IMPROVING TREATMENT ADHERENCE AND OUTCOMES IN INDIVIDUALS WITH PHENYLKETONURIA

by

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ABSTRACT

The objective of this body of research was to (1) survey current self-management skills and treatment knowledge in patients with phenylketonuria (PKU) and (2) evaluate self-efficacy, patient activation, dietary adherence, and blood phenylalanine (Phe) levels in individuals with PKU before and after a 6-month motivational interviewing (MI) intervention.

Patients with PKU aged 7-30 years (n=43) completed one of three age-specific self-management questionnaires during standard metabolic clinic appointments and were invited to participate. Separately, patients with PKU aged 7-35 years (n=31) participated in a 6-month intervention including phone-based MI, goal setting, and a monthly summary. Participants completed stage of change (SOC), self-efficacy, patient activation, and food frequency questionnaires online and obtained monthly blood Phe samples. Demographic data were collected from the electronic medical record. We considered $p<0.01$ as significant when analyzing aim 1 and $p<0.05$ as significant when analyzing aim 2.

Participation in self-management behaviors and treatment knowledge did not increase with age for most measures ($p>0.01$ for all) with only approximately half of adults meeting clinical recommendations. Higher self-management skills and treatment knowledge were not associated with lower blood Phe levels ($R^2=0.249$, $p=0.025$), which may reflect the small sample size.

Most participants were in the action/maintenance SOC for PKU treatment behaviors during the 6-month MI intervention. Self-efficacy significantly increased from baseline (7.4±1.9) to month 6 (8.6±1.3) among adolescent and adult participants ($p=0.002$). There was no increase in patient activation ($p=0.10$) or dietary adherence, though most (n=28/31) reported adherence to medical formula at baseline. Pre-intervention blood Phe slope for all participants ($\beta=0.71$) was not significantly different from the intervention slope ($\beta=0.26$, $p=0.13$). Higher baseline SOC ($\beta=-61.6$, $p=0.005$) and increasing self-efficacy ($\beta=-64.5$, $p<0.001$) were associated with a decreased blood Phe slope.

Self-management skills were lower than clinically recommended and did not consistently increase with age. We demonstrated a significant increase in self-efficacy with MI and, in turn, higher self-efficacy was associated with a reduction in blood Phe levels. Our results suggest strategies to support self-management and increase motivation for behavior change are necessary. Phone-based MI is feasible with a PKU population has potential to increase confidence to engage in self-management behaviors.

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LIST OF ABBREVIATIONS

BH4	tetrahydrobiopterin
BMI	body mass index
CV	coefficient of variation
EF	executive functioning
IEP	individualized education program
IQR	interquartile range
MI	motivational interviewing
PAH	phenylalanine hydroxylase
PAM	patient activation measure
Phe	phenylalanine
PKU	phenylketonuria
SD	standard deviation
SOC	stage of change

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CHAPTER 1

INTRODUCTION

Chronic disease is pervasive. It is the leading cause of death worldwide, predicted to affect 157 million Americans by 2020, and contributes a substantial burden to the current health care system [1, 2]. Public health and health care systems were originally designed to address acute or infectious diseases and are not equipped to address the differing needs of chronic disease management [3-5]. Chronic disease management is, in many ways, more complex than acute management, in which the patient's role is generally passive. Chronic disease management generally requires both medical and lifestyle interventions, and it relies heavily on the patient's ability and willingness to follow medical recommendations away from the hospital or outpatient clinic [4].

Treatment nonadherence is a common and costly phenomenon among individuals with chronic conditions [6-9]. Adherence generally refers to how well treatment recommendations are followed and implies an agreement with recommendations between clinician and patient [10]. However, placing the burden of following treatment recommendations solely on patients also places blame of poor adherence on the patient for lack of self-management skills. Poor treatment adherence does not necessarily reflect a careless or unmotivated patient, but implies current interventions and health care systems are inadequate to facilitate improved adherence [4, 11]. The Chronic Care Model (CCM) was developed to recommend health system changes to improve quality

of care for chronic illness [4].

A key component of the CCM is supporting self-management, which refers to changes in the health system to encourage patient self-management behaviors [4]. This has been supported in several reports, especially in the setting of appropriate transition from childhood to adulthood [11-13]. Rather than focusing on standard education practices that may increase knowledge but not necessarily behavior, the CCM suggests focusing on perceived confidence and skills to manage the disease [4]. Strategies to support self-management include goal setting and problem solving with routine care and use of self-management programs for disease-specific education, which have been shown to improve self-management [14-17]. Ultimately, this model aims to engage patients in their care, set attainable and specific goals, identify potential barriers, and help patients to develop solutions to overcome those barriers.

In the context of chronic illness, the term self-management refers to one's ability to manage the physical and psychological symptoms and implement necessary treatments and lifestyle changes to maintain an acceptable quality of life [18]. Therefore, comprehensive self-management encompasses more than medical and behavioral management, also including role and emotional management [19, 20]. In addition to organizing daily treatments, individuals and families may need to adapt life roles and develop coping strategies to accommodate the chronic illness [19].

Phenylketonuria (PKU), one of the conditions detected on newborn screening, is an often overlooked condition in discussions about chronic disease management. Individuals with PKU are an exemplar of the difficulties associated with improving self-management and treatment adherence in individuals with a lifelong, genetic disease.

Additionally, this condition encompasses the challenges surrounding transition from childhood to adulthood for youth with special health care needs and designing strategies to work with cognitive and/or executive deficits [12].

PKU is a rare disorder with a prevalence of approximately 1 in every 10,000 people [21]. PKU results from phenylalanine hydroxylase deficiency causing impaired phenylalanine (Phe) metabolism. Untreated PKU results in profound intellectual disability [21]. However, the vast majority of individuals with PKU living in the United States are diagnosed on newborn screening and dietary treatment is initiated at birth. A protein-restricted diet and supplemental medical formula are prescribed to maintain blood Phe levels within 120-360 μmol/L throughout life for optimal outcomes [22, 23]. However, many patients exceed the recommended blood Phe range and experience subtle intellectual and/or executive deficits and psychiatric symptoms compared to healthy controls [24-28].

The treatment for PKU is complex and time consuming. The diet requires knowledge of the protein content of foods and the ability to track protein intake and plan meals to meet a specific protein goal. One study reported two major sources of stress for families managing PKU were planning and preparing low protein meals and the social ramifications of the diet [29]. In addition to a highly restrictive diet (e.g., an adult may only tolerate 5-10 grams protein per day), patients are prescribed a medical formula free of phenylalanine, which clinicians recommend to consume in multiple servings daily [30]. This formula is costly, difficult to obtain through insurance, and, for some, unpalatable [31]. Additionally, patients are faced with frequently obtaining blood samples for assessment of blood Phe levels, keeping food records, and attending

metabolic clinic appointments.

The current model for the treatment of PKU, at least in some centers, may not adequately support self-management [10, 32, 33]. This is corroborated by poor treatment adherence reported in this population [34, 35] and a perceived paucity of knowledge among patients with PKU [36]. From a clinical perspective, treatment adherence and metabolic control appear to be better in those who slowly acquired self-management responsibilities, starting at a young age, with continued support from caregivers throughout adolescence compared to those experiencing a rapid transition of self-management responsibilities, typically occurring during adolescence. Strategies to encourage self-management starting at a young age are recommended to facilitate timely and appropriate transition of responsibility to the child [37].

The patient-provider relationship is also a critical component of care. Positively perceived relationships with medical providers have been associated with self-care behaviors in patients with diabetes [38]. The current clinical system often supports direct questioning and giving advice [39]. In other populations, these techniques have been shown to increase resistance and may negatively impact patient-provider communication [40-42]. Additionally, inborn errors of metabolism, such as PKU, are rare disorders with few clinics specializing in their care [43]. Therefore, patients may not have access to an alternative clinic or provider, making it even more critical to maintain rapport. Negative relationships with providers may contribute to loss to follow up. This is a common phenomenon among adults with PKU with an estimated 77% of adults with PKU not receiving treatment from a metabolic center in 2012 [44], which increases the likelihood of inadequate or absent treatment [45].

Successful self-management involves more than the individual; the ability to engage in necessary behaviors must be placed in context of social and environmental settings [11]. For individuals with PKU, this includes individual factors, social and economic factors, treatment options, and health care system factors [44]. These might include cognitive and/or executive functioning skills, family support, access to medically necessary treatments, such as medical formula and low protein foods, and access to a metabolic center [31, 44]. While a system change to support self-management in a larger context is needed, we must also address individual motivation and ability, which has been relatively unexplored in this population.

Strategies to support self-management are needed for patients of all ages with PKU. It may be particularly beneficial during preadolescence and adolescence, as these developmental periods involve dramatic increases in independence and ability to participate in self-care [37]. While it may be assumed that adult patients should already have the required skillset to manage the dietary treatment, disease related stressors change with age, which may require development or review of skills/knowledge to adequately cope with new challenges [36]. However, we must be cautious, as the targeted outcomes of self-management are often derived from the medical team, and may not be congruent with the values of the individual or family [11].

Motivational interviewing (MI) with goal setting may be well suited to facilitate improved self-management [42, 46]. MI is a patient-centered, directive counseling style aimed to resolve ambivalence about change and elicit one's personal motivation for change. While self-management does not merely involve the "self," the patient is a crucial component of chronic disease management. The exploratory nature of MI allows

providers to survey personal goals and values, which may refocus the goal of self-management to reflect the patient's desired outcomes [42]. Additionally, coupling goal setting and action planning with MI provides the opportunity to assess the context of one's ability to engage in targeted self-management behaviors. Providers can assist with problem solving, which is a skill that may be impaired in patients with PKU [47, 48]. Additionally, MI in conjunction with goal setting/action planning may be feasible to incorporate into an outpatient metabolic clinic setting.

Poor treatment adherence is prevalent among individuals with chronic illness, including those with PKU, which results in intellectual and behavioral sequelae. Chronic disease self-management is complex and involves environmental and social factors in addition to the individual. Strategies to support development of self-management skills are needed in PKU care and have been largely unexplored. MI with goal setting offers a means to engage the patient, understand their goals and values, and barriers to change. While this approach does not directly address environmental factors, it allows providers gain an understanding of individual barriers to treatment.

Evaluation of current self-management skills and methods to enhance self-management and treatment adherence would be beneficial to improve long-term outcomes in a PKU population. Additionally, if proved effective, the premise of the proposed intervention could be applied to other chronic diseases and could be transferrable to other metabolic clinics working with a variety of conditions diagnosed through newborn screening programs. This dissertation addressed the following specific aims:

1. Describe self-reported treatment knowledge and participation in age-appropriate self-management skills in patients with PKU.
2. Evaluate changes in patients' reported stage of change, self-efficacy, and patient activation to improve self-management behaviors before and after a motivational interviewing (MI) intervention.
3. Evaluate changes in blood phenylalanine levels and adherence to dietary protein and medical food prescriptions before and after a motivational interviewing intervention.

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CHAPTER 2

SELF-MANAGEMENT SKILLS AND TREATMENT KNOWLEDGE IN PATIENTS WITH PHENYLKETONURIA[1]

2.1 Abstract

2.1.1 Objective

To describe patient-reported self-management behaviors and treatment knowledge in patients with phenylketonuria and explore how these correlate with blood phenylalanine (Phe).

2.1.2 Methods

Participants (n=43) completed an age-specific questionnaire (7-12, 13-17, and 18-30 years) including questions used to construct three scales as overall measures of self-management. Blood Phe levels collected 12 months prior to enrollment were included. Data analysis included descriptive statistics, Spearman correlations, Mann-Whitney U

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test and multivariate linear regression. Significance defined as $p<0.01$.

2.1.3 Results

Participation in self-management behaviors and treatment knowledge did not increase with age for most behaviors ($p>0.01$). Approximately half of adults met clinical recommendations for self-management behaviors. Treatment knowledge was associated with increased participation in corresponding behaviors ($p<0.005$ for all). Higher self-management skills and treatment knowledge were not associated with lower blood Phe levels after controlling for number of blood samples ($R2=0.249$, $p=0.025$), which may reflect our small sample size.

2.1.4 Conclusion

Promotion of self-management skills is important for patients with PKU and may help achieve lower blood Phe levels. Overall, participation in self-management behaviors was lower than clinically recommended. More research is needed to evaluate methods to improve self-management.

2.1.5 Practice Implications

We recommend using the surveys or a similar tool as a checklist in a clinical setting to facilitate discussion of self-management skills.

2.2 Introduction

Phenylketonuria (PKU) is an inborn error of metabolism characterized by a deficiency of the enzyme phenylalanine hydroxylase (PAH), which converts the amino acid phenylalanine (Phe) into tyrosine. PAH deficiency results in elevated blood and tissue concentrations of Phe and a deficiency of tyrosine [1]. Elevated blood Phe

exposure during infancy and early childhood leads to profound intellectual disability, severe behavioral disturbance, and seizures [2, 3]. Since 1964, newborn screening programs in the US identify PKU at birth; severe neurologic impairment is prevented through early initiation of a lifelong Phe-restricted diet and supplemental medical formula. Dietary treatment is designed to reduce blood Phe levels to a therapeutic range (120-360 μmol/L) [4, 5] in order to decrease cerebral Phe concentrations. It is widely accepted that tight control of blood Phe levels throughout life is strongly associated with improved cognitive outcomes [6, 7].

The treatment for PKU involves three primary components: 1) monitoring dietary Phe or protein intake (as a proxy for Phe) [8]; 2) supplementing with a Phe-free protein medical formula to prevent protein malnutrition and improve satiety [9, 10]; and 3) testing blood Phe regularly at home via finger stick. The recommended amounts of dietary Phe and medical formula are based on blood Phe levels, growth, and clinical status [11], while the recommended frequency of blood Phe testing varies from weekly to monthly according to age, adherence to treatment, and blood Phe levels.

An adjunct to a Phe-restricted diet is treatment with tetrahydrobiopterin (BH4), a cofactor to the PAH enzyme, which facilitates PAH folding and stabilizes enzyme activity [12]. Many individuals with PKU taking BH4 have reduced blood Phe levels and increased tolerance to dietary Phe [13]; however, only 40-60% of patients are responsive to BH4 therapy [12, 14].

Successful implementation of a Phe-restricted diet requires a variety of skills and performing multiple tasks throughout the day. The individual must be able to calculate and track milligrams of Phe or grams of protein consumed; manage dietary Phe intake to

stay within a prescribed daily Phe/protein goal; keep detailed food records; prepare and drink medical formula daily; collect regular blood samples via finger sticks; and set and keep regular appointments with a metabolic clinic [15, 16]. Therefore, the treatment for PKU requires ongoing self-management from the patient and/or family.

Self-management describes behaviors aimed to prevent or reduce the impact of illness on one's health [17, 18]. Supporting patient development of self-management behaviors is becoming increasingly recognized as a critical component of primary and specialty care clinics [17, 19, 20]. Increased self-management behaviors have been associated with reduced morbidity in a variety of chronic diseases and with decreased health care utilization in children and adults [21, 22], including for PKU, with improved metabolic control found in patients who assumed personal responsibility for management of their condition [23].

Cognitive and executive functioning (EF) skills impact the ability to engage in self-management behaviors. EF skills facilitate nonstimulus driven control of behavior and emotion for self-regulatory actions [24]. These skills continue to develop well into the second decade of life [25] and include impulse control, mental flexibility, working memory, planning, attention, and self-monitoring [26]. EF abilities are positively associated with self-management skills in other chronic diseases managed with dietary treatment, such as diabetes [24, 27, 28].

While early and continuous treatment prevents severe intellectual disability in PKU, subtle deficits in intelligence and executive skills, and increased emotional and behavioral concerns are frequently reported in individuals with PKU compared to healthy controls [26, 29-33]. These impairments are related to both mean blood Phe

levels and variability in blood Phe levels; greater mean and variation in Phe are associated with increased EF difficulties [6, 34]. Deficits in EF may also impair the ability of an individual with PKU to effectively manage a Phe-restricted diet, including restricting intake of high Phe foods, following a recipe or remembering to drink medical formula.

Preadolescent evaluation and promotion of self-management skills are particularly important in patients with PKU, considering the multiple behaviors needed for successful treatment implementation and the risk of cognitive and EF deficits associated with inadequate adherence to Phe restriction. The objectives of this cross-sectional study were to evaluate patient-reported self-management behaviors and knowledge in a cohort of patients with PKU and to explore how these correlate with blood Phe levels.

2.3 Methods

2.3.1 Participants

Study participants were English-speaking individuals aged 7-30 years diagnosed with PKU on newborn screening and treated since birth. All participants were receiving treatment at the Utah Metabolic Clinic and attended an outpatient clinic visit during the study enrollment period (July 2013-July 2014). Exclusion criteria included intellectual disability (IQ <70), pregnancy (current or within 12 months prior to enrollment), concurrent participation in clinical trial(s), and hyperphenylalaninemia not requiring dietary treatment. Pregnancy was added as an exclusion criteria midway through the study, and pregnant participants who had previously consented were excluded from data analysis. Patients without intellectual disability but with some degree of learning

impairment were invited to participate. Eligibility for an individualized education program (IEP), a written statement for each child with a disability specifying modified academic and functional goals [35], was used as a marker for learning impairment and/or EF deficits. The University of Utah Institutional Review Board approved this study and written consent – and child assent, if appropriate – was obtained for all participants.

2.3.2 Instrument Development

We developed three age-specific questionnaires (7-12 years, 13-17 years, and 18-30 years) to evaluate patients' current self-management behaviors and treatment knowledge. The basis of the survey content was the PKU Self-Management Timeline [16] with additional self-management goals defined by our clinic (Table 2.1). The recommended skills for each age group were based on Piaget's model of cognitive development [16].

We formulated the questionnaires' content standards using expert review from clinicians experienced in treating patients with PKU [36, 37]. We conducted a pilot study and cognitive interviews to assess cognitive standards, referring to the respondents' ability to understand and respond to the questions [36]. Five patients with PKU piloted the questionnaires to identify questions requiring clarification and responses not fitting question intent. We conducted cognitive interviews with three staff members familiar with the PKU diet. They were asked to paraphrase each question in their own words to demonstrate their understanding of the question. Question wording was revised after assessment of content and cognitive standards. In July 2013, the questionnaire was implemented as a clinical tool for all patients with PKU in our clinic.

