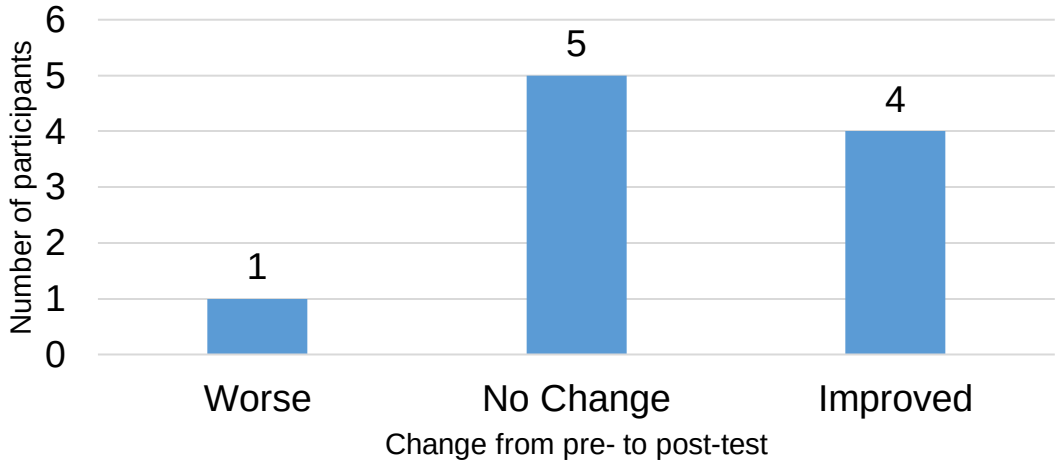


Worse: Participant's total score decreased from pre-test to post-test
No change: Participant reported the same total score on both pre- and post-test
Improved: Participant's total score increased from pre-test to post-test

Question 5: From the list of foods below, which do not need to be counted as part of your daily protein intake?

Of the 10 participant responses, two participants selected the correct answer on the pre-test (20%). Four participants (40%) who answered this question incorrectly on the pre-test chose the correct answer on the post-test. One participant (10%) reversed the correct answer on the pre-test to incorrect on the post-test. The three parts of this question were grouped into one score and graded on a scale from 0 to 3 points. Participants received one point for each question answered correctly to add to a maximum score of 3 out of 3 points. Participants whose scores increased were considered to have an improved score. Although not statistically significant (p=0.375), there was a trend towards improvement in participant response from pre- to post-test. Based on the sample data, 90% of responders (9/10) reported a response that indicated “no change” (n=5) or “improved” (n=4) suggesting that participant’s knowledge did not decline during the month after the education session **(Figure 8)**. In the future, we estimate that an actual proportion between 65 and 98% of subjects would be a reasonable value for those who would indicate “no change” or “improved” after answering this question if this study was to be conducted again, 90% CI [0.65, 0.98].

Figure 8. Distribution of Reponses
Question #5 (n=10): From the lists of foods below, which do not need to be counted as part of your daily protein intake?

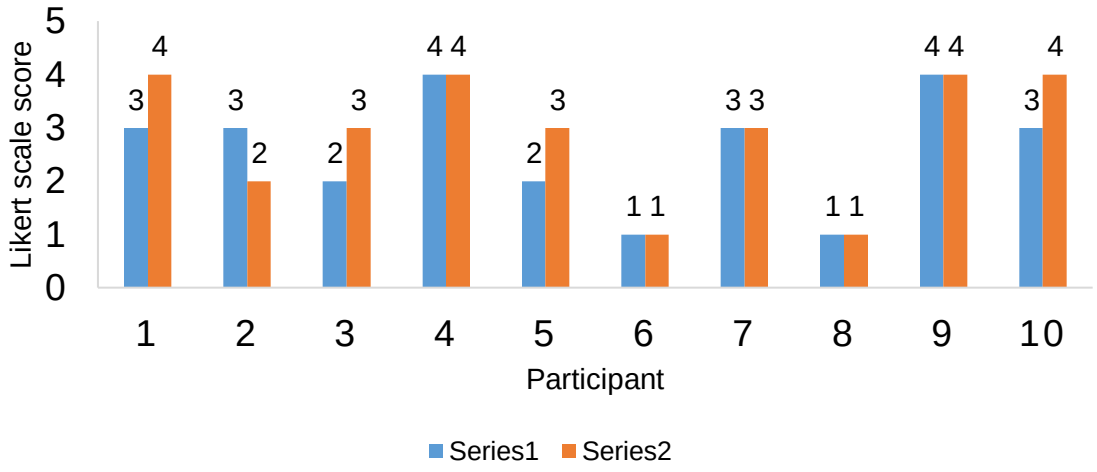


Worse: Participant's total score decreased from pre-test to post-test
No change: Participant reported the same total score on both pre- and post-test
Improved: Participant's total score increased from pre-test to post-test

Question 6: On a scale of 1 to 5, with 1 being extremely likely and 5 being extremely unlikely, how likely are you to track dietary Phe if there was an easier method of tracking?

On the pre-test, two participants chose “very likely”, two participants chose “more likely”, four participants chose “maybe, and two participants chose “more unlikely” to track dietary Phe with an easier method of tracking **(Figure 9)**.

Figure 9. Pre- & post-test likert scale scores (n=10): On a scale of 1 to 5, with 1 being extremely likely and 5 being extremely unlikely, how likely are you to trackdietary phe if there was an easier method of tracking?

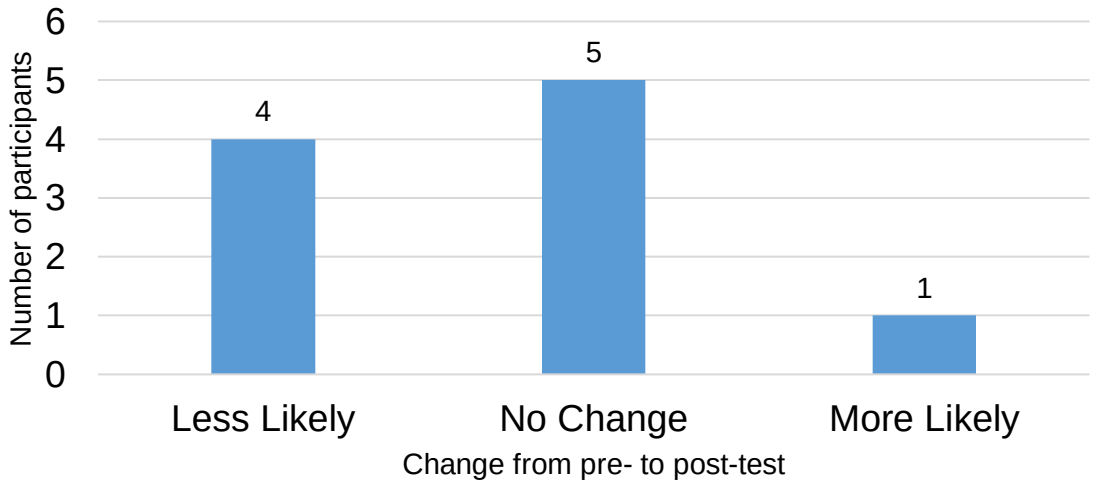


Series 1: Pre-test scores
Series 2: Post-test scores

Of the 10 participant responses, one participant (10%) improved her response to indicate that she was more likely to track dietary Phe and four participants (40%) gave a poorer response to indicate that they were less likely to track dietary Phe. The two participants who responded “very likely” to track dietary Phe with an easier method of tracking on the pre-test also did so on the post-test. Although

not statistically significant (p=0.375), there was a negative trend among participant responses from pre-test to post-test indicating that they would be less likely to track dietary Phe intake, even though an easier method of tracking (i.e. protein counting) was presented in the education session. Based on the sample data, 60% of responders (6/10) reported a response that indicated “no change” (n=5) or “improved” (n=1) motivation to track dietary Phe intake with an easier method of tracking **(Figure 10)**. In the future, we estimate that actual proportions between 35 and 81% of subjects would be reasonable values for those who would indicate “no change” or “improved” after answering this question if this study was to be conducted again, 90% CI [0.35, 0.81].

