

# **Nutritional Management of Aminoacidopathies in Saudi Arabia**

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A thesis submitted for the degree of Doctor of Philosophy

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## Declaration

I, Sadeem Abdulaziz Aljammaz, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

S. Aljammaz.



## Abstract

**Background:** Metabolic disorders are common in Saudi Arabia. Adherence to a special diet is essential to prevent developmental disability in phenylketonuria (PKU). Our aim was to identify the risk factors for non-compliance with treatment of aminoacidopathies and poor outcome in PKU patients at King Faisal Specialist Hospital & Research Centre in Saudi Arabia.

**Methods:** A qualitative study assessed nutritional knowledge, attitudes and practices through interviews (n=5) and focus groups (2) with health care providers, and interviews with patients with aminoacidopathies (6) and families (17). A quantitative study assessed 40 PKU patients by anthropometric measurements, dietary records, phenylalanine blood levels, developmental assessments, and questionnaires with the patients and their mothers. The Vineland-II Adaptive Behaviour Scales were translated into Arabic and adapted to the Saudi culture to be used as the assessment tool to measure outcome. Regression analysis and independent t-tests were used to investigate relations.

### Results:

**Qualitative findings: Major themes identified:** Lack of sufficient services, inadequate dietary knowledge, limited resources for families and dietitians, social and emotional attitudes towards diet, and compliance by the child and mother.

### Quantitative results:

#### *1- Factors contributing to low Vineland-II Adaptive Behaviour Composite score*

**(ABCs): a. Delayed diagnosis:** Mean ABCs ( $\pm 1SD$ ) according to age at start of treatment (Significant difference  $p < 0.0001$ ):

- Diagnosed  $\leq 1$  month: 92.2 ( $\pm 11$ )
- Diagnosed  $> 1$  month: 60.5 ( $\pm 20.6$ )

**b. Disease severity:** There was a significant difference ( $p = 0.008$ ) in the ABCs between patients with Mild PKU (diagnosis phenylalanine 600-1200  $\mu\text{mol/l}$ ) and Classic PKU (diagnosis phenylalanine  $> 1200 \mu\text{mol/l}$ ).

**2- Factors leading to inadequate blood phenylalanine control:** Delayed diagnosis, poor compliance with dietary phenylalanine restriction, and inadequate intake of the prescribed supplement.

**Conclusion:** Newborn screening for PKU has been very successful in improving outcome but this could be further enhanced by targeted improvements in the education and support of families and in the metabolic care services.



## **Dedication**

My cherished Sara...

The infinite sweetness, love, and bliss you bring into my life are my fuel and inspiration. Your absolute support and belief in me that I can help my “other children” is a constant reminder that we should strive to help vulnerable children in any way we can to be well and a source of sparkle and joy to their families.

I believe you have endured the most through this journey of knowledge. You have explored and learnt with me, cooked and prayed for me. I thank you.

This is for you with untellable gratitude and affection.

Love always,

Mama



## Acknowledgements

I am eternally thankful to God for blessing me with the strength and perseverance to achieve this work.

This thesis was possible through the participation of the children, their mothers, and their families. The mothers have demanding lives; they often care for more than one child with PKU, MSUD, or tyrosinaemia. Nonetheless, they were willing to give me hours of their precious time, share their thoughts and hopes, and welcome me into their homes. I am immensely grateful to their patience and generosity.

My utmost gratitude, appreciation, and respect go to my supervisors; Professor Peter Clayton, thank you for your continued guidance, wisdom, and humility; Professor Therese Hesketh, thank you for your constant encouragement, support, and humour. I am forever indebted.

I am grateful to King Saud University, embodied in the College of Applied Medical Sciences, for providing me with a scholarship to pursue this research. I appreciate KFSH&RC for allowing me to carry out the study at their institution. I thank the Department of Medical Genetics at KFSH&RC, especially Dr Zuhair Al-Hassnan, Dr Zuhair Rahbeeni, Dr Muhammed Al-Owain, and Dr Moeenaldeen Al-Sayed for participating in the interviews and for welcoming me into their clinics. I thank the nurses of the metabolic team and the dietitians for their participation in the focus groups. I sincerely appreciate Mr Mohammed Alamoudi for providing the blood results of the patients, and Miss Lina Moncari for her time in providing the developmental assessments available for the patients at KFSH&RC.

I would like to especially acknowledge the great welcome and support I received from the metabolic dietitians at KFSH&RC, Mrs Suhad Almuaigl and Mrs Eman Megdad. They helped in every way possible; they gave me space in their clinic, identified eligible patients, introduced me to the mothers, and retrieved any needed information. I highly appreciate their indescribable kindness and generosity.

My gratitude goes to everyone who participated in the immense task of translating and back translating the different questionnaires and interviews for the study, and the Vineland-II project. I am also grateful to everyone who was involved in testing and piloting the different questionnaires of this study and the adapted Vineland-II.

My appreciation goes to the many individuals who provided assistance in different ways throughout the study; including Dr. Aisha Yousafzai for her help as a second supervisor at the

inception of the study, Mrs Latha Kadalayil for her statistical advice, Dr Peter Foster for supplying the Saudi anthropometric z-scores, and Mrs Alkhansa Alreshood for her assistance in data entry and her skills in entertaining the children during data collection. My gratitude also goes to Dr Kathryn Bond for training me on the administration of the Vineland and the verification of scoring.

I would like to thank my family and friends for their support throughout this journey, for which I will be forever grateful. My parents' unwavering belief in me empowers me. I was fortunate to have my father's unconditional support, and my mother's many abilities at hand along the way, she translated, edited, entertained, and babysat. I am profoundly indebted to them.

I am grateful to my uncles Ahmad and Zeyad Alhokail for their constant assistance. I sincerely appreciate my husband Kalid for allowing me the freedom to realize my ambitions and for his continuous support. I am deeply grateful to my one and only sister, Sofana, the sweetest person ever, who was always available to assist and listen. I thank my brother Salman for always gracing us with his visits and delicious cooking. I thank Ibrahim, Muhammad, and Dana for their continued warmth and caring, and the little ones; Sulaiman, Dlayil, Abdulaziz M, Abdulaziz I, and Abdullah for adding joy to life.

The priceless presence of my close friends; Arwa, Hana, and Rasha, in my world makes it a happier place. Their untiring support humbles me. I also got the pleasure of making new and wonderful friends during the course of this research; I appreciate Alhanouf, Aseel, Asma, Elham, Hadeel, Hessa, and Mai for the many cups of teas we shared.

Last, but by no means least, I am particularly obliged to my dear remarkable brother Omar. His technical savviness and magnificent editing skills came to rescue many a time, no task was ever difficult. You are brilliant!! I ceaselessly thank you...

# Table of Contents

<b>Declaration .....</b>	<b>3</b>
<b>Abstract.....</b>	<b>5</b>
<b>Dedication.....</b>	<b>7</b>
<b>Acknowledgements .....</b>	<b>9</b>
<b>Table of Contents.....</b>	<b>11</b>
<b>List of Tables.....</b>	<b>14</b>
<b>List of Figures .....</b>	<b>16</b>
<b>List of Boxes .....</b>	<b>17</b>
<b>Abbreviations .....</b>	<b>18</b>
<b>Glossary of terms .....</b>	<b>19</b>
<b>1. Introduction.....</b>	<b>21</b>
1.1 Overall aims of the study .....	23
1.2 Research question .....	23
1.3 Research objectives.....	23
1.4 Study design summary .....	24
1.5 Anticipated outcomes.....	25
1.6 Thesis overview .....	26
<b>2. Literature Review .....</b>	<b>29</b>
2.1 Overview of inborn errors of metabolism (IEM).....	30
2.2 Newborn screening for IEM .....	31
2.3 Inborn errors of metabolism and newborn screening in the Middle East ....	35
2.4 Consanguinity in the Middle East.....	40
2.5 Inborn errors of metabolism and newborn screening in Saudi Arabia .....	42
2.6 Nutritional management of IEM.....	52
2.7 The focus of this research .....	57
<b>3. Methods.....</b>	<b>81</b>
3.1 Study site.....	82
3.2 Subjects .....	82
3.3 Ethical considerations .....	83
3.4 Study design.....	83

<b>4. Adaptation of the Vineland-II Scales to Arabic.....</b>	<b>109</b>
4.1 The Vineland Adaptive Behaviour Scales, second edition (Vineland-II)..	110
4.2 Use of the Vineland-II in this study.....	116
4.3 Background information about the Vineland.....	118
4.4 Issues with the Vineland .....	123
4.5 The translation and adaptation of the Vineland-II to the Arabic language and the Saudi Arabian culture.....	126
4.6 The Arabic Vineland-II in the current study.....	133
<b>5. Findings (Phase 1) .....</b>	<b>139</b>
5.1 Services .....	143
5.2 Knowledge .....	151
5.3 Dietary practices and compliance .....	157
5.4 Social issues .....	162
5.5 Needs.....	165
5.6 Newborn screening .....	168
<b>6. Discussion (Phase 1) .....</b>	<b>171</b>
6.1 Services .....	172
6.2 Knowledge .....	174
6.3 Diet.....	176
6.4 Social issues .....	178
6.5 Needs.....	180
6.6 Newborn screening .....	181
<b>7. Results (Phase 2).....</b>	<b>183</b>
7.1 Research group.....	184
7.2 Family Questionnaire.....	185
7.3 Child Questionnaire .....	199
7.4 Assessments and measurements .....	202
<b>8. Discussion (Phase 2) .....</b>	<b>221</b>
8.1 Research group.....	222
8.2 Family Questionnaire.....	222
8.3 Child Questionnaire .....	231
8.4 Assessments and measurements .....	232

<b>9. Conclusions.....</b>	<b>241</b>
9.1 The main risk factors for non-compliance identified from this research...	242
9.2 Key recommendations to overcome the risk factors.....	242
9.3 Products of this study.....	245
9.4 Plans and suggestions for future work.....	246
9.5 Strengths and Limitations .....	247
<b>References.....</b>	<b>251</b>
<b>Appendices.....</b>	<b>291</b>
Appendix 1: Information sheet and consent form.....	292
Appendix 2: Health care providers interview & focus group questions (Phase 1)	296
Appendix 3: Family and child interview questions (Phase 1) .....	303
Appendix 4: Family interview sample (Phase 1).....	307
Appendix 5: List of obtained data (Phase 2).....	314
Appendix 6: Anthropometric data & medical records information (Phase 2) .....	315
Appendix 7: Family Questionnaire (Phase 2).....	318
Appendix 8: Sibling Questionnaire (Phase 2).....	331
Appendix 9: Second 24hr food recall (Phase 2) .....	334
Appendix 10: Child Questionnaire (Phase 2) .....	335
Appendix 11: The items adapted for the Arabic Vineland-II, the adaptations and adjustments, and the reasons for the adaptations .....	337

## List of Tables

Table 1: The acceptable blood Phe levels at KFSH&RC by age group. ....	101
Table 2: The acceptable blood Phe levels in different countries by age group. ....	101
Table 3: A sample of the items adapted for the Arabic Vineland-II, the adaptations and adjustments, and the reasons for the adaptations. ....	131
Table 4: Compliance barriers identified by the health care providers and the families .....	161
Table 5: Knowledge needs as perceived by the families and the health care providers .....	165
Table 6: Age, education level, and occupation of the participating parents (N=24). ....	186
Table 7: Number of children born to mothers and birth order of child with PKU. ...	186
Table 8: Descriptive statistics for number of children born to the mothers, number of children with PKU in the families, and household inhabitants (N=24). ....	187
Table 9: Adherence to formula intake and the causes of difficulty in drinking the formula. ....	188
Table 10: Difficulty of adhering to the PKU diet; opinions of the mothers (N=24), and the barriers to adhering to the PKU diet as recognized by the mothers (N=24). ....	189
Table 11: School attendance, perceived need for special education, and provided special education. ....	189
Table 12: Types of schools the patients attend. ....	190
Table 13: Frequency of going out as a family (N=24) with the child/children with PKU, places that families go to, and the limitations or difficulties that they face when going out due to the child's condition. ....	190
Table 14: Frequency of healthcare visits to KFSH&RC, visits to other facilities, and blood Phe testing, and mothers' perceptions of their children's health. ....	192
Table 15: Mothers' knowledge about some food choices for their children. ....	193
Table 16: Mothers' perceptions of what the dietitian may recommend if blood Phe level was high. ....	193
Table 17: Mothers' knowledge of the risks of prolonged high blood Phe level. ....	194
Table 18: Mothers' beliefs of the length of time needed to follow the PKU diet. ....	194
Table 19: Mothers' preferred ways of information provision and the information source for families regarding PKU. ....	196
Table 20: Wellbeing and support for the mothers, their answers to some quality of life questions. ....	197
Table 21: Understanding of PKU by family and friends. ....	197
Table 22: Food choices for some of the children with PKU (N=12). ....	200
Table 23: The children's understandings of the importance of adhering to PKU diet and formula intake. ....	200

Table 24: The children’s answers to questions regarding going out and diet (N=12). .....	201
Table 25: General descriptive statistics for the variables used in the analyses (N=39). .....	202
Table 26: Mean, standard deviation (SD), and confidence interval (CI) of ABC scores by gender.....	203
Table 27: The acceptable blood Phe level at KFSH&RC by age group.....	204
Table 28: Mean blood Phe level and dietary Phe intake of the patients (N=39). .....	204
Table 29: Pearson product-moment correlation coefficients (r) for formula intake with correlating variables.....	205
Table 30: Pearson product-moment correlation coefficients (r) for mean phenylalanine blood level with different variables. ....	207
Table 31: Multiple regression of mean phenylalanine blood level with correlating variables. ....	209
Table 32: Adaptive Behaviour Composite (ABC) scores for the patients.....	210
Table 33: Pearson product-moment correlation coefficients (r) for ABC scores with different variables. ....	212
Table 34: Multiple regression for the Vineland-II ABC scores with different variables for all the patients (N=38).....	212
Table 35: Linear regression of the Vineland-II ABC scores with age at start of treatment for the patients treated at different age cut-offs. ....	215
Table 36: Univariable linear regression and multiple regression of the Vineland-II ABC scores for the patients treated at $\leq 3.6$ years. ....	216
Table 37: The Vineland-II ABC scores (Mean and SD) according to the age at start of treatment. ....	216
Table 38: PKU categories. ....	217
Table 39: Multiple regression of the Vineland-II ABC scores for the patients diagnosed with Phe blood level $>1200\mu\text{mol/l}$ . ....	217
Table 40: Price comparison between some low protein products and regular products. .....	224
Table 41: Frequency of blood Phe level monitoring in the west. ....	228

## List of Figures

Figure 1: Saudi Arabia. Adapted from (Worldofmaps.net, 2012). .....	27
Figure 2: Flow chart illustrating the different components of Phase 1, methods used, and number of participants in each part. ....	91
Figure 3: The process of the qualitative data analysis as followed in this research. ...	94
Figure 4: Flow chart illustrating the different components of Phase 2, methods used, and number of participants in each part. ....	105
Figure 5: Phase 1 findings organized in themes and sub-themes (derived from 28 interviews and 2 focus groups). ....	142
Figure 6: Mean blood Phe level and age of start of treatment of the patients according to their formula intake (N=39). ....	205
Figure 7: Mean blood Phe level, shown as within or above target range for age, and dietary Phe intake of the patients (N=39). ....	206
Figure 8: Correlation between mean blood Phe level and age at start of treatment for the patients (N=39). ....	207
Figure 9: Correlation between mean blood Phe level and dietary Phe intake for the patients (N=39). ....	208
Figure 10: Correlation between mean blood Phe level and diagnosis Phe for the patients (N=33). ....	208
Figure 11: Mean blood Phe level and dietary Phe intake for early treated patients (N=10). ....	210
Figure 12: The number of patients in each category of the Vineland-II. ....	211
Figure 13: Vineland-II ABC scores for all the patients with their ages at start of treatment (N=38). ....	214
Figure 14: Vineland-II ABC scores for the patients with age of start of treatment ranging from birth until 7 years (N=36) ( $\leq 7$ years was chosen because it removed the two most extreme cases). ....	214
Figure 15: Vineland-II ABC scores for the patients with age at start of treatment ranging from birth until 3.6 years (N=28). ....	215

## List of Boxes

Box 1: Description of the content of the Vineland-II subdomains (Sparrow et al., 2005). .....	113
Box 2: This example illustrates the notable adaptive behaviours in each subdomain of the Vineland-II for a 20 year old patient with a Low adaptive level. ....	114
Box 3: This example illustrates the notable adaptive behaviours in each subdomain of the Vineland-II for a 19 year old patient with a Moderately Low adaptive level.....	115
Box 4: Topics the families are interested to learn more about. ....	195
Box 5: Concerns of the mothers for their children regarding PKU. ....	197
Box 6: Suggestions of and requests by the mothers to improve the healthcare services at KFSH&RC. ....	198

## Abbreviations

<b>ABC scores</b>	Adaptive Behaviour Composite scores
<b>CI</b>	Confidence interval
<b>GMP</b>	Glycomacropeptide
<b>GOSH</b>	Great Ormond Street Hospital
<b>HCP</b>	Health care provider
<b>ICH</b>	Institute of Child Health
<b>IEM</b>	Inborn errors of metabolism
<b>IQ</b>	Intelligence quotient
<b>KFSH&amp;RC</b>	King Faisal Specialist Hospital & Research Centre
<b>LNAA</b>	Large neutral amino acids
<b>MS/MS</b>	Tandem Mass Spectrometry
<b>MSUD</b>	Maple syrup urine disease
<b>N</b>	Number
<b>NBS</b>	Newborn screening
<b>NLNBS</b>	National Laboratory for Newborn Screening
<b>PAH</b>	Phenylalanine hydroxylase
<b>Phe</b>	Phenylalanine
<b>PKU</b>	Phenylketonuria
<b>SA</b>	Sadeem Aljammaz (Principal Investigator)
<b>SD</b>	Standard deviation
<b>SR</b>	Saudi Riyals
<b>WC</b>	Waist circumference
<b>6R-BH4</b>	Tetrahydrobiopterin

## Glossary of terms

**Aminoacidopathies:** Inborn errors of amino acid metabolism result in the build up of one or more amino acids in the blood and urine.

**Finger prick:** A procedure in which a finger is pricked with a lancet to obtain a small quantity of capillary blood for testing.

**Formula:** KFSH&RC use the Ross Metabolic Formula System products, Phenex-I for infants and toddlers and recently started Phenex-II for adults and children above 4 years of age. These are phenylalanine free amino-acid mixtures in powder form. The families are trained to measure the prescribed amount of the powder and reconstitute it with water.

**Free foods:** Foods so low in phenylalanine that they can be permitted without measurement, such as honey, jam, sugars, oils, vinegars, spices, apple juice, some types of candies and sweets, and some fruits and vegetables that contain less than 20–25 mg of phenylalanine in 100g.



# CHAPTER 1

## **INTRODUCTION**

Inborn errors of metabolism have not been a high priority in the health care system in Saudi Arabia in the past, even though collectively they are a significant public health problem in the country (Saadallah & Rashed, 2007). A newborn screening programme has recently begun in Saudi Arabia, it is gradually growing to cover all parts of the country (Al-Odaib et al., 2011). Many children receiving treatment currently were diagnosed in infancy through testing shortly after birth because of an affected sibling. Unfortunately many others were diagnosed late, after their illness had progressed to permanent neurological impairment (Ozand, 1998). Delayed diagnosis, the relatively short safety window of most of the metabolic disorders, combined with the tremendous lack of public awareness both play a part in delayed referrals to appropriate services, and lead to neurological damage in affected infants (Afifi & Abdul-Jabbar, 2007; Al-Gazali, Hamamy, & Al-Arrayad, 2006; and Nasserullah et al., 2003).

Nutritional management - the use of a diet with a reduced content of a specific amino acid or amino acids is the mainstay of treatment for phenylketonuria (PKU) and maple syrup urine disease (MSUD) and it is an important adjunct to drug treatment of tyrosinaemia type 1. However, research concerning nutrition for metabolic disorders in Saudi Arabia is scarce. Basic research to help classify the services, current care practices, nutritional management, and needs of the patients with metabolic disorders and their health care providers is essential, especially with the start of the newborn screening programme. This research will hopefully be a start to assessing these practices and services for patients with aminoacidopathies and their families, and identifying the risk factors associated with unsatisfactory dietary compliance for patients with PKU. This research was carried out with the aim of informing targeted interventions for the benefit of the patients.

## **1.1 Overall aims of the study**

- To describe the current nutritional management of patients with aminoacidopathies in Saudi Arabia.
- To identify the risk factors that lead the patients and their families to have inadequate control over the disorder.
- To use the results of this research to inform appropriate intervention strategies and services for the patients and their families to help them improve compliance.

## **1.2 Research question**

What are the risk factors associated with unsatisfactory nutritional management in a proportion of patients with aminoacidopathies in Saudi Arabia?

## **1.3 Research objectives**

1. To assess the nutrition awareness of the patients with aminoacidopathies (phenylketonuria (PKU), maple syrup urine disease (MSUD), and tyrosinaemia type 1) and their families.
2. To explore the attitudes and practices of the patients and their families with regard to the nutritional management of their disorders.
3. To assess whether current services address the expressed and perceived needs of the patients and their families.
4. To identify the risk factors and the barriers associated with noncompliance with the dietary requirements leading to inadequate metabolic control and high risk of poor outcome for patients with PKU.

## 1.4 Study design summary

This research was a cross-sectional study of a group of patients with aminoacidopathies in Saudi Arabia. It was a 2-phase study design with a mixed method approach; using the sequential exploratory strategy as recommended by Creswell (2009) and Morgan (1998a). Phase 1 was an exploratory qualitative study, and Phase 2 was a quantitative assessment of the risk factors contributing to poor outcome for the patients with PKU at the King Faisal Specialist Hospital and Research Centre (KFSH&RC).

### Phase 1

This phase comprised qualitative research that explored the current status of patients with aminoacidopathies and informed the second phase of the study.

**A. Interviews:** Qualitative data was collected from open and semi-structured interviews:

- Interviews and observations of key informants from the health care team
- Focus groups and interviews with health care providers
- Interviews with the patients
- Interviews with the families of patients

**B. Observations:** Observations were based on purposefully selected participants to examine:

- Formula preparation by patients and carers
- Dietitian counselling sessions
- Doctor clinic sessions

**C. Market survey:** A market survey was conducted to observe the availability and accessibility of the special low protein food products.

**D. Medical records review:** The medical history, developmental assessments and past blood levels were reviewed for the participating patients.

## **Phase 2**

This phase was a quantitative cross sectional survey including:

### **1. *Nutritional assessment: For the patients***

- Anthropometric measures
- Clinical measures: current morbidity data and blood levels
- Diet analysis

### **2. *Questionnaires: For the patients and their families***

- Socio-economic status
- Quality of life
- Nutrition knowledge, attitudes and practices
- Dietary compliance

### **3. *Medical records review:***

- Medical history
- Past blood levels

### **4. *Development assessment: For the patients***

- Past developmental assessments from medical records
- The Vineland-II Survey Interview Form (which involved translating and adapting the Vineland-II to Arabic).

## **1.5 Anticipated outcomes**

- To establish an understanding of the current conditions in various aspects of care for patients with aminoacidopathies in Saudi Arabia.
- To describe the perceptions of the patients and their families towards the services, treatment, education, and support they receive.
- To increase awareness about the importance of compliance with dietary management as an essential part of treatment among the target group.

- To determine the risk factors and barriers leading to inadequate metabolic control for the patients.
- To gain adequate evidence to inform the development of a targeted nutrition management programme to support patients with aminoacidopathies and their families, with a view to expanding the project to include all the patients with metabolic disorders in Saudi Arabia.

## **1.6 Thesis overview**

Chapter 2 presents a review of the literature on MSUD and tyrosinaemia type 1 in general and PKU in particular. Background information about metabolic disorders in the Middle East is reviewed with a focus on Saudi Arabia.

Chapter 3 describes in detail the methods used in this study. The data was collected in Riyadh, the capital of Saudi Arabia (Figure 1), at King Faisal Specialist Hospital and Research Centre (KFSH&RC). KFSH&RC is the main centre that patients with metabolic disorders are referred to from different parts of the country.

Chapter 4 explains the rationale for using the Vineland-II scales in this study. It illustrates the translation and adaptation of the Vineland-II scales to Arabic, and the testing process of the instrument before using it with the patients in this study.

The findings of Phase 1 of this study, which was a qualitative phase, are provided in Chapter 5. The interpretation and discussion of the key findings are presented in Chapter 6. Results of Phase 2, which was a quantitative study, are presented in Chapter 7. The main results are then discussed in view of the relevant literature in Chapter 8. Finally, Chapter 9 concludes with the recommendations arising from this research. The Appendices contain the consent form, Phase 1 interview forms, sample interview, the questionnaires for Phase 2, and the list of adjustments and adaptations to the Vineland-II when translated to Arabic.



Figure 1: Saudi Arabia. Adapted from (Worldofmaps.net, 2012).



## CHAPTER 2

# LITERATURE REVIEW

## **2.1 Overview of inborn errors of metabolism (IEM)**

Inborn errors of metabolism or metabolic disorder are caused by point defects in metabolism. The number of known disorders exceeds 500; they are rare individually, but combined account for a considerable proportion of suffering and illness (Clarke, 2002). Accurate diagnosis is very important for the treatment and prevention of debilitating effects of the disorders (Saudubray, Sedel, & Walter, 2006).

Clarke (2002) describes how metabolic disturbances, due to deficiency of some catalytic or transport proteins, cause the signs and symptoms of disease in patients with inborn errors of metabolism. In many disorders disease is caused by the accumulation of the substrate of an altered enzyme, in some other disorders accumulation of a normally minor metabolite, or deficiency of a product from a specific reaction are the primary causes of disease.

Most inborn errors of metabolism are inherited, and the majority are inherited as single-gene defects, and transmitted in an autosomal recessive manner. Consanguinity increases the probability that the couple are both carriers of a recessive mutation and this increases the likelihood of having children affected with the disorder (Bittles, 2001). Consanguineous marriages are high in small communities that are culturally or geographically isolated; this contributes to the high incidence of some disorders in specific ethnic groups (Al-Gazali et al., 2006; and Clarke, 2002).

In metabolic disorders the onset of clinical symptoms varies from hours after birth to weeks, some disorders even have an onset later in childhood. Incorrect or delayed diagnosis is a common problem in the management of inborn errors of metabolism. Many of the disorders have non-specific signs and symptoms that could be easily attributed to sepsis or other common illnesses. Deterioration of a child without a known reason and without response to common forms of treatment (e.g. antibiotics) is an important indicator for the suspicion of a metabolic disorder (Saudubray, Desguerre, Sedel, & Charpentier, 2006).

## **2.2 Newborn screening for IEM**

Newborn screening (NBS) programmes are established in many countries to identify infants affected by specific diseases before the development of clinical signs and symptoms, thus allowing early medical intervention and treatment to prevent deterioration, disability, or even death. Management of many metabolic disorders developed through recognizing how the point defects in metabolism cause the disease, then attempting by metabolic manipulation, such as dietary, pharmacologic, or other, to neutralize or reverse these effects (Walter & Wraith, 2006). Unfortunately, in some disorders understanding of how the inborn error causes disease is still incomplete (Saudubray et al., 2006).

Newborn screening has achieved a great deal over the past 40 years. Guthrie's development of a simple screening test for PKU had led to the institution of the first PKU screening programme for newborns in the USA (Guthrie, 1961; Guthrie & Susi, 1963; and Jones & Bennett, 2002). It started in the state of Massachusetts in 1962, other states and countries started introducing population screening throughout the sixties and seventies (Levy H.L., 2005; Levy P.A., 2010; and Marsden, Larson, & Levy, 2006). The UK adopted the Guthrie blood-spot screening process in 1969, and shifted from routine screening by many local health authorities to a national level for all newborns (Pollitt et al., 1997).

Newborn screening for PKU has been proven as cost-effective over a decade ago, and has been considered as a fundamental public health programme (Dhondt, Farriaux, Saily, & Lebrun, 1991; Hisashige, 1994; National Institutes of Health Consensus Development Panel, 2001; and Seymour et al., 1997). A review by Lord and colleagues established that in the UK screening for PKU by itself justifies the collection of blood samples from newborns (Lord et al., 1999). Screening for medium-chain acyl-coenzyme A dehydrogenase deficiency (MCADD) and glutaric acidemia type 1 (GA1) has been proven to be worthwhile as well (Marsden et al., 2006; and Wilcken, 2012). It prevents death, disability and alleviates the financial burden of caring for disabled individuals by the community.

The screening technology has advanced tremendously by the introduction of the tandem mass spectrometry (MS/MS) for population screening in the early nineties. It allowed for rapid, reliable, and cost-effective detection of many disorders using a single sample (Chace, DiPerna, & Naylor, 1999; Chace & Naylor, 1999; and Levy P.A., 2010). The significant advancement in MS/MS technology made it an integral part of laboratories. The imperative interactions between laboratories and clinicians became easier, supporting the diagnosis and monitoring process of patients (Strathmann & Hoofnagle, 2011). Many countries started using the MS/MS in extending their newborn screening programmes to include more disorders, including Australia, China, Japan, New Zealand, South Korea, Taiwan, and several European countries (Bodamer, Hoffmann, & Lindner, 2007; Huang et al., 2011; Niu et al., 2010; Schulze et al., 2003; Shigematsu et al., 2002; and Yoon et al., 2003; Wilcken & Wiley, 2008; Wilcken et al., 2009; and Wilson et al., 2012).

In the US, most of the states have had an extended screening programme since the introduction of MS/MS, but there has been considerable variability between states (Therrell & Adams, 2007). In an effort to unify newborn screening between the states the American College of Medical Genetics (ACMG) was commissioned by the Maternal and Child Health Bureau to establish uniform policies for newborn screening for all of the states (Watson et al., 2006). The expert panel of the ACMG recommended mandating screening for 29 core conditions, because there are effective treatments and good knowledge of these conditions. They also identified a secondary target of 25 conditions, as they are incidentally identified when screening for the main conditions or clinically significant but without an effective treatment. Nearly all the states have adopted the new panel of screening (Levy H.L., 2010). The efforts of the ACMG in collaborative improvement of policies related to newborn screening have led to improvements in communications between professionals. Consequently this has led to improving the management of patients with metabolic disorders (Berry, Lloyd-Puryear, & Watson, 2010).

Screening for less severe disorders is still disputed by some researchers (Baily & Murray, 2008; Moyer, Calonge, Teutsch, & Botkin, 2008; Pandor, Eastham, Beverley, Chilcott, & Paisley, 2004; and Pollitt, 2001). Therefore, not every country has expanded newborn screening to cover all the disorders that can be screened for. In

Germany they screen for 12 disorders, in the UK they screen for PKU and MCADD, while in France they only screen for PKU (Klein, 2011; Lindner et al., 2011; and Pollitt, 2009). Pandor and colleagues (2004), in their systematic review of newborn screening for the UK, concluded that there were no justifications for including disorders other than PKU and MCADD to the newborn screening programme in the UK, as only these two disorders meet the criteria for population screening. The main criteria for screening for a condition entail the availability of proper follow-up of positive results, confirmation of diagnoses, availability of treatment, continuous management, and good knowledge of the natural history of the disorders (Kaye & the Committee on Genetics, 2006; Klein, 2011; and Pandor et al., 2004).

In contrast, Downing and Pollitt (2008) argue that the UK has lagged behind other countries in utilizing the MS/MS technology for expanding newborn screening. Especially that there are many disorders with successful treatments, and patients may suffer negative effects with delayed diagnosis (Pollitt, 2009). The main arguments in favour are the cost-effectiveness of early detection and treatment as a result of newborn screening, compared to diagnosis and treatment following presentation of symptoms, and the positive effects of screening on outcome for the patients.

At the same time the extended newborn screening programmes of some countries are criticised of expanding too rapidly. Researchers have debated the benefit and cost effectiveness of expanding newborn screening to include as many detectable disorders as possible. Several of the disorders on some expanded newborn screening programmes are either lacking effective treatment, not needing treatment in infancy, the natural history of the condition is not understood, or long-term data is not available on follow-up of patients with mild disease or pre-symptomatic patients (Baily & Murray, 2008; Coman & Bhattacharya, 2012; and Dhondt, 2010). The ACMG has been criticised for recommending some disorders for newborn screening; disorders that did not meet the screening criteria, nor followed evidence based approach when selected (President's Council on Bioethics, 2008; and Moyer et al., 2008). These researchers advocate the re-evaluation of the recommended disorders and the inclusion of some disorders into pilot studies rather than mandating screening for them, until more evidence is available.

The researchers argue that such rapid expansions of newborn screening programmes to include disorders with many uncertainties are placing unnecessary burdens on the families and the health care systems. Authorities could be spending on expanded newborn screening when it might be more beneficial to spend the money on other health programmes (Baily & Murray, 2008; Levy P.A., 2010; Moyer et al., 2008; and Pollitt, 2007).

The families could also suffer from unnecessary stress and anxiety when faced with a diagnosis of an untreatable disorder, or a disorder with an uncertain outcome (Dhondt, 2010; and Waisbren et al., 2003). In addition to the financial burden they would incur in pursuing treatment possibilities or unneeded treatments (Baily & Murray, 2008; Bennett et al., 2012; and Coman & Bhattacharya, 2012). Bailey and colleagues (2009) recommend providing psychological support to the families with the expansion of newborn screening to conditions that lack clear medical treatments. This is to help the families understand the conditions and to ensure follow-up.

Newborn screening is a fundamental public health programme that is continuously evolving. Many researchers call for international cooperation to benefit from the different experiences in diagnosis, treatment, follow-up and management of these rare conditions (Berry et al., 2010; Dhondt, 2010; Klein, 2011; Pollitt, 2009; and Wilcken, 2010), with the importance of focusing on saving lives, preventing disability, and improving quality of life (Grosse, 2005).

An impressive and important worldwide collaboration is described by McHugh and colleagues (2011). Forty five countries have participated in validating and defining cut-off values for 64 metabolic disorders for newborn screening by tandem mass spectrometry (McHugh et al., 2011). This is significant because different countries have different cut-off ranges for the same disorder on screening (Burgard et al., 2011). This effort has been described as innovative in establishing evidence based cut-off values for newborn screening by MS/MS. These disorders are rare, therefore pooling samples and values from around the world has lead to refining the cut-off ranges for newborn screening, increasing the positive predictive values and reducing false-positive tests (Howell, 2011).

Another achievement of this collaborative project is the development of a recognition software that produces interpretive tools for the conditions that are screened for by MS/MS. The tools work with raw data independently from cut-off values. They helped attain reduction in both false-negative and false-positive results (Marquardt et al., 2012). Such great achievements vastly improve newborn screening programmes and certainly have a positive impact on patients, emphasizing the importance of international collaborations.

### **2.3 Inborn errors of metabolism and newborn screening in the Middle East**

A number of studies have looked at inborn errors of metabolism in the countries neighbouring Saudi Arabia. The incidence of PKU in Turkey is reported to be at 1:5049 (Tunçbilek & Özgüç, 2007). They have a national child health programme for PKU screening. It started in 1986 and gradually increased to cover all urban areas of the country. It is run by the Ministry of Health in collaboration with three University Children's Hospitals (Ozalp et al., 2001). Some of the problems they faced with their screening programme were inadequate sample collection, difficulty in reaching some detected cases, and compliance problems with dietary management. They recognise the need to provide support for the patients of metabolic disorders and their families, and recommend establishing country wide criteria for genetic counselling and patient support. In one effort to improve support Gökmen-Ozel and colleagues (2011) studied the effects of educating the caregivers of patients with PKU at their homes in Turkey. They found that continuous dietary education that incorporates home visits has had a positive effect on lowering the patients' phenylalanine levels.

Some hospitals are doing selective screening for a number of other metabolic disorders. They are finding high numbers of at risk babies to have metabolic disorders, but the numbers are not enough to extrapolate a country wide incidence (Tümer, Biberoglu, Hasanoglu, Ezgu, & Atalay, 2004; and Tunçbilek & Özgüç, 2007). The high incidence of metabolic disorders in Turkey is attributed to the high number of consanguineous marriages, which was found to be in 72% of the families of patients (Tunçbilek & Özgüç, 2007). This rate is much higher than the Turkish

national rate of consanguineous marriages of 22%, the researchers report a declining trend in national consanguinity (Koc, 2008).

There has been newborn screening for PKU in the Gaza strip since 1994, but this is only in the government clinics. Two-thirds of the newborns are delivered at the United Nations Relief and Works Agency for Palestine Refugees in the Near East (UNRWA) clinics and receive healthcare there, where no PKU screening tests are undertaken (Abu Shahla, Abed, & Abu Shahla, 2004). In the year 2000 only 35.5% of newborns were tested for PKU. The researchers note that PKU is a public health problem and the prevalence and incidence of PKU among the population is not known. This compelled them to carry out the first organized study about PKU in the Gaza strip. The overall prevalence of PKU was found to be 6.35/100,000 (1:15,700), with significant inter-regional differences among the different provinces and localities of the Gaza Strip. The highest incidence was in the rural areas at 28.3/100,000 (1:3500), where 60% of the families were of first-cousin marriages. Their results showed that PKU patients have very poor monitoring and weak commitment to blood testing, with only 35.4 % of the patients monitoring their diets monthly. The researchers state the need to improve the Gaza PKU screening, follow-up, and monitoring programmes (Abu Shahla et al., 2004).

Waterston (2004) commended the Gaza team for evaluating their PKU screening programme at such time of struggle when health services usually prioritise health relief rather than prevention. The author recommended the expansion of screening to the UNRWA clinics in the Gaza strip to include all newborns. There is a need there to promote awareness and education among families and health care providers about PKU and screening. In addition, there is a need for funding to train the staff and to provide treatment for the patients, if the programme to be successful.

Newborn screening for PKU has started at the UNRWA clinics in the West Bank in 2006, but not in Gaza (UNRWA, 2006). In 2010 the UNRWA started PKU screening in their clinics in Jordan in collaboration with the Jordanian Ministry of Health (UNRWA, 2010). At the same time Jordan were piloting a national PKU screening programme (Krotoski et al., 2009).

In Lebanon, they have had a private newborn screening programme since 1996 in two university centres (Daher, Beaini, Mahfouz, Cortas, & Younis, 2003; and Khneisser, Adib, Megarbane, & Lukacs, 2008). They screen for PKU, galactosemia, glucose-6-phosphate dehydrogenase deficiency, and congenital hypothyroidism. Nearly 20% of newborns are screened through samples sent from affiliated hospitals around the country. In 2006, the newborn screening laboratory of the Saint Joseph University in Beirut decided to expand their screening programme to include more inborn errors of metabolism utilising the MS/MS technology. The expansion was in collaboration with the Metabolic Laboratory at the Hamburg University Medical Centre in Germany (HUMC). Initially they sent samples to the HUMC for screening. Then by early 2008 they acquired the MS/MS equipment and trained their staff to carry the screening locally, with continued technical support from the HUMC (Khneisser et al., 2008).

Karam et al (2011) declare that only 29% of PKU patients in Lebanon were identified through newborn screening. They stress the need for implementing a national newborn screening programme. There were plans to transfer the newborn screening responsibility to the Ministry of Health in Lebanon and to cover all newborns by 2011 (Krotoski et al., 2009).

Golbahar and colleagues did a selective screening study from 1996 to 2001, in the region of Shiraz, Iran, and found high incidence of PKU (1:3672), tyrosinaemia (1:10,651), and MSUD (1:21,303). They believe these high numbers are mostly attributed to the high rate of consanguineous marriages in the region (Golbahar, Karamizadeh, & Honardar, 2002). In a more recent study, Habib et al (2010) calculated the incidence of PKU in Iran to be at 1:6250. Ghiasvand et al (2009) found high prevalence of PKU among the mentally disabled population in Iran, they consider this to indicate high incidence of PKU among newborns in Iran. The authors believe that the high incidence is due to the high frequency of the PKU allele and the high rate of consanguineous marriages in Iran. They recommend nationwide screening for PKU rather than the current local screening programmes.

First-cousin marriages among Iranians are reported to be around 27.9% in the general population (Saadat, Ansari-Lari, & Farhud, 2004). In a study involving 82 families of PKU patients in Iran, 46 families (56%) were of first-cousin marriages. This lead the

researchers to attribute 50% of the high incidence of PKU in their population to consanguinity (Koochmeshgi, Bagheri, & Hosseini-Mazinani, 2002).

Several studies from Iran were concerned with carrier detection and mutation analysis of PKU in Iran (Hosseini-Mazinani, Koochmeshgi, Khazae-Koohpar, Hosein-Pur-Nobari, & Seifati, 2008; Vallian, Barahimi, & Moeini, 2003; and Zare-Karizi et al., 2011). The researchers hoped to set up diagnostic tests for prenatal diagnosis and carrier detection of PKU among the Iranian population. Zare-Karizi and colleagues (2011) identified the PKU mutations for 124 patients in Iran. Four mutations were found to be most prevalent among the Iranian PKU patients.

The United Arab Emirates (UAE) started PKU screening for newborns in 1995. In an evaluation study of the screening programme, from its start in 1995 to the end of 2000, the incidence for classic PKU in the UAE was calculated to be 1:20,050. Coverage of the newborn screening in 2000 was at 65% of newborns only. The plan was to integrate the newborn screening programme with other health programmes to improve coverage (al-Hosani, Salah, Saade, Osman, & al-Zahid, 2003). The UAE Ministry of Health is planning an expansion of their newborn screening programme to include up to 20 more disorders (Krotoski et al., 2009).

Qatar started a newborn screening programme in 2003 in collaboration with the University Children's Hospital in Heidelberg, Germany (UCH). Samples were sent from Qatar to Germany to be screened. In their evaluation of the programme after screening 25,214 newborns in two and a half years, the researchers calculate the incidence of metabolic disorders in Qatar to be considerably higher than in Germany. The identified patients during this period give an incidence of 1:1327 for metabolic disorders in Qatar, while in Germany the incidence is 1:2517, making the relative risk of having a metabolic disorder in Qatar double that in Germany (Lindner et al., 2007). The UCH provided valuable training and support for the staff in Qatar, as by 2009 it was planned that all newborn screening and diagnoses will be carried out locally in a newly equipped metabolic centre in Qatar (Krotoski et al., 2009; and Lindner et al., 2007).

Organised services for metabolic disorders were instigated in Oman in 1998, without the availability of newborn screening. Joshi and colleagues (2002) reviewed all the

patients diagnosed with metabolic disorders from the start of these services until the end of 2000. Their aim was to identify the prevalence of inborn errors of metabolism in Oman. They calculated the general incidence of metabolic disorders in Oman to be 1:1555, and found that 76% of the patients had consanguineous parents. Currently Oman has newborn screening for a few blood genetic disorders and there are plans to expand it to cover some metabolic disorders (Joshi & Venugopalan, 2007; and Krotoski et al., 2009). Bahrain and Kuwait have newborn screening programmes for one or more disorders and are piloting screening programmes for additional metabolic disorders (Abdel-Hamid, Tisocki, Sharaf, & Ramadan, 2007; AlArrayed & AlHajeri, 2012; Krotoski et al., 2009; and Padilla, Krotoski, & Therrell, Jr., 2010)

Research on inborn errors of metabolism in the region surrounding Saudi Arabia is lacking current updates. However, available research indicates similarities between these countries and Saudi Arabia in the predicaments facing them regarding the management of metabolic disorders. Bayoumi and Yardumian (2006) believe that the reasons hindering the progress of preventative genetic programmes in the Arab Gulf region are not financial, but rather cultural and legal issues. They argue that there is a need for a change in the attitudes of the public, the professionals, and the policies to institute comprehensive programmes. They stress that public debate and education can motivate change and improve awareness about the different needs of patients with metabolic disorders.

Jabbour (2003) recommends coordination among countries in the Middle East, in their efforts to tackle issues of public health. Collaboration would help countries starting newborn screening to pool their resources and expertise, and to enhance the impact of their programmes. Interest in tackling newborn screening and genetic disorders in the Middle East and North Africa (MENA) has grown tremendously in recent years. Many countries either started their own NBS programmes or partnered with other countries for technical support. This is evident through the organisation of a regional conference on strengthening newborn screening in the MENA region in 2006. This was followed by two subsequent conferences in 2008 and 2010 to evaluate the progress of the NBS programmes in the area, share knowledge and experiences, promote collaborations between countries, and encourage population studies that would help establish the incidence of metabolic and genetic disorders (Krotoski et al.,

2009). These meetings are essential to foster relationships and cooperation between nations to help overcome problems that may arise with developing new and challenging programmes.

## **2.4 Consanguinity in the Middle East**

Studies from Saudi Arabia and other countries in the Middle East express the strong associations between consanguinity and some health problems. They include craniofacial anomalies, congenital heart disease, hearing impairments, and autosomal recessive disorders (Abdulrazzaq et al., 1997; Al-Kandari & Crews, 2011; Aziza, Kandasamy, & Shazia, 2011; Becker, Al, Molina, & Paterson, 2001; Bener, Hussain, & Teebi, 2007; El Mouzan, Al Salloum, Al Herbish, Qurachi, & Al Omar, 2008; Ravichandran et al., 2012; and Yunis et al., 2006).

The prevalence of consanguinity in different regions of Saudi Arabia has been reported to be between 51.3% and 57.7% (al-Abdulkareem & Ballal, 1998; Al Husain & Al Bunyan, 1997; and El-Hazmi et al., 1995). A more recent comprehensive study, covering all regions of Saudi Arabia, reports that consanguinity remains high at 56% of all marriages (El-Mouzan, Al-Salloum, Al-Herbish, Qurachi, & Al-Omar, 2007).

This level is similar to the neighbouring Gulf countries with similar social and cultural make up. The United Arab Emirates has a consanguinity rate of 50.5% (Al-Gazali et al., 1997). In Kuwait it is 44.8%, in Qatar 54%, and in Oman 56.3 % (Al-Kandari & Crews, 2011; Bener & Hussain, 2006; and Rajab & Patton, 2000).

Consanguinity in Lebanon and Syria is less than in the Gulf region, but still high at 35.5% and 35.4% respectively (Barbour & Salameh, 2009; and Othman & Saadat, 2009). Consanguinity in Jordan varies between 25.5% and 49% depending on the region, and it has been declining in the younger generations (Hamamy, Jamhawi, Al-Darawsheh, & Ajlouni, 2005; and Obeidat, Khader, Amarin, Kassawneh, & Al, 2010). In Jordan, a study found that 85.9% of patients with autosomal recessive conditions had consanguineous parents (Hamamy, Masri, Al-Hadidy, & Ajlouni, 2007).

The Arab world has high rates of consanguinity. The custom of consanguineous marriages is rooted in the tribal character of the Arab countries and believed to have considerable economic and social advantages (Tadmouri et al., 2009). It is preferred because it provides ease of marriage and assurance in knowing the partner and the in-laws well, which prevents financial, health, or social uncertainties (Bittles, 2001). Consanguineous unions are believed to strengthen family ties, improve the status of women, and be more stable than non-consanguineous unions (AlKhaja et al., 2012; and Modell & Darr, 2002).

Many associate consanguinity with Islam, though it is a cultural norm rather than religious (Modell & Darr, 2002). Islam merely allows cousin marriages, and prohibits uncle-niece and aunt-nephew unions. Consanguinity is not encouraged in any text in the teachings of Islam (AlKhaja et al., 2012; and Bittles, 2001). Indeed, marrying out of the family is encouraged (Al Aqeel, 2007).

Researchers from the Middle East and the West agree that recessive autosomal diseases are evidently more widespread in consanguineous communities (Al-Gazali, 2005; Al-Kandari & Crews, 2011; Bittles, 2001; El-Hazmi et al., 1995; Hamamy et al., 2007; Jaouad et al., 2009; Modell & Darr, 2002; Ozand, Devol, & Gascon, 1992; and Tadmouri et al., 2009). Some Arab tribal groups and villages even have conditions that are confined to them because they descend from limited ancestry (Al-Gazali et al., 2006). Researchers in Saudi Arabia believe that the high level of consanguinity and the tribal nature of marriages have led to the preservation of rare mutations kept in a genetically homogenous population, leaving genetic diseases to thrive (Al-Odaib, Abu-Amero, Ozand, & Al-Hellani, 2003; and Rashed, Rahbeeni, & Ozand, 1999).

The Centre for Arab Genomic Studies maintains a growing database on genetic disorders in Arab populations: the Catalogue for Transmission Genetics in Arabs (CTGA) (AlKhaja et al., 2012; and Tadmouri, Al Ali, Al-Haj, & Al, 2006). Tadmouri and colleagues (2009) found that a high proportion (63%) of the disorders in the CTGA database are autosomal recessive disorders. They present this as clear confirmation of the positive correlation between consanguinity and autosomal recessive diseases in the Arab communities.

Consanguinity, however, is expected to decline globally due to many current social aspects, such as the leaning of younger generations towards smaller family sizes, urbanization, and increased female education. This, with time, will cause a reduction in the prevalence of autosomal recessive disorders (Bittles, 2002; Bittles & Black, 2010; and Hamamy, Al-Hait, Alwan, & Ajlouni, 2007).

Discouraging consanguinity in general to prevent genetic diseases would be ineffective because this ignores that it is a significant and valued social culture in the communities that practice it. The ethics of genetic counselling dictates that customs and traditions, even if not the best for health outcome, need to be respected (Al-Aqeel, 2005; Bittles, 2008; El-Hazmi, 2009; and Meyer, 2005). Therefore, in communities with high levels of consanguinity, researchers consider the best way of tackling it is through directed prospective genetic counselling. It is recommended to identify families at risk of developing autosomal recessive disorders, then offer them genetic counselling, risk information, and provide premarital carrier testing when possible (Abdel-Meguid, Zaki, & Hammad, 2000; Albar, 2002; El-Hazmi, 2004a; Koc, 2008; and Meyer, 2005).

## **2.5 Inborn errors of metabolism and newborn screening in Saudi Arabia**

The Metabolic Services of the Medical Genetics Department at King Faisal Specialist Hospital and Research Centre (KFSH&RC) in Riyadh, Saudi Arabia, is one of the major tertiary care referral centres for metabolic disorders in the region of Saudi Arabia and some neighbouring countries. It has always collaborated with other health care centres in Bahrain, Kuwait, Qatar, Oman, and United Arab Emirates for the diagnosis of genetic disorders (Al-Odaib et al., 2003; and Therrell, 2003).

The disorders seen at KFSH&RC include organic acidaemias, amino acidaemias, fatty acid oxidation defects, and lysosomal storage and peroxisomal disorders among others. In the past the affected infants were identified through diagnosis after symptomatic presentation or through selective screening at KFSH&RC and affiliated hospitals. Selective screening included infants born at these hospitals and infants born

to families with known history of any of the disorders. A newborn screening programme started in 2005 as a pilot, and gradually increased the number of screened newborns each year becoming a national programme in 2011 (more details in the following section).

### **2.5.1 Incidence of IEM in Saudi Arabia**

The true incidence of each metabolic disorder in Saudi Arabia is yet to be identified. There are a few small studies conducted to measure the incidence of metabolic disorders in different regions of the country.

Rashed and colleagues (1999) carried a pilot study of newborn screening using MS/MS at KFSH&RC. They screened 27,624 samples from KFSH&RC and two other Saudi hospitals, and diagnosed 20 cases of metabolic disorders. They reported that this yielded a frequency of 1:1381 live births for a collection of 10 metabolic disorders. This newborn screening continued on a small scale until the start of the national newborn screening pilot programme in 2005 (Saadallah & Rashed, 2007). However, these results need to be interpreted with caution. The study was carried out in hospitals catering for high risk patients; mothers of previously diagnosed children with any metabolic disorder are followed-up here during pregnancy until they give birth to test the new baby. Additionally, KFSH&RC is a tertiary hospital, many infants with unknown diagnoses are referred to it.

Moammar and colleagues (2010) carried out a retrospective study in the Saudi Aramco Medical Centre, a major hospital at the Eastern Province of Saudi Arabia. They reviewed the medical records of Saudi patients at the hospital from 1983 up to 2008, in an effort to measure the incidence of metabolic disorders in that region. They identified 248 patients, who had 55 different metabolic disorders, yielding a prevalence of 1:667. The most commonly seen disorders were lysosomal storage disorders, organic acidopathies, and aminoacidopathies. Nearly all the patients in the study were children from consanguineous marriages. The authors believe that this warrants a prompt expansion of the newborn screening programme. They recommend providing regional treatment and follow-up care facilities with the availability of genetic counselling for the families.

Another retrospective study was conducted by Al Bu Ali and colleagues (2011) in AlAhsa city of the Eastern Province in Saudi Arabia. They reviewed the files of all the babies born in the AlAhsa Maternity and Children hospital from April 2006 till 2009. They identified 43 patients, who had 14 different metabolic disorders, reporting a prevalence of 1:774. The most common metabolic disorders found in this population were 3-methylcrotonyl-CoA carboxylase deficiency and biotinidase deficiency, followed by medium-chain acyl-CoA dehydrogenase (MCAD) deficiency and glutaric acidemia type II.

The Saudi Ministry of Health has reported the rate of metabolic disorders among newborns as 1:1000 (Afifi & Abdul-Jabbar, 2007). This early information from the pilot newborn screening programme speculated that there will be approximately 500 new cases of metabolic disorders each year. This validated the necessity of having a national newborn screening programme, to help reduce harm and disability in the community.

The most recent report about the progress of the newborn screening programme in Saudi was published on the PSCDR website describing progress up to the end of the year 2010 (Al-Odaib et al., 2011). It summarises the expansion plans for the programme, and states that the rate of the 16 disorders screened for is 1:1000 live births after 5 years of increased screening.

The incidence of metabolic disorders in Saudi Arabia is comparable to the reported incidence from the Arab Gulf region, as reviewed in the previous section. However, it is higher than what is reported from Europe and Canada. The overall incidence of metabolic diseases in British Columbia was approximately 1:2500 (Applegarth, Toone, & Lowry, 2000). In Italy the incidence of approximately 200 diseases was reported as 1:2555 (Dionisi-Vici et al., 2002). An incidence of 1:2517 was reported from Germany (Lindner et al., 2007). While in the West Midlands, UK, the overall birth prevalence of metabolic disorders was 1:784 live births (Sanderson, Green, Preece, & Burton, 2006).

One reason for the higher incidence of metabolic disorders in the West Midlands is thought to be the high ethnic diversity of the study population (Sanderson et al., 2006). The other studies reported low ethnic minority groups in their study

populations. Although these studies have included different disorders in their calculations, but they give an understanding of the disease burden in each area. In a previous study in the West Midlands metabolic disorders were reported to be 1:2691 for Whites and 1:318 for Pakistanis (Hutchesson, Bunday, Preece, Hall, & Green, 1998). This demonstrates the variation of incidence among different ethnic groups and the importance of knowing the prevalent disorders in each community to provide adequate services.

In an important step towards obtaining the epidemiological data needed for service planning and provision of care, the Saudi National Genetic and Birth Defects Registry (NGBDR) project started in January 2003. It is funded by the Prince Salman Centre for Disability Research (PSCDR) in collaboration with the KFSH&RC to establish and maintain a national registry of genetic disorders, birth defects, and developmental disabilities in Saudi Arabia (PSCDR, 2012).

### **2.5.2 Newborn screening in Saudi Arabia**

Health care is considered a right for Saudi citizens, thus health services and medications are provided nationally for free. There are ample private health care providers as well. Health services have improved vastly during the past 30 years in Saudi Arabia, but establishing preventative medicine was slow. Services such as premarital screening and newborn screening took a long time to develop, in spite of the high incidence of manageable metabolic disorders in Saudi Arabia. Since 1993 researchers from the KFSH&RC have asserted that the use of new technology such as MS/MS for newborn screening in Saudi Arabia is efficient, cost-effective, and prevents the community from dealing with the emotional and financial burden of caring for many disabled children. They have highly recommended it, especially because KFSH&RC have acquired the technology for diagnostic and selective screening purposes (Nasserullah et al., 1998; Rashed & Ozand, 1993; and Ozand, 1998). Yet it was not until 2005 that a pilot for a national newborn screening programme started in Saudi Arabia.

The pilot started with the aim of screening 50,000 newborns per year from 24 hospitals in the main cities of Saudi Arabia, and gradually involving more hospitals and increasing the number of screened newborns. The disorders screened for are:

Phenylketonuria (PKU), Maple Syrup Urine Disease (MSUD), Arginosuccinase Deficiency (ASL), Citrullinemia (ASD), HMG-CoA Lyase Deficiency (HMG), Isovaleric Acidaemia (IVA), Methylmalonic Acidaemia (MMA), Propionic Acidaemia (PA), Beta-ketothiolase Deficiency (BKT), Methylcrotonyl-CoA Carboxylase Deficiency (3MCC), Glutaric Acidaemia type-I (GA-I), Medium-chain acyl-CoA dehydrogenase deficiency (MCAD), Galactosemia (GAL), Congenital Hypothyroidism (CH), Congenital Adrenal Hyperplasia (CAH), and Biotinidase Deficiency (BD) (Afifi & Abdul-Jabbar, 2007; and Ministry of Health, 2012).

The programme has expanded gradually, screening 130,000 newborns in the year 2011. Samples were sent from 86 hospitals around the country. They predict that by the end of the year 2014 they would be screening all newborns (S. Alabdulmunem, personal communication, May 16, 2012). The latest statistics show that Saudi Arabia has a total of 408 government and private hospitals, more than two thirds with maternity and child services. The number of newborns in Saudi Arabia in the year 2010 was estimated to be just over 600,000 live births (Ministry of Health, 2010).

The Saudi newborn screening programme, now named “The National Programme for Reducing Disability through Early Examination of Infants”, is a collaboration between the Ministry of Health (MOH), KFSH&RC, and PSCDR. Administration is by the PSCDR, supervision and finance are by the MOH, and The National Laboratory for Newborn Screening (NLNBS) is housed at the KFSH&RC and equipped to screen all newborns in the country (Afifi & Abdul-Jabbar, 2007; and Al-Odaib et al., 2011).

The programme was not mandatory, but rather a collaborative effort, where hospitals were asked to collaborate in sending the samples to the NLNBS. It has been announced that in 2012 the programme has become mandatory and all public, military, and private hospitals were urged to ensure their readiness for participation (Ministry of Health, 2011).

The PSCDR has established a secure web portal, to allow direct access for hospitals to the results of newborns screened at their facilities. The aim is to expedite and facilitate the process of conveying the results to the families and their health care providers as quick as possible (Al-Odaib et al., 2011). This is a crucial measure to

employ early in the programme, as timely reporting of positive results is one of the main challenges to newborn screening programmes as discussed by Downing et al (2010). They advocate the use of electronic health information technology to advance the quality and effectiveness of newborn screening.

Abhyankar and colleagues (2010) describe the development of a template for an electronic message to report the results of newborn screening to hospitals and care providers. Several states in the US are implementing this technology, which made communicating results more rapid and effective. Making use of existing technologies would benefit the developing Saudi newborn screening programme. Such technologies could in addition facilitate the dissemination of educational material for the health care providers and the families regarding newborn screening and interpretation of results (Downing, Zuckerman, Coon, & Lloyd-Puryear, 2010).

The PSCDR has also started building a database for the newborn screening results (Al-Odaib et al., 2011). This is important for long-term surveillance of services, quality improvement, and research (Berry et al., 2010; and Kemper et al., 2008). Recording all results in one database will give a true measure of the incidence of each disorder within the screening programme.

With the high incidence of metabolic disorders in Saudi Arabia there are evidently commendable efforts for expanding the newborn screening programme to all newborns in the country. It is crucial to implement a public health education programme to increase the level of public awareness about newborn screening, metabolic disorders, and their management. This is elemental for the understanding and acceptance of a new programme by the community, and ultimately its success (Afifi & Abdul-Jabbar, 2007; and Moammar, Cheriyan, Mathew, & Al-Sannaa, 2010).