Table 2.1. Clinically Recommended Self-Management Skills by Age Group

Age group	Self-management skills
7–12 years	Prepare and consume medical formula with decreasing supervision Identify high and low Phe/protein foods Weigh/measure foods regularly List food items on food records Know target blood Phe values Collect blood Phe samples via finger sticks with supervision
13–17 years	Prepare and consume medical formula with little supervision Independently manage daily dietary Phe/protein intake Independently keep food records Know target and recent blood Phe values Independently collect blood Phe samples via finger sticks
18–30 years	Independently manage all aspects of treatment: Prepare and consume medical formula Manage daily dietary Phe/protein intake Schedule and attend clinic appointments Refill medical formula and/or medication prescriptions Collect regular blood Phe samples via finger sticks

Note. Phe, phenylalanine. Adapted from the PKU Self-Management Timeline [16].

2.3.3 Blood Phenylalanine Levels

Presurvey Phe levels were reported as the mean for all blood Phe levels obtained during the 12 months prior to enrollment. Variation in blood Phe was measured as the coefficient of variation (CV), which is the standard deviation normalized to the mean (SD/mean*100). Blood Phe levels were obtained and measured using two methods as standard of care at ARUP Laboratories in Salt Lake City, UT: 1) dried blood spots on filter paper obtained between clinic appointments were analyzed using tandem mass spectrometry (MS/MS) without chromatographic separation and 2) quantitative plasma amino acids collected during clinic appointments were analyzed using quantitative liquid chromatography and MS/MS (aruplab.com).

2.3.4 Data Collection from Patients

Patients with PKU treated at our center are scheduled for regular clinic appointments every 6-12 months. Eligible participants were identified during weekly pre-clinic rounds. All patients were provided with the age-appropriate questionnaire upon arrival in the outpatient metabolic clinic once per year as a standard of care. Consent was obtained after questionnaire completion; only data from patients who consented were used in the analysis. All patients, including individuals less than 18 years of age, were instructed to complete the questionnaire with limited or no assistance. Caregivers were advised to clarify questions, if needed, but not to provide the answer. Four patients required assistance from a dietitian to answer the questionnaire. After completion, questionnaire responses were discussed with the patient and family in clinic as standard of care.

2.3.5 Data Analysis

Questionnaire responses were summarized using descriptive statistics: continuous variables were reported as mean ± standard deviation, and categorical variables were reported as frequencies. Differences between age groups were assessed using one-way ANOVA for continuous variables and Fisher's exact test for categorical variables.

Three scales were created a priori to evaluate the overall degree of participation in self-management behaviors and treatment knowledge (Appendix A). The behavior scale included two questions, each coded as 1 if the respondent indicated participation in age-appropriate behaviors for preparing medical food and collecting blood samples via finger stick (Table 2.1), 0.25-0.75 if done with some level of assistance (each 0.25 increase represented a questionnaire response option with higher scores reflecting greater independence), or 0 if not done by the respondent. The treatment knowledge scale included three questions coded as 1 or 0, respectively, for the presence of, or absence of, correct PKU self-care knowledge (knowing one's formula prescription, dietary Phe/protein prescription and target blood Phe level range). Responses within 25% of medical formula and dietary Phe/protein prescriptions as recorded in the medical record were coded as 0.5 for the knowledge scale. The individual scales were summed to create the behavior and treatment knowledge scale for an overall measure of self-management. Higher scores correspond to higher levels of self-management behaviors and/or treatment knowledge. There were some additional questions about dietary protein monitoring that we did not include in the scales because these questions differed across the age groups.

We examined the correlation between the self-management scales and presurvey mean Phe and Phe variation in participants aged 10-30 years, using Spearman rank-order

correlation coefficients. We also examined correlation for individual questions about self-care behaviors. The Mann-Whitney U test was used to evaluate differences in pre-survey Phe levels by individual questions about treatment knowledge (coded as yes/no). We excluded patients under 10 years for these analyses because parents have greater control of their treatment. We used multivariate linear regression to evaluate the association between scale variables and presurvey Phe after controlling for potential confounders. Statistical analyses were performed using Stata 13.0 (StataCorp, College Station, TX). Significance was defined as a two-sided p value with alpha of 0.01 to account for multiple comparisons and reduce the risk of type I error.

2.4 Results

During the study period, 61 patients attended clinic and 58 individuals completed the self-management questionnaire; 52 of whom were invited to participate in the study and provided consent. Nine participants were excluded after signing consent, leaving 43 patients for analysis (Fig. 2.1). There were no differences in age, sex, or medical food intake in those excluded after obtaining consent (data not shown).

All participants included in statistical analyses had been prescribed a protein-restricted diet with supplemental medical formula. The majority (82%) of participants receiving adjunct treatment with BH4 were 7-12 years of age despite all patients being offered a trial of BH4. Presurvey Phe levels increased with increasing participant age, as frequently reported in patients with PKU (Fig. 2.2, Table 2.2). One participant did not have a record of blood samples collected during the 12 months prior to enrollment.

Approximately 26% of participants had some degree of learning impairment indicated by eligibility for an IEP (Table 2.2), including 5 participants who were eligible

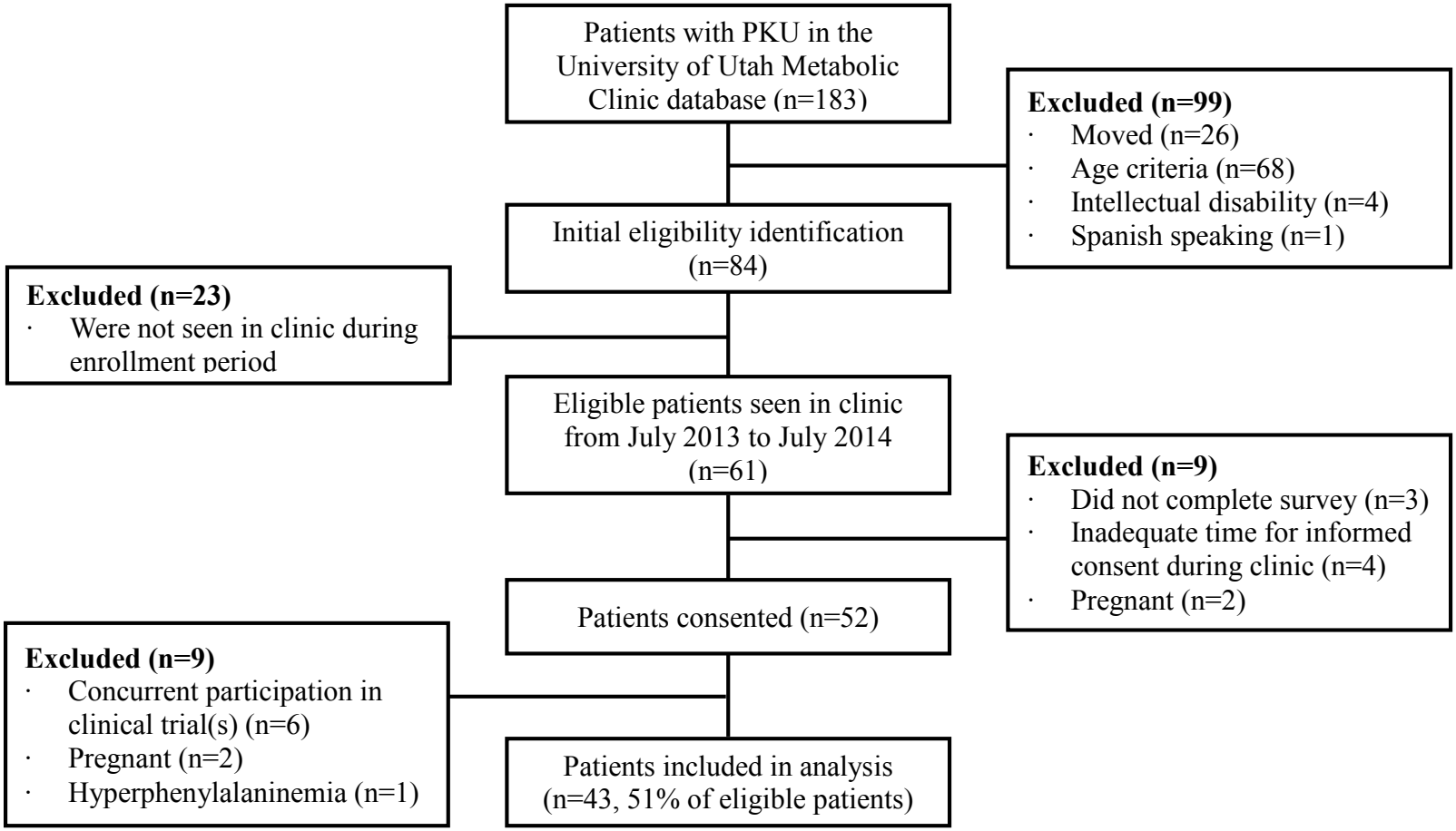

Figure 2.1. Study Enrollment Process

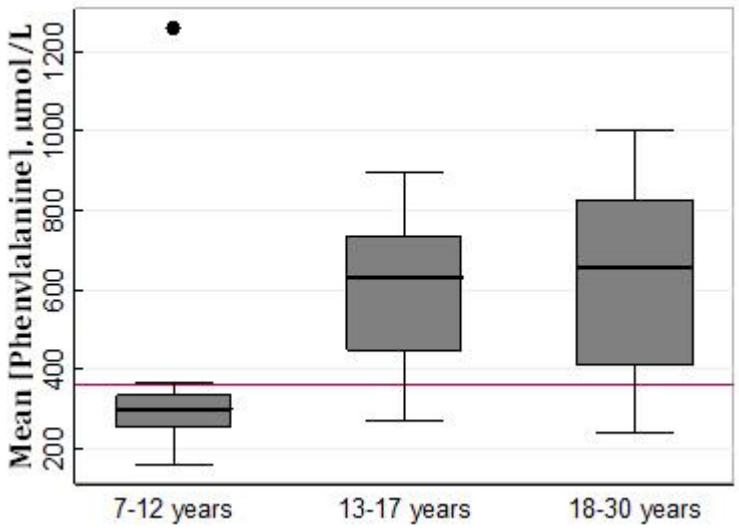

Figure 2.2. Boxplot of Presurvey Mean Phenylalanine Levels by Age Group (N=42). Boxes indicate 25th and 75th percentile, lines within each box represent the median, and the reference line is the upper limit of the therapeutic range for phenylalanine (360 µmol/L). Data source: [5].

Table 2.2. Demographic and Treatment Data for Participants with Phenylketonuria by Age Group Presented as Mean±SD and Frequency

Variable	Total (n=43)	7-12 years (n=21)	13-17 years (n=11)	18-30 years (n=11)	p-value
Age (years)	14.6±5.9	9.6±2	16.3±1.6	22.4±3.6	
Presurvey mean Phe (μmol/L)	464±259	327±222	595±193	612±254	0.001
Presurvey Phe variation (%)[a]	41.2±21.3	45.3±20.8	30±15.7	46.3±25.9	0.36
Number of blood samples over prior 12 months	7.0±4.5	8.8±4.6	5.1±3.4	5.2±4	0.03
Number of food records over prior 12 months	3±3.5	4.2±4.2	1.6±2.3	1.8±1.8	0.07
Overweight/obese[b]	17	4	5	8	0.01
Female	23	12	4	7	0.52
Regular intake of prescribed medical food	39	20	10	9	0.36
BH4 treatment	17	14	3	0	<0.001
IEP eligible[c]	11	5	4	2	0.73

Note. BH4, tetrahydrobiopterin; BMI, body mass index; IEP, individual education program; Phe, phenylalanine; SD, standard deviation

[a]Presurvey Phe variation measured as coefficient of variation (SD/mean*100)

[b]For participants <18 years of age, overweight defined as BMI >85th and <95th percentile on age- and gender-specific growth charts; obesity defined as BMI >95th percentile. Data source: [37, 38]. For adults, overweight defined as BMI of 25-29.9; obesity defined as BMI ≥30.

[c]IEP refers to participants currently or previously eligible for an IEP in school as an indicator of learning impairment.

One-way ANOVA used to determine statistical difference among age groups for continuous variables; Fisher's exact test used for categorical variables. Significant p value with alpha of <0.01.

for an IEP but did not have one in place. Age, presurvey Phe levels, and self-management scales did not differ significantly between those with an IEP and those recommended an IEP (data not shown); therefore, they were combined into one group.

2.4.1 Self-Management Skills

The primary improvement in self-management with increasing age was independent formula preparation (Table 2.3), and most adults reported the correct formula prescription and target blood Phe range. However, few (n=3) adults reported following the clinical guidelines for either medical formula preparation (Table 2.3) or frequency of blood samples (recommended monthly). Participation in related behaviors was higher, as most adolescents (n=7) consumed their formula ≥3 times daily as recommended [38] and most adults (n=8) independently refilled medical formula(s) and/or medication(s).

The majority (n=16) of adolescents and adults reported using one or more reminder strategies to collect blood samples. The frequency of blood samples over the last year was higher for participants who reported a reminder strategy compared to those without reminders (6.3±0.9 and 2.3±0.7 samples, respectively, p=0.010).

Dietary Phe/protein monitoring and knowledge did not increase with age (Table 2.3). Nearly all (n=20) participants 7-12 years of age correctly identified the Phe content of a list of foods as either high or low. Fourteen participants knew how to operate a gram scale and 7 reported regularly weighing/measuring their own foods. Most adolescents did not know their dietary Phe goal, but over half (n=7) reported the ability to independently plan meals to meet their dietary Phe/protein prescription if eating away from home. Approximately half of adolescents and adults monitored Phe/protein intake, which was

Table 2.3. Number of Respondents Reporting Self-Management Behaviors and Treatment Knowledge in a Cohort of Patients with Phenylketonuria

	7-9 years (n=11)	10-12 years (n=10)	13-17 years (n=11)	18-30 years (n=11)	p-value
Medical Formula					
Correctly reported medical formula prescription[a]	4	6	9	9	0.21
Formula preparation					0.01
7 days per week independently	—	4	5	6	
4-6 days per week independently	1	1	2	2	
≤3 days per week independently	7	4	1	1	
Someone else is responsible	3	—	2	—	
Do not drink formula	—	1	1	2	
Dietary Phe/Protein Intake					
Correctly reported Phe/protein prescription[a]	6	6	2	6	0.38
Responsible for food records					0.006
Always keep own food records	—	2	—	NA	
Keep own food records sometimes or assist parents	5	7	4	NA	
Someone else is responsible	4	—	—	NA	
Do not keep food records	2	1	7	NA	
Tracks dietary Phe/protein intake[b]	NA	NA	6	6	1.00
Blood Phe Levels					
Correctly reported target blood Phe range	3	4	7	9	0.06
Collect blood Phe via finger stick					0.09
Always collect sample independently	1	3	5	7	
Sometimes collect sample independently	5	5	4	—	
Someone else is responsible	5	2	1	3	
Do not collect blood samples	—	—	1	1	

Note. NA, item not included in survey; Phe, phenylalanine

[a] Participants able to report current prescription as listed in the medical record

[b] Methods to track dietary Phe/protein intake include one or more of the following: keeping a written record or mental list of foods/protein consumed, limiting the variety of food consumed (protein content of common foods are often memorized), or tracking intake using an application.

predominantly by limiting the variety of food consumed and/or keeping a mental list of Phe/protein consumed.

Females 18-30 years of age (n=7) understood the influence of blood Phe levels on a developing fetus (maternal PKU) [39]. All participants correctly reported the target blood Phe range during pregnancy and most (n=5) reported blood Phe levels should ideally be within the therapeutic range 2-3 months prior to conception.

2.4.2 Self-Management Behaviors, Treatment Knowledge, and Blood Phe Levels

Correlations between individual questions and scales and presurvey Phe levels were assessed with Spearman rank-order correlation coefficients, considering survey data were ordinal. There were no significant associations between self-management measures and presurvey mean Phe or Phe variation (Table 2.4). The difference in pre-survey mean Phe approached significance only for questions assessing dietary Phe/protein knowledge and monitoring (Table 2.5).

Blood Phe levels and self-management were also compared by IEP eligibility. Presurvey mean Phe was not significantly different in participants with vs. without IEP eligibility (614±360 and 412±193 μmol/L, respectively, $p=0.145$). Nor was the combined self-management behavior and knowledge scale (1.8±1.7 and 3.4±1.2, respectively, $p=0.054$).

As expected, knowledge of correct medical formula prescription, dietary Phe/protein prescription, and target blood Phe range were associated with significantly higher participation in their corresponding behaviors ($p<0.005$ for all). However, this association was not consistently significant for other behaviors (i.e., no significant difference in independent formula preparation with knowledge of correct dietary

Table 2.4. Univariate Spearman Rank Order Correlations between Presurvey Blood Phenylalanine Levels and Self-Management Indicators in Participants Aged 10–30 Years

	Presurvey mean Phe	Presurvey Phe variation[a]	Number of blood samples	Number of food records	Prepares formula	Collects own finger stick
Presurvey mean Phe	1.00					
Presurvey Phe variation[a]	-0.443 (0.005)	1.00				
Number of blood samples	-0.298 (0.104)	-0.075 (0.708)	1.00			
Number of food records	-0.236 (0.201)	0.263 (0.177)	0.529 (0.002)	1.00		
Prepares formula	-0.173 (0.359)	-0.028 (0.886)	0.089 (0.628)	-0.261 (0.148)	1.00	
Collects own finger stick	-0.163 (0.381)	-0.341 (0.076)	0.503 (0.003)	-0.017 (0.925)	0.429 (0.014)	1.00

Note. Phe, phenylalanine

[a] Phe variation measured as coefficient of variation (standard deviation/mean*100).

For all correlations, the value of rho is shown followed by the significance (p) within parenthesis.

Table 2.5. Comparison of Unadjusted Presurvey Mean Phenylalanine (Mean±SD) by Treatment Knowledge and Use of Dietary Phenylalanine Monitoring in Participants Aged 10–30 Years

	Group	n	Presurvey mean Phe	p-value[a]
Knows correct medical formula prescription	Yes	24	503±229	0.603
	No	7	616±397	
Knows correct dietary Phe/protein prescription	Yes	14	398±203	0.018
	No	15	635±296	
Knows target blood Phe range	Yes	20	520±231	0.934
	No	11	544±345	
Uses method(s) to track dietary Phe/protein intake	Yes	12	527±193	0.055
	No	9	704±220	

Note. Phe, phenylalanine

[a]p-value calculated using Mann-Whitney U test.