Figure 10. Distribution of Reponses
Question #6 (n=10): On a scale of 1 to 5, with 1 being extremely likely and 5 being extremely unlikely, how likely are you to trackdietary phe if there was an easier method of tracking?



Worse: Participant response changed from “more likely” or “maybe” with pre-test to “maybe” or “less likely” with post-test
No change: Participant reported the same response for both pre- and post-test
Improved: Participant response changed from “less likely” or “maybe” with pre-test to “maybe” or “more likely” with post-test

CHAPTER 5: DISCUSSION

Summary and Conclusions

The 2 main goals of this study were 1. to develop an age-appropriate educational tool, reviewed and approved by metabolic dietitians, that allows adolescents and young adults with PKU to count total protein to manage their metabolic disorder and, 2. to evaluate the effectiveness of the newly-developed educational tool by instructing a cohort of adolescents and young adults with PKU to count protein using this tool and subsequently assessing their knowledge.

Protein counting is a relatively new concept for the dietary management of PKU and involves a simplified approach to the classic nutrition therapy of counting dietary Phe. This simplified approach allows freedom to eat certain fruits, vegetables, and low-protein specialty foods without counting them towards daily dietary Phe intake and, thus, involves less calculation than counting Phe. Multiple studies have shown insignificant changes in blood Phe concentrations with use of a simplified diet, and patients have found it easier to understand and follow than the traditional Phe tracking methods (32-36). The use of protein counting could be especially helpful for adolescents and young adults with PKU who are transitioning to their own self-care and who are motivated to improve and maintain metabolic control throughout life for optimum cognitive functioning. However, at this time there is no standardized method of teaching this new concept to individuals in this age group. This unmet need led to the development

of this educational tool.

Our pilot study with 10 adolescents and young adults found no significant changes in knowledge about protein counting or motivation to use this easier method to track dietary Phe intake after attending the education session. However, there are still important conclusions that can be drawn from the results from this small group of subjects. There was a trend towards improvement in knowledge about protein counting as evidenced by an increase in the number of participants with correct answers on the post-test compared with the pre-test. Interestingly, some participants (n=4) responded that they were “more unlikely” to track dietary Phe with an easier method of tracking (i.e. protein counting) on the post-test; however, responses to post-test question #1b and 2 (shown in Table 4) suggest that these negative attitudes towards the use of protein counting can be attributed to factors other than the effectiveness of the handout and tracking method. Many of the responses reported “laziness” and “too much of a time commitment” as factors that participants did not like about the protein counting method. This may be more related to common adolescent and young adult attitudes and/or behaviors rather than a reflection on the concept of protein counting for diet management.

This idea has been explored in adolescents with diabetes mellitus. Rausch et al. (46) monitored glycemic control in children with type 1 diabetes mellitus who were entering into adolescence and found a significant decline in adherence to medical treatment after following these children for 2 years. Similarly, Kovacs

et al. (47) found that nonadherence to medical treatment began more frequently in middle adolescence (mean age=14 years) suggesting that adolescence is a “high risk” period for treatment noncompliance. However, the predictive factors for treatment adherence in this age group are not well understood suggesting future research is needed to help target effective tools for improved health care management. These findings could be applied to adolescents and young adults with PKU to help improve their treatment compliance.

Assessing the transition and readiness for medical self-management among adolescents and young adults may be an important factor to consider as well. Javalkar et al. (48) assessed health care transition and readiness for self-management among adolescents and young adults diagnosed with various chronic conditions. Some barriers to transition and readiness for self-management included specific factors such as sex, median income, and language. Participants who lived in an area with a greater percentage of females and had a higher median family income had a significantly greater overall readiness to transition to health care self-management (48). Increased age was also found to be related to greater overall readiness to transition suggesting that young adults may be more ready to transition to their own medical self-management than adolescents (48). It may be beneficial to take these factors into consideration when helping transition patients to health self-management and incorporating patient-centered education. The concept of adolescents becoming “active patients” who are involved in the diagnosis and treatment

process is another factor that should be considered. Woynarowska-Soldan et al. (49) explored this idea in teens with chronic diseases and found that this concept was not well understood by this age group. This suggests that the transition to self-management of health care may need to begin at an earlier age in order to establish appropriate habits to promote health throughout life.

Exploration of factors affecting health care adherence is particularly important for adolescents and young adults with PKU in order to maintain optimum cognitive functioning and QOL. Individuals with PKU who are non-compliant often have an extremely difficult time returning to the diet, even if doing so can improve QOL (30). Common reasons for non-compliance with the traditional PKU diet include sociocultural barriers such as poor knowledge of the complicated diet, problems explaining PKU in social situations, and language barriers (25,30). Common deterrents to dietary compliance specifically during adolescence are the power struggle adolescents face with parents and the need to fit in with peers (25,28). However, Sharman et al. (29) found that adolescents commonly identified support from family and friends as an encouraging factor for dietary adherence to maintain “normal” cognitive abilities and Bernstein et al. (37) found that patients considered their families to be the most effective education tool. To be successful in health education of adolescents and young adults with PKU, factors that promote acceptance and QOL need to be considered to help improve knowledge and adherence to dietary treatment.

Strengths and Limitations

The primary limitation of this study was the small sample size which made it difficult to perform higher statistical tests with more power to detect statistical differences between pre- and post-test data. Therefore, it is difficult to conclude the true significance of changes noted among this cohort of adolescents and young adults after the education session. In addition, the pre- and post-tests developed for this study were not validated questionnaires and therefore may contain specific wording of questions that could have been a cause for confusion among participants. Even if there were significant changes found in knowledge and motivation to count protein between the pre- and post-tests, the short follow-up time (1 month) could have made it difficult to assess any true significance of the effectiveness of the educational tool and protein counting method. In addition, the one-time education session was brief (~20 minutes) and only contained information pertaining to the educational tool and its use rather than focusing on specific patient needs and motivation.

Strengths of this study include the development, evaluation, and validation of the educational tool by metabolic RDs across the country providing multiple parties to comment and rate the tool, therefore improving detection of potential weaknesses. The one-on-one sessions with the participants reduced distractions and improved communication between participants and the study coordinator. Use of the teach-back method with 24-hour recalls to practice protein counting was also a strength since it allowed participants to demonstrate their understanding and identify gaps in knowledge that could be addressed before

the end of the session.

Future Directions

This study suggests that protein counting may be an easier method for adolescents and young adults to understand. Because this was a pilot study, we were unable to work with and follow a larger number of participants over time to assess true changes in metabolic control with use of the protein counting tool. However, future research also needs to address the use of more effective methods of health education and address the motivation of adolescents and young adults to improve metabolic control. For example, Singh et al. (50) evaluated the effectiveness of a group education intervention on knowledge, attitudes, and dietary compliance in adolescent girls with PKU attending a summer camp. Significant reductions in dietary Phe intake, blood Phe concentrations, and sense of isolation were measured over the short-term during the camp, although these measures returned to baseline after a one-year period (50).