Educating parents should start before the birth of their infants. Primary health care providers, midwives, and obstetrics need to be educated and involved in educating parents about newborn screening and its importance (Downing et al., 2010). Davis and colleagues (2006) discovered through interviewing new parents and health care providers that they had inadequate information about newborn screening. Parents and providers wanted concise and brief information on newborn screening and agreed that

it should be given before the birth of the baby. The availability of trained health care providers to cater for diagnosed patients from recall after positive results, to education, to follow-up, and management are essential for the success of the programme (Burgard et al., 2011; Howell & Lloyd-Puryear, 2010; and Therrell et al., 2010).

Newborn screening should not be viewed as an end in itself. It should be part of a comprehensive public health programme encompassing follow-up, confirmatory diagnosis, family education, counselling, management, and provision of various services for affected individuals and their families, including continuous evaluation (Kaye & the Committee on Genetics, 2006; and Pass et al., 2000).

Researchers affirm the importance of a timely and well planned follow-up system for the well-being of the patients detected by newborn screening programmes (Downing et al., 2010; and Kuroda & Ito, 1999). Long-term follow-up needs systemic and comprehensive planning to ensure seamless high quality care and treatment throughout life for the patients. This needs continuous staff training, quality assurance, care coordination, updated treatments, and research (Berry et al., 2010; and Kemper et al., 2008).

One of the challenges for the newborn screening programme in Saudi Arabia could be the limited health personnel and resources in small towns and remote villages. Difficulties in managing cases from remote areas were in reaching them and in persuading their families to follow up at specialised centres (Nasserullah et al., 2003). This highlights the need for public education about the newborn screening programme and the disorders, and the need for more specialised health care providers. Many workshops have been organised and training programmes are being developed to improve the knowledge and expertise of health care providers (S. Alabdulmunem, personal communication, May 16, 2012).

Cultural issues, politics, education, technology, and financing will always be challenging obstacles to implementing newborn screening programmes (Saadallah & Rashed, 2007; and Therrell, 2003). Educating policy and decision makers about the benefits of the programme, setting laws and regulations to govern important issues such as confidentiality and accessibility, continuous training for professionals, and

instituting public health education programmes about newborn screening can positively help overcome these challenges (Therrell, 2003; and Therrell et al., 2010).

Quality development and evaluation have been part of the Saudi newborn screening programme due to its participation in the Newborn Screening Quality Assurance Programme (NSQAP) since 2004. The programme is sponsored by the Centres for Disease Control and Prevention (CDC) and the Association of Public Health Laboratories (APHL), and housed in the CDC. The programme provides guidelines, training, consultation, technical assistance, and quality control material for newborn screening laboratories, to help improve their screening accuracy and reliability (Centers for Disease Control and Prevention, 2013; and De Jesús, Mei, Bell, & Hannon, 2010). The Saudi newborn screening programme is also a member of a member of the European Research Network for Evaluation and Improvement of screening, Diagnosis and Metabolism (ERNDIM) Quality Assurance Programme (Al-Odaib et al., 2011).

All the components may not be fully ready in the Saudi newborn screening programme. Nonetheless, it is improving and steadily heading towards reaching the goal of screening all newborns in the country.

### **2.5.3 Schemes implemented in Saudi Arabia to reduce the burden of genetic diseases**

#### **Premarital screening**

Premarital carrier detection for sickle-cell disease and thalassaemia has been implemented in Saudi Arabia since 2002. The Saudi MOH instituted legislation mandating premarital screening from 2004, but it does not prevent identified at risk couples from choosing to take the risk and marry (Al-Odaib et al., 2003; and El-Hazmi, 2004b). Testing for the human immunodeficiency virus (HIV), and the hepatitis viruses B and C (HBV and HCV) was added to the programme in 2008 (Alswaidi & O'Brien, 2009). It was accepted by the community as a step towards prevention, as it enables would-be couples to make informed decisions about marriage and the risks involved (Al-Aama, 2010; Alam, 2006; and Meyer, 2005).

Memish and Saeedi (2011) evaluated the effects of the Saudi premarital screening programme after six years of its implementation. The number of couples who were found to be carriers of sickle-cell or thalassaemia traits and cancelled their marriage plans increased five folds, from only 9% at the start of the programme in 2004 to 52% in 2009. The remaining 48% of couples still went ahead with their wedding plans even though they were carriers and at high risk of having affected children.

Several researchers believe that the timing of the screening test is not optimum. It is usually done after the couple's engagement and just before issuing the marriage certificate; therefore the couple's commitment to each other or their worry of social stigma may be the reason for not cancelling their marriage plans. Other reasons could be the failure of proper referral of carrier couples to genetic counselling, or the couples have been given inadequate information about the risk factors (Al-Aama, Al-Nabulsi, Alyousef, Asiri, & Al-Blewi, 2008; Alhamdan, Almazrou, Alswaidi, & Choudhry, 2007; and Memish & Saeedi, 2011).

The effects of this programme can be improved through providing more information in the media, including information about it in high school and college curriculums, strengthening education about the disease for at-risk couples, encouraging couples to test early on before any wedding plans, and by offering singles the screening test right after high school (Al-Aama et al., 2008; Alhamdan et al., 2007; Ibrahim et al., 2011; and Memish & Saeedi, 2011). Screening could also be offered to the extended family of patients before any plans of marriage (Al-Shahrani, 2009; and Ozand, Odaib, Sakati, & Al-Hellani, 2005).

### **Prenatal diagnosis**

Prenatal diagnosis has been well received among Muslims in many countries, as Islam allows pregnancy termination in the first trimester for health reasons (Modell & Darr, 2002). In Islam, pregnancy termination is permitted if the foetus is diagnosed with a severe and untreatable condition, and both parents agree. This must be carried out before the pregnancy reaches 120 days from conception (Albar, 2002).

Saudi parents accept prenatal diagnosis, and many are starting to accept the idea of pregnancy termination after understanding that religiously it is permitted for severe conditions (Alkuraya & Kilani, 2001; Alsulaiman & Hewison, 2007; and Alsulaiman

et al., 2012). Families affected by a serious condition had more favourable views towards abortion than families who didn't. However, induced abortion is rarely practised in Saudi hospitals. Religious interpretations are strong in the Saudi culture, and abortion conveys ethical dilemmas for many families (Al-Odaib et al., 2003; and Alsulaiman & Abu-Amero, 2013).

### **Pre-implantation genetic diagnosis (PGD)**

PGD is a procedure used for couples at high risk of having children with genetic disorders. It is best suited for monogenic disorders and structural chromosome abnormalities (Geraedts & De Wert, 2009). PGD involves testing of embryos, produced through in-vitro fertilization (IVF), for the genetic disorder. One or two of the unaffected embryos are then implanted into the uterus. It has almost universally assured the delivery of a healthy infant and is recognized as a significant alternative to prenatal diagnosis. It eliminates the dilemma of terminating an affected pregnancy. It has been accepted by families and applied around the world in IVF and PGD centres (Harper & SenGupta, 2012; and Lavery et al., 2002). Nonetheless, it is a challenging procedure, and patients need to understand that risk of misdiagnosis cannot be eliminated (Harton et al., 2011; and Wilton, Thornhill, Traeger-Synodinos, Sermon, & Harper, 2009).

With PGD there is a need for IVF and embryo testing, both are invasive procedures not free from risk. Risks include high patient discomfort, stress and anxiety, reaction to fertility drugs, some embryos may be damaged by the process of cell removal for testing, failure of procedure, miscarriage, ectopic pregnancy, and ovarian hyperstimulation syndrome (Bhattacharya, 2003; El-Hazmi, 1999; Heijnen, Macklon, & Fauser, 2004; and Olivennes, 2003). In addition, there are risks to the infant. These include low birth weight, congenital abnormalities, and peri-natal mortality (Harton et al., 2011).

A few studies have examined the acceptance of PGD among Saudi couples. Most welcomed the idea as a way of preventing the birth of an affected child (Alkuraya & Kilani, 2001; Alsulaiman, Al-Odaib, Al-Rejjal, & Hewison, 2010; and Alsulaiman & Hewison, 2006). Families who had undergone PGD report experiencing more ethical and psychological stress than anticipated (Alsulaiman et al., 2010). PGD is a complex

procedure that continues to evolve and develop with new tools and approaches. It is not an easy process for the families, therefore counselling services should be an integral part of care to help the families through the difficult stages of this technology (Alsulaiman et al., 2010; and Harper et al., 2012).

#### **2.5.4 Knowledge about IEM in Saudi Arabia**

General knowledge and awareness are fundamental issues and it is essential to address them. Al-Essa and colleagues conducted a survey study among randomly selected families with children seen at the clinics of KFSH&RC in Saudi Arabia. The study was to evaluate the knowledge of 500 parents of children with metabolic disorders and it clearly indicated that the majority of parents (over 50%), particularly those with a lower level of education, are unaware of aetiologies, symptoms, inheritance, and therapies for various inborn errors of metabolism. The authors recommend that a broad-based public health education programme is needed in order to secure early referrals, particularly from high-risk families, i.e., families with metabolic disorders, or those who have experienced unexplained infant death (Al-Essa, Ozand, & Al-Gain, 1997). There are no recent measures of current knowledge about IEM in Saudi Arabia, but there have been no major educational programmes to believe that this has vastly improved.

## **2.6 Nutritional management of IEM**

### **2.6.1 Special diets**

The importance of optimal nutrition and dietary manipulation, as an essential part of treatment, needs to be emphasized. Often it is not fully comprehended by families, leading to incomplete compliance with the prescribed diet. In fact, adhering to the special diets require a great deal of effort and adjustment, the diets are absolutely crucial to successful management of a considerable number of metabolic disorders. A special and specific diet is prescribed for each patient with a metabolic disorder that has dietary influences, for example, for patients with inborn errors of protein metabolism (aminoacidopathies) the diet involves restricting the dietary intake of

protein to limit the intake of the amino acid/s (specific to each disorder) that cause the metabolic distress, and substituting this part of the diet with special formulas to provide essential nutrients which have been limited with the restricted diet (Clarke, 2002; and Walter & MacDonald, 2006).

Special diets often mean the difference between developmental disability and normal functioning of individuals with metabolic disorders (Brumm & Grant, 2010; Cockburn & Clark, 1996; and Hoffmann, Helbling, Schadewaldt, & Wendel, 2006). Children with metabolic disorders and their families need to comprehend the genetics of their particular disorders, the treatment of the disorder including the specific dietary restrictions, the reasons for these restrictions and how they work in preventing harmful effects of each disorder. It is important for families to know that the patients will be monitored through regular clinic visits and laboratory tests, be trained to take a blood sample, to adjust the diet to maintain metabolic control, and to handle social situations concerning food. This will help patients recognize that they can be effective individuals in society without compromising their health or being a burden on carers. Nonetheless, compliance with these restricted diets is difficult, and tends to decrease around adolescence. Therefore identifying compliance barriers and learning how to help patients overcome them is an essential aspect of care (MacDonald, Gökmen-Ozel, van Rijn, & Burgard, 2010).

Effective nutritional programmes are in place to support and counsel patients and their families in most of the European countries and North America. They have regular clinic attendance, and when not able to attend patients are trained to send blood samples to their laboratories. Results are then given to the dietitians who can easily communicate these to the patients and families through the phone, and discuss the needed course of action, whether it is to continue with current diet or to implement changes in formula or food intake to improve blood levels. Having such systems in place and training patients and their families in dealing efficiently with them vastly improves the quality of care for each patient, and greatly helps patients and their families in dealing with their disorders. Nutrition counselling and education can be provided in many effective ways; it could be through one to one sessions or in group sessions, with the use of visual aids; such as posters; food models; videos; and stories and games for children (Bernstein et al., 2013; Schwandt et al., 1999; and Williams et

al., 1998). To be most effective education materials need to be adapted to suite the population they are intended for (Winkleby et al., 1997).

Fisch (2000) argued that “The effectiveness of our treatment is always in the shadow of the compliance of our patients” clearly elucidating how essential patient compliance is to outcome. Many studies showed how non-compliance with diet and intake of prescribed protein substitute formulas negatively affect amino acid levels, IQ levels, and cause some vitamins and minerals deficiencies and decreases in bone mineral content (Chang, Gray, & O'Brien, 2000; Huijbregts et al., 2002; Przyrembel & Bremer, 2000; and Robinson et al., 2000).

### **2.6.2 Formula compliance and vitamin and mineral needs**

With all low or restricted protein diets there is a risk of deficiencies in some vitamins and minerals. Current research indicates particular deficiencies when the patients do not comply with their formula intake. Hanley et al (1996) followed 96 adolescents and young adults with PKU in their clinic in Canada; only 66% of them continued with their prescribed dietary therapy, and not all of those had good control or took their formula regularly. They tested 37 of their patients for several micronutrient deficiencies because the formula contains important supplements of vitamins and minerals that are lacking in the low phenylalanine diet, 12 (32%) of them had suboptimal levels of vitamin B<sub>12</sub>; five of those patients were off diet. They recommend periodic monitoring of serum B<sub>12</sub>, red blood cell folate, and ferritin in adolescents and young adults with PKU, and additionally monitoring of methylmalonic acid and homocysteine because they increase with lack of vitamin B<sub>12</sub> and could be good indicators for early detection of B<sub>12</sub> deficiency (Hanley, Feigenbaum, Clarke, Schoonheydt, & Austin, 1996).

Another study reported that 77% of the adult PKU patients in their sample, who are off diet, had biochemical signs of vitamin B<sub>12</sub> deficiency (Hvas, Nexø, & Nielsen, 2006). They have also measured their vitamin B<sub>6</sub> intake through food diaries and found that 71% of the patients get less than the recommended intake. Vitamin B<sub>6</sub> is found in beans, meat, poultry, fish and some fruits and vegetables, but mainly in high protein foods. The authors recommend daily vitamin supplementation for PKU

patients who are off diet and continued dietary management throughout adult life (Hvas et al., 2006).

Robinson and colleagues (2000) found that vitamin B<sub>12</sub> is adequately supplied within the formula or additional supplements for adolescents and adults with PKU on a strict diet, while patients on a relaxed or unrestricted diet had inadequate intake of vitamin B<sub>12</sub>. This was due to their tendency to avoid animal protein because they either find the taste unpleasant or because they recognize it is harmful to them and try to avoid it.

Vugteveen et al (2011) has shown that patients who were continuously treated and have been taking their formula have been found to have functional vitamin B<sub>12</sub> deficiency, which is defined by the authors as an increase of methylmalonic acid levels even if vitamin B<sub>12</sub> levels were normal. They recommend yearly monitoring of serum methylmalonic acid levels in PKU patients to detect B<sub>12</sub> deficiency in the earliest stages. The researchers speculate that finding more vitamin B<sub>12</sub> deficiencies in PKU patients could be due to lower bioavailability of B<sub>12</sub> from the protein substitute formula and due to taking the formula less than three times a day; increased intake of B<sub>12</sub> in one meal reduces its availability (Vugteveen et al., 2011). The main dietary source of B<sub>12</sub> is animal protein. Untreated vitamin B<sub>12</sub> deficiency may lead to a wide range of psychiatric and neurologic problems, some irreversible, in addition to the risk of macrocytic anaemia (Hvas et al., 2006; and Robinson et al., 2000).

Several studies report high incidence of iron deficiency in patients with PKU despite being compliant with the diet and the protein substitute formulas; all patients in these studies had an adequate iron intake within the recommended level (Acosta et al., 2004; Acosta, 1996; Arnold, Kirby, Preston, & Blakely, 2001; Bodley, Austin, Hanley, Clarke, & Zlotkin, 1993; Miranda da Cruz, Seidler, & Widhalm, 1993; and Tavit et al., 2006). The researchers questioned the bioavailability of iron through the protein substitute formula and called for further research. Iron deficiency could affect growth levels and cause cognitive, motor, and behavioural disturbances, therefore the researchers recommended regular monitoring of complete blood counts, haemoglobin, and ferritin for early assessment of any deficiency. One of the previous studies gave iron supplements (5 mg elemental Fe/kg daily) for 4 months to the patients with low iron levels, the patients benefited from this treatment and showed improved levels (Miranda da Cruz et al., 1993).

Only one study looked at vitamin A levels for patients with PKU (Acosta, 1996). All patients had intakes of vitamin A greater than the recommended dietary allowance for age but the plasma retinol concentrations for 48% of them were in the marginal or deficient range. Again the bioavailability of vitamin A from the formula was questioned and further research is warranted.

A few studies looked at selenium levels in patients with PKU and found that high percentages of the patients had low plasma selenium levels, but the patients didn't present any selenium deficiency symptoms (Barretto et al., 2008; Jochum et al., 1997; and MacDonald et al., 2004). This was explained by the low level of selenium in some of the formulas or due to noncompliance with the formula intake. In addition to selenium deficiency Barretto and colleagues found that 37.5% of their patients had below normal levels of erythrocyte zinc even though their intake of zinc was more than the dietary recommended intake. Dietary fibre and phytate content of grains, nuts, and legumes may reduce the bioavailability of zinc by forming insoluble complexes with zinc (Barretto et al., 2008).

Low bone mineralization has been reported in older children with PKU and associated with high levels of blood phenylalanine (Adamczyk et al., 2011; Al-Qadreh et al., 1998; and McMurry, Chan, Leonard, & Ernst, 1992). In all of these studies older children and adolescents who were not compliant with the PKU diet and formula intake had significantly lower bone mineral density than compliant patients and normally developing children. This puts the non-compliant patients at increased risk of not reaching the optimum bone mineral content increasing their risk for fractures and adult osteoporosis. Furthermore, Adamczyk and colleagues (2011) reported that non-compliant patients had significantly lower muscle mass than compliant patients. The researchers recommended continuous dietary compliance with good blood phenylalanine control to protect the bone mineral development of patients with PKU and to reduce the risk of abnormalities in the fat and muscle tissues (Adamczyk et al., 2011; Al-Qadreh et al., 1998; and McMurry et al., 1992).

## **2.7 The focus of this research**

There are a large number of inborn errors of metabolism; it would be too broad and unrealistic to try and address all the disorders in this initial study. The research was thought to be best focused on a group of disorders which has similar nutritional approaches to treatment, and which are of relatively high incidence in Saudi Arabia. Choosing disorders that required dietary management was essential as well, this would guarantee that the outcomes were related to diet and compliance with it and not confounded by other factors.

To accomplish this, the research focused on aminoacidopathies, mainly phenylketonuria (PKU), tyrosinaemia I, and maple syrup urine disease (MSUD) for Phase 1 of the research. As these aminoacidopathies are prevalent in Saudi Arabia and have clear dietary requirements. At the time of the study KFSH&RC had 55 active patients with PKU, 24 with tyrosinaemia I, and 73 with MSUD.

These are all autosomal recessive disorders. In aminoacidopathies there is a need to restrict dietary intake of one or more amino acids which may be toxic themselves or be precursors of toxic metabolites, thus limiting protein intake from food and providing special diets and formulas that provide patients with other essential amino acids, vitamins, minerals, and energy (Walter & MacDonald, 2006). With all low or restricted protein diets there is a risk of deficiencies in some vitamins and minerals, deficiencies should always be assessed in patients and supplements given as needed. Section 2.6.2 above explored this issue in detail.

The clearest of these disorders in outcome is PKU; good dietary compliance is very well correlated to favourable outcome (Donlon, Levy, & Scriver, 2006; and Smith & Lee, 2000). The relationship is clearly defined in PKU between control of the amino acid phenylalanine and the Intelligence Quotient (IQ) levels where IQ is the ultimate outcome measure. Burgard's review of studies of intelligence of patients treated early for PKU showed that IQ level decreases by half a standard deviation for each 300  $\mu\text{mol/l}$  increase in the blood concentration of phenylalanine during pre-school and early school age (Burgard, 2000). In addition, PKU outcome is much less affected by acute illness episodes than MSUD.

For tyrosinaemia I and MSUD the determinants of outcome are less certain and can be affected by other factors; for tyrosinaemia I there is uncertainty around acceptable levels of tyrosine and whether there is a need to avoid low phenylalanine levels, and which of these is negatively related to learning disabilities. MSUD outcome is affected by the severity, duration of the presenting illness and delays in diagnosis. It is also highly affected by acute illness episodes leading to acutely elevated leucine blood levels (Chakrapani & Holme, 2006; and Wendel & de Baulny, 2006). For these reasons Phase 2 of this research focused only on PKU, it is reviewed below in more detail than the other two disorders.

### **2.7.1 Maple syrup urine disease (MSUD)**

MSUD is a disorder of branched-chain amino acid metabolism in which blood concentrations of leucine, isoleucine, and valine are highly elevated. The fundamental defect is in the activity of the branched-chain  $\alpha$ -ketoacid dehydrogenase complex. MSUD is classified as classic, intermediate, intermittent, or responsive to thiamine, all of the patients in this study have classic MSUD (Chuang, Chuang, & Wynn, 2006; and Chuang, Wynn, & Shih, 2006). Around 80% of patients with MSUD have the classical phenotype, they have 2% or less of the normal enzyme activity. The remainder of the patients have the intermediate phenotype with higher residual enzyme activity, and rarely some patients have intermittent manifestation of the disease and some patients respond to dietary treatment with thiamine. Patients with intermediate or intermittent forms of MSUD have a milder clinical course and late onset of the symptoms, but they can experience severe metabolic crises (Simon et al., 2006; and Strauss, Puffenberger, & Morton, 2006).

Early symptoms include vomiting, feeding difficulties, irritability, ketonuria, and the odour of maple syrup in cerumen and urine. Clinical abnormalities for classic MSUD usually manifest within the first week of life (Strauss et al., 2006). Untreated infants with MSUD present with metabolic acidosis, acute encephalopathy, spastic quadriplegia, convulsions, then coma and central respiratory failure. Serious central nervous system conditions may develop in the form of cerebral oedema and death may result from brain-stem compression (de Baulny, Dionisi-Vici, & Wendel, 2012; and Pandor et al., 2004).

Outcome is thought to be most influenced by the severity of illness at diagnosis, the age at diagnosis, and the long-term biochemical control of the branched-chain amino acids (Chuang et al., 2006; Hoffmann et al., 2006; and Naughten, Jenkins, Francis, & Leonard, 1982). Early diagnosis followed by lifelong dietary management can prevent developmental delay, the best outcome is seen when treatment starts before the age of 10 days (Hilliges, Awiszus, & Wendel, 1993; and Kaplan et al., 1991). Researchers advocate the inclusion of MSUD in newborn screening programmes as it allows early diagnosis and management before the onset of severe symptoms, which is fundamental for reducing the risk of brain damage if accompanied with long-term good dietary management (Heldt, Schwahn, Marquardt, Grotzke, & Wendel, 2005; Muelly et al., 2013; and Simon et al., 2006).

Dietary treatment requires following a protein restricted diet with the intake of a special formula free from branched-chain amino acids. This is aimed at limiting the branched chain amino acids to prevent episodes of decompensation while providing sufficient levels for normal development (de Baulny et al., 2012; and Strauss et al., 2006). Patients are susceptible to acute deterioration during acute illness episodes, such as infections, therefore, dietary modifications should be prompted when parents notice behavioural changes, unsteadiness or lethargy (Morris & Leonard, 1997; and Morton, Strauss, Robinson, Puffenberger, & Kelley, 2002). The amino acid leucine is the most toxic, while isoleucine and valine are more tolerated. Dietary protein restriction for the reduction of high leucine blood levels may require cautious supplementation of a small amount of free valine or isoleucine if either of their levels fell below minimum requirements, this is important for normal growth and to prevent amino acid deficiency and the risk of catabolic stress (Chuang et al., 2006; and Morton et al., 2002).

MSUD has been corrected by liver transplantation, although previously it was not considered a better option than strict dietary treatment; due to the risks, uncertain outcome, and cost (Wendel, Saudubray, Bodner, & Schadewaldt, 1999). More successful liver transplantations have been reported in recent years as treatment for MSUD. Researchers report the benefits of liver transplants in effectively controlling the blood levels of the branched-chain amino acids and allowing the patients to be on

normal diets with no restrictions (Chuang et al., 2006; Shellmer et al., 2011; and Strauss et al., 2006).

Liver transplantation does not reverse any cognitive delay caused by MSUD, but it stops the progression of impairment and it provides the patients and their families with the relief from the risks of metabolic crises. Therefore, the best outcome is believed to be when the transplantation is done early in life before experiencing any neurological or intellectual impairment (Mazariegos et al., 2012; Muelly et al., 2013; Shellmer et al., 2011; and Strauss et al., 2006).

Liver transplantation is advised to be decided on each case individually, as circumstances of patients vary, and consideration for a transplant is mostly for patients with severe enzyme deficiency (Mazariegos et al., 2012). Liver transplantation remains complicated and holds the risks of immune suppression, graft complications, and surgery; these are all issues for careful consideration (Chuang et al., 2006; and Strauss et al., 2006). However, in countries with limited availability of the special dietary formula and inadequate management of acute episodes, liver transplantation might be the best option for MSUD patients (Mazariegos et al., 2012).

### **2.7.2 Tyrosinaemia**

There are two types of tyrosinaemia observed in Saudi Arabia, type I (Hepatorenal tyrosinaemia) and type II (Oculocutaneous tyrosinaemia). Tyrosinaemia type I is the type most seen in Saudi Arabia, and all of the patients with tyrosinaemia in Phase I of this study had tyrosinaemia type I.

#### **Tyrosinaemia type I**

Tyrosinaemia type I causes hepatic and renal toxicity. Progressive liver disease is the major complication of untreated tyrosinaemia I, eventually the patients develop liver cirrhosis or hepatocellular carcinoma, or both, in late childhood or adolescence (Chakrapani, Gissen, & McKiernan, 2012). Renal dysfunction is seen in most patients, from mild tubular dysfunction to renal failure. Other common symptoms include rickets, failure to thrive, hepatosplenomegaly, hypotonia, and neurological crises of acute peripheral neuropathy, pain and paresthesia (Chakrapani et al., 2012; Mitchell, Grompe, Lambert, & Tanguay, 2006; and Pandor et al., 2004). The severity

of these symptoms varies, as the disease has a variable phenotype depending on the age at onset of symptoms (Holme & Lindstedt, 1998).

Tyrosinaemia type I is caused by the deficiency of the enzyme fumarylacetoacetate hydrolase (FAH). It is the last enzyme in the catabolism pathway of tyrosine, and it is mainly expressed by the liver and kidneys (Mitchell et al., 2006). Its deficiency stops the process of tyrosine catabolism, which leads to the accumulation of the intermediate metabolites fumarylacetoacetate and maleylacetoacetate, and their reduced derivatives succinylacetoacetate and succinylacetone. These are thought to cause the hepatorenal damage (Chakrapani et al., 2012; and Holme & Lindstedt, 1998).

Tyrosinaemia type I is treated by the drug NTBC (2-(2-nitro-4-trifluoromethyl benzoyl)-1,3-cyclohexanedione), also known as Nitisinone, in addition to dietary restrictions of phenylalanine and tyrosine and the intake of a special dietary formula free from tyrosine and phenylalanine to meet the nutritional requirements of the patients (Chakrapani et al., 2012). NTBC is an inhibitor of the enzyme 4-hydroxyphenylpyruvate dioxygenase which blocks the metabolic pathway of tyrosine at the second step, and inhibits its degradation before reaching the toxic metabolites (Lock et al., 1998). Liver transplantation has been the choice of treatment, but NTBC greatly reduced the need for it. Transplantation is currently indicated for patients with suspected liver cancer or for patients who do not respond to NTBC treatment (McKiernan, 2006).

The first use of NTBC for patients with tyrosinaemia type I was in 1991 by Lindstedt and colleagues (1992). They found marked improvements in the clinical condition of the patients after treatment with NTBC and dietary restrictions of phenylalanine and tyrosine to keep plasma tyrosine level less than 500  $\mu\text{mol/l}$ . It helped in the treatment of renal tubular dysfunction, reduced the need for liver transplants, and for patients who started treatment at an early age it decreased the risk of developing liver cirrhosis and liver cancer (Holme & Lindstedt, 1998; Holme & Lindstedt, 2000; and Lindstedt, Holme, Lock, Hjalmarson, & Strandvik, 1992). The prevention of liver disease when NTBC is started early after birth signifies the importance of having tyrosinaemia type I on newborn screening programmes (McKiernan, 2006; Santra & Baumann, 2008; and Schulze, Frommhold, Hoffmann, & Mayatepek, 2001).

The sources of tyrosine in the body are the diet and the hydroxylation of phenylalanine. Given that the metabolism of tyrosine and phenylalanine is blocked, dietary restriction of these amino acids is essential (Nyhan & Ozand, 1998; and Santra & Baumann, 2008). Dietary treatment accompanies NTBC treatment, and the aim is to keep blood tyrosine level below 400  $\mu\text{mol/l}$ . The diet consists of limiting phenylalanine and tyrosine intake by limiting protein intake and by providing a special dietary formula that provides essential amino acids needed for growth (Mitchell et al., 2006).

NTBC with dietary management is still the best available treatment for tyrosinaemia type I. Studies continue to report the benefits of this treatment for the patients. Larochelle et al (2012) describe the clinical outcome for 78 patients with tyrosinaemia type I in Quebec. They report that the patients who were treated with NTBC in addition to complying with low protein diet did not suffer acute episodes. Additionally, patients detected by newborn screening and treated before one month of age were free from liver disease for the follow up period of the study, over five years.

Couse et al (2011) report improved outcome for their patients in Spain when treated with NTBC and dietary restriction of tyrosine and phenylalanine. Only six patients, out of the 34 in this study, were detected by newborn screening, the remainder were diagnosed after clinical symptoms. Nonetheless, treatment improved their prognosis and none of the patients developed hepatic carcinoma.

A similar experience was reported by Masurel-Paulet et al (2008). They detail the long term effects of treatment with NTBC for 46 patients with tyrosinaemia type I in France. Forty two of the patients were diagnosed after clinical symptoms, 38 of them had liver failure. Treatment with NTBC improved the quality of life and the prognosis for the patients. Two patients developed hepatocellular carcinoma, they were treated after the age of 2 years, this asserts the importance of early treatment. Some of the patients had cognitive problems and school difficulties, the authors report that it is not clear if this is due to noncompliance with the dietary restrictions of tyrosine and phenylalanine, or due to NTBC treatment, or just due to the disease itself. Continued follow up and further investigation is important.

In their review of NTBC, as treatment for tyrosinaemia type I, Santra and Baumann (2008) affirm that NTBC has shown great benefits for the patients, but it requires firm compliance with the dietary restrictions of phenylalanine and tyrosine. Treating patients early with NTBC prevented liver disease, considerably reduced the risk of hepatocellular carcinoma, and improved renal tubular function. Treatment with NTBC improved the symptoms of patients with advanced disease as well. The authors caution that even if patients were on NTBC they should continue to be screened for malignancy in the liver, as the effect of NTBC on reducing the risk of developing hepatocellular carcinoma is not fully clear and needs to be studied further.

### **Tyrosinaemia type II**

Tyrosinaemia type II is rare in Saudi Arabia, and none of the patients were encountered during the data collection of this research. It is caused by a defect in the hepatic tyrosine aminotransferase (TAT); the first enzyme in the catabolism pathway of tyrosine (Mitchell et al., 2006). Tyrosinaemia type II is characterized by causing corneal and skin lesions, in addition to variable degrees of neurological manifestations and learning difficulties, one or all of these effects could be present. Eye symptoms include photophobia, tearing, corneal ulceration, eye pain, and inflammation. Skin lesions are painful hyperkeratotic plaques on the hand palms and feet soles. It is thought that the eye and skin lesions are due to the intracellular accumulation of tyrosine crystals (Chakrapani et al., 2012; and Scott, 2006). Developmental delay occurs in nearly half of the patients with tyrosinaemia II, it has not been linked to age at diagnosis, but it is thought to be affected by very high blood tyrosine levels early in life (Mitchell et al., 2006).

Treatment is through dietary restriction of tyrosine and phenylalanine and the intake of a special dietary formula free from tyrosine and phenylalanine to meet the patients' nutritional requirements. Blood levels of tyrosine below 800  $\mu\text{mol/l}$  resolve the skin and eye symptoms, but there is no definite agreement on an ideal level that allows the best cognitive development and prevents delay, although some researchers suggest 600  $\mu\text{mol/l}$  (Chakrapani et al., 2012; Mitchell et al., 2006; and Scott, 2006).

A report by Al-Essa and colleagues (1998) describes the first four patients with tyrosinaemia II in Saudi Arabia. The patients had skin lesions and mild mental

disability, their eyes were not affected. They were put on dietary restriction of tyrosine and phenylalanine. The patients improved dramatically after complying with the diet and reducing their blood tyrosine level to below 1000  $\mu\text{mol/l}$  (Al-Essa, Rashed, & Ozand, 1998).

### **2.7.3 Phenylketonuria (PKU)**

PKU is caused by a defect in the enzyme phenylalanine hydroxylase (PAH), PAH is required for the conversion of the essential amino acid phenylalanine to tyrosine (Donlon et al., 2006). Without the activity of the PAH enzyme phenylalanine concentrations increase in the blood and reach toxic concentrations in the brain (Blau, van Spronsen, & Levy, 2010; and van Spronsen & Enns, 2010). The expression and activity of PAH is mainly in the liver, but is seen in the kidney as well (Donlon et al., 2006; and Scriver, 2007). Oxygen, iron, and the cofactor tetrahydrobiopterin (BH4) are needed for the activity of PAH (Blau et al., 2010; and Donlon et al., 2006).

The phenylalanine hydroxylase gene has more than 500 different disease causing mutations described, hence the wide spectrum in the genotype and phenotype of the disorder (Scriver, 2007). Variations range between mild defective activity of the enzyme to severe complete inactivation of the enzyme, where blood phenylalanine concentrations could go up to 30 times the normal level. The normal range of blood phenylalanine concentration is 35-120  $\mu\text{mol/l}$  (Walter, Lachmann, & Burgard, 2012). Patients are considered to have mild hyperphenylalaninaemia if their blood phenylalanine levels are 120–600  $\mu\text{mol/l}$ , levels of 600–1200  $\mu\text{mol/l}$  are classified as Mild PKU, and levels over 1200  $\mu\text{mol/l}$  are classified as Classic PKU (Blau et al., 2010).

Progressive developmental delay is the most significant sign of untreated PKU. Other symptoms in untreated or late diagnosed patients include infantile spasms, microcephaly, neuromotor deficits, their eyes, hair and skin would be lightly pigmented compared to their parents, an unusual 'mousy' odour may be observed early in life, and in about a third of the patients other symptoms can manifest such as dermatitis, and seizures. Hyperactivity, behavioural problems, psychiatric symptoms, and decreased executive function is seen in older children and adults (Blau et al.,

2010; MacDonald, Nanuwa, Parkes, Nathan, & Chauhan, 2011; van Spronsen & Enns, 2010; and Walter et al., 2012).

### **2.7.3.1 Main PKU Treatment**

#### **Low phenylalanine diet**

Dietary treatment through the restriction of phenylalanine intake has been the basis of PKU management for the past sixty years. PKU is one of the first metabolic disorders to be understood biochemically and to have a treatment available (Bélanger-Quintana, Burlina, Harding, & Muntau, 2011; and van Spronsen & Enns, 2010). To prevent the symptoms of PKU diagnosis should be made in the neonatal period through newborn screening and treatment should promptly start following confirmation of diagnosis, and continue for life (Donlon et al., 2006).

The main goal of dietary treatment for PKU is to provide a low phenylalanine diet that maintains blood phenylalanine within a reasonable range of 120-360  $\mu\text{mol/l}$ . Limiting phenylalanine blood levels has been established to prevent developmental delay, yet provide enough phenylalanine to meet the need of this essential amino acid for normal growth and body repair (Koch et al., 1996; and Walter et al., 2012). The upper and lower limits of the acceptable blood phenylalanine level differ slightly between countries and changes for different age groups (Blau et al., 2010). Patients keeping their blood phenylalanine levels within the required limits are in metabolic control.

A nutritionally complete low phenylalanine diet is achieved by allowing patients to consume a controlled quantity of low protein natural foods that provide a measured amount of dietary phenylalanine and by consuming a special phenylalanine free protein substitute formula. The formula should provide the needs of amino acids, carbohydrates, fats, vitamins, minerals, and energy. Foods with minimal amounts or free from phenylalanine are allowed without measurements, and all animal protein sources and legumes are not allowed. Low-protein alternatives of some products are available, such as low-protein bread, pasta, and biscuits, they are used to increase dietary variety and provide needed energy. The amount of the allowed dietary phenylalanine is adjusted for each patient until their phenylalanine blood levels

become stable (Feillet & Agostoni, 2010; MacDonald, Gökmen-Ozel, & Daly, 2009; MacLeod & Ney, 2010; and Walter et al., 2012).

It is essential to regularly monitor the phenylalanine blood levels of PKU patients to ensure metabolic control and adherence to diet, and to prevent the harmful effects of high levels (Feillet, MacDonald, Hartung, & Burton, 2010; and van Spronsen & Burgard, 2008). In addition, it is important to monitor the nutritional status of the patients to prevent any deficiencies, since this is a risk with PKU as reviewed previously, especially if the patients were not consuming the prescribed amounts of their formula (Feillet & Agostoni, 2010; and Lammardo et al., 2013).

Researchers also recommend close monitoring of the growth and weight of patients to prevent overweight and obesity (Burrage et al., 2012; and Rocha, MacDonald, & Trefz, 2013). Some studies have found that there are high levels of overweight and obesity among PKU patients, especially in girls (Burrage et al., 2012; and White, Kronmal, & Acosta, 1982), while others report that PKU patients have normal growth and body composition, and overweight and obesity levels are not higher than the levels seen in the normal population (Huemer, Huemer, Moslinger, Huter, & Stockler-Ipsiroglu, 2007; Robertson et al., 2013; and Rocha et al., 2012). Nonetheless, overweight levels are high and increase with age especially for women, Robertson et al (2013) reported overweight in 51% of adult patients with PKU in the UK. Overweight, even if it was similar to the general population levels, may lead to other health problems, which complicates the dietary management for PKU patients. Studies could not identify if obesity in PKU is due to the condition itself, to inadequate metabolic control, or is a result of the dietary treatment (Rocha et al., 2013). More studies are needed to identify the underlying cause of overweight among PKU patients to enable its early prevention.

Adherence to the strict diet of PKU is extremely burdensome and hard for the patients and their families. They face difficult social, emotional, and economical issues relating to the complex dietary management of this disorder (Di Ciommo, Forcella, & Cotugno, 2012; Sharman, Mulgrew, & Katsikitis, 2013; and Simon et al., 2008). Consequently, compliance decreases with age, and becomes more difficult for adolescents to keep metabolic control (Blau et al., 2010; Freehauf, Van Hove, Gao, Bernstein, & Thomas, 2013; MacDonald et al., 2006; and Walter et al., 2002). These

reasons have compelled researchers to seek alternative therapies for PKU to help patients maintain metabolic control for life (Bélanger-Quintana et al., 2011; and Giovannini, Verduci, Salvatici, Paci, & Riva, 2012).

### **2.7.3.2 New treatment options for PKU**

Some new dietary and treatment options have emerged in the past few years, such as glycomacropeptide, large neutral amino acids, and sapropterin dihydrochloride (BH4). They have helped specific patients to reach metabolic control, but they are not suitable for all PKU patients and not available in many countries.

#### **Sapropterin dihydrochloride (BH4)**

Sapropterin dihydrochloride, also known as BH4, is a synthetic form of the naturally occurring tetrahydrobiopterin (6R-BH4), the commercial pharmaceutical name is Kuvan (Burnett, 2007). It was noticed that not only patients with hyperphenylalaninaemia due to tetrahydrobiopterin deficiency (reviewed below) were responsive to the loading test of BH4, some patients with hyperphenylalaninaemia due to PAH deficiency were observed to have lower levels of blood phenylalanine after being given the oral BH4 screening test (Kure et al., 1999; Michals-Matalon, 2008; and Sanford & Keating, 2009).

In combination with dietary management, BH4 is believed to boost residual PAH activity and improve metabolic control. There are several theories on the mechanism of how BH4 works; the main one is that it acts as a pharmacological chaperone. It corrects the misfolding in the PAH enzyme, stabilising it, restoring some of its function, and increasing the amount of active enzyme (Burton et al., 2011; Santos-Sierra et al., 2012; and Staudigl et al., 2011).

Numerous studies have tested the efficiency and safety of BH4 and found that it is effective for some patients with PKU in reducing their blood phenylalanine levels and increasing tolerance to dietary phenylalanine. It had no serious adverse effects and was tolerated well at doses of up to 20mg/kg/day (Burton et al., 2011; Lee et al., 2008; Levy et al., 2007; and Somaraju & Merrin, 2012). Several other studies have tested the use of BH4 with infants and children, they found it to be effective and well

tolerated (Burton et al., 2011; Hennermann, Bührer, Blau, Vetter, & Mönch, 2005; Leuret et al., 2012; and Shintaku et al., 2004).

Keil et al (2013) studied the long-term effects of treating with BH4. They followed up 147 patients with PKU; the patients have been treated with BH4 for at least 6 months and up to 12 years. They found that patients treated with BH4 had improved metabolic control, increased tolerance to dietary phenylalanine, improved compliance with diet and treatment, and many believed they had a better quality of life. They did not report any severe adverse effects to treatment, and minor side effects were gone after reducing the BH4 dose (Keil et al., 2013).

Their results are in agreement with several other studies that have reported on the efficacy of long-term treatment with BH4. Trefz, Scheible, and Frauendienst-Egger (2010) followed 14 patients on treatment for a mean time of 4.6 years, Couce et al (2012) followed 16 patients on treatment for a mean time of 5 years, and Hennermann et al (2005) reported on treating five infants for two years. They have all shown improved metabolic control, significant increase in phenylalanine tolerance, and the ability of many patients to reduce their intake of the protein substitute formula.

It is reported that 20% to 50% of PKU patients are responsive to oral treatment with BH4; most of these patients have mild to moderate PKU (Burnett, 2007; Fiori, Fiege, Riva, & Giovannini, 2005; Keil et al., 2013; Levy et al., 2007; and Lindegren et al., 2013). Patients responsive to BH4 are reported to have lower baseline phenylalanine and phenylalanine/tyrosine ratio than non-responsive patients. Additionally severe mutations were seen more in non-responsive patients (Elsas, Greto, & Wierenga, 2011; and Keil et al., 2013). Nonetheless, there are reports of some patients with severe PAH mutations (classic PKU) responding to BH4 treatment (Fiege & Blau, 2007; Hennermann et al., 2005; and Vernon, Koerner, Johnson, Bergner, & Hamosh, 2010). Therefore, the BH4 loading test is seen as an important test for all patients diagnosed with PKU before initiating treatment (Blau et al., 2009).

Blau et al (2011) recommend that after the diagnosis of PKU, through newborn screening, patients should be screened for BH4 deficiency, and then investigated for their responsiveness to treatment with BH4 through a 24-48 hour loading test. This differs between centres, but usually involves administering a single oral dose of 20

mg BH4/kg body weight/day. The patients are classified as responsive if their blood phenylalanine levels showed a reduction of at least 30% after 24 hours of the loading test, or 48 hours in some centres. This is recommended to be followed by efficiency testing for several weeks to ensure responsiveness and to adjust the dose of BH4 and the dietary phenylalanine intake for each responsive patient to attain optimum metabolic control (Anjema et al., 2013; Blau et al., 2009; and Blau, Hennermann, Langenbeck, & Lichter-Konecki, 2011). Researchers recommend repeating the loading test or extending its trial for non-responsive patient to ensure there are no false negative results and to identify patients who are slow responders to the BH4 treatment (Cerone et al., 2013; Couce, Bóveda, Valerio, Pérez-Munuzuri, & Fraga, 2012; and Staudigl et al., 2011).

Some researchers believe that genotype identification would facilitate predicting BH4 responsiveness (Anjema et al., 2013; Blau et al., 2011; Elsas et al., 2011; Keil et al., 2013; and Utz et al., 2012). This is not always the case, as patients with the same genotype have shown different response to BH4. Therefore, identifying responsive patients according to genotype needs further investigation (Blau et al., 2009; Ponzzone et al., 2010; and Staudigl et al., 2011).

It is important to note that the definition of BH4 responsiveness as blood phenylalanine level reduction of at least 30% is arbitrary. Smaller reductions may still be clinically significant for some patients, especially if they had low baseline phenylalanine levels or were on a strict low phenylalanine diet (Cerone et al., 2013). A survey of clinicians in the USA has shown that they extend the measures of response to include other clinical parameters such as improved behaviour and improved dietary phenylalanine tolerance (Gordon, Thomas, Suter, & Jurecki, 2012). Physicians in Europe are given the freedom to set the criteria of responsiveness for individual patients (MacDonald et al., 2011).

Two studies have evaluated the impact of BH4 treatment on the nutritional status of patients with PKU (Singh, Quirk, Douglas, & Brauchla, 2010; and Thiele et al., 2013). Thiele and colleagues reported that the intake of some micronutrients was particularly below recommendations for the patients who reduced or stopped taking the protein substitute formula as a result of BH4 treatment. The intake of carbohydrates and energy was below the recommendations as well. Singh et al found

that it was important to give micronutrient supplements to the patients who have stopped the protein substitute formula as dietary protein tolerance was increased on BH4 therapy.

Due to the potential risk of nutrient deficiency it is essential to continuously evaluate the nutrient status of patients under BH4 therapy as they relax their diets and reduce their intake of the protein substitute formula. The authors recommend vitamin and mineral supplements during the dietary changes that the patients go through while liberalizing their diets, until they can get sufficient supply of nutrients from natural food. Nutrition education is essential to accompany BH4 therapy, as the dietary recommendations with BH4 is dramatically different than what the patients have been taught since diagnosis with PKU. Each patient should have an individualised nutritional plan due to the variations in BH4 responsiveness among patients (MacDonald et al., 2011; Singh et al., 2010; Somaraju & Merrin, 2012; and Thiele et al., 2013).

Two recent reviews have documented the key issues and recommendations relating to the optimal use of BH4 therapy and dietary treatment for patients with PKU. MacDonald and colleagues (2011) from the UK and nine other European countries formulated a comprehensive guidance for combining BH4 treatment and diet for patients with phenylketonuria. Similarly Cunningham and colleagues (2012), a group of metabolic dietitians and physicians from across the US and Canada, participated in formulating recommendations for the use of BH4 therapy with PKU patients. The researchers based the recommendations on the latest evidence and their clinical experience; it includes guidance on determining BH4 responsive patients, target phenylalanine levels, nutritional monitoring, compliance issues, educating patients and their families on treatment targets and expectations, and the need for further research for long-term outcomes for growth and nutritional adequacy.

In a systematic review of BH4, as an adjuvant treatment of PKU, Lindegren et al (2013) argue that even though many studies have shown the benefit of BH4 treatment, there is still a great need for more research and larger studies. They describe that available evidence does not ascertain the potential effects of BH4 on longer-term outcomes such as nutritional status, behavioural change, executive function, cognitive ability, and quality of life.

Additionally, the cost of BH4 is much higher than dietary therapy, hindering its use in many countries (Burnett, 2007; Couce et al., 2012; and MacDonald et al., 2011). BH4 has caused a big leap in the treatment of PKU, as the first effective non-dietary agent to be approved for treating PKU. Yet not all patients with PKU can benefit from it, due to non-responsiveness, cost, or unknown long-term effects. Dietary treatment continues to be the basis of treatment for the time being.

### **Large neutral amino acids**

Large neutral amino acids (LNAA) have been used with selected PKU patients to improve their metabolic control. LNAA include the essential amino acids valine, isoleucine, leucine, tryptophan, threonine, methionine, and histidine, in addition to tyrosine. Tyrosine becomes an essential amino acid for PKU patients (van Spronsen, de Groot, Hoeksma, Reijngoud, & van Rijn, 2010).

There are several theories for the effect of LNAA supplementation. It may reduce the brain phenylalanine concentrations, since phenylalanine and LNAA use the same transport system, LNAA compete with phenylalanine for transport across the blood-brain barrier. This can obstruct the influx of high levels of phenylalanine into the brain and this may help prevent neurological damage (Lindegren et al., 2012; and Rocha & Martel, 2009). Another treatment theory is that LNAA supplementation would reduce blood phenylalanine levels by competing with the transport of phenylalanine through the carrier protein in the gastrointestinal tract (Lindegren et al., 2012; Matalon et al., 2006; and Matalon et al., 2007). In addition, it has been suggested that LNAA supplementation would be beneficial to PKU patients by increasing their cerebral neurotransmitter synthesis, and by elevating brain levels of essential amino acid other than phenylalanine. There are limited studies to confirm these modalities (van Spronsen et al., 2010).

The systematic review by Lindegren and colleagues (2012) of adjuvant therapies for PKU explained that even though LNAA supplementation for PKU patients has potential benefits, there is insufficient evidence concerning the safety and efficacy of long-term use. They concluded that it is not a feasible treatment alternative to reduce blood phenylalanine levels or increase phenylalanine tolerance for PKU patients. More comprehensive studies are needed to examine the possible benefits, composition, and

dosage of LNAA for all PKU patients (Lindegren et al., 2012; and van Spronsen et al., 2010). In clinical practice, LNAA supplementation is usually offered to patients who are unable to maintain dietary compliance and have chronically elevated phenylalanine blood levels, or adult patients who have been off the PKU diet to help them reach some level of metabolic control. There are several compositions of LNAA available and they do not require FDA approval because they are considered as nutritional supplements. The dosage should be calculated by the medical professional for each individual patient (Camp, Lloyd-Puryear, & Huntington, 2012; Lindegren et al., 2012; and MacLeod & Ney, 2010).

### **Glycomacropeptide**

Glycomacropeptide (GMP) is a natural protein found in cheese whey, and in its pure form it is the only known protein to be naturally free from phenylalanine, which makes ideal for the PKU diet (MacLeod & Ney, 2010). GMP is rich in some essential amino acids, but to be used as a nutritionally complete protein, it needs to be supplemented with the remaining essential amino acids for PKU patients (Laclair, Ney, MacLeod, & Etzel, 2009).

A study by van Calcar and Ney (2012) has shown that an assortment of food products and beverages made from purified and supplemented GMP provided a nutritionally complete and acceptable source of protein for PKU patients. This reduced their need for the protein substitute formula and allowed for more variety in their diet. The GMP products increased the patients' feelings of satiety and enhanced their protein utilization compared with the synthetic protein substitute formula (van Calcar & Ney, 2012).

Nutritionally complete food products made from purified GMP can improve the nutritional management of PKU through improving the variety and taste of the low phenylalanine diet and decreasing the needed amounts of the protein substitute formula. This would help in improving compliance, metabolic control, and quality of life for PKU patients (Laclair et al., 2009; MacLeod & Ney, 2010; and Ney, Blank, & Hansen, 2013). The study by van Calcar and Ney (2012) has established the short-term safety of GMP for PKU patients, but further evidence is needed to identify the long-term efficacy, safety, and effects on nutritional status of GMP products on PKU patients (van Calcar & Ney, 2012; and van Spronsen, 2010).

### **2.7.3.3 Future treatment possibilities**

Several treatment approaches for PKU are being studied in clinical and preclinical trials. These include enzyme therapy, gene therapy, and chaperone molecules. The goal is to find a sustainable treatment for PKU that would reduce blood phenylalanine levels and allow liberation from the strict PKU diet to help the patient achieve a better quality of life.

#### **Enzyme therapy**

Enzyme therapy with phenylalanine ammonia lyase (PAL) is showing promising results in reducing blood phenylalanine levels and may well increase tolerance to phenylalanine for patients with PKU. PAL converts phenylalanine to the harmless metabolite trans-cinnamic acid and trace amounts of ammonia. It has shown positive results in reducing blood levels of phenylalanine in animal models, but the host's immune response prevented a sustained effect after repeating the PAL injections (Sarkissian et al., 1999; and Sarkissian & Gámez, 2005).

Researchers have modified the PAL chemically with polyethylene glycol (PEG), to protect the PAL from immunogenicity, which should lead to a longer and more efficient reduction in blood phenylalanine levels (Gamez et al., 2005; and Gamez et al., 2007). The new formulation (PEG-PAL) has a prolonged plasma half-life and improved activity. Weekly subcutaneous administration of PEG-PAL to PKU mice was effective in achieving and sustaining long-term low blood phenylalanine levels (Sarkissian et al., 2008).

This PEG-PAL formulation is now in clinical trials with PKU patients to test its safety and efficacy. It has completed phase I trials and has entered phase II trials as a possible adjunct treatment for PKU (Belanger-Quintana, Burlina, Harding, & Muntau, 2011; and Sarkissian, Kang, Gamez, Scriver, & Stevens, 2011). The phenylalanine restricted diet may still be needed, but less rigorous.

The PEG-PAL in trials is administered through a subcutaneous injection; offering a non-invasive form would be more desirable since it would be a lifelong therapy for PKU patients. Researchers are working on developing an oral form of the PEG-PAL that can resist intestinal digestion long enough to metabolise phenylalanine in the

intestine before its absorption. In theory oral administration would evade immunogenicity (Kang et al., 2010; Sarkissian et al., 2011).

### **Gene therapy**

Several laboratories are studying the possibility of developing clinical gene therapy for PKU patients. PKU is caused by a defect in the enzyme phenylalanine hydroxylase (PAH), which is due to a mutation in the PAH gene. Gene therapy aims to add a non-mutant copy of the PAH gene into the liver or muscles, through the use of vectors, to produce PAH and correct hyperphenylalaninaemia (Harding & Blau, 2010; and Thöny, 2010).

Liver directed gene therapy, in PKU mice, has been successful in achieving reduction of high blood phenylalanine levels for up to one year, without adverse effects.

However, normal liver cell regeneration leads to the elimination of the gene therapy vector and the loss of PAH expression, preventing the accomplishment of a permanent correction of liver PAH activity (Ding, Georgiev, & Thöny, 2006; Harding et al., 2006; and Rebuffat, Harding, Ding, & Thöny, 2010). Administration of the same vector again was ineffective, because it was destroyed by an immune-mediated rejection developed in the mice in response of the initial vector injection (Rebuffat et al., 2010).

The liver is the predominant metabolic source of PAH normally, but researchers have succeeded in examining the possibility of gene therapy in non-hepatic tissue, such as skeletal muscles. Unlike the liver, muscles provide a stable environment for protein expression due to the lack of ongoing cell regeneration, have large total mass, and have easier accessibility, which theoretically leads to a more sustainable and feasible therapy (Belanger-Quintana et al., 2011; and Thöny, 2010).

Ding and colleagues (2008) managed to achieve sustained and long-term (over one year) reduction of blood phenylalanine levels in PKU mice, through the expression of a complete system that replicated the function of hepatic phenylalanine hydroxylation in the muscle cells. This included the expression of PAH and two biosynthetic enzymes for BH<sub>4</sub> (GTPCH and PTPS) to synthesize enough BH<sub>4</sub> to support phenylalanine metabolism. Researchers suggest that muscle-directed gene therapy

might be a more practical approach for the management of PKU and other inborn errors of metabolism (Ding et al., 2008; and Thöny, 2010).

Immunity against repeated injection of gene therapy vectors is a serious obstacle for application in humans. The success of gene therapy depends on developing a method that leads to permanent gene expression in liver or muscle cells to reach a sustainable therapeutic effect. Gene therapy is a promising treatment option, but it should be thoroughly evaluated before a human trial can be considered (Harding & Blau, 2010; and Thöny, 2010).

### **Chaperone molecules**

Most of the mutations causing PKU impair correct protein folding in the PAH protein, making PKU a suitable candidate for pharmacological chaperones to correct the misfolding (Underhaug, Aubi, & Martinez, 2012). The cofactor BH4 acts as a natural chaperone for PAH, and as discussed earlier, it has shown great results in normalizing blood phenylalanine levels for some patients with mild PKU mutations. The cost of BH4 is high and it is not effective with all PKU patients, therefore, the search for alternative molecules continues. The aim is to find other chaperone compounds that can promote the correct folding of mutant PAH protein, to enhance stabilization or to restore activity, in other mutations of PKU (Santos-Sierra et al., 2012; and Underhaug et al., 2012).

Pey and colleagues (2008) have identified two chaperone molecules that have increased the activity of PAH in mice to levels similar to the BH4 effect, but at a much lower dose. They believe that further examination and modification of these molecules, or other new molecules, has the potential of identifying a more potent pharmacological chaperone with a larger effect on PAH (Pey et al., 2008).

Santos et al. (2012) tested several newly chosen compounds as possible pharmacological chaperones for treating PKU. Two of these compounds increased the activity of PAH and reduced blood phenylalanine levels in PKU mice that are BH4 responsive, one of them even showed double the effectiveness of BH4 treatment (Santos-Sierra et al., 2012). Additional studies are needed to assess if these compounds would also be effective with other PKU mutations.

The field of pharmacological chaperones, though challenging, has shown promising potential for drug development to attain effective molecules that can treat a wider range of patients with PKU and other inborn errors of metabolism. The researchers envision that continued research would hopefully enable patient-tailored treatment by the use of mutation-specific pharmacological chaperones (Pey et al., 2008; Santos-Sierra et al., 2012; and Underhaug et al., 2012).

#### **2.7.4 Maternal phenylketonuria**

Damage to the infants born to mothers with inadequately treated PKU, due to the teratogenic effect of elevated maternal phenylalanine levels, is identified as maternal phenylketonuria syndrome (MPKU) (Koch, Trefz, & Waisbren, 2010). The risk to the infant is proportionate to the level of phenylalanine in the mother's blood. The risks include low birth weight, facial dysmorphism, microcephaly, reduced growth, mental disability, learning difficulties, and congenital heart disease (Donlon et al., 2006; Koch et al., 2010; and Walter et al., 2012).

To protect the infants from these risks, ideally, women with PKU should aim to reach metabolic control few months before conception till the end of pregnancy. The infants of mothers who start dietary phenylalanine restriction before conception have better developmental outcome than the infants of mothers who start after conception (Donlon et al., 2006; Maillot, Lilburn, Baudin, Morley, & Lee, 2008; and Walter et al., 2012). Nonetheless, research has shown that there are many unplanned pregnancies; therefore it is highly advisable for women with PKU of childbearing age to stay on phenylalanine-restricted dietary treatment (Koch et al., 2010; and Rouse & Azen, 2004).

The International Maternal PKU Collaborative Study has stated that maternal blood phenylalanine levels between 120 and 360 $\mu$ mol/l are the most favourable for a good birth outcome (Koch et al., 2003). Their analysis has shown that the IQ outcome for the children was not significantly different between children born to mothers who had reached metabolic control before conception, children born to mothers who had reached control before 10 weeks of pregnancy, or children born to mothers who had mild hyperphenylalaninaemia. Therefore, they concluded that it is best to reach metabolic control when planning a pregnancy, but if the pregnancy was unplanned,

normal outcome for the foetus is still achievable if the control was reached by 8 to 10 weeks of gestation and maintained all through the pregnancy.

However, some researchers believe that to get the best possible outcome for the children maternal metabolic control is vital before pregnancy. In a recent review, Prick and colleagues (2012) has shown that the risks of maternal PKU were significantly linked to mean phenylalanine levels in each trimester, apart from facial dysmorphism, which was linked to the levels in the first trimester only. This indicates that early restriction of phenylalanine intake to reach metabolic control before pregnancy is important, as the face and major organs are developed in the first trimester. Maillot et al (2008) found that it is essential to start metabolic control before conception to prevent congenital heart disease and body malformations.

In addition, it is important to ensure adequate pregnancy weight gain and sufficient intake of vitamins and protein, as they have protective effects against microcephaly and congenital heart disease (Maillot, Cook, Lilburn, & Lee, 2007; and Matalon, Acosta, & Azen, 2003). Frequent monitoring is needed to help avoid fluctuations in blood phenylalanine levels, which was reported to have a negative effect on the infants, even if the mean phenylalanine levels were within the target limits (Maillot et al., 2008).

