Parenting a child with Phenylketonuria (PKU): An exploration of the psychological impact on parents and parenting experience

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THESIS ABSTRACT

This thesis forms part of the examination for the degree of Doctor of Clinical Psychology (ClinPsyD) in the Faculty of Biology, Medicine and Health at The University of Manchester. The thesis has been written by Katie Carpenter and submitted in July 2016 for examination in September 2016.

This thesis focused on the psychological impact and parental experience of caring for a child with an inherited metabolic disorder. Due to treatment advances and early identification, many children diagnosed with inherited metabolic disorders have a favourable prognosis as treatment can prevent many of the most severe consequences. This outcome, however, requires significant input from parents to prevent associated neurological and physical impairment by adhering to strict management regimes. Research has indicated that this is likely to have a psychological impact on parents, but little is known about the further impact on parenting.

Paper 1 provides a comprehensive literature review on the available evidence regarding the psychological impact on parents of caring for a child with an inherited metabolic disorder. Findings indicated that the diagnosis had a lasting psychological impact on parents, although in most cases this is not clinically significant. Ongoing psychological impact varied by the mode of diagnosis, severity of the disorder and perceived care burden. Included studies reported that parents who reported a more significant psychological impact were more likely to show greater levels of concern about their child's disorder and use less adaptive parenting strategies. Implications for health care professionals working with parents are discussed.

Paper 2 provides an interpretative phenomenological analysis of the experience of parents caring for a child with a specific inherited metabolic disorder, phenylketonuria (PKU). Seven parents of children with PKU were interviewed about their experiences of parenting their child. Three main themes emerged: *control, striving for normality and acceptance as a continuum.* Links between the themes were explored to outline a process that parents move through and key implications for clinical practice are identified.

Paper 3 provides a critical reflection of the research process and examines the strengths and limitations of both papers.

DECLARATION

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

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I would like to thank my wonderful partner, my family and my cohort who have provided endless emotional support (and food) throughout this whole process. I would not have made it through without you!

Paper 1

Parenting a child with an inherited metabolic disorder (IMD): A systematic review of the psychological impact on parents

The following paper has been prepared for submission to the *Journal of Child and Family Studies*. The guidelines for authors can be found in Appendix 1. Formatting changes have been made to the current paper to aid readability in this thesis: tables and figures have been inserted within the text, research questions are numbered to add clarity and the discussion section includes subheadings.

Word count: 12,996

Main text: 5, 546 (excluding abstract, tables, figures and references)

ABSTRACT

Parents of children with IMDs have full responsibility for the management of their child's disorder, which can have varying levels of demand. Due to high care demands, responsibility for management and risks involved, it is likely that there is a significant psychological impact on parents caring for a child with an IMD and subsequent changes to their parenting. This study systematically reviewed the research regarding the psychological impact on parents of caring for child with an IMD and reported on the impact this had on their parenting. Clinical implications for healthcare professionals working with parents identified in the literature were reported. A comprehensive search of electronic databases and relevant reference lists was conducted for relevant articles. Studies were included if they reported quantitative measures of psychological impact. Twenty studies met inclusion criteria. Studies were of varying methodological quality and used different measures to assess psychological impact. Findings with regards to psychological impact did not show consistent differences between different IMDs, but varied by mode of diagnosis, child functioning and perceived or actual care burden. High levels of reported stress were associated with greater concern about the disorder and less effective parenting. Studies identified that health care professionals would benefit from improved knowledge and understanding of IMDs and for a greater consideration of the psychosocial impact of caring for a child with an IMD when working with parents. Future research should investigate specific factors that influence psychological impact.

Key words: inherited metabolic disorders, psychological impact, parenting

INTRODUCTION

Inherited metabolic disorders (IMDs) are a set of genetic disorders which involve deficiencies or altered functioning of enzymes in singular metabolic pathways. IMDs are individually rare, but collectively common, with reported incidence rates of 1 in 2500–5000 live births (Martins 1999; Sanderson et al 2006; Seymour, Thomason and Chalmers 1997).

Many IMDs are screened for at birth, as early detection and treatment in the form of restricted diets, drug interventions and enzyme replacement therapy can prevent or reduce the likelihood of toxic accumulations in the brain and body that causes mortality and disability (van Karnebeek and Stockler 2012).

At diagnosis, parents are responsible for the medical management of the IMD. Alongside facing the news of the diagnosis itself, associated risks and prognosis, parents must immediately respond to the increased demands of caring for their child's health needs. Management is life long and can place significant stressors on the family and parents, such as changes to life and routines, significantly increased, complex and time consuming care demands to reduce the risk of metabolic decompensation or neurological damage. These are likely to have an emotional impact on parents as their child's health and development depends on them proving adequate care.

Psychological impact is defined as the effect caused by environmental or biological factors on an individual's psychological health (de Oliveira et al 2013). Examples of psychological impact have been found in research with parents of children with other chronic conditions. Increased levels of stress, anxiety and depression have been found in parents caring for children with autism (Stewart et al 2016), cystic fibrosis (Besier et al 2011; Quitner et al 2014) and diabetes (Streisand et al 2008)

compared to rates observed in the general population suggesting that parents of children with a chronic condition are at risk of reduced psychological wellbeing.

Parents of children with diabetes have reported considerable stress due to the need for constant vigilance, symptom monitoring and strict dietary enforcement to prevent metabolic crises (Sullivan-Bolyai et al 2003). Increased responsibility for treatment management, high care demands and poor adjustment are associated with higher levels of parental stress (Cousino and Hazen 2013). Parents of children with IMDs have reported high levels of burden associated with caring for their child (Gramer et al 2014) suggesting that they might be at risk of experiencing higher levels of stress.

Psychological wellbeing is important in parental adjustment to chronic illness (Vermaes et al 2005). There are well established links between parental distress, parent functioning and development and health outcomes for children; reviews found associations between maternal depression and attachment relationships, behavioural and cognitive outcomes for children (Bernard-Bonnin 2004). Parents with high levels of distress coped less well with demands of parenting, used more maladaptive parenting strategies and instigated fewer routines (Davis et al 2015). Higher rates of anxiety and depression in parents have been linked to poorer treatment adherence in children with cystic fibrosis (Barker and Quittner 2016) and metabolic control in children with diabetes (Eckshtain et al 2010) as well as poorer adjustment outcomes in children with regards to their personal management of the disorder (Cameron, Young and Wiebe 2007). This suggests that the effect of parental psychological adjustment has further reaching impacts on the parenting styles and consequently the child.

This review aimed to provide a comprehensive understanding of the psychological impact on parents of caring for a child with an IMD with reference to anxiety, depression and stress. This will allow for the identification and support of parents to ensure optimum outcomes for themselves and their children. Although many studies in

this area have reported on the impact on families/family functioning, this review focused specifically on the impact on parents. Thus additional aims were to investigate the impact of psychological factors on parenting practices and to identify the recommendations and implication for clinical psychologists and other health care professionals working with these parents. The research questions for this review are:

1) What is the psychological impact of caring for a child with an IMD?
2) What impact do identified psychological factors have on parenting practices?
3) What are the implications for clinical psychologists and other health care professionals working with parents of children with IMDs?

METHODS

Search strategy

An initial scoping exercise was conducted to review the literature and refine the search strategy. Table 1 outlines the search terms used in the systematic search according to PICO (NICE 2012). Search terms for 'population' included all terms associated with parents or care givers. Terms for family were included to ensure that no studies that reported on parents along with families were missed. Search terms for 'intervention' included all variations of 'inherited metabolic disorders' and categories of treatable IMDs with specific disorders identified through newborn screening. Terms for 'outcome' were based on the current literature of other childhood disorders and terms used in similar systematic reviews (Whittemore et al 2012; Zeltner et al 2015).

Inclusion criteria were a) research published on parents (or families/children and parents) of children with IMDs b) published in a peer reviewed journal between 1980 and 2016 c) include at least one quantitative measure of psychological impact for parents. Studies were excluded if they a) did not measure psychological impact on parents b) parent and family outcomes were indistinguishable c) the study was not available in English or d) were conference abstracts or unpublished theses/dissertations.

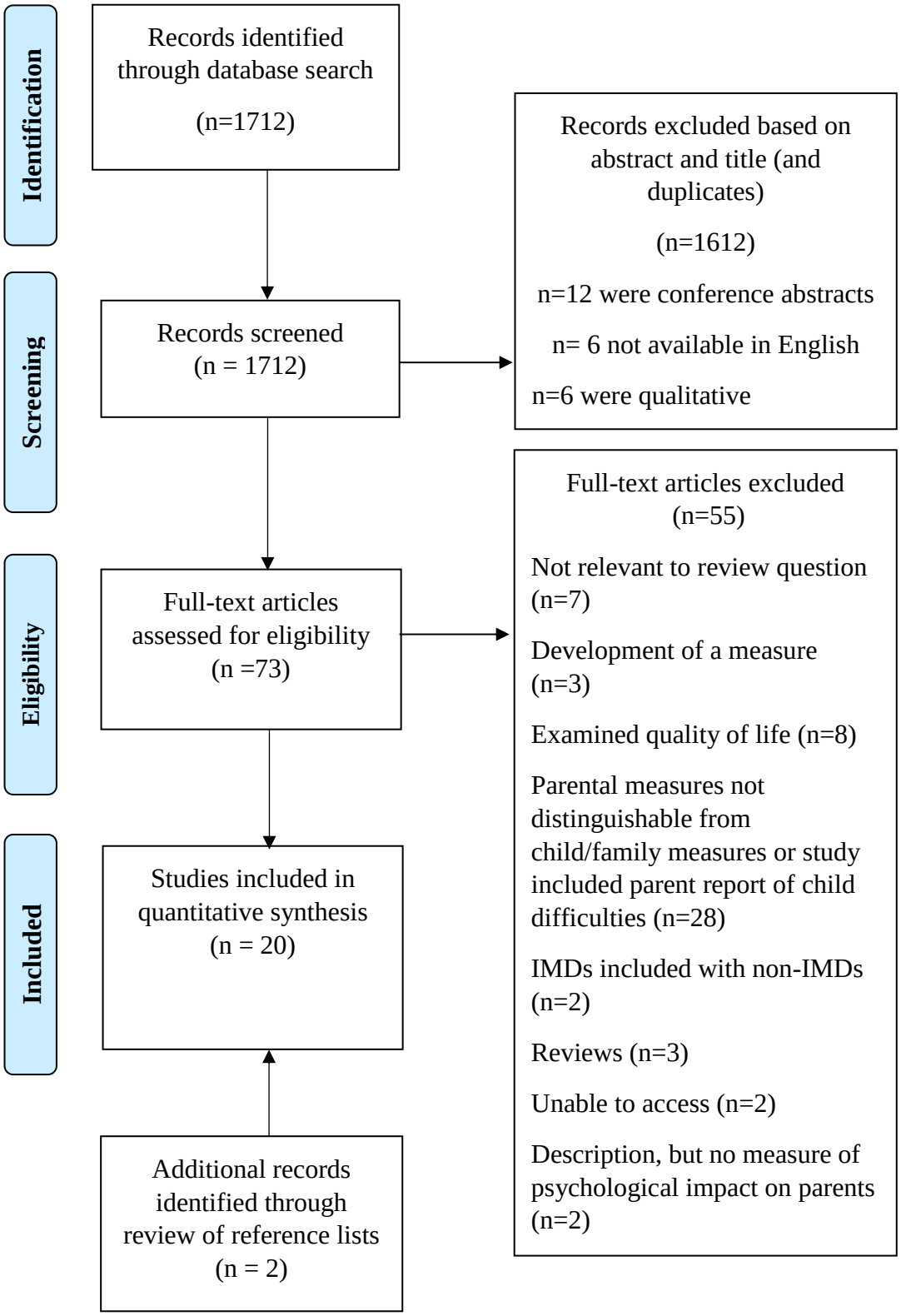
The following databases were searched using the search terms (entered as 'P AND I AND O') in Table 1: CINAHL, Medline, PsycINFO, AMED and Embase. Searches were limited to publications after 1980 (allowing for international implementation of newborn screening)

Table 1: PICO search strategy

	Search terms used
P (Population)	Parent$ or father$ or mother$ or caregiv$ or famil$
I (Intervention)	(Phenylketonuria or (maple and syrup and urine and disease) or (isovaleric and acidemia) or (isovaleric and acidemia) or (isovaleric and aciduria) or (acyl-CoA and dehydrogenase) or (very and long and acyl-CoA and dehydrogenase and deficien$$) or (medium and chain and acyl-CoA and dehydrogenase and deficien$$) or (glutaric and aciduria) or homocystinuria or (inherited and metabolic and disorder) or (inborn and error$ and metabolism) or (intoxication-type and inborn and errors and metabolism) or (urea and cycle) or (organic and aciduria) or (organic and acidemia) or (Inborn and errors and amino and acid and metabolism) or (fatty and oxidisation) or (amino and acid and metabolism))
C (Comparison)	-
O (Outcome)	(wellbeing or (well and being) or well-being or adjustment or adaptation or adaption or adaptive or psycholog* or psychosocial or psychiatr* or social or emotional or (mental and health) or (mental and disorder) or stress or depression or depressive or anxiety or coping)

Figure 1 presents an outline of the search process based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al 2009). Titles and abstracts of all papers returned in the search were screened for inclusion by the first author. Relevant abstracts were selected for full text review (n=73). Full text articles were assessed for eligibility and excluded if they did not meet the inclusion criteria. This was not corroborated by an independent researcher. Fifty-five papers were excluded (see Figure 1). The main reason for exclusion was indistinguishability of parental report from family/child (n=28). Reference lists of included papers were examined, yielding two additional paper; thus, total of twenty studies were included. Data were extracted and entered into a database by the first author. This was not verified by an independent researcher.