Educating adolescents and young adults in a group education setting could be beneficial to improve knowledge and attitudes toward their disease and provide a sense of fellowship. Specifically, for patients followed at the CDRC Metabolic Clinic, this type of education could be incorporated into the Northwest PKU Alliance Family Camp held every August in Antelope, Oregon. It may be of benefit to use this tool in a group education setting with a younger adolescent audience. Having the ability to hold multiple education sessions with younger

participants, to follow participants over a longer period of time, and to use true markers of metabolic control may be a more effective method to applying this educational tool and therefore may lead to improved outcomes with implementing the simplified diet for this age group.

The simplified diet protocol varies vastly among clinics around the world with different clinics using different standards for what foods do and do not need to be counted in the PKU diet (51,52). It is important to standardize the simplified diet among these clinics to make the management of PKU less confusing and improve outcomes for these patients.

With earlier introduction of simplified diet education, earlier transition to self-management of medical care, and encouraged support from parents and peers, adolescents and young adults with PKU could improve their treatment compliance and ultimately their overall QOL. Practitioners need to consider these factors when developing an education strategy for their patients with PKU in this age group.

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APPENDICES

APPENDIX A: Recruitment Letter

IRB Approved: 5/18/2016
Sandra Van Calcar, Ph.D.
Assistant Professor
vancalca@ohsu.edu

OREGON HEALTH & SCIENCE UNIVERSITY
OHSU

School of Medicine

Department of Molecular and Medical Genetics

Mail code: L103
3181 S.W. Sam Jackson Park Rd.
Portland, Oregon 97239-3098
tel 503 494-1682 | fax 503 494-6886

Date:

Dear _____,

We are recruiting subjects for a study entitled *"Development and Evaluation of an Educational Tool to Count Protein for Adolescents and Young Adults with PKU IRB# 15229"*, which will evaluate the effectiveness of a new educational tool designed to teach protein counting as a method of managing PKU. You are being asked to participate in this study because you (or your child) have PKU, are a patient at OHSU and are between the ages of 13 to 25 years. This study will be conducted at Oregon Health & Science (OHSU) Metabolic Clinic. The study is approved by the OHSU Institutional Review Board.

The purpose of this study is to evaluate an educational tool for protein counting by assessing patient knowledge and clinical outcomes. Counting protein is a new system in dietary management of PKU that may be an easier method of counting phenylalanine (Phe) intake. However, there are few educational resources to teach this new method to adolescents and young adults with PKU.

Participation in this study is voluntary. A copy of the informed consent for the study is enclosed which describes the study and what it involves. The study coordinator, Nicole Choyce, will contact you in the next week to answer any questions, see if you (or your child) may be interested in participating and to review the consent form with you. If you have any questions or concerns, I am happy to discuss them with you. My contact information is listed below.

Thank you for considering participating in this research study.

Sincerely,

Sandy Van Calcar, PhD, RD, LD
Dietitian, OHSU Metabolic Clinic
Phone: 503-474-5500
Email: vancalca@ohsu.edu
Oregon Health & Science University
3181 SW Sam Jackson Park Rd. Mail code GH207
Portland, OR 97239

APPENDIX B: Recruitment Telephone Script

IRB Approved: 3/7/2016

IRB#15229

Telephone Recruitment and Screening Script Template

Hello, my name is _____. I'm calling from Oregon Health & Science University about a research study. Am I speaking to _____ (name of recruit or parent/guardian)?

If "no," wait for recruit to pick up, arrange to leave a message, or ask for a time to call back.
If "yes":
I got your phone number from the OHSU Metabolic Clinic. Is this a good time to talk? I expect this phone call will take about 10 minutes.

Arrange to call at another time, if appropriate.

I'm calling about a research study involving individuals with PKU called "Development and Evaluation of an Educational Tool to Count Protein for Adolescents and Young Adults with PKU". The purpose of this study is to evaluate a new educational tool for protein counting by assessing patient knowledge. Letter and consent forms were sent about a week ago to give you details about the study.

I'm calling to see if you have any questions and if you may be interested and eligible to participate in the study. If it looks like you might be eligible, the study will take place during your upcoming appointment in the OHSU metabolic clinic on (insert date). During this time, we will discuss the study with you in more detail and you can decide if you want to participate. You do not have to participate in this study.

Review the study protocol and answer questions.

Before we go on, let me tell you a little bit about your rights as a research subject.

The main risk of answering my questions today is loss of confidentiality. However, we will do our best to keep your information confidential by keeping it coded with a subject identification number and kept on a password-protected computer.

You don't have to answer these questions, and you can choose to stop at any time without penalty. If you have further questions about the study, you can call us at 503-474-5500. If you have questions about your rights as a research subject or research-related injuries, you can call the OHSU Research Intergrity Office at 503-494-7887.

May I go ahead with the eligibility questions?

If no, thank the individual and end the call.
If yes, individual is interested:

Before we discuss the study, I'm going to give a list of things that would PROHIBIT you from being in the study. Please do not indicate if these things apply to you until the end of the list.

IRB#15229

When I'm finished with the list, feel free to ask questions or tell me if you do NOT have any of the following.

The list of criteria presented to a potential subject will depend on his/her sex and age

- Diagnosis of pregnancy
- A nursing mother
- A diagnosis of a concurrent illness
- English is not his/her primary spoken language

If any of those things are true for you, you cannot participate in the study. Does it look like you might still be eligible?

If yes: Document eligibility response and make appointment, if appropriate.
If no:
Thank you for your time.

APPENDIX C: Consent & Assent Forms

IRB Approved: 5/18/2016
Approval Expires: 3/6/2017

OREGON HEALTH & SCIENCE UNIVERSITY

IRB#: __15229_____

MED. REC. NO. _____
NAME _____
BIRTHDATE _____

Clinical Research Consent Summary

TITLE: *Development and evaluation of an educational tool to count protein for adolescents and young adults with PKU*

PRINCIPAL INVESTIGATOR: Sandy Van Calcar, PhD, RD (503) 474-5500

You are being asked to join a research study. You do not have to join the study. Even if you decide to join now, you can change your mind later.

The purpose of this study is to evaluate a new educational tool for protein counting by assessing patient knowledge. Counting protein is a new system in dietary management of phenylketonuria (PKU), and there are few resources for this as an intervention to manage phenylalanine (Phe) intake. We do not know if the protein counting system used in the education tool is better than the usual approach of counting milligrams of Phe for treating PKU.

This study requires 1 visit to the clinic where you will learn how to use the protein counting tool and one phone call one month after the clinic visit to follow-up on your use of this tool. This study will enroll 10-15 adolescents and young adults with PKU, ages 13-25 years, who are currently followed at the OHSU Metabolic Clinic. There is a potential risk for loss of confidentiality involved with participation in this study.

OREGON HEALTH & SCIENCE UNIVERSITY

IRB#: __15229_____

MED. REC. NO. _____
NAME _____
BIRTHDATE _____

Clinical Research Consent and Authorization Form

TITLE: *Development and evaluation of an educational tool to count protein for adolescents and young adults with PKU*

PRINCIPAL INVESTIGATOR:	Sandy Van Calcar, PhD, RD (503) 474-5500
CO-INVESTIGATORS:	Joyanna Hansen, PhD, RD (503) 494-4263 Nicole Choyce, BS (408) 409-0231

SUPPORTED BY: Oregon Health & Science University – Doernbecher Children's Hospital

PURPOSE:
In this form, "you" means you or your child. You have been invited to be in this research study because you have phenylketonuria (PKU). The purpose of this study is to evaluate a new educational tool for protein counting by assessing patient knowledge. Counting protein is a new system in dietary management of PKU, and there are few resources for this as an intervention to manage phenylalanine (Phe) intake. There is a need for age-appropriate educational materials that will teach adolescents and young adults with PKU how to count and track protein as an easier method of dietary management. We do not know if the protein counting system used in the educational tool is better than the usual approach of counting milligrams of Phe for treating PKU.