The high rate of pregnancy while off dietary restrictions among women with PKU reveals that health services for adults with metabolic disorders may be insufficient (Lee, Lilburn, & Baudin, 2003). Preventing the risks of maternal PKU should be a public health concern, as the benefits of newborn screening in preventing disability might be diminished with the increased number of disability related to the outcome of maternal PKU Brown (Brown et al., 2002; and Scriver, 2007).

Education for girls with PKU and their families is essential about the importance of continuing follow up, maintaining metabolic control, and getting reproductive counselling before planning a pregnancy to avoid the risks of maternal PKU syndrome. This effort needs to be shared between the metabolic specialists, paediatricians, gynaecologists, and family doctors. These specialists need to be aware of the maternal PKU syndrome to give the appropriate guidance and support to

females with PKU in childbearing age (Brown et al., 2002; Donlon et al., 2006; Koch et al., 2010; and Walter et al., 2012).

Reaching metabolic control and maintaining it throughout pregnancy is very difficult, especially if the patient was off the PKU diet before pregnancy. Some researchers have recommended the use of sapropterin dihydrochloride (BH4) to help pregnant women with PKU maintain metabolic control, if its safety during pregnancy has been established (Trefz & Blau, 2003). Several reports documented positive outcomes after the use of BH4 in addition to phenylalanine restriction to treat three pregnant women with PKU (Koch, Moseley, & Guttler, 2005; Koch, 2008; and Moseley, Skrabal, Yano, & Koch, 2009). No adverse effects were reported, blood phenylalanine levels were maintained within the recommended range throughout the pregnancies, the infants did not have any of the maternal PKU symptoms, and they showed normal development after follow up (Koch, 2008; Koch et al., 2010; and Moseley et al., 2009). There were no pregnancies among the patients in this study.

#### **2.7.5 Tetrahydrobiopterin (BH4) deficiency**

Another cause of hyperphenylalaninaemia is the deficiency of tetrahydrobiopterin (BH4), which is an essential cofactor in the phenylalanine, tyrosine, and tryptophan hydroxylation reactions. BH4 is also needed for the biosynthesis of nitric oxide and the neurotransmitters serotonin, dopamine, norepinephrine, and epinephrine. Around 2% of patients with hyperphenylalaninaemia worldwide have inherited mutations in the genes encoding for enzymes that are needed for the biosynthesis or regeneration of BH4 (Erlandsen & Stevens, 1999; Hyland, Cotton, Thöny, & Blau, 2006; Scriver, 2007; and Shintaku, 2002).

It has been reported by Blau and colleagues (1996) that disorders of BH4 deficiencies account for 60% of hyperphenylalaninaemias in Saudi Arabia. There are no official statistics on the actual numbers of patients with PKU compared to BH4 deficiencies, but two studies from KFSH&RC in Saudi Arabia reported about their patients. Ozand (1998) reported the diagnosis of 16 patients with Classic PKU and only two patients with BH4 deficiency (6-pyruvoyl-tetrahydropterin synthase deficiency) after screening 26,063 infants in a period of 18 months. In a follow up study, Ozand and colleagues (2005) reported the diagnosis of 42 patients with Classic PKU and 30

patients with BH4 deficiency (6-pyruvoyltetrahydropterin synthase deficiency) over a five year period.

BH4 deficiency disorders are due to impaired synthesis or recycling of the BH4 and are all autosomal recessive disorders (Mitchell, 2000; and Shintaku, 2002). BH4 synthesis defects are due to a deficiency in the enzyme guanosine triphosphate cyclohydrolase (GTPCH) or the enzyme 6-pyruvoyl-tetrahydrobiopterin synthase (PTPS). While BH4 recycling defects are due to a deficiency in the enzyme dihydropteridine reductase (DHPR) or the enzyme pterin-4 $\alpha$ -carbinolamine dehydratase (PCD) (Hyland et al., 2006).

It is important to test patients with hyperphenylalaninaemia for BH4 deficiency to differentiate it from PKU and to distinguish between the different variants of BH4 deficiency. This is done by analysing pterin metabolites in the urine, measuring the DHPR enzyme activity in blood from the newborn screening dried blood spot, and by analysing the level of phenylalanine in blood before and after a BH4 loading test (Blau, Thöny, Spada, & Ponzzone, 1996; Hyland et al., 2006; and Mitchell, 2000).

BH4 deficiencies vary from mild forms of the disease, needing minimal treatment, to severe forms that can be difficult to treat. However, early diagnosis and treatment is effective in providing good outcome for many patients (Blau et al., 1996; and Opladen, Hoffmann, & Blau, 2012). Treatment is by supplementation of BH4 to normalize blood phenylalanine levels, and by replacement therapy of the neurotransmitter precursors 5-hydroxytryptophan and L-dopa (with carbidopa). Additionally, folic acid supplementation and diet are needed for patients with DHPR deficiency (Hyland et al., 2006; and Longo, 2009).

Patients with BH4 deficiency, if untreated, suffer from the symptoms of both hyperphenylalaninaemia and neurotransmitter deficiency. These include microcephaly, seizures, lethargy, irritability, muscular hypotonia, peripheral spasticity, progressive developmental and physical delay, and neurological deterioration (Longo, 2009; Opladen et al., 2012; and Shintaku, 2002). Patients with BH4 deficiency were not included in this study.

Focusing on a single group of disorders, the major aminoacidopathies present in Saudi Arabia, will help develop a model for examining nutrition management, and assessing risk factors associated with unsatisfactory dietary compliance for other disorders. This study can potentially help target future interventions for improving nutritional management of inborn errors of metabolism in Saudi Arabia.

# CHAPTER 3

## **METHODS**

### **3.1 Study site**

The research was carried out at the King Faisal Specialist Hospital & Research Centre in Riyadh, the capital city of Saudi Arabia. The KFSH&RC is the largest tertiary care facility in Saudi Arabia, and one of the largest in the Middle East. The research was undertaken in collaboration with the Medical Genetics Department of KFSH&RC. This department was the first of its kind in Saudi Arabia, and is the main referral centre for patients with inborn errors of metabolism.

### **3.2 Subjects**

Subjects were patients with PKU, tyrosinaemia type I, and MSUD and their families attending care services at KFSH&RC. During the study period the KFSH&RC had on record 67 patients with PKU, 24 patients with tyrosinaemia I, and 73 patients with MSUD. The age range of patients was wide, from infancy to early adulthood (birth to 21 years of age).

#### **3.2.1 Inclusion criteria**

Phase 1: Patients diagnosed with PKU, tyrosinaemia I, or MSUD and their families.

Phase 2: Patients diagnosed with PKU and their families.

#### **3.2.2 Exclusion criteria**

Phase 1: None of the families or patients were excluded.

Phase 2: None of the families or patients were excluded.

### **3.3 Ethical considerations**

The study had minimally invasive procedures. The only additional process to what was routinely followed with the patients and their families at their clinic visits to the KFSH&RC was the interviews in Phase 1 and the questionnaires in Phase 2.

A Consent Form was signed by each participating family (Appendix 1). Participating patients gave verbal assents after their parents' permission. Refusal to participate or the choice to drop out of the study was respected as stated in the Consent Form. To establish confidentiality the patients and their families were assigned codes and no names or identifiable information were entered into the databases.

The study had ethical approval from the UCL Institute of Child Health (ICH) and the KFSH&RC's Research Ethics Committee of their Research Advisory Council. A collaboration agreement was signed between ICH and KFSH&RC.

### **3.4 Study design**

This was a cross-sectional study of a group of patients with aminoacidopathies in Saudi Arabia. It was a 2-phase study design with a mixed method approach; using the sequential exploratory strategy as recommended by Creswell (2009) and Morgan (1998a). Phase 1 was an exploratory qualitative study, and Phase 2 was a quantitative assessment of the risk factors contributing to poor outcome for the patients with PKU at the KFSH&RC.

#### **3.4.1 Preliminary phase**

Before planning for the research I contacted the KFSH&RC; the feasibility of conducting the study at the hospital was discussed with the head of the Research Centre, the Head of the Medical Genetics Department, and the dietitian responsible for patients with metabolic disorders. Prior to the data collection process for Phase 1 of the study I met with some of the medical genetics doctors, the dietitian, and the laboratory technicians responsible for handling the blood samples and running the

tandem mass spectrometer (MS/MS), used for measuring blood levels of amino acids, to informally discuss the project and familiarize myself with their work. It was important to observe them in their work environment and to observe some of the patients and their families to be able to formulate the questions of the interviews (Silverman, 2006). Having spent my clinical nutrition internship at the KFSH&RC made this phase much easier, as I am acquainted with the way their clinics are conducted and have good rapport with the dietitians and many of the nurses there.

### **3.4.2 Phase 1**

This phase was a qualitative study that explored the current status of care and nutritional management of patients with PKU, tyrosinaemia I, and MSUD and their families at KFSH&RC and informed the second phase of the study.

**A. Interviews:** Qualitative data was collected from semi-structured interviews (Appendix 2, 3, and 4):

- Interviews with key informants from the health care team
- Focus groups with supporting health care providers
- Interviews with the patients
- Interviews with the families of patients

**B. Observations:** Observations were based on purposefully selected participants to examine:

- Formula preparation by patients/carers
- Dietitian counselling sessions
- Doctor clinic sessions

**C. Market survey:** A market survey was conducted to observe the availability and accessibility of the special low protein food products that are needed for the diets of the patients.

**D. Medical records review:** The medical history, developmental assessments and past blood levels of the patients were reviewed.

### **3.4.2.1 Phase 1 study sample**

Purposive sampling (non-probability sample) was used for this qualitative phase. Participants were chosen purposefully because they had particular experiences or characteristics which are reflective of the sampled population and were the best to enlighten the researcher about the study question (Creswell, 2007; and Patton, 2002). This enabled detailed exploration and understanding of the central themes being studied (Mays & Pope, 1995). All health care providers directly involved in the management of the patients were identified and included as key informants in addition to supporting health care providers. The families were interviewed until the data reached redundancy and no new information was generated (Creswell, 2007; and Ritchie, Lewis, & Elam, 2003).

Stakeholders identified at KFSH&RC:

- Health care providers: medical genetics doctors, nurses, metabolic disorders dietitians, and general dietitians.
- Patients: patients with PKU, MSUD, or tyrosinaemia I.
- Families: families or carers of patients with PKU, MSUD, or tyrosinaemia I.

### **3.4.2.2 Phase 1 data collection**

Qualitative research in this study was conducted as an essential preliminary to the quantitative research in Phase 2. The purpose was to provide an understanding of the current situation and to reach aspects of behaviours and attitudes that quantitative methods cannot reach (Creswell, 2009). Pope and Mays (1995) emphasized that in areas that have had little or no previous investigations, as is the case for this study, qualitative research is a prerequisite for good quantitative research. The framework approach was recommended for this form of research (Pope, Ziebland, & Mays, 2000), this is described in detail below in section 3.4.2.4 Phase 1 data analysis.

The research in this phase was based on 4 components. The flow chart in Figure 2 illustrates these components:

**A. Interviews (Knowledge, attitudes, and practices study):** Comprehensive information on the current status at the Medical Genetics Department at the KFSH&RC were gathered through:

- **Key informants from the health care providers:** Interviews and observations of key informants such as the metabolic disorders specialist dietitians and the physicians who represent the main points of contact with the patients and their families. Interviews covered their perceptions on care and health services, relationships with other health care providers, relationships with patients and their families, perceived nutrition knowledge of patients and carers, suggested dietary management, and compliance issues. The key informants were chosen because they had particular knowledge and insight related to the study question (Patton, 2002) (Appendix 2).
- **Health care providers:** Focus groups with health care providers (HCP) who support the main health care providers such as the nurses and the general dietitians. General dietitians may see patients with metabolic disorders during the weekend shifts or they may cover for the metabolic dietitians when needed. Discussions included perceptions of the provided health services, interrelations between health care providers and families, nutrition knowledge, management, and compliance issues (Appendix 2).
- **Families:** Interviews with the families included mothers, fathers, carers, and siblings when available. Interviews and discussions looked at metabolic disorders, acceptance, perceived nutrition and diet knowledge, management, compliance barriers, hospital services, relationships with health care providers, and relationships with other families affected by metabolic disorders in order to determine knowledge, attitudes, and practices. The interview schedule is shown in Appendix 3, and a sample of an interview is in Appendix 4.
- **Patients:** Interviews with the patients explored knowledge of their disorders, perceived nutrition and diet knowledge, compliance barriers, hospital services, and relationships with health care providers and others (Appendix 3).

## **The interview formats**

### **Interviews**

Open-ended interviews allow the researcher to explore participants' thoughts, feelings, and perspectives (Patton, 2002). The standardized open-ended interview is the type of interview used in this study. Open-ended interviews have the advantage of being structured, but at the same time flexible. They have an interview schedule with specific questions and topics to cover but this structure is flexible in its sequence allowing the topics to be covered in the order that is most suitable for the participant, and allow the responses to be explored and probed further by the researcher (Silverman, 2005).

The construction of the questions in the interviews in this study followed the rules and suggestions described by Patton (2002), for example, how to avoid leading questions and dichotomous questions. This was aided by the experience of the language used and information gathered during observations of the clinics at KFSH&RC. Questions in the family and child interviews were created from clinical experience and from issues raised through the interviews with health care providers. The interviewing strategy followed the recommendations of Legard, Keegan, and Ward (2003).

### **Focus groups**

In qualitative research it is recommended to use more than one method of data collection for triangulation, as explained in section 3.4.2.5 below. In addition to the one-to-one interviews with key informants, focus groups were conducted with the general dietitians' group and the nurses' group. Focus groups are focused informal group discussions by a small group of people to gather opinions on specific issues, moderated by the researcher, who asks open-ended questions to the whole group and then moderates the discussions (Krueger & Casey, 2000; and Morgan, 1998b).

An advantage of the focus groups is the interaction among the participants, listening to others and responding, thus enriching the discussion (Finch & Lewis, 2003; and Patton, 2002). Another advantage of focus groups is that it facilitates the collection of data from a homogenous group of participants in a relatively short period of time (Wilkinson, 2008). Focus groups are also beneficial in providing the foundation for subsequent questionnaire development (Krueger & Casey, 2000). The procedures and

protocols for conducting focus groups in this research followed the recommendations in the focus group references by Krueger (1998), Krueger and Casey (2000), and Morgan (1998c).

### **The interview process**

The health care providers' interviews were carried out in English, as this is the official language used at the hospital by all health care providers. Interviews with the families and the patients were carried out in Arabic, except for one interview which was done in English; because the mother didn't speak Arabic well and English was her first language. The interviews were held in a quiet meeting room to minimise distractions. The opportunity for interviewees to ask questions was always provided. I conducted and facilitated all of the interviews and focus group sessions.

The interview schedules were all designed in English. The family and patient interview schedules were translated to Arabic then back translated to English; to test the accuracy and validity of the content and meaning (Ercikan, 1998). The translation and back translation were done by two independent translators. The back translated interview forms were compared to the original English forms; there was good agreement between the two English versions.

The interview questions for the health care providers were pre-tested with other non-participating health care providers and the questions for the families and the patients were tested with four Saudi families, and then piloted with three of the families at KFSH&RC. This was necessary to ensure clarity and comprehensibility of the questions asked, relevance and coverage of the research problem, and to monitor the length of the interviews and comfort of the interview setting (Creswell, 2007). Two of the questions needed to be modified to clarify them.

The next steps, in line with the recommended protocols for the interviews and the focus group sessions, were followed in every session after general introductions and consent signing:

- I asked permission to record the session.
- I confirmed confidentiality of the interviews, and participants' freedom to not answer a question when uncomfortable to do so.

- I briefly went over the purpose and objectives of the study with the participants and how the results are planned to be used.
- I told them the maximum amount of time expected for the session to last.
- I gave them opportunity to talk and ask questions at the end, even if not research related; the objective was to have them leave feeling good.

## **B. Observations:**

- ***Formula and diet preparation:*** Formula and diet preparations by mothers were observed to get a clear perception of their practices.
- ***Dietitian counselling sessions:*** The metabolic disorders dietitians were observed at random counselling sessions to ascertain how the families are counselled and learn about their relationships with the dietitians.
- ***Doctor clinic sessions:*** The metabolic disorders doctors were observed at random clinics to determine how the families are counselled and learn about their relationships with the doctor.

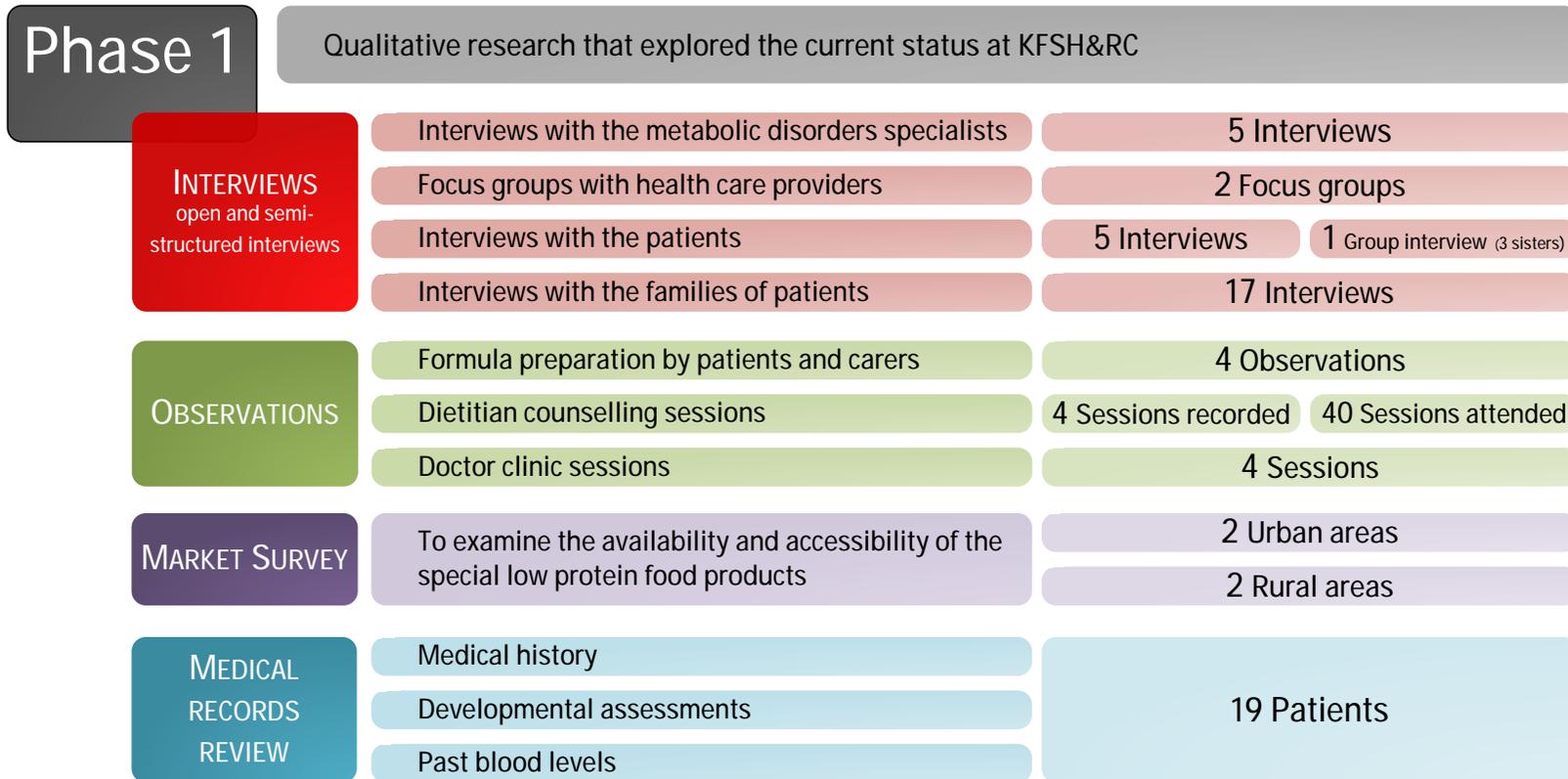
## **The observations**

The purpose of the observations is to get a direct personal experience of the participants' environments and behaviours (Creswell, 2009; and Patton, 2002). Patton described several other advantages for direct observations; they provide better understanding of the context in which participants interact, give the opportunity to notice things and routines that may be missed by participants and not mentioned in interviews because they are routinely immersed in them, help learn about things that the participants might not be keen to mention in interviews, and finally observations give the researcher an objective view of the settings away from the participants' perceptions (Patton, 2002). The settings, actions and behaviours of the observed individuals at the research site were recorded in field notes, these notes were then incorporated in the qualitative data analysis.

**C. Market survey:** The major markets in four areas -two urban areas and two rural areas- were surveyed to form an awareness of the low protein products available

and accessible for patients with aminoacidopathies. The products could be ready-to-eat products such as low protein bread, breakfast cereals and biscuits, or ingredients to make low protein dishes such as low protein flour, pasta and rice. These areas were believed to be representative enough of the Saudi market.

**D. Medical records review:** The medical history, developmental assessments, and past blood levels of the relevant amino acids for a sample of patients from each disorder, were recorded. The purpose of this process was to get a preliminary idea of trends in compliance among patients before embarking on Phase 2 of the study and to test the quantitative analysis procedure.



**Figure 2: Flow chart illustrating the different components of Phase 1, methods used, and number of participants in each part.**

### **3.4.2.3 Phase 1 data management**

The principal investigator (SA) facilitated the sessions. The sessions were audio tape-recorded. All of the interviews with the health care providers and the children were audio recorded, for the interviews with the families seven out of the seventeen declined audio recording their interviews. The families' answers in these interviews were written down during the interview by the principal investigator then reviewed with them at the end of the interview to ensure accuracy of the written notes. The interviews were transcribed verbatim by the principal investigator. The Arabic interviews were translated to English for analysis. The translation was done by the principal investigator and another translator to check for accuracy and validity through the discussion of their translations till agreement was reached on the content and meaning of the final translation. The aim was to be as closely representative as possible of the Arabic transcripts (Birbili, 2000). Both people who translated the interviews were from Saudi Arabia, fluent in Arabic and English, and familiar with the cultures of Saudi Arabia and the United Kingdom.

Findings from the interviews, focus groups, and observations of this phase were used for triangulation (refer to section 3.4.2.5); to see how much health care providers and families agree on issues concerning the care of patients (Fontana & Frey, 2003). Findings from this phase were compared to the related results from Phase 2 of this study.

### **3.4.2.4 Phase 1 data analysis**

#### **Quantitative analysis**

Amino acid blood levels were obtained from patients' medical records and were entered for analysis into SPSS 15.0 for Windows (SPSS Inc., 2006). Approximately six past blood levels were available for nine patients with PKU, five patients with tyrosinaemia I, and five patients with MSUD. Descriptive, correlation and regression statistics were used to test the associations and relationships of the blood levels over time and with related variables. This was to test the analysis process and prepare for Phase 2 of this study.

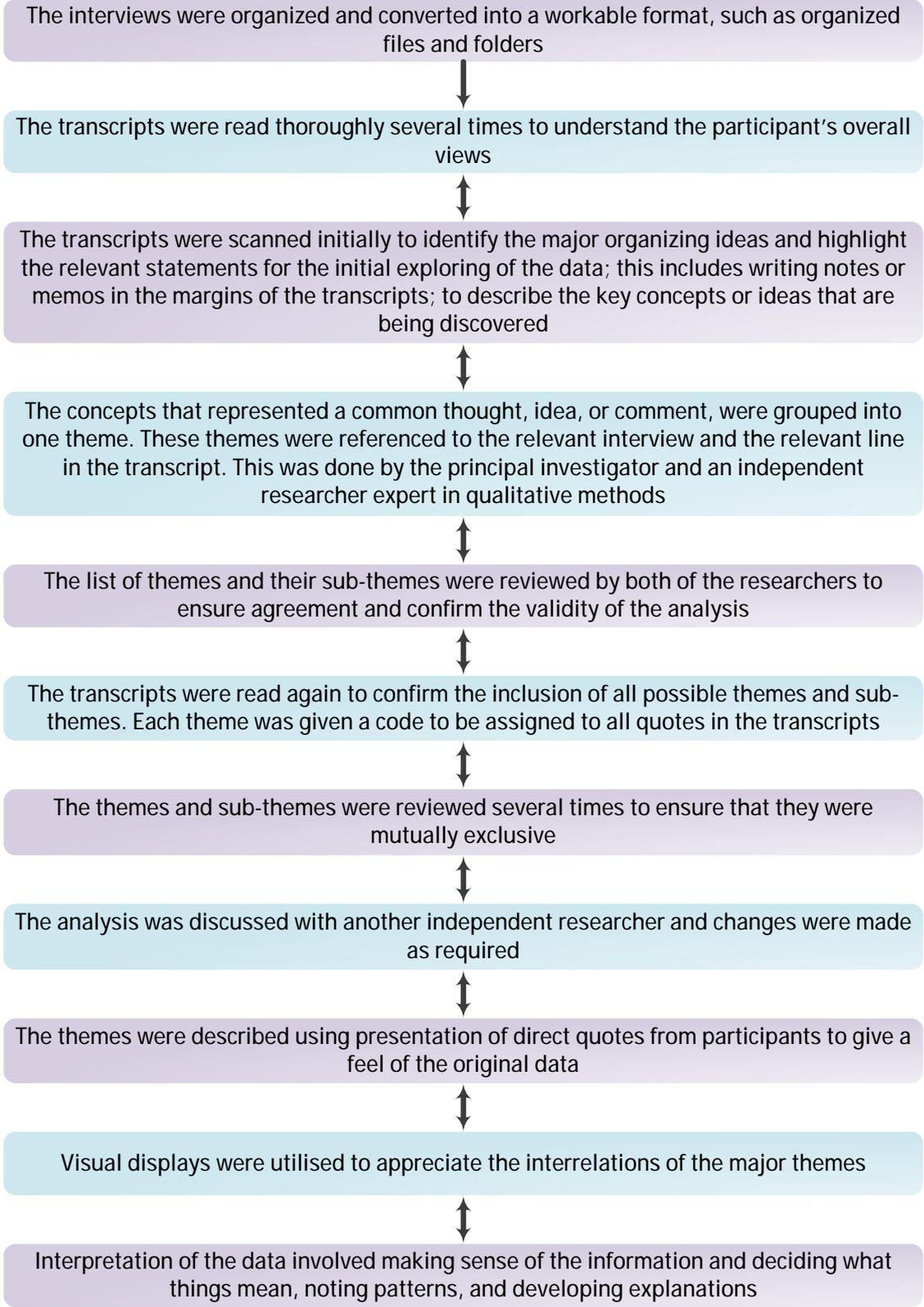
## **Qualitative analysis**

The qualitative data were analysed using the concept of analytic hierarchy in a thematic framework approach to enable the best interpretation of meaning (Spencer, Ritchie, & O'Conner, 2003). This approach is recommended where the analysis needs to be linked with quantitative findings, as in this study (Pope et al., 2000). Guidelines from qualitative researchers such as Creswell (2007), Silverman (2005) and Denzin and Lincoln (2003) on thematic data analysis were incorporated. The process of the analysis is represented in Figure 3.

This thematic framework of coding allowed for a dynamic content analysis based on understanding the evidence and interpretation of meaning. Going backward and forward repeatedly within the data to identify the key concepts and themes from the interview texts and refine the developed analytical account.

The concepts that represented a common thought, idea, or experience were grouped together to form one theme. Each theme was then organised into sub-themes; a hierarchical organization of the data in each theme. This was carried out until the data was all organised into independent themes. This was done by the principal investigator and a researcher expert in qualitative analysis. The list of themes and their sub-themes were then reviewed by both of the researchers, this step is important to ensure agreement on the conceptualisation and classifications of the themes and to confirm the validity of the analysis. The analysis was discussed with another independent expert researcher and changes were made when required. The emerging analytic concepts facilitate the enhancement of the final analytical findings.

The findings are presented in Chapter 5; they are arranged in the major themes that have emerged from the data. The themes were described using presentation of direct quotes from participants to give a feel of the original data. These steps were performed manually using Microsoft Office Word and Microsoft Office Excel spread sheets, as depicted in Figure 3.



**Figure 3: The process of the qualitative data analysis as followed in this research.**

### 3.4.2.5 Triangulation

Triangulation has been recommended and used to strengthen the research study and add to its credibility by mixing methods which provide varied ways of looking at the same issue (Patton, 2002). Four types of triangulation have been described in the literature: data triangulation, a range of data sources are used for the study; methodological triangulation, more than one method is employed to study one phenomenon; theory triangulation, a combination of viewpoints are utilized to investigate a data set; and investigator triangulation, various researchers are used to counteract the potential bias of a single researcher (Denzin & Lincoln, 2003; Patton, 2002; and Silverman, 2006).

With triangulation the research benefits from adding the strength of one method to the strength of the other methods used reducing any weakness in one method (Creswell, 2009). Triangulation provides cross data validation, corroboration, and test for consistency in results (Patton, 2002). One example of triangulation advantages is to reduce research bias when information and data are gathered from more than one source such as interviews and observations which could help in avoiding biased or untrue responses and it gives a richer, more comprehensive image of the issue under study (Foss & Ellefsen, 2002; and Patton, 2002). Another use of triangulation, that is applicable for this study, is the use of qualitative quotes that support or do not support the quantitative results (Creswell, 2009). However, some researchers state that the benefit of triangulation is only in its ability to expand and deepen the comprehension of the subject under study and to give a more complete depiction of the phenomenon, and not essentially to validate the data (Ritchie, 2003).

Three types of triangulation have been used in this study. First, *data triangulation*, combining data from interviews, focus groups, observations, and document analysis in Phase 1, and combining data from questionnaires, assessment measurements, and document analysis in Phase 2. The second type of triangulation used is *methodological triangulation*, in which both qualitative and quantitative methods have been used in this study in an effort to get well validated and substantiated results. The third type of triangulation used in some stages of this research is *investigator triangulation*, more than one researcher was employed at various parts of the study, in Phase 1 the principal researcher (SA) and two other researchers checked the thematic

analysis of the qualitative data to ensure agreement on themes. In Phase 2 several researchers worked on the translation and back translation of the Vineland-II survey, because the process of translation and its validation require more than one researcher.

#### **3.4.2.6 Applications of Phase 1 results**

Findings from the data collected in this phase were used to inform the structuring of the questionnaires for Phase 2 of the study. Creswell (2009) has recommended this sequential approach, using the accounts and themes that have emerged from the initial qualitative data collection phase to construct a questionnaire that is based on the views of the participants and key informant to be used in the second phase with a wider range of participants and with quantitative components.

### 3.4.3 Phase 2

Phase 2 was a quantitative cross sectional survey. The purpose of Phase 2 was to identify the risk factors for patients with aminoacidopathies in Saudi Arabia that lead to poor nutritional control of the disorder and hence unsatisfactory blood amino acid levels and a poor neuropsychological outcome. The qualitative findings of Phase 1 from the purposive sample were used to develop the questionnaires; ensuring context specific questions were included and posed to a larger sample group.

A feasibility decision was made to determine whether Phase 2 would focus on one metabolic disorder (PKU) or all three disorders. Out of the three disorders (PKU, MSUD, and tyrosinaemia I) PKU has the clearest relation between dietary compliance and outcome in terms of developmental ability (Donlon et al., 2006). Therefore it was decided to focus Phase 2 on PKU patients and their families. The forms and questionnaires used in Phase 2 are in Appendices 5 to 10.

This phase included:

**A. *Nutritional assessment:***

- Anthropometric measures
- Clinical measures: current morbidity data and blood levels
- Diet analysis

**B. *Questionnaires (For the patients and their families), covering:***

- Socio-economic status
- Quality of life
- Nutrition knowledge, attitudes and practices
- Dietary compliance

**C. *Medical records review:***

- Medical history
- Past blood levels

**D. *Development assessment:***

- Past developmental assessments from medical records
- The Vineland-II Survey Interview Form

### **3.4.3.1 Questionnaire development and pilot**

The Family and Child Questionnaires were developed after studying the findings of Phase 1 of this study. The main themes and issues that were raised by the families and the health care providers were used to inform the development of the questions. The questions were constructed using information and the vocabulary learnt through Phase 1 findings and by following the guidelines described by Oppenheim (1992) and Peterson (2000). It was designed as a structured questionnaire with limited responses and only few open ended questions, this has the advantage of reducing the time needed from the interviewee, limiting the interviewer bias, and can be administered either as a face-to-face interview or by the phone (Creswell, 2009; and Peterson, 2000).

The initial Family Questionnaire contained 106 items covering questions about socio-economic status, health, education, social activities, attitudes and practices, disorder and nutrition knowledge, dietary habits, personal concerns, seeking help, and getting information. It had a section for diet history (24 hour recall) and food frequency questionnaire. A simple Child Questionnaire was developed to find out the children's perspectives and knowledge of the disorder and their diet, it included 11 questions. The metabolic dietitian and one of the metabolic clinic doctors read the questionnaires and gave their feedback, which was incorporated within the process of improving the questionnaires.

It was then important to pilot the questionnaires to refine and develop the questions, to ensure that they are clear and serve the purpose of the research (Oppenheim, 1992). The pilot was essential to test for the duration and the setting of the interview as well. The Child Questionnaire was piloted with three patients; one question appeared to be redundant so it was deleted and one question needed rewording to improve clarity. Then it was re-tested with 4 more patients and it was received well in both clarity and duration; none of the children misunderstood any of the questions and none of them seemed agitated or bored by the end of the questionnaire.

The Family Questionnaire was piloted with 5 families and was found to be too long. The mothers felt that some of the questions were irrelevant, some were not easy to understand, and the food frequency questionnaire was too long and tedious for them; only two mothers completed it. After considering the mothers' comments and

reviewing their responses to ensure they actually answer what is asked, twenty two questions were deleted from the questionnaire, seven questions were reworded and modified, and an “other” category was added to all possible questions so the respondents would not feel limited to the listed choices. The food frequency questionnaire was cancelled, as the mothers were not used to it and did not see the benefit of it. They were more comfortable with the 24 hour recall, as this is what they are used to giving at the dietitian’s clinic. Therefore it was kept and it was used twice for most of the patients. The modified Family Questionnaire was re-piloted with 3 families; it was well-received. Only the order of a few questions was changed, after the second pilot, to improve the sequential flow of the questionnaire. As many families have more than one child with PKU a Sibling Questionnaire was created; it only included the questions pertaining to the patients, so the mothers would not have to answer the other questions more than once.

### **Family Questionnaires**

The Family Questionnaire and Sibling Questionnaire (Appendices 7 and 8) were administered in an interview format to ensure completion of all the questions. Several of the mothers had low literacy levels and therefore it was not feasible to give them a questionnaire to complete in writing. Also due to the many appointments the families need to attend at their visit to the hospital and the length of the questionnaire sometimes it was necessary to start it at the hospital with the mother but complete it by phone when she was relaxed in her home environment and not stressed about being late at hospital or missing their return travel. The questionnaire had a few open ended questions, and there are several limitations to having the participants answer them in writing; they might not answer an open-ended question, because it takes more effort than selecting from a list of answers; it also depends on their writing skills, and the researcher cannot probe to extend the responses if needed (Creswell, 2007; and Oppenheim, 1992). Therefore administering the questionnaires in a structured interview format was considered to be the best method with this population. It helped to overcome the known drawbacks of using a questionnaire, such as low response rate, not answering all the questions, misunderstanding some questions, respondent literacy issue, and respondent motivation (Gillham, 2000).

## **Child Questionnaire**

School age patients with the ability to communicate with others were asked to participate to answer the Child Questionnaire (Hameen-Anttila, Juvonen, Ahonen, Bush, & Airaksinen, 2006; and Knox & Burkhart, 2007). After getting the parent's consent the Child Questionnaire was explained to the child and a verbal assent was taken from each participating child. The child was then taken to another room for the interview or to a quiet side within the clinic while the mother talked with the dietitian. The questionnaire was conducted in a structured interview format. The questions focused mainly on the child's dietary choices, knowledge and attitudes towards the diet (Appendix 10).

### **3.4.3.2 Phase 2 study sample**

All the patients diagnosed with PKU who have their medical care and follow up at KFSH&RC were invited to participate in the study.

### **3.4.3.3 Phase 2 data collection**

A research assistant was hired to assist with some data collection in this phase (anthropometric measurements and medical records reviews). She was also needed to entertain and engage the children while I interviewed the parents to answer the questionnaire. The flow chart in Figure 4 illustrates the four components in this phase of the study:

**A. Nutritional assessment:** A comprehensive clinical assessment of the nutritional status of each patient with PKU was carried out:

- ***Anthropometric measurements:***

Height, weight, waist circumference, mid-upper arm circumference, and triceps skin-fold thickness.

- ***Clinical measures:***

Morbidity data: Illnesses or admissions to hospitals were recorded to take into account the changes in blood levels due to illness.

**Blood level:** The blood levels of phenylalanine (Phe) were monitored throughout the study whenever the patients were required to send a blood sample. The analytical method used at KFSH&RC to determine blood levels of phenylalanine is tandem mass spectrometry (MS/MS). This test is standard and reliable, with high sensitivity and specificity for PKU (Strathmann & Hoofnagle, 2011; and Wilcken, 2006). Internationally there is no consensus on the desired target levels of amino acids for aminoacidopathies; there are variations between clinics in different countries. The target blood levels of phenylalanine for PKU followed at KFSH&RC\* are shown in Table 1, and the target levels in other countries are listed in Table 2.

**Table 1: The acceptable blood Phe levels at KFSH&RC by age group.**

Age Group	Phe $\mu\text{mol/l}$
<2 years	120 - 350
2-6 years	120 - 450
>6 years	120 - 600

**Table 2: The acceptable blood Phe levels in different countries by age group.**

Age groups (years)	Phe $\mu\text{mol/l}$			
	UK <sup>1,2</sup>	Germany <sup>3</sup>	France <sup>4</sup>	USA <sup>5</sup>
< 7	120 - 360	40 - 240	120 - 300	120 - 360
7 -9	120 - 480	40 - 240	120 - 300	120 - 360
10 - 12	120 - 480	40 -900	< 900	120 - 360
13 - 15	120 - 700	40 -900	< 900	120 - 600
16 - 18	120 - 700	40 - 1200	< 900/1200	120 - 600
>18	120 - 700	40 - 1200	< 1200/1500	120 - 900

<sup>1</sup>Blau, van Spronsen, & Levy, 2010. <sup>2</sup>Medical Research Council, 1993. <sup>3</sup>Burgard et al, 1999.

<sup>4</sup>Abadie et al, 2005. <sup>5</sup>National Institutes of Health Consensus Development Panel, 2001.

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\* Gold standards for target Phe blood levels are not available for PKU. Target levels differ from one country to another.

- ***Diet analysis:*** The phenylalanine content and the quality of the diet for the patients were assessed through taking two 24 hour food recalls for the patients' intakes from their mothers.

**B. Questionnaires:** The Family and Patient pre-tested questionnaires (Appendix 7, 8 and 10 ) were administered with the mothers and the patients:

- ***Socio-economic status:*** Information from the structured questionnaire was used to assess indicators of the socio-economic status of the families; such as employment, parental education, level of monthly spending, number of siblings, number of siblings with the same disorder, and medical history.
- ***Aspects of quality of life:*** Information from the questionnaire was used to assess aspects of the quality of life, social behaviour and wellbeing of the patients and their families.
- ***Nutrition knowledge, attitudes and practices:*** Information from the questionnaire was used to assess medical history, level of care, level of disorder knowledge, level of nutrition knowledge, attitudes and practices of the patients and their families towards the diet and the nutritional management of their disorders.
- ***Dietary compliance:*** Compliance with dietary treatment was monitored through reviewing dietary patterns using the 24 hour recalls and answers to related questions in the Family Questionnaire. The families were asked in the questionnaire about the difficulties they experience in following the diet, and if they were not following the diet the barriers and reasons for that. Understanding their struggles will help us help the families in overcoming these difficulties.

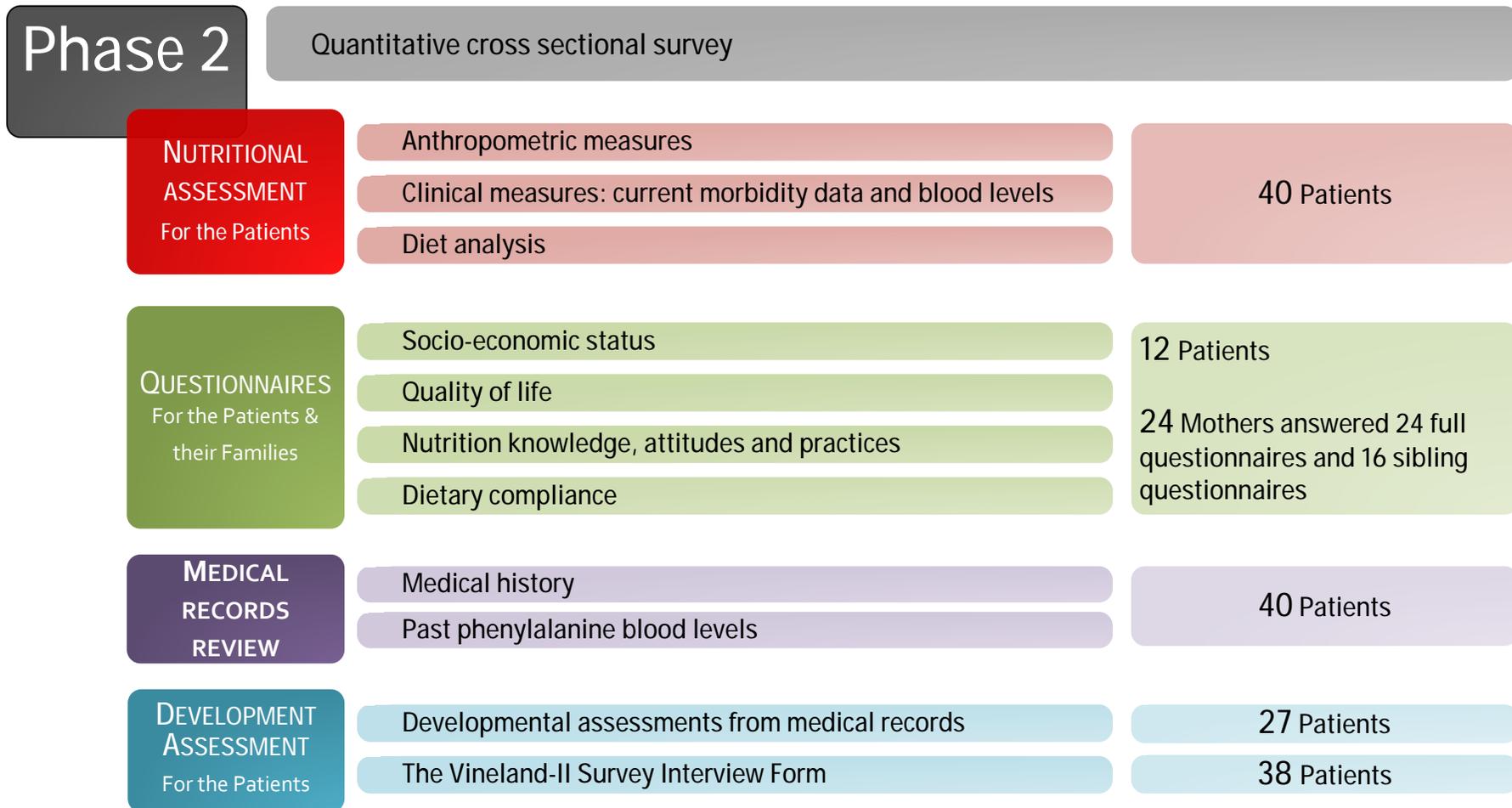
### **C. Medical records review:**

- ***Medical history:*** The medical history of each patient was reviewed and any medical problem was recorded.
- ***Past blood levels:*** Past blood levels of the amino acid phenylalanine were obtained from the medical records for the patients to look at patterns of blood levels over time and to establish an understanding of patients' diet management and compliance history.

### **D. Development assessment:**

- ***Past developmental assessments from medical records:*** All of the developmental assessments done for the patients were noted and final reports copied for analysis.
- ***The Vineland-II Survey Interview Form:*** Many of the patients (13 out of 40) had not had any kind of developmental assessment done; therefore it was decided to use the Vineland-II with all of the patients for better analysis. Chapter 4 describes the rationale for using the Vineland-II, the translation, adaptation, and testing process of the instrument.





**Figure 4: Flow chart illustrating the different components of Phase 2, methods used, and number of participants in each part.**

#### **3.4.3.4 Phase 2 data management**

Quantitative data was double entered, for accuracy, into PASW Statistics 18 for Windows (SPSS Inc., 2009) for analysis. Correlation, regression, t-test and analysis of variance statistical techniques were used to generate models and explore statistical relationships in this risk factor analysis (Kirkwood & Sterne, 2003; Pallant, 2007; and Tabachnick & Fidell, 2007). All tests were set to an alpha level of 0.05 (confidence level of 95%).

#### **3.4.3.5 Phase 2 data analysis**

##### **1. Questionnaires**

Data from the Family Questionnaire and Child Questionnaire (Appendix 7, 8 and 10) were summarised for all participants through frequencies and percentages. Descriptive statistics were used to determine the mean and standard deviation of key indicators. The data included gender, age at diagnosis, education levels, social life, health care practices, and knowledge about PKU. Age, education level and employment status for the mothers and the fathers, household information, including monthly spending and other indicators of socio-economic status were summarised and tabulated. Knowledge of families regarding PKU was summarized and frequencies of the correct answers were tabulated. Families' concerns and suggestions were listed.

##### **2. Assessments and measurements**

###### **i. Normality testing**

Preliminary analyses were performed to ensure the assumption of normality was not violated. Dependant variables were tested for normality using the Kolmogorov-Smirnov statistic, histograms, and Normal Probability Plots of the regression standardized residuals. The data was normally distributed thus parametric statistics were used for the analysis.

## **ii. Gender differences**

An independent-samples t-test was conducted to determine if there were any differences between male and female patients in terms of the Vineland-II score, age at start of treatment, diagnosis phenylalanine level, mean blood phenylalanine level, and dietary phenylalanine intake.

## **iii. Anthropometric measurements**

Z-scores were calculated for length/height-for-age, weight-for-age, and BMI using the Saudi age and gender specific reference values (Foster & Kecojević, 2010). The one-sample t-test was used to compare the z-scores with the Saudi reference standards (Al Herbish et al., 2009; El-Mouzan, Al-Herbish, Al-Salloum, Qurachi, & Al-Omar, 2007). Three patients were over the age of the reference data (over 19 years of age), the BMI was calculated for them and compared to the WHO classification (WHO, 2000).

The mid-upper-arm circumference (MUAC) and triceps skin-fold thickness (TST) measurements were used to calculate the upper arm fat area (UFA). Due to the absence of Saudi references the UFA and TST were compared to the USA reference data (Addo & Himes, 2010; and Mahan & Escott-Stump, 2003). The waist circumference (WC) measures were compared to the UK reference data (McCarthy, Jarrett, & Crawley, 2001) due to the unavailability of a Saudi reference for WC as well.

## **iv. Dietary intake**

The dietary phenylalanine content of patients' diets was calculated using the references used at KFSH&RC: the Nutrition Support Protocols (Acosta & Yannicelli, 2001) and a reference developed at KFSH&RC by the dietitians for the local foods. The daily dietary intake of phenylalanine for patients was used in an independent-samples t-test to compare difference in intake between patients with acceptable mean blood Phe levels and patients with high mean blood Phe levels. The Pearson product-moment correlation coefficient test and multiple regression analyses were used to investigate the relations between the dietary Phe and the mean blood Phe levels and the Vineland-II scores.

#### **v. Outcome measures analyses**

Descriptive statistics were used for the main variables used in the analyses (minimum, maximum, mean, and standard deviation). The independent-samples t-test was conducted to determine if there were any differences between the patients who were treated early ( $\leq 1$  month of age) and patients who were treated late ( $> 1$  month of age). It was also used to determine if any differences existed between patients with Mild PKU (diagnosis Phe 600-1200  $\mu\text{mol/l}$ ) and patients with Classic PKU (diagnosis Phe  $> 1200$   $\mu\text{mol/l}$ ), and between patients with adequate formula intake and patients with unsatisfactory formula intake.

The Pearson product-moment correlation coefficient, linear regression, and multiple regression tests were utilised to determine the relations and associations between the Vineland-II scores, age at start of treatment, diagnosis Phe level, mean blood Phe level, dietary Phe intake, and the socio-economic status indicators. There were few missing data values and they were treated as missing in the analyses. Imputation of missing values in a small sample is not recommended (Kirkwood & Sterne, 2003).

## CHAPTER 4

# **ADAPTATION OF THE VINELAND- II SCALES TO ARABIC**

## **Introduction**

During the process of this research it became apparent that many of the participating patients had not had any developmental assessment done, and those that had, were not all assessed by the same tool making comparisons impossible. Therefore, the Vineland-II was chosen to be used with all of the patients to facilitate analysis. This chapter describes the rationale for using the Vineland-II, the translation and adaptation of the Vineland-II scales to Arabic, and the testing process of the instrument.

### **4.1 The Vineland Adaptive Behaviour Scales, second edition (Vineland-II)**

The Vineland-II is a measure of adaptive behaviour for individuals from birth to 90 years of age (Sparrow, Cicchetti, & Balla, 2005). Adaptive behaviour is defined as the age-appropriate conceptual, social, and practical skills learned and needed by people to function in everyday living (Schalock et al., 2007). Adaptive behaviours include skills needed for daily life activities such as washing, brushing teeth and hair, toileting, dressing, playing, food handling, following rules, being able to work, managing money, having personal responsibility, communicating and having social skills.

The Vineland-II is designed to aid in diagnosing and classifying intellectual and developmental disabilities in a range of conditions including autism spectrum disorder, emotional and behavioural disturbances, many genetic disorders, disorders causing developmental delay, and many other physical, mental, and injury-related conditions. It is an important tool for determining the eligibility of a child for special services through measuring the child's development. It provides valuable information to help develop educational, intervention, or treatment plans and programmes through identifying strengths and weaknesses of individuals. The Vineland-II facilitates monitoring and reporting progress of individuals during such programmes. In addition the Vineland-II has been recommended for use in research when the development and functioning of participants need to be examined (Sparrow et al., 2005).

The Vineland-II has three versions of the scales:

- 1. Two survey forms:** The Survey Interview Form and the Parent/Caregiver Rating Form provide a targeted assessment of adaptive behaviour in four domains: Communication, Daily Living, Socialization and Motor Skills (Motor Skills for children <7 years of age only), with sub-domains in each domain. It also includes an optional Maladaptive Behaviour Index designed to assess problem behaviours. The Survey Interview Form is administered to a parent or caregiver using a semi-structured interview format and the Parent/Caregiver Rating Form uses a rating scale by the parent or caregiver. An Adaptive Behaviour Composite score is provided when all domains are administered. It is a standardised score and describes the individual's overall functioning.
- 2. The Expanded Interview Form:** This form provides an in-depth assessment of the previous four domains of adaptive behaviour. It is useful in facilitating the preparation of individual educational or treatment programme planning.
- 3. The Teacher Rating Form:** This form assesses the adaptive behaviour in the four domains but focuses on content that teachers would observe in classroom settings in addition to basic academic performance (Sparrow et al., 2005).

The Survey Interview Form, without the optional Maladaptive Behaviour Index, was translated and adapted for the use in this research study.

### **The Vineland-II scores**

The Vineland-II uses standard scores to describe functioning. A standard score tells the distance of the individual's raw score from the mean raw score of a normative reference population, taking into account the standard deviation of the distribution of raw scores. The standard score scale of the Vineland-II has been normalised and has a mean of 100 and standard deviation of 15 (Sparrow et al., 2005).

The Vineland-II defines five adaptive levels for the scores of the Adaptive Behaviour Composite (ABC), the domains, and the subdomains. These adaptive levels describe an individual's performance using virtually universal terms.

## **The Vineland-II adaptive levels**

### **- Low (20-70):**

A score in this level is lower than 97% of the individuals in a given age.

### **- Moderately low (71-85):**

A score in this level is lower than 84% of the individuals in a given age.

### **- Adequate (86-114):**

A score in this level indicates normal adaptive functioning. It includes about 68% of the individuals in a given age from the normative reference population.

### **- Moderately high (115-129):**

A score in this level is higher than 84% of the individuals in a given age.

### **- High (130-160):**

A score in this level is higher than 97% of the individuals in a given age.

The Vineland-II consists of four main domains each with sub-domains. The Vineland-II manual gives a description of the sub-domains, listed in Box 1 on the following page (Sparrow et al., 2005). In Box 2 and Box 3 there are two examples illustrating the most notable adaptive behaviours in each subdomain for two patients. The first patient has a Low adaptive level, and the second patient has a Moderately Low adaptive level on the ABC score levels. It is important to note that other patients within the same adaptive levels would differ slightly in their behaviours within each subdomain, as the Vineland-II ABC score is a composite of all of the domains.

**Box 1: Description of the content of the Vineland-II subdomains (Sparrow et al., 2005).**

**1. Communication Domain:**

**Receptive:** How the individual listens and pays attention and what he or she understands.

**Expressive:** What the individual says, how he or she uses word and sentences to gather and provide information.

**Written:** What the individual understands about how letters make words, and what he or she read and writes.

**2. Daily Living Skills Domain:**

**Personal:** How the individual eats, dresses, and practices personal hygiene.

**Domestic:** What household tasks the individual performs.

**Community:** How the individual uses time, money, the telephone, the computer, and job skills.

**3. Socialization Domain:**

**Interpersonal relationships:** How the individual interacts with others.

**Play and leisure time:** How the individual plays and uses leisure time.

**Coping skills:** How the individual demonstrates responsibility and sensitivity to others.

**4. Motor Skills Domain:**

**Gross motor:** How the individual uses arms and legs for movement and coordination.

**Fine motor:** How the individual uses hands and fingers to manipulate objects.

**Box 2: This example illustrates the notable adaptive behaviours in each subdomain of the Vineland-II for a 20 year old patient with a Low adaptive level.**

**1. Communication Domain:**

**Receptive:** He follows two part instructions, but would not listen to a story for 15 minutes.

**Expressive:** He has conversations that last at least 10 minutes and explains ideas in more than one way. He knows own telephone number when asked, but does not say complete address. He cannot describe long-term goals.

**Written:** He can read and understand material of at least second grade level and can put words in alphabetical order, but cannot write simple correspondence of three sentences or more.

**2. Daily Living Skills Domain:**

**Personal:** He can shower by himself, can find and use appropriate public restrooms, and cares for minor cuts. He cannot use a thermometer to take own temperature or another's, cannot take medicine as directed, or arrange doctor appointments.

**Domestic:** He is careful when using sharp objects, he clears breakable items from own place at table, and can use simple appliances such as a toaster or a bottle opener. He cannot use microwave, tools, or vacuum. He does not clear table fully or use household cleaning products correctly.

**Community:** He demonstrates understanding that some items cost more than others, can tell time by the half hour on an analog clock, and can make telephone calls to others. He cannot evaluate quality and price when selecting items for purchase, does not count change after purchase, and does not have computer skills to carry out complex tasks such as accessing the internet or word processing.

**3. Socialization Domain:**

**Interpersonal relationships:** He uses words to express happiness or concern for others, acts when others need help such as holding a door open or picking up a dropped item, and recognises likes and dislikes. He does not meet friends regularly, he is not careful when talking about personal things, and he does not understand hints or indirect cues in conversations.

**Play and leisure time:** He asks permission before using objects belonging to others, and can go places with a group of responsible friends. He cannot follow rules in complex games or sports and does not show good sportsmanship.

**Coping skills:** He acts appropriately when introduced to strangers, refrains from talking with food in mouth, and accepts helpful suggestions from others. He does not say sorry after hurting another's feelings, does not control anger or hurt when plans change for reasons that cannot be helped, and does not understand that gentle teasing with family is a form of humour or affection.

**4. Motor Skills Domain:** The patient is older than required for this domain.

**Box 3: This example illustrates the notable adaptive behaviours in each subdomain of the Vineland-II for a 19 year old patient with a Moderately Low adaptive level.**

**1. Communication Domain:**

**Receptive:** His level is adequate for this subdomain; he follows instructions given earlier, understands the sayings that are not meant to be taken word for word, and can listen to informational talk for at least 30 minutes.

**Expressive:** His level is adequate for this subdomain; he gives complete home address, gives complex directions to others, and describes a realistic long-term goal.

**Written:** He can read and understand at least sixth-grade level material, and at least two newspaper articles per week, but does not write advanced correspondence of 10 sentences or longer and does not edit or correct own written work before handing it in.

**2. Daily Living Skills Domain:**

**Personal:** He can use a thermometer, seek medical help in an emergency, and follow directions for medical treatment or diet, but does not keep track of medications well enough and cannot always arrange doctor appointments.

**Domestic:** He can clear the table fully, use household cleaning products correctly, use a sharp knife, and clean one or more rooms other than own bedroom. He does not prepare basic food that requires cooking and cannot perform maintenance tasks.

**Community:** He evaluates quality and price when selecting items for purchase, counts change after purchase, obeys time limits for breaks, and notifies school when he will be late or absent. He has limited computer skills to carry out a few complex tasks such as accessing the internet or word processing. He does not use a bank account, cannot travel for at least five miles to familiar or unfamiliar destinations alone using a bike, public transport, or driving, and does not earn money.

**3. Socialization Domain:**

**Interpersonal relationships:** His level is adequate for this subdomain; he is careful when talking about personal things, he understands hints or indirect cues in conversations, he cooperates with others to plan or be part of an activity, and he goes out in single and group outings.

**Play and leisure time:** His level is adequate for this subdomain; he follows rules in complex games or sports, he plans activities with more than two things to arrange, and he goes places with friends without adult supervision.

**Coping skills:** His level is adequate for this subdomain as well; he keeps secrets, thinks about what could happen before making decisions, and uses caution when encountering risky social situations.

**4. Motor Skills Domain:** The patient is older than required for this domain.

## **4.2 Use of the Vineland-II in this study**

### **4.2.1 The need for a uniform outcome measure for all the patients**

After the data collection for Phase 2 was completed and the analysis had been commenced, it became evident that the developmental assessments of the patients, obtained from their medical records at KFSH&RC, were inconsistent and incomparable. The patients were assessed using one or more of the following tools:

- \* The Bayley Scales of Infant and Toddler Development.
- \* The Leiter International Performance Scale.
- \* The Test of Nonverbal Intelligence (TONI).
- \* The Beery-Buktenica Developmental Test of Visual-Motor Integration (Beery VMI).
- \* The McCarthy Scales of Children's Abilities.
- \* The Vineland Adaptive Behaviour Scales (Vineland ABS).

There was no apparent system for the use of this array of assessment tools. Diversity in the available developmental test results made sound analysis impossible. Dividing the patients into groups according to their age at assessment proved difficult because there was no consistency in using the same assessment tool at any specific age-group for the patients, and it was not possible to combine the results of different tools in one analysis. Dividing the patients into groups according to the type of assessment tool resulted in groups of very small numbers making the statistical analysis impossible. In addition, 13 patients had not had any developmental assessment done at KFSH&RC or elsewhere.

The problem of the inconsistent data on development was discussed with Dr Kathryn Bond, a clinical psychologist who works with PKU patients at Great Ormond Street Hospital (GOSH). She recommended that a new assessment be undertaken for all the patients using the Vineland-II. It has been used successfully for patients with PKU, and it has the ability to identify developmental delay through an easy and straight forward survey form with the mothers or caregivers; it is designed to be administered through an interview or to be given to the caregiver to fill out. Dr Bond provided training on administering, scoring and interpreting the Vineland-II results.