Figure 1: Flowchart demonstrating PRISMA search strategy



Quality assessment

Due to the diverse designs of included studies, the Quality Assessment Tool for Studies with Diverse Designs (QATSDD) was selected (Sirriyeh et al 2012). This tool allows for the assessment of a body of research that addresses similar research questions using different methodological approaches and has shown good reliability and validity (Sirriyeh et al 2012).

All fourteen items of the QATSDD were rated by the first author on a four-point-scale ranging from 'not at all' (0) to 'complete' (3) to provide a total score (maximum score=42). Four studies (20%) were independently rated by another researcher to establish inter-rater reliability (k= 0.70).

RESULTS

Characteristics of studies

Twenty studies were included which are summarised in Table 2. Fourteen studies were cross-sectional studies examining measures of psychological impact in parents of children with IMDs compared to parents children without IMDs (n=5), parents of children with other disorders (n=3) or no control group (n=6). One study was a prospective cohort study (Waisbren et al 2003), examining parental and child health outcomes in two clinical groups (IMDs diagnosed by newborn screening compared to clinically identified), one study was correlational (Waisbren et al 2004), one study was a retrospective cohort study examining parental trauma at two time points (Read 2004), one study was both correlational and cross sectional (Brown, Crowe and Boneh 2015), one study was an observational situational analysis (Ievers-Landis et al 2005) and one used an experimental design (Fehrenbach and Peterson 1989). Sample sizes of parents

varied greatly (range 11-263) across a range of IMDs, although PKU was the most represented in the studies (n=12 specifically examined PKU[1]). In seven studies, measuring the psychological impact was not the primary aim of the study. The majority of studies were from the USA (n=12), although other countries were represented (see Table 1).

[1] A glossary has been provided in Appendix 4 outlining clinical features, management and prognosis of all inherited metabolic disorders referenced.

Table 2: Methodological details of included studies

No.	Study	Country	Design	Inherited Metabolic Disorders (IMDs) examined	No of parents (n)	Parent and child characteristics	Quality Score (out of 42)
1	Kazak, Reber & Snitzer (1988)	USA	Cross sectional	Phenylketonuria (PKU)	45	Parents of children with PKU (n=45). Mean age of mothers 28.8 years, mean age of fathers 32.7 years, number of years in education; mothers 12.9, fathers 31.1. Mean age of children 3.1 years.	30 (71%)
2	Fehrenbach & Peterson (1989)	USA	Experimental	Phenylketonuria	30	Mothers (90%) and fathers (10%) split into good (n=19) and poor (n=11) treatment compliance groups. Mean age of parents 32.29. No mean age of children reported (range 6m- 16 years).	26 (62%)
3	Vetrone et al (1989)	Italy	Cross sectional	Phenylketonuria	20	10 married couples who had a child with PKU. No mean ages or other characteristics reported.	10 (24%)
4	Hendrikx et al (1994)	Netherlands	Cross sectional	Phenylketonuria	22	No parent characteristics reported. Age range of children 9-13 years, mean IQ 92.09 (normal range).	16 (38%)
5	Cederbaum et al (2001)	USA	Cross sectional	Urea Cycle disorders (UCDs)	118	Mothers (76%) and fathers (24%). Mean age of parents 226 years. Mean age of child at diagnosis 24.8 months.	28 (66%)
6	Read (2003)	USA	Cross sectional	Phenylketonuria	78	Parents of children with PKU (n=29), parents of children with mitochondrial disease (n=29).	28 (66%)

No.	Study	Country	Design	Inherited Metabolic Disorders (IMDs) examined	No of parents (n)	Parent and child characteristics	Quality Score (out of 42)
						Mean age of mothers, 38 years. 76% married, Mean age of children 8.8 years	
7	Waisbren et al. (2003)	USA	Prospective cohort study	MCADD, SCADD, VLCADD, LCHADD, Fatty acid oxidisation disorder, propionic acidemia, methylmalonic acidemia, argininosuccinic acidemia, 3MCC deficiency, citrullinemia, isovaleric acidemia, Methyl/butyl CoA dehydrogenase deficiency, glutaric acidemia type I and II, tyrosinemia I, arginase deficiency, cobal C deficiency, cartinine palmitoyltransferase II deficiency	83	Parents of children with IMDs identified by newborn screening (NBS) (n=50) or clinically identified (n=33). NBS group: 74% of parents married, mean age of child at diagnosis 5 days, mean age of child 9 months, 'low social position' 28%, ethnicity 78% white. N=1 child performed in intellectual disability range. Clinically identified group: 85% of parents married, mean age of child at diagnosis 4 months, mean age of child 34 months, 'low social position' 42%, ethnicity 88% white. N=8 children performed in intellectual disability range.	29 (69%)
8	Jusiene & Kucinskas (2004)	Lithuania	Cross sectional	Phenylketonuria	37	No parent characteristics reported. Children aged between 4-14 years, mean age 9 years.	15 (36%)
9	Read (2004)	USA	Retrospective cohort study	Phenylketonuria	83	Mothers (94%), and fathers (6%). Mean age of parents 38 years. Time	32 (76%)

No.	Study	Country	Design	Inherited Metabolic Disorders (IMDs) examined	No of parents (n)	Parent and child characteristics	Quality Score (out of 42)
						since diagnosis/finding out they are a gene carrier (1-46 years). Mean age of children not reported.	
10	Waisbren, et al (2004)	USA	Correlational	Phenylketonuria, Galactosemia, argininosuccinic acidemia, glutaric acidemia types I & II, MCADD, Maple Syrup Urine Disease	263	Parents of children with IMDs identified by NBS (n=139) or clinically identified (n= 124). 89% mothers, 10% fathers, 1% other caregiver. Ethnicity: white (91%), Hispanic (6%) African American (2%). Marital status: 75% married. Mean age of children 8.5 years. Mean age of child at diagnosis: 2 months (NBS group) 9.5 months (clinically identified group)	29 (69%)
11	Boles et al (2005)		Cross sectional	IMDS (categorised into mildly/severely affected) Severely affected: Methylmalonic acidemia, propionic acidemia, Maple Syrup Urine Disease, glutaric acidemia type I, 3-hydroxy-3-methyl glutaryl co-enzyme A Lyase deficiency and glucose transporter deficiency	17	No parent or child characteristics reported.	18 (43%)

No.	Study	Country	Design	Inherited Metabolic Disorders (IMDs) examined	No of parents (n)	Parent and child characteristics	Quality Score (out of 42)
				Mildly affected: Phenylketonuria , VLCADD, galactosemia, methylmalonic acidemia, isovaleric acidemia, tyrosinemia type I-			
12	Ievers-Landis et al (2005)	USA	Observational (situational analysis)	Phenylketonuria	19	Mothers (95%) and fathers (5%). No other parent characteristics reported. Mean age of child 9.9 years.	33 (79%)
13	Lord, Wastell & Ungerer (2005)	Australia	Cross sectional	Phenylketonuria	126	Mothers (51.6%) and fathers (48.4%). Mean age mothers 34.03 years, mean age of fathers 37.62 years. 52% of mother and 58% of fathers had completed at least one year of tertiary education. 49% of mothers and 95% of fathers were employed, 26% and 45% in technical or professional occupations. All participants were married. Mean age of children 5.41 years.	35 (83%)
14	Packman et al (2007)	USA	Cross sectional	Maple Syrup Urine disease (MSUD)	55	Mothers (56.4%) and fathers (43.7%). Mean age of mothers 41 years, mean age of fathers 43 years. 84% of parents married. Mothers' education: 26.0% eleventh grade or less, 24.0% high school diploma or equivalent, 50.0% college	28 (66%)

No.	Study	Country	Design	Inherited Metabolic Disorders (IMDs) examined	No of parents (n)	Parent and child characteristics	Quality Score (out of 42)
						or graduate school. Fathers' education: 28.6% eleventh grade or less, 26.5% high school diploma or equivalent, 44.9% college or graduate school. Bimodal peaks in socioeconomic status (low and middle ranges). Ethnicity: 70.8% white, 18.8% native American, 2.1% Asian, 2.1% Ashkenazi Jewish, 2.1% biracial. Mean age of children 11 years.	
15	Lord, Ungerer & Wastell (2008)	Australia	Cross sectional	Phenylketonuria	99	Mothers (52.5%) and fathers (47.5%). Mean age of mothers 35.5 years, mean age of fathers 38.0 years. 56% of mothers and 94% of fathers were employed. 50% of mother and 60% of father had completed tertiary education, 23% and 51% of mothers and fathers were in technical or professional occupations. Mean age of children 6.6 years.	35 (83%)
16	Storch et al (2008)	USA	Cross sectional	Glycogen Storage Disorder Type I	31	Parents of children with GSD. Mean age of children 11.1 years.	32 (76%)
17	Torkelson & Trahms (2010)	USA	Cross sectional	MCADD	11	Parents of children with MCADD (diagnosis by NBS). 90% mothers, 10% fathers. Mean age of mothers	31 (74%)

No.	Study	Country	Design	Inherited Metabolic Disorders (IMDs) examined	No of parents (n)	Parent and child characteristics	Quality Score (out of 42)
						30.6 years, mean age of fathers 32.9 years. 90.8% of mothers and 56.4% of fathers had either vocational training or were college graduates. 46.5% of mother worked full time, and 18.2% worked part time. Mean age of children 25.8 months.	
18	Mahmoudi-Gharaei, Mostafavi & Alirezaei. (2011)	Iran	Cross sectional	Phenylketonuria	49	59.2 % mothers, 40.8% fathers of children with PKU. All parents were married. Mean age of child 9.84. Mean age of diagnosis 4.72 years, mean age diet commenced 5.87 years.	25 (60%)
19	Brown, Crowe & Boneh (2015)	Australia	Cross sectional and correlational	NBS: MMA (1), Isovaleric acidemia (1), propionic acidemia (1), glutaric acidemia (6), Maple Syrup Urine Disease (1), VLCADD (6) Clinically identified: Glycogen Storage Disorder I (2), III (1), isovaleric acidemia (1), orthinine transcarbamylase deficiency (2)	22	Age range of parents 28-50 years. Mean socio-economic status score 6.6. Age range of children 3-16 years. One child functioning with intellectual disability range.	33 (79%)
20	Gunduz et al (2015)	Turkey	Cross sectional	Phenylketonuria	61	Mothers (70.5%) Fathers (29.5%). Mean age of parents 34.3 years. 39.5%	25 (60%)

No.	Study	Country	Design	Inherited Metabolic Disorders (IMDs) examined	No of parents (n)	Parent and child characteristics	Quality Score (out of 42)
						and 72.2% of mothers and father were educated to college/university levels. Mean age of children 6.5 years.	

Quality ratings

The maximum quality rating score was 42. The quality scores of the studies were varied with a mean of 26.9 (SD=7) and a range of 10-35 (24% to 83%). These are presented in Table 2. Due to the small evidence base of psychological research in parents of children with IMDs, all studies were retained to provide a comprehensive account of the available literature.

Psychological impact on parents

Psychological impact was examined both at the point of diagnosis and through the care process. The impact on parenting was then examined, followed by the recommendations for healthcare professionals working with parents elicited from all papers reviewed.