This study requires 1 visit to the clinic or 1 in-home visit and one follow up phone call one month after the scheduled visit.

This study will enroll 10-15 adolescents and young adults with PKU, ages 13-25 years, who are currently followed at the OHSU Metabolic Clinic.

PROCEDURES:
The study session will be scheduled during your usual clinic visit to the Metabolic Clinic or a scheduled in-home visit. You will be given a pre-test upon arriving for the scheduled visit. The pre-test will include questions to assess your knowledge and interest in protein counting as a potentially easier way for you to count your Phe intake. There will also be a question regarding your preferred method for future contact (mail, email, or both). The scheduled education session will last approximately 30 minutes. During the first 15 minutes, use of the education tool will be explained to you and you may ask any questions you might have. You will be asked to write down everything you eat and the amounts you eat for 24 hours prior to coming in for your visit. You will use this and the phenylalanine prescription from your medical records during the remaining 15 minutes of your session to practice the protein counting method that was taught to

you. You will be asked to teach the use of the educational tool back to the study investigator as you understood it.

One month after the scheduled session, you will be mailed or emailed a post-test. The post-test will include similar questions to the pre-test to assess any changes in your knowledge and your use of the protein counting method. You will also receive a brief follow-up telephone call as a reminder to complete and return the post-test evaluation within one to two weeks of receiving the test.

	Visit 1 Day 1	Follow up Day 30
Discussion about the study and signing consents	X	
Pre-test	X	
Educational Session	X	
Post-test & follow up phone call		X
Total time	1 hour	15-30 minutes

RISKS AND DISCOMFORTS:
Some of these questions may seem personal or embarrassing. They may upset you. You may refuse to answer any of the questions that you do not wish to answer. There is a potential risk for loss of confidentiality by being involved in this study.

BENEFITS:
You may or may not personally benefit from being in this study. However, by serving as a subject, you may help us learn how to benefit patients in the future.

ALTERNATIVES:
You may choose not to be in this study. You do no need to participate in the research study to receive treatment for PKU from the OHSU Metabolic Clinic.

CONFIDENTIALITY
We will take steps to keep your personal information confidential, but we cannot guarantee total privacy. All data will be entered and stored into an OHSU encrypted computer. Participants will be assigned numbers and will have no identifiers associated to them. The original questionnaires will be stored in a locked cabinet in the principal investigator's office and kept until all data is analyzed and published.

We will create and collect health information about you as described in the Purpose and Procedures sections of this form. Health information is private and is protected under federal law and Oregon law. By agreeing to be in this study, you are giving permission (also called authorization) for us to use and disclose your health information as described in this form.

The investigators, study staff, and others at OHSU may use the information we collect and create about you in order to conduct and oversee this research study.

Under Oregon law, suspected child or elder abuse must be reported to appropriate authorities.

We may release this information to others outside of OHSU who are involved in conducting or overseeing research, including the Office for Human Research Protections, a federal agency that oversees research involving humans. They may also be permitted to review and copy your records.

Data from this study may be shared with other investigators at OHSU for future research studies. All identifying information about you will be removed from the data before it is released to any other investigators.

None of the information collected and created in this study will be placed in your OHSU medical record.

We will not release information about you to others not listed above, unless required or permitted by law. We will not use your name or your identity for publication or publicity purposes, unless we have your special permission.

When we send information outside of OHSU, they may no longer be protected under federal or Oregon law. In this case, your information could be used and re-released without your permission.

We may continue to use and disclose your information as described above indefinitely.

COMMERCIAL DEVELOPMENT:
Information obtained from you in this research may be used for commercial purposes, such as making a discovery that could, in the future, be patented or licensed to a company, which could result in a possible financial benefit to that company, OHSU, and its researchers. There are no plans to pay you if this happens. You will not have any property rights or ownership or financial interest in or arising from products or data that may result from your participation in this study. Further, you will have no responsibility or liability for any use that may be made of your information.

COSTS: There will be no cost to you or your insurance company to participate in this study.

LIABILITY:
If you believe you have been injured or harmed as a result of participating in this research and require treatment, contact Sandy Van Calcar, PhD, RD at (503) 474-5500.

If you are injured or harmed by the information collected, you will be treated. OHSU does not offer any financial compensation or payment for the cost of treatment if you are injured or harmed as a result of participating in this research. Therefore, any medical treatment you need may be billed to you or your insurance. However, you are not prevented from seeking to collect compensation for injury related to negligence on the part of those involved in the research. Oregon law (Oregon Tort Claims Act (ORS 30.260 through 30.300)) may limit the dollar amount that you may recover from OHSU or its caregivers and researchers for a claim relating to care or research at OHSU, and the time you have to bring a claim.

If you have questions on this subject, please call the OHSU Research Integrity Office at (503) 494-7887.

PARTICIPATION:
If you have any questions, concerns, or complaints regarding this study now or in the future, contact Sandy Van Calcar, PhD, RD at (503) 474-5500.

This research is being overseen by an Institutional Review Board ("IRB"). You may talk to the IRB at (503) 494-7887 or irb@ohsu.edu if:

- Your questions, concerns, or complaints are not being answered by the research team.
- You want to talk to someone besides the research team.
- You have questions about your rights as a research subject.
- You want to get more information or provide input about this research.

You may also submit a report to the OHSU Integrity Hotline online at https://secure.ethicspoint.com/domain/media/en/gui/18915/index.html or by calling toll-free (877) 733-8313 (anonymous and available 24 hours a day, 7 days a week).

Your participation in this study is voluntary. You do not have to join this or any research study. You do not have to allow the use and disclosure of your health information in the study, but if you do not, you cannot be in the study.

If you do join the study and later change your mind, you have the right to quit at any time. This includes the right to withdraw your authorization to use and disclose your health information. If you choose not to join any or all parts of this study, or if you withdraw early from any or all parts of the study, there will be no penalty or loss of benefits to which you are otherwise entitled, including being able to receive health care services or insurance coverage for services. Talk to the investigator if you want to withdraw from the study.

If you no longer want your health information to be used and disclosed as described in this form, you must send a written request or email stating that you are revoking your authorization to:

Sandy Van Calcar, PhD, RD
Asst. Professor, Department of Molecular and Medical Genetics
Oregon Health and Science University
3181 Sam Jackson Park Rd.
Mailcode GH 207
Portland, OR 97239
vancalca@ohsu.edu

Your request will be effective as of the date we receive it. However, health information collected before your request is received may continue to be used and disclosed to the extent that we have already acted based on your authorization.

The information we will collect from you will not be stored with your name or any other identifier. Therefore, there will not be a way for us to identify and destroy your materials if you decide in the future that you do not wish to participate in this research.

We will give you any new information during the course of this research study that might change the way you feel about being in the study.

Your health care provider may be one of the investigators of this research study and, as an investigator, is interested in both your clinical welfare and in the conduct of this study. Before entering this study or at any time during the research, you may ask for a second opinion about your care from another metabolic dietitian who is in no way involved in this project. You do not have to be in any research study offered by your care providers in the Metabolic Clinic.

SIGNATURES:

Your signature below indicates that you have read this entire form and that you agree to be in this study.

_____ _____
Signature of Subject Date
(Or Parent/Guardian if subject is under 18)

_____
Printed Name of Subject
(Or Parent/Guardian if subject is under 18)

_____ _____
Signature of Person Obtaining Consent Date

_____
Printed Name of Person Obtaining Consent

Subjects 15-17 years of age:

Your signature below indicates that you agree to be in this study.