Phe/protein goal).

Performing one self-management behavior was not consistently associated with participation in other self-management behaviors (Table 2.4). Participants who reported using one or more methods to track dietary Phe/protein intake were more likely to independently prepare medical formula (p=0.004) but not to collect blood samples (p=0.056).

Self-management behavior and knowledge scales were negatively correlated with presurvey mean Phe levels (Fig. 2.3), though not reaching statistical significance. A potential confounder of this association was the number of blood samples, considering it is associated with self-management behaviors and impacts a 12-month average; therefore, we controlled for it in a multivariate linear regression. Age was not included in the model despite being a predictor of blood Phe concentrations [34, 40-42], as it is mostly related to behavioral factors as opposed to biological mechanisms. After controlling for number of blood samples, the combined behavior and knowledge scale model accounted for 24.9% of the variance in presurvey mean Phe, though increased self-management behaviors and treatment knowledge was not significantly associated with lower blood Phe levels (Beta=-95; p=0.024).

2.5. Discussion and Conclusion

2.5.1 Discussion

Multiple studies have described poor treatment adherence in PKU and sequelae of elevated Phe concentrations [6-8, 40, 41, 43]. However, few have examined individual treatment knowledge and participation in self-management behaviors and how these relate to blood Phe levels [23, 44, 45]. Here, we present participant-reported self-

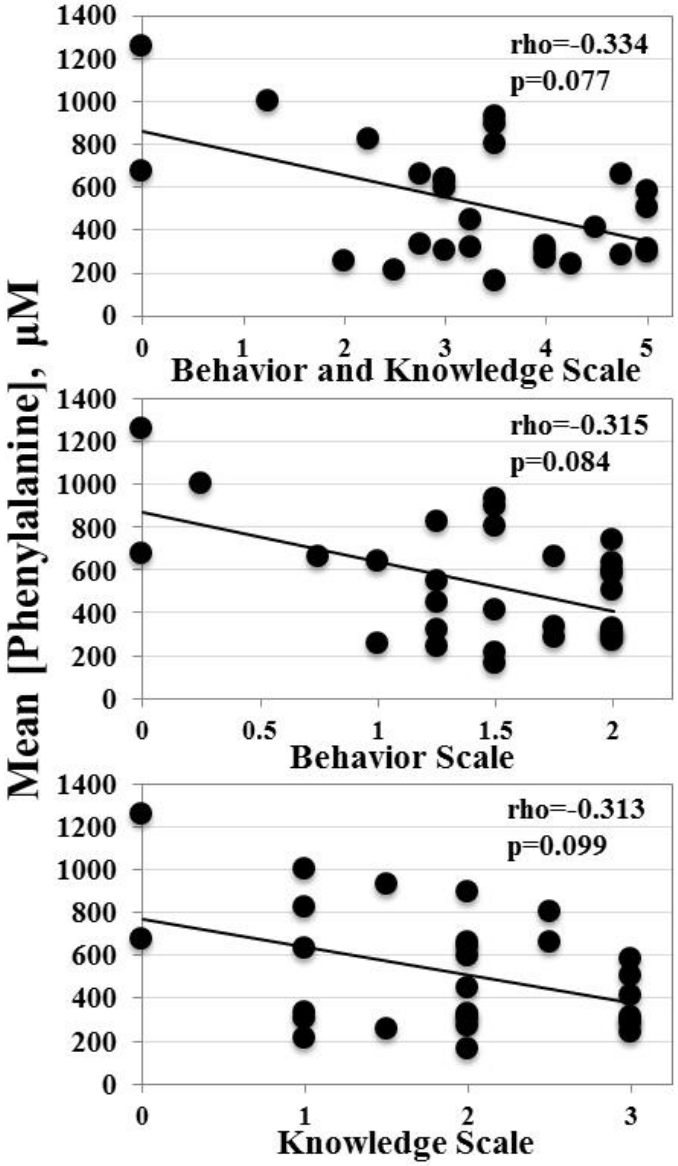

Figure 2.3. Spearman Rank-Order Correlations between Presurvey Mean Phenylalanine Concentrations and Scale Variables in Participants Aged 10-30 Years. Three scale variables were created to capture self-management behaviors (formula preparation and blood sample collection via finger stick) and treatment knowledge (knowledge of formula prescription, dietary phenylalanine/protein goal, and target blood Phe range), as well as the combined behavior and knowledge scale.

management skills in patients among three different age groups ranging from 7-30 years.

Overall participation in self-management behaviors in our sample was lower than clinically recommended (Tables 2.1 and 2.3). Others have reported similar difficulties in adherence to treatment recommendations. In individuals with diabetes, only 54% of children and adolescents and 51% adults adhered to treatment guidelines [46, 47]. Additionally, an association has been reported between patient nonadherence and the complexity of specific therapies [15]. The treatment regimen for PKU is complex and must be followed day after day. Of 19 caregivers of a child with PKU, the majority reported difficulty adhering to recommended medical formula goals (53%) and dietary Phe/protein goals (84%) [45].

More 7-12 year olds in our sample engaged in age-appropriate management of dietary Phe/protein intake compared to older participants, whereas adolescents and adults demonstrated more self-sufficiency in formula preparation and blood sample collection (Table 2.3). Younger participants likely had increased parental assistance to monitor Phe/protein intake and provider emphasis on food records. Only 55% (n=12) of adolescent and adult participants regularly monitored dietary Phe intake, probably reflecting an increased social life and meals away from home. This result is comparable to a previous study reporting 45% of adolescents and adults with PKU correctly reported their dietary Phe/protein goal [44].

Treatment knowledge was related to increased participation in corresponding self-management behaviors in our sample. In contrast, another study found that an increase in knowledge did not lead to a concomitant increase in treatment adherence among 32 patients with PKU over 6 months [44]. Our results may reflect motivated

participants who, in order to manage their condition, were more likely to have knowledge of treatment goals. While knowledge alone may not be sufficient to initiate behavior, an understanding of the multifaceted treatment for PKU is necessary for appropriate management.

Current evidence indicates adherence to one aspect of a treatment regimen does not imply adherence to all treatment components [8, 48]. We observed participation in selective self-management behaviors (Table 2.3) and an inconsistent association among self-management behaviors (Table 2.4). However, it is possible that certain behaviors are better indicators of overall self-management than others. In our sample, participants who reported using a method to monitor dietary Phe/protein intake, arguably the most time consuming treatment component, were significantly more likely to prepare formula independently ($p=0.004$). Therefore, those who monitor Phe/protein intake may be more likely to participate in other self-management behaviors.

We anticipated participation in self-management behaviors and increased treatment knowledge to help achieve lower Phe levels. After controlling for number of blood samples, higher self-management skills and treatment knowledge were not significantly associated with lower mean blood Phe levels. However, the combined scale in this study did not include a measure of dietary Phe/protein monitoring, inclusion of which may have strengthened the model based on our univariate analysis. This is consistent with a previous report that increased difficulty with adherence to formula and dietary Phe/protein goals was associated with higher blood Phe levels ($p=0.03$ and 0.05, respectively) [45]. There was no association between self-management and variation in blood Phe, but we did not collect a longitudinal self-management measure that would

indicate participants' consistency in following recommendations, thus informing our measure of blood Phe variation.

There are several obstacles for the development of self-management skills in individuals with PKU. First, no mechanism exists to provide concurrent feedback on the influence of dietary Phe/protein consumption on blood Phe levels [49] or the effect of high blood Phe levels on long-term cognitive functioning [6]. A home blood Phe monitor capable of producing immediate results is not currently available, and many metabolic clinics receive blood Phe results 3-10 days after collection. Additionally, individuals may not experience or recognize symptoms of elevated Phe levels, which may reduce incentive to maintain Phe levels within the recommended range.

External influences, such as clinic-guided dietary changes and parental control over food intake may reduce autonomy and motivation to engage in self-care [23, 50]. Parental knowledge of PKU dietary management also impacts blood Phe levels and likely self-management skills. Two studies described maternal knowledge of dietary treatment using the same questionnaire [51, 52]. Lower maternal knowledge of dietary Phe exchanges was correlated with higher blood Phe levels in children 1-15 years of age ($p=0.043$) [51] and lower overall dietary knowledge was associated with higher blood Phe levels in children 5-6 years of age ($p<0.001$) [52].

Lastly, cognitive and/or executive impairments can inhibit development of self-management skills [27, 28, 53]. Elevated blood Phe levels increase the risk for learning problems [54], which may then impair self-management abilities, though this was not demonstrated in our sample. One study reported lower measures of self-care in adults with PKU compared to healthy controls, which may be related to subtle cognitive

deficits [55]. This suggests individuals with PKU may require additional structure to achieve self-management goals, also demonstrated in this cohort with an increase in the number of blood samples with the use of a reminder strategy.

Willingness and ability to engage in self-management behaviors is complex and influenced by a myriad of cognitive, psychological, and social factors. Strategies such as motivational interviewing, increasing personal agency, and action planning have also been used to enhance self-management in other chronic diseases with some success [23, 56-58]. Future research is needed to evaluate these techniques to enhance engagement in self-management behaviors in patients with PKU.

2.5.2 Limitations

The results of this study should be interpreted in the context of its limitations. The self-management surveys were created by investigators and were not validated in a large sample, which is challenging considering the rarity of PKU. Rather, the surveys met content and cognitive standards and were piloted in a small patient sample. The study design introduced the potential for selection and self-report bias towards inclusion of patients who regularly attended clinic (the site of ascertainment); therefore, study participant characteristics may differ from those of patients lost to follow up or attending clinic infrequently. Additionally, all measures of self-management were based on participant-report. Participants may have over-reported participation in self-management behaviors based on social desirability, as suggested by previous studies reporting alterations in Phe/protein intake prior to blood draws in patients with PKU [8, 15]. During survey completion by participants, caregivers were requested to limit their assistance to question clarification; however, this process was not directly monitored,

creating the potential for caregivers influencing the participants' answers. The generalizability of results is also limited to the extent that educational practices and clinical management at our clinic may differ from other clinics. Lastly, given our small sample size, we can only suggest associations and larger studies will be important to identify which factors are important.

2.5.3 Conclusion

Early and ongoing promotion of self-management skills is an important component of care for patients with PKU. Increased patient self-care has been linked to improved health outcomes in PKU and other chronic diseases. However, this was not demonstrated in our study, which may simply reflect small a sample size. Dietary Phe/protein knowledge and monitoring appeared to be the strongest individual factors associated with blood Phe levels and participation in other self-management behaviors; however, these factors did not increase from childhood to adulthood. Treatment knowledge may not be sufficient to influence behavior despite being critical to successful self-management. Overall, participation in self-management behaviors in this study was lower than is clinically recommended. More research is needed to determine the best methods to encourage patient self-management and to further explore the benefits of increased self-management in this population.

2.5.4 Practice Implications

We encourage use of the surveys presented in this study or a similar tool to facilitate discussions about age-specific self-management skills with patients and their families. Our clinic used the surveys in this manner in addition to evaluating current self-management behaviors. Patients completed the survey in the clinical setting while

waiting for providers. Providers reviewed the patients' responses to survey questions during routine clinic appointments, which inherently created a structure in which to discuss the primary topics of self-management with each patient.

The self-management measures most often associated with other positive behaviors were dietary Phe/protein intake knowledge and monitoring. This behavior was practiced in only about half of adolescent and adult participants. Tracking Phe/protein intake is tedious and may pose difficulties for individuals with learning impairments. This indicates a need for additional education and resources to facilitate dietary Phe/protein intake monitoring, especially considering its primary contribution to blood Phe concentrations.

2.6 Acknowledgements

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CHAPTER 3

PHONE-BASED MOTIVATIONAL INTERVIEWING TO INCREASE SELF-EFFICACY AND PATIENT ACTIVATION IN INDIVIDUALS WITH PKU[2]

3.1 Abstract

3.1.1 Objective

To evaluate self-reported patient activation and self-efficacy in individuals with phenylketonuria (PKU) before and after a 6-month motivational interviewing (MI) intervention.

3.1.2 Methods

Participants (n=31) were 7-35 years of age and were divided into three age groups (preadolescents, adolescents, and adults). Participants completed online questionnaires assessing current stage of change (SOC), patient activation, and self-efficacy. The intervention included monthly phone-based MI, goal setting, and a monthly

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summary. Data were analyzed with descriptive statistics and mixed effects linear regression.

3.1.3 Results

Most participants were in the action/maintenance SOC for PKU treatment behaviors. Patient activation and self-efficacy were significantly different by age group ($p<0.01$ for both). Self-efficacy significantly increased from baseline to month 6 among adolescents and adults (7.4±1.9 and 8.6±1.3, respectively, $p=0.002$). There was no increase in patient activation ($p=0.10$).

3.1.4 Conclusion

The results of this study suggest phone-based MI is a potential method to increase self-efficacy for PKU self-management behaviors in adolescents and adults with PKU.

3.1.5 Practice Implications

MI is a potentially beneficial tool for metabolic clinics treating patients with PKU of a variety of ages. Additionally, pairing goal setting with MI may help reduce intellectual/executive barriers to implementing dietary treatments once the individual is motivated to take action.

3.2 Introduction

Poor treatment adherence has been described across a variety of behaviors and chronic diseases [1-4], including phenylketonuria (PKU) [5-7]. PKU is an inherited disorder of phenylalanine (Phe) metabolism causing intellectual/executive function deficits and behavioral disturbances [8-10]. PKU is typically diagnosed via newborn screening and lifelong treatment is initiated at birth. Treatment is multifaceted, and

successful management of PKU involves daily monitoring of dietary Phe or protein intake, consumption of a Phe-free medical formula, weekly to monthly monitoring of blood Phe levels via finger stick, and regular food records and appointments with a metabolic clinic [11]. The treatment is designed to maintain blood Phe levels within a therapeutic range (120-360 μmol/L) [12], which improves cognitive and behavioral outcomes, quality of life, and reduces health care expenditures [13-17].

Adherence to daily medical and/or dietary regimens is difficult to maintain, and becomes increasingly more difficult as treatment complexity increases [18, 19]. The ability to adhere to treatment recommendations in PKU may be further impaired by subtle cognitive deficits [10, 20]. In a study of 19 families with PKU, all children reported problems following the diet and 91% reported problems drinking medical formula primarily due to issues with the daily regimen, lack of treatment knowledge, palatability, and social aspects of the diet. Many of the strategies for dealing with problems related to protein intake (73% of strategies) and formula intake (43% of strategies) were maladaptive and were correlated with elevated blood Phe levels [21].

Individuals are also faced with different adherence challenges at different ages. A qualitative study of 37 individuals with PKU aged 8-31 years reported age-related themes regarding their perception of having PKU. The preadolescents were gaining more awareness of PKU and learning to deal with peer confrontation; adolescents were acquiring self-management responsibilities and dealing with shifting relationship with parents; and young adults were developing autonomy and self-reference and later focusing on how PKU affects jobs, relationships, and future children [22]. Perhaps partly due to fluctuating difficulties with treatment, adherence and metabolic control declines

with age [5, 6, 8, 9, 23] with approximately 20% of adolescents and adults with PKU maintaining blood Phe levels within the therapeutic range [8].

Strategies to facilitate behavior change are needed to address the challenges with treatment adherence in individuals with PKU and other chronic diseases. Two potential mediators of behavior change include patient activation and/or self-efficacy. Increased patient activation and self-efficacy have been repeatedly associated with improved self-management behaviors, health outcomes, and reduced health care costs among individuals with a variety of chronic diseases [19, 24-31], suggesting practitioners should foster these attributes in their patients.

Patient activation has become a topic of interest in recent years. An activated patient has the knowledge, skills, confidence, and motivation to manage his/her own health. High activation was associated with increased self-management in 479 adults with hypertension, diabetes, and arthritis [28]. Similar to stages of change (SOC), patient activation occurs on a continuum of four levels with individuals theoretically proceeding through each level to become effective self-managers. However, patient activation differs from SOC in that it is not specific to one behavior and it encompasses knowledge and skills, which are not directly addressed in SOC [32].

Self-efficacy is defined as the belief that one can successfully implement a behavior required to achieve the desired outcome [33]. Meta-analyses have reported positive associations between self-efficacy and participation in recommended self-care in adults with type 1 and 2 diabetes and adherence to antiretroviral therapy in individuals with HIV [19, 31]. In a cohort of 357 adolescent females, goals to make healthy food choices were not translated into action unless the individual had high self-efficacy

($p<0.01$) [30]. Increased parental self-efficacy regarding medical formula intake ($p=0.007$) and raising a child with PKU ($p=0.028$) was also associated with improved blood Phe levels in children with PKU [34].

Tailored interventions based on an individual's self-reported SOC or patient activation have been shown to be more effective in improving activation, self-efficacy, and health behavior change compared to more traditional approaches [26, 35-38]. Motivational interviewing (MI) is commonly used in conjunction with SOC to provide tailored counseling based on one's readiness to change. MI is a patient-centered, collaborative style of communication designed to elicit intrinsic motivation for change. MI explores ambivalence while supporting patient autonomy in order to reduce resistance and elicit change talk from the patient [39-43].

There are multiple studies and meta-analyses supporting the effectiveness of MI to improve self-efficacy, self-management behaviors, and health outcomes when compared to controls (no treatment, standard of care, or information only) [44-49]. One meta-analysis reported improved self-efficacy with MI interventions in patients with diabetes, cardiovascular disease, or smoking, producing an overall effect size of 1.39 (95% CI 1.09-1.78, n=7 studies) [47]. Other improvements have been found in self-monitoring (blood sugar, food intake, and exercise), glycemic control, blood pressure, cholesterol, HIV viral load, and body weight [47, 50, 51]. MI has also demonstrated positive results in a variety of settings, such as phone-based MI [44, 52-54], and age groups, including children and parents, adolescents, and adults [48, 49, 55, 56].

We hypothesize the use of phone-based MI in conjunction with monthly goal setting will increase patient activation and self-efficacy in participants with PKU.

Patients with PKU may benefit from more dynamic interaction with providers, as this genetic disease requires lifelong treatment. The current study evaluated self-reported SOC, patient activation and self-efficacy before and after a 6-month intervention comprised of monthly phone-based MI delivered by a metabolic dietitian, goal setting, and a monthly summary.