Table 3: Quality scores on QATSDD for each study

QATSDD item	**Study number** Scores for each item (0= no consideration/mention, 1= limited consideration/mention, 2= general consideration/mention 3= specific consideration/mention)																			
Criteria	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
1. Explicit theoretical framework	3	3	3	1	3	3	2	2	3	3	2	3	3	3	3	3	3	2	3	2
2. Clear statement of aims/objective	3	2	1	2	2	3	3	2	2	3	1	3	3	3	3	3	3	3	3	3
3. Description of research setting	3	3	3	2	2	3	3	3	2	3	3	3	3	2	3	3	3	3	3	2
4. Sample size considered in terms of analysis	0	0	0	0	2	0	0	0	0	1	0	0	2	0	2	3	1	0	1	0
5. Representative sample of reasonable size	2	2	1	3	3	0	2	2	3	2	2	2	2	3	2	2	2	1	2	2
6. Clear procedure for data collection	3	3	1	1	2	2	3	0	3	2	1	3	3	2	3	1	2	1	2	3
7. Clear rationale for choice of tools	3	0	0	0	1	3	2	0	3	2	1	2	3	2	3	3	3	3	3	3

QATSDD item	**Study number** Scores for each item (0= no consideration/mention, 1= limited consideration/mention, 2= general consideration/mention 3= specific consideration/mention)																			
Criteria	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
8. Detailed recruitment data	3	3	0	0	1	1	3	0	3	2	0	2	1	1	1	2	3	2	1	1
9. Statistical assessment of reliability and validity of tools used	1	3	0	0	1	1	3	0	3	1	0	2	1	1	1	1	1	1	1	1
10. Fit between research question and method of data collection	3	2	1	2	2	2	3	2	2	3	2	2	3	2	3	3	3	3	3	2
11. Fit between research question and method of analysis	3	2	0	2	2	3	3	2	3	3	2	3	3	2	3	3	3	3	3	2
12. Justification for analytical method used	1	2	0	0	3	3	0	0	3	2	1	1	3	3	3	2	1	2	3	2
13. User involvement in design	0	0	0	0	2	0	0	0	0	0	0	3	0	2	0	0	0	0	0	0

QATSDD item	**Study number** Scores for each item (0= no consideration/mention, 1= limited consideration/mention, 2= general consideration/mention 3= specific consideration/mention)																			
Criteria	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
14. Strengths and limitations critically discussed	3	3	0	1	1	3	2	1	3	2	3	3	3	1	3	3	3	1	3	3
TOTAL SCORE	**30**	**26**	**10**	**16**	**28**	**28**	**29**	**15**	**32**	**29**	**18**	**33**	**35**	**28**	**35**	**32**	**31**	**25**	**33**	**25**

Table 4: Main findings of the studies

Study	Aims related to review	Psychological construct examined	Measures used	Main findings related to parents	Implications for health care professionals working with parents identified in the paper
Kazak, Reber & Snitzer (1988)	Compare rates of parental psychological distress, marital satisfaction, parenting stress, family cohesion and adaptability in parents of children with PKU to healthy controls	Parent anxiety and depression, parenting stress	Langner Symptoms Checklist, Parenting Stress Index (PSI)	Parents of children with PKU did not reported significantly different levels of distress to norms. Mothers reported significantly higher levels of distress than fathers. Parents of children with PKU did not reported significantly different levels of parenting stress compared to norms. Although parents of children with PKU reported slightly higher scores, this was within normal range.	No implications for working with parents identified.
Fehrenbach & Peterson (1989)	Examine role of parental problem-solving in treatment compliance, and to examine the	Parent stress	Subjective rating of parent stress (Likert scale). Number of problem	Parents' problem solving abilities related to PKU specific challenges was reduced in conditions of high stress. Parents in good compliance group demonstrated more and better quality problem solving strategies than parents in poor compliance group, but both	Health care professionals should help parents improve problem solving skills, particularly in 'high stress' situations.

Study	Aims related to review	Psychological construct examined	Measures used	Main findings related to parents	Implications for health care professionals working with parents identified in the paper
	impact of stress on problem solving and treatment compliance		solving strategies generated and researcher rated quality of problem solving.	groups reduced in high stress condition. Parents in good compliance group rated the high stress situations as subjectively less stressful than parents in poor compliance group.	
Vetrone et al (1989)	Describe parents' reactions to discovery of PKU, psychological difficulties in managing PKU.	Anxiety, depression and reaction to diagnosis	Unspecified 50 item questionnaire.	6/10 parents reported anxiety, depression and shame. This was linked to fears about PKU and the effect on their child. Parents felt embarrassed in food related situations. Mothers reported more guilt about passing on gene. Parents reported depression and shock following diagnosis which was stronger in mothers. These parents seemed more PKU and diet centred rather than child-centred and were deemed less attuned to their child's needs.	Communication of the diagnosis is important and information given should be correct. Health care professionals should be aware of signs of psychological distress in parents following the diagnosis as this predicts later adjustment. Psychological support should be offered to parents during the first few months after diagnosis.
Hendrikx et al (1994)	Extent to which the treatment and	Parent perception of child	Child Behaviour Checklist	Significant differences between parents of children with PKU and parent of healthy controls with respect to parental	No implications or recommendations made.

Study	Aims related to review	Psychological construct examined	Measures used	Main findings related to parents	Implications for health care professionals working with parents identified in the paper
	management of PKU imposes an emotional burden on early treated PKU patients and the parenting practices of their parents.	behaviour and parenting styles	(CBCL), Block and Block child rearing practices report	rearing style. Parents exerted more restrictive and nurturing rearing styles than norms. Parents of children with PKU reported their children as more hyperactive and less socially competent and there was a correlation between hyperactivity (measured by CBCL) and restrictive parenting styles.	
Cederbaum et al (2001)	Assess psychosocial needs and outcomes of families with Urea Cycle Disorders (UCDs)	Reaction to diagnosis, current stressors, changes in daily activity, effect on relationship with partner	Questionnaire (30 items), devised for this study.	Parents experienced many negative emotions at the point of diagnosis: fear (72%), anger (22.5%), guilt (20%), disappointment (24%), concern (64%), relief (29%), and sadness (54%). 92% and 48.5% of parents identified 'emotional' and 'mental' stressors, including thoughts about the death of their child daily (50%) and at least weekly (75%) and considerable concern about getting medication, administering it and worrying about side effects (67%).	Health care professionals need to understand the nature of parent's concerns and fears in order to help them understand and cope with their child's diagnosis and future. Ambiguity in communication or lack of knowledge from health care professionals was identified as a significant stressor. Medical professionals need to be aware of UCDs so that people with expertise and knowledge of UCDs can be available to answer questions to reduce parent

Study	Aims related to review	Psychological construct examined	Measures used	Main findings related to parents	Implications for health care professionals working with parents identified in the paper
				Parents also reported positives of their experience: 63% reported being more compassionate, 25% had become activists, 67.5% felt more patient, 42% reported an 'awakened' world view.	stress. Health care professionals should keep their knowledge should be kept up to date.
Read (2003)	Investigate stress and other demands placed on parents of children with PKU compared to parents of children with mitochondrial disease	Parental stress and degree of worry about IMDs	PSI, Likert scale	Mothers of children with PKU reported lower levels of parenting stress that mothers of children with mitochondrial disease and norms. Mothers of children with PKU reported lower levels of concern about their child than mothers of children with mitochondrial disease. Suggested that better availability of support and knowledge about PKU contributed to reduced parental stress. Most PKU food is covered by insurance and most children with PKU relatively unimpaired compared to children with mitochondrial disease.	Physical care should be supplemented with interventions that reduce parental stress, such as support group, individual counselling, improved nurse-family relationships and social programmes that offer financial support to cover cost of care if parents are struggling. Develop and promoted web-based resources for parents (chat rooms, forums, list-serves and websites) to better connect them with health care professionals and other parents.
Waisbren et	Compare	Parental stress	PSI	Parents of children with IMDs	Parents needed more information and

Study	Aims related to review	Psychological construct examined	Measures used	Main findings related to parents	Implications for health care professionals working with parents identified in the paper
al. (2003)	parenting stress and developmental and health outcomes of children between groups of parents who's child had been diagnosed with IMDs through newborn screening (NBS) or clinically identified			identified by newborn screening (NBS) reported significantly less overall parenting stress than parents of children with IMDs identified clinically (CI). Higher numbers of parents in CI group reported levels of parenting stress in the clinical range (48%) compared to parents in NBS group (2%). Parents of children in NBS group reported greater satisfaction with social relationships. Maternal stress increased as child functioning and satisfaction with social support decreased. There was no differences found in fathers' scores. Parents who rated their understanding of the NBS process as low reported more stress.	education about NBS procedures prior to the birth of their child to reduce stress. Primary care physicians need better education about IMDs as face to face contact with knowledgeable professionals was shown to reduce stress. Parents should be offered consultation sessions with a genetic counsellor who can provide information about genetic carrier status and aid reproductive decisions.
Jusiene & Kucinskas (2004)	Evaluate behavioural and emotional problems of children with PKU in Lithuania and	Parent strategies for coping with stress, reaction and adjustment to child's disease,	Coping Strategies Questionnaire, structured questionnaire (developed for this	Parents report significant emotional reactions to the diagnosis of PKU in their child. 27% felt guilty or blamed themselves, 35% concealed the diagnosis from others, 38% felt angry with themselves/others/god, 95% felt very confused and distressed, 68% took	Health care professional working with parents should consider parental psychological adjustment and coping. Possible interventions with parents who are identified as struggling are education, psychological counselling

Study	Aims related to review	Psychological construct examined	Measures used	Main findings related to parents	Implications for health care professionals working with parents identified in the paper
	analyse these problems in the context of parental psychological adjustment and coping with the child's disease.	child behaviours.	study) that consisted of questions about parental adjustment and relations with child, (CBCL)	a long time to accept the child's disease. Parents of children with PKU use fewer detachment strategies. No other significant difference in coping strategies used between parents of children with PKU and healthy controls. 59% reported 'indulging' their child. Parental feelings of guilt and anger were significantly related to indulgence of the child, which in turn predicted internalising and total problems in children as measured by CBCL.	and 'other forms' of assistance.
Read (2004)	Examine psychological impact on parents of discovering they are gene carriers for PKU	Trauma reactions at point of diagnosis/discovery of carrier status, and current time point	Impact of Event Scale	IES scores highest at point of diagnosis (comparable to sample of women recently diagnosed with breast cancer) and reduce over time. No correlation between scores on scale, change in scores over time or with parent age, number of years since diagnosis or health/development of child.	Parents should be offered genetic counselling to discuss the implications of being a gene carrier.
Waisbren, et al (2004)	Examine predictors of parenting	Parental stress	PSI	Overall parental stress for sample was comparable to normative means. Parents of children with IMDs	Interventions targeting child functioning, social support and actual or perceived difficulties with meeting

Study	Aims related to review	Psychological construct examined	Measures used	Main findings related to parents	Implications for health care professionals working with parents identified in the paper
	stress in parents of children who's IMDs had been identified clinically or by NBS			identified by newborn screening (NBS) reported lower scores of parenting stress than parents of children with IMDs identified clinically (CI). 32% of the overall sample reported clinically significant levels of parenting stress (above 84th percentile). Child development was correlated with parenting stress, and related to timing of diagnosis and treatment. Parents in NBS reported finding it easier to meet their child's needs than parents in CI group (95% vs 60% respectively), and were reported greater amounts of and satisfaction with social support. Child's adaptive functioning, parental satisfaction with social support and perceived difficulties meeting child health needs predicted parental stress.	child's health care needs could reduce parent stress.
Boles et al (2005)	Compare depression in	Anxiety, depression,	Beck Anxiety Inventory	Depression and anxiety scores were lower in mothers in the IMD group than	No implications reported

Study	Aims related to review	Psychological construct examined	Measures used	Main findings related to parents	Implications for health care professionals working with parents identified in the paper
	mothers of children with IMDs and mothers of children with mitochondrial disease	evidence of mental health conditions	(BAI), BDI, Questionnaire for Mothers of Children with Metabolic Disease (designed for study)	the mitochondrial disease (MD) group. In the IMD group, depression and anxiety scores were greater in mothers of severely affected children rather than mildly affected children. 7 of 9 mothers in mildly affected IMD group had very low anxiety and depression scores. Lower rates of maternal mental health problems in mothers of children with IMDs that mothers of children with MD (12 v 40%) which was statistically significant when suspected mental health problems were included.	
Ievers-Landis et al (2005)	Describe dietary challenges faced by children and adolescents with PKU and their caregivers and assess type of	Affective intensity of reactions to dietary challenges Parental coping styles	Likert scale-problem frequency, intensity and affective intensity, Researchers coded parenting styles as adaptive or	53% of caregivers reported formula problems and 84% reported diet problems. 16% of caregivers reported using authoritarian strategies to solve formula problems, 37% reported using authoritarian strategies to solve dietary problems. Parent ratings of frequency, difficulty and affective intensity of problems and perceived effectiveness of strategies	Health care professionals have a role in helping parents to help their children manage emotional demands of PKU whilst still maintaining good treatment adherence. Health care professionals could use the measures from this study to assess challenges with treatment adherence to determine if parents need help with medical management or the emotional