_____ _____
Signature of Subject Date

_____
Printed Name of Subject

IRB Approved: 3/7/2016
Approval Expires: 3/6/2017

OREGON HEALTH & SCIENCE UNIVERSITY

Child Assent Form

IRB# 15229

TITLE: *Development and evaluation of an educational tool to count protein for adolescents and young adults with PKU*

PRINCIPAL INVESTIGATOR: Sandy Van Calcar, PhD, RD (503) 474-5500

CO-INVESTIGATORS: Joyanna Hansen, PhD, RD (503) 494-4263
Nicole Choyce, BS (408) 409-0231

This research study was explained to me. I know how it may or may not help me. I also know that this study will help doctors learn more about phenylketonuria (PKU). To be sure that I know what is going to happen, the investigator will ask me the following:

1. To explain what I will do and what will happen in this study.
2. If I have any questions or want to know anything else about this study or (insert name of condition).
3. To explain some of the good and bad things that might happen to me if I enter this study.

I have thought about being a part of this study. I have asked and received answers to my questions. I agree to be in this study. I know that I don't have to agree to be in the study. Even though I agree to be in it now, I know I may feel differently later on and can ask to stop being in the study. I know that I may talk with my parents and/or doctor about not being in this study at any time.

Name/signature:_____ Date:_____

Document Control No.: IRB-CAS-01
Original Date: 12/04/2002; Revision Date: 3/7/2012

APPENDIX D: Education Tool Review Additional Comments

PKU Protein Counting Education Tool Review: Additional Comments

Evaluation #1:

- Header: 'Starches, Grains Cereals and Breads (Not low protein medical foods): does your clinic call the specialty low protein foods 'medical foods'? I think of metabolic formulas = medical foods not the specialty foods.
- The columns for Avoid high protein foods; tabulate to align cheese after cottage after the bullet check mark; it might read easier..
- Nice handout overall! Please put a date and your name for authorship credit so will know for future versions.

Evaluation #2:

- Where do you list the specialty low protein cheese; some types have 0 gm or 1 gm of protein (and can be found in regular grocery store)...these are important to list (ALL cheese is currently listed as a red light high protein food).
- Maybe insert a single page with “My Protein Allowance” that reinforces “I can have all these free foods, plus ____ grams of protein, per my RD's instructions”
- Add to free foods to clarify that: free foods are = <75 mg phe/100g serving
- Thanks will be lovely to have a handout tool to help us to teach our parents/patients.

Evaluation #3:

- Would move ½ cup portion box to the pages where the list of foods is located.
- Why are free foods <75 mg when you have them count foods with 1 gm protein/50 mg phe?
- Recommend adding box on front page with space to fill in individual's protein allowance
- Include broader food groups on avoid list, i.e. nuts, soy, legumes/beans

Evaluation #4:

- I would repeat the ½ cup portion information with different lists
- Suggest organize high protein foods in a less random fashion. Include chicken. Nuts. Quinoa.
- Suggest in mention of the Servings per container part of the food label. Many get confused by this.
- There are lots of free Web resources for nutrition data – consider adding those.

- Consider adding pictures of meals with the protein content vs just individual foods.

Evaluation #5:

- On the lists of foods, what about regular pasta, rice?
- I know the numbers fell into place this way, but it seems weird that tater tots are “moderate” and French fries are “high” – maybe change the portion sizes so they're in the same category. Or comment on it as a teaching opportunity
- for the AVOID list, I might split this further – truly high protein foods (eggs, meat, etc.) and “pretty high” moderate foods (all those grains)
- English muffins is on the AVOID list and ½ English muffin is on the Grains list
- Some other things that might need another look – 3 Oreo cookies is okay but donuts (even a donut hole?) are not.
- Whoops, I just now saw rice and spaghetti – I think maybe there could be a box that describes how they might (or might not fit) – like maybe say ¼ cup rice = x gm protein
- Perhaps work through the example of the nutrition facts label (add or circle the protein and say 3 x 50 = 150. You can estimate that 2/3 cup of this food has about 150 mg phe
- For the apps, I'd spell it out a bit more – you can use these apps to find the protein content and then estimate phe
- how many goldfish in ½ cup (all the other foods were clear to me, but the goldfish spread on the plate wasn't how I'm used to seeing them as a parent – I guess I could count them....)
- Not a big deal at all, but the “white bread” seemed pretty brown. (Guessing it's not whole grain, but maybe just say bread??)
- Nice work!! This will be helpful to families!

Evaluation #6:

- Very well done

Evaluation #7:

- This looks really nice, a few thoughts – what do you think about the label reading in the front, where you introduce “protein counting”
- Can you repeat the indication of the ½ cup portions on each of the pages where it is relevant?
- In the “Free Food” section – what do you think about “Most” instead of “All” where there are exceptions.
- In addition, how about a list of the “Free fruits” and “Free veggies” to give them ideas
- What do you think about “Avoid” foods on a separate page?

Evaluation #8:

- A well put together handout. I like the more specific foods (i.e. 10 Ritz crackers vs 2 whole wheat crackers). I find specific, concrete examples are important for this population.
- Content-wise it seems good. I would remove the “flax milk” from the dairy alternatives that are 1 gm as I believe this is very close to 0 gm per 8 oz. serving.

Evaluation #9:

- Overall, excellent. It is a bit long yet is a good synthesis of several currently available tools.
- I really like the high list. It is very concise.
- Is there a way to model the moderate and high lists in this manner?
- I would use this tool for my patients.
- Pg. 2 – it says “NOT low protein medical food”. I’m not sure how that relates, and it’s really not low protein, just PHE free or minimal PHE? Perhaps a general statement somewhere that MF is a separate thing.
- Pg3 – in the AVOID list I think nuts and nut butters (in addition to peanut butter) and eggs should be added. And I don’t think I would put regular breads on the AVOID list – especially now that we have people with higher tolerance w/ Kuvan
- General – should specialty low protein foods be addressed somewhere?
- AND when the text is wrapped for a listed item, I would line up the left margins instead of the way it is, so: Item 1 is typed, Item 2 is typed but longer so text is wrapped. But would be easier to read if margins are aligned within the list.

Changes made to PKU Protein Counting Education Tool prior to use in clinic (based on additional comments):

- The columns for Avoid high protein foods; tabulate to align cheese after cottage after the bullet check mark; it might read easier..
- Where do you list the specialty low protein cheese; some types have 0 gm or 1 gm of protein (and can be found in regular grocery store)...these are important to list (ALL cheese is currently listed as a red light high protein food).
- Maybe insert a single page with “My Protein Allowance” that reinforces “I can have all these free foods, plus ____ grams of protein, per my RD's instructions”
- Would move ½ cup portion box to the pages where the list of foods is located.
- Include broader food groups on avoid list, i.e. nuts, soy, legumes/beans

- for the AVOID list, I might split this further – truly high protein foods (eggs, meat, etc.) and “pretty high” moderate foods (all those grains)
- English muffins is on the AVOID list and ½ English muffin is on the Grains list
- In the “Free Food” section – what do you think about “Most” instead of “All” where there are exceptions.
- What do you think about “Avoid” foods on a separate page?
- I would remove the “flax milk” from the dairy alternatives that are 1 gm as I believe this is very close to 0

APPENDIX E: Educational Tool

A Guide to Protein Counting for PKU

What is protein counting?

This may be an easier method to track your daily Phe intake.

50 milligrams Phe=1 gram Protein

Your daily **protein** allowance: _____ gm(s)

All foods in the lists are 1/2 cup portions unless otherwise noted.