3.3 Methods

3.3.1 Participants

Study participants were individuals aged 7-35 years, diagnosed with PKU on newborn screening and treated within 1 month of birth. All participants were English speaking and had Internet access at home. Exclusion criteria included 1) intellectual disability (ID, IQ<70), 2) pregnancy, as excess Phe is teratogenic and requires different treatment guidelines [12], 3) hyperphenylalanemia not requiring dietary treatment, and 4) concurrent participation in clinical trial(s) testing enzyme substitution therapy. Patients were identified and recruited through the Utah Metabolic Clinic from December 2013 to July 2014. Participants were compensated monetarily for their time. The University of Utah Institutional Review Board approved this study and written consent – and child assent, if appropriate – was obtained for all participants.

3.3.2 Measures

3.3.2.1 Stages of Change

The research team compiled a questionnaire to assess participants' current SOC based on the format of previous questionnaires shown to be reliable [57, 58] (Appendix B). Treatment of PKU is complex and multiple behaviors contribute to blood Phe levels [59]; therefore, we assessed SOC for three behavioral domains, including meeting

dietary Phe/protein goals, meeting medical formula goals, and making healthy food choices. Healthy food choices do not affect Phe levels to the same extent as Phe/protein and medical formula goals. However, inclusion of this domain provided an opportunity to discuss other areas of improvement for those already meeting Phe/protein and formula goals and to provide options for those who may not be ready to discuss working towards Phe/protein or formula goals. Participants were asked to select the most important behavior from a list within each behavioral domain (Table 3.1). If none of the items pertained to the participant, he/she could write in another behavior of interest. For each domain, the SOC was scored on a progressive scale that ranged from "1" (absence of the desire to change behavior) to "5" (presence of the desire to maintain a changed behavior). The corresponding numbers to the participant's SOC are as follows: precontemplation=1, contemplation=2, preparation=3, action=4, and maintenance=5.

3.3.2.2 Patient Activation

Activation was measured with the abbreviated Patient Activation Measure (PAM-13). This questionnaire measures perceived knowledge, ability, and confidence to manage one's health [32]. PAM-13 scores range from 0 to 100, and this score can then be divided into four levels of activation [60]. The levels reflect a patient's belief that he/she should play an active role in self-care and collaborate with providers (level 1), knowledge about one's disease and its treatment (level 2), confidence to support new behaviors (level 3), and ability to maintain lifestyle changes in times of stress (level 4) [32]. The PAM-13 was validated in a cohort of adults (n=1515) and has not been validated in children [32]. Patient activation was included in this study considering it measures perceived knowledge and skills in addition to confidence, which are critical to

Table 3.1. List of Behavioral Targets for Stage of Change Questionnaire

Domain	List of behaviors
Dietary Phe/protein	Count how much Phe/protein I eat Keep diet records Plan meals beforehand Watch my portion sizes Prepare meals at home
Medical formula	Drink all formula every day Drink formula several times per day Make my own formula Bring my formula to school/work Try a different formula or try to improve the taste of my current formula
Healthy food choices	Eat more fruits/vegetables Drink fewer sweetened drinks (soda, juice) Eat out less often (restaurants, fast food) Eat fewer "junk foods" (chips, cookies, candy) Cook meals at home more often

Note. Phe, phenylalanine. Participants were asked to “Choose the single most important thing you could personally do to meet your goals” for each domain.

successful PKU management. Also unlike the SOC and self-efficacy questionnaires, it is not behavior specific, allowing a more general measure of activation for self-care.

3.3.2.3 Self-Efficacy

Self-efficacy was measured with a modified version of the 8-item Diabetes Self-Efficacy Scale developed at the Stanford Patient Education Research Center [61, 62]. Items were ranked on a 10-point Likert scale ranging from 1 (*not confident*) to 10 (*totally confident*). The total score reflected the average of the eight items rather than the sum to maintain the original metric. The wording of items 2, 5, 6, and 8 was revised to apply to someone with PKU (e.g., substituting "blood sugar" with "phenylalanine"). The topic of items 1 and 4 was replaced with statements regarding the ability to consume medical formula and collect blood samples, as the original topics (frequent meals and exercise) were not meaningful to the management of PKU (Appendix C).

3.3.2.4 Blood Phenylalanine

Participants collected a blood Phe sample via finger stick at baseline and were asked to collect monthly blood samples as part of standard of care monitoring during the study.

3.3.3 Interventions

3.3.3.1 Monthly Summary

A monthly PDF was emailed to participants to summarize previous responses (Appendix D). It displayed each participant's current SOC for selected behaviors within the three domains, monthly goal, prescribed protein intake, and average protein intake over the past month estimated from a validated food frequency questionnaire [63].

Participants received the summary prior to phone-based MI with instructions to review the information prior to the call, though they were not required to view the summary during the conversation.

3.3.3.2 Phone-Based Motivational Interviewing

Participants were contacted by phone once per month during the 6-month intervention. Author Krista Viau delivered the MI intervention. The interventionist received more than 30 hours of MI training via workshops, individual coaching and expert practice feedback. The sessions were audio recorded and a random sample was reviewed by author Michael Adelman, who was also trained in MI, to evaluate reliability of the MI intervention and give practice feedback. Calls were made after metabolic clinic staff received monthly blood Phe results, generally 5-10 days after sample collection. For participants less than 18 years of age, telephone counseling was conducted with either (1) the caregiver and participant concurrently or (2) participant alone followed by a verbal summary provided to the caregiver.

The interventionist reviewed topics on the summary and the participant's blood Phe result at the beginning of the session. After the initial discussion, participants were asked if he/she would like to focus on anything in particular the following month. A list of options was presented if the participant did not have a particular topic in mind. MI techniques aimed to understand the participant's goals and values, barriers to change, and elicit personal motivation for change were used during the session to explore potential behaviors to target and, if appropriate, to create a monthly goal.

3.3.3.3 Monthly Goals

Topics for monthly goals were derived from the discussion, particularly participant change talk. While current SOC for behavioral domains were discussed during the phone conversation, the participant had the option of choosing a goal that was separate from the behaviors selected on the SOC questionnaire. Each month participants were asked if they would like to form a goal, though they were reminded they could choose to maintain current health if they did not identify a specific change they were ready to implement. If the participant was interested in creating a goal, the interventionist assisted to design goals that were specific and measureable according to guidelines [64]. The interventionist reviewed the participant-reported progress of the previous month's goal, and discussed next steps during the following month's telephone conversation.

3.3.4 Data Collection

Study data were collected and managed using the REDCap electronic data capture tools hosted at University of Utah [65]. Participants were instructed on questionnaire completion during the in-person baseline visit. All questionnaires were emailed to participants and completed online using REDCap survey tools. Participants under 18 years of age were asked to complete the questionnaires with a caregiver. Krista Viau clarified individual responses with participants over the phone as needed. The SOC and food frequency questionnaires were administered monthly. Patient activation and self-efficacy questionnaires were completed at baseline and months 3 and 6. Participants were asked to collect blood samples the same day as questionnaire completion.

Demographic and treatment information including date of birth, sex, current protein and medical formula prescriptions, blood Phe results collected within 6 months

prior to enrollment, and eligibility for an individualized education program (IEP) were obtained from the electronic medical record. IEP eligibility was used as a proxy for the presence of learning problems. Adult participants were classified based on previous IEP eligibility.

3.3.5 Data Analysis

Demographic, questionnaire and monthly goal data were summarized using descriptive statistics: continuous variables were reported as mean ± standard deviation if normally distributed and median (interquartile range (IQR)) if not normally distributed, and categorical variables were reported as frequencies. Differences between data at baseline were assessed via Fisher's exact test for categorical data and one-way ANOVA for continuous data. Correlation between total goals created and total goals achieved was assessed with Spearman correlation coefficients due to the small sample size.

Due to repeated measurements in each participant, we used random effects linear regression to evaluate differences between IEP eligibility, age categories, and number of goals created and achieved. Random effects linear regression was also used to compare baseline patient activation and self-efficacy to month 3 and month 6 scores, controlling for potential confounders. We used an intention-to-treat analysis. Statistical analyses were performed using Stata 13.0 (StataCorp, College Station, TX). Significance was defined as a two-sided p-value with alpha of 0.05.

3.4 Results

Forty-six percent of patients invited to participate enrolled in the study (Fig. 3.1). Participants fell into three age categories, preadolescents (7-12 years), adolescents (13-17 years), and adults (18-35 years, Table 3.2). Approximately half (n=17) of

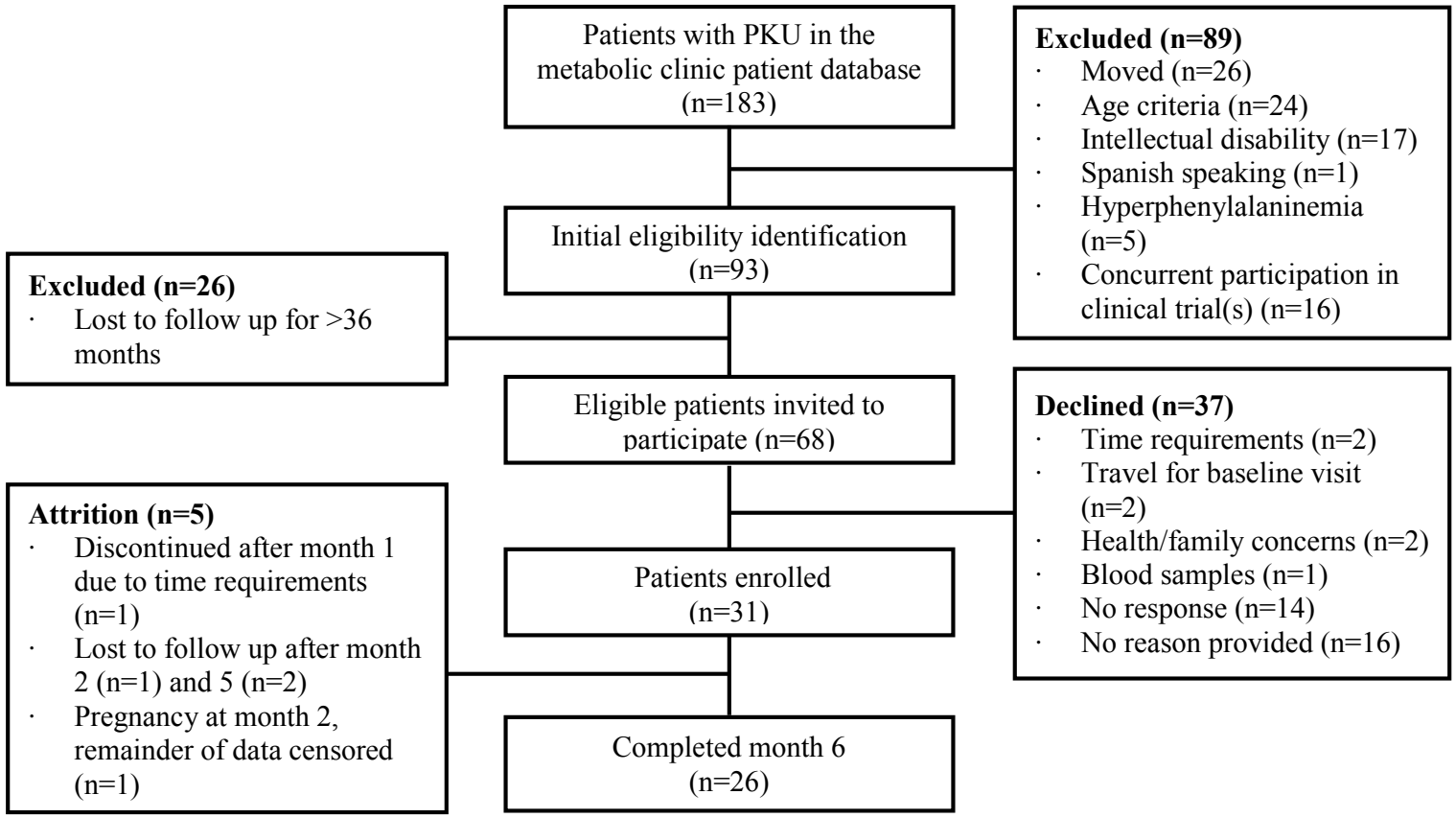

Figure 3.1. Flow Chart of Participant Recruitment, Enrollment, and Retention. Patients in the metabolic clinic database include all known patients in Utah who have been seen in our clinic and a portion of patients from surrounding states, including Idaho and Wyoming.

Table 3.2. Demographic and Baseline Treatment Information for Participants with PKU, Presented as Median (IQR) or Frequency

	Total n=31	Preadolescent (7-12 yrs) n=11	Adolescent (13-17 yrs) n=5	Adult (≥18 yrs) n=15	p-value[c]
Age (years)	17.2 (9.8-26.5)	9.5 (7.5-11.5)	16.4 (15.1-16.8)	26.5 (20.4-30.2)	
Baseline Phe Level (μM)	390 (209-579)	317 (140-433)	573 (495-865)	491 (226-686)	0.13
Female	22	8	1	13	0.032
Overweight/Obese	16	2	3	11	0.016
IEP[a]	7	2	1	4	1.00
Taking Medical Food[b]	28	10	5	13	1.00
BH4 Treatment	14	8	1	5	0.09

Note. BH4, tetrahydrobiopterin; IEP, individualized education program; IQR, interquartile range; Phe, phenylalanine

[a] Participants currently or previously eligible for an IEP in school as an indicator of learning impairment.

[b] Participants reporting regular medical food intake at enrollment.

[c] Differences between groups assessed with Fisher's exact test for categorical data and one-way ANOVA for continuous data.

participants' blood Phe concentrations were above the therapeutic range at baseline (120-360 μmol/L) [12], which was significantly different between the age categories (p=0.036). Participants completed a median of five (4-6) of the 6 monthly phone-based MI sessions with the median duration of 13 minutes (10.5-16). Thirty-one participants completed baseline questionnaires, 28 completed month 3 questionnaires, and 26 completed month 6 questionnaires.

3.4.1 Stages of Change

At baseline, most participants reported being in action or maintenance stages (Table 3.3). There was no significant difference in baseline SOC between age categories for any domain (data not shown). No participants were precontemplative for all three behavioral domains. The majority of participants' SOC remained stable throughout the intervention. SOC related to Phe/protein goals increased over the intervention for 7 participants and decreased for 5 participants; medical formula goals increased for 4 participants and decreased for 2 demonstrated participants; and healthy choices increased in 6 participants and decreased for 3 participants. All participants who decreased their SOC at month 6 were in the action or maintenance stages at baseline and 3/7 had selected a different behavior at month 6 compared to baseline.

Participants indicated their current SOC for one behavior per month within each domain. Most chose different behaviors throughout the intervention (n=20 for Phe/protein goals, n=13 for formula goals, and n=20 for healthy choices). The number of different behaviors selected for the three behavioral domains were not significantly associated with the SOC for that domain. Hypothesis testing was not performed for change in SOC across the intervention, as the behavior for each domain was not static.

Table 3.3. Baseline Stage of Change for Three Behavioral Domains

	Phe/Protein Goals	Formula goals	Healthy food choices
Precontemplation	1	—	—
Contemplation	6	—	5
Preparation	5	5	5
Action	5	6	10
Maintenance	14	20	11

Note. Baseline stage of change reflects the behavior with each domain selected by each participant.

3.4.2 Monthly Goals

Participants created a total of 118 goals during 150 cumulative counseling sessions. Goals varied throughout the intervention with a median of three (2-4) distinct goals per participant. Of these, 58.4% of goals were achieved per participant report. The number of different goals was not correlated with the percentage of goals achieved (p=0.80). Monthly goals were not always consistent with the behaviors selected on the SOC questionnaire. Nearly one-third (31.4%) of participant goals were focused on Phe/protein intake, 22% medical formula intake, 5.1% regular BH4 intake, 21.2% healthy choices, 17.8% exercise, and 2.5% nonhealth related topics. The total number of goals created and the number of goals achieved during the intervention were not significantly different by IEP eligibility (p=0.36 and p=0.59, respectively) and were not associated with baseline stage of change, patient activation, or self-efficacy scores (data not shown).

3.4.3 Patient Activation and Self-Efficacy

At baseline, most participants had patient activation scores reflecting high activation levels 3 and 4; Fig. 3.2), and had moderate self-efficacy scores (Table 3.4 Participants completing the intervention and those who discontinued prior to 6 months (Fig. 3.1) had similar median patient activation scores (71 (53-78) and 69 (50-73), p=0.94) and self-efficacy scores (7.9 (5.4-8.8) and 7.3 (5.1-8.8), p=0.64) at baseline. Over the course of the study, 4 participants maintained their baseline activation scores, 15 participants increased activation scores, and 4 participants decreased activation scores. Total self-efficacy scores increased for 19 participants during the intervention and decreased for 7 participants.

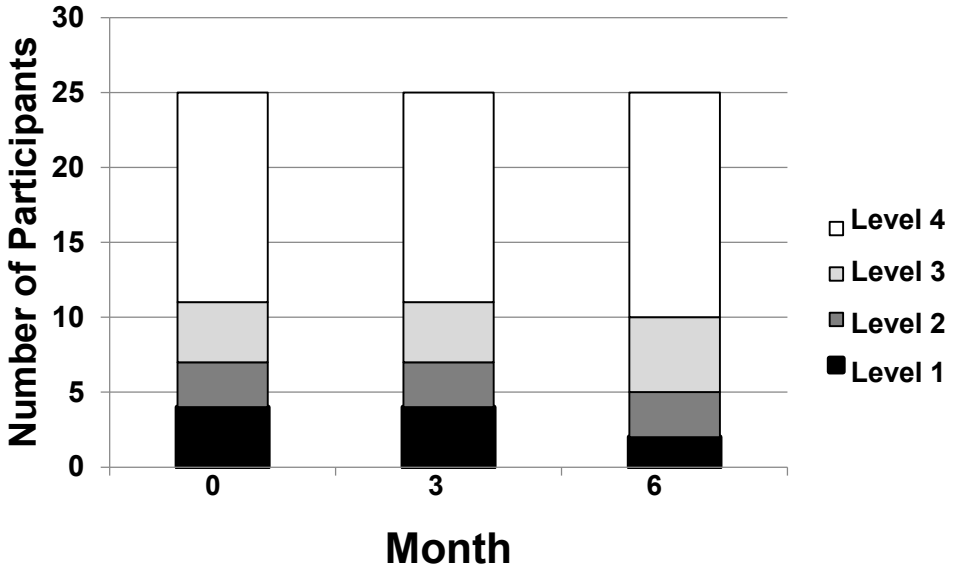

Figure 3.2. Patient Activation Levels for Participants at Baseline, Month 3, and Month 6 (n=25). Excludes participants with missing patient activation scores at month 3 or 6 (n=6). Level 1 reflects a belief that taking an active role is important; level 2 reflects confidence and knowledge to take action; level 3 reflects taking action; and level 4 reflects the ability to maintain changes under stress. Data source: [32].