#### **4.2.2 Rationale for using the Vineland-II**

The Vineland-II measures the important behaviours and skills needed for adaptive functioning; it is not a measure of cognitive functioning, so it does not provide an Intelligence Quotient (IQ) score as many of the papers in the literature report for PKU patients.

Cognitive ability and IQ scores are considered to be relatively stable over time for children older than 5 years of age (Shevell, Majnemer, Platt, Webster, & Birnbaum, 2005; and Sparrow et al., 2005), while functional outcomes can improve or deteriorate according to interventions or changes in the environment (Sparrow et al., 2005).

Assessing functional outcomes for the patients serve in setting realistic expectations for them where eventual outcome can be modified with improved access to available resources and planned interventions that are targeted to minimize disability (Shevell et al., 2005). This gives the Vineland-II an advantage for planning specific educational interventions for the patients, but at the same time there is a theoretical possibility that the Vineland-II scores might be influenced by access to special education currently received by some individual patients who would be included in the research.

Assessment of an individual's daily functioning is increasingly becoming an important outcome measure to identify for patients. Research has shown that it is essential to utilize assessment tools that evaluate children's development through daily activities and functioning which, at the same time, are age appropriate and sensitive to different cultures and social settings; this is in order to adequately identify the support vital for the children and their families to achieve functional independence (Hogan, Rogers, & Msall, 2000; and Ottenbacher et al., 2000). Msall (2005) argues that focusing on the medical impairments and developmental disabilities of children portrays their deficits and does not account sufficiently for their skills in functional adaptation and their daily performance in their environments. In two reviews of measuring functional outcomes the authors recommended functional assessment of children as an important part of the evaluation. It captures the children's typical performance in their own environments, demonstrating both their strengths and challenges, and it facilitates planning the supports they need (Msall & Tremont, 2002; and Msall, 2005).

Assessing the current function of patients with PKU in this study serves to indicate how the disorder is affecting the patients' everyday lives. The Vineland-II satisfies the recommended criteria discussed above. It gives a score for the typical functioning and performance of the patients, the Adaptive Behaviour Composite score; this score can be used in statistical analyses with the different variables that are believed to affect the outcome for patients with PKU, such as age at diagnosis and start of treatment, level of blood Phe at diagnosis, mean of blood Phe levels and dietary Phe intake.

One of the advantages of the Vineland-II is that it does not cause any burden to the patients; they are not involved in the assessment, the Survey Interview Form of the Vineland-II is carried out with the mother or the primary caregiver of the patient (Sparrow et al., 2005). It has been shown that the mother or the primary caregiver is a valid and reliable source of information. There is a very high correlation between independent assessments of adaptive behaviour levels for patients and the estimation of these levels by primary caregivers (Sparrow & Cicchetti, 1985). Interviewing the mothers should prove straightforward as they had been previously interviewed by me and a good rapport had been established. Another advantage was that interviews could be done over the phone (Limperopoulos, Majnemer, Steinbach, & Shevell, 2006).

### **4.3 Background information about the Vineland**

The Vineland ABS and the updated Vineland-II\* have been widely and effectively used in clinical and research settings for the past 26 years (Middleton, Keene, & Brown, 1990; Sparrow, Balla, & Cicchetti, 1984; Sparrow & Cicchetti, 1985; and Sparrow et al., 2005). It has been used with patients with PKU (Kalkanoglu et al., 2005; Lee et al., 2009; and Matthews, Barabas, Cusack, & Ferrari, 1986), children with Down syndrome (Kishnani et al., 2010), children with neurodevelopmental disabilities (Msall, 2005), and individuals with autism (Carter et al., 1998; Freeman, Del'Homme, Guthrie, & Zhang, 1999; Kanne et al., 2010; Kraijer, 2000; Paul et al., 2004; and Ray-Subramanian, Huai, & Ellis, 2011). It has also been used to study the effects of early maltreatment of children on their development (Becker-Weidman,

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\* The Vineland-II was updated in 2005 with new norms, improved items, expanded age range, and improved overall organisation of the domains and sub-domains.

2009) and to compare the similarities and the differences in the adaptive behaviours of several common genetic syndromes (Di Nuovo & Buono, 2011).

#### **4.3.1 The Vineland and PKU**

The Vineland scales have been used with some patients with PKU at GOSH and KFSH&RC, and there are several reports of research studies that have used the Vineland with patients with PKU. It was used with PKU patients in two double blind placebo-controlled studies (Kalkanoglu et al., 2005; and Lee et al., 2009). Both studies involved untreated adult PKU patients who were diagnosed late and had severe intellectual disabilities. Lee and colleagues tested the benefits of phenylalanine restricted diet on their group in the UK. The Vineland was part of the assessment process at several points of this trial. The other study by Kalkanoglu and colleagues looked at the effects of phenylalanine-free essential amino acid tablets on the performance of their group of PKU patients in Denmark. They used a simplified version of the Vineland to assess their patients at specified intervals.

Matthews (1986) used the Vineland to demonstrate that early treated children with PKU had deteriorated in social functioning after discontinuing the low phenylalanine diet at the age of 5.5 years on average; the scores of these patients were negatively correlated with their blood phenylalanine levels. In one report of the Maternal PKU Collaborative Study Waisbren and colleagues (2000) used the Vineland, among other tests, to assess the children of mothers with PKU. Their objective was to establish how the development of these children is affected by the timing of dietary treatment and metabolic control, or lack of it, of the mothers during pregnancy.

#### **4.3.2 The relation of the Vineland to other scales**

The Vineland-II validation studies, reported by Sparrow and colleagues (2005), show a very high correlation between the Vineland-II and the Vineland ABS, indicating a high degree of consistency between the two scales. The Vineland-II scales have retained most of the original items in the Vineland ABS. It has been improved by deleting a few items related to behaviours that are no longer common, by adding new items to expand the age range of the tool, and by increasing the density of the items in the first 3 years of life to improve the measure of adaptive behaviour in this

vulnerable period of development. The updated items also reflect the changes in culture and incorporate new knowledge about development. Having this strong relationship between the Vineland-II and the Vineland ABS is essential. It allows the transfer of the experiences gained from using the Vineland ABS for many years to the Vineland-II, and permits the research carried on with the Vineland ABS to support the Vineland-II as well (Sparrow et al., 2005).

Several studies have demonstrated high concurrent validity and correlation between the scores of the Vineland ABS and different tests of intelligence. Middleton et al (1990) examined the relation between the scores of the Vineland ABS and that of the Scales of Independent Behaviour (SIB), which is another measure of adaptive behaviour, and found high correlation between them ( $r = 0.83$ ). Sattler (2002) and Rosenbaum et al (1995) report good correlation between the Vineland ABS and several tests of intelligence, language, motor functions and academic achievement.

The authors of the Vineland-II report its validity in its ability to support the diagnosis of a range of disorders and describe deficits and levels of adaptive performance (Sparrow et al., 2005). To confirm this, individuals with intellectual disability, autism, emotional or behavioural disturbance, attention deficit hyperactivity disorder, learning disability, and visual or hearing impairments were assessed with the Vineland-II. Individuals in each of these clinical groups were previously diagnosed and assessed by the appropriate clinical or psychometric assessments particular to each diagnosis, for example the Autism Diagnostic Interview-Revised or the Autism Diagnostic Observation Schedule for autism patients, and the Wechsler Intelligence Scale for Children for mental disability patients. The scores were compared with a normally developing reference group. The Vineland-II differentiated between the clinical groups and the normal group, it identified the adaptive deficits found in the patients and distinguished between the different levels of severity in each disorder (Sparrow et al., 2005). This provided evidence that the Vineland-II would be a good measure to use with patients with PKU.

#### **4.3.3 Developmental assessment tools used for assessing patients with PKU**

Research and studies involving patients with PKU have used many different tools to assess the developmental levels of the patients. There is no consensus on the best tests

to be used with patients with PKU which makes comparability of research results somewhat limited. Formerly IQ tests were the main measures to assess the effects of PKU on patients. Lately the patients are assessed more through neuropsychological evaluations (Griffiths, Demellweek, Fay, Robinson, & Davidson, 2000). This includes behavioural, cognitive, language, motor, and executive functioning assessments, as a distinct psychosocial profile for patients with PKU is still unidentified (Weglage, 2000).

DeRoche and Welsh (2008) carried out a meta-analysis of 33 studies from 1980 to 2004. They were studies that investigated executive function and intelligence for early treated patients with PKU. There were many tools used to assess intelligence in the analysed studies, but there was no significant difference between their results. However, there was a significant difference between the results of executive function studies that were analysed. The difference was in the measurement tools and date of the study, more recent studies showed a higher incidence of executive function deficits and some executive function test tools reported more deficits than others. The authors pointed out that the research community has no agreement on the best tool to measure the executive function domain for PKU patients (DeRoche & Welsh, 2008).

In another meta-analysis, Burgard (2000) reviewed longitudinal studies that looked at the IQ of early treated patients with PKU. Smith and Knowles (2000), in a systematic review, looked at the research that studied behaviour for early treated patients with PKU. Various tools to measure intelligence and behaviour were used in these reviewed studies as well. Below are the tools used in the reviewed studies (Burgard, 2000; DeRoche & Welsh, 2008; and Smith & Knowles, 2000), however this is not a comprehensive list of all the tools used for patients with PKU.

#### **Tools used to assess intelligence:**

- \* Stanford Binet
- \* Cultural Fair Intelligence test
- \* Wide Range Achievement test (WRAT)
- \* Colombia Mental Maturity Scale (CMMS)
- \* Wechsler Intelligence Scale for Children (WISC)
- \* Wechsler Intelligence Scale for Children- Revised (WISC-R)
- \* Wechsler Preschool and Primary Scales of Intelligence (WIPPSI)

- \* Wechsler Adult Intelligence Scale (WAIS)
- \* Wechsler Adult Intelligence Scale-Revised (WAIS-R)
- \* Hamburg Wechsler Intelligenztest für Kinder (HAWIK, German WISC)
- \* Hamburg Wechsler Intelligenztest für Kinder-Revision (HAWIK-R, German WISC-R)
- \* Hannover Wechsler Intelligenztest für das Vorschulalter (HAWIVA, German WIPPSI)
- \* Hamburg Wechsler Intelligenztest für Erwachsene- Revision (HAWIE-R, German WAIS-R)
- \* Terman-Merril method
- \* Raven's Progressive Matrices

#### **Tools used to assess executive function:**

- \* Amsterdam Neuropsychological Test
- \* Behavior Rating Inventory of Executive Function (BRIEF)
- \* Contingency Naming Task
- \* Wisconsin Card Sorting Task (WCST)
- \* Stroop Tests
- \* Rey complex Figure Task
- \* Tower Tests
- \* Continuous Performance Task
- \* Corsi-Millner
- \* California Verbal Learning Test
- \* Design Fluency Task
- \* Luria-Nebraska
- \* McCarthy Scales
- \* Thurstone Letter Fluency
- \* Other experimental executive function measures created by different authors

#### **Tools used to assess behaviour:**

- \* Rutter Behaviour Scale for Teachers (RBST)
- \* Persönlichkeitsfragebogen für Kinder (PFK, German Personality Questionnaire for Children)
- \* Freiburger Persönlichkeits-Inventar (FPI, German Freiburg Personality Inventory)
- \* Mannheimer Biographical Inventory (MBI)
- \* Mannheimer Eltern Interview (MEI)
- \* The Minnesota Multiphasic Personality Inventory (MMPI)
- \* Mobility Inventory (MI)

Waisbren and White (2010) called for or the use of what their group have named as the “Uniform Assessment Method” for PKU. It is a battery of specific tests and tools to be used with patients with PKU to screen for problems in adaptive behaviour, social/emotional function and executive function. The tests are the Adaptive Behavior Assessment System - Second Edition (ABAS-II) for patients 0-2 years; the Behavior Rating Inventory of Executive Function (BRIEF) and Behavior Assessment System for Children - Second Edition (BASC-II) for patients 2-17 years; and for adult patients the BRIEF, Beck Anxiety Inventory (BAI), and Beck Depression Inventory - Second Edition (BDI-II). The authors recommended that these specific tests be used in PKU clinics in routine visits, they do not need to be administered by psychologists and they take less than an hour to be administered. This would identify patients who need further assessments early on, provide long-term monitoring of PKU outcome, and provide a uniform source of results and research data that is from a uniform set of assessment tools across many clinics. They then recommended another battery of tests for patients who are identified to need further assessments and for high risk patients (Waisbren & White, 2010). This appears to be a good idea for all PKU clinics to follow, but there is no evidence yet that this has become regular practice.

## **4.4 Issues with the Vineland**

### **4.4.1 Availability of the Vineland in Arabic**

Although the Vineland ABS has been used for many years at the KFSH&RC it had never been officially translated into Arabic or adapted to the local culture. One of the lead authors of the Vineland, Professor Sara Sparrow, visited the KFSH&RC in 1996 to train the team at the Neuropsychology Clinic there on using the tool. She trained them on the administration, scoring, and interpretation of the Vineland ABS and on how to change some of the items to fit the Saudi culture without losing the meaning of the questions. They have been using it since then with many families including some families with PKU patients.

The psychologists were translating the items in the Vineland verbally when they administered it with the caregivers and they adapted any irrelevant questions to what

was more appropriate to the culture in Saudi Arabia. This might have served them well in their clinical setting but it would not work in a research setting; consistent translation and adaptation was definitely required.

A search was undertaken for an official translation of the Vineland-II or the Vineland ABS in several medical centres and universities in Saudi Arabia, United Arab Emirates, Kuwait, Jordan, Lebanon and Egypt. Unfortunately none of these institutions had had it translated officially; many were using it by translating the questions orally while they administered the tool for each patient, as is the practice in the KFSH&RC. Therefore a decision was made to formally translate the Vineland scale into Arabic.

#### **4.4.2 Translation and adaptation of the Vineland to other languages**

The Vineland has been translated and adapted to other non-western cultures. Goldberg and colleagues (2009) translated the Vineland ABS into Vietnamese. In the processes of its adaptation, 17 items of the scale were reworded to be more relevant to the Vietnamese culture and one item, regarding the use of irregular plurals, was eliminated because it didn't have an equivalent in the Vietnamese language. They tested the translated and adapted instrument with 120 normally developing children and 31 children with intellectual disabilities; it was successful in distinguishing between the two groups. They affirmed that the Vietnamese Vineland is reliable and valid for the use within the Vietnamese culture. The authors stated that the cultural adaptation of the Vineland was flexible and successful, and they recommended further adaptations of the Vineland to other cultures to benefit from this tool (Goldberg, Dill, Shin, & Nguyen, 2009).

The Vineland was also translated and adapted to the Indonesian culture by Tombokan-Runtukahu and Nitko (1992). Seven items of the Vineland ABS were modified to incorporate content that is more relevant to the Indonesian culture, and seven items were eliminated because they were unsuitable to the Indonesian culture and were difficult to substitute. The authors tested the translated and adapted instrument with 43 normally developing children and 43 children with intellectual disabilities. They were satisfied that the adapted instrument was reliable and valid for

use in Indonesia and that it has similar psychometric qualities to the original English version (Tombakan-Runtutahu & Nitko, 1992).

Zhang et al (2006) examined the Vineland ABS, among other instruments, as a tool for the initial screening for autism for Chinese children. The authors did not translate the Vineland but inspected/scrutinized each item in the scales based on their Chinese cultural perspective to judge if the Vineland is appropriate to be used within a Chinese culture or not. They reported that 12 items are unsuitable for Chinese families and they need to be adapted to give valid results.

#### **4.4.3 Translation and adaptation of standardized assessment tools to Arabic and different Arab cultures**

Many assessment tools have been translated from the original English form to the Arabic language. With the translation, the tools have been culturally adapted to the local Arab culture of the study populations including several in Saudi Arabia (Al-Ansari & Bella, 1998; Brown & Al-Khayal, 2006; and Malki, Mesallam, Farahat, Bukhari, & Murry, 2010), in other Arab countries (Harifi et al., 2011; Sabbah, Drouby, Sabbah, Retel-Rude, & Mercier, 2003; Saleem & Natour, 2010; and Shehab, al-Jarallah, & Moussa, 1998), or, through collaboration between several Arab countries (El Meidany, El Gaafary, & Ahmed, 2003; el Miedany, Youssef, & el Gaafary, 2003; and Madi, Al-Mayouf, Grainger, & Bahabri, 2004). The researchers have all produced Arabic instruments valid for use in their cultures.

For example, Al-Ansari and Bella (1998) have translated the Revised Denver Pre-screening Developmental Questionnaire (R-PDQ). They made changes to it to adapt it to the Saudi culture and validate it for the use with Saudi children. Shehab et al (1998) translated the Health Assessment Questionnaire (HAQ) to Arabic and adapted it to for use in Kuwait. Another study translated and adapted the HAQ to the culture of a collection of Arab countries in North Africa and the Middle East including Saudi Arabia (El Meidany et al., 2003). The Childhood Health Assessment Questionnaire (CHAQ) has been translated and culturally adapted as well. It was validated in Egypt and Saudi Arabia (el Miedany et al., 2003; and Madi et al., 2004). In Lebanon the short form 36 health survey (SF-36) was adapted to their Arab culture as a quality of life measure (Sabbah et al., 2003).

## **4.5 The translation and adaptation of the Vineland-II to the Arabic language and the Saudi Arabian culture**

### **4.5.1 Translation and cultural adaptation of instruments**

Many surveys and instruments are developed in English and, when proved successful, they are translated to numerous different languages. Translation of well-established instruments has the advantage of saving time, money, and energy that could be spent on developing a new instrument in each language (Hambleton & Patsula, 1998; and Peters & Passchier, 2006). It also has the benefit of facilitating cross-cultural awareness and comparability between research results from different countries (Lloyd et al., 1998; and Yu, Lee, & Woo, 2004) and examining any similarities or differences between cultures (van de Vijver & Hambleton, 1996).

It is established that literal or simple translation of instruments from one language to another is ineffective due to the various differences between languages and cultures, therefore cross-cultural adaptation of instruments is recommended (Ercikan, 1998; Hilton & Skrutkowski, 2002; Scientific Advisory Committee of the Medical Outcomes Trust, 2002; van de Vijver & Hambleton, 1996; and Yu et al., 2004).

Cultural and language adaptations involve adapting the instruments to suit specific regions, countries, and diverse life-styles. The translated instrument must be relevant to the culture of the target population and equivalent to the concepts of the original instrument while capturing the same concepts cross-culturally (Guillemin, Bombardier, & Beaton, 1993; Hilton & Skrutkowski, 2002; and Peters & Passchier, 2006). The adaptation should reflect the meaning and maintain the relevance of the original instrument so it does not alter what the items are intended to measure (Ercikan, 1998).

One of the most recommended and used approaches for cross-cultural translation is forward and back translation (Ercikan, 1998; Hambleton & Kanjee, 1995; Hilton & Skrutkowski, 2002; and Peters & Passchier, 2006). It involves translating the instrument from the source language to the target language. A second translator then takes the translation and translates it from the target language back into the source language. Finally the original instrument and the back-translated version are

compared and any discrepancy or ambiguity in meaning clarified (Beaton, Bombardier, Guillemin, & Ferraz, 2000; Ercikan, 1998; and Peters & Passchier, 2006). One of the important aims of this comparison should be to attain conceptual equivalence (Bowden & Fox-Rushby, 2003).

Swaine-Verdier et al (2004) recommend a “two panel” approach as a thorough technique for translating and adapting instruments. One panel of 5-7 people is recruited to translate and adapt the instrument, and another panel of 5-7 lay people to test the adapted instrument. Other researchers suggest the use of an additional third panel for back-translation (Peters & Passchier, 2006). Combining translation techniques have been reported to produce positive results (Maxwell, 1996; and Peters & Passchier, 2006).

It is recommended to have at least two translators and they should have excellent knowledge of English and the target language (Hambleton & Patsula, 1998; and Maxwell, 1996). However, to translate and adapt instruments effectively, it is not enough that the translators are proficient at the language, it is essential that they have adequate knowledge of the culture of the research population (Hambleton, 2005; Hambleton & Patsula, 1998; and Vulliamy, Lewin, & Stephens, 1990).

To ensure appropriate translation it is important to pre-test and pilot the translated instrument in the new target culture (Beaton et al., 2000; and Birbili, 2000). This is essential to verify the validity and reliability of the translated instrument (Peters & Passchier, 2006).

#### **4.5.2 The translation and cultural adaptation process for the Vineland-II**

The translation and cultural adaptation of the Vineland-II followed the guidelines recommended by Beaton and colleagues (2000). They recommend following a series of rigorous stages to achieve high quality cross-cultural adaptation and to come up with an equivalent and applicable tool.

The Vineland-II was translated into Classic Arabic. This is not the same as spoken Arabic but it is the official Arabic used in all the written forms in Saudi Arabia and other Arab countries. It is the form of Arabic that is taught in schools, and it is widely understood in the Arab world. It can be easily read out in any local dialect.

The following process summarizes the translation and adaptation procedures we undertook with the Vineland-II, ten individuals were involved in this process:

1. The Vineland-II was translated in Saudi Arabia at a professional translation agency that specializes in translating scientific English documents to Arabic. It was also translated by an independent professional translator, who is a native Arabic speaker proficient in English.
2. An independent assessor and I reviewed the initial translations to examine content, semantic and conceptual equivalence with the English version. We suggested some modifications and alternative translations to some items.
3. We met with the independent translator and discussed the two available versions of the translation. Discrepancies were resolved to create one mutual translation. This was done to ensure that the Arabic items gave the same meanings as the English items, not by literal translation of the words from English to Arabic but by using words that are more appropriate in giving the meaning in the Arabic language.
4. Two experts in Arabic linguistics reviewed the Arabic translation to ensure correct grammatical structure and punctuation of the Arabic items. They did not have any knowledge of the English version.
5. The Arabic Vineland-II was back-translated from Arabic to English by two other independent translators. One was an English literature and linguistics specialist and the other was a health care professional, both were not familiar with the original Vineland-II in English.
6. The translators and I discussed and compared the back-translations with the original English Vineland-II to ensure conceptual equivalence and to identify any translation errors. The two back-translations had high agreement with the original. We identified few discrepancies between the original and the two back-translations and discussed them with the first translator. This led to modification of a few items in the Arabic translation to improve compatibility with the English meanings.

- 7.** We adapted some items and examples in some items to fit with the culture of Saudi Arabia, such as replacing some words or activities by others that better represent the local culture (e.g. changed Western names to Arabic names and changed some Western activities to activities that are practised more in Saudi Arabia). Section 4.5.3 below lists these adaptations in detail. The two translators and I are from Saudi Arabia and have first-hand experience of its cultural norms. We have all lived for at least 2 years in the USA, and, therefore, are also familiar with the cultural norms that provide the basis for the Vineland-II.
- 8.** The Arabic Vineland-II was checked for its cultural adaptation and comprehensibility by a senior clinical neuropsychologist at Riyadh Armed Forces Hospital and a senior neuropsychology technician at KFSH&RC (who has been using and adapting the Vineland ABS -first edition- since 1996 with patients at KFSH&RC). Their comments were incorporated into the Arabic Vineland-II.
- 9.** One of the Arabic language experts checked the linguistic and grammatical structure again.
- 10.** A technical expert worked to arrange the Arabic Vineland-II in a comparable style as the original English Vineland-II. I wanted the Arabic version to have the same organization and aesthetics as the original, so people who have used the English Vineland-II would easily find their way using the Arabic version.
- 11.** To test the language of the Arabic Vineland-II, its understandability, acceptability, and clarity to different people, I read it to two women and gave it to three other people to read it through. They were not familiar with it previously and they were asked to give their feedback on any item they didn't understand or which was ambiguous. A few items were highlighted; we discussed these items till we reached agreement on the best way to reword them or add more information to clarify the meaning.
- 12.** The Arabic scales were piloted on normally developing children of both genders and different age groups to test all the items on the Arabic Vineland-II. Section 4.5.4 below describes this pilot study.

### **4.5.3 Adaptations to the Vineland-II in the Arabic version**

A couple of adaptations were carried out all through the Vineland-II:

1. All mention of miles, feet, and inches were changed to kilometers, meters, and centimeters, as these are the measurements used in the region.
2. All the Western names in the Vineland-II were changed to local Arabic names.

Some examples of the adaptations and adjustments are listed in Table 3 below.

Specific adaptations for each item, or adaptation of the example in an item and the reason for the adaptation, are detailed in Appendix 11.

**Table 3: A sample of the items adapted for the Arabic Vineland-II, the adaptations and adjustments, and the reasons for the adaptations.**

<b>Page Number</b>	<b>Item Number</b>	<b>Item in English Vineland-II</b>	<b>Adaptation</b>	<b>Reason</b>
5	11	Points to at least three five minor body parts when asked (for example, fingers, elbows, teeth, toes, etc.).	Replaced the word “toes” with “thumb”	Language: translation of toes is “feet fingers”, and fingers were included already
6	12	Names at least three objects (for example, bottle, dog, favourite toy, etc.).	Replaced “Dog” with “Cat”	Cultural: cats are a more common pet
7	38	Pronounces words clearly without sound substitutions (for example, does not say “wabbit” for “rabbit”, “Thally” for “Sally,” etc.).	Replaced examples using the word “chair”.	Language: this example can illustrate the point of letter substitution better in Arabic. Chair in Arabic is pronounced as “kursi” the substitution could be “tursi”
8	52	Describes a short-term goal and what he or she needs to do to reach it (for example, says, “I want to get an A on my test, so I’m going to study hard”; etc.).	Replaced “A” with “high grades”	Cultural: different grading system
9	6	Identifies all printed letters of the alphabet, upper-and lowercase.	Replaced “upper- and lower case” with “different forms”	Language: Arabic does not have upper or lower cases but letters change forms according to their place in words
10	19	Wipes or blows nose using tissues or handkerchief.	Replaced “handkerchief” with etc.	Language: tissue and handkerchief are translated to the same word in Arabic
12	8	Helps prepare foods that require mixing and cooking (for example, cake or cookie mixes, macaroni and cheese, etc.).	Replaced “macaroni and cheese” with “macaroni and tomato sauce”	Cultural: this is a more common dish
	9	Uses simple appliances (for example, a toaster, can opener, bottle opener, etc.).	Deleted the example “Bottle opener”	Language: the previous example of can opener translates the same as bottle opener
16	37	Goes on group dates.	Replaced “dates” with “gatherings or meetings”	Cultural: there is no dating in Saudi, but meetings with friends without parents is acceptable
18	24	Plays simple games that require keeping score (for example, kickball, pickup basketball, etc.).	Replaced examples of games with more common ones	Cultural

#### **4.5.4 Testing of the Arabic Vineland-II**

For the purpose of this research a small pilot study was done to ensure the reliability and validity of the Arabic version of the Vineland-II. The pilot was done for 15 normally developing children; it was administered with 5 mothers in a face to face interview and with 10 mothers in a phone interview. All of the children were considered normally developing children, 7 were male and 8 were female. Their ages ranged from 4 months up to 16 years. The Vineland-II has 383 items that cover adaptive behaviour from birth to 16 years of age and over, mothers would be interviewed about the behaviours relevant to their children's age group rather than go through the whole scales. Therefore it was necessary to have two to three children in every age group to ensure coverage of all the items more than once.

The tested children all had ABC scores within the normal "Adequate" level of the Vineland-II except two. One child had a score in the "Moderately High" level and the other had a score in the "Moderately low" level. This was expected because the child with high scores was classified as gifted by his school. As for the other child, his mother indicated that he was spoiled and everything was done for him, being the youngest in a large family, and she thought he was slow in progress compared to his siblings at his age (2 years). The ability of the Arabic Vineland-II to distinguish these two children out of the group was very encouraging and a testament to its validity.

The best measure of validity is to administer another adaptive behaviour instrument to the same group of children and compare the results with their scores from the Arabic Vineland-II. This was beyond the scope of the current research; nonetheless it should be carried out before using the Arabic Vineland-II on a larger scale.

Two small scale reliability tests were done. The first, to ensure that the Arabic Vineland-II is reliable in measuring what the English Vineland-II intends to measure, both the Arabic and the English versions were administered with bilingual mothers of four children. All of the four children had similar scores yielding the same adaptive behaviour level on both the Arabic and the English Vineland-II.

The second was a measure of test-retest reliability, the Arabic Vineland-II was administered twice with the mothers of three of the children, there was 7-10 days

between the first and second administration. The children had almost the same scores on both administrations of the Arabic Vineland-II.

The numbers in this pilot study were too small to consider it a validation study for the wider use of the Arabic Vineland-II in Saudi Arabia. However, for the purposes of this study, it was believed to provide sufficient evidence to go ahead and use the Arabic Vineland-II for the patients in this research. Further reliability and validity tests with larger numbers and varied developmental levels need to be carried out on the Arabic Vineland-II to ensure the appropriateness of its use with the wider population in Saudi Arabia and other Arab countries.

## **4.6 The Arabic Vineland-II in the current study**

### **4.6.1 Administration of the Arabic Vineland-II**

The families in this study live in different parts of Saudi Arabia. Travelling to these different parts to administer the Vineland-II was not feasible, and waiting for them to attend their appointments at the KFSH&RC and administer the Vineland-II then would have taken a very long time to accomplish, as many patients only come to clinic every 6 months. Furthermore there was no guarantee that the families would be able to complete the Vineland-II interview due to a full day of clinic appointments and arrangements for travel home that could not be changed, as had been experienced in the data collection period.

Administration of the Arabic Vineland-II by phone was therefore considered.

Limperopoulos et al (2006) examined the equivalence reliability of the Vineland Adaptive Behaviour Scales; their objective was to test if the scores of the Vineland obtained by in-person interviews were comparable to scores obtained by phone interviews through a cross-sectional comparative design. They establish that the in-person interview scores were highly correlated with the phone interview scores ( $r = 0.99$ ), indicating that administering the Vineland through phone interviews gives results consistent with the in-person administration. They have examined the Vineland ABS not the updated Vineland-II, but given that there is a very high correlation between the Vineland-II and the Vineland ABS (Sparrow et al., 2005), it

was assumed that this consistency between phone and in-person interviews would still be present. It is vital to have tools that can give reliable and comparable results when administered through face to face interviews and through phone interviews, this makes gathering data easier, more flexible, and cost effective, it facilitates continuous monitoring of progress and improves access to families in remote areas (Limperopoulos et al., 2006; and Msall & Tremont, 2002).

It was decided best to administer the Vineland-II with the mothers and caregivers over the phone. I had established a good rapport with the families when I met them and the patients during the data collection of Phase 2, and I had talked to them over the phone at least two times to follow up and to take the 24 hour diet recalls. I had had many more contacts when the mothers had more than one child with PKU.

I carried out all of the Vineland-II phone interviews. Administration of the Vineland-II was according to the outlined instructions in the manual (Sparrow et al., 2005). I was trained to conduct and score the Vineland-II by Dr Kathryn Bond, a clinical psychologist working at GOSH. In addition, I had numerous discussions concerning the administration of the Vineland in Arabic with Ms Lina Moncari, the neuropsychology technician at KFSH&RC who administers the Vineland. She gave me valuable tips and insights.

The average time spent on the phone with the mothers for each patient was two hours and twenty minutes. This included introduction of the Vineland-II and the reasons for administering it, conversing with the mothers and listening to their complaints and difficulties with PKU, administering the Vineland-II, and reporting back the scores to the mothers who requested them.

#### **4.6.2 Scoring and interpretation of the Arabic Vineland-II results**

The scoring of the Vineland-II was done by Dr Bond and me to ensure accuracy, and then we discussed the interpretation of the results. We decided that for the purposes of this research the Vineland-II Adaptive Behaviour Composite score (ABC score) would be used in the analyses. The ABC score is defined as a global measure of adaptive functioning. Statistically it is the most dependable general estimate of adaptive functioning as it is based on all of the items in every domain (Sparrow et al., 2005). Further analysis of the scores of each domain may prove valuable for future

research. These scores would facilitate identifying each patient's strengths and weaknesses and are good for monitoring and re-evaluating them periodically to help the patients improve in their daily functioning with planned interventions.

#### **4.6.3 Correlation of the Vineland-II scores with scores from other assessments for the patients**

Twenty seven of the patients had had at least one assessment completed at the Neuropsychology Clinic at the KFSH&RC. The scores they had are from one of these assessment tools: the Beery VMI, the Leiter, the TONI, the Bayley, the McCarthy, and the Vineland ABS. To explore the association between the Vineland-II and other assessments I ran correlation test between the Vineland-II ABC scores for each of the patients with the latest scores they had from previous assessments.

The Pearson product-moment correlation coefficients between the Vineland-II scores and the other scores was high ( $r = 0.92$ ,  $p < 0.0001$ ). This indicated that the Vineland-II had successfully identified the level of development for each patient, as it was in agreement with the scores of other tests.

#### **4.6.4 Experience with the Arabic Vineland-II after its administration**

Although Saudi society and culture are very different to the American culture, much of the day to day routine is very similar. The main differences in culture were the games and sports of choice, and issues with regard to dating and the places to go out to. These were easily modified as described in section 4.5.3 above.

After administering the Arabic Vineland-II with the mothers of the patients in this study there was no need for additional modifications in relation to culture except for two items. One is concerned with writing and sending letters, packages or greeting cards, as it is becoming less practised by Saudis unless in businesses. As this behaviour is expected at an older age only few of the patients reached this item on the Vineland-II, a couple of mothers answered by saying their children sent emails. This item needs to be tested further with a larger sample and modified as required or substituted with another example more relevant to the culture.

The other issue is related to coin use. The use of coins in the Saudi Arabian currency is not fundamental as it is with the pound, dollar or euro, and when used only the 50 halala and 25 halala coins are used (halala is the Saudi equivalent of a pence or cent, Saudi currency: 1 Riyal = 100 halala). Many of the larger shops are starting to abandon the use of coins and many would give out a pack of gum if the change was less than a complete Riyal, instead of giving the change back in coins. We did not change this item in the initial adaptation because we were under the impression that the coins were still in good use in many small grocers and local shops, but most of the mothers reported no use of the coins. This might not be the case in other Arab countries.

Most of the families in this study live in cities or small towns; I didn't find any difference between them in administering the Arabic Vineland-II. Nonetheless it was administered to only 38 children in this study. Some cultural differences may come up if administered with larger numbers of families from villages or rural areas.

One area that needs to be looked at closer is the acquisition of language skills across age. The language skill items in the Vineland-II relate to the rate of learning the English language at different ages. When translating and testing the Vineland-II, we discussed this issue and came to the agreement that the questions are asked at the right ages even for Arabic. Validating the Arabic translation on a larger number of normally developing children will give better evidence for this.

#### **4.6.5 Request for the Arabic Vineland-II**

Researchers from the Yale University Child Study Centre approached me requesting the Arabic translation of the Vineland-II, after hearing about it through Prof Sara Sparrow. They intended to use it with children in Saudi Arabia in a collaborative research project between them and the King Faisal University in Saudi Arabia.

## **Summary**

This chapter portrayed the translation of the Vineland Adaptive Behaviour Scales (Vineland-II) to Arabic, the adaptation of the scales to the culture of Saudi Arabia, and the testing process of the instrument in Arabic with Saudi families. This chapter also described how the Arabic translation of the Vineland-II was administered, scored, and interpreted for this research study.

The results of the Vineland-II Adaptive Behaviour Composite scores for the patients in this study are shown and analysed with other variables from Phase 2 of this study in Chapter 7. These results are then discussed in Chapter 8.



## CHAPTER 5

# FINDINGS (PHASE 1)

## **Introduction**

This chapter describes the findings of the qualitative study from Phase 1 of this research. The aim of this phase was to gain an understanding of the current situation of the patients with aminoacidopathies at KFSH&RC with a view to inform the quantitative and second phase of this study. The findings here were used to structure the questionnaires for Phase 2, and this was then used with a larger number of participants and with quantitative components following the sequential approach recommended by Creswell (2009).

### **The interviews**

**Interviews with health care providers:** There were five interviews with the key informants: three interviews with the metabolic medicine doctors, one interview with the senior metabolic dietitian, and one interview with two dietitians; the metabolic dietitian in training and the dietitian who covers the metabolic clinic when both the metabolic dietitians are not available.

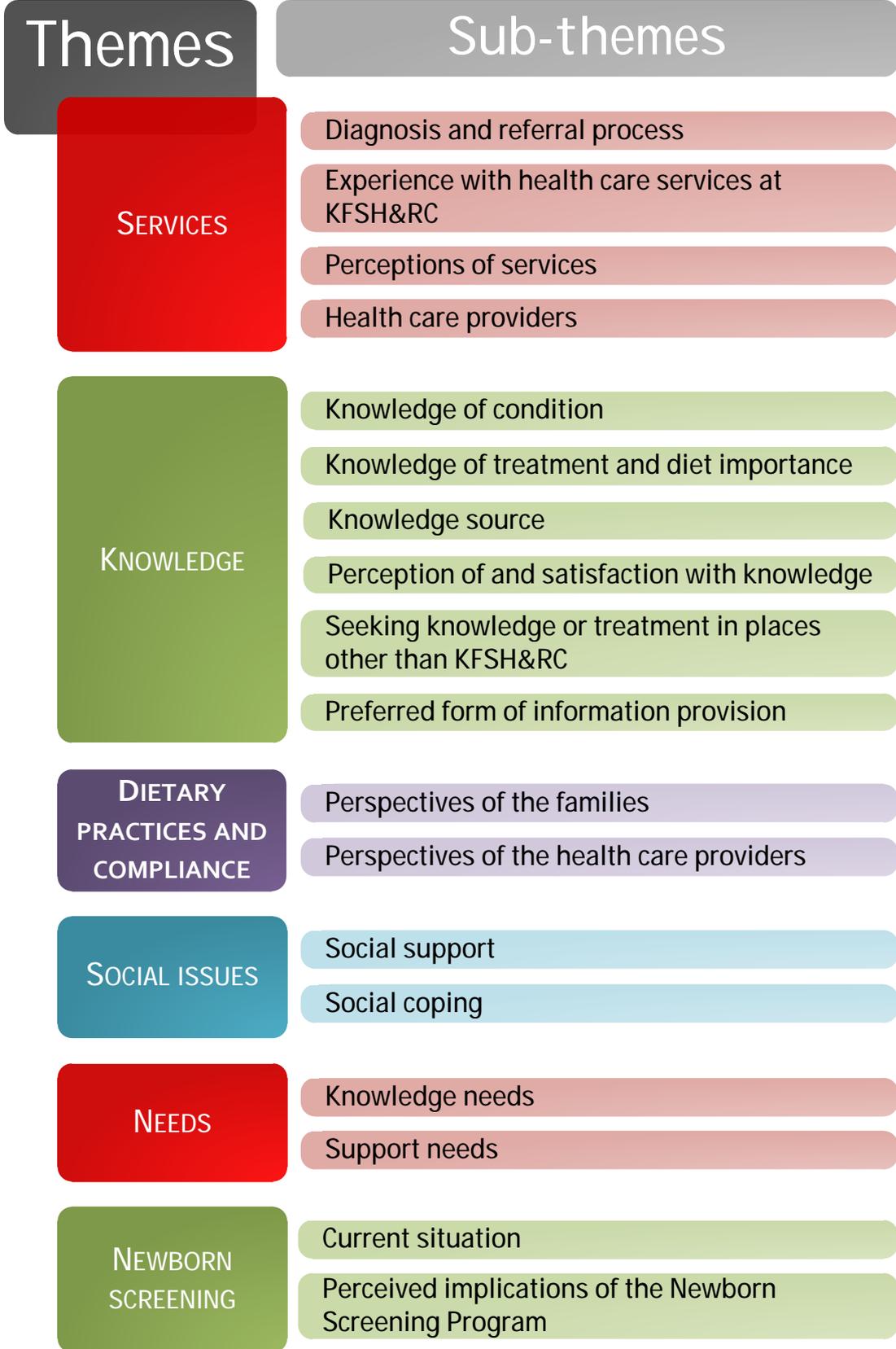
**Focus groups with health care providers:** There were two focus group sessions. One was with 5 general dietitians who work at the hospital and occasionally see patients with aminoacidopathies. The other was with 7 nurses who work at the metabolic clinic.

**Interviews with patients:** Eight patients were interviewed. There were five interviews with individual patients and one group interview with three sisters. They had MSUD, PKU, or tyrosinaemia type I. Their average age was 11.6 years, with a range of 7 to 16 years of age.

**Interviews with families:** There were 17 interviews with families of patients with MSUD, PKU, or tyrosinaemia type I. The families, in between them, had 41 affected children with one of these aminoacidopathies. The interviews were mainly with the mothers and some of the fathers contributed.

Six major themes were identified from the interviews, focus groups, and observations. Each theme encompasses the related subject ideas, concepts, and experiences that were identified from the data. Each theme is then organised into sub-themes, which is a hierarchical organization of the data in each theme. Figure 5 shows the themes and their sub-themes.

The analysis process of deriving these themes is described in the Methods chapter (Qualitative analysis under section 3.4.2.4). The key findings and concepts identified from the participants' perspectives within each theme are presented with examples of direct quotations from the interview texts as evidence. Each quote is followed by the unique code of the person who said it and where it appeared in the transcribed text for reference.



**Figure 5: Phase 1 findings organized in themes and sub-themes (derived from 28 interviews and 2 focus groups).**

## 5.1 Services

### 5.1.1 Diagnosis and referral process

Parents and health care providers had strong views on the process of diagnosis and referral. The doctors believe early diagnosis is improving in Saudi Arabia with the introduction of newborn screening. However, most of the patients in this study were diagnosed late or were diagnosed early through selective screening of families with a known history of a disorder. Many of the families talked about the anguish and distress they and their children have endured due to misdiagnosis or delayed diagnosis. Out of the 17 interviewed families 14 families have lost a child or more, or have a disabled child due to delayed diagnosis of the metabolic disorder they had (Nine families have lost 15 children, and 11 families have 13 delayed children). They talked a lot about “constant crying”, “hospitalizations”, “pain”, “coma”, and “dying”.

*“He was diagnosed at birth. I have a daughter before him; she has the same disorder, but was diagnosed late...” MSUD Parent F9, 13*

*“Six before her and they all died! They all had the same disorder but we did not know, they were not properly diagnosed.. After we discovered her and got to know her smell; the smell of her sweat and urine, the same things and symptoms that she went through the children before her went through. They were not diagnosed at the hospital.” MSUD Parent F13, 17*

When a metabolic disorder was diagnosed in a family all their newborns would be screened after that. Some families think they were fortunate to have their newborns at hospitals that were involved in the new newborn screening programme.

*“If the family has a history of a disorder once the mother gets pregnant they will follow her up at the hospital.” Dietitian D, 51*

*“ I have two daughters, the first daughter, after the first week of birth at the Military Hospital, in Jeddah, they were suspicious of the blood test; they said we should repeat the blood analysis and send it to Riyadh to be sure. From Riyadh they said she has high amino acids and she should not breast feed milk from her mother. My second daughter, soon after delivery we asked for blood test because the doctor told us that her siblings may have the same disorder. They sent the blood test to Riyadh and they said she has amino acids like her sister.” MSUD Parent F12, 10*

*“She was diagnosed at 11 days of age, and she is the first with this disorder. We have two other normally developing children.” PKU Parent F7, 13*

The health care providers considered that the referral system was good when the family has a known history of the disorder. However, they reported that problems arose in identifying and dealing with new cases, due to limited expertise of general paediatricians in the field of Metabolic Disorders in most parts of the country. Nevertheless, they believe the situation has improved in recent years with early referrals due to training of some paediatricians at KFSH&RC's Medical Genetics Department and the start of the newborn screening programme.

*“Referral comes from two sources; either through the newborn screening if they are born here, or referral from hospitals across the country. So usually physicians outside this hospital send Tandem MS if the patients are sick or suspected to have metabolic disease they send the metabolic screening to the hospital and if it comes positive they contact us...”*  
Doctor R1, 15

*“It is much better in the last two years than when we first started; because some physicians started to come to our hospital to take their fellowship which includes metabolic disorders.”* Dietitian D, 73

### **5.1.2 Experience with health care services at KFSH&RC**

#### **Frequency of clinic visits**

Patients are seen at different intervals, depending on their doctor's schedule and on their case. The dietitian and some doctors like to see the patient weekly for the 1<sup>st</sup> month, then twice a month, then every 1-3 months after the age of 3 months, then every 6 months after the age of 1 year if they were stable. But often the clinic schedule is full or the patients do not want to schedule the doctor's visit on a different day than the dietitian, so their visits become further apart.

*“For the 1<sup>st</sup> month we see the new patient weekly and do the necessary changes in the diet....but if everything is stable we see them every 2 weeks during the second and third month of life. This is the way of some of our doctors, others follow different schedules. I prefer this way and I follow it when I schedule for the patients. After that we see them monthly or every 3 months.”* Dietitian D, 110

*“My clinic again, is very busy, so I do a less often follow-up for all the people.”* Doctor R2, 33

*“When she was first diagnosed we came every 2-3 months and now every 6 months.”* PKU Parent F15, 94

### **Access to health care providers and contact between visits**

Usually families can reach their doctor or the metabolic dietitian by phone or pager, or even their mobile phones, but it is not always easy to get through to them. Some families who live in Riyadh just come to the hospital when they need to.

*“Sometimes the clinic is so busy, sometimes we can't answer them [phone calls], but usually we answer them as much as possible.”* Dietitian D2, 153

*“We also receive calls at night sometimes even, after working hours on our pagers or mobile phones.”* Dietitian D, 151

*“Calling is not that easy, it is hard to get the dietitian on the phone; they don't transfer the calls easily.”* PKU Parent F4, 78

*“When I need something I come.”* MSUD Parent F10, 121

The dietitians and the doctors do not have the time to regularly call and follow up with the patients. Therefore they ask the families to call after having a blood test to check the levels and discuss any changes needed in the diet.

*“I ask them to call me, they call and we check the labs and discuss any needed changes.”* Dietitian D, 136

*“We do not contact them, they usually contact us. So we ask them to send the samples and to call us 1 week or 10 days after that, because we have dozens and dozens of these patients; for MSUD we have a huge population. So if you just keep tracking you need one person doing nothing but this, it is a huge list!”* Doctor R1, 79

### **Referral to the metabolic dietitian and follow-up appointments**

Referral to the metabolic dietitian is considered essential and it is regular procedure for all patients as soon as they are diagnosed. Some families need to see her more often than the doctor but due to travel issues they usually schedule the dietitian's appointment on the same day as the doctor's appointment.

*“They diagnose the disorder and refer the patient right away to the metabolic dietitian. And we start with the patient from day one if born at KFSH, if the patient is from outside the hospital we do as much as we can to communicate with other hospitals to start the diet as soon as possible, as soon as they contact us.”* Dietitian D, 20

*“When she first got sick and we saw the doctor he transferred us here [to the dietitian].”*  
MSUD Parent F11, 121

*“Always [see dietitian] with the doctor’s appointment”* MSUD Parent F10, 154

### **Blood amino acid level tests**

Families are asked to have regular blood tests to check the relevant amino acid levels for their children, but that is not always easy for the families when they live far from the hospital. They usually just do a blood test when they come to see the doctor at clinic, or few days before the clinic visit if they live in Riyadh.

*“It depends on the situation and diagnosis. I like to ask for blood levels before the clinic time, just to get the results so I can decide on this in the clinic... I tell them to come before each clinic visit to do blood levels... My philosophy is to ask for it before to be more practical in making necessary changes. Some physicians do the blood tests at the same day, they may forget to communicate results or leave it till next visit.”* Doctor R3, 60

*“I had to pay a lot for sending the blood samples to Riyadh and got tired of that.”* PKU Parent F16, 94

### **5.1.3 Perceptions of services**

#### **Services at KFSH&RC**

Patient care at KFSH&RC was satisfactory to most families. It is viewed as providing good services for the patients and their families with few exceptions. The long waiting times at the hospital to be seen by the doctor and the dietitian were the most voiced complaint. Families mentioned that the health care providers are very busy and overworked and they think this reduces quality time with them. Another problem for many of the families who do not live in Riyadh, where KFSH&RC is located, was travelling to get to their appointments (only six of the interviewed families live in Riyadh).

*“Sometimes we come on the appointment and we are seen right away, and some other times we are delayed. We stay for 3 or 4 hours!”* MSUD Parent F11, 78

*“I feel that [the dietitian] is over worked and I don’t have time to ask her every question that I want to ask her.”* PKU Parent F7, 146

*“The difficulties are in the transportation, no one is available to bring me from Kharj [a*

*town 2 hours drive from Riyadh].*” (Mother became tearful) MSUD Parent F8, 57

*“A lot of time is wasted in the airport. This is my dilemma. Now we finished from the dietitian and we will have to wait to see the doctor. It takes too long for seeing the doctor!”*  
PKU Parent F16, 155

From the point of view of the patients they like the crayons they are given at the clinic to colour and the cafeteria at the hospital, but they dislike coming to the hospital because of the blood test and they do not like the fact that there are no playground or play facilities for them at the hospital.

*“I don’t like to come because of the needle prick”* PKU Patient P4, 39

*“It is better not to come here. I don’t like the blood tests. I only like them to take my weight and pressure.”* MSUD Patient P13, 20

*“There are no swings... If they had swings, we would’ve played.”* PKU Patient P16b, 12

On the other hand, the health care providers at KFSH&RC perceived the services as “inadequate” due to limited availability of dietitians trained in the field of metabolic disorders, limited time for patient counselling, limited specialized staff, limited educational material, and language barriers between families and non-Arabic speaking staff. A positive aspect seen in KFSH&RC services is that the special diet formulas prescribed for metabolic disorders are given free of charge.

*“It is inadequate [hospital service], I think.”* Dietitian D, 472

*“I think they are fairly good, except that the only thing is that they are strained. Of course, there is room for improvement in what could be provided.”* Doctor R2, 217

*“If the system doesn't help you, doesn't provide you with clinics, with more staff then you cannot say that your system is efficient! You cannot describe it as efficient!”* Doctor R1, 272

*“There should be somebody to guide these people; they come from faraway places. There should be somebody to coordinate them to assist and so forth. It is a lot of stress for them.”*  
Nurse N1, 253

*“They have to sit there with the child for how many hours, but you know we cannot help it if the clinics are very busy - 20, 25, 30 to 40 patients a day and everybody has to wait to be seen!”* Nurse N2, 169

*“Of course it is great for them to get the formula free, because otherwise it would be costly!”* Dietitian D, 484

## **Services at health care facilities other than KFSH&RC**

Services at health care centres other than KFSH&RC were perceived as satisfactory for general health care, but unsatisfactory in relation to providing care related to metabolic disorders. That was especially evident in the lack of expert dietitians.

*“If the doctors in other cities know what to do they don’t refer the patients to our doctors, but there are no dietitians. So even if we didn’t see the patient they send all the needed information for the dietitian at KFSH&RC to do the formula calculations and dietary requirements.”* Dietitian D, 96

*“We tell the doctors [in other cities] that she has PKU. Of course, no one knows much about this illness, we alert them about some medications that she should not take.”* PKU Parent F15, 140

### **5.1.4 Health care providers**

#### **Health care providers involved in patient care**

The patients and their families are regularly seen by the metabolic team, which consists of the specialist doctors, the metabolic dietitians and the nurses. They are referred to other specialist such as the psychologist, neurologist, and social worker as needed.

*“The doctors, dietitians, nurses [the metabolic team].”* Dietitian D2, 448

*“We involve the neurologist, ophthalmologist, and paediatricians. Sometimes our problems go to other systems like the liver, kidneys, and other parts of the body, so we involve related healthcare providers. We involve also other medical services like social services”* Doctor R2, 126

#### **Relationships between health care providers, families and patients**

Relationships with health care providers were viewed as good and satisfactory by the families. The patients’ relationships with the health care providers were not as clear, some felt they were listened to and their opinions mattered and some felt that they were not involved.

*“I used to feel shy, but then a woman told me not to be shy and be honest with them, and that is what I did. The doctor does his best.”* MSUD Parent F8, 83

*“I like the dietitian, I always see her and she explains everything to me, I understand her and she teaches me, but the foreigner dietitians before her I didn’t understand them*

*because of the language.*” MSUD Parent F13, 144

*“No, I don’t tell them what I like.”* (referring to communication with doctors) PKU Patient P4, 49

*“He [the doctor] speaks English and I only understand Arabic.”* MSUD Patient P13, 16

Relationships and communication between the different health care providers within the metabolic team appear to be good. The relationships of the health care providers with the families and the patients were portrayed as good and strong as well.

*“My relationship with the physicians and nurses is rather strong.”* Dietitian D, 455

*“We have a good rapport with them [doctors and dietitians].”* Nurse N5, 346

*“I feel I have a very strong relationship with them [families and patients], at the hospital they call them my kids!”* Dietitian D, 266

*“I hope it is good. I try to make my best to deliver a good care... I try to listen to them. I try to establish a good rapport, establish good trust...”* Doctor R2, 99

### **Work setting for the metabolic team**

All of the doctors, dietitians, and nurses in the metabolic team agreed that the metabolic clinics were very busy with high work load, long hours, and high stress. There were four main doctors and two dietitians in the metabolic team, with rotating nurses and trainees. There were 7 clinic sessions per week for the metabolic disorders, each session was 4 hours long and covered by one doctor, one medical trainee, one dietitian, and two nurses or three if the patient numbers were high. The number of patients varied from 10 to 24 per clinic session.

*“It is very strenuous, you need the dedication.”* Dietitian D2, 22

*“You know the coordination for the patients, coordination for education; we are so busy every day you know our practice goes from 8am to 6pm sometimes finishing at 7 or 8pm.”* Nurse N1, 411

*“It is difficult for us during the clinic, because at the same clinic we need to deal with the patient in front of us, deal with the patients on the phone, and deal with the patient who is*

*waiting outside the door, and it is only one person in the clinic, it is really too much. If we have help in the clinic, at least a clerk or a training dietitian, it would help a lot in giving better care to the patients and reducing strain on the dietitian.”* Dietitian D, 129

*“The only thing they [hospital administration] are thinking about is that the load is covered and the patients are seen. They don't care how you are covering it, if you are being killed by covering this load or not!!”* Dietitian D, 532

*“My clinic is very busy, let us say the average number we see per clinic is 24, out of the 24 I would say, 10 to 12 will be aminoacidopathy cases.”* Doctor R2,26

The main dietitian has been working with metabolic disorders for the over 10 years and she has trained the second dietitian. Both are highly motivated and well respected at the Medical Genetics Department, but overworked with the high load of duties. Workload is a major stress factor; nonetheless, they enjoy the work and have good job satisfaction.

*“Thank God when I'm working with these patients I don't feel it's a hospital duty. I work with them because I like them, I like this area, and I am enjoying it.”* Dietitian D, 537

*“Sometimes I go up to the clinic from 8am and don't go down till 6pm. The whole day is with them but still I'm happy because I see the results of what I am doing.”* Dietitian D, 543

*“Definitely it would be satisfying!”* General dietitian FD, 124

## 5.2 Knowledge

### 5.2.1 Knowledge of condition

The knowledge of the families about their children's conditions appeared to be limited to knowing that it is genetic and it is related to protein intake. Only three families knew more detailed information about the conditions, and their knowledge was through their research and reading from the internet or available books. Most children knew the name of their conditions, but didn't appear to understand a great deal beyond that, such as the reason for their blood testing or how would they be affected by high amino acid levels in the blood.

*"I don't have a complete knowledge, but I do know it is genetic, because of the family relation between me and her mother."* PKU Parent F4, L16

*"I don't know anything about his disorder!"* MSUD Parent F14, L15

*"No, I don't understand."* PKU Patient P4, L36. When asked: "Do you understand what the doctors or your parents tell you about your condition PKU?"

*"Protein"* PKU Patient P16b, L27. When asked: "What do you know about your condition? Do you know what is it called?"

Knowledge of metabolic conditions among general health professionals in the country is perceived to be limited but improving for paediatricians due to the fellowship programme that is now offered at the Medical Genetics Department at KFSH&RC and the out-reach clinics at different cities from this department as well. As for other health care providers working with children with inborn errors of metabolism, such as dietitians and nurses, they report that there are no training programmes about metabolic disorders or knowledge-improvement opportunities available other than occasional symposiums and lectures.

*"Oh, very limited...very limited! If you are talking about specialists in metabolic diseases, our services are probably the only one across the country that provides comprehensive care to those patients..."* Doctor R1, 325

*"We have the fellowship programme here, at KFSH&RC at the medical genetics department...Only doctors who choose to come here are trained; this is the only facility*

*that trains in this field.*” Doctor R2, 244

*“I think it is better than before, but still not the optimum you want to hear or see... We are getting more invitations for talks and symposiums.”* Doctor R3, 216

*“No, if they want teaching at least they would send a dietitian to be trained... But there is no interested dietitian till now. I feel if you are interested in something you will really nag to go to learn it. The problem is everybody is feeling that the metabolic nutrition is ‘oh something nobody can do it’. It is just real calculations. You need to concentrate and to have the ability to listen, and the ability to be patient with these kinds of patients.”* Dietitian D, 598

## **5.2.2 Knowledge of treatment and diet importance**

Families seemed to have good knowledge about their children’s treatment and good comprehension of diet importance in managing the conditions (PKU, MSUD, and tyrosinaemia I). Most of the children interviewed showed fair knowledge of the treatments and formulas they were taking, but not all seemed to be fully aware of the diet importance.

*“Doctors told me if she didn’t follow the diet she will get convulsions, become lethargic, and her brain will be different.”* MSUD Parent F11, 110

*“When I really comply with her diet I see that my daughter becomes proper, good in her head... Sometimes when I’m sick or something and they don’t give her the diet correctly you will see something wrong with her either her gait wobbly or her hand shaking or eyes rolling, I can feel she is not all right.”* MSUD Parent F13, 175

*“If we don’t follow the diet the brain will be affected and acidity increases.”* PKU Parent F2, 89

*“NTBC and the formula.”* Tyrosinaemia I Patient P6, 24. In answer to, “Can you tell me something about your treatment?”

Health care providers agree on the importance of the diet and the dietitian’s role in the management of these disorders. Non-metabolic dietitians admit that their knowledge of the metabolic diets is very limited.

*“Very important, especially the acidopathies, without a dietitian we cannot manage them! It is a very vital role for the management.”* Doctor R2, 187.

*“Diet is a very big part of the care really; because if they don’t stick to their diet they*

*might die. That's what I hear over and over from Doctor Ozand, he will be screaming to the mothers, 'How come you didn't come back!'... Doctor Ozand stresses the importance of the dietary supplement or treatment.” Nurse N1, 63*

*“If the patient was newly diagnosed it would be difficult for us to calculate the formula... We would need to consult the metabolic dietitian.” General dietitian FD, 79*

### **5.2.3 Knowledge source**

Knowledge sources regarding the aminoacidopathies for families were limited to health care providers at KFSH&RC; namely doctors and the metabolic dietitians. Only three of the interviewed families read books or searched the internet for additional information, while the majority (82% of interviewed families) believed that the hospital was the only source for information pertaining to their children’s conditions.

*“Only from the doctor. When I come here the doctor and the dietitian tell me.” PKU Parent F16, 103*

*“There is no source except the dietitian. For this disease the only source is the hospital.” MSUD Parent F5, 120*

Health care providers believed they were the main source of information for families as well. The reason for that is thought to be the unavailability of information resources in the Arabic language and the low literacy levels in many families.

*“I think their knowledge depends on what we tell them; very few can go and research about their disorder. Till now there is no material in Arabic, all the resources are in English, and it is difficult for most of them to read English.” Dietitian D, 317*

*“We have different kinds of patients. Most of the patients of these diseases in Saudi Arabia come from tribal areas. Most of them if you give something to read, I don’t think they read it. With the new generation they look in the internet and prepare questions for you, but most of our patients (90%) they get the knowledge from what you give them.” Doctor R3, 127*

Health professionals not specialized in metabolic disorders get their knowledge about specific conditions from the internet, literature review, the Ross Protocol manual for metabolic nutrition, lectures, and by asking the metabolic team.