"FREE" Foods

- ✓ Most fruit, except dried fruit
- ✓ All fruit juices
- ✓ Most vegetables, except those listed (see page 3)
- ✓ Most vegetable juices, except those listed (see page 3)
- ✓ All low protein breads/pasta/rice/baked goods
- ✓ All sauces/condiments/dressings <1 gm protein per serving
- ✓ Flax milk (8 oz)

1

Vegetables and Dried Fruit

Low 1 gm	Moderate 2 gm	High 3 gm
✓ Arugula ✓ Broccoli ✓ Dried fruit (1/4 cup) ✓ Mushrooms ✓ Nori Seaweed (8 sheets)	✓ Asparagus ✓ Avocado ✓ Baked potatoes (1/4) ✓ Cooked spinach (1/8 cup) ✓ Hash browns ✓ Mustard greens ✓ Peas ✓ Sweet potatoes/ yams ✓ Tater tots (10)	✓ Artichoke hearts ✓ Brussels sprouts ✓ Corn ✓ French fries (12) ✓ Mashed potatoes ✓ Sun-dried tomatoes

All foods in the lists are 1/2 cup portions unless otherwise noted.

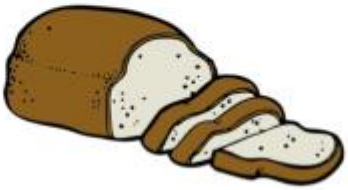
Dairy Alternatives

Low
1 gm

- ✓ Almond milk (8 oz)
- ✓ Cashew milk (8 oz)
- ✓ Coconut milk/yogurt/ice cream (8 oz)
- ✓ Quinoa milk (8 oz)
- ✓ Rice milk (8 oz)
- ✓ Daiya Cheddar/Provolone/Swiss cheese (1 slice)

Starches, Grains, Cereals & Breads (NOT low-protein medical foods)

Low 1 gm	Moderate 2 gm	High 3 gm
✓ Corn flakes cereal ✓ Corn tortilla-6" (1) ✓ Gluten-free tortilla-6" (1) ✓ Graham crackers (1 sheet) ✓ Rice cereals ✓ Whole wheat crackers (2) ✓ Quaker Chewy Granola Bar (1)	✓ Animal crackers (8) ✓ Bran flakes cereal ✓ Bread, white/wheat/ raisin/potato (1 slice) ✓ Cheese Nips (15) ✓ Chips Ahoy Chewy Chocolate Chip Cookies (2) ✓ Chow mein noodles ✓ Corn grits ✓ Croutons ✓ Frozen waffles (1) ✓ Hamburger bun (1/2 bun) ✓ Hotdog bun (1/2 bun) ✓ Oreo cookies (3) ✓ Pancake-4" (1) ✓ Saltines (5) ✓ Potato chips (1 oz) ✓ Pop tart (1) ✓ Rice cakes (2 cakes) ✓ Rice noodles ✓ Ritz crackers (10) ✓ Wheat Thins (10)	✓ Bread stuffing ✓ Corn bread-2x2" ✓ Couscous ✓ English muffin (1/2 muffin) ✓ Flour tortilla-6" (1) ✓ Goldfish ✓ Italian bread (1 slice) ✓ Oatmeal ✓ Rye bread (1 slice) ✓ Whole wheat tortilla-6" (1)



All foods in the lists are 1/2 cup portions unless otherwise noted.

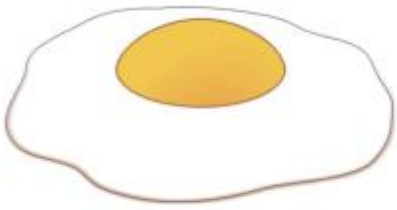
AVOID these high protein foods

Very high

- ✓ Edamame
- ✓ Eggs
- ✓ Fish/shellfish
- ✓ Meat/Poultry
- ✓ Cheese (all types)
- ✓ Cottage cheese
- ✓ Cow's milk
- ✓ Frozen Yogurt
- ✓ Goat's milk
- ✓ Ice cream
- ✓ Oat milk
- ✓ Sour cream
- ✓ Yogurt
- ✓ Nuts/Seeds

High

- ✓ Granola
- ✓ Hamburger Helper
- ✓ Macaroni
- ✓ Rice
- ✓ Spaghetti
- ✓ Beans/Legumes
- ✓ Soy burgers
- ✓ Soy milk
- ✓ Bagels
- ✓ Croissant
- ✓ Donuts
- ✓ French toast
- ✓ Pita bread
- ✓ Soft pretzel
- ✓ Cliff Bar
- ✓ Luna Bar
- ✓ Peanut butter
- ✓ Power Bar



Label Reading

1 gram of protein = 50 milligrams of Phe

Nutrition Facts

Serving Size 2/3 cup (55g)
Servings Per Container About 8

Amount Per Serving

Calories 230	Calories from Fat 40
	% Daily Value*
Total Fat 8g	**12**%
Saturated Fat 1g	**5**%
Trans Fat 0g	
Cholesterol 0mg	**0**%
Sodium 160mg	**7**%
Total Carbohydrate 37g	**12**%
Dietary Fiber 4g	**16**%
Sugars 1g	
Protein 3g	
Vitamin A	10%
Vitamin C	8%
Calcium	20%
Iron	45%

* Percent Daily Values are based on a 2,000 calorie diet. Your daily value may be higher or lower depending on your calorie needs.

	Calories:	2,000	2,500
Total Fat	Less than	65g	80g
Sat Fat	Less than	20g	25g
Cholesterol	Less than	300mg	300mg
Sodium	Less than	2,400mg	2,400mg
Total Carbohydrate		300g	375g
Dietary Fiber		25g	30g

Serving Size

Protein per serving

Additional Resources

Below are a list of resources that you can access with your smart phone or other mobile device.

These are helpful tools for items without a nutrition facts label.

Mobile Apps:

- ✓ MyFitnessPal
- ✓ Fooducate
- ✓ Food Facts
- ✓ Simply Soups, Sauces and Smoothies

Web Resources:

- ✓ HowmuchPhe.org

Serving Sizes

1/4 Baked Potato
2 gm Protein

1/2 cup Mashed Potatoes
3 gm Protein

1 small bag Lay's Potato Chips
2 gm Protein

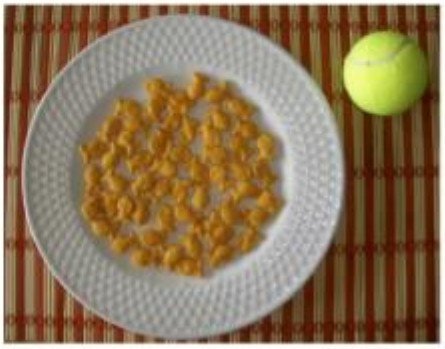
About 12 French Fries
3 gm Protein

1/2 cup Roasted Red Potato
3 gm Protein

About 10 Tater Tots
2 gm Protein

Serving Sizes

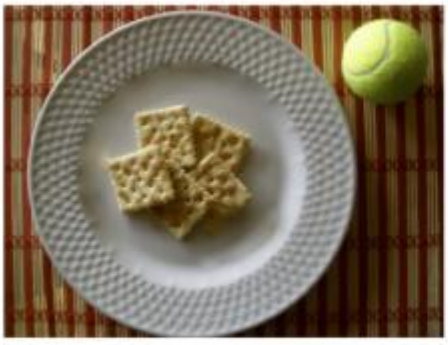
1/2 cup Peas and Carrots
2 gm Protein



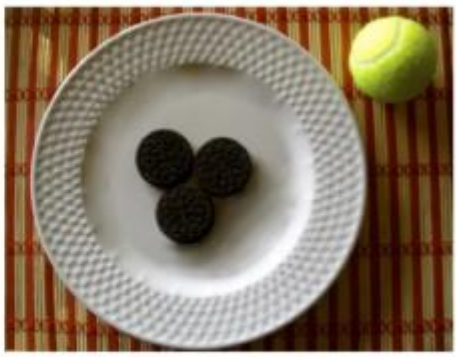
1/2 cup Goldfish Crackers
3 gm Protein

1 Corn Tortilla
1 gm Protein

1 slice White Bread
2 gm Protein



5 Saltine Crackers
2 gm Protein



3 Oreo Cookies
2 gm Protein

APPENDIX F: DANEH Checklist

Nutrition Education Handout Checklist

Scoring Criteria

Content:

Current, accurate, and consistent with USDA Dietary Guidelines and MyPlate

(required 'yes' for approval)

Yes ☐

Check "yes" if the content promotes current, evidence-based recommendations, and is consistent with USDA Dietary Guidelines and MyPlate.