Study	Aims related to review	Psychological construct examined	Measures used	Main findings related to parents	Implications for health care professionals working with parents identified in the paper
	solutions to these problems and their efficacy. To determine the associations of ratings of reported problems and solutions to dietary adherence.		maladaptive.	used to manage these correlated with treatment adherence (phe-levels) in diet domains, but not formula related domains. More reported problems and less effective strategies was associated with worse adherence. Caregivers who reported using authoritarian practices perceived their strategies as less effective. Caregivers of older children with worse treatment adherence, with fewer financial resources were more likely to use authoritarian practices to manage dietary challenges.	support of their child. The clinical interview could be shortened and adapted for use in clinical settings to review problems and solutions in management of PKU. Caregivers' management of disorder specific problems should be carefully reviewed to determine and appropriate referrals to psychological services made to improve problem solving abilities and decrease reliance on maladaptive parenting strategies.
Lord, Wastell & Ungerer (2005)	Examine trauma reactions in parents of children with PKU.	Trauma reactions Parent concerns Partner relationships	Impact of Events scale (IES), PKU checklist, Intimate Bond measure	Most mothers report low to moderate frequency of trauma reactions and a small minority reported a high intensity of trauma. Small proportion of fathers than mothers experience a moderate or high level trauma reaction, although younger father experience higher levels of trauma reactions. Higher levels of trauma reactions were found in mothers whose partners were perceived as	Parents should be offered counselling at the point of diagnosis (as crisis support and to prevent trauma symptoms). Clinicians providing counselling should be aware of the variation in emotional impact on mothers and fathers. Trauma responses should be routinely assessed. The IES could be used to identify parents at high risk of PTSD or

Study	Aims related to review	Psychological construct examined	Measures used	Main findings related to parents	Implications for health care professionals working with parents identified in the paper
				unsupportive. Parents experience intrusive thoughts and feelings more frequently that avoidant reactions. Trauma reactions seemed to diminish over time but this was not a strong trend. Overall trauma reactions were lower that trauma reactions of parents of children surviving cancer, but not significantly so. Parents demonstrated low to moderate concerns about PKU. Significant positive correlation (r=0.62) was found between full scale IES scores and PKU checklist scores suggesting trauma reaction was related to level of concern.	adjustment difficulties. When trauma responses are severe, parents should be offered appropriate clinical interventions that incorporate reorganisation of the emotional processes (e.g. CBT for PTSD). Interventions with mothers should focus on support from partner and social relationships. Counselling approaches that promote 'mutual understanding' of the emotional impact of the diagnosis should be offered to parents who experience their partners as unsupportive. This would facilitate co-operation of parents in management of PKU. Parents lacking social support would benefit from opportunities to explore their support needs with health care professionals who can facilitate access to targeted programs that strengthen social support and support groups.

Study	Aims related to review	Psychological construct examined	Measures used	Main findings related to parents	Implications for health care professionals working with parents identified in the paper
Packman et al (2007)	Ascertain psychosocial issues faced by families of children with MSUD, including sources of stress for parents. Describe Quality of life and psychosocial adjustment of children with MSUD.	Reaction to diagnosis, current stressors, changes in daily activity, effect on relationship with partner assessed using questionnaire	Questionnaire (30 items), devised for this study (adapted from Cederbaum's 2001 questionnaire).	Parents experienced many negative emotions at the point of diagnosis. fear(74.5%), anger (21.6%), guilt (23.5%), disappointment (33.3%), concern (88.2%), relief (37.3%), sadness (52.9%), shock (41.2%) Parents reported significant emotional stressors (78.4%) coming from sources such as financial and insurance concerns (75%), problematic interactions with medical staff (60%) and educational staff (30%).	Health care professionals need to understand parents' reactions to the diagnosis of their child and their fears about their child in order to best support then to understand and cope with it. Health care professionals have a role in educating teachers and school personnel about the child's special needs relating to MSUD. Health care professionals need to support parents in many aspects of their needs, including finances, health care coverage, resources, time management child care and dietary management. MDT working essential to support families (geneticist, genetic counsellors, nutritionists, psychologists and individual with expertise in financial/insurance matters, social work) Children and parents should be offered

Study	Aims related to review	Psychological construct examined	Measures used	Main findings related to parents	Implications for health care professionals working with parents identified in the paper
					professional individual or family therapy if they are distressed. Access to support groups should be promoted. Health care providers need to validate feelings of children and parents and provide interpersonal support, reassurance and maintain hope.
Lord, Ungerer & Wastell (2008)	Assess parental resolution of the diagnosis of PKU, and examine relations between resolution of the diagnosis and adjustment on outcomes for parents and children. Examine the relationship between	Emotional reaction to the diagnosis, Parent adjustment and coping, Child adjustment	Reaction to Diagnosis Interview (RDI) , Ways of coping questionnaire , Hunter Opinions and Personal Expectations Child Behaviour Checklist (CBCL)	Most parents were resolved to the diagnosis (69% of mothers and 77% of fathers). There was no association between category of resolution and age of child. Resolution was not a function of time since birth. Resolved parents had lower scores on the Malaise inventory. Low levels of personal hopefulness were associated with higher scores on the Malaise inventory, but resolution class was not significantly associated with personal hopefulness. Resolution and personal hopefulness predict stress.	Health care professionals need to acknowledge the emotional impact of the diagnosis on parents. Health care professionals should be aware of indicators of lack of resolution (persistent distress, avoiding talking about diagnosis and problems) and make referrals for psychological support as appropriate. Assessment of parental reaction to diagnosis should an integrated part of clinical care. The RDI could be adapted and used for psychosocial assessment with parents. Unresolved parents should be offered

Study	Aims related to review	Psychological construct examined	Measures used	Main findings related to parents	Implications for health care professionals working with parents identified in the paper
	parent resolution and other coping variables. Compare variance in parent and child outcomes explained by resolution with personal hopefulness and coping strategies			Resolution class was not significantly associated with child behaviour, but this was predicted by parental perceptions of severity of PKU and levels of personal hopefulness. Parents use a wide range of coping strategies. Resolution was not related to how parents cope, other than escape avoidance in mothers.	counselling aimed at relieving diagnosis related grief. Counselling should also promote a more balanced view of child's future. Supporting resilience and hopefulness may contribute to more effective parenting and more positive perceptions of child.
Storch, et al (2008)	Assess quality of life and psychosocial functioning of children with GSD I and their parents.	Parent distress, Parent stress	Brief Symptom Inventory (BSI), Pediatric Inventory for Parents (PIP)	Parental stress was higher in parents caring for a child with GSD than parents of healthy controls as measured by the PIP. Parents of children with GSD parents showed more symptoms of anxiety and depression as measured by BSI. Parents reported increased frequency and severity of distress related to caring for a child with special needs.	Families would benefit from consultation with paediatric psychologists to learn adaptive ways to manage the extra responsibility of caring for their child and for parents' psychosocial functioning to be monitored. Parents would benefit from support to learn strategies to manage personal distress whilst attempting to balance the

Study	Aims related to review	Psychological construct examined	Measures used	Main findings related to parents	Implications for health care professionals working with parents identified in the paper
				Parents' ratings of difficulties in children are higher than children's self-ratings.	challenge of caring for their child and maintaining a normal lifestyle. Parents and children would benefit from professional assistance in identifying appropriate developmental opportunities to ensure parents are not being overly restrictive.
Torkelson & Trahms (2010)	Assess parenting stress in parent of children with MCADD	Parental stress and parent perceptions of illness.	PSI, Questionnaire designed for this study	Parents of children with MCADD report significantly lower levels of parenting stress than norms.	Family and professional support and information were identified factors that alleviated stress. Lack of or conflicting information, interactions with primary health care providers, current and future concerns were factors that increased stress. Low levels of parental stress were deemed to be due to feelings of competence due to high levels of support and clear guidance about treatment and management.
Mahmoudi-Gharaei, Mostafavi & Alirezaei.	Assess Quality of life, depression, anxiety and	Depression, anxiety and stress	Depression, Anxiety and Stress Scale (DASS)	High levels of depression, anxiety and stress in parents Depression (% of parents in each range) Normal- 42.9%, Mild- 8.2%,	None identified

Study	Aims related to review	Psychological construct examined	Measures used	Main findings related to parents	Implications for health care professionals working with parents identified in the paper
(2011)	stress in parents of children with PKU.			Moderate- 20.4%, Severe- 10.2%, Very severe 18.4% Anxiety (% of parents in each range): Normal- 49.9%, Mild-12.2%, Moderate-8.2%, Severe- 8.2%, Very severe 24.5%. Stress (% of parents in each range): Normal- 42.9%, Mild-14.3%, Moderate-18.4%, Severe- 10.2%, Very severe 14.3%.	
Brown, Crowe & Boneh (2015)	Explore levels of coping and management of parents of children with IMDs and the relationship with children's cognitive, behavioural and social outcomes	Parental anxiety and depression Parent coping and support	Kessler 10 Distress scale, Parent experience of Childhood Illness (PECI)	Most (16/22) parents were well adjusted. Small number reported high levels of distress. Two parents were at moderate risk of distress, one was in the high risk range, and two parents were in the very high risk range for distress. Of the four parents who reported higher levels of distress, three had children who were diagnosis clinically with an IMD. Parental coping was better than parents of children with brain tumours. Poorer parent coping was associated with more	Health care professionals could use PECI to screen for parents who are struggling to cope in the clinical setting. Families need a multidisciplinary team (unspecified professions) to support them, and the MDT should consider biopsychosocial factors when supporting families.

Study	Aims related to review	Psychological construct examined	Measures used	Main findings related to parents	Implications for health care professionals working with parents identified in the paper
				emotional symptoms in children. Age of child was a factor that affected distress.	
Gunduz et al (2015)	Compare anxiety and depression in parents of children with PKU compared to healthy controls	Anxiety, depression	State Trait Anxiety Inventory (STAI), Beck Depression Inventory (BDI)	Depression and anxiety scores were higher for PKU parents than controls. Mothers reported significantly higher levels of anxiety and depression than fathers of children with PKU and parents of healthy controls. Number of affected children, gender of child, or age of child did not affect scores. There was no correlation between anxiety and depression and age of parent. Parents with lower educational level reported higher levels of anxiety and depression. Lower educational status was the only independent factor associated with depression and anxiety. Parents of children with intellectual disabilities reported higher levels of depression and anxiety than neurologically unaffected children. 68.8% reported a financial burden.	Health care professionals should establish supportive relationships with parents and maintain therapeutic communication.

Study	Aims related to review	Psychological construct examined	Measures used	Main findings related to parents	Implications for health care professionals working with parents identified in the paper
				Parents who struggled to provide low protein food reported higher levels of depression and anxiety than parents who reported finding it easy to provide this. Parental depression was found to correlate with anxiety scores on both the STAI-S/T (r=0.523, r=0.440 respectively).	

Psychological impact upon diagnosis of child

Six studies specifically examined the psychological impact on parents of their child being diagnosed with an IMD. Being confronted with a diagnosis of an IMD caused significant emotional responses in parents in all the studies. Parental reactions included fear, confusion, concern, sadness and shock, as well as anger, guilt and disappointment (Cederbaum et al 2001; Jusiene and Kucinkas 2004; Packman et al 2007) and reactions of shock, depression, discomfort and powerlessness were stronger in mothers (Vetrone et al 1989). Parents reported trauma reactions to both the diagnosis (Lord, Ungerer and Wastell 2008) and to the news that they were carriers of the genetic disorder passed down to their children (Read 2004), although feelings of guilt regarding genetic transmission was more pronounced in mothers (Vetrone et al 1989). Although most parents experienced low to moderate trauma reactions, a small minority reported high scores on trauma measures, comparable to parents of children who had survived cancer (Lord, Wastell and Ungerer 2005) Mothers reported higher levels of traumatic symptoms than fathers and higher levels of intrusive rather than avoidant trauma reactions were observed, and this was correlated with amount of concern about the disorder (Lord, Wastell and Ungerer 2005), suggesting an association with greater perceived or actual severity of the disorder. The psychological impact did not vary by disorder, suggesting that these are common reactions to a diagnosis of a disorder, rather than to a specific disorder, however it should be noted that due to variations in newborn screening programmes by country, not all children were diagnosed pre-symptomatically.

Ongoing psychological impact

Sixteen of the studies examined the ongoing psychological impact of caring for a child with an IMD. Eight studies reported on measures of stress in parents, and eight reported measures of anxiety and depression.