*“We research on them when we encounter them.”* General dietitian FD,59

*“Doctors [as source of information], if you ask them questions, they are really going to answer you.”* Nurse N1, 139

#### **5.2.4 Perception of and satisfaction with knowledge**

Some families perceived themselves as having good knowledge of their children’s conditions and good understanding of their dietary requirements, and they were satisfied with their knowledge (n= 9). Other families were not as confident; they felt they did not have enough information or good understanding of the conditions or the dietary requirements (n= 8).

*“Yes, I’m not scared anymore; I have a grasp on it.”* PKU Parent F7, L28

*“A little bit [understand disorder], I don’t understand it very well, I know the diet only.”* MSUD Parent F9, L25

*“Not really [good understanding], but I think I understand what I need to know.”* Tyrosinaemia I Parent F6, L45

In agreement with this, health care providers see that some families have good comprehension of the conditions while others have only the minimum knowledge. This is thought to be due to different literacy levels and knowledge of the English language among families.

*“I think they grasp the minimum of that. Lots of them here have a level of education that does not allow them to go and seek the full knowledge and the information you would like them to have. It is not accessible sometimes or not in the language they understand. I would say they understand the ‘yes’ and ‘no’ and to follow the example, if they want of course. But in terms of prognosis, they are behind.”* Doctor R2, 138

*“Clearly there is a big difference between those who can speak English and those who cannot. They can communicate with you very well. They will tell you for example: ‘Why did you do succinylacetone’, ‘What is the result’, they would contact me through the Internet*

*and email me. So there is a big difference in types of care between these two different kinds of populations, if you would say.” Doctor R1, 172*

*“Most of them know their [dietary] restrictions.” General dietitian FD, 199*

*“Some of them with low education we need to explain more.” Dietitian D2, 302*

### **5.2.5 Seeking knowledge or treatment in places other than KFSH&RC**

Many families had particular queries about their children’s conditions; they wanted to know more, but very few actually took action and tried to search for answers. This was also true in regard to seeking treatment in other places. Most families believed that KFSH&RC was the only place for treating their children, only two families travelled abroad to seek other opinions.

*“I would like to know how does acidity rise, soon after he eats one thing or after eating many things will it accumulate and rise?” MSUD Parent F9, 127*

*“I want to learn more about the disease. I have heard once the patient makes it to adulthood it resolves, but people at the hospital say ‘no’; because these are enzymes in the blood and they don’t go, so I don’t know!” MSUD Parent F5, 40*

*“Thanks to Allah, the doctors are sufficient for me.” MSUD Parent F11, 154*

Health care providers and observation confirm that there is low interest in researching and seeking information from families and general health care providers not specializing in metabolic disorders.

*“People have to be trained on how to get needed information. That is why ‘knowledge-wise’ we are not mature here. They don’t have more information in the rest of the world, but when they need it they know how to find it and that is the difference!!” Doctor R2, 249*

### **5.2.6 Preferred form of information provision**

Families showed interest in the idea of receiving new and additional information and messages to take home. The preferred method of receiving information differed according to literacy levels. Many families requested video or audio tapes to have as information sources in addition to requests for more leaflets and printed material with pictures. Some parents asked for lectures to attend and have open discussions.

*“Cassette tapes to hear are better; because I can’t write or read.”* Parent F14, 120

*“By cassette, video tape and pictures.”* Parent F1, 131

*“By video tape we can watch and listen, and face to face meetings, I mean someone explains and if I didn’t understand I can ask.”* Parent F6, 234

## 5.3 Dietary practices and compliance

### 5.3.1 Perspectives of the families

#### Diet

Dietary knowledge and practices of most of the families appeared to be derived from the recommendations that they receive from the dietitians. Food choices, likes, dislikes, knowledge of allowed and non-allowed foods and compliance were expressed. Many of the children knew what food should be avoided and the main permitted foods in their diets and said that their mothers prepared these foods for them. Two of the children were not sure about the food that they should avoid.

*“She is prohibited from all foods of animal origin, and allowed vegetarian food only.”*  
PKU Parent F4, 40

*“When we visit others he eats salads or potatoes, he knows his food.”* MSUD Parent F10, 48

*“Biscuit allowed, a little, not too much, because it would affect my brain. Cake has high protein, and I don’t eat tea biscuits. Cheese is forbidden and eggs are not good for me.”*  
MSUD Patient P13, 43

*“I don’t eat meat or food containing proteins.”* PKU Patient P6, 49

Some mothers confessed that they try their best to follow the diet but did not always manage to comply. They understood the importance of following the diet, but the difficulty of following such a limited diet was overwhelming for some mothers.

*“Fruits and allowed food she doesn't eat, because she is fed up with them too.”* PKU Parent F15, 72

*“I don’t really follow it, I won’t lie to you. Their instructions are very strict... I feel sorry for him; I feel that he needs to eat a bite of meat once in a while. I want to give him from the food his siblings eat; you know a mother’s heart.”* MSUD Parent F5, 127

*“She gets frustrated when she sees her sisters eat anything they like-cheese or meat- and she can’t.”* PKU Parent F4, 30

## **Formula**

Another difficulty the families faced was with the formula; many of the children would not drink it easily, especially if they were diagnosed late. Nonetheless, the mothers tried hard because they saw the positive effect it has on their children. On observation, the mothers prepared the formula as directed by the dietitian. None of the interviewed children complained about the formula, they all said that they drink what is given to them. Only three said they helped their mothers to prepare their formula.

*“I give her Cornflakes for breakfast with a cup of tea. Her formula milk has a strong smell she can’t eat it with it.”* MSUD Parent F13, 97

*“The formula she doesn’t accept it unless it’s mixed with juice or flavouring like Tang.”* MSUD Parent F3, 75

*“We notice if they do not take their formula they become abnormal in their balance.”* MSUD Parent F12, 113

## **Barriers to compliance**

The families identified several barriers to complying with the diet and formula. Limited dietary choice was the major barrier; there were no low protein food products available for the children to offer them a variety of choices. The children become bored of the diet and start trying other foods that should be avoided. This was confirmed through the market survey. There were no low protein products available, only low protein flour was found in one specialty store and it was sold at 12 times the price of regular flour.

Other barriers included children unsupervised around food at school or social occasions, time needed to prepare the patient’s meals in addition to the family’s meals, the need to travel from their towns to get to the hospital, and emotional barriers where the mothers feel sorry for their children and give them non-allowed food. The identified barriers are in Table 4 in the following section.

*“They got bored with the same breakfast, lunch, and diner, even though we are doing our best to give them food similar to ours.”* MSUD Parent F12, 41

*“I need the special food from the U.S. so she can eat from it freely. They have special food that is low in amino acids.”* MSUD Parent F3, 60

### **5.3.2 Perspectives of the health care providers**

#### **Diet**

Diet is a major concern as it is crucial in the management of aminoacidopathies. The importance of prompt dietary intervention is stressed and explained to families as soon as they are diagnosed. Dietary counselling for the patients had to be adapted to the culture and customs of life in Saudi Arabia. The dietitian explained that the use of measuring scales was not common because the hospital does not provide them and they are costly for the families to get. Families were trained to use scoops for measuring the needed amount of formula. Breast feeding is common in Saudi Arabia, but the dietitian found expressing breast milk to give the baby a measured amount was not a welcomed practice by the mothers, so they were instructed not to breastfeed.

*“The measuring scales are too expensive for the hospital to give to families, and even if it was given to them there is no interest to use it...”* Dietitian D, 196

*“Here if you tell them breast-feed measured amounts, they will just carry the baby on the breast and feed it, so we don’t allow it at all for any one.”* Dietitian D, 185

#### **Formula**

Issues related to the special dietary formula were evident through the interviews and observations. The dietitians reiterated what some of the families have said regarding the difficulty of getting their children to drink the entire prescribed amount of formula. The provision of free formula by KFSH&RC is considered a blessing but also a potential problem should the hospital run out of stock. Although a rare event, this could put patients at risk because there is no other source for the formulas in the market.

*“There isn’t any other way [to get formula]. It has to be through the hospital and they have to come to get it.”* Doctor R2, 133

#### **Compliance**

Compliance with appointments, formula, and diet emerged as essential aspects concerning patient care. The dietitians perceived that most patients comply with 60-70% of the diet. Some of the families failed to realize the importance of watching and

recording the dietary intake of their children and a few families would not travel to come to the nutrition appointment if it was scheduled on a different day than their appointment with the doctor. Some of the perceived factors affecting compliance were the type of disorder, early or late diagnosis, and frequency of follow-up.

*“Patients are different; some ignore the dietitian’s appointment, if they don’t have a doctor’s appointment they do not come at all, although the importance of the diet is explained to them by the doctors!!”* Dietitian D, 121

*“Many will not bring it [food record]; they would say ‘Oh my God! Every time you want us to bring it!?’ or ‘Every time you ask us these questions?’ They don’t understand that I need this information to calculate how much they are eating...”* Dietitian D, 212

*“...for any patient if they are diagnosed early and take the formula early and get used to the formula, so there is no problems they will get used to it because they don’t know the taste of the other foods, but when they are diagnosed late already there is problem later to the restricted diet, it is more difficult.”* Dietitian D2, 331

*“Tyrosinaemia & MSUD are more towards the compliance group. The reason is if they find that by restricting their food and following their diet they will prevent acute episodes... they will stick to it.”* Doctor R2, 160

Some of the barriers identified by health care providers were personal issues that needed to be dealt with by the families, but they recognize that unfortunately many barriers were beyond the family control. Such limitations in resources and unavailability of products become barriers for providing optimum services, which hinder compliance. The barriers to compliance identified by the health care providers and the families are listed in Table 4. The dietitian empathized with the families in regard to the difficulties they face in following a restricted diet.

*“Sometimes the families will come and say ‘We are fed up, what can we give them?’ I can understand their frustration because there is nothing in the market for them.”* Dietitian D, 258

**Table 4: Compliance barriers identified by the health care providers and the families**

<b>Compliance Barriers</b>
Limited product availability
Limited educational materials
Limited nutrition experts
Limited counselling time
Limited knowledge about the disorders and the diet
Travel to Riyadh to get to KFSH&RC
Language barriers
Formula unavailable in local areas
Financial and time burden of preparing a special diet
Social barriers: unsupervised patients at schools and social occasions
Emotional barriers: feeling sorry for the child, depression, anxiety, stress
Cultural issues: over-protection of child, wanting the child to be equal to others

Measures to facilitate compliance were implemented by the hospital, such as paying for travel expenses of the families when they attend appointments and providing housing when they cannot afford it. The health care providers recognized that continuous follow-up, reinforcement and having more than one child with the same disorder were factors that improved compliance. They acknowledged that more efforts were needed to tackle all the barriers to compliance.

*“The hospital pays travel expense for the mother, the father and the patient. Even if they need to come back just to take the formula we give them follow-up slip, so their travel will be paid for.”* Dietitian D, 309

*“Education, establishing trust with the family, and reinforcement -positive reinforcement- over time, all would help.”* Doctor R2, 181

*“I think the most important reason for compliance is if the family knows the nature of the disease... For some families, their first child with the disorder is mentally disabled, due to late diagnosis... So these families know the outcome so they are compliant with their other diagnosed children.”* Doctor R3, 169

*“Reinforcement, continuous follow-up, like clinic visits are very important. Reinforcement!”* General dietitian FG, 313

## 5.4 Social issues

### 5.4.1 Social support

Many parents seek social support from family members or even the metabolic dietitian. This is necessary due to the pressures they encounter when dealing with metabolic disorders on daily basis.

*“After Allah we have my sister, she does her best. She loves them and treats them well.”*

MSUD Parent F12, 46

*“The dietitian does her best. When I talk to her with a problem she advises and tries to help out, but I feel it is not in their hands. They say foods with minimal protein are all right, but you know they are kids and they need more. Food like cheese and eggs are totally forbidden, but I can see in their eyes that they want to eat these foods when they see someone or their brother [healthy brother] eating from it. This is my dilemma, it breaks my heart.”* Tyrosinaemia I Parent F6, 76

There are no support group services available for the families at KFSH&RC. Some of them ask the health care providers about other families with children with the same diagnosis in an effort to connect with others in the same situation.

*“Some of them ask for it, sometimes we have the numbers to give them to contact each other, if they agree, and if they see each other in the waiting area...”* Dietitian D, 497

### 5.4.2 Social coping

#### Diet in social settings

Social coping skills and adaptations were very important for the families and patients to help them cope with the dietary isolation that the children have to live with. Most families found some coping strategies for feeding their children in social settings, such as taking their food with them or selecting appropriate food from what is offered in a social occasion or a restaurant. Nonetheless, some families found it hard to go out or socialize with the affected child.

*“We take her food with us. Her condition didn’t prevent us from going out.”* PKU Parent F4, 43

*“Nothing special [when going out], I leave them like other children, they know well not to eat meat, and they only eat rice and other things. Thanks to Allah I don’t worry about them regarding meat and such foods, even if they visit others. You know, some people offer children food, they say no thanks we can’t eat this, they know.”* Tyrosinaemia I Parent F6, 93

*“We try not to go for social visits a lot, but if we did, we take their meal with us. We prefer our family to visit us.”* MSUD Parent F12, 57

*“I don’t go out; I just stay at my family’s house.”* MSUD Parent F8, 47

## **Education and school enrolment**

Children with mild development disabilities were placed in mainstream schools.

Families explain their children’s condition to schools, which in most instances are cooperative with the families. Few families complained that their schools were not as accommodating as desired.

*“Yes [teachers know about her condition], they call us when they have something to ask about.”* PKU Parent F15, 84

*“To some extent [school cooperative], not that great!”* Tyrosinaemia I Parent F6, 105

The situation was not as easy for the families of children with moderate or severe developmental disabilities. It was hard for them to find special education schools in their areas and some schools would not accept them, either due to their dietary restrictions or due to the severity of their disability.

*“The eldest was not accepted in school [special education school].”* PKU Parent F16, 128

*“No, we enrolled her in a private school but we saw she wasn’t benefiting; it wasn’t a special education school and the tuition was expensive so we took her out.”* MSUD Parent F13, 112

Children are coping differently at school and with friends. Some have no problems with telling friends about their conditions and diets, while others prefer not to mention it.

*“Yes, they know. [Friends know about patient’s condition]”* PKU Patient P4, 96

*“No [friends at school don’t know about formula], at home they know.”* PKU Patient P15, 92

## Family issues

There were many stresses and fears facing the families. One recurrent fear was pregnancy and having other affected children, another was living far from where services are available.

*“She is the first one. We have a healthy boy and her, and that's it, we stopped.”* PKU Parent F15, 20

*“No, it's just pregnancy; I'm thinking about it but scared [of having another child with Tyrosinaemia].”* Tyrosinaemia I Parent F17, 170

*“Originally we are from out of Riyadh, and we can go back, but because of the boys' appointments we thought it would be better to stay here.”* Tyrosinaemia I Parent F6, 149

Health care providers were aware that families faced many stresses and frustrations at the hospital and at their homes. These included long waiting times at the hospital, social stresses, financial burdens, limited dietary choices for their children, unavailability of many local services, and the fear of having more affected children. Frustrations were mainly due to service barriers faced by families as well as health care providers.

*“The waiting time!”* Dietitian D, 278

*“The nature of these diseases, the fear that it's inherited diseases; genetics. They will panic when they know it might affect other members of their family in the future, even they worry about the previous kids! Even if they are healthy and normal. Situations of formula, diet in the families, the socio economic status, if the father works or mother works, all of these stress the family.”* Doctor R3, 99

*“Every day they ask us if there is any new food that is allowed.”* Dietitian D2, 254

*“It is too much for the family if they have four or five kids with the same problem.”* Nurse N2, 162

## 5.5 Needs

### 5.5.1 Knowledge needs

The families and the health care providers called repeatedly for the need to understand more and to improve the knowledge of these metabolic conditions. This improvement was thought to be needed in many different aspects, for both the families and the health care providers. Table 5 lists the knowledge needs voiced by families and different health care providers.

*“I want to know about the adult cases of this condition, see how they lived, and learn from them. We are always worried about the future.”* Parent F15, 193

*“I wish and it would be great if there was an Arabic website about MSUD available for us.”* Parent F3, 222

*“I wish there could be workshops for the families.”* Dietitian D, 442

*“Training, training is really important, even if I have the manual, it is very difficult for me.”* General dietitian FD, 149

**Table 5: Knowledge needs as perceived by the families and the health care providers**

<b>Knowledge needs perceived by the families</b>
More information to understand the conditions better
More information about disease prognosis and the future
Detailed nutrition information
More information on dietary choices
Contraception counselling
More general information about care and education of patients
<b>Knowledge needs perceived by the health care providers</b>
Improve general public awareness of metabolic disorders
Workshops for families to improve their knowledge of metabolic disorders
Better patient education
Better training for dietitians
Continuous training for staff
Better education for health professionals in general around the country

### 5.5.2 Support needs

The families indicated that support was needed to assist them in dealing with the metabolic disorders. The families felt isolated, not knowing other families dealing with the same disorders, they asked about them and wished for support groups. They wanted to get to know others and learn about their experiences. Many of the families wished for financial support and support at home with their children, this was especially evident with the mothers of children with disabilities. Some of the families asked for more support for the dietitians so they would get more time during their appointments with them.

*“We can exchange different experiences, learn from each other and talk about our difficulties, it will be kind of a support for us, and that will bring us some comfort. People who have their hands in the fire are not like who don’t! Many think there is no patient except their child but when you see others with sick children you accept your situation. Thanks to Allah.”* Parent F13, 224

*“I thought of bringing in a house helper, but how can I pay her wages?”* Parent F16, 104

*“Financial stress as we have four children with the same disease.”* Parent F1, 35

*“I think they need a lot more, and also dietitians, they need more, they are over worked and under staffed!”* Parent F7, 130

The health care providers echoed the families’ views in their need for family support groups and provision of more supportive services. At the same time they expressed that they themselves require support in many aspects to aid them in providing optimal services. They needed an increase in the number of dietitians and other staff specialised in working with patients with metabolic disorders. This would support them in increasing the number of clinics to see the patients, which would reduce the numbers of patients per clinic session and would give them more time for counselling and educating the families. They agreed that there is a great need for providing the special low protein food products for the families or providing financial support for the families to be able to afford such products.

*“I feel that the family support groups is one of the most important things that would help the patient to know more and have better communication with each other and not only with us as medical staff.”* Dietitian D, 366

*“These patients need social services, support groups which are not provided. They need psychological assessments, psychological input from different aspects... There is only one neuropsychologist in the whole hospital and the waiting list for him is up to nine months to one year!”* Doctor R1, 282

*“We need more clinics, we need more metabolic dietitians...”* Dietitian D2, 482

*“There are no special food products for the patients; they can only get it through the internet, which is very expensive!”* Doctor R2, 221

## 5.6 Newborn screening

### 5.6.1 Current situation

The National Newborn Screening Programme in Saudi Arabia has started, and it is in its early phases. The health care providers agreed that the programme was long overdue and it still needs to grow and reach smaller towns to cover all newborns in the country. There are concerns among health care providers in regard to the insufficient planning for this programme

*“...unfortunately most of our patients are mentally disabled!! Because we don’t have the newborn screening programme across the country and the vast majority of our patients come from referral hospitals, local hospitals outside this hospital.”* Doctor R1, 204

*“We should have started this programme a long time ago!”* Doctor R1, 311

*“It’s excellent if all the members are there; if one angle is not there it will collapse!”*  
Dietitian D, 574

### 5.6.2 Perceived implications of the newborn screening programme

Health care providers all agreed that the impact of newborn screening is good because early diagnosis can prevent deterioration in many patients. At the same time they predicted that the programme will increase their work load at KFSH&RC. They had concerns regarding the readiness of health care providers around the country and the availability of services for new cases. It was strongly articulated that training of health care providers is fundamental for the success of this programme.

*“I think it would be more rewarding... And less stressful on our part, good we saved that beautiful baby.”* Nurse N2, 388

*“I think the impact would be good. Diagnosis of some metabolic diseases early on can make a lot of difference, provided that these patients receive good care at the time of diagnosis!”* Doctor R2, 235

*“Impact on our practice will be bigger load, unless they would think about education and training programmes!”* Dietitian D, 609

*“We will be overloaded with cases! We are already overloaded... I think if the Ministry of Health and the health care in this country do not appreciate the importance of genetics and*

*the importance of this kind of diseases and the high frequency and incidence of these disorders in this country...we will have great difficulty!” Doctor R1, 346*

*“Screening is not a test it is a programme; from getting the results to getting the patients and treating them. It is part of the programme to train people to deal with these cases. You can’t screen without the facility to treat!!” Doctor R3, 231*

## **Summary**

The thematic analysis of the interviews and the focus groups in this phase resulted in the emergence of six major themes. The observations supported these themes. The themes are mutually exclusive in their evidence, but they are all interrelated and have an impact on one another.

The findings from this phase gave vital insights into the circumstances and struggles of the patients with aminoacidopathies, their families, and the health care team managing their treatment in Saudi Arabia. It provided valuable information to help understand the condition of current health care management at KFSH&RC. This was the first time that this form of enquiry has been carried out with a population of patients with metabolic disorders in Saudi Arabia. The next chapter discusses the implications of these findings and how it helped shape the creation of the questionnaire for Phase 2 of this study.



# CHAPTER 6

## **DISCUSSION (PHASE 1)**

## **Introduction**

The qualitative study in Phase 1 provided a wealth of information about the situation of patients with aminoacidopathies at KFSH&RC from the perspectives of the families, the patients, and their health care providers. Their knowledge, attitudes, and practices were explored. The results informed the development of comprehensive questionnaires for the use with the patients with PKU and their families in Phase 2 of the research, as recommended in the literature (Creswell, 2009; Pope & Mays, 1995; Pope et al., 2000; and Thomas et al., 2004).

### **6.1 Services**

Early diagnosis and referral to treatment were important issues that came up from the interviews with the families and the health care providers. Early diagnosis and treatment is essential to prevent illness and disabilities in patients with aminoacidopathies (Abadie et al., 2005; Burgard et al., 1999; Medical Research Council Working Party on Phenylketonuria, 1993; Schulze, Frommhold, Hoffmann, & Mayatepek, 2001; and Simon et al., 2006). Early diagnosis is improving in Saudi Arabia; currently the Saudi Newborn Screening Programme is in its formative years, and it is gradually expanding to increase the number of screened newborns (Afifi & Abdul-Jabbar, 2007; and Ministry of Health, 2012).

Families mentioned that the health care providers were very busy and overworked which increased waiting time at the hospital, reduced quality time with the families during hospital visits, and reduced access to the staff when needed between scheduled appointments. From the patients' point of view, these waiting times were boring. The waiting areas are bland with no play facilities or activity corners for the children. Providing a fun and relaxed environment for the patients when they visit the hospital, in addition to alleviating boredom, reduces the fear and anxiety that many children feel upon entering hospitals. This is an essential part of providing a positive experience for the patients and their families (Doverty, 1992; and Jun-Tai, 2008). This could improve their interest in attending appointments and following the recommendations that they hear from the health care providers (Sylva, 1993).

The busy schedules of the health care providers lead to scheduling follow-up appointments after longer than ideal intervals. This is in disagreement with the recommendations of increasing accessibility to health care providers and increasing patient monitoring to improve adherence to diet and metabolic control of phenylalanine blood levels (Feillet & Agostoni, 2010; Feillet et al., 2010; van Spronsen & Burgard, 2008; Wappner, Cho, Kronmal, Schuett, & Seashore, 1999; and Wendel & Langenbeck, 1996).

Another side to this concern is the follow-up with the dietitian. The interviews showed that the importance of the role of the metabolic dietitian was emphasized by the health care providers. This was understood by the families but not put into practice by having regular appointments to see the dietitian and monitor the blood amino acid levels for their children. Regular and close nutrition monitoring is essential for optimum outcome (Feillet & Agostoni, 2010). The burden of travel for many of the families leads to combining all the appointments (i.e. doctor, dietitian, and blood test) on one visit to the hospital every 6 or 9 months.

Another cause of infrequent follow-ups could be the limited number of metabolic dietitians. Two dietitians alternate to cover the clinics and inpatient care, therefore there are not enough clinic appointment slots to cover frequent follow-up appointments. In addition, when families are given appointments with the dietitian only, many do not show up because they do not find it easy or worth the trip to travel to Riyadh for one appointment. This wastes valuable time from the metabolic nutrition clinic. Therefore the dietitians schedule their appointments to coincide with the doctors' appointments only. This reduces nutritional monitoring.

This is both a service and a compliance issue that should be investigated further to understand from more of the families their perspectives regarding frequent follow-ups and nutritional monitoring. Improving the local health care services for metabolic disorders is key, so the families would not need to travel to Riyadh so often. Local family physicians and dietitians can provide regular health care, family support, monitoring, and coordination with specialists. Training them on the circumstances that need referral to specialised medical management will instil confidence in their care (Casey, 2013). This might be a solution for improving nutritional follow-up and

monitoring which, as mentioned earlier, is recognized to help improve metabolic control.

## **6.2 Knowledge**

Knowledge of the conditions (MSUD, tyrosinaemia type 1, and PKU) by the families and the patients was not optimum. The families were well aware of the treatments, formulas and the importance of dietary restrictions for their children. Their knowledge fell short when it came to understanding details about the disorders that their children have: the long-term prognosis, the minor side effects, or future expectations in terms of education, employment, marriage and pregnancy. Their knowledge appeared centered on the present needs of care. This could be a consequence of the busy schedules of the metabolic doctors and dietitians. They appear to focus their time with the families on informing them of what they need to be doing at the present for the best health care for their children. Detailed information about the disorders or extra information regarding the future may be viewed as too technical for the families, or as unnecessary details that may confuse the families, or merely the time constraint of the busy clinic schedule does not allow for it. Similar experiences were reported in two other qualitative researches involving patients with PKU or their families (Awiszus & Unger, 1990; and Ievers-Landis et al., 2005).

The families were keen to obtain more information and many felt a strong need to know about the future for their children. Providing adequate information and education for the families and the patients to fully comprehend their disorders may help in the acceptance process of having a lifelong disorder, as not accepting the disorder may lead to bad metabolic control (Crone et al., 2005). Knowing that they can learn to control many aspects of their disorders may empower them to improve their skills to deal with problems related to their diet and treatment, and therefore, through modifying behavior, they would improve their compliance (Ievers-Landis et al., 2005). The patients may also benefit a great deal if they were given the opportunity to learn more about their disorders and the importance of their dietary restrictions and formula intake (Bekhof et al., 2005; and Feillet et al., 2010). Good understanding of one's illness has been shown to have a positive improvement in

adherence to treatment or at least reduce deviation from the required treatments (Landolt, Nuoffer, Steinmann, & Superti-Furga, 2002; van Spronsen & Burgard, 2008; and Vegni, Fiori, Riva, Giovannini, & Moja, 2010).

Antshel and colleagues (2004) found that families and patients with internal attribution styles, where they construe the cause of events as due to personal factors, have better compliance with treatment than families with external attribution styles. People with external attribution styles perceive their conditions as controlled by external factors, which may be explained by their limited knowledge of their disorders. Improving the families' knowledge and understanding of the disorders could be helpful in arming them against attributing control of their disorders to external factors, and therefore may improve their adherence to the diet.

Knowing more about the views of more of the families through the questionnaire in Phase 2 would verify if this was a true need for the families. The number of patients who were interviewed in Phase 1 was small (8 children), insufficient to judge the knowledge of the patients. Therefore learning further about the patients and their knowledge in regards to their conditions and dietary needs would be valuable in understanding their knowledge needs and to informing the recommendations.

The knowledge source regarding the disorders, for nearly all of the families, was limited to what was provided by the staff at the hospital. Learning from the families what they need to know and what form of information provision appeals to them most would help in improving the information provision practices at KFSH&RC. This would hopefully have a positive impact on improving the knowledge and comprehension of the families regarding their children's conditions and dietary needs. It is important to offer different tools and sources of information to the families and the patients, and to involve them, so they can find the most suitable ways for them to learn and to improve their confidence and satisfaction with their knowledge and comprehension (Bernstein et al., 2013; Durham-Shearer, Judd, Whelan, & Thomas, 2008; and Vegni et al., 2010).

The language barrier was another important issue to address. Nearly all the information available about aminoacidopathies is in English, and only a few families can fully comprehend it. This limits the information that can be accessed by the

families to the few leaflets that were written and offered by the dietitians at KFSH&RC in Arabic. Translating a whole variety of information including recipes or creating a website in Arabic to present information related to the disorders for the families was seen as an extra work load that the dietitians' time and that their schedules do not permit.

For comprehensive care and to help the patients and their families understand their conditions and adhere to the recommendations, the hospital would need to provide them with ample information in the Arabic language. In addition to the medical information this should include recipes and food serving ideas that are not just translated, but suited to the food culture in Saudi Arabia and uses the food products that are available in the country. Many western recipes call for ingredients that are not available in Saudi Arabia for the families. The need for this service was evident from the qualitative findings.

The health care providers expressed the opinion that the knowledge of other health care providers, who are not specialized in metabolic disorders, such as family doctors or general pediatricians, was not sufficient to take care of the patients at their local clinics. They agreed on the need to improve the knowledge of other health care providers and to train more dietitians in the field of metabolic disorders. This could definitely have a positive impact on advancing the services provided for the families and it could improve the quality of the time spent with the families (Nasserullah et al., 2003).

### **6.3 Diet**

Dietary compliance appeared to be a central issue for the families. The difficulty and restrictions of the diet was a cause of anxiety and frustration for many of the mothers. Some did not comply due to incomplete understanding of the grave consequences of noncompliance, and some just felt sorry for their children and believed that this restricted diet is unjust. Jusienė and Kučinskis (2004) evaluated Lithuanian children with PKU and their parents in regard to their coping and psychological adjustment to the illness. They reported that the parents may pity their children and therefore indulge them with foods that are not allowed. Feeding and nourishing to them was

associated with love and care, so feeding the child with PKU differently could be interpreted as unfair (Jusienė & Kučinskas, 2004). This explanation was heard repeatedly from the families in Saudi Arabia.

The formula, like the diet, was reported to be difficult to consume by many of the families. Though the interviewed patients did not complain about it or report hating it, this could be because they knew they should be drinking it, and chose not to report that they miss some doses. Formula intake is crucial for keeping good metabolic control and for providing essential amino acids. Not drinking it has detrimental effects for the patients (Acosta et al., 2004; Adamczyk et al., 2011; MacDonald et al., 2004; and Tavit et al., 2006).

Ievers-Landis and colleagues (2005) investigated the challenges of the dietary treatment for PKU that are faced by the patients and their families. Nearly all of the interviewed children declared having problems and challenges with following the diet and drinking the formula. Most of their interviewed caregivers reported problems with the diet and half of them had problems with their children's consumption of the formula. Di Ciommo and colleagues (2012) interviewed children, adolescents, and young adults with PKU about their experiences with adherence to diet. The main concerns were fear of social stigma and social limitations due to their restricted diet. The need to adhere to the PKU diet negatively affected their quality of life. These are a couple of the few qualitative studies that have been done for patients with PKU, and their findings are comparable to the findings from this qualitative study.

The families have identified many barriers to their adherence to the diet and formula intake. The difficulties with the diet and formula intake are challenges that many of the families of patients with metabolic disorders have been documented to face (Bernstein et al., 2013; Bilginsoy, Waitzman, Leonard, & Ernst, 2005; Demirkol, Gizewska, Giovannini, & Walter, 2011; and MacDonald, 2000).

The health care providers at KFSH&RC reported more noncompliance from patients with PKU, since they do not get acute symptoms due to high blood phenylalanine levels. Patients with MSUD had better compliance due to the immediate effects they experience after noncompliance. This is reported for MSUD due to the acute episodes or metabolic crises that the patients would get due to high blood levels of leucine that

result from noncompliance or acute illnesses (Morton et al., 2002; and Strauss et al., 2010).

The health care providers reiterated the compliance barriers that the families have mentioned and added a few more that prevented them from providing the best service for their patients. Some dietary related services are not available for the families, such as continuous nutritional management at their local towns, continuous education, and low protein products to offer the patients a wider variety of food choices. Under such circumstances the recommendations for the families must be adjusted according to their individual needs. The health care providers were already making some adjustments according to the culture of the area. Some researchers suggest instructing the families to follow the diet strictly, but to be slightly flexible when there is noncompliance with the formula, however, the continuation with the dietary restrictions without taking the formula could lead to nutrient deficiencies (Brenton, 2000; and Crone et al., 2005).

It was important to learn and find out more about the barriers of compliance that the families and the patients face. This information is essential to help find ways to overcome these barriers. This qualitative study revealed that more efforts are necessary to tackle the service barriers that the health care providers recognized as hindering the patients' compliance with diet and formula intake.

## **6.4 Social issues**

Having a life long illness to deal with requires a lot of adjustments by the families (Awiszus & Unger, 1990; Brenton, 2000; and Dellve, Samuelsson, Tallborn, Fasth, & Hallberg, 2006). Some of the families found coping mechanisms that worked for them in dealing with dietary restrictions, while some families struggled with these issues. Research found that when families internalize the problems they face and find coping strategies, their children tend to have better metabolic control (Antshel, Brewster, & Waisbren, 2004; and Awiszus & Unger, 1990). Learning through the questionnaire how many parents struggle with coping and managing their children's conditions, then identifying the best practices to improve their situations may immensely help the metabolic control of the patients at KFSH&RC.

The lack of family support services for the parents and the patients, to share their difficulties and stresses with each other, increases the feelings of defeat and confusion that some of the families have. Many of the families seek social support from other close family members, but due to the limited knowledge about these disorders, many turn to the dietitians, even for issues not related to diet. Identifying vulnerable families who are in need for support is vital for a comprehensive care provision. It is important to empower the parents to maintain a social support system because it improves their coping skills and quality of life (Fidika, Salewski, & Goldbeck, 2013).

Some of the prominent issues that bothered the mothers were the fear of having additional affected children and living far from KFSH&RC. Provision of genetic counselling services and focused education about family planning may help ease the stress regarding future pregnancies (Albar, 1999; Al-Gazali, 2005; and Meyer, 2005).

Living far from the relevant health services was voiced as a barrier to compliance. The monitoring of blood levels tends to be less frequent, and in some instances if the formula runs out there are no other places but KFSH&RC to get it. If the families are not organized enough to arrange for someone to get more supply of the formula before they run out, their child could be without formula for a few days. Some families cannot arrange that and they end up waiting several days until their appointment at KFSH&RC, then they travel for the appointment and get their supply. Patients are usually given enough supply to last them until their following appointments, but delaying the appointment or extra intake of the formula may cause the need for additional supply before the follow-up appointment. This is another reason for providing more specialised care at other centres around the country. Then the families would have somewhere closer to home to go to for general follow-up, dietary counselling, blood level monitoring, and formula supply.

Another important aspect of the social life for the families is the schooling system. The families struggle with finding appropriate schools for their children, whether they have learning disabilities or not. Mainstream schools that cater for children with mild learning disabilities are increasing, but they can still only be found in the main large cities in Saudi Arabia (e.g. Riyadh, Makkah, Jeddah, Medina and Dammam). Special education and rehabilitation schools for children with moderate to severe learning disabilities are available, but again limited to the main cities and have long waiting

lists to get into them. Due to this some of the families have to travel long distances to get their children to school and some of the families have moved to the larger cities for their children to be in school. This situation leaves the families with limited choices, either move to a major city or keep their child at home; neither is an easy choice.

Even when the patients do not have learning disabilities, the families have some difficulties explaining their cases to the schools regarding the dietary restrictions for their children. Not all schools show cooperation in this regard, there is no governmental mandate of care between the health care system and the education system. The entire burden falls on the families to convince the schools that their children can fit in with other children with the help of some education to the teachers and the students about the disorders and the dietary restrictions.

This is a daily battle that the families need not fight. Frustrations were mainly due to service barriers faced by the families as well as the health care providers. Knowing more about these barriers and finding the best ways to overcome them are fundamental to providing the best care for the patients.

## **6.5 Needs**

Through the interviews and observations, many service, support, knowledge, and education needs were evident, as discussed earlier. These needs revealed how imperative it was to have a better and more detailed understanding of the situation of the patients of metabolic disorders and their families, to enable appropriate planning for improvements.

Support was clearly needed by the families and the patients to assist them in dealing with their daily struggles in relation to their disorders. Services such as family support groups, home visits, and home support for the families with children with disabilities may give the families better motivation and continuous reminders to comply with the recommendations and metabolic control. Many studies have demonstrated the effectiveness of support groups for patients with metabolic disorders and their families. Meeting other patients has been shown to provide social, psychological, and

metabolic advantages and positive influences (Awiszus & Unger, 1990; Bernstein et al., 2013; Brenton, 2000; MacDonald et al., 2010; Vegni et al., 2010; and Wappner et al., 1999).

Knowledge needs were equally pointed out by the families and the health care providers on many different aspects of the disorders. Therefore it was important to learn through the questionnaires if these knowledge needs were shared by many other mothers and to find out their preferred ways of meeting these needs.

The health care providers highlighted the need for improving the awareness of other health care providers, and providing training for more dietitians. They acknowledged the need to support the metabolic clinic to improve its services by adding more staff to enable them to spend more time with each patient. In addition, the provision of low protein food products, in their opinion, would improve their level of service. These are in line with recent recommendations for improving compliance (MacDonald et al., 2010).

## **6.6 Newborn screening**

The newborn screening programme in Saudi Arabia started in 2005 as a pilot. It started in twenty four of the main hospitals in Saudi Arabia with the aim to screen up to 50,000 newborns per year. It has expanded gradually, screening 130,000 newborns in the year 2011 (S. Alabdulmunem, personal communication, May 16, 2012). The programme has become mandatory in 2012 (Ministry of Health, 2011), and it is predicted that all newborns will be screened by the end of 2014\*.

The perceptions of the health care providers about this programme were that the readiness and training of the relevant health care providers around the country were not optimum. A review of the effectiveness and benefit of the Saudi newborn screening programme agrees with these perceptions and anticipates challenges for the public health system in Saudi Arabia. It primarily expresses concern that the interconnections between primary health care services and specialists are limited,

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\* Detailed information about the newborn screening programme in Saudi Arabia can be found in Chapter 2 Literature Review, section 2.5.2.

especially for small villages and remote areas. It affirms the importance of training of staff and planning a thorough referral system to ensure proper follow-up of identified patients (Afifi & Abdul-Jabbar, 2007).

Nasserullah and colleagues (2003) reported their experience with screening for sickle cell disease and other hemoglobinopathies in the Eastern area of Saudi Arabia. They asserted that shortage of staff and low levels of knowledge were the main barriers to successful newborn screening. In another report from the Eastern Province of Saudi Arabia, Moammar et al (2010) reviewed the prevalence of inborn errors of metabolism in that region. They stressed the importance of expanding the newborn screening programme and providing regional follow-up, treatment, and genetic counselling for the families to advance the quality of care. It is absolutely essential to have adequate services to meet the needs that arise from implementing a country wide screening programme (Berry et al., 2010; and Therrell, 2003).

## **Summary**

A wealth of information was gained from this qualitative study. All of the above issues informed the development of the questionnaires for Phase 2. The questionnaires were to investigate and include the opinions of more patients with PKU and their families. The questionnaires were not divided into sections according to the findings from Phase 1, but were designed to be flowing in meaning and relevance to cover all the significant issues that came out in Phase 1.

The health care providers directly involved with the care for patients with aminoacidopathies were all interviewed in Phase 1 of this study. Therefore, they were not interviewed further in Phase 2, which focused only on the patients and their families. The views and suggestions of the health care providers were incorporated into the final recommendations of this research.

# CHAPTER 7

## **RESULTS (PHASE 2)**

## **Introduction**

This chapter presents the results from Phase 2 of this research. Results are presented in four sections: the research group, data from the Family Questionnaire, data from the Child Questionnaire, and data from the different assessments and measures done with the patients.

### **7.1 Research group**

The King Faisal Specialist Hospital and Research Centre had 67 patients with PKU on record. Four of these patients have emigrated; 18 have not visited the hospital for two years or more, and were unreachable. Five refused to participate: three were siblings in one family who did not want to participate. The fourth was a sibling of two patients who participated in the study; the mother did not want to include him because he was doing well. The last one was as well a sibling of two patients who participated, but she was a newborn and the mother didn't want to include her.

The remaining 40 patients all participated in the study. The patients' ages ranged from 1 month to 21 years. Their ages at diagnosis ranged between 2 days and 17.5 years. Twenty six patients are female and 14 are male. The questionnaire was answered by the mothers except for two families; the step mother answered one and the eldest sister answered the other.

Two of the families had another child with PKU (in each case the first child with PKU) in addition to the participating child. Both were not patients at KFSH&RC, and therefore it was not possible to include them in the study. They were diagnosed late and were profoundly delayed, and they have been placed in assisted care facilities.

## 7.2 Family Questionnaire

### 7.2.1 Socio-economic status

The 40 patients are from 24 families\*. Five families each have three children with PKU, ten have two children with PKU, and nine have one child with PKU\*. All the children live with both of their parents, except one child; she lives with her father and step mother. Five families live in extended households, the remainder nuclear. Eighty percent of the families live in urban areas, 15% in peri-urban areas, and 5% in rural areas. Fifteen families (37.5%) live in Riyadh, other families live in cities or towns that are a 3 to 14 hour drive to Riyadh (45 min – 2 hr flight).

There is a wide range in parents' education and occupations, although most mothers are homemakers. Table 6 shows parents' ages, education level, and occupation. The monthly spending of the families varies, most families (66.7%) spend less than 5000 Saudi Riyals per month (1 Pound Sterling = 6 Saudi Riyals SR). The average spending in Saudi Arabia is SR 4700 (Saudi Central Department of Statistics & Information, 2007). Table 7 and Table 8 give details of the number of children born to mothers, the number of children still alive, birth order of child with PKU, and statistics of household inhabitants.

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\* When the information in the analysis is related to the parents it is shown in the tables as a total of 24, when the information is related to the patients, the total is 40.

\* Four children not included in the study: two declined, and two were not patients at KFSH&RC, as explained in the research group section.

**Table 6: Age, education level, and occupation of the participating parents (N=24).**

		Frequency (%)	
		Father	Mother
<b>Age</b>	26-30	0 (0%)	3 (12.5%)
	31-35	2 (8.3%)	7 (29.2%)
	36-40	7 (29.2%)	8 (33.3%)
	41-45	7 (29.2%)	4 (16.7%)
	46-50	3 (12.5%)	1 (4.2%)
	>50	5 (20.8%)	1 (4.2%)
	<b>Total</b>	<b>24 (100%)</b>	<b>24 (100%)</b>
<b>Education level</b>	Read & write	0 (0%)	1 (4.2%)
	Primary school	2 (8.3%)	4 (16.7%)
	Middle school	2 (8.3%)	5 (20.8%)
	High school	6 (25%)	7 (29.2%)
	Less than Univ. Dip	3 (12.5%)	3 (12.5%)
	University	10 (41.7%)	4 (16.7%)
	Higher graduate degree	1 (4.2%)	0 (0%)
<b>Total</b>	<b>24 (100%)</b>	<b>24 (100%)</b>	
<b>Occupation category</b>	Professional	13 (54.2%)	5 (20.8%)
	Technician	4 (16.7%)	1 (4.2%)
	Worker	2 (8.3%)	0 (0%)
	Military officer	2 (8.3%)	0 (0%)
	Unemployed	1 (4.2%)	0 (0%)
	Retired	2 (8.3%)	0 (0%)
	House-wife	0 (0%)	18 (75%)
<b>Total</b>	<b>24 (100%)</b>	<b>24 (100%)</b>	

**Table 7: Number of children born to mothers and birth order of child with PKU.**

		Frequency (%)
<b>Number of children born to mother</b>	2	1 (4.2%)
	3	6 (25%)
	5	3 (12.5%)
	6	6 (25%)
	7	4 (16.7%)
	8	2 (8.3%)
	9	1 (4.2%)
	10	1 (4.2%)
	<b>Total</b>	<b>24 (100%)</b>
<b>Birth order of child with PKU</b>	1	8 (20%)
	2	5 (12.5%)
	3	7 (17.5%)
	4	6 (15%)
	5	6 (15%)
	6	4 (10%)
	7	1 (2.5%)
	8	1 (2.5%)
	9	1 (2.5%)
	10	1 (2.5%)
<b>Total</b>	<b>40 (100%)</b>	

**Table 8: Descriptive statistics for number of children born to the mothers, number of children with PKU in the families, and household inhabitants (N=24).**

Statistics	Number of children born to mother	Number of children with PKU	Number of children in the household	Number of adults in the household*
Mean	5.58	1.83	3.96	4.88
Mode	3 and 6	2	3	3
Std. Deviation	2.145	.761	2.074	1.985
Minimum	2	1	1	2
Maximum	10	3	10	8

\*Includes adult siblings

### 7.2.1.1 Food budget

The fathers are the main food buyers (15/24). The food budget for half of the families (12/24) in this study is within the average food expenditure for all Saudi families, which is 447 Saudi Riyals (SR) per week (Saudi Central Department of Statistics & Information, 2007). Ten families spend much more on food than the national average. This high spending is due to ordering low protein products from abroad, as they are not available in the Saudi market.

### 7.2.2 Diet and formula

#### 7.2.2.1 Food and formula preparation

The primary carer for all patients is the mother, except for the one child whose parents are divorced; the domestic helper is the primary care giver. The secondary carer is mostly the sister when available, the father, or a domestic helper.

The patient's meals are prepared separately from the family meals in most families (21/24), only three families cook their own food to be suitable for their child with PKU. Meals are usually prepared by the mothers, except for three families where the domestic helper prepares the meals. Formula is mainly prepared by the mothers as well (31/40); only two children, who are siblings, are given a chance to make their formula with their mother. Most mothers prepare the formula just before the child needs to drink it (18/40), or prepare the prescribed amount for the whole day and leave it in the fridge for the child to drink from (17/40). Most of the mothers need less than 5 minutes to prepare the formula. Some of the flavours that the mothers add to

the formula to improve its taste are salt, instant coffee, orange juice, honey, and mostly sugar.

### 7.2.2.2 Formula intake

Most of the children drink their formula 2 to 3 times a day (19/40). Others drink their formula 4 to 5 times a day or whenever hungry (12/40). The remaining 9 only drink their formula occasionally or never (Table 9). Drinking the formula is not easy for all children, 16 children have difficulty drinking their formula. The mothers believe the smell and taste of the formula are the main reasons of this difficulty. All causes of difficulty and the frequency in which they are mentioned by the mothers are listed in Table 9.

**Table 9: Adherence to formula intake and the causes of difficulty in drinking the formula.**

		Frequency
<b>Drink formula</b>	Always	23
	Usually	8
	Occasionally	7
	Never	2
	<b>Total</b>	<b>40</b>
<b>Difficulty causes</b>	Smell of formula	9
	Taste of formula	8
	Fed up with the formula	3
	Consistency of formula	2
	Will not drink formula when sick	1

### 7.2.2.3 Diet adherence

Only three of the mothers felt that complying with the PKU diet is easy, others felt it was difficult or even very difficult (Table 10). The mothers face many barriers to adhering to the diet; children being unattended around food and children's insistence on eating banned foods are the two main barriers. Table 10 lists all the barriers faced by the mothers. Only two mothers felt that they did not have any barriers to comply with the diet.

**Table 10: Difficulty of adhering to the PKU diet; opinions of the mothers (N=24), and the barriers to adhering to the PKU diet as recognized by the mothers (N=24).**

<b>Diet adhering</b>	<b>Frequency</b>
Easy	3
Difficult	11
Very difficult	10
<b>Total</b>	<b>24</b>

<b>Barriers</b>	<b>Frequency (%)</b>
Child unattended around food	13 (54.2%)
Child's insistence on eating banned food	11 (45.8%)
Social visits	9 (37.5%)
School teachers or pupils	8 (33.3%)
Other children or friends of child	8 (33.3%)
Family members: siblings, grandparents, aunts, or uncles	7 (29.2%)
Limited dietary choices	7 (29.2%)
Refusal to eat what's offered	1 (4.2%)
Has a big appetite	1 (4.2%)
Limited knowledge of diet	0 (0%)

### 7.2.3 Education and social life

#### 7.2.3.1 School attendance

Seven of the children (17.5%) are under school age, and 6 (15%) do not go to school - due to unavailability of specialist schools to cater for their learning disabilities in their areas. Twenty seven of the children (67.5%) go to school. More than half of the children who go to school (16/27) are thought to need special education by their mothers. Most of them get some type of special education or special classes, although not always as appropriate as the mothers wish (Table 11). The schools the children attend are regular schools, regular schools with special education classes, or special education schools. They are a mix of private and public schools (Table12).

**Table 11: School attendance, perceived need for special education, and provided special education.**

	<b>Frequency (%)</b>		<b>Total</b>
	<b>Yes</b>	<b>No</b>	
<b>Go to school</b>	27 (67.5%)	13 (32.5%)	<b>40 (100%)</b>
<b>Need special education</b>	16 (59.3%)	11 (40.7%)	<b>27 (100%)</b>
<b>Get special education</b>	14 (51.9%)	13 (48.1%)	<b>27 (100%)</b>

**Table12: Types of schools the patients attend.**

School Type	Frequency (%)
Public school (regular)	6 (22.2%)
Public school (has special education classes)	5 (18.5%)
Private school (regular)	7 (25.9%)
Private school (has special education classes)	3 (11.1%)
Special education school	6 (22.2%)
<b>Total</b>	<b>27 (100%)</b>

### 7.2.3.2 Social activities

Most of the families go out at least once a week accompanied by their children with PKU (Table 13). Mainly they go out for family visits, but a large number take their children out for recreational outings and shopping as well (Table 13). One mother rarely goes out; she finds it very difficult to deal with her child when out, she stays home with him and they go out for their hospital appointments only. Nearly half of the families face difficulties or limitations when going out with their children. The main limitations they endure being the diet and difficulty in dealing with the child in public (Table 13).

**Table 13: Frequency of going out as a family (N=24) with the child/children with PKU, places that families go to, and the limitations or difficulties that they face when going out due to the child's condition.**

Go out with child	Frequency
Daily	1
Weekly	18
Monthly	4
Rarely	1
<b>Total</b>	<b>24</b>
<b>Places to go to accompanied by child</b>	
Family visits	23
Family recreation outings	21
Shopping	15
Other places	0
<b>Outing limitations</b>	
Child's diet	6
Difficulty with child	5
General anxiety (worried about child)	4
Embarrassment	2
Disability of child	2
Formula	1
Influence of others	1
Child's condition	0
Other limit: child becomes ill after outing	1

#### **7.2.4 Health care practices**

Most of the patients visit KFSH&RC twice a year, but the frequency of visits varies and ranges up to 12 visits a year (Table 14). This usually depends on the health status and age of the patient. Ninety percent of the patients visit other facilities for general health care, such as dental care and intercurrent illnesses. Table 14 lists the frequency of these visits. There is a difference in the frequency of testing phenylalanine blood level between patients, although many of them will have a blood test only when they visit KFSH&RC every six months (Table 14). Most of the mothers perceived that their child's health is excellent or good in general, only 4 children are perceived to have fair health (Table 14).

Five of the patients have other health problems in addition to PKU (two have glucose-6-phosphate dehydrogenase deficiency, one has insulin dependent diabetes, one has myoclonic encephalopathy, and one has a ventricular septal defect). All of these conditions are managed with PKU and do not have an effect on child development except in the case of one patient who has myoclonic encephalopathy, which impairs development. Therefore he was excluded from the analyses involving development and assessments. Data from his mother's questionnaire was kept in this analysis because it covered her knowledge, concerns, and care for her child in relation to PKU.

**Table 14: Frequency of healthcare visits to KFSH&RC, visits to other facilities, and blood Phe testing, and mothers' perceptions of their children's health.**

		<b>Frequency (%)</b>
<b>Appointment frequency at KFSH per year</b>	1	2 (5.0%)
	2	16 (40.0%)
	3	9 (22.5%)
	4	7 (17.5%)
	6	2 (5.0%)
	12	4 (10.0%)
	<b>Total</b>	<b>40 (100%)</b>
<b>Frequency of visits to another healthcare facility</b>	Once a month	4 (10%)
	Every 3 months	8 (20%)
	Every 6 months	19 (47.5%)
	Never (only go to KFSH)	4 (10%)
	Other	5 (12.5%)
	<b>Total</b>	<b>40 (100%)</b>
<b>Frequency of sending blood to KFSH&amp;RC for Phe level</b>	Once a month	2 (5%)
	Every 3 months	9 (22.5%)
	Every 6 months	19 (47.5%)
	Other	10 (25%)
	<b>Total</b>	<b>40 (100%)</b>
<b>Mother's perception of child's health</b>	Excellent	23 (57.5%)
	Good	13 (32.5%)
	Fair	4 (10%)
	Poor	0 (0%)
	<b>Total</b>	<b>40 (100%)</b>

## 7.2.5 Knowledge

### 7.2.5.1 Knowledge about PKU

Many of the mothers perceived their knowledge of PKU to be good or excellent (17/24), but there were some who felt they do not understand the condition well enough (7/24). More mothers though (21/24) were confident in their knowledge of the dietary requirements of PKU. Nearly all the mothers understood the importance of their children's compliance to the diet and formula intake; only one mother felt that following the diet is not important to her child's health and another mother felt that both the formula and diet are somewhat important but not fundamental to her child's health. All the mothers knew the basics of the dietary restrictions; that is fruits and vegetables are allowed, while meats and dairy products are not allowed. Two of the mothers thought that lentils are allowed in the diet when they are not, due to their high protein content, and one mother did not know if they were allowed or not. Similarly

two of the mothers thought that diet drinks were allowed and didn't know that they had phenylalanine in them (in the sweetener, aspartame), and two of the mothers didn't know if they are allowed or not (Table 15). When the mothers need information regarding the PKU diet many call the dietitian to ask (15/24), some of the mothers (8/24) would look for the information in the written material that they have and some (7/24) would wait till their next appointment to ask the dietitian. Only one mother said she would look for dietary information on the internet.

**Table 15: Mothers' knowledge about some food choices for their children.**

Is it all right for a child with PKU to eat or drink:	Frequency (%)		
	Yes	No	Do not know
Dates (allowed)	24 (100%)	0 (0%)	0 (0%)
Meat stew (not allowed)	0 (0%)	24 (100%)	0 (0%)
Lentils (not allowed)	2 (8.3%)	21 (87.5%)	1 (4.2%)
Diet cola (not allowed)	2 (8.3%)	20 (83.3%)	2 (8.3%)

The mothers' perceptions of what the dietitian would recommend if their children had high blood Phe levels were mostly correct. They were aware that the child needs to drink all the prescribed formula, reduce dietary protein intake, and in some cases the dietitian might increase the formula intake to cover the child's needs when some food choices are reduced (Table 16). Most of the mothers, but not all, knew that a prolonged elevated blood Phe level would cause permanent learning disability for their children. Some understood that elevated levels cause hyperactivity and only a few believed that high levels would cause irritability. Table 17 lists the risks of prolonged high blood Phe levels as perceived by the mothers. Most of the mothers believed that the PKU diet is to be followed for life, as recommended by the KFSH&RC specialists. Still, some believed that it is only needed until their children grow up or are cured from this disorder (Table 18).

**Table 16: Mothers' perceptions of what the dietitian may recommend if blood Phe level was high.**

If high Phe level (correct answer)	Answered correctly (%)
Reduce the formula (no)	24 (100%)
Increase dietary protein intake (no)	24 (100%)
Reduce dietary protein intake (yes)	22 (91.7%)
May increase the formula (yes)	6 (25%)
Ask if ill (yes)	1 (4.2%)
Ask about the diet (yes)	1 (4.2%)

**Table 17: Mothers' knowledge of the risks of prolonged high blood Phe level.**

<b>Risk of prolonged high Phe level in blood</b> (correct answer)	<b>Answered correctly (%)</b>
Permanent learning disability (yes)	19 (79.2%)
Hyperactivity (yes)	7 (29.2%)
Irritability (yes)	3 (12.5%)
Illness (no)	21 (87.5%)
Paralysis (no)	23 (95.8%)
No effect (no)	24 (100%)
<b>Other risks perceived by the mothers</b>	<b>Frequency</b>
- Low/decreased concentration	5
- Aggressiveness/anger	4
- Change in hair colour	2
- Sleep problems	2
- Seizures	1
- Nausea	1
- Coma	1
- Death	1

**Table 18: Mothers' beliefs of the length of time needed to follow the PKU diet.**

<b>Diet Period</b>	<b>Frequency (%)</b>
All his/her life	17 (70.8%)
Until he/she grows up	4 (16.7%)
Until he/she is cured	2 (8.3%)
Don't know	1 (4.2%)
<b>Total</b>	<b>24 (100%)</b>

### 7.2.5.2 Seeking information

The families wanted to learn more about many issues relating to PKU. Learning more about diet choices and what the future holds for their children were highest on their lists. They wanted to understand the effects of PKU on growth, puberty, marriage, and pregnancy. They wanted more information about food choices and recipes to improve their children's limited diet. Some families just wanted to understand the condition and its effects on brain and development. They were interested to learn about other patients similar to their children; how they are doing, how their families are coping, and how they are at school. A few families also were interested in learning about new advances in research in terms of a cure or a medicine for PKU that would improve dietary choices or replace the formula.

Box 4 lists some of what the families are interested in learning about. When asked how they would like to have this information provided to them most preferred the material to be given to them on videos, pamphlets, or CDs to take home; to watch, read, or listen to in their own time and keep as a reference. Many families were also interested in having a designated time that they can easily reach their health care provider by phone to ask any question they might have. All the ways of information provision according to preference of mothers are listed in Table 19. The main sources of information for families currently are the doctors and the dietitians (Table 19).

**Box 4: Topics the families are interested to learn more about.**

**Future**

- Do his food choices now affect him negatively in the future?
- How can I prevent them from getting worse, in their brain functions?
- How are other patients doing mentally, when they grow up?
- How to deal with them at puberty?
- Her future when she grows up.
- Her growth and puberty.
- What to do in the future. What is the future like for them?
- Pregnancy issues.
- Understand future of PKU.
- When they grow up and get married how would PKU affect them in the future?
- Would like to understand if there would be improvements in the future.
- What will happen when she grows up?

**Diet**

- Diet.
- Understand more about the formula and how it benefits my son.
- How to improve the diet choices from the allowed food, to introduce new recipes.
- More information about the diet in the future.
- The diet is very limited, how to improve it?
- Know about more options of food.
- More information about allowed foods.
- Something to help with the diet.
- How to count protein grams in food items?
- What kinds of food can we give them more of?

**Condition**

- How does it affect their brains?
- How are other children here doing?
- I need to understand her condition.
- Know more about dealing with learning disability.
- More information about this disorder.
- Is the stress level of the child affected by their phenylalanine blood level?
- I would like to meet and know about older children similar to my daughter, what happened to them, how are the families coping, how are the schools?

**New advances in PKU**

- Information about new improvements.
- Would there be medications instead of the formula and diet?
- I would like to know about any advances.