Table 3.4. Individual Self-Efficacy Scores by Question for Participants with Phenylketonuria, Presented as Mean±SD

Variable	Baseline (n=31)	Month 3 (n=28)	Month 6 (n=26)	Change in mean scores
You can do all the things necessary to manage your PKU on a regular basis.	7.0±2.2	7.5±2.1	8.0±2.3	+1.0
You can follow your diet when you have to prepare or share food with other people who do not have PKU.	7.5±2.5	7.5±2.0	8.5±1.4	+1.0
You can choose the appropriate foods to eat when you are hungry (for example, snacks).	7.5±2.4	7.9±1.4	7.9±1.8	+0.4
You can poke your finger to collect a blood sample every month at a minimum.	7.7±2.9	8.0±2.8	7.8±2.7	+0.1
You can do something to prevent your blood phenylalanine levels from increasing.	6.7±2.4	7.1±2.4	7.5±2.5	+0.7
You know what to do when you blood phenylalanine level goes lower or higher than it should be.	7.1±2.8	6.9±2.4	7.7±2.6	+0.6
You can judge when changes in your illness mean you should visit the doctor.	6.3±2.7	6.3±2.8	7.1±2.7	+0.8
You can control your PKU so that it does not interfere with the things you want to do.	7.9±2.3	8.0±1.7	8.6±1.6	+0.7

Note. 1=not confident and 10=totally confident. Questions from modified version of the Stanford Diabetes Self-Efficacy Scale [62].

Self-management responsibilities increase with age [66] and a concomitant increase in activation and self-efficacy are expected. In our participants, patient activation and self-efficacy scores were significantly different between age categories ($p<0.01$ for both). The mean activation score was 61.4±18.5 for preadolescents, 70.5±18.9 for adolescents, and 74.5±14.6 for adults. The mean self-efficacy score was 6.7±1.7 for preadolescents, 7.7±1.5 for adolescents, and 8.1±1.7 for adults.

The change in patient activation and self-efficacy was assessed with random effects linear regression. IEP eligibility was not included in the model, as it was not significantly associated with patient activation or self-efficacy in bivariate regression models ($p=0.83$ and 0.33, respectively). Considering the difference in mean activation and self-efficacy between age groups, we stratified the analysis by age category. However, adolescents and adults were combined into a single category, as there were only 5 participants in the adolescent category. After controlling for age, patient activation did not significantly change over the course of the intervention ($\beta=5.1$, $p=0.10$; Fig. 3.3A). This was consistent with results after stratifying by age group ($p=0.19$ for preadolescents and $p=0.24$ for adolescents/adults). However, self-efficacy scores significantly increased from baseline to month 6 ($\beta=0.68$, $p=0.017$; Fig. 3.3B). After stratifying by age group, the adolescent and adult age group demonstrated a significant increase in self-efficacy from baseline to month 6 ($\beta=1.06$, $p=0.002$), though this was not found in the preadolescent age group ($\beta=0.13$, $p=0.79$).

3.5 Discussion and Conclusion

To our knowledge this is the first study to use motivational interviewing and goal setting to influence stage of behavior change, activation, and self-efficacy in patients

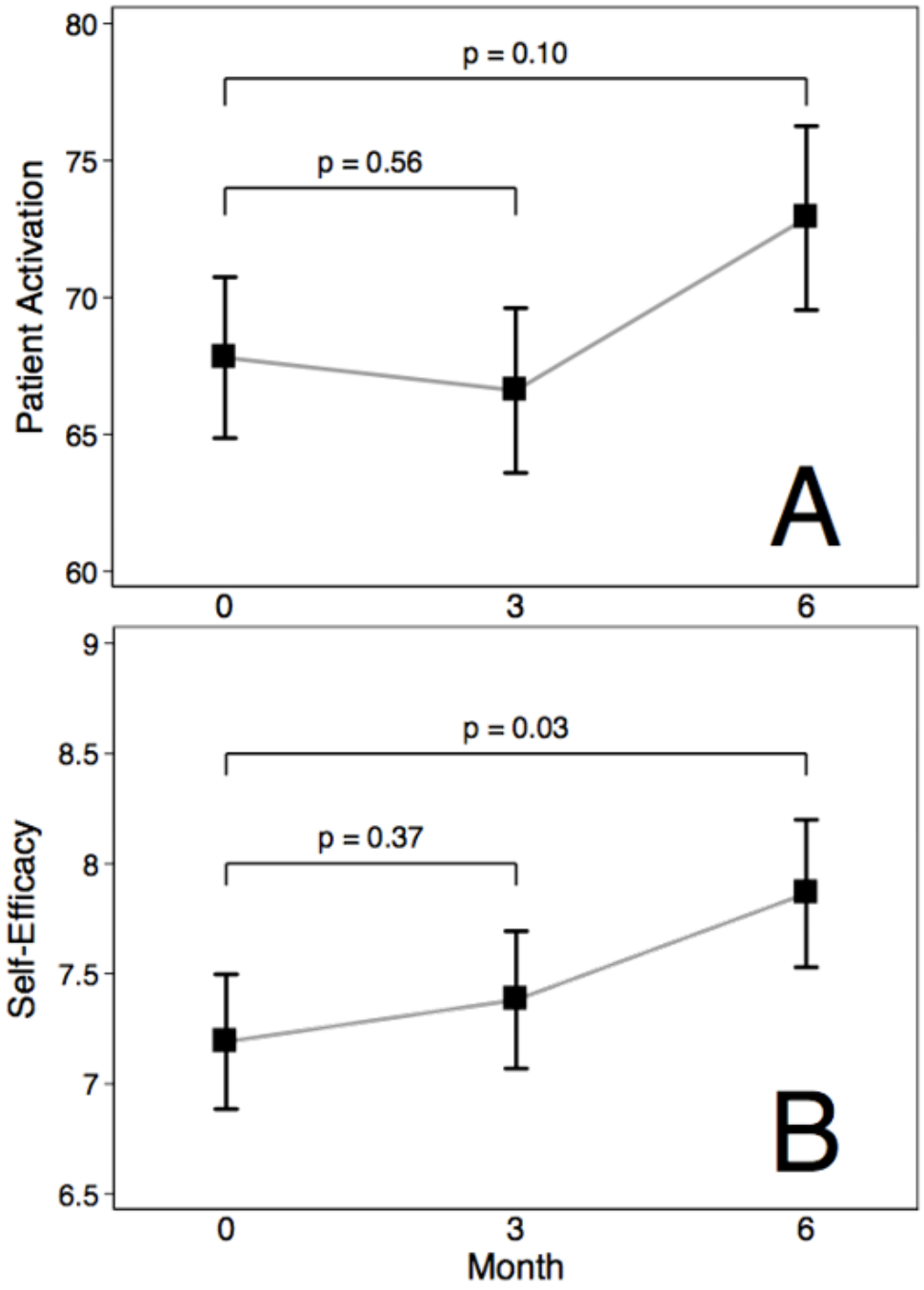

Figure 3.3. Predicted Means ± Standard Error for Patient Activation (A) and Self-Efficacy (B) for All Participants from Baseline to Month 3 and Month 6. Random effects linear regression used to estimate slope in patients with PKU. Patient activation was scored from 0-100 and self-efficacy was scored from 1-10; with both measures, higher scores reflected increased activation or self-efficacy.

with PKU. Patients' knowledge and engagement in their own care are crucial for chronic disease management. The treatment for PKU is complex, and many with PKU have subtle intellectual and/or executive deficits; therefore interventions that increase motivation and confidence in managing one's health are ideal for individuals with PKU. Our primary finding was a significant increase in self-efficacy to manage a variety of behaviors involved in the treatment of PKU after the 6-month MI intervention.

MI has demonstrated positive outcomes with a variety of age groups [47-49]. Our sample included participants aged 7-35 years. While it is crucial to engage younger patients in their care and provide opportunity for skills mastery [59, 67, 68], we noted differences in the efficacy of MI in the youngest participants compared to adult participants. This may be explained by their developmental stage, which often includes a lesser understanding of illness-related concepts, expressive language skills, and ability tolink current behavior with past events or long-term goals when compared to adolescents and adults [69]. Therefore, programs targeting preadolescents would likely be most effective when involving both parents and children in the MI intervention [48]. In contrast, MI is well suited for adolescence considering this period is typically characterized by ambivalence, desire for autonomy, and development of self-identity [69-71]. Despite age-related challenges, including younger participants is important to increase self-management behaviors and reduce the likelihood of poor treatment adherence later in life.

We assessed each participant's current SOC prior to the monthly MI intervention. This provided context regarding the participant's current readiness to take action and provided a starting point for therapeutic discussion. The majority of our participants were

in action/maintenance stages for medical formula goals (Table 3.2). This indicates our population adhered to formula recommendations more often than other behavioral domains, which is also consistent with our clinical experience.

Most participants changed their selected SOC behaviors over the 6-month period (Table 3.1), which demonstrates the flexibility of the intervention. The exploratory nature of MI may encourage participants to select a behavior they had not considered previously. While flexibility is important in MI, this design limited our ability to follow up on the change in SOC for each behavior. Therefore, we were unable to determine if a change in SOC behaviors reflected a lack of readiness for the behavior change or successful implementation of the behavior. Future studies might collect SOC for a variety of specified self-management behaviors in order to determine if MI facilitates increasing readiness to change over time.

The majority of participants had high activation scores throughout the intervention (Fig. 3.2). PAM scores did not significantly increase from baseline to month 6 (Fig. 3.3A). PAM-13 was validated in adults and our sample had a large percentage of participants in the preadolescent (35%) and adolescent (16%) age groups. While we do not expect a preadolescent or even adolescent population to agree with some of the PAM-13 statements (e.g., “When all is said and done, I am the person who is responsible for taking care of my health”) [32], there was also no significant change in activation scores for participating adults ($p=0.32$). This suggests the 6-month MI intervention did not have a significant impact on overall patient activation in this sample and/or that the PAM-13 may not be the appropriate tool for this population to reflect a difference in perceived confidence and readiness to manage one’s health.

Self-efficacy for tasks relating to PKU management significantly increased over the 6-month MI intervention (Fig. 3.3B). However, the change was not significant at month 3, indicating change in self-efficacy may take time to develop. The significant change in self-efficacy was only found for adolescent and adult participants' self-efficacy and not for preadolescents. This may be related to the expected self-management skills at varying ages. Adolescents and adults have greater self-management responsibilities compared to younger participants; therefore, confidence regarding specific skills related to PKU management may have a greater potential to increase in older participants.

It is possible that the increase in participant-reported self-efficacy reflected regression to the mean, in which repeated measurements are less extreme than the first measurement. In our sample, 5 participants had baseline self-efficacy scores in the lower half of the range (score ≤ 5) and were mostly preadolescents (n=4). However, there was no significant increase in self-efficacy in the preadolescent group, suggesting regression to the mean was not the underlying cause of reportedly increased self-efficacy. The best method to account for potential regression to the mean is inclusion of a randomized control group [72].

Previous research has shown a positive association between self-efficacy and participation in action planning and self-monitoring in adults [73, 74]. We were unable to determine if the increase in self-efficacy in our population was due to a specific component of the intervention (MI, goal setting, monthly summary) or the intervention as a whole. However, our results did not show an association between goal setting and self-efficacy. It is possible that the participants with greater confidence were already

engaging in recommended behaviors, and thus chose to maintain current health rather than create a monthly goal.

For most participants, outcome measures increased over the course of the intervention. However, SOC, activation, and self-efficacy decreased for a few participants. For SOC, we are unable to compare baseline to month 6 as participants selected different behaviors. Reported decreases in patient activation or self-management may reflect questionnaire fatigue and/or regression to the mean. Additionally, several of these participants cited life stressors impairing their ability to adhere to treatment recommendations during the intervention, though they completed the intervention. We were unable to compare this to participants who discontinued the study, though baseline data were similar. Many patients, particularly adults, are lost to follow up with an estimated 77% of adults with PKU were not followed by a metabolic clinic in 2012 [75]. Maintaining patient rapport and engagement is a fundamental part of the treatment plan. Use of MI may help achieve these goals and subsequently increase the likelihood of patients continuing with treatment into adulthood [76].

Subtle intellectual and/or executive deficits may impair one's ability to manage the complex treatment for PKU. Studies in other populations have reported a negative association with executive functioning and self-management and/or treatment adherence [77, 78]. In contrast, our results did not show a significant difference in number of goals created or achieved, patient activation, or self-efficacy scores between individuals with or without learning problems. While many individuals with PKU have subtle cognitive/executive deficits, we suggest MI remains a potentially beneficial tool. MI originated and has been demonstrated to be effective in the substance abuse field [55, 79,

80], which has increased rates of mental illness and executive deficits [81], and has been successfully used to increase engagement in patients with a traumatic brain injury [82]. Although the current study excluded individuals with ID, these findings support further exploration of MI as a potential intervention to facilitate treatment adherence in individuals with PKU and more severe intellectual deficits.

3.5.2 Limitations

The design of this study introduced potential for selection and self-report bias. Many adults with PKU were lost to follow up in our clinic and may have different characteristics than patients currently attending a metabolic clinic. Additionally, those that declined participation may have lower baseline SOC compared to participants. Self-reported data may also be overestimated, also suggested in a recent meta-analysis of MI interventions showing self-reported outcomes had greater effect sizes compared to objective outcomes [47]. Additionally, rather than a separate control group, participants acted as their own control, which addressed participant matching but failed to control for a potential Hawthorne effect. The reliability of the MI intervention was evaluated and practice feedback provided. However, the intervention was delivered by one dietitian, and needs to be replicated with other interventionists to evaluate its reliability and generalizability. The questionnaires used in these studies were modified and/or used in populations not meeting the age criteria in the original validation studies, which increased the risk of systematic bias. Additionally, learning impairment was measured with IEP eligibility, which may not include all participants needing an IEP and, conversely, potentially include participants with an IEP for less substantial learning impairment. Lastly, PKU is a rare disease; therefore the target population number was

small, reducing power. The study included preadolescent, adolescent, and adult participants to increase the study population. However, these factors limit our ability to determine the efficacy of this intervention. Studies with larger sample sizes in each age group are needed to understand the impact of phone-based MI on patient activation and self-efficacy.

3.5.3 Conclusion

The 6-month phone-based MI intervention, in conjunction with goal setting and a monthly summary, was associated with a significant increase in self-efficacy for PKU self-management behaviors among adolescent and adult participants. Our results indicate patient self-efficacy takes time to develop, as there was no significant difference in self-efficacy after 3 months. This association was not found for patient activation. Measures of SOC identified that the majority of participants were currently performing or maintaining self-care behaviors. The results of this study suggest phone-based MI is a potential method to increase self-efficacy in adolescents and adults with PKU. Additional research is needed to further evaluate the efficacy of MI in a larger cohort of patients with PKU and with different age groups.

3.5.4 Practice Implications

Results from this study suggest MI is an appropriate tool to enhance self-efficacy for PKU self-management behaviors. Self-efficacy may increase the likelihood of treatment adherence in patients with PKU, as has been reported in other chronic diseases. Additionally, pairing goal setting and action planning with MI may help patients construct an individualized and feasible plan once they are prepared to take action. While not demonstrated in this study, this pairing may also increase confidence through

mastery experiences [73].

MI may be beneficial with patients of a variety of ages, though developmental stage and differing stressors related to PKU management need to be considered. We recommend using an MI intervention with both parents and children or preadolescents with PKU to facilitate confidence and behavior change, considering self-management responsibilities begin early in chronic disease. Adolescents may respond to the autonomy support emphasized in MI. Additionally, MI may be a beneficial addition to initiatives aiming to engage adult patients lost to follow up in a metabolic clinic [75]. The patient-centered nature of MI has potential to maintain patient rapport and keep patients engaged in a metabolic clinic.

3.6 Acknowledgements

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CHAPTER 4

A NOVEL APPLICATION OF MOTIVATIONAL INTERVIEWING TO IMPROVE TREATMENT ADHERENCE IN PHENYLKETONURIA[3]

4.1 Abstract

4.1.1 Objective

The objective of this study was to demonstrate the efficacy of a 6-month phone-based motivational interviewing (MI) intervention to reduce blood phenylalanine (Phe) slope and improve diet adherence in individuals with phenylketonuria (PKU) using a before-and-after design.

4.1.2 Methods

Participants (n=31) were 7-35 years of age and completed stage of change (SOC), self-efficacy, and food frequency questionnaires online. Pre-intervention blood Phe levels collected within 6 months of enrollment were compared to blood Phe during the

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intervention. The intervention included monthly phone-based MI, goal setting, and a monthly summary. Data were analyzed with descriptive statistics, Fisher's exact test, Mann-Whitney U test, and mixed effects linear regression.

4.1.3 Results

There was no significant change in dietary adherence over the intervention, though the majority of participants (n=28/31) reported adherence to medical formula at baseline. After controlling for baseline SOC and learning problems, the pre-intervention blood Phe slope for all participants (β=0.71) was not significantly different from the intervention slope (β=0.26, p=0.13) and not different based on age (p=0.77). Higher SOC at baseline (β=-61.6, p=0.005) and self-efficacy (β=-64.5, p<0.001) were associated with a decrease in blood Phe slope.

4.1.4 Conclusion

This study suggests MI is feasible in a PKU population and lends support to the link between SOC, self-efficacy, and behavior change. SOC and self-efficacy may be future targets for behavioral interventions to improve metabolic control in patients with PKU. However, a larger sample size and longer follow-up are needed to further explore potential benefits of MI in this population.