No ☐

Check "no" if the content is based on outdated information (including MyPyramid).

Comments: _____

_____

Promotes relevant health issues for target audience

Yes ☐

Check "yes" if the content addresses a relevant health issue of the target audience (i.e., reducing sodium for African-American audiences).

No ☐

Check "no" if the content is not relevant to the target audience (i.e., eating organic fruits and vegetables for low-income audiences).

Comments: _____

_____

Clear purpose

Yes ☐

Check "yes" if it is immediately clear what the handout will tell you or how it can help you.

No ☐

Check "no" if you have to read much of the content before you realize what the handout will tell you or how it can help you.

Comments: _____

_____

Total Content Score _____

(3 possible 'yes' responses)

Behavior Focus:

One or two main themes

Yes ☐

Check "yes" if the handout contains no more than two main themes. For example, a handout with ten strategies to shop on a budget has one main theme, shopping on a budget.

No ☐

Check "no" if the handout contains three or more main themes. For example, a handout that covers tips for healthy snacks, physical activity, and bedtime routines contains three main themes.

Comments: _____

_____

Specific examples of desired behavior

Yes ☐

Check "yes" if the handout clearly instructs a person what to do, and how to do it through specific examples. For example, "Play active games with your kids, like hide-and-go-seek, double Dutch jump rope, or tag."

No ☐

Check "no" if the handout provides vague recommendations without specific examples of desired behavior. For example, "Be more physically active."

Comments: _____

_____

Total Behavior Focus Score _____
(2 possible 'yes' responses)

Cultural Sensitivity:

Culturally appropriate content for target audience

Yes ☐

Check "yes" if the handout is intended for a general audience and includes many cultural food and behavior practices. Check "yes" if the target audience is a specific culture, and the handout includes appropriate food and behavior examples for that culture.

No ☐

Check "no" if the handout is intended for a general audience and does not include culturally diverse food and behavior practices. Check "no" if the target audience is a specific culture and the handout does not represent appropriate food and behaviors for that culture.

Comments: _____

_____

Culturally appropriate images for target audience

Yes ☐

Check "yes" if the handout is intended for a general audience and includes images that respectfully represent many cultures, including the people, places and foods pictured. Check "yes" if the target audience is a specific culture, and the handout includes images of people, places, and foods from that culture.

No ☐

Check "no" if the handout is intended for a general audience and does not include images that respectfully represent many cultures. Check "no" if the target audience is a specific culture and the handout does not include appropriate images representing that culture.

Comments: _____

_____

Total Cultural Sensitivity Score _____
(2 possible 'yes' responses)

Written Word:

Simple, common words

Yes ☐

Check "yes" if simple, common words are used frequently, with limited use of abbreviations, acronyms, and technical jargon.

No ☐

Check "no" if complex and unfamiliar words are used frequently or if abbreviations, acronyms, and technical jargon appear excessively.

Comments: _____

_____

Positive messages

Yes ☐

Check "yes" if messages focus mostly on the positive behavior desired, i.e. "do this."

No ☐

Check "no" if the messages focus mostly on the negative behavior to change, i.e. "don't do this."

Comments: _____

_____

Active voice, second person (you/your), conversational tone

Yes ☐

Check "yes" if the handout refers to the second person (i.e. "you/your"), stays in the present tense, and uses a conversational/friendly tone. For example, "Offer healthy and tasty after school snacks for your kids, like grapes or cheese sticks."

No ☐

Check "no" if handout refers to the third person, uses the past tense, and/or is too formal. For example, "Parents need to provide nutrient-dense foods in-between meals for their children and adolescents."

Comments: _____

_____

Repetition of key words and/or new concepts

Yes ☐

Check "yes" if key words and/or new concepts are repeated effectively for reinforcement, or if repeating key words is not necessary (i.e. for a very short handout).

No ☐

Check "no" if repeating key words and/or new concepts would be effective for reinforcement, but are missing.

Comments: _____

Total Written Word Score _____
(4 possible 'yes' responses)

Organization and Readability

Logical order, most important message first

Yes ☐

Check "yes" if the information is displayed in a logical order, with the most important messages listed first.

No ☐

Check "no" if information is disorganized, and/or the most important messages do not appear until later in the handout.

Comments: _____

_____

Short paragraphs

Yes ☐

Check "yes" if each paragraph is short (60 words or less) and only contains one topic. Check "yes" if the handout does not contain paragraphs.

No ☐

Check "no" if each paragraph is long (over 60 words) and/or contains two or more topics.

Comments: _____

_____

Space around headings and text

Yes ☐

Check "yes" if there is a ½ inch margin around the perimeter of the handout and has at least a double space before headings.

No ☐

Check "no" if the margins are less than ½ inch around the perimeter of the handout and/or there is little space before headings.

Comments: _____

_____

Blocks of text are left-justified

Yes ☐

Check "yes" if blocks of text are left-justified.

No ☐

Check "no" if blocks of text are centered or right-justified.

Comments: _____

_____

Bullets, numbers, and tables
Yes ☐
Check "yes" if bullets, numbers, and/or tables appear often.
No ☐
Check "no" if the handout contains mostly text, and few bullets, numbers, or tables.
Comments: _____

_____

Several informative headings/subheadings
Yes ☐
Check "yes" if several headings/subheadings are present to help identify what the text will tell you next.
No ☐
Check "no" if few headings/subheadings are present, and/or if the headings/subheadings do not inform you what the text will tell you next.
Comments: _____

_____

Easy to read font
Yes ☐
Check "yes" if font is at least 12 point, and is serif (with feet, like Times Roman) or sans serif (without feet, like arial).
No ☐
Check "no" if font is smaller than 12 point, and is fancy or curly.
Comments: _____

_____

Important text is bolded or underlined if necessary
Yes ☐
Check "yes" if emphasizing text, bolding and underlining are used. Check "yes" if no emphasis of text is needed, (i.e. for a very short handout).
No ☐
Check "no" if emphasizing text uses all caps or italics.
Comments: _____

_____

Purposeful and relevant images

Yes ☐

Check "yes" if images show instruction or the desired behavior, are placed near relevant text, and include captions when necessary to describe the behavior or emphasize a point.

No ☐

Check "no" if images do not show instruction or the desired behavior, are not placed near relevant text, or do not include captions as necessary.

Comments: _____

_____

5th grade reading level

Yes ☐

Check "yes" if handout is written at or below a 5th grade reading level.

No ☐

Check "no" if handout is written at a 6th grade reading level or higher.

Instructions for determining reading level in Word:

1. Set up readability program:
   a. Click Review
   b. Click Spelling & Grammar
   c. Click Options
   d. Select Show readability statistics
2. Select, copy, and paste text into Word.
3. Under Review, click Spelling and Grammar Check.
4. Look for the Flesch-Kincaid **Grade Level** of the bottom of the Spelling and Grammar box.