**Table 19: Mothers' preferred ways of information provision and the information source for families regarding PKU.**

<b>Form of information provision</b>	<b>Frequency (%)</b>
Video tapes/ DVDs	24 (100%)
Written material (e.g. pamphlets)	21 (87.5%)
Designated time to call HCP to answer specific questions	21 (87.5%)
Audio cassettes / CDs	18 (75%)
Informal sessions with healthcare providers (HCP) during clinic visits	17 (70.8%)
Group lectures	16 (66.7%)
Email	2 (8.3%)
Email with doctors & professionals out of Saudi Arabia	1 (4.2%)
Website regarding PKU in Arabic	1 (4.2%)
<b>PKU information source</b>	
Doctor	22 (91.7%)
Dietitian	21 (87.5%)
Internet	7 (29.2%)
Another person with same diagnosis	5 (20.8%)
Books	4 (16.7%)
Nurse	2 (8.3%)

### **7.2.6 Personal concerns**

The mothers had many concerns for their children regarding PKU (Box 5). Most of the mothers were concerned about the diet; its difficulty to comply with, limitations of choices, and the inability to control their children around food. The unknown future was a big concern for the mothers as well; they worry about their children's development, ability to complete school and have proper education, puberty issues, and the ability to lead a normal adult life. Some mothers were concerned about the increased weight of their children due to the continued intake of Phenex-I after 2 years of age. Phenex-I is a Ross product formula that is designed for infants and toddlers with PKU. Until recently (2010) KFSH&RC had only Phenex-I available for all PKU patients, providing older children with higher energy content than their needs and causing an overweight problem for them. This issue was resolved when the administration at KFSH&RC finally listened to the pleas of the dietitians and the families and started importing Phenex-II.

The mothers feel isolated and alone in dealing with PKU, not all have family support when needed. Nearly all felt that caring for a child with PKU makes them depressed or stressed. Many felt that it affects their own health (Table 20). Some mothers think that PKU is not understood clearly by their family and friends (Table 21), most of

them would like their families to know more about PKU. All the mothers except one welcomed the idea of having a family support group for PKU.

**Box 5: Concerns of the mothers for their children regarding PKU.**

- Difficulty with diet
  - Diet compliance
  - Control of Phe blood level
  - Want special schools that understand metabolic disorders to control the children’s eating and prevent eating food from friends
  - To protect her child the mother avoids social gatherings
- The future
  - Brain function
  - Education
  - Puberty
  - Marriage and having children
- Weight increase due to Phenex-1 use
- General worry, worry about health and condition
- Worry about child’s disability
- Worry about taking care of child properly
- Feel sad for child
- Formula difficulties

**Table 20: Wellbeing and support for the mothers, their answers to some quality of life questions.**

Wellbeing and support questions	Yes	
	Frequency (%)	
Do you think caring for a child with PKU affects your health?	10	(41.7%)
Do you think caring for a child with PKU makes you sad, depressed or stressed?	21	(87.5%)
Do you have a family member(s) available to help you when you need help?	17	(70.8%)
Would you want a family member(s) to know more about your child’s illness?	19	(79.2%)
Would you be interested in joining a family support group?	23	(95.8%)

**Table 21: Understanding of PKU by family and friends.**

Rate the degree to which your child’s condition is understood by	Frequency (%)			
	Does not apply to me	Misunderstood	Understood	Completely understood
Your spouse	0 (0%)	1 (4.2%)	6 (25.0%)	17 (70.8%)
Other children	1 (4.2%)	0 (0%)	9 (37.5%)	14 (58.3%)
Family members	0 (0%)	5 (20.8%)	15 (62.5%)	4 (16.7%)
Friends	10 (41.7%)	2 (8.3%)	11 (45.8%)	1 (4.2%)

### 7.2.7 Suggestions and requests for service improvement

All the mothers had some suggestions and requests on ways to improve health care and services for their children (Box 6). The two key requests that most mothers asked for were to reduce the waiting time at the clinic and to provide some low protein food products to improve diet choices. The families' concerns, need for information, suggestions, and requests all echo the findings from Phase 1 of this study.

#### Box 6: Suggestions of and requests by the mothers to improve the healthcare services at KFSH&RC.

##### **Hospital and care issues**

- Reduce the long waiting time at KFSH&RC.
- Waiting time in the hospital is very long, there are many things to do on the same appointment day; lab work, paper work, see the doctor, then the dietitian. All is very tiring for me and the children especially that we come travelling on the same day.
- We have difficulties in obtaining the formula because they do not send it by mail, so we have to send someone to Riyadh to get it, and that is not always easy, and it is not available where we live.
- Blood level results not given to us easily, we have to call several times to be able get them. I hope this could improve.
- Do the blood test at the clinic rather than the lab. They take blood from the arm at the lab and they hurt the children, they should only do a prick at clinic.
- I do not benefit from visiting the doctor; they keep asking the same questions but do not give me new information or educational material.
- I wish that reception and nursing staff become nicer, they are rude sometimes.
- The non-Arabic speaking staff are rude sometimes.
- A call from the dietitian periodically to check on the patients.
- A call from the hospital to remind us with our appointments.
- Provide health care in our area.

##### **Diet issues**

- Provide low protein food products to allow more food options.
- Give more dietary guidelines and specific diets.
- Try to find a solution for those children with high Phe blood levels.

##### **Social issues**

- The children need to meet each other and see other kids with the same disorder.
- Provide schools that understand their conditions and diet.
- If the hospital could help in providing an exercise area for the kids to help them to keep acceptable weights or even if they only provide swimming sessions for them.

##### **Information provision**

- More research about genetic disorders.
- Provide the latest information available about PKU and any medication for it.
- Educate young people about these disorders before marriage.

## **7.3 Child Questionnaire**

### **7.3.1 Participants**

Twelve children answered the questionnaire out of the 27 children who go to school. The main reason for not participating was time constraint. The families either had another appointment at the hospital to attend or needed to leave the hospital as soon as they were able to travel back to their homes. Their mothers barely had time to answer the main questionnaire and asked to forego the child's questionnaire.

The average age of the children who participated was 10.6 years ( $SD = 3.07$ ). They all went to school and had good communication ability. Their Vineland-II ABC scores were a mix of adequate and low levels (mean = 76.82,  $SD = 13.77$ ).

Most of the children answered all the questions, but two of the children didn't answer two questions each and one child didn't answer three questions. Two of them were uncomfortable when asked about their feelings on their diet and formula and chose to skip to the following question. The third child didn't understand a couple of questions; I repeated them in a different format, but she lost interest and wanted another question.

All the children enjoyed the questionnaire chat and the attention it brought. Many continued on telling stories and recipes, or complaining about the diet restrictions and bargaining with me to ask the dietitian to allow some restricted foods to be added to their diets.

### **7.3.2 Dietary practices and knowledge**

When asked about their food choices, all the children, except one, listed low protein foods (Table 22). One child listed chicken and beans among his food choices. Seven children listed French fries or chips as favourites; French fries are allowed in restricted amounts, but many children eat more than the amount prescribed by the dietitian. The mothers say that their children do not like vegetables. Potatoes are the

only thing they like to eat, although they are, like rice and bread, restricted to specific amounts per day.

The children’s knowledge about their dietary restrictions and allowances was good. All of them knew that fruits and vegetables are freely allowed while dairy products and meats are not allowed. They knew that they should not eat milk chocolate or drink diet soda. The main foods they were confused about were chickpeas and French fries. Chickpeas are one of the highly consumed legumes in the Saudi diet; they are eaten as “hummus” (mashed chickpeas mixed with yogurt and sesame seed paste). It is high in protein and not allowed for PKU patients. Only five children knew it was not allowed while three thought it was a freely allowed food. French fries was thought to be a free food by half of the children, only four knew that it is a low protein food and restricted to a limited amount per day as prescribed by the dietitian. Most of the children seem to understand the importance of drinking the formula and complying with the diet (Table 23).

**Table 22: Food choices for some of the children with PKU (N=12).**

<b>What do you like to eat?</b>
Apple, banana, grapes, and cucumber
Salad, rice, pineapple, chips, and French fries
Rice, formula, and grape leaves stuffed with rice
French fries and ketchup, pizza, and lollypops
French fries and rice
Biscuits, formula, and chips
Rice and bread
Potatoes and salad
French fries, chicken burger, cabbage and carrots salad, and beans salad
Green beans, banana, pasta, and chips
Apple, orange juice, and bread (made from rice)
Salads, corn salad, French fries, cocktail juice, and mango with melon juice

**Table 23: The children’s understandings of the importance of adhering to PKU diet and formula intake.**

	Frequency			Total
	Very important	Somewhat important	Not important	
What do you think is the importance of drinking your formula?	10	0	1	11
What do you think is the importance of eating your specific diet?	9	3	0	12

### 7.3.3 Social life

Nearly all the children go out with their families to visit others or to go shopping. Only four of the children perceive themselves as different from other children because of PKU. Ten of the twelve children do not choose their daily food, and only two of the twelve feel that it is difficult to eat differently from others (Table 24).

**Table 24: The children's answers to questions regarding going out and diet (N=12).**

	Yes
Do you go out shopping with your family?	11
Do you go out with your family to visit others?	12
When you are playing with other children do you feel you are different from them?	4
Do you choose your food?	2
Is it difficult that you have to eat differently from others?	2
It is okay to drink only some of your formula?	2

## 7.4 Assessments and measurements

Several assessments and measurements were taken for the children: 24 hour food recall, mean blood phenylalanine level, the Vineland-II questionnaire, and anthropometric measurements. This section includes the results of these assessments and the results of analysing the relations between them, including the children's phenylalanine levels at diagnosis, and ages at treatment initiation. The main descriptive statistics for these variables are listed in Table 25. One of the 40 children was excluded from these analyses because he has myoclonic encephalopathy, which impairs development confounding the results in relation to PKU. Data from 39 patients is included in this section.

**Table 25: General descriptive statistics for the variables used in the analyses (N=39).**

	N	Missing	Minimum	Maximum	Mean	SD
<b>ABC score</b>	38	1	23	112	68.84	23.22
<b>Diagnosis Phe</b> ( $\mu\text{mol/l}$ )	33	6	235*	2770	1487.88	736.25
<b>Age at start of treatment</b> (Years)	39	0	0.005	17.6	2.45	3.41
<b>Mean blood Phe level</b> ( $\mu\text{mol/l}$ )	39	0	245	1764	791.79	318.37
<b>Dietary Phe intake</b> (mg/day)	39	0	88	1551.5	466.45	335.01

\*Taken early after birth due to sibling affected with PKU, subsequent blood Phe levels were in range of PKU.

### 7.4.1 Gender differences

There was no significant difference between male and female patients in the main outcome measure, the Vineland-II Adaptive Behaviour Composite (ABC) scores (Table 26), or the other main variables in the analyses. Therefore they were analysed as one group.

**Table 26: Mean, standard deviation (SD), and confidence interval (CI) of ABC scores by gender.**

Gender	ABC Score		
	Mean	SD	95% CI
Male	65.69	26.411	(49.73 - 81.65)
Female	70.48	21.774	(61.49 - 79.47)

### 7.4.2 Anthropometry

The study children had significantly higher Body Mass Index (BMI) z-scores than the Saudi reference population ( $p=0.001$ ,  $t=3.73$ ). The BMI z-scores varied from -1.76 to 3.28 (Mean=0.72, SD=1.12). The height-for-age z-scores (Mean=-0.10, SD=1.23) and weight-for-age z-scores (Mean=0.52, SD=1.42) were not significantly different from the Saudi reference population (El-Mouzan et al., 2007). Three of the patients were over 19 years of age, which is over the reference data age group. The BMI was calculated for them. One female was underweight (BMI=16.98), one male was within normal weight (BMI=18.81), and one male was class 2 obese (BMI=39.95) (WHO, 2000).

The triceps skin-fold thickness (TST), available for 26 of the study patients, ranged from 4mm to 18mm (<5<sup>th</sup> percentile to 90<sup>th</sup> percentile). The upper arm fat area for them ranged from 0.75cm<sup>2</sup> to 32.5 cm<sup>2</sup> (<5<sup>th</sup> percentile to 95<sup>th</sup> percentile). The waist circumference (WC) measurements were available for 33 patients, but due to the age range of the UK reference data (5-17 years) only 25 patients were included in this analysis. The WC ranged from 451mm to 1230mm (5<sup>th</sup> percentile to >95<sup>th</sup> percentile). Twelve (48%) of the 25 patients had WC over the 90<sup>th</sup> percentile, indicating high number of patients with high level of abdominal fat tissue. The use of over the 90<sup>th</sup> percentile for WC as a cut-off for overweight was defined as a reliable marker in

several studies (Garnett, Baur, Srinivasan, Lee, & Cowell, 2007; McCarthy, Ellis, & Cole, 2003; and Ness-Abramof & Apovian, 2008).

### 7.4.3 Diet and formula intake

#### Dietary phenylalanine intake

Twenty four hour food recall was taken twice for 35 patients. Four patients had one 24 hour food recall; their mothers were unreachable for the second recall. Patients are allowed up to 400 mg of dietary phenylalanine per day if their blood Phe levels were within the acceptable limits (Table 27). Only 21 of the 39 patients had a dietary Phe intake within the prescribed limit (less than 400 mg per day) (Table 28).

**Table 27: The acceptable blood Phe level at KFSH&RC by age group.**

Age Group	Phe $\mu\text{mol / l}$
<2 years	120 - 350
2-6 years	120 - 450
>6 years	120 - 600

**Table 28: Mean blood Phe level and dietary Phe intake of the patients (N=39).**

	Frequency (%)	
	Yes	No
Dietary Phe intake within daily limit	21 (53.8%)	18 (46.2%)
Mean blood Phe within limit for age	10 (25.6%)	29 (74.4%)

#### Formula intake

Compliance with the formula intake was better than the dietary compliance; 30 (77%) of the patients had good formula intake. This means they always or usually drank their prescribed amount of formula. The remaining nine did not drink their formula or only drank some of it occasionally. Seven of the non-compliant patients were diagnosed late, after 2.5 years of age. The age at start of treatment was significantly different between the patients who were compliant with formula intake and the patients who were not compliant ( $p = 0.024$ ,  $t = -2.36$ ,  $df = 37$ ) (Figure 6).

The formula intake status of patients was highly correlated with the mean blood Phe level; the patients who were non-compliant with formula intake had higher mean blood Phe levels ( $r = -0.525$ ,  $p = 0.001$ ). The age of patients at the start of treatment

and their dietary Phe intake were significantly associated with formula intake as well (Table 29).

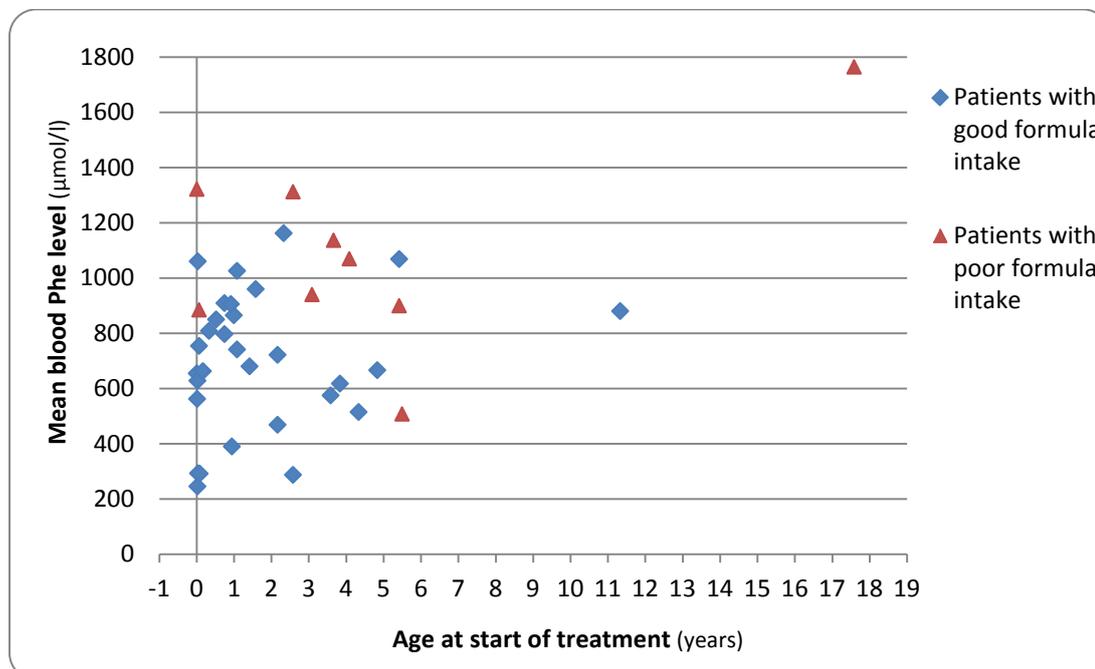
**Table 29: Pearson product-moment correlation coefficients (r) for formula intake with correlating variables.**

Formula intake correlation with:	Correlation coefficient (r)	P-value (2-tailed)	Number of patients in each analysis
Mean blood Phe level ( $\mu\text{mol/l}$ )	-0.525	0.001	39
Age at start of treatment (years)	-0.361	0.024	39
Dietary Phe intake (mg/day)	-0.360	0.024	39

#### 7.4.4 Mean blood phenylalanine level

##### A. Mean blood phenylalanine level and formula intake

The mean blood Phe level was significantly lower ( $p = 0.001$ ,  $t = -3.75$ ,  $df = 37$ ) for the patients who were compliant with their formula intake (Mean = 701, SD = 248.5) than the mean Phe level for the patients who were not compliant with their formula intake (Mean = 1093, SD = 353.4) (Figure 6).



**Figure 6: Mean blood Phe level and age of start of treatment of the patients according to their formula intake (N=39).**

## B. Mean blood phenylalanine level and dietary phenylalanine intake

Only 10 of the patients (25.6%) had mean blood Phe level within the acceptable limits for age (Table 1 and Table 28). The remaining 29 patients had higher levels, nine of them their mean blood Phe level was over 1000 $\mu$ mol/l. The dietary Phe intake was significantly lower ( $p < 0.0001$ ,  $t = 3.88$ ,  $df = 37$ ) in patients who had mean blood Phe level within the acceptable limits for age (Mean dietary Phe = 250.1 mg/d, SD = 114) than in patients who had levels above limits for age (Mean = 541.1 mg/d, SD = 354.5) (Figure 7).

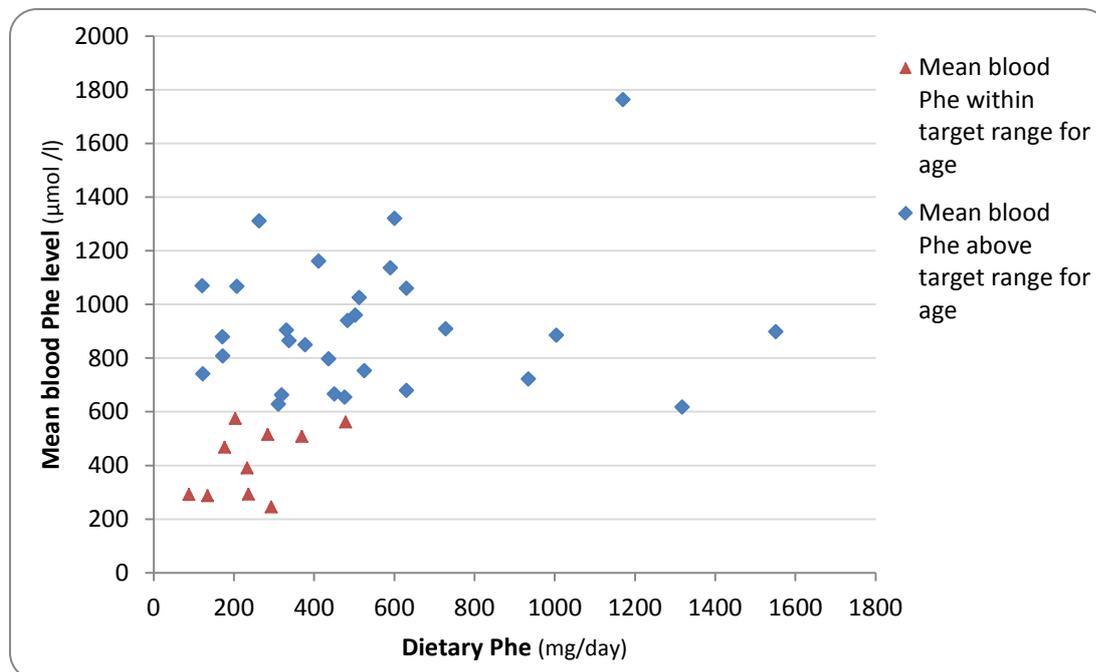


Figure 7: Mean blood Phe level, shown as within or above target range for age, and dietary Phe intake of the patients (N=39).

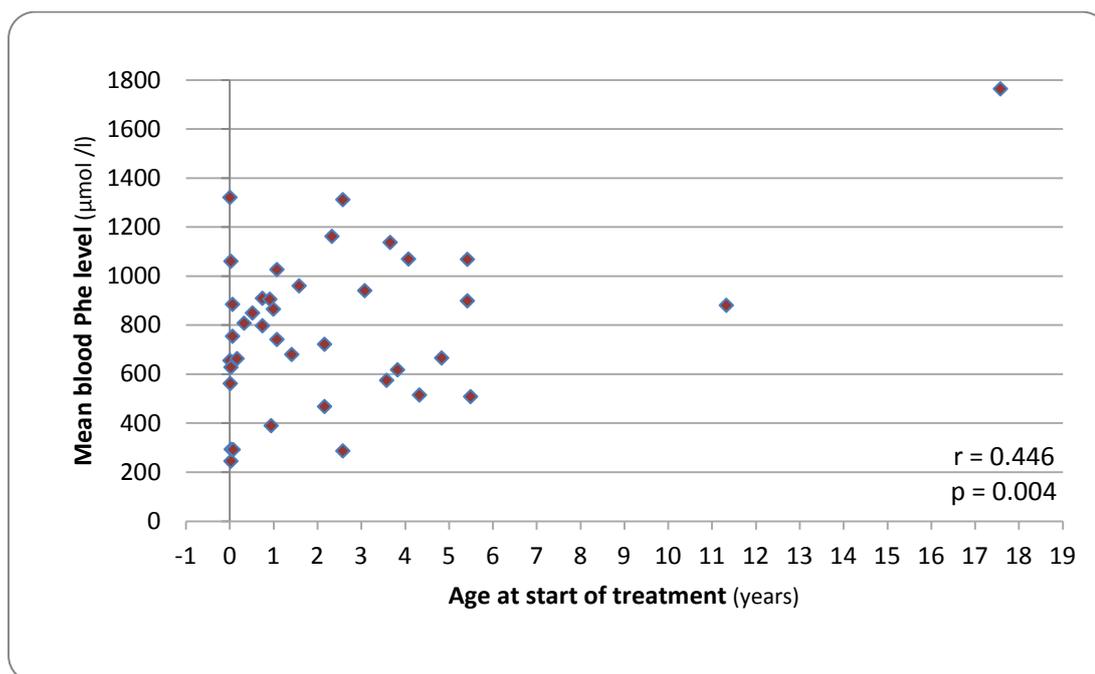
## C. Mean blood phenylalanine level correlation and regression (associations and relationships with other variables)

Significant statistical associations were found between the mean phenylalanine blood level and two variables - the age of the patient at the start of treatment and the patient's phenylalanine dietary intake. This was demonstrated by analysis of the Pearson product-moment correlation coefficients ( $r$ ) for the mean phenylalanine blood level with different variables (Table 30, Figure 8). Nearly 20% of the variation in the mean phenylalanine blood level is explained by the age of the patient at treatment

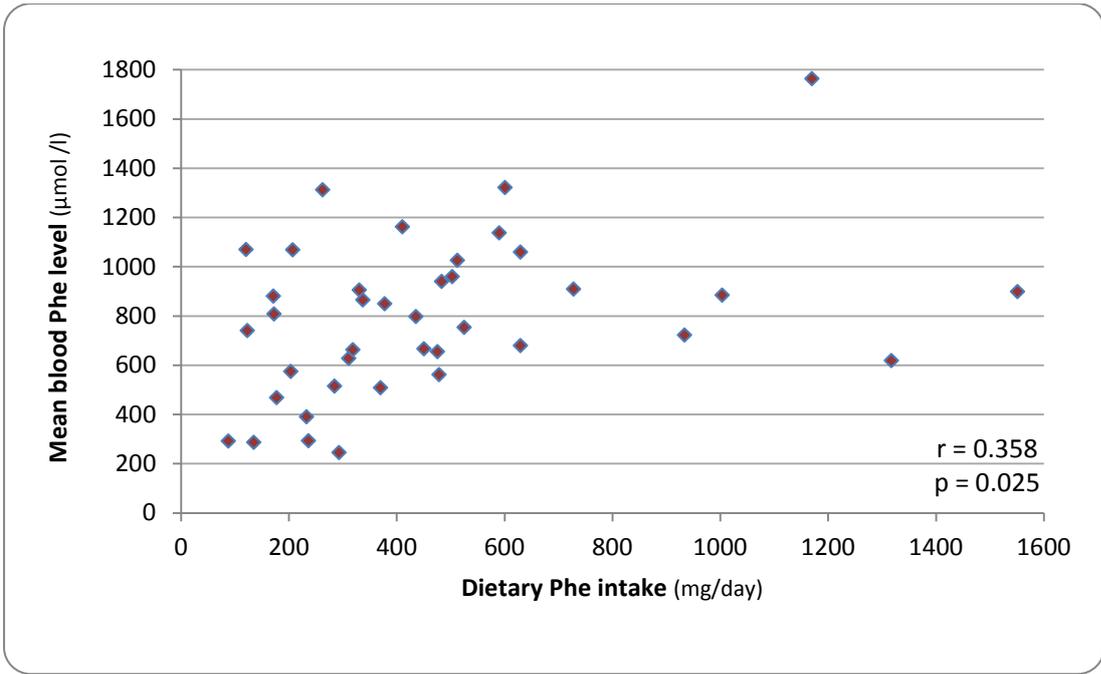
initiation and nearly 13% is explained by phenylalanine dietary intake. There was a weak non-significant correlation between the Phe blood level at diagnosis with the mean blood Phe level (Table 30, Figure 10); therefore it was not included in further analyses.

**Table 30: Pearson product-moment correlation coefficients (r) for mean phenylalanine blood level with different variables.**

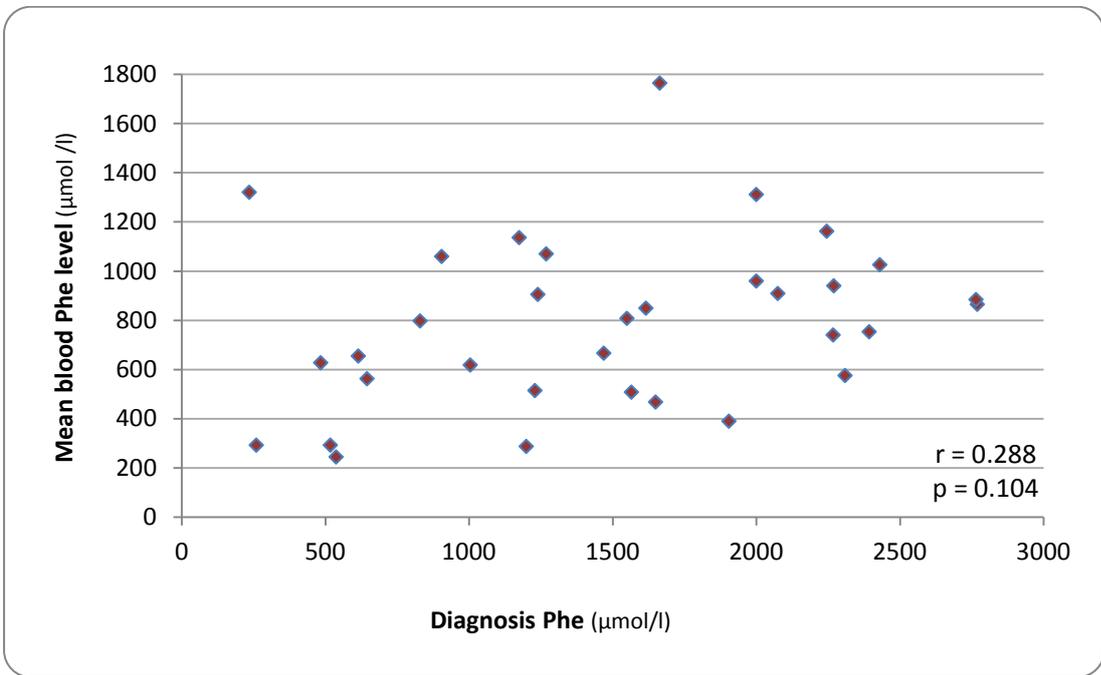
Mean phenylalanine blood level correlation with:	Correlation coefficient (r)	P-value (2-tailed)	Coefficient of determination (% of shared variance)	Number of patients in each analysis
Age at start of treatment (years)	0.446	0.004	19.9%	39
Dietary Phe intake (mg/day)	0.358	0.025	12.8%	39
Diagnosis Phe blood level ( $\mu\text{mol/l}$ )	0.288	0.104	8.3%	33



**Figure 8: Correlation between mean blood Phe level and age at start of treatment for the patients (N=39).**



**Figure 9: Correlation between mean blood Phe level and dietary Phe intake for the patients (N=39).**



**Figure 10: Correlation between mean blood Phe level and diagnosis Phe for the patients (N=33).**

The two variables correlating with blood phenylalanine concentrations (age of patients at treatment initiation and dietary intake of phenylalanine) were further analyzed in a standard multiple regression model to describe the relationships. The statistical significance of the model was high ( $p=0.005$ ). The co-linearity diagnostics showed that the model did not violate the non-multicollinearity assumption. The model's  $R^2$  was 0.259, indicating that this model explained 25.9% of the variance in the mean phenylalanine blood level (Adjusted  $R^2=0.218$ ).

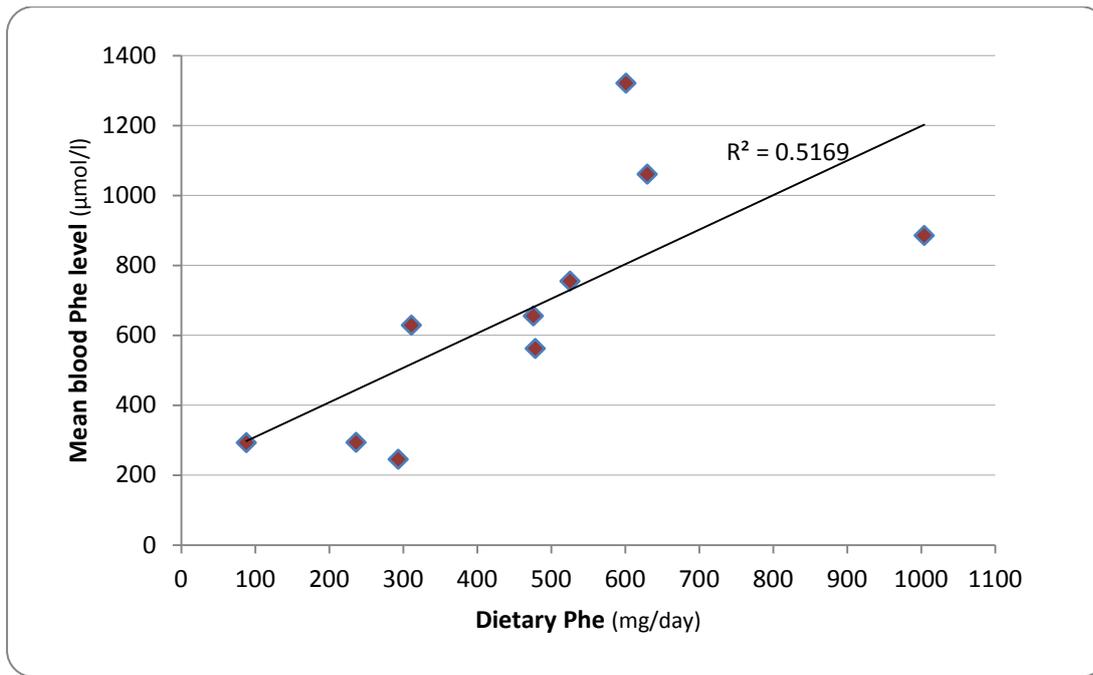
Table 31 lists the results of each variable in this model. The standardized coefficients, Beta, compare the contribution of each variable to explaining the variation in mean Phe level. The strongest contribution was made by the variable, age at start of treatment (Beta=0.376,  $p=0.016$ ). Dietary Phe intake, although correlating with mean Phe level, lost its significance in this multiple regression model when controlling for age at treatment initiation. The next paragraph looks at the early diagnosed patients separately.

**Table 31: Multiple regression of mean phenylalanine blood level with correlating variables.**

N=39	Coefficient B	Standard Error for B	Standardized coefficient Beta	P-value	95% CI for B	$R^2$ / Adjusted
Age at start of treatment (years)	35.154	13.931	0.376	0.016	(6.902 - 63.406)	0.259 /0.218
Dietary Phe intake (mg/day)	0.242	0.142	0.255	0.097	(-0.046 - 0.529)	

#### **D. Mean blood phenylalanine level for early diagnosed patients**

Ten of the patients were diagnosed and treated early ( $\leq 1$  month of age). For this group of patients the mean blood Phe level showed a significant positive correlation with dietary Phe intake ( $r = 0.719$ ,  $p = 0.019$ ,  $R^2 = 0.516$ ) (Figure 11). Due to the small number of patients further analysis was not possible.



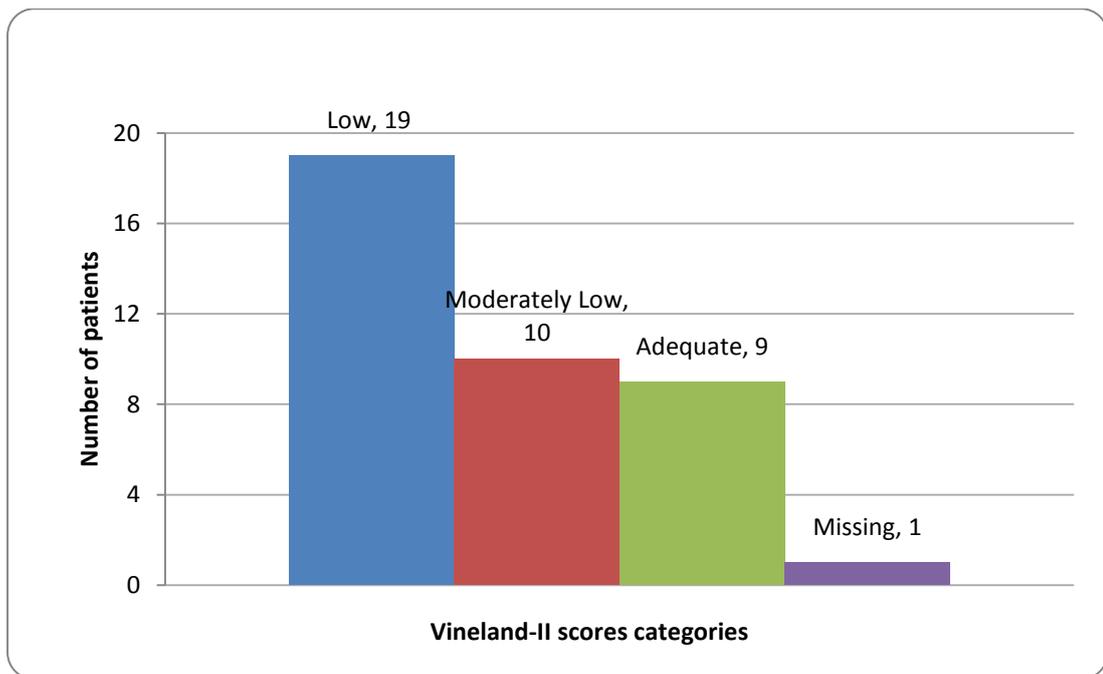
**Figure 11: Mean blood Phe level and dietary Phe intake for early treated patients (N=10).**

#### 7.4.5 The Vineland-II scores (the outcome measure)

Thirty eight out of the 39 patients had a completed Vineland-II assessment interview done with their mothers. One patient’s mother was unreachable and the Vineland-II score was treated as missing in the analysis. Table 32 and Figure 12 show a summary of results from Vineland-II Adaptive Behaviour Composite (ABC) scores for patients.

**Table 32: Adaptive Behaviour Composite (ABC) scores for the patients.**

ABC score	Number of patients (%)
Low (20-70)	19 (48.7%)
Moderately Low (71-85)	10 (25.6%)
Adequate (86-114)	9 (23.1%)
Missing	1 (2.6%)
<b>Total</b>	<b>39 (100%)</b>



**Figure 12: The number of patients in each category of the Vineland-II.**

#### **A. The Vineland-II scores associations and relationships with other variables**

The relationships of the Adaptive Behaviour Composite score (ABC) of the Vineland-II (as the dependant variable) were examined with all the variable factors that were thought to have an influence on the ABC scores (as independent variables):

1. Phenylalanine blood level at diagnosis
2. Age of patients at treatment initiation
3. Mean of blood phenylalanine level
4. Dietary intake of phenylalanine

There was a strong negative association (correlation) between Vineland-II scores and age of patients at the start of their treatment ( $r=-0.56$ ,  $p< 0.0001$ ) indicating lower scores are associated with older age at treatment initiation. Vineland-II scores also correlated with phenylalanine blood level at diagnosis and mean of blood phenylalanine levels as shown in Table 33. The coefficient of determination shows that 31% of variation in the Vineland-II ABC scores can be explained by the age of patients at the start of treatment.

**Table 33: Pearson product-moment correlation coefficients (r) for ABC scores with different variables.**

ABC score correlation with:	Correlation coefficient (r)	P-value (2-tailed)	Coefficient of determination (% of shared variance)	Number of patients in each analysis
Age at start of treatment(years)	-0.560	<0.0001	31.4%	38
Diagnosis Phe blood level( $\mu\text{mol/l}$ )	-0.451	0.010	20.3 %	32
Mean blood Phe level( $\mu\text{mol/l}$ )	-0.330	0.043	10.9 %	38
Dietary Phe intake(mg/day)	-0.203	0.222	4.1 %	38

These variables were further analyzed in a standard multiple regression model to describe the relationships with the Vineland-II scores more precisely. The statistical significance of the model was high ( $p = 0.002$ ). The co-linearity diagnostics showed that the model did not violate the non-multicollinearity assumption. The model's  $R^2$  was 0.456, indicating that this model explained 45.6% of the variance in the ABC scores (Adjusted  $R^2 = 0.376$ ).

Table 34 lists the results for each variable in this model. The standardized coefficients, Beta, compare the contribution of each variable to explaining the variation in ABC scores. The strongest contribution was made by the variable age at start of treatment (Beta = -0.505,  $p = 0.004$ ), followed by the level of phenylalanine at diagnosis (Beta = -0.383,  $p = 0.016$ ). When adjusting for all the variables in this multiple regression model the significant association between the mean blood Phe level and Vineland-II scores, seen in correlation, disappeared.

**Table 34: Multiple regression for the Vineland-II ABC scores with different variables for all the patients (N=38).**

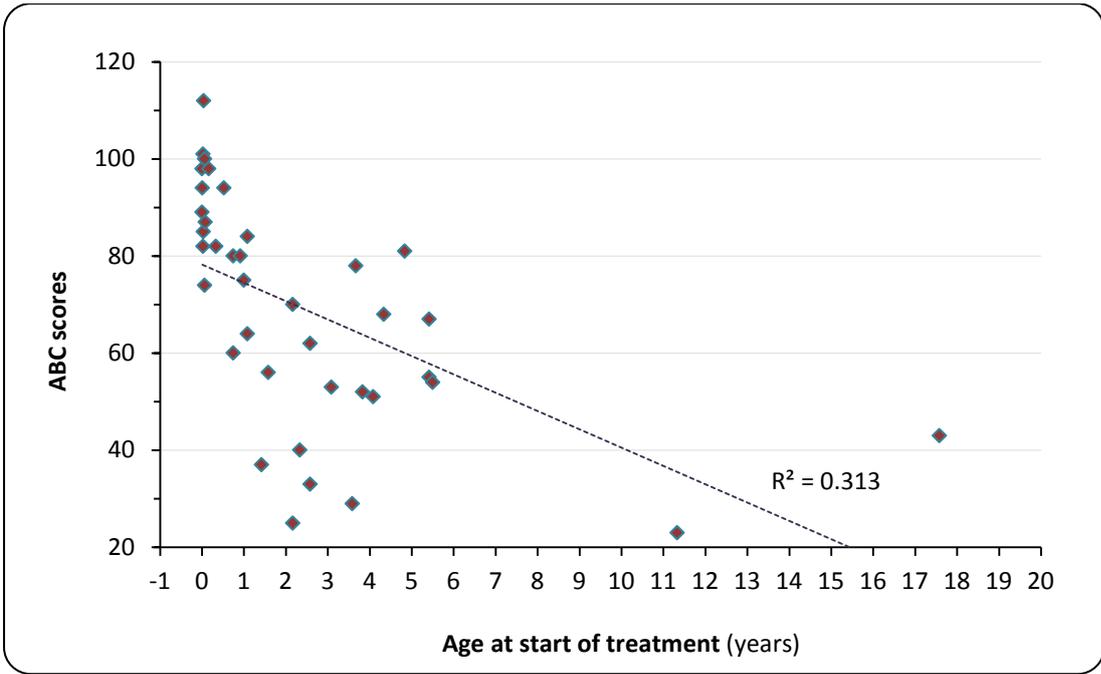
ABC scores	Coefficient B	Standard error for B	Standardized coefficient Beta	P-value	95% CI for B	$R^2$ / Adjusted
Age at start of treatment (years)	-3.439	1.090	-0.505	0.004	(-5.676- -1.201)	0.456 /0.376
Diagnosis Phe ( $\mu\text{mol/l}$ )	-0.012	0.005	-0.383	0.016	(-0.022- -0.002)	
Mean blood Phe level ( $\mu\text{mol/l}$ )	0.001	0.011	0.019	0.914	(-0.024-0.027)	
Dietary Phe intake (mg/day)	-0.002	0.012	-0.036	0.819	(-0.024-0.019)	

## **B. The Vineland-II scores and the age at start of treatment**

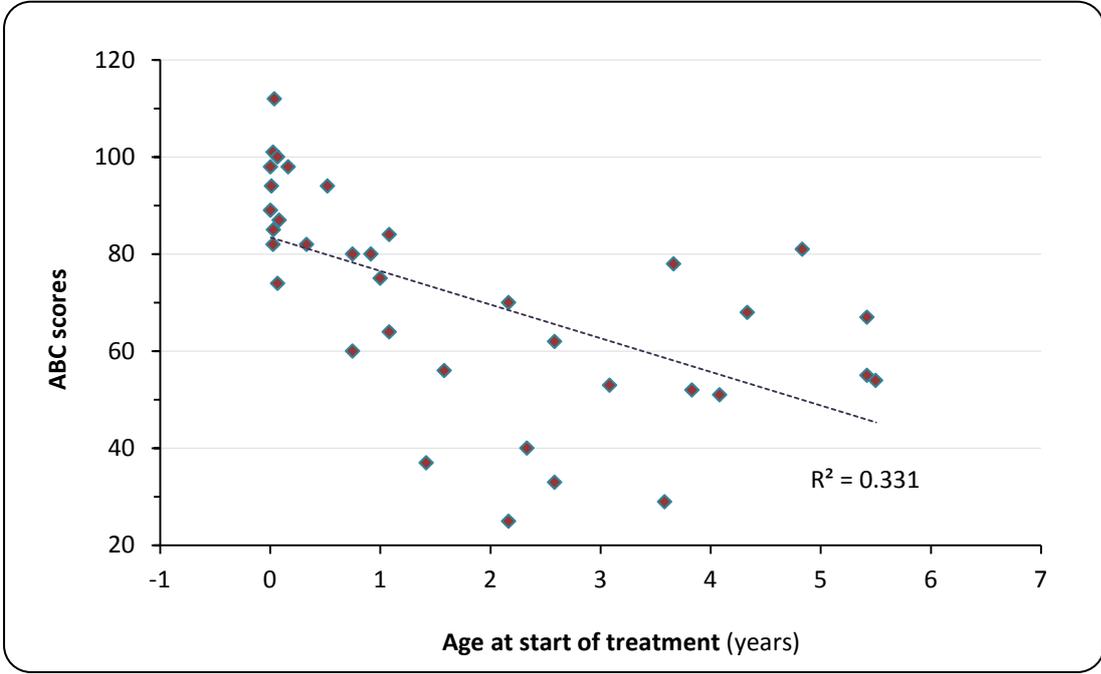
The age at start of treatment had the strongest effect on the Vineland-II scores. Further examination of the linear relationship showed that linearity was very strong between the age at start of treatment and Vineland-II for an age at start of treatment of up to 3.6 years (Table 35). After that age the relation becomes not as linear (lower value for  $R^2$ ), although still highly significant ( $p < 0.001$ ) (Figure 13, Figure 14, and Figure 15). Therefore the regression analysis was repeated to include patients who started treatment at the age of 3.6 years or below (Table 36).

For this group of patients, treated at 3.6 years of age or less, the most significant variables shown by univariate regression analysis to have an effect on the ABC scores were age at the start of treatment ( $p < 0.0001$ ) and phenylalanine blood level at diagnosis ( $p = 0.007$ ) (Table 36). However, fitting the same variables into a multiple regression model (Table 36), to account for confounders, seems to remove the significant association of phenylalanine blood level at diagnosis and illustrates that the dietary intake of phenylalanine is a significant predictor of the outcome measure the Vineland-II scores ( $p = 0.033$ ).

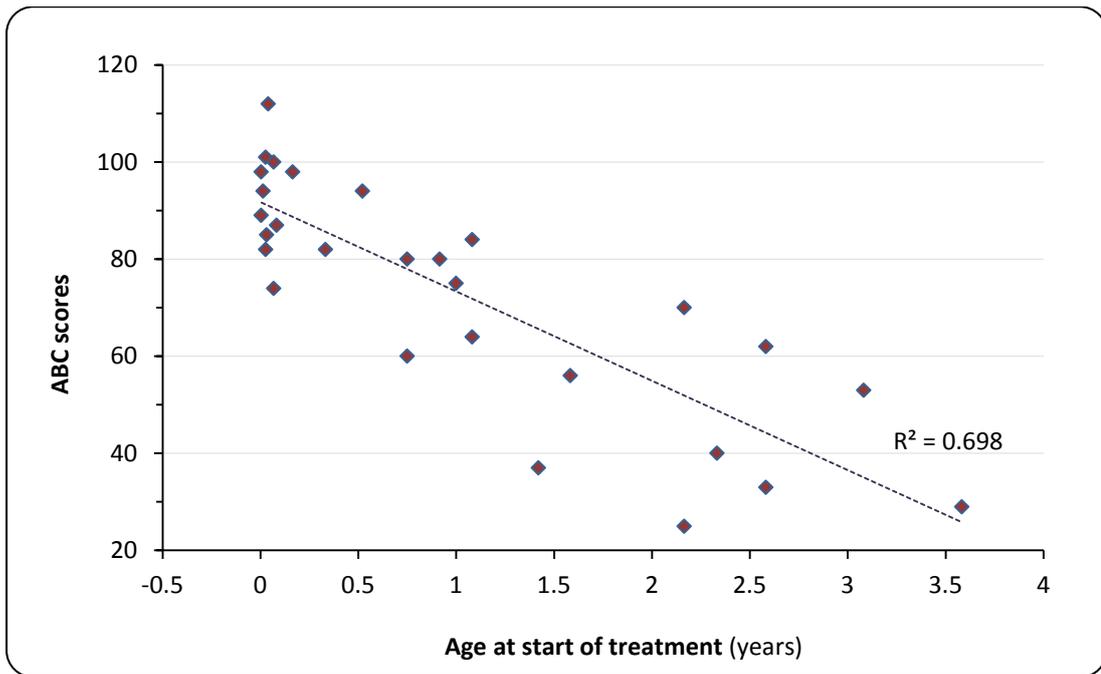
The statistical significance of the model was high ( $p < 0.0001$ ). The model's  $R^2$  was 0.80, indicating that this model explained 80% of the variance in the ABC scores for patients treated at 3.6 years of age or below (Adjusted  $R^2 = 0.760$ ). Age at the start of treatment made the strongest contribution to the dependent variable (ABC scores), as illustrated by the standardized coefficient (Beta) = -0.855. There was a loss of 19 points on the Vineland-II ABC score with every year of delay in treatment (Coefficient B = -19.173) (Table 36).



**Figure 13: Vineland-II ABC scores for all the patients with their ages at start of treatment (N=38).**



**Figure 14: Vineland-II ABC scores for the patients with age of start of treatment ranging from birth until 7 years (N=36) ( $\leq 7$  years was chosen because it removed the two most extreme cases).**



**Figure 15: Vineland-II ABC scores for the patients with age at start of treatment ranging from birth until 3.6 years (N=28).**

**Table 35: Linear regression of the Vineland-II ABC scores with age at start of treatment for the patients treated at different age cut-offs.**

ABC scores	Coefficient B	Standardized coefficient Beta	P-value	95% CI for B	R <sup>2</sup> / Adjusted
All ages at start of treatment (years) N=38	-3.811	-0.560	<0.0001	(-5.72- -1.90)	0.313/0.294
Age at start of treatment ≤ 7 years* N=36	-7.01	-0.575	<0.0001	(-10.48- -3.54)	0.331/0.311
Age at start of treatment ≤ 3.6 years N=28	-18.745	-0.836	<0.0001	(-23.71- -13.78)	0.698/0.687

\* ≤ 7 years was chosen because it removed the two most extreme cases

**Table 36: Univariable linear regression and multiple regression of the Vineland-II ABC scores for the patients treated at  $\leq 3.6$  years.**

ABC scores Patients diagnosed $\leq 3.6$ years	Univariable				Multivariable			
	Coeff't B	P-value	95% CI for B	R <sup>2</sup> / Adjusted	Coeff't B	P-value	95% CI for B	R <sup>2</sup> / Adjusted
Age at start of treatment (years) N=28	-18.745	0.000	(-23.71-13.78)	0.698 / 0.687	-19.173	0.000	(-24.81 -13.53)	0.800 / 0.760
Diagnosis Phe ( $\mu\text{mol/l}$ ) N=25	-0.015	0.007	(-0.026-0.005)	0.276 / 0.245	0.000	0.930	(-0.008 -0.007)	
Mean blood Phe level ( $\mu\text{mol/l}$ ) N=28	-0.026	0.099	(-0.058-0.005)	0.101 / 0.067	-0.007	0.446	(-0.027 -0.013)	
Dietary Phe intake (mg/day) N=28	-0.020	0.328	(-0.062-0.021)	0.037 / 0.000	-0.028	0.033	(-0.053 -0.003)	

### C. Comparison of Vineland-II scores for early and late treated patients

There was a significant difference ( $p < 0.0001$ ,  $t=6.07$ ,  $df = 30$ ) in the Vineland-II ABC scores for early treated patients ( $\leq 1$  month of age) and late treated patients ( $>1$  month of age) (Table 37). The magnitude of the difference between these two groups is large, as indicated by the large effect size shown by eta squared = 0.506. This represents 50.6% of the variance in the ABC scores is explained by age at treatment. Guidelines for interpreting eta squared values were taken from Pallant (2007).

**Table 37: The Vineland-II ABC scores (Mean and SD) according to the age at start of treatment.**

Age at treatment	Number of patients (%)	Mean ABC scores	SD
Started treatment $\leq 1$ month of age	10 (25.6%)	92.2	11.01
Started treatment $> 1$ month of age	29 (74.4%)	60.5	20.59
<b>Total</b>	<b>39 (100%)</b>	-	-

#### 7.4.6 Classic and Mild PKU

Twenty two patients had diagnosis phenylalanine blood levels of more than  $1200\mu\text{mol/l}$ , consistent with Classic PKU (Guldberg et al., 1998; and Smith & Lee, 2000), 11 patients had levels  $\leq 1200\mu\text{mol/l}$ , and 6 patients did not have a diagnosis level on their medical records. For this analysis patients with diagnosis levels of phenylalanine  $>1200\mu\text{mol/l}$  are classified as Classic PKU patients, and patients with diagnosis levels of phenylalanine  $\leq 1200\mu\text{mol/l}$  are classified as Mild PKU patients (Table 38). At the KFSH&RC the distinction between Classic and Mild PKU is not

made and the care protocol for all patients is the same. None of the patients in this study have hyperphenylalaninemia (Phe levels of 300-600  $\mu\text{mol/l}$ ), as they are not put on dietary restrictions or followed up by dietitians at KFSH&RC. Both groups were analysed separately in a standard linear regression then in a multiple regression model. The Vineland-II ABC score was the dependent variable with the same previous independent variables:

- (1. Age of patients at treatment initiation, 2. Mean of blood phenylalanine level,
3. Phenylalanine blood level at diagnosis, 4. Dietary intake of phenylalanine).

**Table 38: PKU categories.**

Category	Number of patients (%)
Mild PKU	11 (28.2%)
Classic PKU	22 (56.4%)
Missing diagnosis Phe level	6 (15.4%)
<b>Total</b>	<b>39 (100%)</b>

### A. Classic PKU

The most significant factor having an influence on the Vineland-II ABC scores in this group is the age of patients at treatment initiation. In the univariate linear regression age at the start of treatment of the patients had a significant effect on the ABC scores (Coefficient B = -2.463,  $p = 0.034$ ). Then when analysing the variables in a multiple regression model, which takes into account all the other related variables to test for confounders, its significance became stronger (Coefficient B = -3.887,  $p = 0.016$ ). All values are summarised in Table 39.

**Table 39: Multiple regression of the Vineland-II ABC scores for the patients diagnosed with Phe blood level  $>1200\mu\text{mol/l}$ .**

ABC scores, patients with diagnosis Phe $>1200\mu\text{mol/l}$	Coefficient B	Standard error for B	Standardized coefficient Beta	P-value	95% CI for B	R <sup>2</sup> / Adjusted
Age at start of treatment (years)	-3.887	1.437	-0.732	0.016	(-6.93- -0.84)	0.431/ 0.289
Mean blood Phe level ( $\mu\text{mol/l}$ )	-0.015	0.015	-0.255	0.322	(-0.046-0.016)	
Diagnosis Phe ( $\mu\text{mol/l}$ )	-0.015	0.010	-0.385	0.131	(-0.036-0.005)	
Dietary Phe intake (mg/day)	0.044	0.019	0.610	0.036	(0.003-0.085)	

## **B. Mild PKU**

In this group of patients, two variables (the age of the patient at treatment initiation and the dietary intake of phenylalanine) had a significant effect on the Vineland-II ABC scores in a univariate linear regression analysis for each; both had a p-value of 0.027. However, when analysed in a multiple regression model with the other correlating variables (mentioned above), to account for confounders, this significant effect was lost and none of the variables appear to be a significant predictor of the Vineland-II scores for patients with mild PKU.

## **C. The Vineland-II scores comparison between Mild and Classic PKU patients**

There was a significant difference ( $p = 0.008$ ,  $t = 2.84$ ,  $df = 30$ ) in the Vineland-II ABC scores for Mild PKU patients (Mean = 85.27, SD = 17.39) and Classic PKU patients (Mean = 65.38, SD = 19.51). The magnitude of the difference between the groups is large, as indicated by the effect size statistic (eta squared = 0.212) (Pallant, 2007). This represents 21.2% of the variance in the ABC scores is explained by PKU severity.

### **7.4.7 Socio-economic status effect on outcome**

The socio-economic status indicators had no significant effects on the Vineland-II ABC scores of the patients, their mean blood Phe levels, or their dietary Phe intake. The socio-economic status indicators that were investigated were: age, education level, and occupation of the fathers and the mothers, monthly spending, family size, the number of children with PKU in the family, and the number of unaffected children in the family.

### **7.4.8 The effect of special education on the Vineland-II scores**

Fourteen out of the 27 patients who go to school receive some form of special education. Six of the children were in special education schools, they were all diagnosed late and have low Vineland-II scores. Eight children go to regular schools that have one or more special education sessions every day. The sessions are usually to improve skill or performance on specific subjects that the children find difficult,

usually maths. Six of those children have low scores on the Vineland-II and two have moderately low scores. The potential effect of special education on the Vineland-II scores was not clear or measurable from the available data. The patients didn't have previous Vineland-II scores to compare with the current scores, and they are all within the low level of the Vineland-II scores, so even if special education had a positive effect it was not enough to move the children from the low level to the adequate level of the Vineland-II.

#### **7.4.9 Observations and comments during the Vinland-II interviews**

Many of the mothers of patients who attended school said their children had difficulties in mathematics and in memorizing (13/27). During the Vineland-II interview, when the questions were related to reading and writing, the mothers added that their children usually have problems in the maths class and needed extra help. Many also said memorizing poetry and verses from the Qur'an was very difficult for their children. The mothers were not asked about these issues specifically during the interview, but since it came up as a problem very often faced by the children, it should be acknowledged, and may be investigated further in future research.



# CHAPTER 8

## **DISCUSSION (PHASE 2)**

## **Introduction**

This study explored the management of PKU in Saudi Arabia in order to understand the situation of the patients and their families and to answer the study question: “What are the risk factors associated with unsatisfactory nutritional management of patients with aminoacidopathies among a group of patients in Saudi Arabia?”

This chapter examines the results of Phase 2 to identify the answer to the study question. The results of the study are discussed in relation to the literature.

### **8.1 Research group**

The group of PKU patients in this study is unique. They are a mixture of patients diagnosed at different ages, some diagnosed late, some diagnosed through familial selective screening and some diagnosed through the newly introduced new born screening programme. They are all treated by the same medical team, aiming for the same blood phenylalanine target levels.

The age range of the group is large (21 years). This study wanted to explore and understand the situation in Saudi Arabia for PKU patients in particular and patients with metabolic disorders in general. No other study has attempted this in the country, therefore it was essential to include all available patients and not only focus the study on a specific age group.

### **8.2 Family Questionnaire**

#### **8.2.1 Family size**

The family size in Saudi Arabia is larger than the average family size in the UK and the west (Population Reference Bureau, 2012). In the UK the fertility rate is estimated at 1.97 children per women (Zumpe, Dormon, & Jefferies, 2012) while the current overall fertility rate for Saudi women is 3.3 children, and the average number of children for Saudi women aged 45-49 years is 5.6 children (Saudi Central Department of Statistics & Information, 2007). The culture still encourages large families; the fact

that overall fertility rate is not as high as the rate for the 45-49 age group probably reflects the fact that there are high numbers of young couples in Saudi Arabia who will continue to have additional children.

The families in this study have a higher fertility rate than the Saudi average. They have a very similar fertility rate to the older Saudi women, although only one of the mothers is in that age range. The mean number of children born to mothers in this study is 5.58, and more than 60% of the families have 2 children or more diagnosed with PKU. Having a child with PKU does not seem to affect the choices of the families to have more children.

It would be interesting to explore the reasons behind parents choosing to have large families. Is it just cultural or does a diagnosis of a metabolic disorder lead to an increase in family size? One reason could be that they are trying to have a son without the disorder. Knowing the reasons would be important given that the more children a family decides to have, the greater chance there is that they will have more affected children.

Burns et al (1984) explored the effects of PKU on families' decisions on having more children or not in the US. Among the main influencing factors they found were the birth order of the child with PKU; if it was the first then the families were more inclined to have at least one more child. The age of the parents was another factor; younger parents often had additional children after the child with PKU. When the families were asked if PKU was a reason for not having more children, families with lower levels of knowledge about PKU and families with a male child affected with PKU were more inclined to give PKU as a reason for not having more children. That could be because more PKU-aware and knowledgeable families felt more confident in their ability to deal with PKU, and families with a female child may still desire to have a male child (Burns, Azen, Rouse, & Vespa, 1984). This was the only study in the literature that looked at this aspect. In the Saudi culture, having a male child to carry the family name is very important and an extremely compelling reason for them to have more children.