4.2 Introduction

Phenylketonuria (PKU) is a challenging chronic disease to manage, requiring patients and families to perform multiple, interrelated tasks on a daily basis. Hence, there are several barriers to optimal and lifelong treatment, such as habitual consumption of medical formula, diligent monitoring of dietary phenylalanine (Phe)/protein intake,

keeping frequent food records and obtaining blood samples [1, 2]. Recently, there have been improvements in availability and taste of protein foods and medical formulas as well as new treatment options [2, 3]. However, for many individuals with PKU, the diet remains highly restrictive. Therefore, it is not surprising that treatment adherence declines with age, resulting in increased blood Phe concentrations [4]. Sequelae of elevated blood Phe levels, such as learning problems and reduced achievement, slowed processing speed, increased executive functioning deficits, increased anxiety and emotional disorders develop as many adolescents and young adults liberalize or abandon dietary Phe restriction [4-10].

There are a myriad of factors influencing one's ability to adhere to treatment guidelines and manage their own care [2, 11, 12]. Self-efficacy, problem solving and coping skills are required to deal with the physical, social, and psychological consequences of a chronic illness [12-14]. In PKU, deficiencies in self-management skills contribute to poor treatment adherence and detrimental cognitive and neuropsychological outcomes [15-17].

Poor treatment adherence is not specific to individuals with PKU; rather it is a prevalent phenomenon among individuals experiencing chronic illness [18-21]. Increased self-management and treatment adherence are associated with improved health outcomes and reduced health care expenditures [22-25]. Despite these benefits, it is a common finding that prescriptions are not filled, healthy lifestyle choices are not implemented, and/or self-management behaviors are lacking [21, 26-29]. The discrepancy between potential health benefits and actual behavior change may be due, in part, to ambivalence, which is a normal part of change. An ambivalent individual has

both arguments for and against change [30]. Traditionally, our health care system responds to ambivalence with direct questioning, giving advice, and attempting to convince patients to change their behaviors [31, 32]. These strategies often lead to increased resistance to change and leave both practitioners and patients frustrated [33, 34].

Motivational interviewing (MI) is a patient-centered, directive counseling style that explores ambivalence to elicit intrinsic motivation for behavior change [30]. The foundation of MI is an atmosphere of collaboration, compassion, evocation, and acceptance. MI employs strategies, such as reflective listening, supporting patient autonomy to decide whether or not to change, and reducing resistance. Whereas in the traditional model direct questioning and giving advice are normative, MI suggests collaboration among experts, where the provider is the expert on the condition/treatment and the patient is the expert on himself or herself [30]. This structure allows practitioners to elicit and reinforce change talk, in which the patient states reasons for change. The practitioner guides the patient and helps them identify discrepancies between their current actions and their desired outcomes, creating opportunity for the patient to develop motivation to change.

Meta-analyses consistently demonstrate a modest, positive association between MI and health outcomes despite differences in targeted health behaviors, delivery settings, and provider type [35-38]. In medical settings, participants receiving MI were 1.55 times more likely to have positive outcomes compared to controls [35]. A similar result was noted in pediatric populations (effect size: 0.28 (95% CI 0.24-0.32)) with 95% of studies reporting a positive impact of MI compared to controls [37]. It has been used

effectively as the sole intervention, in combination with other programs, and as a method to increase engagement in other programs, such as educational programs or cognitive behavioral therapy [37, 39].

Intermediate outcomes, such as self-efficacy and progressing through stages of change (SOC), are common targets of behavior change interventions, as they are theorized precursors to actual behavior change [40]. Self-efficacy reflects confidence to successfully engage in a behavior, and SOC reflects one's readiness to engage in a behavior, ranging from precontemplation to maintenance [40]. Meta-analyses have shown an association between MI and self-efficacy [35], as well as between self-efficacy and self-management behaviors [41, 42]. In patients with diabetes, self-efficacy and perceived autonomy support, which is a key element of MI, were associated with improved glycemic control, better perceived health, and self-management behaviors. [43-46]. This has also been shown in PKU, with positive associations between parental self-efficacy and perceived internal locus of control and better metabolic control in children with PKU [47, 48].

Treatment adherence and subsequent metabolic control decrease with age in individuals with PKU [4, 49, 50]. MI has been associated with improved self-efficacy and health outcomes in chronic disease [35]. We hypothesize that the use of MI techniques will improve treatment adherence and metabolic control in a PKU clinical population. This study seeks to demonstrate the effectiveness of 6-month intervention with phone-based MI, goal setting, and a monthly summary to improve treatment adherence and reduce blood Phe levels using a before and after study design.

4.3 Methods

4.3.1 Participants

Patients aged 7-35 years, diagnosed with PKU on newborn screening and treated since birth were recruited. All participants were English speaking and had Internet access at home. Exclusion criteria included 1) intellectual disability (IQ<70), 2) pregnancy, and 3) concurrent participation in clinical trial(s) testing enzyme substitution therapy. Patients were identified and recruited through the Utah Metabolic Clinic from December 2013 to July 2014. The University of Utah Institutional Review Board approved this study and written consent – and child assent, if appropriate – was obtained for all participants. Participants were provided financial compensation for their time.

4.3.2 Measures

4.3.2.1 Blood Phenylalanine

Participants were asked to collect monthly blood Phe samples via finger stick as standard of care during the study. In addition to the standard monthly sample, during months 3 and 6, participants were asked to collect an unannounced blood Phe sample within 24 hours of the request. The random date was generated in Excel. All additional blood samples collected via finger stick during the study were also included in statistical analysis for the intervention Phe levels. Blood samples obtained at the baseline visit and up to 6 months prior to enrollment were used for the pre-intervention comparison. Pharmacological treatments for PKU, including a synthetic form of tetrahydrobiopterin (BH4) and recombinant phenylalanine ammonia lyase conjugated with polyethylene glycol (rAvPAL-PEG), have the potential to alter blood Phe levels independent of dietary treatment [51, 52]. Therefore, a portion of the blood Phe levels from individuals

who initiated and/or discontinued BH4 (n=5) or rAvPAL-PEG (n=2) during the 6-month pre-intervention period. All levels included in statistical analysis were consistently on or off the medications listed above. Additionally, treatment guidelines and dietary Phe tolerance during pregnancy differ from a nonpregnant adult. Therefore, blood Phe levels obtained while pregnant during the pre-intervention period were also excluded from statistical analysis (n=1). Blood samples collected from finger sticks were analyzed at ARUP Laboratories in Salt Lake City, UT using tandem mass spectrometry without chromatographic separation. Blood Phe concentrations obtained from quantitative analysis of plasma amino acids collected via venipuncture were excluded as the analysis method differed.

4.3.2.2 Food Frequency Questionnaire

The Food Frequency Questionnaire (FFQ) © 2012 BioMarin Pharmaceutical Inc. was used to evaluate participants' average protein intake. The accuracy of this tool for assessment of quantity and quality of protein was validated in a PKU clinical population aged 12 years and older [53]. The FFQ was used in place of 3-day food records, which are standard to assess dietary intake in PKU. The FFQ is a comparatively fast method to assess protein intake and allows quantification of protein from distinct food categories. It may also alleviate collection of food records as a barrier to treatment [53, 54]. This tool was designed to assess average protein intake from medical formula and 12 food categories over the preceding month in individuals following a low protein diet. Food categories include low protein foods, vegetables, fruits, breads and grains, snack foods, beans, nuts and seeds, milk and yogurt, cheese, eggs, meat, and fast food/restaurants.

4.3.2.3 Stages of Change and Self-Efficacy

The SOC questionnaire followed the format used in previous studies [55, 56] and is described in more detail in Chapter 3, Appendix A. We assessed current SOC for three behavioral domains: meeting dietary Phe/protein goals, meeting medical formula goals, and making healthy food choices. SOC for the healthy food choices domain is not described further in this study, as it has a lesser impact on blood Phe levels. For each domain, participants were asked to choose the behavior that was most important to them from a list (e.g., "Drink formula several times per day") or could add their own behavior. Current SOC was assessed for the selected behaviors. For each domain, the SOC was scored on a progressive scale that ranged from "1" (absence of the desire to change behavior) to "5" (presence of the desire to maintain a changed behavior).

Self-efficacy was measured with a modified version of the eight-item Diabetes Self-Efficacy Scale developed at the Stanford Patient Education Research Center [57, 58]. Revisions were made to include self-management items relevant to PKU (described in Chapter 3, Appendix B). Items were ranked on a 10-point Likert scale ranging from 1 (*not confident*) to 10 (*totally confident*); the total score averages the results of the eight items.

4.3.3 Interventions

4.3.3.1 Monthly Summary

A monthly summary was emailed to participants to summarize previous responses (SOC and monthly goal). It also illustrated average protein intake over the last month compared to the amount prescribed and an overview of current sources of dietary protein (Fig. 4.1). Participants received the summary prior to phone-based MI with

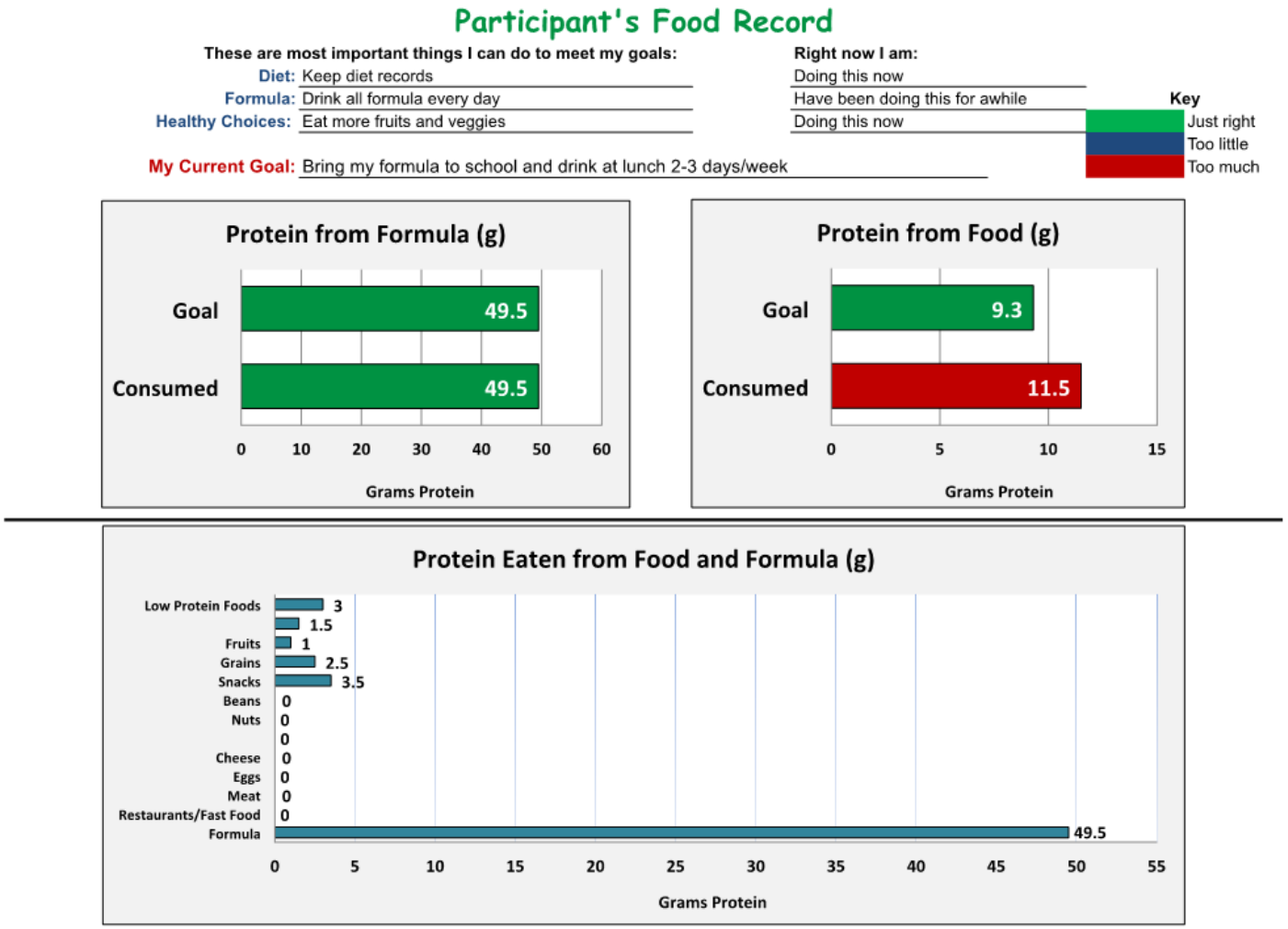

Figure 4.1. Monthly Summary Emailed to Participants. This summary reflects current stage of change for three behavioral domains, monthly goal, and average protein intake compared to the prescribed amounts.

instructions to review the information prior to the call. Participants were not required to view the summary during the conversation.

4.3.3.2 Phone-Based Motivational Interviewing

Participants were contacted by phone once per month during the 6-month intervention. Author Krista Viau received over 30 hours of MI training via workshops, individual coaching, and expert practice feedback prior to initiating the MI intervention. Michael Adelman, a triple board resident (pediatrics, general psychiatry, child psychiatry) trained in MI, reviewed a random sample of audio-recorded MI sessions with Krista Viau to evaluate reliability of the MI intervention and provide practice feedback. Calls were made after metabolic clinic staff received monthly blood Phe results, generally 5-10 days following sample collection. For participants less than 18 years of age, telephone counseling was conducted with either (1) the caregiver and participant concurrently or (2) participant alone followed by a verbal summary provided to the caregiver.

The MI intervention differed from standard of care reporting of blood Phe results. The standard in our clinic generally involves relaying the laboratory values to the patient (or parent if the patient is less than 18 years), assessing potential requirements for dietary changes, and offering advice if needed. In this study, the interventionist reviewed topics on the monthly summary and the participant's blood Phe levels at the beginning of the session. After providing this information, participants were asked if he/she would like tofocus on anything in particular the following month. A list of options was presented if the participant did not have a particular topic in mind. MI techniques aimed to understand participants' goals and values, barriers to change, and elicit personal

motivation for change were used during the session to explore potential behaviors to target and, if appropriate, to create a monthly goal.

4.3.3.3 Monthly Goals

Goal setting is part of the MI planning process and should only occur when the participant is ready to do so [30]. Topics for goals were derived from the discussion, predominantly from participant change talk. Monthly goals did not always align with behaviors selected on the SOC questionnaire. If the participant was ready to form a monthly goal, the interventionist helped him/her form a specific and measureable goal according to guidelines [59]. Participants had the option of maintaining current health if they did not identify a specific goal they were ready to implement. During the following month's telephone conversation, the interventionist reviewed the participant-reported progress of the previous month's goal and discussed next steps.

4.3.4 Data Collection

Study data were collected and managed using the Research Electronic Data Capture (REDCap) tools hosted at University of Utah [60]. Participants were instructed on questionnaire completion during the in-person baseline visit. All questionnaires were emailed to participants and completed online using REDCap survey tools. Participants under 18 years of age were asked to complete the questionnaires with a caregiver. Krista Viau reviewed individual responses requiring clarification with participants over the phone. The FFQ and SOC questionnaires were administered monthly. The self-efficacy questionnaire was completed at baseline, month 3, and month 6. Participants were asked to collect the blood sample on the same day as questionnaire completion.

The following demographic and treatment information were obtained from the

electronic medical record: date of birth, sex, current protein and medical formula prescriptions, blood Phe results collected within 6 months prior to enrollment, and eligibility for an individualized education program (IEP), which suggests the presence of learning problems. Participants were designated as IEP eligible in this study if they had ever had an IEP and/or had been recommended for an IEP by a psychologist working within the metabolic clinic.

4.3.5 Data Analysis

Demographic, phenylalanine, and questionnaire data were summarized using descriptive statistics: continuous variables were reported as mean ± standard deviation if normally distributed or median and interquartile range (IQR) if not normally distributed, and categorical variables were reported as frequencies. Baseline SOC for both Phe/protein and medical formula behavioral domains (score 1-5) were summed to create a total SOC score ranging from 2-10. Differences in data without repeated measurements were assessed with Fisher's exact test and Mann-Whitney U test.

For the nutritional outcomes with repeated measurements within the same participant, a random intercept and random slope mixed effects linear regression model was fitted to the percentage protein consumed compared to prescribed with an unstructured variance-covariance structure. The predictor variables included time (days), intervention (baseline vs. post), and either Phe/protein SOC or medical formula SOC.

Given that there were repeated measurements of blood Phe across time within the same participant, a mixed effects linear regression model was fitted to the data. The model was fitted with random intercepts and random slopes across time for participants with an unstructured variance-covariance structure. The predictor variables included time

(days), intervention (pre vs. post), and time x intervention interaction term. It also included two covariates, continuous baseline stage of change and IEP (eligible vs. not eligible).

Statistical analyses were performed using Stata 13.0 (StataCorp, College Station, TX). Significance was defined as a two-sided p-value with alpha of 0.05.

4.4 Results

Participant enrollment and retention are described in Fig. 3.1. Participants completed a median of five (4-6) of the planned six phone-based MI sessions with the median duration of 13 minutes (10.5-16). Eleven participants were preadolescents (7-12 years), 5 were adolescents (13-17 years), and 16 were adults (18+ years). All participants were prescribed a low protein diet with medical formula, though 3 participants reported rarely drinking medical formula at baseline. There was no significant difference in pre-intervention Phe levels between those taking formula <3 and ≥3 times daily (p=0.71). While the majority of participants were in the action or maintenance SOC for behaviors related to metabolic control (Table 3.3), approximately half of participants' blood Phe levels exceeded the recommended range at baseline (120-360 μM) [61].

When compared to the median (IQR) Phe levels of the 37 patients who declined participation (319 μM (176-504)), participant median pre-intervention Phe levels were not significantly different (357 μM (193-573), p=0.12). However, 15 patients who declined participation did not have results available for comparison, as 13 patients had not collected blood Phe samples and two had concurrent conditions affecting Phe concentrations. Age distribution (preadolescent, adolescent, and adult categories) was not significantly different from participants (p=0.16), although sex (71% female vs. 44%

female) differed between participants and nonparticipants ($p<0.01$).

4.4.1 Average Protein Intake

For all participants, the median medical formula intake was 100% (100-100%) of the amount prescribed, and natural protein intake was 114.3% (91.7-146.9%) of the amount prescribed throughout the intervention. For most, over 75% of total protein consumed came from medical food, and nearly 25% of natural protein came from snack foods (Fig. 4.2). The majority of participant responses (58.3%) to the FFQ indicated consuming medical formula in three or more servings per day and 10% of responses indicating formula intake in one serving per day.