In relation to stress, parenting stress was a significant factor in the development of further psychological distress. Studies reported caring for a child with an IMD had an effect on stress in parents (n=8). Degree of parental stress varied by disorder severity, mode of diagnosis and gender of parents. Parents of children with PKU and MCADD indicated less parenting-related stress compared to parents of healthy controls (Read 2003; Torkelson and Trahms 2010) or stress levels that were not significantly different to those reported by healthy controls (Kazak, Reber and Snitzer 1988). However, Torkelson and Trahms (2010) noted that parents demonstrated significantly higher rates (54%) of defensive responding compared to norms (15%). The majority of the studies examined the impact on mothers only, had limited number of fathers participating or did not differentiate maternal and paternal responses, thus limited information regarding gender differences could be elicited.

The amount of parenting stress reported varied by the impact of the disorder on the child. Parents of children with PKU (a relatively stable disorder) reported significantly less stress than parents of children with other disorders which have higher care needs and greater impact on children's functioning, such as mitochondrial disease, and IMDs like Glycogen Storage Disorder type I (Read 2003; Storch et al 2008). Parents of children with Glycogen Storage Disorder type I (GSD I) reported higher rates of parenting stress and increased severity and frequency of distress related to caring for their child (Storch et al 2008). Levels of parenting stress increased as child functioning decreased (Waisbren et al. 2003). However, one study

reported higher levels of parenting stress in parents of children with PKU in Iran (Mahmoudi-Gharaei, Mostafavi and Alirezaei 2011).

Parenting stress was affected by the mode of diagnosis. Two studies compared rates of parenting stress in parents of children with IMDs who had been diagnosed by newborn screening or clinically identified following symptomatic presentation in the neonatal period (Waisbren et al 2003; 2004). Parenting stress was significantly higher when IMDs had been diagnosed clinically, and parents of children who had been diagnosed by newborn screening indicated stress levels comparable to general population (Waisbren et al 2003). This study showed that children diagnosed by newborn screening had better health and developmental outcomes, but also noted that consistent with other studies parenting stress increased as child functioning decreased. Parents of children with GSD I, which is clinically identified reported higher levels of stress (Storch et al 2008). Brown and colleagues (2015) found that parents of children diagnosed clinically were at greater risk of parenting stress along with other psychological disorders such as anxiety and depression.

In relation to symptoms of anxiety and depression, the reported scores on measures for parents of children with IMDs was varied. Four studies reported higher levels of anxiety and depression in parents of children with IMDs (PKU and GSD I) compared to parents of healthy controls or the general population (Gunduz et al 2015; Mahmoudi-Gharaei, Mostafavi and Alirezaei 2011; Storch et al 2008; Vetrone et al 1989). Despite findings that a significant percentage of parents of children with PKU reported moderate to very severe levels of depression and anxiety respectively (Mahmoudi-Gharaei, Mostafavi and Alirezaei 2011), Gunduz and colleague (2015) noted that despite significant differences in scores, parental scores were in the ‘mild’ ranges for depression and just above clinically recommended cut offs for anxiety.

There was mixed evidence regarding gender differences in parental anxiety and depression scores. Vetrone and colleagues (1989) identified that mothers reported stronger 'feelings' of depression (although not quantified) and higher scores of anxiety and depression were reported by mothers compared to fathers (Kazak, Reber and Snitzer 1988; Mahmoudi-Gharaei, Mostafavi and Alirezaei 2011), whereas Lord and colleagues (2008) failed to find any differences. Anxiety and depression varied by severity of disorder: parents of children with neurological impairment reported higher scores of anxiety and depression (Gunduz et al 2015) and mothers of children who were less severely affected by their IMD reporting low, or very low scores on measures of anxiety and depression (Boles et al 2005). Low levels of anxiety and depression were noted in parents of children with IMDs (Boles et al 2015; Brown, Crowe and Boneh 2015; Kazak, Reber and Snitzer 1988); however, this was affected by whether children were diagnosed following illness, or pre-symptomatically. Lord and colleagues (2008) also found that parents who were not accepting of their child's diagnosis reported higher levels of anxiety and depression. Direct comparison of outcomes for studies was not possible, due to lack of consistent tools used to measure anxiety and depression.

Impact on parenting

Eight studies explored the impact of parental psychological factors on parenting. In particular, the psychological impact on parents and its role in further psychological distress (with reference to adjustment, acceptance and coping) and subsequent impact on parenting strategies was examined.

Parental coping strategies did not differ from those used by parents of healthy controls (Jusiene and Kucinkas 2004; Lord, Ungerer and Wastell 2008). Poorer

parental coping was related to more emotional symptoms in children (Brown, Crowe and Boneh et al 2015; Packman et al 2007). A lack of acceptance of the diagnosis was considered to contribute to increased stress over time and to increase levels of anxiety and depression in parents of children with IMDs (Lord, Ungerer and Wastell 2008). Levels of distress (trauma, stress) were related to the parent's level of concern about the disorder (Lord, Wastell and Ungerer 2005; Read 2003) which had an impact on parenting, because studies suggested that parents who have increased concerns about the disorder showed elevated levels of stress, anxiety and depression and demonstrated more maladaptive parenting strategies including restrictive or overprotective (Hendrikx et al 1994; Jusiene and Kucinkas 2004; Storch et al 2008), authoritarian (Ievers-Landis et al 2005) or over-indulgent (Jusiene and Kucinkas 2004) parenting styles.

Unresolved parents and parents who reported high levels of negative affective reactions were considered to be less able to sensitively respond to their child's emotional needs and put appropriate boundaries into place (Lord, Ungerer and Wastell 2008), more likely to be 'diet centred' rather than 'child centred' (p 346 Vetrone et al 1989) and to use fewer, more authoritarian management strategies that were perceived as less effective at the expense of listening to their child's concerns and working collaboratively (Ievers-Landis et al 2005). Parents who reported higher levels of personal hopefulness also reported fewer child behaviour problems; however, parental resolution was not related to child behaviour problems (Lord, Ungerer and Wastell 2008).

Parents who reported high levels of distress were more likely to overestimate their child's difficulties, reported more negative perceptions of their child (Hendrikx et al 1994; Storch et al 2008) and produced fewer, poorer quality problem solving strategies with regards to dietary management (Fehrenbach and Peterson 1989). This

resulted in more restrictive or overly nurturing parenting, and parents gave their child fewer opportunities to engage in developmental and social activities (Storch et al 2008). The greater use of maladaptive parenting styles (over-indulging) was associated with greater parental rating of child behaviour problems (Jusiene and Kucinkas 2004). Parents who reported less distress about the diagnosis and caring for their child described fewer child behaviour problems (Jusiene and Kucinkas 2004; Lord, Ungerer and Wastell 2008) and they indicated a better ability to use more as well as better quality and adaptive (authoritative rather than authoritarian) management strategies with regards to treatment regimens (Fehrenbach and Peterson 1989; Ievers-Landis et al 2005).

Implications for health care professionals working with parents

Four studies did not make recommendations for health care professionals working with parents of children with IMDs (potentially due to assessment of psychological impact on parents not being the primary aim of many studies). Most papers made suggestions without specific guidance. Overwhelmingly, the studies suggested that the psychological wellbeing of parents should be considered as part of care provided to a child with IMDs.

Studies identified the need for better education and information for parents regarding newborn screening procedures from professionals prior to the birth of their child (Waisbren et al 2003). Medical professionals in contact with parents need improved and up-to-date knowledge and understanding of IMDs and to be clear in their communication with parents. A lack of information and knowledge from professionals unfamiliar with IMDs increased stress for parents (Cederbaum et al 2001; Torkelson and Trahms 2010), whilst face-to-face contact and supportive

relationships with knowledgeable professionals reduced stress (Gunduz et al 2011; Read 2003; Torkelson and Trahms 2010; Waisbren et al 2004). This was particularly important at diagnosis (Vetrone et al 1989).

Studies emphasised the need for health care professionals to support parents so they can meet a variety of needs, not just the medical management of their child's disorder and consider biopsychosocial factors. Alongside clear guidance and management plans related to the IMD, health care professionals need to consider supporting parents with financial/insurance related concerns, resources, time management, child care and the education of other professionals involved in their child's care (Cederbaum et al 2001; Packman et al 2007; Read 2004; Torkelson and Trahms 2010). Studies indicated the need for multidisciplinary support for parents to meet these needs, including geneticists, genetic counsellors, nutritionists, psychologists, social work and individuals with expertise in financial advice (Brown, Crowe and Boneh 2015; Packman et al 2007).

The importance of emotional support for parents was indicated. Studies reported that an acknowledgement and understanding of parental distress would better help parents cope (Cederbaum et al 2001; Lord, Wastell and Ungerer 2005; Packman et al 2007; Vetrone et al 1989). Professionals should listen to and validate parents' feelings and concerns about their child and provide interpersonal support and reassurance (Cederbaum et al 2001; Packman et al 2007), whilst helping promote hope and a balanced view of the child's disorder to promote more positive perceptions of the child (Packman 2007 et al; Waisbren et al 2003).

Social support was identified as a significant predictor of parental psychological distress (Kazak, Reber and Snitzer 1988; Lord, Wastell and Ungerer 2005; Read 2003; Waisbren et al 2003). Thus it was recommended that health care professionals promote access to and utilisation of social support in the form of

support groups, interventions that target and strengthen social support and the development of web-based resources to connect parents with health care professionals and other parents (Lord, Wastell and Ungerer 2005; Packman et al 2007; Read 2003).

Studies endorsed the need for improved screening and monitoring of parental psychosocial functioning as part of clinical care. Health care professionals working with parents should be aware of gender differences in psychological responses (Lord, Wastell and Ungerer 2005; Lord, Ungerer and Wastell 2008). Studies recommended that psychological impact should be assessed at the point of diagnosis (Lord, Wastell and Ungerer 2005; Vetrone et al 1989) and at regular intervals for parents struggling to cope and adjust (Brown, Crowe and Boneh 2015; Jusiene and Kucinkas 2004; Storch et al 2008), accept the diagnosis of their child (Lord, Wastell and Ungerer 2005) or showing ongoing trauma responses (Lord 2008, Ungerer and Wastell). Health care professionals could also review current management strategies and affective reactions to disorder specific challenges with parents to assess whether additional support is needed (Ievers-Landis et al 2005).

An increased awareness of when to refer parents who are struggling for more specialised interventions/support to assist either with practical or emotional management was highlighted. Roles for genetic counsellors (Packman et al 2007; Read 2004; Waisbren et al 2003) and clinical psychologists were indicated, to help parents learn adaptive ways to manage the extra caring responsibilities alongside managing their own distress (Storch et al 2008), improve child functioning (Waisbren et al 2004), decrease stress and increase problem solving abilities related to dietary management and promote use of adaptive parenting strategies (Fehrenbach and Peterson 1989; Ievers-Landis et al 2005; Storch et al 2008).

Parents could be offered psychological support around the point of diagnosis (Lord, Wastell and Ungerer 2005; Vetrone et al 1989) and parents who show high levels of negative affect should be offered individual counselling, family therapy or couple counselling (Jusiene and Kucinkas 2004; Lord, Wastell and Ungerer 2005; Lord, Ungerer and Wastell 2008; Packman et al 2007; Read 2003). More specific psychological interventions for parents experiencing high levels of distress should be aimed at resolving trauma symptoms and promoting healthy acceptance of the diagnosis (Lord, Ungerer and Wastell 2008). Interventions that promote more balanced views of the child's future, promote hopefulness and resilience in parents were indicated to improve parenting (Lord, Ungerer and Wastell 2008).

DISCUSSION

For most parents the psychological impact is not above clinical thresholds; however, a small but significant minority experienced high levels of psychological distress. Ongoing psychological impact did not appear to vary by disorder; however, mode of diagnosis affected psychological outcomes for parents. Parents with children diagnosed with IMDs clinically as opposed to by newborn screening showed significantly elevated rates of stress, possibly due to poorer health and developmental outcomes for children (Waisbren et al 2003), however it should be noted that not all countries offer the same newborn screening programmes, which may affect the outcomes reported. The literature identified diagnosis of IMD following illness, impairments in child functioning and high perceived or actual severity of IMD and care burden as potential risk factors for parental distress. Psychological impact appeared to vary by gender, with more mothers reporting higher levels of psychological distress than fathers across all studies, consistent with findings of

parents of children with chronic health conditions (Van Oers et al 2014). These findings may reflect the tendency of mothers to be main care givers and thus are responsible for food and medical provision, and may worry more about the child than fathers.