### 8.2.2 Food choices and food budget

Within the Saudi culture the responsibility for buying food lies mainly on the men of the household. This was demonstrated by the families in this study where over 60% of the fathers bought the food. This may pose a problem regarding appropriate food choices if the communications between the mothers and the fathers are not very clear. This could then lead to unintentional high availability of foods that should be avoided and limited availability of free foods in the home, ultimately encouraging non-compliance (Neumark-Sztainer, Story, Perry, & Casey, 1999; and Story, Neumark-Sztainer, & French, 2002). The mothers are the ones going to clinic with their children, talking to the dietitian, being educated on what to feed their children and what to avoid. Often the fathers are at the hospital with the family, but they are usually busy dealing with necessary paper work and future appointments, therefore on most occasions they are not present during the dietitian's appointments.

Low protein food products (such as low protein pasta, biscuits, flour, rice, and bread) are not given to patients by KFSH&RC and are not available in the local markets. In the UK, most of these products are available on prescription from the National Health Service (Paediatric Formulary Committee, 2012). This takes away the burden of locating and buying these products from the families. These special low protein products are very costly. Depending on the product the price could be from 4 to 20 times the price of a comparable regular product.

Table 40 lists the prices of some low protein products compared to the average prices of similar regular products in the UK.

**Table 40: Price comparison between some low protein products and regular products.**

Product type	Price of low protein products from different companies	Price of comparable regular products
Breakfast cereal flakes 375g	£6.39	£1.80
Chocolate chip cookies 100g	£5.64	£0.66
Cream-filled biscuits 125g	£2.13	£0.25
Cake bars 6×40g	£5.10	£1.35
Rice pudding 4×69g	£5.60	£0.75
Plain flour mix 1kg	£13.54	£0.70
Pasta 500g	£6.35	£0.55
Rice 500g	£6.87	£0.80

All the families are very keen that their children benefit from these products, but not all know how to get them or can afford them. Some families, through individual internet search, found some American and European companies that will ship low protein products to Saudi Arabia. This comes at a huge financial burden for them, especially as these companies usually only agree to ship orders in bulk and not just for individual use. Therefore, several of these families have organized to order together and plan orders for special occasions and celebrations in Saudi Arabia, such as Eid and Ramadan. For the families that can afford these special low protein products, their average spending on food is way above the Saudi National average (Refer to Results, Chapter 7, section 7.2.1.1).

These special low protein food products are essential for the wellbeing of patients with PKU, they are important in helping patients achieve satisfactory blood phenylalanine levels (Ahring et al., 2009). They should be treated as medical food and prescribed for children as part of their treatment (Millner, 1993). Availability of these products should lead to much better dietary compliance, especially as the mothers currently find it very difficult to follow the diet with its restrictions, and one of the main compliance barriers they face is their children's insistence on eating foods they should avoid. When low protein products are available for these children this should definitely help in satisfying their needs and cravings by providing a diet with more variability and some similarity to that of unaffected family members and friends (Singh, Kable, Guerrero, Sullivan, & Elsas, 2000).

### **8.2.3 Formula intake**

The formula is a fundamental part of the PKU diet and treatment (Medical Research Council Working Party on Phenylketonuria, 1993). It provides up to 85% of the patients' protein needs and the essential vitamins and minerals which are lacking in the low phenylalanine diet (MacDonald et al., 2006). As detailed in the literature review, studies have shown that patients with PKU would be at high risk of developing essential amino acids or micronutrient deficiencies if they are not taking their formula regularly and at the same time avoiding animal protein because they are not used to such foods and find the taste unpleasant or because they recognize it is harmful for them and try to avoid it.

Deficiencies of vitamin B<sub>12</sub>, vitamin B<sub>6</sub>, iron, selenium, and zinc have been frequently reported for patients with PKU who are mostly non-compliant (Acosta et al., 2004; Arnold et al., 2001; Barretto et al., 2008; Hanley et al., 1996; Hvas et al., 2006; Jochum et al., 1997; MacDonald et al., 2004; Miranda da Cruz et al., 1993; Robinson et al., 2000; and Tavit et al., 2006). Low bone mineral density and reduced muscle mass has been reported for non-compliant patients with PKU as well (Adamczyk et al., 2011; Al-Qadreh et al., 1998; and McMurry, Chan, Leonard, & Ernst, 1992). The researchers recommended continued dietary management throughout adult life and regular monitoring to assess deficiencies early, and some authors recommended daily vitamin and mineral supplementation for PKU patients who are off diet.

Untreated vitamin B<sub>12</sub> deficiency may lead to a wide range of psychiatric and neurologic problems, some irreversible, in addition to the risk of macrocytic anaemia (Robinson et al., 2000; and Hvas et al., 2006). Iron deficiency could affect growth levels and cause cognitive, motor, and behavioural disturbances (Acosta et al., 2004; and Arnold et al., 2001). Low bone mineral density increase risk for fractures and adult osteoporosis (Adamczyk et al., 2011). Deficiencies of essential amino acids may have detrimental consequences and also contribute to high Phe levels, as results from this study have shown that low formula intake lead to increased blood Phe levels (section 8.4.2 below).

Seventy seven percent of the patients reported good compliance with formula intake; 57% of them reported always drinking all the prescribed amount of formula daily, and 20% reported usually drinking it daily. Many of the patients (16) had difficulties in drinking their formula (Table 9 in Results, Chapter 7). This seems to be a common and recurring issue with PKU patients at different parts of the world, even when using different types and brands of formula or protein substitutes, as generally their smell and taste are not appetizing (Prince, McMurray, & Buist, 1997). In the UK, MacDonald et al (1997) found only 38% of patients consume their prescribed protein substitute daily. In Germany Schulz and Bremer (1995) found that 20% of the adolescents and young adults in their study had stopped taking the formula.

Only two children in this study, who are siblings, were given the opportunity to mix their own formula. The other children were not trained to prepare the formula by their mothers or at the clinic, many of the mothers didn't trust their children to make up the

formula properly and it didn't occur to some that they could teach their children how to prepare the formula. Clinic time is very busy and there are no sessions available for training children and adolescents on diet and formula preparation. When children and adolescents are involved in choosing their meals and preparing them, they are more likely to consume what they have prepared and eat healthier options (Birch & Fisher, 1998; Larson, Perry, Story, & Neumark-Sztainer, 2006; and Larson, Story, Eisenberg, & Neumark-Sztainer, 2006). This might be very helpful in compliance with consuming the formula as well. Many of the children had difficulties drinking their formula; having the responsibility of mixing it and choosing a flavour to add to it might be a good incentive for them to consume it all.

Finding ways to involve the patients and empower them to improve compliance with formula intake is an important part in PKU management and treatment. As this is a universal problem, learning from the experiences of other successful centres may help find ways to work with patients at KFSH&RC to overcome their difficulties. Given that deficiencies contribute to poor outcome it is highly recommended to provide regular monitoring of trace minerals and vitamins in addition to blood Phe levels for patients with PKU at KFSH&RC. Regular monitoring of micronutrient levels for the patients and teaching the families about micronutrient deficiencies and their deleterious, and sometimes irreversible, effects may motivate them to be more compliant with formula intake.

#### **8.2.4 Diet adherence**

Only 21 (53.8 %) patients reported dietary intake of Phe within the allowed daily limit (<400mg/day). Adhering to the PKU diet was difficult for nearly all the families at KFSH&RC, 21 out of 24 families found it difficult to comply with the diet (Table 10 in Chapter 7 described the difficulties). The PKU diet is highly restricted and difficulties with the diet are commonly reported in the literature (Crone et al., 2005; Feillet & Agostoni, 2010; Fisch, 2000; MacDonald, 2000; Medical Research Council Working Party on Phenylketonuria, 1993; van Spronsen & Enns, 2010; and Wappner et al., 1999).

To improve dietary adherence it is necessary to work with the families and the patients to overcome their barriers to adherence (Bernstein et al., 2013; MacDonald et al., 2010; and MacDonald et al., 2011). In this group the main reasons for noncompliance seem to all materialize when the children are not under the mother's strict supervision. Targeting dietary education sessions and materials to the patients themselves would improve comprehension of the diet and its importance to their health and wellbeing, which could highly improve compliance (Feillet et al., 2010). Shifting the responsibility of dietary choices to the patients when they are at an appropriate age may also empower the patients and improve compliance, especially when combined with social support and behaviour modification strategies (Demirkol et al., 2011; Singh et al., 2000; and van Spronsen & Burgard, 2008).

### 8.2.5 Blood phenylalanine level monitoring

Blood Phe level monitoring at specific regular intervals is recommended and practiced in Europe and the USA. Table 41 lists the recommended frequency of Phe monitoring in different countries.

**Table 41: Frequency of blood Phe level monitoring in the west.**

Frequency of Monitoring	Age (years)		
	UK <sup>1</sup>	Germany <sup>2</sup>	USA <sup>3</sup>
Weekly	≤4	≤4	≤1
Fortnightly	4-10	4-12	1-12
Monthly	>10	12-17	>12
Every 2-3 months	-	>17	-

<sup>1</sup>Medical Research Council, 1993. <sup>2</sup>Burgard et al, 1999. <sup>3</sup>National Institutes of Health Consensus Development Panel, 2001.

The doctors and the dietitians at KFSH&RC encourage the families to monitor their children's blood Phe levels monthly, but this rarely happens. The blood tests are usually done just before or at the day of their appointments at KFSH&RC, which are usually every 6 months for most of the families. The blood Phe levels from such tests may not be representative of the actual Phe levels because the families probably improve the patient's diet before the blood test. This is natural; the families do not want to be labelled as noncompliant, as described by Weglage et al (1992) and

Bilginsoy et al (2005). More frequent monitoring would provide a better picture of typical blood Phe levels (Demirkol et al., 2011).

Many of the families do not live in Riyadh, where KFSH&RC is located. They are not trained to do the finger prick blood sampling at home to mail blood samples on the filter paper (Guthrie cards) to the KFSH&RC laboratory. Therefore they have to go to a hospital in their area to get a blood sample taken and sent to KFSH&RC. The burden of setting this up and explaining to hospitals the need for these samples falls on the families. Therefore many are deterred from this procedure and just wait for their follow-up appointments every 6 months at KFSH&RC.

Regular monitoring of the blood Phe level helps the families and the patients to understand the effects of diet and formula intake and helps them gain better control of their Phe levels (Bilginsoy et al., 2005; Feillet et al., 2010; Wappner et al., 1999; and Wendel & Langenbeck, 1996). It is important to have a specific protocol for regular blood Phe level testing at KFSH&RC, and set in place measures to help implement it. These might include educating the families about the importance and benefit of regular monitoring, and training them to do a finger prick at home to mail the blood samples, or liaising with regional hospitals to facilitate the process of sending the blood samples from the families' towns to KFSH&RC.

Many researchers recommend the introduction of self-monitoring of Phe levels by the patients (Bekhof et al., 2005; van Spronsen & Enns, 2010; and Wendel & Langenbeck, 1996), as this gives the patients more realization of their ability to control and influence their Phe levels, essentially educating them on how to improve their compliance.

### **8.2.6 Knowledge about PKU**

The knowledge of the mothers about PKU and its diet could be described as good with some need for improvement. The families are given the basic information about PKU but it seems to concentrate only on the day-to-day management. This is evident by the families' high level of interest in learning more about the disorder; how it could affect their children's brains, what the future holds for their children, how they can improve those prospects, and how to improve their diet.

More detailed education sessions, support groups, cooking demonstrations of special PKU recipes, improved educational materials, and easier access to health care providers all may help the families to keep on track and to improve their adherence to diet (Bernstein et al., 2013; MacDonald et al., 2010; and Waisbren et al., 1997). These provisions would help support all patients with aminoacidopathies and not just PKU patients.

The provision of regular family support groups for PKU and other metabolic disorders is much needed at KFSH&RC. The families are interested in joining support groups and the health care providers at KFSH&RC view them as a positive additional service. Support groups would provide a safe and relaxed environment for the families to improve their knowledge about their children's disorder, share their experiences, discuss their concerns, bring family members or friends to learn more about PKU, and provide an opportunity for the families to meet one another (Awiszus & Unger, 1990; and Brenton, 2000). They also provide a great opportunity for the children to meet other children with their same diagnosis, and learn that they are not alone in their struggles with PKU.

### **8.2.7 Concerns and suggestions of the mothers**

The mothers had many concerns regarding their children's care and wellbeing. They also had many suggestions that they thought would improve the service provided to them at KFSH&RC and give their children a more positive experience. All these concerns, suggestions, and requests for information by the families echo the findings of Phase 1 of this study, presented in Chapters 5 and 6. Those findings were from families of children with PKU as well as families of children with other aminoacidopathies, who share the services and similar dietary restrictions.

Listening to the families and addressing their needs is a significant part of the management and treatment of chronic conditions. This improves the relationship between the families and the health care providers; in turn this leads to positive attitudes towards the recommendations of health care providers and better compliance with these recommendations by the families (Bekhof et al., 2003; Bilginsoy et al., 2005; Crone et al., 2005; Taanila, Jarvelin, & Kokkonen, 1998; and Vegni et al., 2010).

## **8.3 Child Questionnaire**

It was a great pleasure having the opportunity to interview some of the children. They showed good comprehension and communication skills with great enthusiasm to be heard, qualities that would enable them to be more involved in the management of their disorder.

### **8.3.1 Knowledge and diet adherence**

Most of the education and instruction during the clinic is directed to the mothers with occasional involvement of the children when they are available. Nearly all the children in this study did not mix their own formula and were not trusted to choose their own food, although they showed good basic knowledge of the PKU diet. The main confusion seemed to be around chickpeas, eaten as hummus. Many of the children thought they were allowed to eat hummus and did not know it was part of the “beans” group. This could be attributed to the translated educational material given to the families. These do not include a specific mention of “hummus” as a high protein food to avoid. Translated materials can frequently miss country-specific dietary habits and preferences. Having educational materials developed locally to include common food choices and habits is essential.

Involving and engaging the children in the care process during their hospital visits will improve their knowledge and understanding of their condition and dietary requirements. As discussed earlier, giving the children some autonomy in their own health management, at an appropriate age, can have a positive effect and improve their dietary compliance (Bilginsoy et al., 2005; Medical Research Council Working Party on Phenylketonuria, 1993; van Spronsen & Burgard, 2008; and Waisbren et al., 1997).

### **8.3.2 Diet adherence and adolescence**

It is especially important to empower the adolescents and give them a sense of their ability to achieve good control because compliance is known to decline in adolescence (Antshel et al., 2004; Freehauf et al., 2013; MacDonald et al., 2011;

Medical Research Council Working Party on Phenylketonuria, 1993; and Walter & White, 2004). Patients during adolescence may refuse to follow their restricted PKU diets, as it is normal to act against limits and rules in this age group, but Crone and colleagues (2005) explain that the increase in blood Phe levels during adolescence could be due other factors in addition to decreased compliance. Decreased protein needs after a period of increased growth and hormonal changes may play a part in their increased blood Phe levels (Crone et al., 2005). Levy and Waisbren (1994) recommend developing support programmes targeting PKU patients during adolescence. Their research showed that positive perceptions towards treatment and social support with the PKU diet during adolescence are closely related to good dietary adherence, and support programmes helped achieve that.

## **8.4 Assessments and measurements**

### **8.4.1 Anthropometry**

There was a trend in this group of PKU patients towards overweight and obesity as evident from the BMI and waist circumference (WC) levels. This is in concurrence with recent findings showing increased body fat, overweight, and obesity in children with PKU (Albersen et al., 2010; and Burrage et al., 2012).

There is consistent evidence that waist circumference, as indicative of central adiposity, is related to cardiovascular disease risk factors in children (Katzmarzyk et al., 2004; Maffeis, Pietrobelli, Grezzani, Provera, & Tato, 2001; and Savva et al., 2000) and diabetes mellitus and mortality in adults (Ness-Abramof & Apovian, 2008). Katzmarzyk et al (2004) have hypothesized that waist circumference in childhood could be used to predict adulthood disease outcomes, after more research, as has been demonstrated for BMI, while McCarthy (2006) recommends that WC should be measured routinely in clinical and epidemiological settings. However some studies still do not support the need to measure waist circumference in children, in addition to BMI, especially before puberty (Cameron, Jones, Griffiths, Norris, & Pettifor, 2009; Garnett et al., 2007; and Reilly et al., 2010). The National Institute for Health and Care Excellence in the UK does not recommend the use of waist circumference as a

routine measurement in children and young people, but suggests it could be used in some situations to give additional information on the risk of developing long-term health problems (National Institute for Health and Care Excellence, 2006). Due to the increased trend towards obesity in PKU patients it might be beneficial to have WC measurements as routine practice to identify at risk patients and prevent further health complications in this population, especially as it is an easy measurement to take and does not need equipment other than a measuring tape.

#### **8.4.2 Factors affecting mean blood phenylalanine level (determinants of blood Phe level)**

- Age of patient at start of treatment
- Dietary intake of phenylalanine
- Formula intake

The strongest factor affecting the blood Phe level of the patients was their age at the start of treatment; the highest Phe levels were reported for the late treated patients. These patients had moderate to severe developmental delay due to late treatment; therefore their families may not have been strict in adhering to the diet or formula intake, which could explain the higher blood Phe levels. Another reason could be that they have not been treated by the health care providers as aggressively as the other patients with less or no developmental delay. Treatment of late diagnosed patients can be beneficial. Lee et al (2009) and Gassió et al (2003) studied the effects of following a phenylalanine restricted diet on late diagnosed adults; they showed that it had positive effects on the quality of life for the patients and their families. Trefz et al (2000) showed that late treated patients with PKU had improved intelligence level after treatment with a phenylalanine restricted diet. However these effects are much less obvious than the effects of treatment on an infant diagnosed and treated continuously from the first month of life, and this probably has an impact on the enthusiasm of parents and carers for pursuing a difficult form of treatment.

The dietary Phe intake was significantly different between patients with acceptable blood Phe levels and patients with high blood Phe levels, illustrating the documented relation between dietary Phe intake and blood Phe levels (Blau et al., 2010; and

Burgard et al., 1999). This relation for the whole group of patients lost some strength when adjusting for age at the start of treatment in the multiple regression model; this could be attributed to the group not being homogenous in regard of age at diagnosis and treatment. When looking at the early diagnosed and treated patients the association between mean Phe blood level and dietary Phe intake is significant, corroborating what is reported in the literature.

Compliance with formula intake, as discussed earlier, is essential for good blood Phe level (Medical Research Council Working Party on Phenylketonuria, 1993). In this study the patients with good formula intake had better mean blood Phe level than the patients who did not comply with formula intake. The patients who were diagnosed late were more likely not to comply with formula intake. This could be due to two issues; firstly the patients not being able to acquire a taste for the formula as it was introduced to them late, so they struggle to accept it or refuse to drink it (Donlon et al., 2006; and Owada, Aoki, & Kitagawa, 2000). Secondly this could be due to the fact that late diagnosed patients are delayed and their families do not see an immediate and clear benefit of treatment with the formula, as a result they may have low motivation and consequently are not very strict in having their children drink the formula when they refuse it or struggle to drink it.

#### **8.4.3 The outcome measure: what determines the Vineland-II ABC scores?**

- Age at diagnosis and treatment
- Phenylalanine level at diagnosis (disease severity)
- Dietary phenylalanine intake

The main goal of examining all the aspects of PKU management at KFSH&RC in this study was to find out what gives the patients there the best outcome. The ultimate goal of treatment and management of patients with PKU is to get the best developmental outcome and prevent intellectual impairment (Brumm & Grant, 2010).

The major determinant of outcome, measured by the Vineland-II ABC score, was age at diagnosis - the younger the patient at the time of diagnosis and treatment, the better the score. As reviewed earlier, this has been recognized by many researchers leading to emphasis on the huge importance of early diagnosis through newborn screening,

and early treatment, to prevent permanent learning disabilities. This has been central to the construction of guidelines for PKU management in the UK, the US, Germany and France (Abadie et al., 2005; Burgard et al., 1999; Medical Research Council Working Party on Phenylketonuria, 1993; and National Institutes of Health Consensus Development Panel, 2001).

Patients treated within the first month of life scored in the adequate range of the Vineland-II (Mean score = 92.2), while patients treated after one month of age had much lower scores (Mean score = 60.5). This has been described since 1968 by Dobson and colleagues (1968). In their retrospective study they found that treatment by 1 month of age yielded better IQ outcome than treatment after one month of age. They found the same results in a later analysis of a subsample from the US PKU Collaborative Study (Dobson, Williamson, Azen, & Koch, 1977). Later research found even earlier treatment leads to better IQ results, and guidelines currently in the UK, USA and Europe recommend treatment as soon as possible after birth (Abadie et al., 2005; Burgard et al., 1999; Medical Research Council Working Party on Phenylketonuria, 1993; and National Institutes of Health Consensus Development Panel, 2001).

The relation between the scores of the Vineland-II and the age at the start of treatment was strongest in linearity up to an age of start of treatment of 3.6 years. After that age the relation was still highly significant but less linear. It can be argued that the early years of life are the most vulnerable to progressive damage leading to an increased degree of developmental delay (Koch & Wenz, 1987; and Smith, Beasley, & Ades, 1990). Dobson and colleagues (1968) found similar observations to this study, the greatest impairment in their group was seen when dietary treatment started after 3 years of life. In another study by Smith et al (1991), they found that the greatest effect of increased blood Phe levels on intelligence occurred up to 4 years of age, then from 5 to 8 years of age the negative effect was still present but less severe, as seen in the group of patients in this study after the age of 3.6 years. This demonstrates that treatment in the first few months of life is the most essential to prevent permanent cognitive damage (Blau et al., 2010; and Burgard, 2000).

The second most important determinant of the Vineland-II score was the Phe level at diagnosis which is a marker of disease severity (see next section below). A third

determinant of the Vineland-II score identified by some of the analyses was the dietary Phe intake as calculated from the 24 hour diet recall. This was significant only in the multiple regression analysis for the patients treated at 3.6 years of age or younger, and was of weaker significance than that of the age of the patient at treatment. Similarly the effect of mean blood Phe level on outcome was significant in simple linear regression but that was lost in the more robust test of multiple regression, when all the influencing factors are included.

This group of patients is not homogenous; it is a mix of early and late diagnosed patients, with different severity of disease, some are on a strict diet and some are not. Therefore strong significant association of the outcome measure with the dietary intake of Phe and blood Phe levels such as is documented in the literature was not seen in this group. The Medical Research Council (1993) reported that poor quality of Phe control is linked to intellectual impairments during pre-school years. Burgard (2000) in a meta-analysis of longitudinal PKU studies concluded that patients who were treated early and had had good Phe control had the best outcome and near normal IQ scores. Smith and Knowles (2000) in a review of some PKU studies stated that bad Phe control is associated with lower IQ and behavioural problems. Aoki (2003) and Aoki et al (2007) reported that after long-term follow-up of patients with PKU in Japan the IQ was shown to be negatively related to blood Phe levels, and therefore stricter guidelines were introduced for the PKU diet. Dawson and colleagues (2011) showed that reaction time in adults with PKU was significantly related to their blood Phe levels and dietary control.

Many studies report the clear effect of Phe dietary intake and blood level on the developmental outcome for patients with PKU. Normally dietary Phe intake is a measure of compliance: if the recommended Phe intake is 400 mg per day and the patient is ingesting 1,000 mg per day, this is likely to lead to higher blood Phe levels and a lower Vineland-II score. However for this group of patients the strongest significance in correlation, simple linear regression, and multiple regression was seen for the age of the patients at the start of treatment. This could be attributed to the fact that 74% of the patients in this group were diagnosed late, and therefore the effect of not starting treatment early is very strong on outcome, lowering the Vineland-II score, whether the patients were compliant with the diet or not. Another reason may be that

dietary Phe intake is a marker of disease severity: in a patient with mild disease and satisfactory Phe levels, the dietary Phe intake recommended by the clinic doctor and dietitian will be higher and still the outcome measure will not be affected negatively.

#### **8.4.4 Classic and Mild PKU: Effects on outcome**

The severity of disease was a factor affecting patients' development and causing lower scores on the Vineland-II in this study. The level of developmental damage has been shown to depend on the severity of the disease (Koch et al., 2002; and Smith & Beasley, 1989); although some patients are very susceptible to increased levels of blood Phe concentrations while others do not seem to be affected by it (National Institutes of Health Consensus Development Panel, 2001; and van Spronsen & Enns, 2010). Therefore it was essential to classify the patients in this study according to their disease severity to identify the factors affecting the Vineland-II ABC scores in each group.

Classifying this group of patients into Classic PKU and Mild PKU revealed that the age at treatment initiation had a significant negative effect on the scores of the Vineland-II for the Classic PKU group. This was not the case for the Mild PKU group. The patients with mild disease were protected from severe developmental delay even when they were treated late or had higher than the desired range of blood phenylalanine on treatment. As a group their mean Vineland-II scores were much better than the patients with Classic PKU. The severity of the disease is clearly an important factor affecting the development of patients.

#### **8.4.5 Socio-economic status effects on outcome**

It has been suggested that higher levels of education and better knowledge of PKU by parents of patients lead to better compliance and outcome for patients (Cotugno et al., 2011; MacDonald et al., 2008; and van Spronsen, 2010). The level of education of the mothers and fathers of the patients in this study, and their level of knowledge about PKU, did not have any effect on outcome. Olsson et al (2007), similarly, failed to find a relationship between parents' education level and their children's blood Phe levels. Bekhof and colleagues (2003) tested if parents' knowledge of PKU and its diet

improved blood Phe levels and compliance; their level of knowledge was not significantly related to good control. They speculated that knowledge is influenced by psychosocial and emotional factors before it can be translated into behaviour towards compliance. This has been described by Durham-Shearer and colleagues (2008) as well. The authors suggested that knowledge improvement should be combined with other interventions to reach a positive effect on outcome, all while involving the patients in the development of these interventions (Durham-Shearer et al., 2008; and Singh et al., 2000).

Holtzman and colleagues (1986) reported, from the US Collaborative Study of children with PKU, that unemployment in the families was one of the factors causing bad control of Phe levels in their children. There was only one unemployed father in this study sample, not enough to test a relation between unemployment of the parents and the quality of Phe control. Eighteen (75%) of the mothers identified themselves as house-wives, there was no relation between their status and the quality of Phe control in this study.

#### **8.4.6 Mathematical skills and recall memory of patients**

Mathematical skills and memorization (e.g. memorizing passages from the Qur'an) seemed to be problematic for many of the PKU patients who attended regular mainstream schools, even when they had good control. Patients with PKU have frequently been described as having difficulties with mathematics. Berry and colleagues found that early treated patients with PKU had similar achievement scores to their non-PKU siblings except in arithmetic scores, which was lower for the PKU group (Berry, O'Grady, Perlmutter, & Bofinger, 1979). Such difficulties continued to be described in the literature either through studies or as reports by PKU patients and their families, regardless of their quality of dietary and blood Phe control (Azen et al., 1991; Pennington, van Doorninck, McCabe, & McCabe, 1985; Schmidt, Burgard, & Rupp, 1996; and Tiefenthaler, 2000). Feillet and colleagues (2010) suggest addressing the specific learning needs of these patients between the health care providers and the schools. It is necessary to provide the children with additional supportive services such as allowing them to use calculators or giving them more time during tutoring and tests (Feillet et al., 2010).

Memorization or recall memory problems for PKU patients are not reported in the literature as much as executive function deficits. White and colleagues (2001) reported impaired abilities in memory and learning in children with early treated PKU, and this impairment was more evident in older children. In contrast, another study did not find any significant difference in recognition and recall memory between early treated adults with PKU and controls (Channon, German, Cassina, & Lee, 2004).

Janzen and Nguyen (2010) reviewed the limited research available on non-executive cognitive abilities in patients with early treated PKU. In regard to long-term and recall memory they found mixed reports; some research reporting deficits and some reporting normal ability. The authors speculate that these discrepancies in the findings are due to the different tools used to assess learning and memory in the different studies. Impairments were highlighted when the tools testing them required the patients to use executive function strategies, which are commonly reported to be impaired in patients with PKU (Janzen & Nguyen, 2010). Learning and recall memory appear to be under investigated in individuals with PKU, it is difficult to conclude if they may suffer from a genuine deficit due to PKU or if it is more of a consequence of their impaired executive abilities.

It could as well be that the Western curricula, especially for younger school age children, does not require memorization skills as early as in Saudi Arabia, therefore it is not reported as a deficit. Arabic poetry and the Qur'an are taught from the first grade onwards; both subjects require a lot of memorization which was a cause of difficulty for many of the patients in this study. Janzen and Nguyen (2010) recommend developing specific strategies for patients suffering from learning and recall memory difficulties. They suggest the use of day planners or memory notebooks, making lists, using mnemonic devices, and dividing compound information into more controllable parts.

## **Summary**

There are many potential risk factors causing unsatisfactory control of PKU in Saudi Arabia and leading to developmental delay, but it has been evident from this research that the strongest factor affecting the development of a child with PKU is the age at diagnosis and treatment initiation. This demonstrates the unparalleled importance of the newborn screening programme. The other main causes of developmental delay are the severity of the disease, the quality of dietary control, and formula intake. The severity of the disease cannot be changed but ought to be determined to guide each patient's treatment plan. Given that the PKU treatment involves following a very strict low protein diet and drinking the protein substitute formula, improving compliance with formula intake and the quality of dietary control is vital.

# CHAPTER 9

# CONCLUSIONS

## **Introduction**

A number of risk factors for non-compliance and key recommendations have emerged from the results of this study. The recommendations are predominantly focused on overcoming the compliance barriers and enhancing the care experience of the patients and their families. Furthermore, the results of this study point to other areas that deserve additional research.

### **9.1 The main risk factors for non-compliance identified from this research**

1. The families are dissatisfied; they feel their concerns and needs are not fully met.
2. The need for social support and family support groups.
3. Lack of detailed educational sessions for the families, educational sessions targeting the patients, and cooking demonstrations of special PKU recipes.
4. The children are not being involved and engaged in the care process.
5. Lack of easy access to the health care providers.
6. Lack of regular blood Phe level monitoring, and monitoring of micronutrients.
7. Unavailability of low protein food products.

### **9.2 Key recommendations to overcome the risk factors**

#### **1. Training for health care providers:**

**a.** Training for more staff at KFSH&RC as their workload is high and will be increasing with the newborn screening programme underway. More staff are needed to adequately serve the patients and their families.

**b.** Training for health care providers at local hospitals and health care centres around the country to enable them to deal with the basic care and follow-up for the patients locally. This would reduce the strain on the KFSH&RC services. Having adequate local services provides regular access to health care providers and services. This would improve monitoring of the patients' blood levels and nutritional intake,

allowing for prompt adjustments on the dietary advice according to the levels and needs of the patients.

Local services would also provide the opportunity for regular support to the families, in terms of continuous education, opportunity for family support groups, and meeting other families from the same area with similar diagnoses. This would succeed if there were enough families locally or at least within the same province, where the commute to the health care centres would be easy.

## **2. Information and education for the patients and their families:**

**a. Varied information resources:** There are limited information resources in Arabic for the families. This study showed that the families were interested in gaining more knowledge about the disorders and the diet. Many families requested video or audio tapes in addition to leaflets and printed material with pictures to have as information sources. Some parents asked for workshops to attend and have open discussions. Providing the families with a variety of materials in Arabic, in addition to organizing detailed education sessions and cooking demonstrations of special low protein recipes would improve their access to information. These can be helpful for the staff training as well.

**b. Targeted education for the patients:** Tailoring dietary education materials and sessions to the patients' needs improves their comprehension of the diet and its importance to their wellbeing, which could highly improve compliance (Feillet et al., 2010). Empowering the patients by involving them and giving them the responsibility of their dietary choices, at appropriate ages, may improve compliance especially when combined with adequate support (Singh et al., 2000; and van Spronsen & Burgard, 2008).

**c. Websites in Arabic:** Many of the families access the internet but the language barrier prevents them from accessing relevant information. There are no websites targeting this population in Arabic. There are family forums that a few of the mothers use to chat to each other and learn from their experiences. Sometimes they invite an expert to contribute, but that is not a constant source of information for them. Offering websites with efficient information that cater for the patients and the

parents is essential for improving information access. Websites overseen by the KFSH&RC or the Ministry of Health would ensure reliable resources.

**3. Improve monitoring:** More rigorous and regular monitoring of the diet and Phe levels would help the families and the patients understand the effects of diet and formula intake and help them gain better control of their Phe levels (Demirkol et al., 2011; and Giovannini et al., 2012). Collaborations with local health care facilities and providing the families with prepaid postage envelopes to regularly send dried blood spots on Guthrie cards may encourage regular blood testing.

**4. Enhance developmental assessments:** Having a clear system for regular referrals to the psychologist for continuous developmental assessments would benefit many of the children and provide the parents with feedback to support compliance. Consistency in the use of assessment tools and tests would benefit future research and longitudinal comparisons.

**5. Offer alternative protein substitutes:** Providing more than one choice for the formula may reduce some of the difficulties in drinking it and improve compliance (MacDonald et al., 1997).

**6. Provide low protein food products:** These products are essential in helping the patients comply with their diets and attain better blood Phe levels. Having a variety of low protein food choices satisfies the patients' needs and cravings by offering a diet with more variability and some resemblance to that of unaffected family members and friends (Ahring et al., 2009; and Singh et al., 2000).

**7. Organise support programmes:** Support groups are greatly needed. The families showed high interest in joining support groups. Meeting other families has been shown to provide social, psychological, and metabolic advantages and positive influences for both the patients and their families (Brenton, 2000; MacDonald et al., 2010; Vegni et al., 2010).

Providing support for the children to equip them to be more involved in their own health management has constructive results and improves their dietary compliance (Bilginsoy et al., 2005; and van Spronsen & Burgard, 2008). Developing support

programmes particularly targeting adolescents is essential, as compliance is known to decline at this age (MacDonald et al., 2011; and Walter & White, 2004).

**8. Develop policy to involve schools:** Schools are integral in the lives of the patients. Child development plans are not available between the schools, the parents, and the health care providers. Policy and programme development to ensure school engagement in the development plans for the patients are essential. This would provide needed support from the schools to the families and entice school cooperation with dietary requirements.

**9. Provide play facilities:** The children spend many tiring hours at the KFSH&RC. Providing play facilities for the patients and their siblings while waiting for their appointments would offer them some enjoyable time and provide respite for their families. This would help in making the experience of going to the hospital less stressful for the families, leaving them more focused at clinic time.

### **9.3 Products of this study**

**1. A comprehensive questionnaire:** The developed questionnaire can be used for future studies with other patients with aminoacidopathies or other metabolic disorders.

**2. The Arabic Vineland-II:** The Vineland-II is an important tool, and having it in Arabic is invaluable to advance the assessment of children in the Arab world.

**3. An Arabic website for PKU:** I have started the process of planning a website that would provide basic dietary information about PKU in Arabic, with sections for both the patients and the parents. It would be beneficial to follow this by exploring the possibilities of collaborating with KFSH&RC or the Saudi Ministry of Health on expanding it to cover all relevant metabolic disorders.

## **9.4 Plans and suggestions for future work**

- 1.** Further research is needed to examine the quality of life for the patients with metabolic disorders and their mothers. This research included some questions related to that aspect and results showed that their quality of life is affected. Jusienė and Kučinskas (2004) pointed out that stressed parents have children who struggle. Understanding what the families go through would help organise support and counselling for them.
- 2.** Develop educational material for each disorder. Having a variety of educational material developed locally to include common food choices and habits is essential.
- 3.** Develop targeted nutrition management programmes, informed by the results of this study, to support patients with aminoacidopathies and their families. This can then be expanded to include all the patients with metabolic disorders in Saudi Arabia.
- 4.** Reaching the teachers of the patients was not feasible in this study. Carrying out research to investigate the teachers' perspectives in addition to the accounts of the parents and the patients would give a broader picture about the risk factors. Involving the teachers would aid in the development of the needed policy for coordinating between schools and health care providers.
- 5.** Development of public education programmes to improve the public awareness of the newborn screening programme in Saudi Arabia and to educate them about the screened disorders.
- 6.** Finally, an essential next step for me is to validate the Arabic Vineland-II with a larger sample, and work with the Vineland-II developers to publish the Arabic version.

## 9.5 Strengths and Limitations

### 9.5.1 Strengths of the study

1. **Study design:** Preceding the quantitative study with a qualitative study provided an understanding of the current situation and aspects of behaviours and attitudes that quantitative methods cannot obtain. This approach strengthens the study and adds to its credibility (Creswell, 2009; and Patton, 2002).
2. **Language and cultural knowledge:** The principal investigator, Sadeem Aljammaz, being from Saudi Arabia provided fluency in the language and familiarity with the culture of the participants. This allowed for ease of communication and valuable comprehension of social cues.
3. **Data collection:** The interview data was collected by one researcher (the principal investigator Sadeem Aljammaz), and the Vineland-II was administered by the same investigator as well. This limited data collection bias or differences that might occur when more than one researcher is involved in data collection.
4. **The Vineland-II translation and adaptation:** Translating the Vineland-II and culturally adapting it to the area was a major undertaking. It provided a reliable tool that gave uniform and comprehensive assessment of the patients in this study. Administering the Vineland-II and not using the available results of developmental assessments done by other health care providers gave stronger information. This also provided an Arabic tool that can benefit future studies.

### 9.5.2 Limitations of the study

1. **The Hawthorne effect:** This is the researcher's impact on participants (Pope & Mays, 1995). To limit that effect and in an effort to put the respondents at ease so they would talk freely, time was given before the interviews to establish rapport with respondents, and it was made clear that the principal investigator (SA) was not part of the KFSH&RC's hierarchy (Creswell, 2007; and Fontana & Frey, 2003).

2. **Sampling:** Sampling the families and patients for Phase 1 of the study was done till reaching a point of saturation (where we expect no significantly new information) in an attempt to gather as wide a range of opinions as possible in that situation (Creswell, 2007; and Ritchie et al., 2003). Therefore with such qualitative enquiry it is not feasible to plan for a sample number in advance. For Phase 2 the sample size was relatively small, but included all the available PKU patients at the KFSH&RC.
3. **Observation:** Observations of formula preparation by families were done at KFSH&RC; this might not be truly reflective of their home environment situation. Observing families and patients at the clinics might have altered their normal interactions with the dietitian or the doctor (Patton, 2002). Nonetheless KFSH&RC is a training hospital and families are generally used to having at least one trainee paediatrician or dietitian in the clinic.
4. **Market survey:** Surveying more areas than the two urban areas and two rural areas, that were explored, was not feasible. These were believed to be sufficiently representative of the Saudi market.
5. **Dietary intake:** Although the 24 hour food recall is the most practical method for measuring dietary intake for this sample, it is not the most accurate or definitive measure of Phe intake. The mothers know what their children with PKU should and should not eat, so they may not fully report high Phe intake.
6. **Past Phe blood levels:** Unfortunately most patients had their blood tests at irregular intervals which made some analyses impossible.
7. **Development assessments:** Not having uniform and consistent assessments for all of the patients at the KFSH&RC was problematic, but this was overcome by administering the Vineland-II.

## **Conclusion**

This has been the first study in Saudi Arabia to qualitatively examine the perceptions of the patients, their families, and their healthcare providers about their aminoacidopathy disorders. It was followed by a quantitative study to identify the risk factors for non-compliance. The results offered initial understanding of the barriers to dietary compliance, and provided direction for future research investigation with different metabolic disorders. This research journey was enlightening and an inspiration to continue to advocate for the needs of patients with metabolic disorders.



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# Appendices

## Appendix 1: Information sheet and consent form

<p>مستشفى الملك فيصل التخصصي ومركز الأبحاث</p> <p>KING FAISAL SPECIALIST HOSPITAL AND RESEARCH CENTRE</p>	
<p><b>Title of Proposal:</b></p> <p style="text-align: center;"><b>Nutritional Management of Amino Acidopathies in Saudi Arabia</b></p> <p><b>Part I – Research Participant Information Sheet:</b></p> <p><b>A. Purpose of the Research:</b> You and your child are being asked to participate in a research study. The purpose of this research is to identify the risk factors leading to unsatisfactory nutrition management and control for patients with amino acidopathies, specifically Phenylketonuria (PKU), Tyrosinemia, and Maple Syrup Urine Disease (MSUD). You and your child qualify for participation in this study because your child is diagnosed with PKU, Tyrosinemia, or MSUD.</p> <p><b>B. Description of the Research:</b> In this project you –and your child if possible- will be interviewed and asked some questionnaires, we will access some information from your child's medical records, we will record the usual growth measurements and amino acid blood levels taken from your child during a regular clinic visit, and we will interview you during a hospital visit to get information regarding your child's diet. We would need to meet with you two or three times during the period of this study, which will be approximately 18 months. These meetings will be when you bring your child to the clinic visit. We would like to enrol all KFSH&amp;RC patients' with PKU, Tyrosinemia, and MSUD and their families in this study; the number is approximately 150 patients.</p> <p><b>C. Potential Benefits:</b> Participating in this research will help the researchers understand risk factors and problems as so ciated with the nutritional management of patients with PKU, Tyrosinemia, and MSUD. This information will help increase awareness</p>	<p style="text-align: right;"><b>عنوان البحث :</b></p> <p style="text-align: right;">دور التغذية في علاج أمراض الأحماض الأمينية في المملكة العربية السعودية</p> <p style="text-align: right;"><b>الجزء الأول – معلومات للمشاركة في البحث:</b></p> <p style="text-align: right;"><b>أ. الغرض من البحث:</b> الغرض من البحث هو تحديد المسببات المؤدية إلى تغذية غير منضبطة للمرضى المصابين بالأمراض الوراثية الاستقلابية، خاصة مرضى (بي كي يو PKU ، وإم إس يو دي MSUD ، و تيروسينيميا Tyrosinemia). أنتم مؤهلون للمشاركة في هذه الدراسة لأن طفلكم مصاب بإحدى الأمراض الثلاثة السابق ذكرها.</p> <p style="text-align: right;"><b>ب. وصف البحث:</b> ستتم مقابلة كل من الأم و الأب والطفل في هذا البحث للإجابة على الأسئلة كما سيتم رصد بعض المعلومات الطبية ذات العلاقة من الملف الطبي للطفل. وسيتم تسجيل ومتابعة وقياسات النمو لطفلك وسيتم ملاحظة نتائج تحاليل الدم لمعرفة معلومات ذات علاقة بغذاء طفلك. سيتم الاجتماع بكم مرتين أو ثلاثة خلال فترة هذه الدراسة والتي مدتها 18 شهراً تقريباً، وهذه الاجتماعات ستتم خلال مراجعتكم لعيادة الطبيب . نود مشاركة كل مرضى (بي كي يو PKU ، وإم إس يو دي MSUD ، و تيروسينيميا Tyrosinemia) وعائلاتهم في هذه الدراسة وعدد المرضى تقريباً 150 مريض .</p> <p style="text-align: right;"><b>ج. الفوائد المحتملة:</b> مشاركتك في هذا البحث ستساعد الباحثين بعون الله تعالى على كشف بعض الغموض وحل المشكلات المتعلقة بالتغذية للمرضى المصابين بالأمراض</p>
<p><b>ORA A C</b></p> <p>(ORA 5.1.5.1) 23 Oct 2000</p>	<p style="text-align: center;"><b>إقرار بالموافقة على المشاركة في الأبحاث التي تتطلب استعمال دواء/جهاز/ أو إجراءات خاصة</b></p>
<p>For ORA Official Use Only <b>INFORMED CONSENT FOR RESEARCH INVOLVING THE ADMINISTRATION OF DRUGS, USE OF DEVICES OR PERFORMANCE OF PROCEDURES</b> This Consent Document is approved for use by the Research Ethics Committee of KFSH&amp;RC From: _____ To: _____ RAC#: _____</p>	
Page 1	

مستشفى الملك فيصل التخصصي  
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about the importance of nutrition as part of treatment and to help develop a nutrition management program to support patients with amino acidopathies and their families.

الوقاية الاستباقية. كما أن نتائج هذا البحث ستحسن بعون الله من فهم وإتباع أفضل أساليب التغذية للتعامل مع المرضى المصابين بالأمراض الوراثية الاستقلابية.

**D. Cost/s:**

Participants will not be responsible for financial costs related to this study. Refreshments, children's activities and care will be provided during interviews.

د. التكاليف:  
ليس هنالك أي التزام مادي على المشاركين في هذه الدراسة وسيتم تزويد المشاركين بالمطربات وتزويد الأطفال بالعناية المناسبة خلال المقابلات.

**E. Termination of Participation:**

You may discontinue participation in the study at any time without penalty or loss of benefits to which you are otherwise entitled.

هـ. إنهاء المشاركة:  
لكم الأحقية الكاملة في الخروج من الدراسة بدون أية تأثير على حقوقكم وعلاجكم القام في المستشفى.

**F. Voluntary Participation:**

Participation in this study is voluntary. You will suffer no penalty nor loss of any benefits to which you are otherwise entitled should you decide not to participate. Withdrawal from this research study will not affect your ability to receive alternative methods of medical care available at KFSH&RC.

و. المشاركة التطوعية:  
للمشاركة في هذه الدراسة طوعيه وإذا قررت عدم المشاركة فإنا لن نتعرض لأي مضايقات أو لفقدان حقاك المشروع في المعالجة، كما أن قرارك بالانسحاب من الدراسة لن يؤثر على تلقيك خدمة علاجية بديلة متوفرة في مستشفى الملك فيصل التخصصي ومركز الأبحاث.

**G. Confidentiality:**

Your identity and medical record, as a participant in this research study, will remain confidential with respect to any publications of the results of this study. Furthermore, your medical record may be reviewed by the Research Advisory Council or the agency sponsoring this research in accordance with applicable laws and regulations.

ز. السرية:  
كمشارك في هذه الدراسة ستكون هويتك ومعلومات ملفك الطبي سية في جميع المنشورات المتعلقة بنتائج الدراسة، ويمكن الاطلاع عليه من قبل المجلس الاستشاري للأبحاث أو الجهة الداعمة للدراسة في حدود النظم والقوانين المطبقة بهذا الخصوص.

**H. Contact Person(s):**

You may call the Section of Assurance & Compliance, Office of Research Affairs at 442-4724 for general

ح. الأشخاص الذين يمكن الاتصال بهم:  
في حالة وجود أي استفسار عليك الاتصال على قسم رقابة وجودة

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To: \_\_\_\_\_

RA/C#: \_\_\_\_\_

(ORA 5.1.5.1)  
23 Oct 2000

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التي تتطلب استعمال دواء/جهاز/ أو إجراءات خاصة

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questions concerning research at KFSH&RC or

research subjects' rights. For any specific questions with regard to this study please contact Dr. Zuhair Al-Hassnan or Ms Sadeem Aljammaz at telephone # 464-7272 Ext. 39164, Pager # 4281.

A signed copy of the consent form will be given to you.

البحوث في مكتب فثون الأبحاث على هاتف رقم 24724 لتوجيه أي أسئلة عامة تتعلق بالبحوث بمستشفى الملك فيصل التخصصي أو تتعلق بحقوق المشارك. وفي حالة وجود أسئلة محددة تتعلق بهذا البحث نرجو الاتصال على الدكتور زهير الحصنان أو سديم الجماز على هاتف رقم 464-7272 تحويلة رقم 39164 أو جهاز نداء رقم 4281. سيتم تزويدك بنسخة موقعة من هذا الإقرار.

**PART II - Authorization for Participation in This Research:**

Patient Name: \_\_\_\_\_

MRN #: \_\_\_\_\_

1. I acknowledge that I have read, or had explained to me in a language I understand, the attached Research Participant Information sheet and that Dr Al-Hassnan or Ms Sadeem Aljammaz has explained to me the nature of the research described in the Research Participant Information Sheet as well as any benefits reasonably to be expected. I have had the opportunity to ask any questions I had with respect to the research and all questions I asked were answered to my satisfaction.

2. I confirm that I have read, or had read to me, the foregoing authorization and that all blanks or statements requiring completion were properly completed before I signed.

Patient/Surrogate: \_\_\_\_\_ Date: \_\_\_\_\_

الجزء الثاني: تفويض بالمشاركة في البحث الطبي:

اسم المريض: \_\_\_\_\_

رقم الملف الطبي: \_\_\_\_\_

1. أقر بأنني قد قرأت - أو قد شرحت لي بلغة أفهمها - جميع المعلومات المتعلقة بالمشاركة بالبحث والرفقة، وأن الدكتور/ زهير الحصنان أو سديم الجماز قد أوضح لي ماهية البحث المذكور في نموذج المعلومات للمشاركة والغرض منه والفوائد المرجوة منه. كما أنه قد أتيحت لي الفرصة الكافية لعرض الأسئلة فيما يتعلق بالبحث الطبي وتلقيت الإجابات الكافية عنها.

2. بهذا أؤكد بأنني قد قرأت (أو قرأ لي) هذا التفويض وأن جميع المعلومات اللازمة قد تمت تعبئتها بدقة قبل توقيع علي.

التوقيع: \_\_\_\_\_ التاريخ: \_\_\_\_\_

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إقرار بالموافقة على المشاركة في الأبحاث  
التي تتطلب استعمال دواء/جهاز/ أو إجراءات خاصة

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ومركز الأبحاث

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الاسم: \_\_\_\_\_  
Print Name: \_\_\_\_\_

صلة القرابة: \_\_\_\_\_  
Relationship: \_\_\_\_\_

3. I confirm that I have accurately translated and/or read the information to the subject or his/her surrogate. **3. أُؤكِّد بأنِّي قد قرأتُ/ ترجمت جميع المعلومات المذكورة بدقة للمريض أو لولي أمره.**

توقيع الشاهد: \_\_\_\_\_  
Witness Signature: \_\_\_\_\_

الاسم: \_\_\_\_\_  
Print Name: \_\_\_\_\_

رقم البطاقة: \_\_\_\_\_  
KFSH&RC ID #: \_\_\_\_\_ Date: \_\_\_\_\_

4. I have fully explained to the above patient/ relative/ guardian the nature and purpose of the research, the benefits reasonably to be expected. It is my understanding that the above patient/ relative/ guardian understands the nature, purposes, benefits, and risks of participation in this research before signing of this informed consent. I have also offered to answer any questions the above patient/ relative/ guardian might have with respect to the research and have fully and completely answered all such questions. **4. أفر بأنِّي قد فرحت بصورة كاملة للمريض / أو قيه (ولي أمره) طبيعة والغرض من البحث. من المفهوم لديّ بأن المريض المذكور أعلاه (أو قيه أو ولي أمره) قد فهم طبيعة الدراسة وأهداف منها والفوائد والمخاطر المترتبة على المشاركة فيها قبل توقيعهم على الموافقة بالمشاركة. وقد قمت بتوضيح استعدادي للإجابة على جميع أسئلة المريض/ قيه/ ولي أمره عن موضوع الدراسة وقدمت فعلاً بالإجابة كاملة على جميع الأسئلة بطريقة واضحة ومرتضية.**

توقيع الباحث الرئيسي: \_\_\_\_\_  
Signature of Principal Investigator: \_\_\_\_\_

الاسم: \_\_\_\_\_  
Print Name: \_\_\_\_\_

الوظيفة: \_\_\_\_\_  
Title: \_\_\_\_\_

التاريخ: \_\_\_\_\_  
Date: \_\_\_\_\_

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التي تتطلب استعمال دواء/جهاز/ أو إجراءات خاصة

## Appendix 2: **Health care providers interview & focus group questions** **(Phase 1)**

### **1. Dietitian interview**

#### **Patient care:**

1. What are your duties as a dietitian at KFSH&RC?
2. How do you view your work as “the metabolic disorders dietitian” at KFSH&RC?
3. What/who are the patients that you see?
4. I am particularly interested in patients with aminoacidopathies (PKU, MSUD, and Tyrosinaemia I), how often do you see such patients?
5. How are they referred to you?
6. How many patients do you see per day/clinic?
7. How often do you see each patient?
8. How often do you contact the carers between clinic visits? Do they contact you?
9. What happens in your clinic (in detail please) when you are with a patient?
10. How many or what percentage of these patients are with disabilities?
11. Is there a difference in your management of patients with disabilities? How?
12. How would you describe your relationships with the patients and their families?
13. What are the pressures and stresses families face?

#### **Diet:**

14. What is your opinion about the knowledge and understanding of patients and carers regarding the causes, symptoms and treatments of the disorders they have?

15. What do you think about the nutrition knowledge of patients and carers regarding the nutrition management of their disorders?
  - Carers' views
  - Children's views
16. What are your suggestions and ideas regarding the nutrition management for these patients?
17. How is the compliance of the patients with their prescribed diets?
18. In your opinion, what are the reasons for compliance or non-compliance with diet?
  - Do you think family issues could be a factor?
  - Social aspects, education, or economic factors?
19. How do you think compliance can be improved?

**Services:**

20. How would you describe your relationships with other health care providers involved in the care of patients with metabolic disorders?
21. Do you think you are adequately involved in the management of patients?
22. What is your opinion about the hospital's services for patients with metabolic disorders and their families?
23. Do you think these services have room for improvements?
24. What do you think could be provided to improve services?
25. Do you think you have enough support?
26. What do you think about the national screening programme pilot? What do you think its impact might be? How in your opinion dieticians around the country would handle IEM?

## **2. Doctor interview**

1. I am particularly interested in patients with aminoacidopathies (PKU, MSUD, and Tyrosinaemia I), how often do you see such patients?
2. How are they referred to you?
3. How many patients do you see per day/clinic?

### **Patient care:**

4. How often do you see each patient?
5. How often do you contact the carers between clinic visits?
6. Do patients contact you between clinic visits? How do you address their needs?
7. How often do you ask for blood levels?
8. How do you communicate results to carers?
9. What is the protocol you follow in your clinic (in detail please) when you are with a patient?
10. How would you describe your relationships with the patients and their families?
11. What are the pressures and stresses families face?
12. Do you involve any other health care providers in the care of your patients?
13. If yes, who and how?

### **Diet:**

14. What is your opinion about the knowledge and understanding of patients and carers regarding the causes, symptoms and treatments of the disorders they have?
15. What do you think about the nutrition knowledge of patients and carers regarding the dietary management of their disorders?
  - Carers' views
  - Children's views
16. What are your suggestions and ideas regarding the nutrition management for these patients?

17. In your opinion, what is the importance of the dietician to the care of these patients?
18. How is the compliance of the patients with their prescribed diets?
19. In your opinion, what are the reasons for compliance or non-compliance with diet?
  - Do you think family issues could be a factor?
  - Social aspects, education, or economic factors?
20. How do you think compliance can be improved?

**Services:**

21. How would you describe your relationships with other health care providers involved in the care of patients with metabolic disorders?
22. What is your opinion about the hospital's services for patients with metabolic disorders and their families?
23. Do you think these services have room for improvements?
24. What do you think could be provided to improve services?
25. What do you think of the national screening programme pilot and its impact on the country?
26. How do you think is the knowledge of physicians around the country regarding IEM?
27. Do you think the national screening programme has any implications for your practice as a doctor and for the wider clinical practice?
28. Have I missed anything? Would you like to add anything? Thank you.

### **3. General dietitians' focus group**

#### **Experience:**

1. Were you ever involved in the management of patients with inborn errors of metabolism?
2. What is your previous experience with IEM? (Professional training etc.)
3. What is your knowledge about inborn errors of metabolism?
4. Where did you get your knowledge from?
5. Are there particular experiences you want to share with the group?
6. If you had had an experience, how did you deal with it, how did you manage, were you able to easily get help/support?

#### **Patient care:**

7. How do you find dealing with patients with inborn errors of metabolism?
  - what aspects of care are satisfying
  - what aspects are difficult
8. What in your opinion would help you in dealing with these patients?
9. Where do you get information on the subject when you need it?

#### **Diet:**

10. What is your opinion about the knowledge and understanding of patients and carers regarding the causes, symptoms and treatments of the disorders they have?
11. What do you think about the nutrition knowledge of patients and carers regarding the nutrition management of their disorders?
  - Carers' views
  - Children's views
12. What are your suggestions and ideas regarding the nutrition management for these patients?
13. How is the compliance of the patients with their prescribed diets?
14. In your opinion, what are the reasons for compliance or non-compliance with diet?
  - Do you think family issues could be a factor?
  - Social aspects, education, or economic factors?
15. What are the pressures and stresses families face?

16. How do you think compliance can be improved?

**Services:**

17. How would you describe your relationships with other health care providers involved in the care of patients with metabolic disorders?

18. What do you think about the services provided for patients and their families?

19. What do you think could be provided to improve services?

20. What do you think about the national screening programme pilot?

#### **4. Nurses' focus group**

##### **Experience:**

1. What are your previous experiences with IEM?
2. What are your roles/duties in the metabolic clinic?
3. What is your knowledge about inborn errors of metabolism?
4. What is your knowledge about nutritional aspects of care for IEM? (formula preparation)

##### **Patient care:**

5. Do families ask you for information?
6. Where do you get your knowledge/training from? Do you find it easy to get needed information?
7. How would you describe your relationships with the patients and their families?
8. What are the pressures and stresses families face?
9. How is the compliance of the patients with their prescribed diets?
10. In your opinion, what are the reasons for compliance or non-compliance with diet?  
- Do you think family issues could be a factor?  
- Social aspects, education, or economic factors?
11. How do you think compliance can be improved?

##### **Services:**

12. How would you describe your relationships with other health care providers involved in the care of patients with metabolic disorders?
13. What is your opinion about the hospital's services for patients with metabolic disorders and their families?
14. What do you think could be provided to improve services?
15. What is your knowledge about the national screening programme pilot?
16. Do you think the national screening programme has any implications for your practice as a nurse and for the wider clinical practice?

## Appendix 3: Family and child interview questions (Phase 1)

### Family interview

Date:

Diagnosis:

Interviewer:

Interviewee:

Start time:

### General start:

1. Tell me about your child please. Probe: when diagnosed, is s/he first in the family with this illness, etc.
  - 1a. What do you know about your child's illness?
  - 1b. Who explained the disorder to you?
  - 1c. Do you think you have good and enough understanding of this disorder?
2. Where do you get your information from?

### Social:

3. How do you and your child cope with this condition?
  - 3a. What are the main difficulties and pressures facing you? (**Probe:** stress, depression, frustration)
  - 3b. Who supports you and your child? Do you seek support?
4. Describe the treatment your child receives?
  - 4a. Tell me more about the diet.
  - 4b. When you go out and during social occasions, what do you do?
  - 4c. Does your child go to school?

4d. Do the teachers know about his/her condition? Are they cooperative/helpful? (**Probe**)

**Clinical care:**

5. How often do you come to KFSH&RC?
  - 5a. Do you find it easy to meet all appointments? Or do you have problems in attending?
  - 5b. What difficulties do you have?
  - 5c. How much time do you spend at the hospital when coming to visit the metabolic clinic?
  
6. Tell me about your experience during your clinic visits here?
  - 6a. Who are the health care providers that you visit during your appointments here at the hospital?
  - 6b. Do you have enough time with each of them?
  
7. Who are the health care providers that you visit at your local health clinic?
  - 7a. How is the care there?
  
8. How do you contact health care providers when you need them between clinic visits?
  - 8a. How would you describe your relationships with different health care providers?

**Diet:**

9. What do you think is the importance of the diet to your child's wellbeing?
10. How would you rate your understanding of the nutrition requirements of your child?
11. Where do you get your nutrition knowledge from?
12. When were you referred to a dietician?
13. How often do you visit the dietician?
14. Do you follow the dietician's instructions on diet?

15. Do you have barriers to following the diet? What are they?

**Probe:**

- Time and effort to make formula and organise diet
- Products not found in market.
- Financial, expenses.

**Services:**

16. Have you met other families who have children with similar conditions?

16a. Would you like to meet other families? **Probe**

17. What is your opinion about the hospital services provided for you and your child?

18. What further information are you seeking regarding your child's condition and /or care?

18a. In what form would you prefer to have that information?

19. Have you sought treatment in other places?

Thank you for your time and participation.