When compared to baseline, there was no significant difference in the percentage of medical formula or natural protein consumed in relation to the amounts prescribed during the intervention after controlling for SOC for medical formula or Phe/protein goals ($p=0.89$ and $p=0.99$, respectively). In the same model, SOC for medical formula goals was significantly associated with percentage formula consumed ($\beta=5.4$, $p=0.027$), though SOC for Phe/protein goals was not significantly associated with percentage natural protein consumed ($p=0.12$). We also included the natural protein goal in the dietary Phe/protein model, as the degree of dietary restriction may impact one's ability to follow recommendations. Lower protein tolerance was associated with increased percentage of natural protein consumed compared to the goal after controlling for the intervention, time, and SOC ($\beta=-3.7$, $p=0.015$).

4.4.2 Blood Phenylalanine Concentrations

The median number of blood Phe samples collected in the 6 months pre-intervention was three (2-5) samples. Seven participants only had their baseline level for

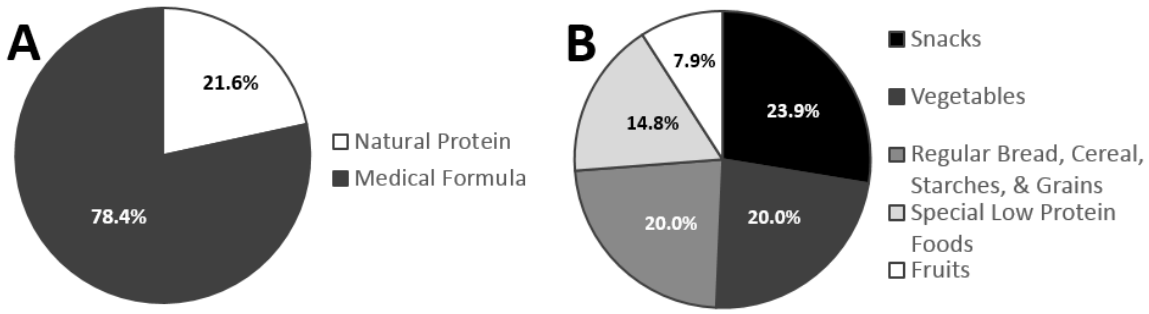

Figure 4.2. Median Distribution of Protein Intake for All Participants. Protein intake calculated with the Food Frequency Questionnaire, which estimated participants' average protein intake over the last month. (A) Median percent of total protein intake from medical formula (phenylalanine-free protein) and natural protein (food). (B) Median percent of natural protein intake (not including medical formula) by food category.

the pre-intervention comparison. Baseline Phe was not significantly different between those with pre-intervention Phe samples and those with only a baseline sample (p=0.31). During the course of the intervention, participants collected a median number of seven (6-8) blood Phe samples.

Unannounced blood Phe samples were collected during months 3 and 6 due to the potential for individuals to alter dietary intake prior to collecting a blood sample [1, 2]. Unannounced samples were collected 15.4±4.1 days apart from the scheduled sample during month 3 and 13.2±6.0 days apart during month 6. The unannounced Phe levels collected at months 3 (n=17/27) and 6 (n=19/26) were not significantly different from the scheduled blood collection dates during the same month (p=0.96 and p=0.37, respectively).

Change in Phe was evaluated with a mixed effects linear regression model. We included baseline SOC (Phe/protein and medical formula domains) and IEP eligibility in the model, as both were significantly associated with blood Phe slope in bivariate regression models (data not shown). IEP eligibility was not associated with Phe slope after controlling for the effect of the intervention and baseline SOC (β=132.4, p=0.12). Blood Phe levels increased prior to enrollment and during the intervention (Fig. 4.3A). The pre-intervention blood Phe slope (β=0.71) was not significantly different from the intervention slope (β=0.27, p=0.13). However, higher baseline SOC (β=-63.7, p=0.005) was significantly associated with a decrease in blood Phe slope.

There is a known effect of age on blood Phe levels as individuals adapt to a social life and assume self-management responsibilities [4]. Mean pre-intervention blood Phe levels among preadolescents (228±165 μM), adolescents (618±243 μM), and adults

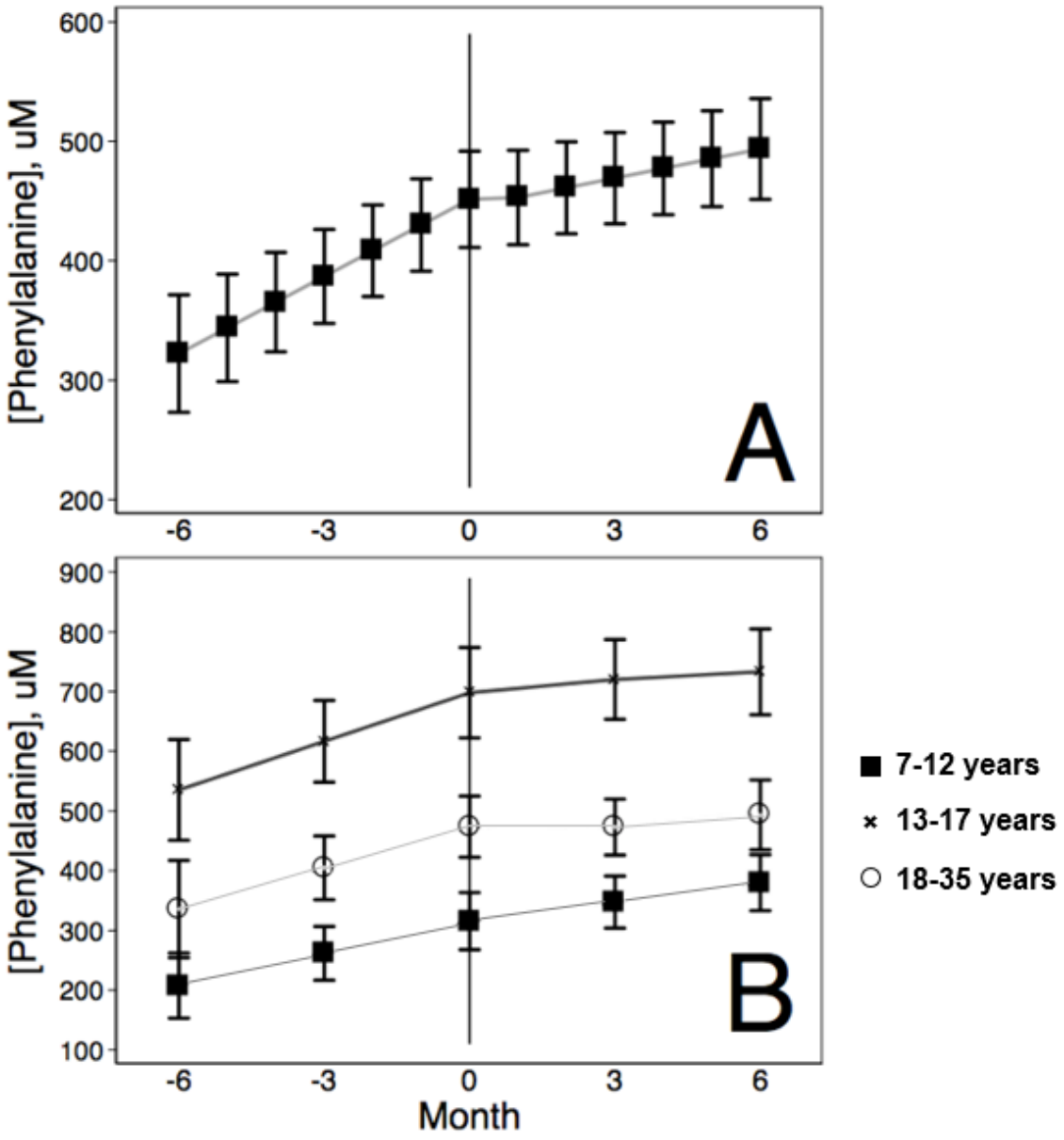

Figure 4.3. Predicted Slope in Blood Phenylalanine (Mean ± Standard Error) 6 Months Pre-intervention and During the Intervention. Mixed effects linear regression model predicted the slope after controlling for baseline stage of change and eligibility for an individualized education program. (A) Pre-intervention slope for all participants (β=0.71) compared to the intervention slope (β=0.27) was not significantly different (p=0.13). (B) Pre-intervention and intervention slopes for each age category were not significantly different from the adult group (p=0.69 for preadolescents and p=0.73 for adolescents).

(457±236 μM), significantly differed by age group ($p<0.001$). Considering differences in mean Phe by age category, we tested a three-way interaction variable between age category, intervention, and time. The pre-intervention and intervention slope for blood Phe was not significantly different for either preadolescent or adolescent groups when compared to the adult group ($p=0.69$ and $p=0.73$, respectively, Fig. 4.3B).

We also assessed the effect of changing self-efficacy scores on the blood Phe slope during the intervention. Baseline self-efficacy was not significantly associated with blood Phe slope ($p=0.49$) pre-intervention and during the intervention. However, after including all self-efficacy scores during the intervention, self-efficacy was significantly associated with blood Phe slope during the intervention ($\beta=-64.5$, $p<0.001$). We were not able to assess the interaction term in this model, considering self-efficacy was only collected at three time points (baseline, month 3, and month 6). Self-efficacy was not kept in the main model because it restricted our ability to compare pre-intervention and intervention blood Phe slopes.

4.5 Discussion

This study contributes to our understanding of the relationship between motivational interviewing and behavior change in the context of chronic disease management and supports the link between SOC, self-efficacy, and health outcomes. Practitioners have identified the need for improved education and motivational strategies to promote self-management behaviors in PKU [2, 5, 62-64] with a goal of maintaining optimal metabolic control throughout life [61]. However, few studies have explored methods to increase patient motivation in a PKU population [65, 66]. This is the first study, to our knowledge, describing the use of MI with a PKU clinical population to

improve treatment adherence and metabolic control in participants with PKU.

Treatment adherence was assessed based on participant-reported medical formula and natural protein intake, as appropriate intake of these nutrients is the foundation of PKU dietary management [67]. Self-management skills related to dietary treatment are often lacking [29], as reported in Chapter 2 with only approximately half of adolescents and adults with PKU reportedly preparing and consuming medical formula every day (n=11/22) and tracking protein intake (n=12/22). Our results did not show a significant change in adherence to medical food intake during the MI intervention. However, the majority of participants were consuming 100% of their formula prescription. Timing of medical formula intake is also an important factor in blood Phe control and variation [68]. The majority of participants consumed formula in multiple servings daily, though we did not see a difference in pre-intervention Phe levels between those taking formula <3 and ≥ 3 times daily.

Adherence to natural protein prescription also did not increase during the intervention. We adjusted for protein tolerance in this model, and higher protein tolerance was associated with improved adherence to goals. The FFQ estimates of average protein intake have been shown to be less accurate than a 3-day food record (mean error rate of 7%) and do not correlate well with a singular blood Phe level [53]. The main purpose of using the FFQ vs. food records was to reduce barriers to collecting dietary information, and to illustrate total protein intake as well as the sources of dietary protein in order to facilitate discussion with the participant.

The primary outcome of interest in this study was change in blood Phe levels before and during a 6-month intervention. Participants' blood Phe levels were increasing

during the 6 months preceding enrollment for all age categories (Fig. 4.3). This could be partly due to increasing age and rapid increases in Phe have been noted in adolescents [50]. Changes in treatment or life stages may also contribute. In our sample, 2 participants were discontinuing rAvPAL-PEG, 1 participant was entering adolescence, 2 were entering adulthood, and 1 participant was returning to a pre-pregnancy dietary Phe tolerance prior to enrollment.

After accounting for baseline SOC and learning problems, the change in blood Phe levels was not significantly different during the intervention when compared to the pre-intervention slope ($p=0.13$, Fig. 4.3). It is possible that behavioral changes required to decrease blood Phe levels would require a longer follow-up period. In addition to the amount of effort and motivation required to initiate and maintain behavior change, achieving good metabolic control requires multiple behaviors. For example, if someone starts keeping food records but does not drink formula regularly, they are progressing but it may not make a substantial impact on blood Phe levels. There are also several factors that influence a blood Phe result unrelated to treatment adherence, including illness, growth, and diurnal variation [69-72].

Baseline SOC for Phe/protein and medical formula goals was significantly associated with change in blood Phe levels over time. Research in asthma and physical activity has demonstrated an increase in SOC with MI interventions [73, 74], which may then facilitate behavior change [75]. Our results are consistent with a previous report summarizing three randomized controlled trials showing an association between higher baseline SOC for fat intake and progression towards action over 12-24 months in adolescents and adults [76]. In a group of adolescents with PKU (n=16), successful

completion of a 4-month intervention was negatively associated with baseline Phe levels (r=0.49), which may be related to baseline SOC [65]. Evaluating SOC for behaviors contributing to metabolic control may be useful in a clinical setting to quickly determine readiness to change and to tailor recommendations accordingly.

While the three age groups had different mean Phe levels, the change in blood Phe slope pre-intervention and intervention was not significantly different between age categories (Fig. 4.3B). This suggests the intervention was not more effective in one age category. The majority of MI research has been conducted with adolescents and adults, and interventions involving children typically involve both parents and children [37]. MI's focus on supporting autonomy may be particularly effective in adolescents to help resolve ambivalence and increase self-efficacy [18, 77]. However, more research is needed to explore the effect of MI among different ages.

Previous studies have demonstrated an association between self-efficacy and behavior change across a multitude of domains, and MI may be a means to increase self-efficacy for target behaviors [35, 41-47, 78]. Our results indicate increasing self-efficacy for PKU management behaviors was significantly associated with a decrease in blood Phe levels. Self-efficacy is particularly important considering the multiple behaviors needed to achieve appropriate blood Phe levels. There is evidence suggesting participation in one self-management behavior increases the chance of participation in other behaviors, possibly due to achieving mastery in one area that translates elsewhere [79, 80]. Strategies aimed to increase mastery experiences, such as goal setting and action planning may be beneficial to increase self-efficacy and reduce blood Phe levels.

It is clear that elevated blood Phe levels contribute to cognitive and executive

function deficits in PKU [16, 81]. While we did not see an association with slope in blood Phe and learning problems after controlling for other factors, intellectual and executive deficits have been associated with decreased self-management behaviors in other chronic diseases [11, 82]. Due to the potential for these deficits, individuals with PKU may need additional help to adopt recommended self-management skills and achieve therapeutic blood Phe levels. Additionally, IEP eligibility is only a proxy for learning impairment and more thorough assessment of cognitive deficits may be warranted to further explore this relationship.

MI may be beneficial with a PKU population for several reasons. The treatment for PKU is complex, but regardless of the existing skillset, MI may be used to further develop motivation for chronic disease management. MI has been used effectively as the sole intervention to elicit intrinsic motivation to change and also as a method of engaging patients in other educational programs. It is an ideal tool to help patients prioritize in the face of competing obligations, as it allows practitioners to elicit values and topics of importance from the patient (e.g., potential ramifications of the diet on social life), which increases rapport and can lead to productive discussion. Lastly, consequences of elevated Phe levels accumulate over time and are not always apparent to the individual [5, 17]. MI can help address this by developing discrepancy between values and behaviors [30].

We propose MI is feasible for PKU patients followed by outpatient metabolic clinics despite potential barriers, such as time constraints and training processes. MI can be successfully delivered in a single session or in several shorter sessions [35]. Research has shown positive outcomes with brief MI interventions [83, 84], and brief MI has been implemented into some general practice visits, which are notably short encounters. Our

phone-based MI intervention was designed to be accessible for patients who do not live locally, a commonality among many metabolic centers [85, 86]. Several studies have demonstrated benefits of phone-based MI interventions to improve SOC and health behaviors [74, 84, 87, 88]. Additionally, while MI started with interventionists trained in psychology, the delivery of MI has expanded to a variety of healthcare providers, including physicians, dietitians, and nurses [37, 89]. Considering the primary treatment for PKU is nutrition therapy, in our study, a metabolic dietitian delivered the phone-based MI intervention.

The training process is a common barrier to implementation, considering the amount of training required to become proficient in MI [90, 91]. While acquiring MI skills takes time, training practitioner(s) within a metabolic clinic may be worth the investment considering its association with positive health outcomes. Additionally, there is some evidence that simply adopting the MI spirit (collaboration, evoking the patient's own motivation, and honoring autonomy) and reducing MI nonadherent behaviors (confronting, giving advice without permission, and giving orders or imperatives) have been associated with positive outcomes [78, 92]. This suggests practitioners can have a positive impact in a clinical setting by implementing MI principles.

Additional research is needed to evaluate the impact of MI to improve adherence and metabolic control in a PKU population. A multicentered trial evaluating the MI is warranted in order to enroll an adequate sample size for a controlled trial considering PKU is a rare disease. Longer intervention and follow-up are also recommended. It may take longer than 6 months to achieve a significant difference in blood Phe levels, and the sustainability of the intervention should be assessed.

4.5.1 Limitations

Several factors may have affected our ability to evaluate the efficacy of the MI intervention. Our sample size was small (n=31), which reduces the power to detect significant associations. However, PKU is a rare disease, and the original patient pool (n=183) comprised all known patients with PKU in Utah and a portion from surrounding states. Due to the rarity of PKU, participants acted as their own control in the before-and-after study design, which limited our ability to control for the effect of increased observation on treatment adherence. We collected two unannounced blood Phe samples to help address this and the potential for participants to alter dietary intake in the days prior to a blood sample, which were not significantly different from scheduled Phe samples.

There was potential for selection bias, considering we had a number of individuals lost to follow up (n=26) and declining participation (n=37). Nearly all of our participants were currently drinking medical formula, which may not be representative of most individuals with PKU, especially adults. Additionally, it was difficult to compare blood Phe levels between our sample and those declining participation, as approximately 40% of patients did not have Phe levels available for comparison. However, recruitment included mailing flyers to last known addresses and advertising on Facebook through a local PKU community to reach those who were not attending clinic regularly.

The questionnaires were altered or were not administered in the same manner as their original use. Our measures of SOC and self-efficacy were altered to reflect meaningful statements to individuals with PKU. We measured average protein intake over the last month with an FFQ that participants completed online. This tool was validated with an in-person administration with individuals ≥ 12 years of age [53].

Participants were contacted to clarify responses after FFQ completion, but we were unable to determine if FFQ online administration was as accurate as in-person administration. Lastly, the results of the FFQ were emailed to participants as a monthly summary (Fig. 4.1), though we were unable to assess if participants viewed the summary sheet and if it contributed to the effect of the intervention.