Cultural factors may influence the psychological impact on parents. Parents who reported highest levels of psychological distress were from Iran and Turkey where rates and impact of IMDs are reportedly higher than the other papers due to consanguineous marriage and lack of robust national neonatal screening (Erdem and Teksen 2013; Pourfarzam and Zadhoush 2013). Higher levels of distress in parents could be related to the presentation of neurological damage in children due to delayed diagnosis and treatment (Mahmoudi-Gharaei, Mostafavi and Alirezaei 2011) and high rates of perceived difficulties providing low protein food due to health insurance coverage (Gunduz et al 2015); both risk factors for increased psychological distress. Socio-political and contextual factors present in countries like Iran and Turkey (such as civil unrest) could affect provision of health care and parental wellbeing and limitations of measures should be considered as there is evidence of cultural variations in expression of distress (e.g., higher rating of somatisation and exaggeration of symptoms, see Uluşahin, Başoĝlu and Paykel 1994).

Given the evidence of the psychological impact on parents caring for a child with an IMD, psychological distress in parents should be appropriately screened for as part of the care provided to families. It should be noted that studies have found that parents' psychological symptoms may not be related to children's metabolic control (Jaser et al 2009; Medford et al 2016 submitted for review) and thus may go undetected. Parental stress was highly associated with anxiety and depression (Gunduz et al 2015) and negatively associated with personal hopefulness (Lord, Ungerer and Wastell 2008). Similar findings were reported by Horton and Wallander

(2001) who found that hope and social support were negatively associated with distress in parents of children with chronic conditions, and hope moderated stress related to child disability and parental maladjustment. This suggests that parental hopefulness was a resilience or protective factor against the psychological impact of caring for a child with an IMD and could be amenable to intervention, although no studies in this area have been conducted. Clinicians working with parents can encourage a hopeful attitude in parents retaining a positive focus when speaking to parents.

Social support is a significant predictor of parental wellbeing in IMDs and other chronic conditions (Fidika et al 2013; Speechley and Noh 1992; ten Hoedt et al 2011; Waisbren et al 2004). Interventions that promote access to or utilisation of social support, making and maintaining social relationships and promoting parental self-development and self-care could prove beneficial for parental mental health. Evidence for this has been found in parents of children with juvenile arthritis and diabetes (Horton and Wallander 2001; Turner et al 2001) so increased social support could reduce care burden and psychological impact on parents of children with IMDs

Perception of severity and difficulties in meeting child's needs was a predictor of parenting stress (Waisbren et al 2003). Evidence that perceptions of severity are linked to higher rates of parental stress, anxiety and depression has been found in parents of children with other conditions such as ASD (Keenan et al 2016), congenital heart disease (DeMaso et al 1991) and intellectual disability (Hassall, Rose and McDonald 2005). Perceptions of severity and increased perception of need for high levels of control are also risk factors for burnout in mothers of chronically ill children (Lindstrom, Aman and Norberg 2011). This suggests an important role of parental cognitions and illness representations in the psychological impact of caring for a child with IMDs, consistent with cognitive and illness representation theory

(Diefenbach and Leventhal 1996; Lazarus and Folkman 1984). Inventions that modify perceptions of difficulties (e.g., CBT informed interventions), with practical support to help parents better meet their children's needs (e.g., problem solving) could be beneficial in reducing stress by promoting parental self-efficacy.

Acceptance of the diagnosis was found to reduce stress, anxiety and depression, suggesting a vital role of acceptance of the IMD in the process of psychological distress. Research with parents of children with intellectual disabilities found that mothers who were more accepting reported fewer psychological adjustment problems, and acceptance was negatively associated with anxiety, depression and stress (Lloyd and Hastings 2007). Parents who were not resolved to (or accepting of) the diagnosis showed significant higher levels of stress, anxiety and depression. Health care professionals should be aware of indicators of poor parental adjustment because they have links to increased use of maladaptive parenting strategies, such as restrictive, authoritarian, or permissive or lax parenting (Jones and Prinz 2005; Rezendes and Scarpa 2011; Sanders and Woolley 2005). A review of 34 studies by Whittemore (2012) found that parental anxiety and depression produced different parenting and management strategies, with parents reporting high levels of depression demonstrating more family conflict and less consistent and warm parenting and reduced levels of monitoring and involvement in management, and parents reporting higher levels of anxiety demonstrating more controlling and overprotective parenting with increased parental monitoring, although anxious parents reported less self-efficacy. Although restrictive or authoritarian strategies may contribute to good treatment adherence, they may be motivated by high levels of psychological distress in parents, and lead to less than optimal health and emotional outcomes for children, such as lower autonomous motivation for treatment adherence and reduced positive affect (Cameron, Young and Wiebe 2007). This has been

specifically noted in parents of children with PKU. Macdonald and colleagues (1997) found that parents of children with PKU who were preoccupied with the dietary management were less attuned to their child's behavioural signals and more likely to use coercive parent strategies during feeding, which increased subsequent feeding problems.

The findings of this review indicated that interventions for parents may be beneficial for parents who present with high levels of psychological distress and maladaptive parenting strategies. A review of psychological interventions for parents of children with chronic illness found problem solving therapies (enhancing social competence through constructive problem solving, attitudes and skills) had the most beneficial effect on both adaptive parenting behaviour and parental mental health (Ecclestone et al 2015). Turner et al (2001) found that residential interventions for parents of children with juvenile arthritis, providing disease-related information and social and emotional support reduced parental stress and improved parental psychological wellbeing. Interventions with parents of children with diabetes have found that parenting courses around general parenting as well as illness specific conflict resolution strategies in parents of children with diabetes improved parenting skills decreased parental depression and anxiety but not stress (Doherty, Calam and Sanders 2013; Sassman et al 2012;). According to Morawska, Calam and Fraser (2015), interventions for parents of children with chronic illness should include illness specific psycho-education, strategies for effective illness management, provide information to help parents understand links between illness, parenting and child adjustment and promote effective management of child emotional and behavioural problems. Parenting interventions that encompass these could be beneficial for parents of children with IMDs.

Strengths and limitations of the study

Some limitations need to be acknowledged which related to measurement variability, reliance on cross-sectional and self-report data and some differences in how the studies conceptualised and operationalised psychological impact. Due to the range of measures used to assess psychological impact, statistical pooling of the results was not possible. Results were mixed regarding the ongoing psychological impact, although variations were to be expected due to the mode of diagnosis, clinical presentation, subsequent care burden, degree to which treatment will ameliorate neurological or physical damage and prognosis within the disorders reviewed, although not all studies reported on these factors. However, a benefit of the study was the diversity of IMDs included, which allows greater generalisability of the findings. All sampling appeared to be opportunistic or self-selected, which should be considered in interpretation of the findings and most samples were small which is not surprising considering the low prevalence rates of the IMDs in question. This had an impact on quality rating of the studies, because researchers had to recruit available numbers rather than required numbers for statistical power. However, it should be noted that specific IMDs are rare, and thus there is a reduced pool of participants to recruit from and as such these are relatively good sample sizes for the prevalence rates.

Future research

More multi-site longitudinal research with parents of children with IMDs is required to capture how the psychological impact might change over time, and very few qualitative studies exist that would allow access to parents' experience of the psychological impact. Future research could focus on investigating specific factors

that influence psychological impact on parents, such as age of child, amount of service provision and subsequent psychological impact on parents. At present, there has been no research into interventions with parents of children with IMDs, and this would be beneficial area of future research. Furthermore, no studies into parents of children with IMDs have examined concepts, such as parental self-efficacy or competence, which have been linked to stress, anxiety and depression, and parenting practice (Jones and Prinz 2005; Rezendes and Scarpa 2011; Sanders and Woolley 2005) in parents of children with other conditions. As high parental stress has been linked to feelings of incompetence (Dellve et al 2006), future research could address this in parents of children with IMDs.

Conclusion

The findings of this review indicate that there is a significant psychological impact on parents of children with IMDs. This is greater at the point of diagnosis and influenced by mode of diagnosis, and child, parent and social factors. Findings indicate that parents who experience a greater psychological impact are at risk of using less effective parenting strategies. Health care professionals can a significant role in supporting parents and reducing this impact.

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Paper 2

Parenting a child with phenylketonuria (PKU): An interpretative phenomenological analysis of parents' experiences

The following paper has been prepared for submission to the *Journal of Genetic Counselling.* The guidelines for authors can be found in Appendix 5. Changes have been made to the current paper to aid readability of the thesis: Tables and figures have been inserted within the text.

Word count: 12,109

Main text: 6, 748 (excluding abstract, tables, figures, quotes and references)

ABSTRACT

Phenylketonuria (PKU) is a rare inherited metabolic disorder which can cause neurological damage if left untreated. PKU is identified through newborn screening, and treatment begins immediately which prevents these severe consequences. When a child is diagnosed, parents must assume immediate responsibility for the management of PKU and prevention of neurological damage. Quantitative studies have identified significant psychosocial stressors for parents but little is known about how the parents experience this process. This study aimed to explore the experiences of parents of children with PKU under the age of two. Seven parents were interviewed about their experiences, and interpretative phenomenological analysis was used to analyse the data. Three main themes were identified: *control, striving for normality and acceptance.* Links between the themes and processes underpinning the results were explored with relation to existing literature and theories from a clinical psychology perspective. A key role of acceptance was identified in parents' experiences. Clinical implications and suggestions for further research are discussed.

Keywords: phenylketonuria, parents, experience, interpretative phenomenological analysis, qualitative.

INTRODUCTION

Phenylketonuria (PKU) is an inherited metabolic disorder (IMD) with a prevalence of 1 in 10,000 births (Williams, Mamotte and Burnett 2008; National Society for Phenylketonuria 2014). People with PKU cannot metabolise phenylalanine which is found in many protein-rich foods. This enzyme can accumulate in the brain and blood, causing damage to the brain and nervous system and can cause intellectual disability and epilepsy. Neurological damage can be prevented if treatment in the form of a strict, phenylalanine restricted diet and amino acid supplements is started immediately and continued throughout childhood. Life-long adherence to this treatment regime has been recommended (National Society for Phenylketonuria 2014), which has ameliorated the most severe consequences of PKU (Al-Hafid and Christodoulou 2015).

The management of PKU places significant demands on parents, who supervise and monitor the nutritional intake of their child, attend regular appointments and submit regular blood tests. Parents of children with IMDs report significant burden on the family (Gramer et al 2014) and challenges include time constraints, stress related to preparation of special diet, keeping records of blood results and restrictions on social life (Bilginsoy et al 2005; Eijgelshoven et al 2013) along with emotional, mental and interpersonal stress (Cederbaum et al 2004; Packman et al 2007). Parents of children with IMDs have reported stress related to dietary provision, the 'threat' of metabolic crisis, coping with uncertainty and the unknown, difficulties managing life transitions and struggling for improvement in care (Khangura et al 2015; Read 2003; Storch et al 2005; Zeltner et al 2016).

When their child is diagnosed with an IMD, parents are expected to adapt and cope (Abindin 1990) and integrate parenting tasks with tasks related to their child's

disorder, whilst managing their own emotions and adjusting to the diagnosis, prognosis and management of their child's disorder (Turner-Henson, Holoday and Swan 1992). Children require higher levels of care, and common concerns about providing competent care may be exacerbated by illness demands and the tasks of caring may interfere with opportunities for normal developmental experiences. There is a strong association between high burdens of care (actual and perceived) and parental stress (Calderon et al 2011; Cousino and Hazen 2013) and evidence to suggest that parents of children with a chronic illness with high burdens of care experience higher levels of emotional distress and poorer adjustment (Cadman et al 1991).

Reports of parenting stress in parents of children with PKU has been mixed; despite significant care demands parents report lower or similar levels of stress and quality of life compared to parents of healthy control children and other inherited metabolic disorders (Kazak, Reber and Snitzer 1988; ten Hoedt et al 2011), although parents of younger children reported impaired quality of life (Fidika et al 2013; ten Hoedt et al 2011), possibly due to dependency and care needs of younger children.

Research has explored the experience and process of parenting in other chronic conditions; parents of children with diabetes reported 'constant vigilance' and adjustment process in their parenting, moving from 'incompetence to skill' in managing the disorder, moving from sadness to action with active participation in parenting and a creation of a 'new normal' (Gray 1997; Sullivan-Bolyai et al 2003). Parents of children with chronic illness have also reported constant anxiety, feeling overwhelmed, loss of support and contact with 'outside world', struggling with the diagnosis, the challenges faced at critical times in the child's life, and needing to take charge and advocate for their child's care (Coffey 2006). Themes of worry, limitations on parents and perceived lack of support have been noted along with

positive experiences with the disease (Butler et al 2007; Mellin et al 2006; Sullivan-Bolyai et al 2003; Sullivan-Boyai et al 2006).