Assure participant of confidentiality.

End:

## **Child interview**

Date:

Interviewer:

Interviewee:

Start time:

1. Why do you come here?
2. What do you know about your illness?
3. Do you understand what the doctors or your parents tell you about it?
4. What do you like or dislike about coming to the hospital?
5. Can you tell me something about your treatment?
6. Do you give your opinion about your treatment or diet?
7. Do you think your opinion matters to the doctors or to your family?
8. What is your favourite food?
9. Do you choose your food?
10. Do you know what you are allowed to eat and what you are not allowed to eat?
11. Is it easy to stick to this diet?
12. Do you take formula?
13. Who prepares it? Do you have a role in preparing it?
14. Is it easy to take? Why?
15. Do your friends know about it? How do you deal with friends?
16. Is there anything you would like to ask me or tell me?

Thank you for your time and participation.

End:

## Appendix 4: Family interview sample (Phase 1)

Date:

Diagnosis: **MSUD**

The interview was tape recorded and conducted with the mother at the dietitian's clinic. The patient (13 years old) was colouring and her older brother came towards the end and gave a few comments.

Interviewer: S=Sadeem

Interviewees: M=Mother and B=Brother of patient.

Start: 03:05 p.m.

**S. Tell me about your daughter, when was she diagnosed?**

M. A week after birth.

**S. Is she your first affected child?**

M. She is the seventh.

**S. How many of your children are affected with this disorder?**

M. Six before her and they all died! They all had the same disorder but we did not know, they were not properly diagnosed. One lived up to her 4<sup>th</sup> year at the hospital, but she really suffered, she disabled and blind.

**S. You mean 6 children died without knowing their diagnosis?**

M. I know their illness, now I know it was the same disease. After we discovered her and got to know her smell; the smell of her sweat and urine, the same things and symptoms that she went through the children before her went through. They were not diagnosed at the hospital.

**S. How many children who are not affected do you have?**

M. Three boys and two daughters.

**S. Are they older or younger than this daughter?**

M. Different ages.

**S. What do you know about her condition?**

M. They are fine when they are born, nothing wrong. At the 5<sup>th</sup> day of breast feeding they start to constantly cry then get convulsions and close the eyes and mouth. Nothing gets into their mouths, not milk, water or anything. They become stiff. At the hospital some slip into a coma, some don't. They don't feed like other infants, the hospital gave them special feeding, I don't know what it was. They stay at the hospital; they don't come out with me.

**S. How did you know about your daughter?**

M. I delivered her by caesarean section, and the doctors were suspicious because I had a daughter before her and an American doctor at the hospital in Dhahran suspected that she had the disorder, we got two affected children after her. The doctor there told

us that we might get affected children in the future; one child might be affected and one might not be. Here, Dr. Ozand did an operation on her and dialysis; she stayed 45 days at KFSH, and was started on formula and a special diet, which we follow till today.

**S. When this daughter was born, how did you realize she had the disease? Was the blood test done right away?**

M. She was born in Yanbu. The doctor called KFSH, and on her 5<sup>th</sup> day of birth she slipped into a coma. She was airlifted to KFSH in Riyadh from Yanbu.

**S. Who explained her condition to you?**

M. The doctor in Yanbu.

**S. Do you think you understand your daughter's condition?**

M. Yes I do, from the smell of their body fluids, smells like fenugreek, when I start smelling that distinctive smell in the baby's sweat and urine I know it is the disease, I even smell my grandchildren to know.

**S. Are there any grandchildren affected with the disorder?**

M. No, thank God.

**S. Do you feel you have a full understanding of the condition?**

M. Yes, I do. Her cousin has MSUD as well.

**S. Where do you get your information about the condition?**

M. Once the baby is born, I observe them and I know if they got the disease or not. First I know by the constant crying, and then the distinctive smell, most important the sweat and urine smell. The convulsions come from the 5<sup>th</sup> day after the proteins increase from breast feeding.

**S. How do you deal with the disorder? What are the difficulties you face? Do you face difficulties?**

M. Of course, the food difficulties! She is older now and sees what we eat and other people eat. She asks for food that is not allowed. She says; why don't you give me from your food? I am your daughter! You don't love me! You don't want me! You know, her food is very limited.

**S. Do you need support?**

M. Yes. I am tired, my knees are bad, and I recently had surgery in my neck. I can't keep up with her, she tires me. I can't catch up with her when she grabs food and runs. She runs upstairs and I can't go after her.

**S. Does she grab food and run away?**

M. Yes, like she grabs bread and runs away with it.

**S. Is there anybody who helps or supports you?**

M. My daughters try to help out, but they are married; one lives in Kharj, and the other is in Jeddah, sometimes I have a house helper.

**S. Describe the treatment your daughter takes?**

M. Vitamins and iron tablets.

**S. Tell me about her diet in detail?**

M. I give her Cornflakes for breakfast with a cup of tea. Her formula milk has a strong smell she can't eat it with it. I cook for her lunch two spoons of rice with carrots, courgettes and tomatoes. Dinner is the same or tomato and cucumber salad, this is her food.

**S. What about the formula?**

M. Her milk.

**S. Does she drink it?**

M. Yes.

**S. How do you manage when you go out or during social occasions?**

M. I take her food and her formula with me. I just have to.

**S. Does she go to school?**

M. No, we enrolled her in a private school but we saw she wasn't benefiting; it wasn't a special education school and the tuition was expensive so we took her out.

**S. Were you not happy with the school?**

M. She was not doing well at all, she didn't learn anything.

**S. How many times do you visit KFSH?**

M. Since the day she was born. She is 13 years old now.

**S. How many times in the year?**

M. Since her birth appointments were every 2 weeks, then every month, then 2 and 3 months and currently it is every 6 months.

**S. Is it easy to attend the clinics at KFSH or are there difficulties?**

M. Yes it is becoming difficult for us. Her dad and I are old, and tired, and we have to travel from Dammam. We used to live in Yanbu and travelled from there as well.

**S. You mean difficulty of travelling?**

M. Yes, of course the travelling difficulties and the preparation of her food, I have to cook for her. For the formula I have to take 2 thermoses one cold with ice to preserve the formula, and one with hot water to heat it up for her to drink it. I do get tired.

**S. How much time do you spend at the hospital?**

M. Differs, 3-4 hours, depending on the number of patients that day.

**S. What is your experience when you attend the clinic? Which healthcare providers do you see?**

M. The doctors change, we used to see Dr. Ozand, then Dr. Al-Owain, then Dr. Zahrani, and others. Even our dietitian Suhad there used to be 4 before her.

**S. Who else do you see beside the doctor? Do you see the dietitian?**

M. I like the dietitian, I always see her and she explains everything to me, I understand her and she teaches me, but the foreigner dietitians before her I didn't understand them because of the language.

**S. Do you feel you spend enough time with the doctor and the dietitian?**

M. Yes, thanks to God. They ask me about her and I explain, and they take her height, weight and blood test. The dietitian asks about how I feed her.

**S. Who are the health care providers you visit in your area?**

M. We have a copy of her medical report; we show it to the doctors if she gets a cold, it's difficult. They should take care and just give her medicine for fever and antibiotics.

**S. How is the quality of their care?**

M. It is fine, but they don't know about her disorder, they say we heard of but don't know how to deal with it. They are not at the level of KFSH yet.

**S. How do you contact health care providers between clinic visits?**

M. We only call the dietitian when we run out of the formula, we call and my son picks it up for us. We don't call the doctor.

**S. Is that easy for you?**

M. Yes it is easy, thank God.

**S. How are your relationships with the doctors and the dietitian?**

M. The dietitian, thanks to God! She does her best and gives us the formula. The doctor writes the blood tests and the treatment. They all do a great job, I have no problems.

**S. What do you about the importance of the diet to your daughter's condition?**

M. When I really comply with her diet I see that my daughter becomes proper, good in her head.

**S. By proper do you mean stable or normal?**

M. Yes stable [laughs due to dialect differences]. Sometimes when I'm sick or something and they don't give her the diet correctly you will see something wrong with her either her gait wobbly or her hand shaking or eyes rolling, I can feel she is not all right.

**S. So, you feel the diet is important for her?**

M. Of course, if the diet is right she becomes good.

**S. How would you rate your understanding of her diet?**

M. Yes I do understand her diet.

**S. Where do you get your information from?**

M. I've memorised it.

**S. From where did you get the information before you memorised it?**

M. They told me about the diet, and I follow it, I don't add or deduct.

**S. When were you referred to the dietitian?**

M. Since the day she was born.

**S. How many times you visited the dietitian?**

M. With the doctor's appointments, currently every 6 months.

**S. Do you follow the dietitian's instructions?**

M. Yes I do, if I don't it affects my daughter and her health.

**S. Are there any barriers for following the diet? Like time, effort or finances?**

M. Yes, when we travel it is a problem; there are many things that affect her, not me. When traveling we need to carry a lot of stuff for her feeding; her food, water and a cooker, we have to take everything.

**S. Did you meet other families who have children with similar conditions?**

M. Yes, her cousin. Suhad knows her.

**S. It there anyone else?**

M. There is but not with the same disorder.

**S. In the family?**

M. Not from our family, but in the neighborhood.

**S. Are they following the same diet?**

M. I am not sure about their diet.

**S. Didn't you ask them about their experience?**

M. I asked them, they say they follow what the dietitians told them, I don't know what. I know they use the same formula, because when they ran out one time, they took a can from me, that was in Dammam.

**S. Would you like to meet other families with the same condition?**

M. Yes, I do wish to. We can exchange different experiences, learn from each other and talk about our difficulties, it will be kind of a support for us, and that will bring us some comfort. People who have their hands in the fire are not like who don't! Many think there is no patient except their child but when you see others with sick children you accept your situation. Thanks to *Allah*.

**S. What is your opinion about the hospital services provided for you and your daughter?**

M. I think it is great, and like to thank them for that.

**S. Is there further information you would like to know about your daughter's condition and care?**

M. I want to know more about the diet.

**S. In what form would you prefer to receive this information in, such as in video, cassettes or written material?**

M. I think video is the best way, so I can watch and listen to understand, if I just listen may be things would be said and I don't understand.

**\*Her eldest son who drove them to the hospital came into the room towards the end of the interview and joined in.**

B. My mother suffers. The dietitian gives us a list of allowed food products, we go to the supermarket and find stuff they didn't tell us about so we avoid them, she [the patient] is a child and sometimes wants stuff, all the kids chew gum and she wants like them. This is the problem we suffer; the dietitian gives us a list of may be 10 products and we follow that; but there are new stuff all the time!

M. If she finds candy she wants it, if she finds Pepsi she wants it as well.

B. It became a hassle, when the kids bring sweets and we tell her no this is not good for you! She suffers from that the most.

**S. So you want to know exactly which items are allowed and those that are not allowed?**

B. Yes, we want to know all the allowed food items in the supermarket. I am afraid we are saying no to items that she is permitted to eat! Yesterday I took the kids with me to the supermarket everyone chose something and she kept saying I want this or that and I'd tell her no, just take what is allowed. There could have been something allowed for her but we don't know!

**S. Right, that might happen if you don't know.**

B. This is the problem! My mother brought today a crisp wrapper to show it to the dietitian, my sister wants to have it.

M. She saw it on TV and with other kids. It is from corn and I read the protein portion is 6 but I am not sure if it is safe for her. Here at the reception she was given this juice; I told her not to drink it till we ask the dietitian to be sure.

B. All foods have protein but we want to know the exact allowed amounts.

**S. Did you search for treatment somewhere else?**

M. No, I just bought her vitamins two years ago, other than that no way.

**S. Thank you all, I appreciate your time.**

End: 03:30 p.m.

**Comments on F#13 interview:**

I approached the mother while she was at the waiting area. She came with her son, a young man, and her daughter, the patient. She agreed right away to participate in the research, but she said “I’m illiterate; I can barely right my name!”

I read the consent form for her and explained it and she wrote her name at the signature line.

I gave the patient some colouring paper and crayons with the mother’s approval. She said that colouring will occupy her daughter while she talks to me.

Although the mother is illiterate, she seemed to understand her daughter’s diet and its importance. They seemed to be a caring family. The brother came in at the end and expressed his concern regarding the different food products and sweets allowed for his sister, they prevents her from eating different sweets and gums from other children and feels sorry for her. He wanted to know all the allowed products.

This shows that different family members are involved in the patient’s care and diet.

## Appendix 5: List of obtained data (Phase 2)

<b>List</b>	<b>Completed</b>	<b>Missing data</b>
<b>Consent form given to parent</b>		
<b>Consent form in MR</b>		
<b>Measurements taken</b>		
<b>Interview</b>		
<b>24 hrs food record #1</b>		
<b>24 hrs food record #2</b>		
<b>MR review</b>		
<b>Copy of developmental assessments</b>		
<b>Past blood levels</b>		

**Appendix 6: Anthropometric data & medical records information  
(Phase 2)**

**A. Anthropometric measurements**

**Date:**

<b>A1. Height / Length</b>	_____ cm
<b>A2. Weight</b>	_____ kg
<b>A3. Mid Upper Arm Circumference</b>	_____ mm
<b>A4. Triceps Skin Fold Thickness</b>	_____ mm _____ mm _____ mm Ave: _____ mm
<b>A5. Waist Circumference</b>	_____ mm

**B. Information obtained from medical records**

<b>MR1. Child's name:</b>	<b>MR2. MR #:</b>	
<b>MR3. Date of birth:</b>	<b>MR4. Age:</b>	
<b>MR5. Sex:</b> 1. Male      2. Female	<b>MR6. Age at diagnosis:</b>	
<b>MR7.1 Phenylalanine concentration at diagnosis:</b> _____ $\mu\text{mol/l}$	<b>MR7.2 Date:</b>	
<b>MR8.1 Age at start of treatment:</b>	<b>MR8.2 Date:</b>	
<b>MR9. Medical problems:</b>		
<b>MR10. Morbidity in the past two weeks:</b>	<b>1. Yes</b>	<b>2. No</b>
If yes: <b>MR10.1 What?</b>		
<b>MR11. Did the child undergo developmental assessment:</b> <b>1. Yes</b> <b>2. No</b>		
If yes <b>MR12. Date of developmental assessment:</b>		
<b>1<sup>st</sup> report:</b> _____	<b>2<sup>nd</sup>:</b> _____	<b>3<sup>rd</sup>:</b> _____
<b>4<sup>th</sup>:</b> _____	<b>5<sup>th</sup>:</b> _____	<b>6<sup>th</sup>:</b> _____
<b>MR13. At what age:</b>		
<b>1<sup>st</sup>:</b> _____	<b>2<sup>nd</sup>:</b> _____	<b>3<sup>rd</sup>:</b> _____
<b>4<sup>th</sup>:</b> _____	<b>5<sup>th</sup>:</b> _____	<b>6<sup>th</sup>:</b> _____
<b>MR14. Is phenylalanine blood level taken at the day of interview:</b> <b>1. Yes</b> <b>2. No</b>		
If yes: <b>MR14.1 Phe level:</b> _____ $\mu\text{mol/l}$	<b>MR14.2</b> <b>Phe/Tyrosine ratio:</b>	<b>MR14.3 Date:</b>
<b>MR15.1 Last phenylalanine blood level:</b> _____ $\mu\text{mol/l}$	<b>MR15.2</b> <b>Phe/Tyrosine ratio:</b>	<b>MR15.3 Date:</b>

**MR#:****Name:****Past blood levels:**

<b>Date</b>		<b>Phenylalanine blood level <math>\mu\text{mol/l}</math></b>		<b>Phenylalanine /Tyrosine Ratio</b>	
MR16.		MR16a.		MR16b.	
MR17.		MR17a.		MR17b.	
MR18.		MR18a.		MR18b.	
MR19.		MR19a.		MR19b.	
MR20.		MR20a.		MR20b.	
MR21.		MR21a.		MR21b.	
MR22.		MR22a.		MR22b.	
MR23.		MR23a.		MR23b.	
MR24.		MR24a.		MR24b.	
MR25.		MR25a.		MR25b.	

## Appendix 7: Family Questionnaire (Phase 2)

## Family Questionnaire

استبانة العائلة

## 1. Identification information

101. Date \ التاريخ:			
102. Interviewee \ المشارك:	<input type="checkbox"/> Mother \ الأم	<input type="checkbox"/> Other \ آخر: _____	
103. Home phone number \ رقم هاتف المنزل:			
104. Mobile number \ رقم الجوال:			
105. Address \ مقر الإقامة:			
106. Town \ البلد:	1. Urban \ مدينة	2. Rural \ قرية	3. Peri-urban \ شبه مدينة

## 2. Socio-economic Status

الأب \ Father

201. Age (yr) \ العمر:							
<21	21-25	26-30	31-35	36-40	41-45	46-50	>50
202. Education- What is the highest level of schooling that you have completed: ؟ أكملها المستوى العلمي: ما هي آخر مرحلة دراسية							
1. None \ لا يوجد		2. Read & write \ يقرأ ويكتب					
3. Primary School \ الابتدائية		4. Middle school \ المتوسطة					
5. High School \ الثانوية		6. Less than Univ. Dip. \ دبلوم دون الجامعي					
7. University \ الجامعة		8. Higher degree \ دراسات عليا					
203. Occupation \ الوظيفة: _____							
1. Professional \ مهني		2. Technician \ فني		3. Worker \ عامل			
4. Student \ طالب		5. Military officer \ عسكري		6. Unemployed \ غير موظف			
7. Retired \ متقاعد		8. Other \ أخرى: _____					

## Mother \ الأم

<b>204. Age (yr) \ العمر:</b>							
<21	21-25	26-30	31-35	36-40	41-45	46-50	>50
<b>205. Education- What is the highest level of schooling that you have completed:</b>							
المستوى العلمي: ما هي آخر مرحلة دراسية أكملتها؟							
1. None \ لا يوجد	2. Read & write \ تقرأ وتكتب						
3. Primary School \ الابتدائية	4. Middle school \ المتوسطة						
5. High School \ الثانوية	6. Less than Univ. Dip. \ دبلوم دون الجامعي						
7. University \ الجامعة	8. Higher degree \ دراسات عليا						
<b>206. Occupation \ الوظيفة: _____</b>							
1. Professional \ مهنية	2. Technician \ فنية	3. Worker \ عاملة					
4. Student \ طالبة	5. Unemployed \ غير موظفة	6. Retired \ متقاعدة					
7. House-wife \ ربة منزل	8. Other \ أخرى: _____						
<b>207. Marital Status - Which of the following best describes you now:</b>							
الحالة الاجتماعية: أي الآتي ينطبق عليك الآن:							
1. Single \ غير متزوجة	2. Married \ متزوجة						
3. Divorced/separated \ مطلقة/منفصلة	4. Widowed \ أرملة						

## Family information

<b>208. What is your family's approximate monthly spending \</b>								
ما هو إجمالي إنفاق الأسرة خلال الشهر تقريبا:								
1. <1000	2. 1000-2999	3. 3000-4999	4. 5000-6999	5. 7000-8999				
6. 9000-10999	7. 11000-14999	8. >15000	9. Don't know \ لا أعلم					
<b>209. Family Type \ نوع العائلة:</b>								
1. Nuclear \ نووية			2. Extended \ ممتدة					
<b>210. Number of people living in the household \ عدد الأفراد المقيمين في المنزل:</b>								
<b>210.1 Number of adults \ عدد البالغين:</b>								
0 1 2 3 4 5 6 7 8 9 $\geq 10$								
<b>210.2 Number of children \ عدد الأطفال:</b>								
0 1 2 3 4 5 6 7 8 9 $\geq 10$								
<b>211. Number of children born to mother \ عدد الأطفال المولودين للأم:</b>								
0 1 2 3 4 5 6 7 8 9 $\geq 10$								
<b>212. Number of children alive \ عدد الأطفال الأحياء:</b>								
0 1 2 3 4 5 6 7 8 9 $\geq 10$								
<b>213. Birth order of affected child \ ترتيب الطفل المصاب حسب الولادة:</b>								
0 1 2 3 4 5 6 7 8 9 $\geq 10$								

<b>214. Number of children with disorder   عدد الأطفال المصابين :</b>		
0 1 2 3 4 5 6 7 8 9 $\geq 10$		
<b>215. Who is the primary care giver   من هو المسئول الأول عن تقديم الرعاية للطفل</b>		
1. Mother\الأم	2. Father\الأب	3. Sister\الأخت
4. Grandmother\الجددة	5. Domestic helper\الخادمة المنزلية	
6. Other\أخرى: _____		
<b>216. Who is the secondary care giver   من هو المسئول الثاني عن تقديم الرعاية للطفل</b>		
1. Mother\الأم	2. Father\الأب	3. Sister\الأخت
4. Grandmother\الجددة	5. Domestic helper\الخادمة المنزلية	
6. Other\أخرى: _____		

### 3. Health related questions

<b>301. What was your child's age at diagnosis   كم كان عمر طفلك عند التشخيص</b>			
1. ___ days\أيام	2. ___ weeks\أسابيع	3. ___ months\أشهر	4. ___ years\سنوات
<b>302. How many times have you attended appointments at KFSH&amp;RC in the past year?</b>			
كم عدد مرات حضورك للمواعيد في مستشفى الملك فيصل التخصصي و مركز الأبحاث خلال السنة الماضية؟			
0 1 2 3 4 5 6 7 8 9 10 11 $\geq 12$			
<b>303. How often do you visit a health care facility with your child other than KFSH?</b>			
كم عدد المرات التي تزورين فيها مركزاً طبياً آخر مع طفلك؟			
1. Once a month   مرة بالشهر			
2. Every 3months   كل ثلاثة أشهر			
3. Every 6months   كل ستة أشهر			
4. Never (only go to KFSH)   مطلقاً، لا أذهب لغير مستشفى الملك فيصل التخصصي			
5. Other   أخرى: _____			
<b>304. How often do you send blood samples for your child/children?</b>			
كم مرة ترسلين عينات دم لطفلك/أطفالك؟			
1. Once a month   مرة بالشهر		2. Every 3months   كل ثلاثة أشهر	
3. Every 6months   كل ستة أشهر		4. Other   أخرى: _____	

**305. What do you expect the dietitian to do if your child's blood phenylalanine level was high?**

ماذا تتوقعين أن تفعل أخصائية التغذية في حال ارتفاع مستوي حمض الفينيل ألانين (الحموضة) في دم طفلك؟

- Increase the formula \ زيادة خلطة الحليب
- Reduce the formula \ تقليل خلطة الحليب
- Increase protein from food \ زيادة البروتين في الغذاء
- Reduce protein from food \ تقليل البروتين من الغذاء
- Ask if the child was ill \ تسأل إن كان طفلك مريضاً
- Don't know \ لا أعلم
- Other \ أخرى: \_\_\_\_\_

**306. What do you think is the risk for your child if his/her blood phenylalanine level was constantly high?**

ما الخطر المعرض له طفلك بنظرك عندما يكون مستوى حمض الفينيل ألانين بالدم مرتفع باستمرار؟

- No effect \ لا يؤثر
- Irritability \ الشعور بعدم ارتياح
- Illness \ المرض
- Hyperactivity \ زيادة النشاط والحركة
- Permanent learning difficulties \ صعوبات تعلم دائمة
- Paralysis \ شلل
- Don't know \ لا أعلم
- Other \ أخرى: \_\_\_\_\_

**307. How would you describe your child's health in general \ كيف تصفين صحة طفلك عموماً؟**

1. Excellent \ ممتازة      2. Good \ جيدة      3. Fair \ وسط      4. Poor \ سيئة

**308.1 Is there any other problem your child suffers from \ هل يعاني طفلك من مشاكل أخرى؟**

1. Yes \ نعم      2. No \ لا

**308.2 If yes, specify \ إذا كانت الإجابة نعم، حددي:**

**309.1 Has your child been ill in the past 2 weeks \ هل مرض طفلك خلال الإسبوعين الماضيين؟**

1. Yes \ نعم      2. No \ لا

**309.2 If yes- What was the illness \ إذا كانت الإجابة نعم، مم كان يعاني؟**

- Cold \ زكام       Fever \ حرارة       Cough \ كحة       Diarrhea \ إسهال
- Vomiting \ تقيؤ       Other \ أخرى: \_\_\_\_\_

**310. Did your child give a blood sample today \ هل أخذت عينة دم لطفلك اليوم؟**

1. Yes \ نعم      2. No \ لا

#### 4. Development related questions

<p><b>401. Does your child go to school \ هل يذهب طفلك للمدرسة ؟</b> 1. Yes \ نعم 2. No \ لا</p>
<p><b>If no, go to section 5 \ اذهبي لفقرة 5</b></p>
<p><b>If yes \ نعم</b> إذا كان الجواب نعم:</p> <p><b>402. Which year of school \ بأي سنة دراسية طفلك ؟</b></p> <p>Nursery\حضانة KG1\روضة KG2\تمهيدي 1 2 3 4 5 6 7 8 9 10 11 12</p>
<p><b>403. What is the school \ ما هي المدرسة ؟</b> _____</p> <p>1. Public school (regular)\مدارس حكومية</p> <p>2. Public school with special education classes\مدارس حكومية بها تعليم خاص</p> <p>3. Private school (regular)\مدارس أهلية</p> <p>4. Private school with special education classes\مدارس أهلية بها تعليم خاص</p> <p>5. Special education school\مدارس تأهيل أو تعليم خاص</p> <p>6. Other \ أخرى: _____</p>
<p><b>404. Do you think your child needs special education \ هل تعتقد أن طفلك بحاجة لتعليم خاص ؟</b></p> <p>1. Yes \ نعم 2. No \ لا</p>
<p><b>405. Does your child receive any special education at school \ هل يتلقى طفلك أي تعليم خاص في مدرسته ؟</b></p> <p>1. Yes \ نعم 2. No \ لا</p>
<p><b>If no \ إذا كان الجواب لا</b></p> <p><b>406. Why not \ لم لا يتلقى تعليماً خاصاً ؟</b></p>

#### 5. Social activities questions

<p><b>501. How often do you as a family go out with your child \ كل كم تخرجون مع طفلك كأسرة ؟</b></p> <p>1. Daily \ يومياً 2. Weekly \ اسبوعياً 3. Monthly \ شهرياً 4. Rarely \ نادراً</p>
<p><b>502. Where do you go \ إلى أين تذهبون ؟</b></p> <p><input type="checkbox"/> Family visits \ زيارات العائلة</p> <p><input type="checkbox"/> Outings \ فسخ</p> <p><input type="checkbox"/> Shopping \ تسوق</p> <p><input type="checkbox"/> Other \ أخرى: _____</p>
<p><b>503. Do you have limitations or difficulties when going out due to your child's condition ?</b></p> <p>هل تواجهون تقييداً أو صعوبات عند الخروج بسبب حالة طفلك؟</p>

1. Yes \ نعم 2. No \ لا

**504. If yes- is it due to \ فهل ذلك بسبب \ إذا الجواب نعم،**

- Illness \ المرض  Diet \ الحمية  Formula \ الخلطة  
 Embarrassment \ الإحراج  
 Influence of others \ تأثير الآخرين  
 Disability of child \ الإعاقة لدى الطفل  
 Difficulty with child \ صعوبة التعامل مع الطفل  
 General anxiety (worried about child) \ مخاوف عامة (قلق على الطفل)  
 Other \ أخرى: \_\_\_\_\_

## 6. Attitudinal / practices questions

**601. How would you rate your knowledge about your child's condition?**

كيف تقيمين معرفتك بحالة طفلك؟

1. Excellent \ ممتازة 2. Good \ جيدة 3. Fair \ وسط 4. Poor \ سيئة

**602. How would you rate your knowledge about your child's dietary needs?**

كيف تقيمين معرفتك باحتياجات طفلك الغذائية؟

1. Excellent \ ممتازة 2. Good \ جيدة 3. Fair \ وسط 4. Poor \ سيئة

**603. What do you think is the importance of your child drinking the special formula?**

باعتقادك، ما أهمية شرب طفلك للخلطة الخاصة؟

1. Very important \ مهم جداً 2. Somewhat important \ مهم نوعاً ما 3. Not important \ غير مهم

**604. What do you think is the importance of your child eating his/her specific diet?**

برأيك، ما أهمية التزام طفلك بتناول حمية غذائه الخاصة؟

1. Very important \ مهم جداً 2. Somewhat important \ مهم نوعاً ما 3. Not important \ غير مهم

**605. How do you find adhering to the diet \ كيف تجددين الالتزام بالحمية الغذائية \**

1. Very easy \ سهل جداً 2. Easy \ سهل 3. Difficult \ صعب 4. Very difficult \ صعب جداً

**606. Which of the following you recognize as a barrier to following the diet for your child:**

أي من الأمور الآتية يعيق من اتباع طفلك للحمية الغذائية:

- Family members; siblings, grandparents, aunts, or uncles \ أفراد العائلة (أخوان، أجداد، أعمام، أخوال)
- Social visits \ الزيارات الاجتماعية
- School; teachers or pupils \ المدرسة (مدرسين وطلاب)
- Other children, friends of child \ أطفال آخرين، أصدقاء الطفل
- Limited dietary choices \ الاختيارات الغذائية المحدودة
- Child unattended around food \ عدم مراقبة الطفل وهو حول الطعام
- Child's insistence on eating forbidden food \ إصرار الطفل على الأكل من الأغذية الممنوعة
- Limited knowledge of diet \ المعرفة المحدودة بالنظام الغذائي
- Other \ أخرى: \_\_\_\_\_
- No barriers \ لا يوجد عوائق

**607. For how long do you think your child should follow this diet?**

إلى متى باعتقادك يجب أن يتبع الطفل هذه الحمية الغذائية؟

1. Few years \ بضع سنوات
2. Until he/she grows up \ حتى يكبر
3. Until he/she is cured \ حتى يشفى
4. All his/her life \ طوال حياته
5. Don't know \ لا أعلم
6. Other \ أخرى: \_\_\_\_\_

**608. If you had a question regarding the diet, what would you do:**

ماذا تفعلين إذا كان لديك سؤال عن الحمية الغذائية؟

- Wait till the next appointment. \ الانتظار للموعد القادم
- Call the dietitian to ask. \ الاتصال بأخصائية التغذية للسؤال
- Try to find some information to read. \ محاولة البحث عن معلومات مقروءة
- Don't know. \ لا أعلم
- Other \ أخرى: \_\_\_\_\_

## 7. Knowledge questions:

Statement	True	False	Don't know
701. It is all right for a child with PKU to eat dates. لا بأس أن يأكل الطفل المصاب بـ (بي كي يو) التمر.	1	2	3
702. It is all right for a child with PKU to eat rice with meat stew. لا بأس أن يأكل الطفل الرز مع مرققة اللحم.	1	2	3
703. It is all right for a child with PKU to eat lintels. لا بأس أن يأكل الطفل العدس.	1	2	3
704. It is all right for a child with PKU to drink diet cola. لا بأس أن يشرب الطفل دايت كولا.	1	2	3

## 8. Dietary habits

<p><b>801. Who usually buys the food for the family</b> \ من هو المسؤول عن شراء المواد الغذائية \ للعائلة?</p> <p>1. Father \ الأب      2. Mother \ الأم      3. Grandparent \ الجد أو الجدة 4. Both parents \ كلا الوالدين      5. Driver \ السائق      6. Other \ أخرى: _____</p>
<p><b>802. What is your food budget</b> \ ما هي الميزانية المخصصة للغذاء</p> <p>1. &lt; 500 per week \ أقل من ٥٠٠ ريال بالأسبوع      2. 500-1000 per week \ ٥٠٠ - ١٠٠٠ ريال 3. &gt; 1000 per week \ أكثر من ١٠٠٠ ريال بالأسبوع      4. Don't know \ لا أعلم</p>
<p><b>803. Who usually prepares food for the family</b> \ من يحضر الطعام للعائلة عادةً</p> <p>1. Mother \ الأم      2. Father \ الأب      3. Grandparent \ الجد أو الجدة      4. Domestic helper \ الخادمة      5. Other \ أخرى: _____</p>
<p><b>804. Is the child's food prepared separately</b> \ هل يتم تحضير طعام الطفل منفصلاً عن طعام العائلة?</p> <p>1. Yes \ نعم      2. No \ لا</p>
<p><b>805. Who usually prepares food for the child</b> \ من يحضر الطعام للطفل عادةً</p> <p>1. Mother \ الأم      2. Father \ الأب      3. Grandparent \ الجد أو الجدة      4. Domestic helper \ الخادمة      5. Other \ أخرى: _____</p>
<p><b>806. Who prepares the formula for the child</b> \ من يحضر الخلطة للطفل</p> <p>1. Mother \ الأم      2. Father \ الأب      3. Grandparent \ الجد أو الجدة 4. The child \ الطفل      5. Domestic helper \ الخادمة      6. Other \ أخرى: _____</p>
<p><b>807. How long does it take to prepare the formula</b> \ كم من الوقت يستغرق تحضير الخلطة</p> <p>1. &lt;5min \ أقل من ٥ دقائق      2. 5-10min \ ٥ - ١٠ دقائق      3. 10-15min \ ١٠ - ١٥ دقيقة 4. 15-20min \ ١٥ - ٢٠ دقيقة      5. &gt;20min \ أكثر من ٢٠ دقيقة</p>
<p><b>808. How do you prepare the formula</b> \ كيف يتم تحضير الخلطة</p> <p>1. Prepare a batch for 2 days. \ تحضير كمية تكفي ليومين 2. Prepare batch for one day. \ تحضير كمية تكفي ليوم واحد 3. Prepare batch for half a day. \ تحضير كمية تكفي لنصف يوم 4. Prepare an amount just before drinking. \ تحضير كمية قبل تناولها بقليل 5. Other \ أخرى: _____</p>

<p><b>809. What are the ingredients of your child's formula \ ما هي مكونات خلطة طفلك ؟</b></p> <p>1. _____ml water      2. _____scoops Phenex 1      3. _____ scoops Polycose</p> <p>4. _____scoops Pro-Phree      5. Other \ أخرى:_____</p>
<p><b>810. Does your child drink all of his/her formula \ هل يشرب طفلك الخلطة كاملة ؟</b></p> <p>1. Always \ دائماً      2. Usually \ عادةً      3. Occasionally \ أحياناً      4. Never \ أبداً</p>
<p><b>811. How many times per day does the child drink the formula \ كم مرة باليوم يشرب الطفل الخلطة ؟</b></p>
<p><b>812. How much formula does the child drink each time \ ماهي كمية الخلطة الي يشربها الطفل في كل مرة ؟</b></p>
<p><b>813. Total amount of formula the child drinks per day \ مجموع كمية الخلطة التي يشربها الطفل باليوم :</b></p>
<p><b>814. Does your child have difficulty drinking the formula \ هل يعاني طفلك من صعوبة في شرب الخلطة ؟</b></p> <p>1. Yes \ نعم      2. No \ لا</p>
<p><b>815. If yes: Why \ إذا كان الجواب نعم، لماذا ؟</b></p> <p><input type="checkbox"/> Taste \ الطعم      <input type="checkbox"/> Smell \ الرائحة      <input type="checkbox"/> Consistency \ الكثافة      <input type="checkbox"/> Other</p> <p>أخرى:_____</p>

## 9. Diet history

901. Twenty four hour food recall \ ساعة الماضية \ طعام الطفل خلال ال ٢٤

Food item / Time of day نوع الغذاء/الوقت خلال اليوم	Quantity الكمية
First thing in the morning \ أول شيء \ صباحاً:	
Breakfast \ الإفطار:	
Morning snack \ وجبة خفيفة بالصباح:	
Lunch \ الغذاء:	
Afternoon snack \ وجبة خفيفة بالمساء:	
Dinner \ العشاء:	
Before bed time snack \ وجبة خفيفة قبل النوم:	

902. Do you cook with fat/oil \ هل تقومين باستخدام الزيت أو الدهن في طهي الطعام \

1. Yes \ نعم 2. No \ لا

If yes \ إذا كان الجواب نعم :

903. What type of fat do you use \ أي نوع من الدهون تستخدمون \

Vegetable oil \ زيت نباتي  Butter \ زبدة  Ghee \ سمن  Other \ أخرى: \_\_\_\_\_

## 10. Personal concerns

<p><b>1001. What are your main concerns for this child (PKU) \ ما شاغلك الأساسي \</b>  <b>بخصوص طفلك المصاب؟</b></p> <p>1. _____  2. _____  3. _____</p>																																			
<p><b>1002. Do you think caring for a child with PKU affects your health?</b>  <b>هل تعتقد أن الاهتمام بطفل مصاب بـ (بي كي يو) يؤثر على صحتك؟</b></p> <p>1. Yes \ نعم 2. No \ لا</p>																																			
<p><b>1003. Does it make you sad, depressed or stressed \ أو الكآبة، أو الضغط؟</b></p> <p>1. Yes \ نعم 2. No \ لا</p>																																			
<p><b>1004. Do you have a family member(s) available to help you when you need help? (Probe: with care for this child or other responsibilities around the house)</b>  <b>هل يوجد من يستطيع تقديم المساعدة لك من أفراد عائلتك عند حاجتك لذلك؟ (تحفيز: سواء المساعدة برعاية طفلك أو المسؤوليات المنزلية الأخرى)</b></p> <p>1. Yes \ نعم 2. No \ لا</p>																																			
<p><b>1005. Rate the degree to which your child's illness is understood by:</b>  <b>قيمي لي درجة فهم مرض طفلك من قبل:</b></p> <table border="1"> <thead> <tr> <th></th> <th></th> <th>Does not apply to me لا ينطبق علي</th> <th>Misunderstood غير مفهوم</th> <th>Understood مفهوم</th> <th>Completely understood مفهوم تماماً</th> </tr> </thead> <tbody> <tr> <td>1005.1</td> <td>Your spouse زوجك</td> <td>0</td> <td>1</td> <td>2</td> <td>3</td> </tr> <tr> <td>1005.2</td> <td>Your children أطفالك</td> <td>0</td> <td>1</td> <td>2</td> <td>3</td> </tr> <tr> <td>1005.3</td> <td>Other family members باقي أفراد العائلة</td> <td>0</td> <td>1</td> <td>2</td> <td>3</td> </tr> <tr> <td>1005.4</td> <td>Friends الأصدقاء</td> <td>0</td> <td>1</td> <td>2</td> <td>3</td> </tr> </tbody> </table>								Does not apply to me لا ينطبق علي	Misunderstood غير مفهوم	Understood مفهوم	Completely understood مفهوم تماماً	1005.1	Your spouse زوجك	0	1	2	3	1005.2	Your children أطفالك	0	1	2	3	1005.3	Other family members باقي أفراد العائلة	0	1	2	3	1005.4	Friends الأصدقاء	0	1	2	3
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1005.4	Friends الأصدقاء	0	1	2	3																														
<p><b>1006. Would you want a family member(s) to know more about your child's illness?</b>  <b>هل تودين أن يعرف أفراد عائلتك أكثر عن حالة طفلك؟</b></p> <p>1. Yes \ نعم 2. No \ لا</p>																																			

## 11. Getting help

<b>1101. Where are you currently getting your information about PKU from?</b> من أين تحصلين على معلوماتك عن (بي كي يو) حالياً؟	
1101.1	<input type="checkbox"/> Doctor \ الطبيب
1101.2	<input type="checkbox"/> Nurse \ الممرضة
1101.3	<input type="checkbox"/> Dietitian \ أخصائية التغذية
1101.4	<input type="checkbox"/> Another person with the same diagnosis \ شخص آخر يعاني من نفس المرض
1101.5	<input type="checkbox"/> Books \ كتب
1101.6	<input type="checkbox"/> Internet \ انترنت
1101.7	<input type="checkbox"/> Other \ أخرى: _____
<b>1102. Would you be interested in joining a family support group?</b> هل لديك الاهتمام بالانضمام الى مجموعة دعم العوائل؟ 1. Yes \ نعم 2. No \ لا	
<b>1103. List the topics you wish to learn more about:</b> حددي المواضيع التي ترغبين في معرفة المزيد عنها: 1. _____ 2. _____ 3. _____ 4. _____	

<b>1104. How would you prefer to obtain this information?</b> ما هي الطريقة التي ترغبين بها الحصول على تلك المعلومات؟				
1104	<b>Form of information provision</b> وسيلة تقديم المعلومات	<b>Yes</b> نعم	<b>No</b> لا	<b>Don't</b> لا أدري
1104.1	Formal group lectures محاضرات جماعية رسمية	1	2	3
1104.2	Informal sessions during clinic visits from a member of your health care team جلسات غير رسمية خلال زيارة العيادة من أحد أعضاء الفريق الطبي	1	2	3
1104.3	Cassettes to listen to at home الاستماع الى شريط تسجيل في المنزل	1	2	3

1104.4	Videotapes to view at home مشاهدة شريط فيديو في المنزل	1	2	3
1104.5	Written material (e.g. pamphlets) مواد مكتوبة (مثال: منشورات)	1	2	3
1104.6	A designated time period during which you could phone a health professional to answer specific questions الاتصال بأحد المختصين خلال وقت محدد للإجابة عن أسئلة محددة	1	2	3
1104.7	Other: أخرى			

**1105. Please list suggestions on how we could improve your health care:**

الرجاء سرد اقتراحاتكم لكيفية تطوير الخدمات الصحية المقدمة لكم:

1. \_\_\_\_\_
2. \_\_\_\_\_
3. \_\_\_\_\_

**1106. Do you have any questions?**

هل لديك أية أسئلة؟

**1107. May I contact you within the next couple of weeks to ask you few questions?**

هل يمكنني أن اتصل عليك خلال الأسبوعين القادمين لأسألك بعض الأسئلة؟

1. Yes \ نعم، لا مانع نعم، 2. No \ لا

**Thank you very much for you time...**

أشكرك كثيراً على وقتك

## Appendix 8: Sibling Questionnaire (Phase 2)

Date:

## 2. Socio-economic Status

213. Birth order of affected child \ ترتيب الطفل المصاب حسب الولادة  
0 1 2 3 4 5 6 7 8 9 ≥10

## 3. Health related questions

301. What was your child's age at diagnosis \ كم كان عمر طفلك عند التشخيص؟

1. \_\_\_\_ days \ أيام 2. \_\_\_\_ weeks \ أسابيع 3. \_\_\_\_ months \ أشهر 4. \_\_\_\_  
years \ سنوات

303. How often do you visit a health care facility with your child?

كم عدد المرات التي تزورين فيها مركز طبي آخر مع طفلك؟

1. Once a month \ مرة بالشهر  
2. Every 3months \ كل ثلاثة أشهر  
3. Every 6months \ كل ستة أشهر  
4. Never (only go to KFSH) \ مطلقاً لا أذهب لغير مستشفى الملك فيصل التخصصي  
5. Other \ أخرى: \_\_\_\_\_

307. How would you describe your child's health in general \ كيف تصفين صحة طفلك  
عموماً؟

1. Excellent \ ممتازة 2. Good \ جيدة 3. Fair \ وسط 4. Poor \ سيئة

308.1 Is there any other problem your child suffers from \ هل يعاني طفلك من مشاكل  
أخرى؟

1. Yes \ نعم 2. No \ لا

308.2 If yes, specify \ إذا كانت الإجابة نعم، حددي:

309.1 Has your child been ill in the past 2 weeks \ هل مرض طفلك خلال الإِسبوعين \  
الماضيين؟

1. Yes \ نعم 2. No \ لا

309.2 If yes- What was the illness \ إذا كانت الإجابة نعم، مم كان يعاني؟

Cold \ زكام  Fever \ حرارة  Cough \ كحة  Diarrhea \ إسهال  Vomiting \ تقيؤ  
 Other \ أخرى: \_\_\_\_\_

#### 4. Development related questions

<p><b>401. Does your child go to school \ هل يذهب طفلك للمدرسة \</b> 1. Yes \ نعم 2. No \ لا</p>
<p><b>If no, go to section 8 \ إذا كان الجواب لا، اذهبي لفقرة 8</b></p>
<p><b>If yes \ إذا كان الجواب نعم:</b></p> <p><b>402. Which year of school \ بأي سنة دراسية طفلك \</b>  Nursery \ حضانة KG1 \ روضة KG2 \ تمهيدي 1 2 3 4 5 6 7 8 9  10 11 12</p>
<p><b>403. What is the school \ ما هي المدرسة \</b> _____</p> <p>1. Public school (regular) \ مدارس حكومية  2. Public school with special education classes \ مدارس حكومية بها تعليم خاص  3. Private school (regular) \ مدارس أهلية  4. Private school with special education classes \ مدارس أهلية بها تعليم خاص  5. Special education school \ مدارس تأهيل أو تعليم خاص  6. Other \ أخرى: _____</p>
<p><b>404. Do you think your child needs special education \ هل تعتقد أن طفلك بحاجة \</b> لتعليم خاص  1. Yes \ نعم 2. No \ لا</p>
<p><b>405. Does the child receive any special education at the school \ هل يتلقى طفلك أي \</b> تعليم خاص في مدرسته  1. Yes \ نعم 2. No \ لا</p>
<p><b>If no \ إذا كان الجواب لا:</b></p> <p><b>406. Why not \ لم لا يتلقى تعليم خاص \</b></p>

#### 8. Dietary habits

<p><b>809. What are the ingredients of your child's formula \ ما هي مكونات خلطة طفلك \</b></p> <p>1. _____ml water 2. _____scoops Phenex 1 3. _____ scoops Polycose  4. _____scoops Pro-Phree 5. Other \ أخرى: _____</p>
<p><b>810. Does your child drink all of his/her formula \ هل يشرب طفلك الخلطة كاملة \</b></p> <p>1. Always \ دائماً 2. Usually \ عادةً 3. Occasionally \ أحياناً 4. Never \ أبداً</p>
<p><b>811. How many times per day does your child drink the formula \ كم مرة باليوم \</b> يشرب الطفل الخلطة</p>
<p><b>812. How much formula does your child drink each time \ ماهي كمية الخلطة الي \</b> يشربها الطفل في كل مرة</p>
<p><b>813. Total amount of formula the child drinks per day \ مجموع كمية الخلطة التي \</b> يشربها الطفل باليوم</p>

814. Does your child have difficulty drinking the formula | هل يعاني طفلك من صعوبة في شرب الخلطة؟

1. Yes | نعم 2. No | لا

815. If yes: Why | إذا كان الجواب نعم، لماذا؟

Taste | الطعم  Smell | الرائحة  Consistency | الكثافة  Other | أخرى: \_\_\_\_\_

## 9. Diet history

901. Twenty four hour food recall | طعام الطفل خلال الـ ٢٤ ساعة الماضية

Food item / Time of day نوع الغذاء/الوقت خلال اليوم	Quantity الكمية
First thing in the morning   أول شيء صباحاً:	
Breakfast   الإفطار:	
Morning snack   وجبة خفيفة بالصباح:	
Lunch   الغذاء:	
Afternoon snack   وجبة خفيفة بالمساء:	
Dinner   العشاء:	
Before bed time snack   وجبة خفيفة قبل النوم:	

## Appendix 9: Second 24hr food recall (Phase 2)

Date:

طعام الطفل خلال الـ ٢٤ ساعة الماضية | Twenty four hour food recall

Food item / Time of day نوع الغذاء/الوقت خلال اليوم	Quantity الكمية
<b>First thing in the morning</b>   أول شيء صباحاً	
<b>Breakfast</b>   الإفطار:	
<b>Morning snack</b>   وجبة خفيفة بالصباح	
<b>Lunch</b>   الغذاء:	
<b>Afternoon snack</b>   وجبة خفيفة بالمساء	
<b>Dinner</b>   العشاء:	
<b>Before bed time snack</b>   وجبة خفيفة قبل النوم	

## Appendix 10: Child Questionnaire (Phase 2)

## C. Child Questionnaire

## استبانة الاطفال

Date:

General questions أسئلة عامة	Yes نعم	No لا
C1. Do you go out shopping with your family? هل تذهب للتسوق مع الأهل؟	1	2
C2. Do you go out with your family to visit others? هل تذهب مع الأهل لزيارة الآخرين؟	1	2
C3. Do you choose your food? هل تقوم باختيار طعامك؟	1	2
C4. What do you like to eat? ماذا تحب أن تأكل؟ 1. 2. 3. 4.		
C5. When you are playing with other children do you feel you are different from them? عندما تلعب مع الأطفال الآخرين هل تحس أنك مختلفا عنهم؟	1	2
C6. Is it difficult that you have to eat differently from others? هل تجد صعوبة في ضرورة أكلطعام مختلف عن الآخرين؟	1	2
C7. What do you think is the importance of drinking your formula? في اعتقادك ما مدى أهمية تناول خلطة الحليب؟ 1. Very important \ مهم للغاية 2. Somewhat important \ مهم بعض الشيء 3. Not important \ غير مهم		
C8. What do you think is the importance of eating your specific diet? في اعتقادك ما مدى أهمية الالتزام بالحمية الغذائية المخصصة لك؟ 1. Very important \ مهم للغاية 2. Somewhat important \ مهم بعض الشيء 3. Not important \ غير مهم		
C9. It is okay to drink only some of your formula? (لا مانع) أن تتناول فقط جزءا من خلطة الحليب المخصصة لك؟ هل مسموح	١	٢

**C10. Knowledge questions:**

أسئلة المعلومات

I'll list some food items and you tell me if the food is a free food (you can eat as much as you like from it), if it is a low protein food (you can eat measured amounts from it), or if it is a forbidden food:

سأقوم بسرد بعض أنواع الأطعمة وأريدك أن تحدد أيا منها يعتبر طعاما مسموحا (أي تستطيع أن تأكل منه كما تشاء)، أو طعاما يحتوي على نسبة قليلة من البروتين (تستطيع أن تأكل منه كمية محدودة)، أو طعاما ممنوعا (لا تأكل منه أبدا):

	<b>Food item</b> الأطعمة	<b>Free food</b> طعام مسموح	<b>Low protein</b> طعام قليل البروتين	<b>Forbidden food</b> طعام ممنوع	<b>Don't know</b> لا أعلم
C10.1	Apples التفاح	1	2	3	4
C10.2	Carrots الجزر	1	2	3	4
C10.3	Chick peas الحمص	1	2	3	4
C10.4	Cheese الجبن	1	2	3	4
C10.5	Chicken الدجاج	1	2	3	4
C10.6	Chocolate الشكولاته	1	2	3	4
C10.7	Dates التمر	1	2	3	٤
C10.8	Diet Pepsi دايت بيبيسي	1	2	3	4
C10.9	Lollypops حلوى سكر (مصاصة)	1	2	3	4
C10.10	Seven-up سفن اب	1	2	٣	٤
C10.11	French fries البطاطس المقلىة	1	2	3	4

**Appendix 11: The items adapted for the Arabic Vineland-II, the adaptations and adjustments, and the reasons for the adaptations**

Page No.	Item No.	Item in English Vineland-II	Adaptation	Reason
5	7	Points to at least three major body parts when asked (for example, nose, mouth, hands, feet, etc.).	Replaced the word “hands” with “head”	Cultural: a more common example is to ask children about their heads
	11	Points to at least three five minor body parts when asked (for example, fingers, elbows, teeth, toes, etc.).	Replaced the word “toes” with “thumb”	Language: translation of toes is “feet fingers”, and fingers were included already
	12	Follows instructions with two actions or an action and two objects (for example, “Bring me the crayons and paper”. “Sit down and eat your lunch”; etc.).	Replaced the word “crayons” with “pens”	Language: no clear translation for crayons, pens in Arabic imply pens, pencils and colouring pens or crayons
	18	Understands sayings that are not meant to be taken word for word (for example, “Button your lip”; “Hit the road”; etc.).	Added explanation for sayings; “button your lip” meaning shut your mouth	Language
6	12	Names at least three objects (for example, bottle, dog, favourite toy, etc.).	Replaced “Dog” with “Cat”	Cultural: cats are more common as pets
	17	States own first name or nickname (for example Latisha, Little Sister, etc.) when asked.	Replaced “little sister” with a more common nick name	Cultural
	18	Uses phrases with a noun and a verb (for example, “Katie Stay”; “Go home”; etc.).	Replaced “go home” example with a more common one	Language: used clearer example in Arabic
	22	Asks questions beginning with what or where (for example, “What’s that”; “Where doggie go?; etc.).	Replaced “doggie” with “father”	Cultural

Appendix 11: The items adapted for the Arabic Vineland-II, the adaptations and adjustments, and the reasons for the adaptations

Page No.	Item No.	Item in English Vineland-II	Adaptation	Reason
7	36	Uses regular past tense verbs (for example, walked, baked, etc.); may use irregular past tense verbs ungrammatically (for example, "I runned away"; etc.).	Only one type of past tense available in Arabic	Language
	38	Pronounces words clearly without sound substitutions (for example, does not say "wabbit" for "rabbit", "Thally" for "Sally," etc.).	Replaced examples using the word "chair". Chair in Arabic is pronounced as "kursi" the substitution could be "tursi"	Language: this example can illustrate the point of letter substitution better in Arabic
8	50	Uses irregular plurals correctly (for example, children, geese, mice, women, etc.).	Replaced examples with common ones relevant to plural type in Arabic	Language
	52	Describes a short-term goal and what he or she needs to do to reach it (for example, says, "I want to get an A on my test, so I'm going to study hard"; etc.).	Replaced "A" with "high grades"	Cultural: different grading system
	54	Describes a realistic long-range goal that can be done in 6 months or more (for example, says, "I want to buy a bike, so I'll babysit and run errands to earn enough money to buy it"; etc.).	Replaced "babysit and run errands" with "work"	Cultural: babysitting is not common. The word "work" in Arabic implies any uptake of work in general
9	4	Points or writes using correct orientation (for example, in English from left to right; in some languages from right to left or top to bottom).	Mentioned Arabic language writing direction as example	Language
	6	Identifies all printed letters of the alphabet, upper-and lowercase.	Replaced "upper- and lower case" with "different forms"	Language: Arabic does not have upper or lower cases but letters change forms according to their place in words
	7	Prints at least three simple words from example (for example, cat, see, bee, etc.).	Replaced examples with more commonly used ones in Arabic	Language
	10	Prints at least 10 simple words from memory (for example, hat, ball, the, etc.).	Replaced examples with more common ones	Language
10	19	Wipes or blows nose using tissues or handkerchief.	Replaced "handkerchief" with etc.	Language: tissue and handkerchief are translated to the same word in Arabic

Appendix 11: The items adapted for the Arabic Vineland-II, the adaptations and adjustments, and the reasons for the adaptations

Page No.	Item No.	Item in English Vineland-II	Adaptation	Reason
11	25	Brushes teeth.	Added “with toothbrush”	Language
	32	Bathes or showers and dries self.	Used one word for “Bathes or showers”	Language
12	8	Helps prepare foods that require mixing and cooking (for example, cake or cookie mixes, macaroni and cheese, etc.).	Replaced “macaroni and cheese” with “macaroni and tomato sauce”	Cultural: this is a more common dish
	9	Uses simple appliances (for example, a toaster, can opener, bottle opener, etc.).	Deleted the example “Bottle opener”	Language: the previous example of can opener translates the same as bottle opener
	10	Uses microwave oven for heating, baking, or cooking (that is, sets time and power setting, etc.). You may mark “N/O” for No Opportunity if there is no microwave in the home.	Deleted “baking”	Language: in Arabic cooking also implies baking
	12	Use tools (for example, a hammer to drive nails, a screwdriver to screw and unscrew screws, etc.).	Replaced “screw, unscrew” with one word	Language
13	4	Counts at least 10 objects, one by one.	Deleted the phrase “one by one”	Language
	12	Identifies penny, nickel, dime, and quarter by name when asked; does not need to know the value of coins.	Changed wording to be “Recognizes metal coin categories and refers to its names when asked, does not need to know value of coin”	Cultural: coins do not have the US names. Kept it generic, different areas may have different names for coins.
	18	States value of penny (1 cent), nickel (5 cents), dime (10 cents), and quarter (25 cent)	Changed wording to be “defines value of coin when asked (for example: half a Riyal = 50 halala)” Riyal is the Saudi currency.	Cultural
14	26	Carries or stores money safely (for example, in wallet, purse, money belt, etc.).	Deleted the word “purse”	Language
	28	Obeys curfew parent or caregiver sets.	Changed to “obeys orders of parent or caretaker on returning home on the specified time”	Language
	41	Manages own money (for example, pays most or all own expenses, uses checks or money orders for purchases as needed, etc.).	Deleted “money orders”	Cultural: rarely used

Appendix 11: The items adapted for the Arabic Vineland-II, the adaptations and adjustments, and the reasons for the adaptations

Page No.	Item No.	Item in English Vineland-II	Adaptation	Reason
16	22	Uses words to express happiness or concern for others (for example, says, "Yeah! You won"; "Are you all right/"; etc.).	Replaced "yeah!" with "great"	Language
	24	Recognizes the likes and dislikes of others (for example, says, "Chow likes soccer"; "Susie doesn't eat pizza"; etc.).	Replaced names to "my brother" and "my sister"	Language
	30	Chooses not to say embarrassing or mean things or ask rude questions in public.	Added "inappropriate"	Language
	31	Places reasonable demands on friendship (for example, does not expect to be a person's only friend or to have the friend always available, etc.).	Rephrased to be "understands reasonable friendship parameters"	Language
	37	Goes on group dates.	Replaced "dates" with "gatherings or meetings"	Cultural: No dating in Saudi, but meetings with friends without parents is acceptable
	38	Goes on single dates.	Replaced "dates" with "gatherings or meetings"	Cultural
17	16	Plays informal, outdoor group games (for example, tag, jump rope, catch, etc.).	Deleted "informal"	Language: "informal" is implied within the Arabic sentence
	18	Follows rules in simple games (relay races, spelling bees, electronic games, etc.).	Replaced examples of games with more common ones in the area	Cultural
	20	Plays simple card or board game based only on chance (for example, Go Fish, Crazy Eights, Sorry™, etc.).	Replaced examples of games with more common ones in the area	Cultural
18	24	Plays simple games that require keeping score (for example, kickball, pickup basketball, etc.).	Replaced examples of games with more common ones	Cultural
	26	Plays more than one board, card, or electronic game requiring skill and decision making (for example, Monopoly™, Cribbage, etc.).	Deleted "cribbage"	Cultural: cribbage is not played in the region
	27	Goes places with friends in evening with adult supervision (for example, to a concert, lecture, sporting event, movie, etc.).	Deleted "concert" and "movie" and used more common examples	Cultural: no opportunity to go to concerts or movies

Appendix 11: The items adapted for the Arabic Vineland-II, the adaptations and adjustments, and the reasons for the adaptations

Page No.	Item No.	Item in English Vineland-II	Adaptation	Reason
18	28	Follows rules in complex games or sports (for example, football, soccer, volleyball, etc.).	Deleted "football" (American football)	Cultural: not played
	30	Plans fun activities with more than two things to be arranged (for example, a trip to a beach or park that requires planning transportation, food, recreational items, etc.)	Replaced example	Cultural
	31	Goes places with friends in evening without adult supervision (for example, to a concert, lecture, sporting event, movie, etc.).	Deleted "concert" and "movie" and used more common examples	Cultural
19	12	Changes voice level depending on location or situation (for example, in a library, during a movie or play, etc.).	Replaced example with "in library or when close to someone sleeping"	Cultural
	29	Is aware of potential danger and uses caution when encountering risky social situations (for example, binge during parties, Internet chat rooms, personal ads, etc.).	Replaced example "binge drinking parties" with "late night parties"	Cultural
20	13	Climbs on and off low objects (for example, chair, step stool, slide, etc.).	Replaced "step stool" with "step"	Language
	27	Catches on beach ball-sized ball with both hands from a distance of 2 or 3 feet.	Explained "beach ball" as an air filled ball with a size of 45 cm	Clarification
21	4	Squeezes squeaky toy or object.	Added explanation for "squeaky"	Language
22	32	Unlocks dead-bolt, key, or combination locks that require twisting.	Deleted "dead-bolt"	Language