4.5.2 Conclusion

Phone-based motivational interviewing, delivered by a metabolic dietitian, with monthly goal setting is feasible for clinical use in patients with PKU. There was no significant change in dietary adherence or blood Phe slope during the intervention. Higher baseline SOC for Phe/protein and medical formula goals was significantly associated with lower blood Phe levels. Additionally, increasing self-efficacy scores were significantly associated with improved metabolic control. It is possible that a longer follow up period is needed to demonstrate change in blood Phe levels. However, it is encouraging to see inverse associations between SOC, self-efficacy, and metabolic control in PKU, as these intermediate outcomes may be targets of future behavioral interventions. Additional research is warranted to further evaluate MI in a larger sample size and a longer duration of follow-up to further explore the utility of MI in this population.

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CHAPTER 5

CONCLUSION

Phenylketonuria (PKU) requires lifelong treatment with strict dietary control of phenylalanine (Phe) or protein intake with supplemental medical formula to avoid sequelae of inadequately treated PKU, including subtle intelligence and executive functioning deficits, slowed processing speed, psychological and behavioral problems, and poor nutrient intake [1-6]. Unfortunately, PKU patient adherence to treatment goals begins to decrease after early childhood with subsequently elevated blood Phe levels [7-9]. Concomitantly, self-management skills are often not transitioned from parent to child at an early age, resulting in a suboptimal skillset in adolescents and adults [10]. Compared to the plethora of research demonstrating the link between elevated blood Phe levels and brain dysfunction [3-5, 11-18], relatively few studies have assessed strategies to support development of self-management skills to enable treatment adherence in PKU populations [19-22]. This body of research indicated that:

1. Self-management skills and treatment knowledge in patients with PKU aged 7-30 years were generally less than clinically recommended and did not consistently increase with age. Additionally, in our small sample, report of using more self-management skills and accurate treatment knowledge were not significantly associated with lower mean Phe levels.

2. Adolescent and adult participants of a 6-month intervention with phone-based motivational interviewing (MI) and goal setting demonstrated a significant increase in self-efficacy for PKU self-management skills. Presence of learning problems was not associated with lower self-efficacy.
3. Higher self-efficacy and baseline readiness to change were associated with lower blood Phe levels during the phone-based MI intervention. Our results suggest MI is feasible with a PKU population.

There are many barriers to developing self-management skills and adhering to recommended therapies in individuals with PKU and other chronic conditions. Treatment nonadherence in PKU may reflect lack of immediate symptoms reducing motivation to adhere to daily therapies [12], increasing manifestation of cognitive and psychological impairments that develop over time [12], an artifact of current developmental phase (e.g., adolescence) [23], poor transition of self-management responsibilities, and/or decreasing motivation for self-care in the face of competing obligations. Additionally, current health systems may not adequately support patient adherence to recommended therapies.

Routine measures to support development of self-management skills are needed for patients with PKU. In our clinic, the self-management questionnaires acted as a checklist for anticipatory guidance. Review of the questionnaires allowed providers to easily evaluate current skills and knowledge and facilitate discussion with families on the primary topics of self-management in an outpatient clinical setting. MI techniques also have the potential to increase motivation to initiate and/or maintain behavior change to prevent negative health outcomes in PKU and other chronic conditions.

Strategies to support self-management should be age specific. Upon completion

of the MI intervention, it was apparent modified questionnaires and techniques were needed in the preadolescent age group compared to older participants. Considering the degree of parental assistance at this age, interventions targeting both the patient and parent are recommended. Developing self-management skills remains critical in this age group, as ability to assume responsibility for self-care increases, and it provides opportunity to instill self-management skills before facing increased independence over food choices during adolescence and adulthood.

Our results suggested MI would be a viable option for individuals with PKU with or without learning problems. Fundamental features of PKU include subtle intellectual deficits with more pronounced executive function deficits [13], which have been proposed to be a substantial barrier to following the dietary regimen [24]. MI has been used in other populations with cognitive/executive functioning issues [25-27] and methods to adapt MI for those with mild intellectual disability have recently been explored [28]. Additionally, combining goal setting/action planning with MI may help patients with executive deficits problem solve and carry out a behavior once they are motivated to take action. Collecting a robust cognitive and executive evaluation at baseline would provide a means to evaluate MI at varying levels of cognitive impairment. Further evaluation would be required for use of MI with individuals with PKU and intellectual disability, an exclusion criterion for the current studies.

The use of MI with individuals with PKU deserves further exploration. The studies described here are merely an introductory evaluation of MI in a PKU population. Therefore, the opportunities for research assessing MI and other strategies to support self-management in this field are expansive. The results of the current studies should be

reevaluated with a randomized study design and larger sample size, which would have alleviated many of the limitations of the current studies. Extending the duration of the intervention and/or follow-up is also recommended to see if change in Phe levels requires more time to occur and if the effects of the intervention are maintained. The studies presented here also highlight a need for validated tools to assess self-management, SOC, or self-efficacy in a PKU population.

We recommend evaluating MI in subgroups of patients with PKU and other inborn errors of metabolism. In preadolescents, an MI intervention could be used with both parents and children to increase engagement in self-management programs. At this age, learning impairment may not yet be apparent [12], which may reduce motivation for both parents and children to maintain adherence to the strict diet. Additionally, the patient-centered focus of MI may appeal to older patients who are returning to clinic and/or to help prevent loss to follow up, which is a substantial issue in the adult PKU population [29]. Lastly, exploration of MI and other strategies to support self-management in a PKU population could be applied to other inborn errors of metabolism, many of which share treatment principles and are also treated at metabolic centers.

This body of research explored methods to prevent negative consequences of inadequate self-management and treatment adherence. Public health aims to prevent disease and promote health for the population. PKU is an exemplar of the difficulties associated with improving self-management and treatment adherence in populations affected with a lifelong, genetic disease. We cannot readily prevent the occurrence of PKU, as it is a genetic condition; however, early identification and treatment through newborn screening, one of the most effective public health programs, prevents profound

intellectual disability. Additionally, there is potential to prevent or reduce the negative outcomes associated with inadequately treated PKU. While we studied a rare disease, the results offer implications for the health care system caring for this population and other inborn errors of metabolism.

The results of this dissertation suggest MI is a feasible, potentially beneficial counseling style to use with individuals with PKU. Participants' self-management skills were less than clinically recommended and did not consistently increase with age. MI with goal setting and a monthly summary was associated with increased self-efficacy regarding PKU management, and increased self-efficacy was associated with an improvement in metabolic control. While the executive deficits and behavioral aspects of PKU add another layer of complexity to treatment adherence, methods to support self-management and increase motivation for behavior change are still necessary. Motivational interviewing has potential to increase motivation and confidence to engage in self-management behaviors in a PKU population.

5.1 References

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APPENDIX A

COMPOSITION AND CODING FOR SELF-MANAGEMENT SKILLS AND TREATMENT KNOWLEDGE SCALES

BEHAVIOR SCALE – POTENTIAL SCORE 0-2					
10-12 Years		**13-17 Years**		**18-30 Years**	
Do you help prepare your formula or even prepare it by yourself?		**Do you prepare your own formula?**		**Do you prepare and drink your formula regularly?**	
-I weigh/mix my formula myself every day (7 days per week).	**1**	-I weigh/mix my formula myself every day (7 days per week).	**1**	-I prepare and drink my formula every day (7 days per week).	**1**
-I weigh/mix my formula myself most days (4-6 days per week).	**1**	-I weigh/mix my formula myself most days (4-6 days per week).	**1**	-I prepare and drink my formula most days (4-6 days per week).	**0.75**
-I weigh/mix my formula myself sometimes (≤ 3 days per week).	**0.75**	-I weigh/mix my formula sometimes (≤ 3 days per week).	**0.5**	-I prepare and drink my formula sometimes (≤ 3 days per week).	**0.5**
-I help my parents weigh/mix my formula.	**0.5**	-My parents weigh/mix my formula every day.	**0.25**	-No, I do not prepare my formula but I drink it.	**0.25**
-My parents weigh/mix my formula every day.	**0.25**	-No, I do not drink formula.	**0**	-No, I do not drink formula.	**0**
-No, I do not drink formula.	**0**				
Have you tried pricking your own finger to get a blood sample?		**Do you collect your own finger stick blood samples at home?**		**Do you collect your own finger stick blood samples at home?**	
-Yes, I am an expert!	**1**	-Yes, I always collect my finger stick sample myself.	**1**	-Yes, I collect them at least monthly (12+ times per year).	**1**
-Yes, I have tried it 1-2 times.	**1**	-Yes, I sometimes collect my finger stick sample myself.	**0.75**	-Yes, I collect them at least every other month (6-11 times per year).	**0.75**
-No, I have never tried it.	**0**	-Yes, but I still need some help from my parents.	**0.5**	-Yes, I collect them every once in a while (≤5 times per year).	**0.25**
		-No, but I know how to collect a finger stick sample.	**0.25**	-No, but I know how to collect a finger stick sample.	**0.5**
		-No, I have never tried it.	**0**	-I don't collect finger stick samples.	**0.25**
		-I don't collect finger stick samples.	**0**		**0**

KNOWLEDGE SCALE – POTENTIAL SCORE 0-3					
7-12 Years		**13-17 Years**		**18-30 Years**	
What is your formula prescription?		**What is your formula prescription?**		**What is your formula prescription?**	
-Correct	**1**	-Correct	**1**	-Correct	**1**
-Within 25% of prescription	**0.5**	-Within 25% of prescription	**0.5**	-Within 25% of prescription	**0.5**
-Incorrect/Don't know	**0**	-Incorrect/Don't know	**0**	-Incorrect/Don't know	**0**
What is your daily PHE/protein prescription?		**What is your daily PHE/protein prescription?**		**What is your daily PHE/protein prescription?**	
-Correct	**1**	-Correct	**1**	-Correct	**1**
-Within 25% of prescription	**0.5**	-Within 25% of prescription	**0.5**	-Within 25% of prescription	**0.5**
-Incorrect/Don't know	**0**	-Incorrect/Don't know	**0**	-Incorrect/Don't know	**0**
What is your goal range for blood PHE levels?		**What is the recommended blood PHE range for you?**		**What is the recommended blood PHE range for you?**	
-Correct	**1**	-Correct	**1**	-Correct	**1**
-Don't know	**0**	-Don't know	**0**	-Don't know	**0**

APPENDIX B

STAGE OF CHANGE QUESTIONNAIRE

We would like to know what you think is most important to help you meet your personal health goals. Please choose the items that are most important to you at this time. Keep in mind that it does not have to be something you are currently doing.

Phe/Protein Goals

What do you think is the single most important thing you could do to meet your PHE/PROTEIN GOALS? Please select one.

- Count how much Phe/protein I eat
- Keep diet records
- Plan meals beforehand
- Watch my portion sizes
- Prepare meals at home
- Other (please specify)

Are you making this change now?

- Yes
- No

Please mark the following statement that best applies to you.

- No, and I do not plan to make this change.
- No, but I plan to make this change in the next 6 months.
- No, but I plan to make this change in the next 30 days.
- Yes, I have been making this change for LESS than 6 months.
- Yes, I have been making this change for MORE than 6 months.

Formula Goals

What do you think is the single most important thing you could do to meet your FORMULA GOALS? Please select one.

- Drink all formula every day
- Drink formula several times per day
- Make my own formula
- Bring my formula to school/work
- Try a different formula or try to improve the taste of my current formula
- Other (please specify)

Are you making this change now?

- Yes
- No

Please mark the following statement that best applies to you.

- No, and I do not plan to make this change.
- No, but I plan to make this change in the next 6 months.
- No, but I plan to make this change in the next 30 days.
- Yes, I have been making this change for LESS than 6 months.
- Yes, I have been making this change for MORE than 6 months.

Healthy Choices

What do you think is the single most important thing you could do to MAKE HEALTHY FOOD CHOICES? Please select one.

- Eat more fruits/vegetables
- Drink fewer sweetened drinks (soda, juice)
- Eat out less often (restaurants, fast food)
- Eat fewer "junk foods" (chips, cookies, candy)
- Cook meals at home more often
- Other (please specify)

Are you making this change now?

- Yes
- No

Please mark the following statement that best applies to you.

- No, and I do not plan to make this change.
- No, but I plan to make this change in the next 6 months.
- No, but I plan to make this change in the next 30 days.
- Yes, I have been making this change for LESS than 6 months.

Yes, I have been making this change for MORE than 6 months.

APPENDIX C

COMPARISON OF ORIGINAL SELF-EFFICACY SCALE TO REVISED COPY USED IN THE CURRENT STUDY

We would like to know how confident you are in doing certain activities. For each of the following questions, please choose the number that shows how confident you are that you can do these tasks regularly at this point in time where 1 = not confident at all and 10 = totally confident.

Original Scale	Revised Scale
1. How confident do you feel that you can eat your meals every 4 to 5 hours every day, including breakfast every day?	1. How confident do you feel that you can do all the things necessary to manage your condition on a regular basis?
2. How confident do you feel that you can follow your diet when you have to prepare or share food with other people who do not have diabetes?	2. How confident do you feel that you can follow your diet when you have to prepare or share food with other people who do not have PKU?
3. How confident do you feel that you can choose the appropriate foods to eat when you are hungry (for example, snacks)?	3. How confident do you feel that you can choose the appropriate foods to eat when you are hungry (for example, snacks)?
4. How confident do you feel that you can exercise 15 to 30 minutes, 4 to 5 times a week?	4. How confident do you feel that you can poke your finger to collect a blood sample every month at a minimum?
5. How confident do you feel that you can do something to prevent your blood sugar level from dropping when you exercise?	5. How confident do you feel that you can do something to prevent your blood phenylalanine levels from increasing?
6. How confident do you feel that you know what to do when your blood sugar level goes higher or lower than it should be?	6. How confident do you feel that you know what to do when you blood phenylalanine level goes lower or higher than it should be?
7. How confident do you feel that you can judge when the changes in your illness mean you should visit the doctor?	7. How confident do you feel that you can judge when changes in your illness mean you should visit the doctor?
8. How confident do you feel that you can control your diabetes so that it does not interfere with the things you want to do?	8. How confident do you feel that you can control your PKU so that it does not interfere with the things you want to do?

APPENDIX D

MONTHLY SUMMARY

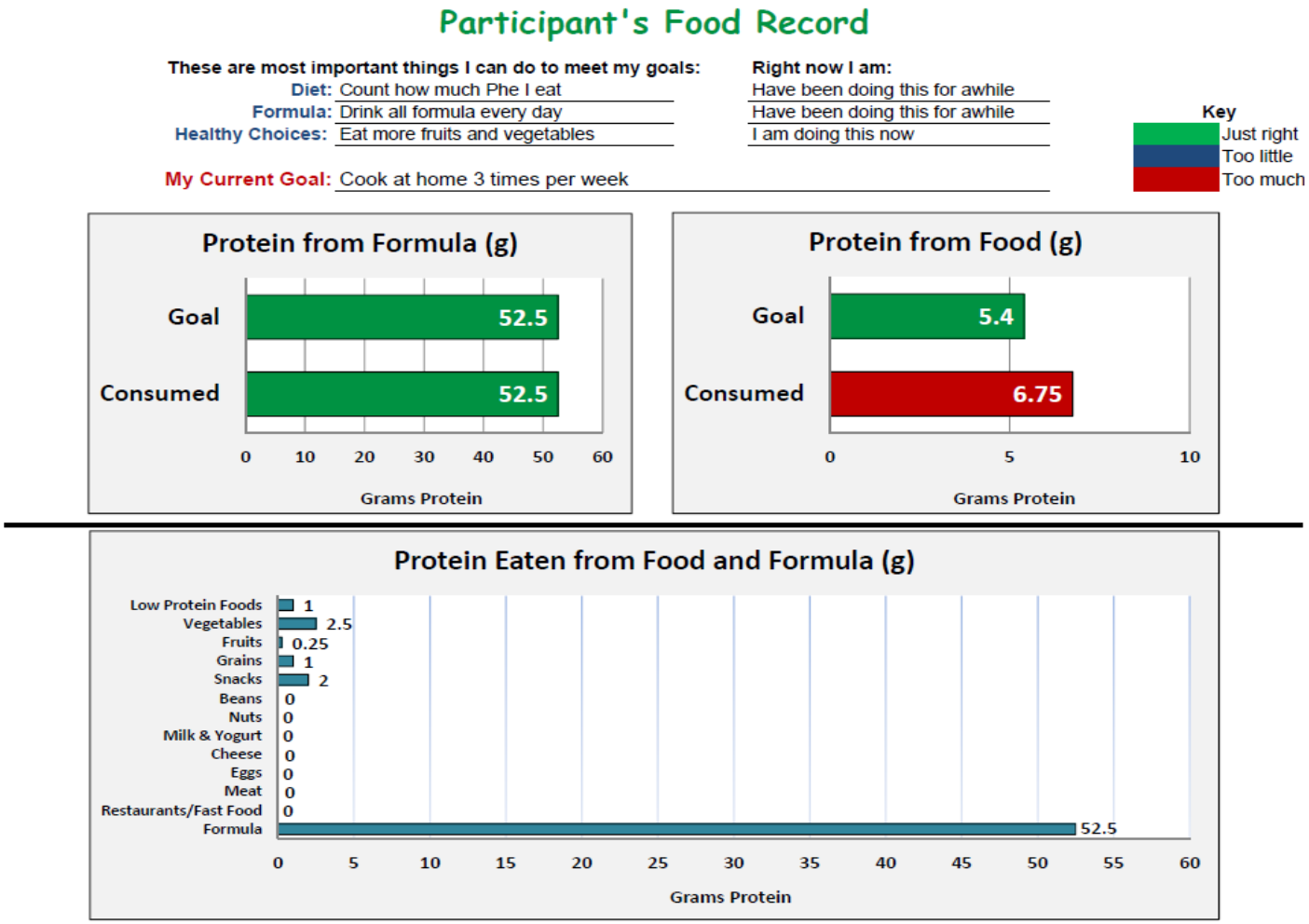

Figure D.1. Summary Sheet Emailed to Each Participant Monthly Prior to the Phone-Based MI Intervention. Information includes current stage of change for selected behaviors, monthly goal, prescribed protein and protein consumed over the last month based on results of the FFQ.