Comments: _____

_____

Total Organization and Readability Score _____
(10 possible 'yes' responses)

Appendix G: Evidence Table

Executive Functioning and Getting Back "On Diet"					
Author	**Year**	**Citation**	**Population**	**Methods**	**Results**
Cotugno, G	2011	Cotugno G, Nicolo R, Cappelletti S, Goffredo BM, Dionisi Vici C, Di Ciommo V. Adherence to diet and quality of life in patients with phenylketonuria. Acta Paediatr 2011;100:1144-9.	41 early-treated patients affected by PKU aged more than 3 years old	Cross-sectional design with three-days of dietary assessment, QoL questionnaires for patients <18 years old and Short Form for adults were completed.	Phe intake was significantly in excess of prescribed if mothers had a lower level of education. Adherence was not correlated with age. Metabolic control was obtained in 41.5-51.2% of the patients depending on the target. QoL was reduced in children and adolescents. There was no significant correlation between adherence and QoL
Guest, JF	2013	Guest JF, Bai JJ, Taylor RR, Sladkevicius E, Lee PJ, Lachmann RH. Costs and outcomes over 36 years of patients with phenylketonuria who do and do not remain on a phenylalanine-restricted diet. J Intellect Disabil Res 2013;57:567-79.	The Health Improvement Network database (a nationally representative database of patients registered with general practitioners in the UK).	A computer-based model to estimate the incidence of co-morbidities and the levels of healthcare resource use and corresponding costs over the 36 years.	47% of patients discontinued their phenylalanine-restricted diet between 15 and 25 years of age. Of these, 73% remained off diet and 27% restarted a restricted diet at a mean 30 years of age.Patients had a mean 12 general practitioner visits per year and one hospital outpatient visit annually, but phenylalanine levels were only measured once every 18 to 24 months.

Ten Hoedt, AE	2011	Ten Hoedt AE, de Sonneville LM, Francois B, ter Horst NM, Janssen MC, Rubio-Gozalbo ME, Wijburg FA, Hollak CE, Bosch AM. High phenylalanine levels directly affect mood and sustained attention in adults with phenylketonuria: a randomised, double-blind, placebo-controlled, crossover trial. J Inherit Metab Dis 2011;34:165-71.	9 continuously treated adults with PKU	Randomised, double-blind placebo-controlled; Two 4-week supplementation periods; 1: mimicking normal dietary intake, 2: placebo in randomly allocated order via a randomisation coding list in a double-blind cross-over design. A set of neuropsychological tests was administered at the end of each study period. Patients and a friend or relative, completed weekly Profile of Mood States questionnaires, evaluating the patients' mood.	Mean plasma Phe levels were significantly higher during Phe supplementation compared with placebo (p = 0.008). Neuropsychological tests demonstrated an impairment in sustained attention during Phe supplementation
Nutrition Education					
Bernstein, LE	2014	Bernstein LE, Helm JR, Rocha JC, Almeida MF, Feillet F, Link RM, Gizewska M. Nutrition education tools used in phenylketonuria: clinician, parent and patient perspectives from three international surveys. J Hum Nutr Diet 2014;27 Suppl 2:4-11.	A total of 888 responses were collected from three surveys. Participants from 17 countries, in Europe; North America (USA and Canada); Mexico; Argentina; Turkey; Australia; and Africa (Tunisia).	The first two surveys were distributed through the Metabolic Dietitians ListServe, and the third survey was distributed by international clinics and the National PKU Alliance website	A consistent decline in 'parents as role models' as an educational tool was observed starting at age 10 years. Patients responded they feel their families are the most effective form of education, whereas handouts were selected as the least effective educational tool by patients. Parents responded they feel the most effective educational tool is one-on-one counselling. Patients and parents show a desirable trend in wanting to attend group clinic.

Ten Hoedt, AE	2011	Ten Hoedt AE, Hollak CE, Boelen CC, van der Herberg-van de Wetering,N.A., Ter Horst NM, Jonkers CF, Wijburg FA, Bosch AM. "MY PKU": increasing self-management in patients with phenylketonuria. A randomized controlled trial. Orphanet J Rare Dis 2011;6:48,1172-6-48.	Thirty-eight patients aged ≥ 1 year	10 month randomized controlled trial. Patients were randomized into a study group (1) or a control group (2). Group 2 continued the usual procedure: a phone call or e-mail by a dietician in case of a deviant Phe value.	There were no significant differences in mean Phe value, percentage of values above recommended range or in frequency of blood spot sampling for Phe determination between the pre-study period and the study period in each group, nor between the 2 groups during the periods. All patients and/or parents expressed a high level of satisfaction with the new way of disease management.
Simplified Diet					
Sweeney, AL	2011	Sweeney AL, Roberts RM, Fletcher JM. Dietary protein counting as an alternative way of maintaining metabolic control in phenylketonuria. JIMD Rep 2012;3:131-9.	18 participants with PKU	Phase 1: participants were randomised to continue counting Phe unit exchanges or changed to counting gm protein exchanges, using a new diet chart developed in-house. Foods containing < 20mg Phe per serving were now considered "free." Phase 2: participants educated to use an updated version of the in-house diet chart - in this version foods containing < 50mg Phe per serving were considered "free."	Phe levels over 6months were comparable to pre-study levels. Four participants had a significant improvement in blood Phe levels, nine showed no significant change and one participant's levels were significantly higher.

MacDonald, A	2003	MacDonald A, Rylance G, Davies P, Asplin D, Hall SK, Booth IW. Free use of fruits and vegetables in phenylketonuria. J. Inherit. Metab. Dis. 2003;26:327–338.	15 subjects with PKU, ages 1 to 24 years	Three-part prospective 15-week study with week 1: free use of fruits and vegetables 0-50 mg Phe/100 gm serving; week 2: free use of fruits and vegetables 51-75 mg Phe/100 gm serving; week 3: free use of fruits and vegetables 76-100 mg Phe/100 gm serving.	Blood Phe concentrations were not adversely affected by free use of fruits and vegetables 51-100 mg Phe/100 gm serving
Rohde, C	2012	Rohde C, Mutze U, Weigel JF, Ceglarek U, Thiery J, Kiess W, Beblo S. Unrestricted consumption of fruits and vegetables in phenylketonuria: no major impact on metabolic control. Eur J Clin Nutr 2012;66:633-8.	14 children, ages 2 to 10 years, with PKU	Cross-over design with a 2 week period of traditional counting method and 2 week period of free fruit and vegetable consumption	Mean Phe intake significantly increased during the 2 weeks of free fruits and vegetables (58 mg/day), but mean blood Phe remained stable. Fruit and vegetable intake did not increase.
Rohde, C	2014	Rohde C, Mutze U, Schulz S, Thiele AG, Ceglarek U, Thiery J, Mueller AS, Kiess W, Beblo S. Unrestricted fruits and vegetables in the PKU diet: a 1-year follow-up. Eur J Clin Nutr 2014;68:401-3.	19 children, ages 2 to 10 years, with PKU	Free use of fruits and vegetables for all patients and monitoring of diet and blood Phe concentrations at 6 months and 12 months	Mean Phe intake significantly increased at 6- (68 mg/day) and 12 months (70 mg/day), but mean blood Phe concentrations remained stable. Frequency of Phe concentrations above the recommended range remained stable.

Zimmerman, M	2012	Zimmerman M, Jacobs P, Fingerhut R, Torresani T, Thony B, Blau N, Baumgartner MR, Rohrbach M. Positive effect of a simplified diet on blood phenylalanine control in different phenylketonuria variants, characterized by newborn BH4 loading test and PAH analysis. Mol Genet Metab 2012;106:264-268.	80 patients with classical PKU, moderate PKU, mild PKU, and mild hyperphenylalanemia	Cross-over design with use of free fruits and vegetables <100 mg Phe/100 gm serving	Median Phe levels of the simplified diet group did not differ significantly to the median Phe levels of the classical diet group.