Little is known about the experience of parents caring for a child with PKU. PKU represents a different challenge for parents, because it is identified at birth when the child is asymptomatic, and if managed well patients can remain symptom free. Quantitative studies have identified the challenges faced by parents in maintaining this, but not how these are experienced by parents. Parents of children with PKU reported significant emotional challenges early on in their child's life, despite an absence of ill health, including grief and trauma reactions alongside caring for their new baby (Awiszus & Unger 1990; Lord, Ungerer and Wastell 2008) suggesting that this is a critical time for parents. During early childhood, the child's brain is developing, and cognitive, emotional, social and motor skills are developing (Centre for Disease Control and Prevention 2013). The weaning process begins which represents a major challenge for parents given the importance of dietary management and the child's increasing development and independence (MacDonald et al 2012) and parents are beginning to entrust the care of their child to others (e.g., nursery).

Currently, although research suggests that this time period could be a particular challenge for parents of children with PKU, there is little research exploring their lived experiences, the processes parents go through in adjusting to and coping with these challenges, and how they make sense of their experience. Qualitative enquiry will achieve this because it provides a rich descriptive account of the phenomena under investigation (Elliot, Fischer and Rennie 1999). This study aimed to explore the lived experience of parenting a child with PKU in the first two years, with the added intention that the findings would enable health professionals to gain a better understanding of the subjective experience of parents caring for a child

with PKU. These insights should provide a better understanding of how health care professionals may be able to intervene.

METHOD

Theoretical framework

Interpretative Phenomenological Analysis (IPA; Larkin, Smith and Clifton 2006; Smith, 1999; Smith and Osborne 2008) was followed. IPA looks at how people make sense of their experiences and the significance they attach to their experiences (Smith, Larkin and Flowers 2006). IPA was deemed an appropriate way to explore the experiences of parents'.

Participants and recruitment

Ethical approval was granted by University and NHS Ethics Committees (ref 15/NW/0454 see Appendix 7). Purposive sampling was used with parents and carers of children with PKU. Study design, protocols and participant materials were discussed with and approved by the National Society for Phenylketonuria (NSPKU). Parents with children under the age of two were recruited from PKU clinics in the North of England. After assessment by the clinical team, parents were excluded if there were other significant family stressors (for example, other serious medical problems within the family or other significant caring responsibilities) and did not speak English.

Eligible participants were sent postal information packs. In addition, posters and adverts were placed in waiting rooms, Facebook groups and NSPKU newsletters

(see Appendix 15). Parents who wished to participate returned consent forms, and interviews were booked accordingly.

Interviews

Parents were interviewed in their own homes using a semi-structured interview schedule, which allowed for probing and further exploration of arising areas of importance for participants (Smith 2009). The interview schedule was developed through reviewing the available literature and in discussion with the clinical team; it was approved by the NSPKU. Four areas were identified as prompts for parents: experience of the diagnostic process, processes of parenting, challenges and coping, support (see Appendix 13).

Data analysis

Data were analysed using IPA, according to Smith and Osborn's (2008) guidelines. All interviews were audio-recorded and transcribed verbatim by the first author and listened to again to ensure validity. Analytic diaries were kept by the first author to enable reflection on pre-conceptions and ideas. Two researchers (KC and DS) undertook each stage of data analysis independently. All transcripts were re-read a number of times, and each researcher's reflections on the transcripts were noted and bracketed to ensure that data-led interpretations were derived. Each transcript was analysed line by line (descriptive coding) to elicit key meanings, understandings and matters of importance to the participants (an example of this can be found in Appendix 17). Linguistic and conceptual comments were made on the data. Frequent patterns in responses were identified firstly within individual transcripts and then across all transcripts to develop themes (subordinate themes). Relationships between

themes were drawn out by two researchers (KC and DS) and organised through discussion to provide a detailed narrative of the analysis. Each stage was discussed by two researchers to ensure that interpretations were plausible, coherent and grounded in the data. The final interpretation was corroborated by anonymous data excerpts and finalised by the research team.

Reflexive positioning

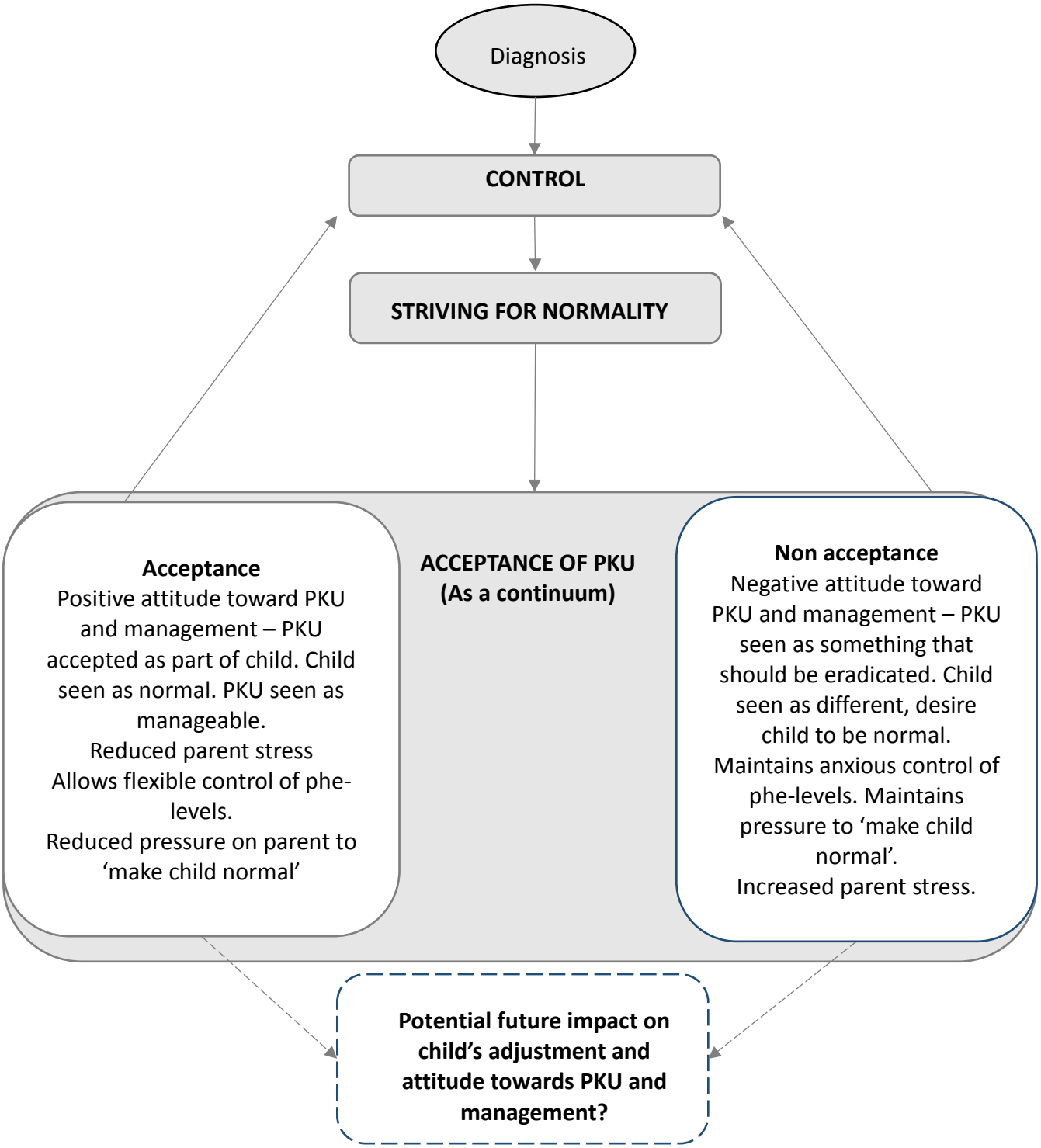
It is widely acknowledged that researchers bring their own preconceptions, expectations, knowledge and experiences to the research process. Reflexivity is an important part of qualitative research and is an attempt by the researcher to acknowledge how this may inform or influence processes and outcomes in order to maintain the integrity of the research and allow for greater transparency and replicability (Smith, Flowers and Larkin 2009). The author was undertaking a doctoral training course in clinical psychology, part of which was constituted by this research. The author had come from a predominantly clinical background prior to training, and although not a parent herself had two years experiencing working with parents of children with intellectual and developmental disabilities, which included a significant amount of post-diagnostic support for parents whose children had just been diagnosed with autism. The wider research team comprised of a health psychologist and a clinical psychologist, both of whom were parents and active researchers in the area of parenting. The author wanted to ensure that research produced clinically relevant recommendations, and the aim of the study (along with a linked project) were to use the findings to inform the development of a group for parents of children with PKU at one of the sites. The interpretative process is likely to have been influenced by these experiences, and knowledge and experiences of

using and applying psychological models and understanding experiences from a clinical psychology perspective.

RESULTS

Eighteen packs were sent out. One participant declined to participate (6%). Two parents consented to participate, but were unable to be contacted using the details provided (11%). Six mothers and one father consented to participate (39%). No information was available for participants who did not respond (44%). They were interviewed in their home and interviews lasted on average 106 minutes (range 62-137 minutes, SD=27.7). All participants were white British, married and living with their partner and child(ren). The sample size of seven was appropriate for IPA studies (Smith, Flowers and Larkin 2009). Theoretical sufficiency was obtained within this sample, comparable to other IPA studies of parents of children with chronic conditions (Schweitzer et al 2012; Smith et al 2006; Smith, Jarman and Osborn 1999). Three superordinate themes: *Control, Striving for Normality and Acceptance as a continuum* and 11 subordinate themes were identified. The three superordinate themes were closely associated with each other; first parents described a process of gaining control over the management of PKU to ensure their child was healthy and to prevent neurological damage, then establishing a 'normal' life for their child to minimise the impact of PKU on the child. The following stage of acceptance of PKU was described as a continuum, with parents' experiences falling into acceptance or non-acceptance of different aspects of PKU. The potential impact of parents' experiences and attitudes on their child's adjustment in the future is considered in the discussion. Figure 1 illustrates these themes and processes. Illustrative quotes can be found below each theme. Pseudonyms have been used to protect the participants' identity.

Figure 1: Diagrammatic representation of superordinate themes



Superordinate theme 1: Control

As parents were expected to gain immediate control of their child's blood phe-levels, irrespective of their emotional reaction, and maintain this through strict dietary control, the requirement of control manifested itself in many aspects of the parents' lives. Three subordinate themes were identified: *Fears of the consequences of non-compliance, increased personal responsibility, emotional and social consequences of control.*

Fears of the consequences of non-compliance

All parents experienced worry about being unable to control blood levels due to the serious consequence of non-compliance with the dietary treatment. The threat of brain damage was ever present, especially soon after diagnosis.

Alice: *"Some days would be good because you'd think "it's fine, it's just a diet and blah de blah"... and then you have other days when you think, well what happens if she doesn't stick to her diet… and what happens if we don't.. and you know them things that go through your head... …… you don't want your child to have any kind of brain damage do you?"*

Parents felt uncertainty about how effectively they managed the diet due to a lack of immediately observable effects of raised phe-levels and reliance on feedback from blood tests as a marker of success. This fear was exacerbated when confronted with dietary challenges, such as their child not wanting to eat or refusing supplements.

Nina: *"... I just can't help thinking, when his bloods are high... there's got to be something happening to his brain, it's got to have some sort of impact, that toxic build up..... I just don't know… so yeah it's scary..."*

Increased parental responsibility

Parents described feeling overwhelmed by the demands of care that were placed on them immediately following diagnosis. All parents reported feeling some guilt for passing down a genetic disorder.

Jemima: *"... you are their main carer and you do all the hard work as you would a normal child, so obviously... it's [child] who has the PKU but for the first good few years of their life.. it's the parents that are working hard to keep everything within range"*

Jemima: "*I felt so many emotions... I felt... my main one was guilt... like… like I felt guilty... once I'd found out that it was genetic.."*

Parents assumed exclusive responsibility for preventing neurological damage. As fear of relinquishing control by allowing others to care for their child reduced the amount of support they were able to access, support from family members was a source of both relief and further stress depending on the perceived competence of the carer to care adequately for the child. There was a reluctance to allow or burden others to care or prepare food for their child unless parents were sure they were capable of managing the diet, which all parents reported caused them to delay putting their child into nursery.

All parents reported that they adjusted their working patterns, the majority sent prepared food along with the child, and all had invested time teaching relatives and professionals before they allowed them to care for their child. Parents described this as necessary to reduce the burden on others and to alleviate their own anxieties about handing over control of their child to someone else.

Amy: "*I would have gone back part time, but it definitely impacted when they were asking me to do a third day. Because I probably would have had a third day but... I just felt that it would take away... firstly I would have had to put her in nursery and at that point I definitely wasn't ready to trust someone else with her."*

"*I think I'm quite... I like to take ownership of it... so I suppose the food diary helps me with that... erm... I like to be in control of it... so it's very much reliant on me... like... [husband] doesn't really take... much involvement at all... in... the management of his he... his diet... but... I suppose that's just how I've dealt with it... I've taken it on control... and... I'm sort of in charge..."*

Emotional and social consequences of control

Despite good self-reported treatment adherence, parents experienced continued pressure to maintain good blood-phe levels. Social situations involving food increased parental stress, anxiety and the need for 'constant vigilance' to ensure their child did not eat restricted food. Parents felt varying levels of need to 'protect' their child from situations where restricted food was accessible. All parents expressed guilt for either feeding or denying their child certain foods.

Amy: "*I remember the first one, making it and just thinking, how can I give my child this? How can I… feed my child something that smells so bad, something that I wouldn't even dream of drinking?"*

All parents reported some degree of frustration and anxiety when their child did not eat 'planned' food, for example if they had planned to give a certain number of protein exchanges for that meal and the child refused to eat it, and stress about

recalculating exchanges if their child had eaten some of the meal but required alternative food.

Some parents described feeling of failure if they were unable to provide varied, low protein food that their child would eat, and all parents felt some degree of this when blood results were high.

Emma: "*Well I'm on the phone crying, I get her on facetime (gesturing to mum)... you tell him mum, will you speak to him mum... and I don't want him to see that I'm upset, and frustrated and that I can't do it.. and then I feel like I'm... as a parent I've let him down".*

Strains on relationships were increased when this happened, because parents doubted themselves and suspecting others (partner, family members, and professionals) of giving their child something they were not supposed to have by accident when levels were high. This resulted in reduced availability and utilisation of support, which increased the burden for parents. Parents who could confidently leave their child with others felt less anxious and found time to relax.

Nina: "*I think we had three weeks where... his bloods were high... not off the record high, but higher than they should have been and higher out of the safe range... and... it was a bit like... urgh... are we doing something wrong... are they doing something wrong... and then you start to doubt the mums, you know like... and I kind of... questioning my mum, saying, are you giving him anything to drink, because aspartame... is... is... full of phenylalanine... I'm like... are you giving him something just really innocently... like a different kind of juice or... and I've had her checking all these sort of labels... in the house... and she's like, I promise you I only give him what you give me..."*

Ben: "*I find myself at work thinking... hmm I wonder what's going on now, I wonder if she's had her food, I measured it out but I wonder if she's given them or.. you know... has she given her some milk or something like that... some cow's milk to settle her. You don't know. You just think because they aren't there with us when we're talking to the doctors and stuff like that... it does... it's a challenge for me to try and wipe that out,"*

The necessity of being organised and planning meant parents lost the joy of spontaneity and were less able to engage in social activities (such as eating out). All parents were concerned that the requirements of following the diet would cause others to judge them due to a lack of understanding about PKU and its management.

Alice: "*We've got to watch haven't we, what she's doing, whereas if people have no understanding of it at all, they'll just… they'll think I'm some mad woman, you know like... going... if she starts picking something up, I'm like "NO YOU CAN'T EAT THAT" thinking I'm some kind of crazy woman, who doesn't let her kid eat… certain things.."*

Emma: "*So I could be in the supermarket for hours, and not even realise, it feels like 5 minutes to me cos I'm constantly checking everything... at first, when he was first born, I got into trouble, once, not into trouble, but I got questioned and frisked, because they thought I was a shop lifter because I spent that long in there.. looking..."*

Superordinate theme 2: Striving for normality

Parents did not want PKU to define their child or them as a family. The next step, following maintaining control over blood-phe levels and the management of PKU, was to minimise the impact of PKU on the child to ensure that they were able to live a 'normal' life. The reported impact of PKU on the life of parents was varied. All

parents wanted to ensure that PKU did not dominate their child's life, although this could have a paradoxical effect by dominating the parents' life. Four subordinate themes were identified: *a different healthy child, fears of child feeling different, effortful creation of a 'normal' life, achievement.*

A different, healthy child

Most, but not all parents felt their child was normal, but with a different diet and that PKU was only a small part of their child. Parents reflected on their child occupying a 'liminal space' between being healthy and ill (Diesen et al 2015) due to their child having a serious disorder but not being ill or having anything wrong due to the asymptomatic nature of well-managed PKU.

Jemima: *"I don't want to tiptoe around [child] and his condition... he needs to know why he can't have it... and you know... even though it's going to be a bit rough at times, that it is only food.. and... you know... there's more important things but... yeah it's hard to explain to a child why they are different and with him coming up to two... and I think he's realising he's a bit different now... but we're going to make that as positive as we can"*

Alice "*they all said that you know, it's fine, she'll just grow up to be a normal little girl, just on a special diet kind of thing"*

Amy "*Obviously we understand the seriousness of it, but it's so important for me and [husband] that we don't let it take over… don't let it define he.... it's just something that she has, it's not... doesn't make her who she is"*

Fear of child feeling different

Parents described that PKU was invisible until occasions where food was present. As food was viewed as an important part of social life, parents expressed concerns about their child fitting in, being treated differently compared to others or that their child would feel different to others or be excluded.

Jemima "*I worry about [child] going to high school... I worry about him being in primary school and being picked on... food is such a social side of your life these days... everyone goes out for tea… and stuff like that and it breaks my heart to think you know... that's gonna be difficult for [child]"*

Ben "*I mean once you're told by the doctor, look don't worry, there's people with this... this... disorder… illness, not sure... what we should be calling it really.. And they still live perfectly normal lives... cos that's all you want to hear about for your child... is that they'll live as close to a normal life as possible."*

Concerns were present and future based; parents considered both the social impact of PKU later in their child's life (e.g. at parties, school) and how they would cope with the increased demands of minimising this. Parents feared their child missing out on opportunities because of their PKU and felt determined to prevent this from happening. Parents were concerned their child would feel different within the family. Parents were navigating challenges, such as eating together, considering the impact on siblings and striking a balance that was fair to their child and did not affect family members.

Nina "*but it was hard to accept that he was going to have a different… kind of life if you like… and then I kept thinking really far in the future like… thought about when he wants to go to parties… and… other kids are eating cake and… he can't join in…*

and you know… when he's a teenager and they all go to McDonald's and he… he's just got to sit there with a little bag of fries…"

Amy *"…and when I speak to the hospital about that, they always say, take it one day at a time. Don't think about what she will have for a takeaway when she's 12. Don't think about that yet, think about today. But obviously you do think about that, you do think about what will she have when she's 12 and all her friends are ordering pizza what will she do?"*

Effortful creation of a normal life

All parents felt that PKU should not restrict their child from any normal activities. Fear of their child not being or feeling normal, motivated parents to strive to prevent or minimise any feelings of 'difference' arising from the diagnosis and management of PKU. Parents felt responsible for minimising the impact of PKU for the child. It was important to parents that the food their child ate looked similar to food others were eating.

Nina: "*The fruit and veg thing is kind of a big... is a biggie , because I like the fact that I can give them both a plate of fruit and there's no difference... there's no distinction between what they're eating... it's just the same."*

Amy: "*That's the key thing that it's helpful with, and sharing recipes, that's helpful. And lots of people do PKU and non-PKU versions and show you things you can eat together."*

Family routines were changed to ensure the child did not feel left out (e.g., not eating food the child could not have in front of them, not eating out in

restaurants). Parents experienced moment of sadness in situations that highlighted that their child was different, despite their best efforts, which motivated them to work harder to reduce this difference and their sadness.

Amy: "*But... and a lot of the time as well, [husband]'s mum and dad have her quite a bit, so at a weekend we'll either wait until she's in bed to have our tea, because we don't want to eat in front of her because we feel bad, or she'll go round there and we'll have our tea early and we'll go and pick her up, so she'll be there for an hour or so whilst we eat our tea.. just so we're not eating in front of her"*

However, difficulties in acquiring low-protein foods were considered a barrier to achieving 'normality'. Making or buying food that looked normal placed a burden on time, resources and finances. In order to make their child feel normal and included and keep them healthy, parents were required to give their child 'special treatment', and attempts at minimising the impact of PKU on the child increased the impact on parents.

Ben: "*... give [child] that reflects or looks like something that her friends are having... so when she does get to school, it's not obviously different to what everyone else is having… therefore it goes under the radar."*

Achievement

Alongside the challenges of providing a 'normal life' for their child, parents described many positive aspects despite PKU being acknowledged both as a serious and manageable disorder. Seeing their children develop normally and do things that other children did, and seeing other children with PKU doing 'normal' things gave

parents hope and reassurance that PKU had a minimal impact on their child's life, both at present and in the future.

Nina: "…*and he is... you know... he's completely met all his milestones... exceeded them in some places, so... you know... he's just a completely normal boy on this diet"*

Lucy: "…*and I can see him doing exactly the same as the other children... and they don't even know he has PKU... but he's still... just normal... you know... I find that really positive... erm... finding... you know going to a restaurant and finding something on a menu... that they do something that he can have, I find that really... I find that like a happy moment... erm. Finding something in the supermarket that he can have, that's like a really positive moment... like... I've just recently found, Tesco do some white chocolate buttons that he can have... and it's like woo! So I buy loads... erm... just little things like that I suppose, make me... give me a bit of a boost"*

Parents reflected on their ability to overcome challenges, such as taking the blood, cooking, going on holiday and returning to work and integrate it into their family life.

Jemima: *"To watch him eat something I've cooked is great….. cos it's such a major thing I think… erm... yeah.. Because it's all I'm ever thinking about... trying to think of new things for him and... Things he might enjoy... then I make something and he really likes it and I think "yeah, I've cracked it I've done it, I'm doing a good job."*

Lucy: "*We went on holiday with him... so that was lovely and I feel much happier about that now... I kind of... I was very nervous about it... but I'm really glad that we did it... and I'm determined to... not let it stop him in life... and that's sort of my outlook "*

Amy: *"I would be quite stressed about her needing it at certain times, but now I'm much more confident and relaxed, but then… I didn't know if I'd got the dose right for the Anamix [supplement] with the protein… I think I was too structured with it, but that's just what we'd been told to do so was just following that really. Yeah and then… I did just get on with it and then it very soon just became part of how it was."*

Despite challenges, parents felt the effort required to create a normal life was worthwhile and they valued reassurance that they were doing a good job. Parents described that seeing their child develop like any other child and enjoying food they had cooked made their considerable efforts meaningful. Most parents felt proud of their increasing confidence and competence in managing the demands of the diet and treatment and reported that the stress they experienced was not pervasive.

Superordinate theme: Acceptance of PKU as a continuum

Acceptance was the next stage once parents had successfully gained control of phe-levels, minimised the impact on the child and seen for themselves that PKU did not have an overwhelming impact on their child or their family. Parental acceptance of PKU was described as a continuum that parents could move along as they faced new challenges. Parents described themselves as at different points along this continuum as represented by the following five subordinate themes: *acceptance of diagnosis and management, lack of knowledge, understanding and information, support from others, becoming the expert, gratitude.*

Acceptance of diagnosis and management

Parents gave almost identical account of their feelings at the diagnosis, including hope that the results were wrong, shock, anxiety and sadness that their apparently healthy child had something wrong with him or her.

Jemima: "*Denial was my other massive thing... I just didn't want to believe... he was different... erm…… (Long pause) but yeah... I think I came across alright... but inside for a long time, I struggled a lot for a long time with [child]'s diagnosis…"*

Nina: "*I'm not depressed... I'm just sad, because of my baby, but not in a depression state... I'll get over it... but I've got to come to terms with it, because it's different and… you know... it was a big shock..."*

Parents expressed the need to come to terms with the diagnosis, although there were varying degrees of acceptance between parents. Some saw PKU as a hated or undesirable thing existing within their child. They wished that their child did not have the disorder, or that it could be eradicated and were constantly hoping for a cure or radical improvements in treatment in order to make their child 'normal'.

Emma: "*Well I ask about it every time I go. About this Kuvan [medication]... and [the] doctor explained to me that [child] can have the Kuvan if he wants on a trial for 6, 7 years… and his exchanges can go up from 13 to 30 a day. It's massive. So he says, when he explained it to me… if he wants it he can possibly go on it... but do you want him to grow to the age of 9 eating completely normal, and then at 9 having to say you can't have it no more, it was just a trial and now you've got to have your prescription food and go back to the way you were.. because they can't offer it on prescription"*

Other parents accepted PKU and its management as only a small part of their child and their life, and embraced what they had to do to manage PKU rather than try to remove it.

Alice: "*Obviously if she… I wish, no I don't wish she didn't have it, but it would be easier if she didn't have it… wouldn't it like.. for the worry and stuff but it's not I don't… think, I don't think… oh I hate PKU and grrr... Like I said she's my little girl and I'll do anything for her…. and so I am doing... you just get on with it..."*

Amy: "*I gave myself that day to kind of wallow and feel sorry for myself and that was it. It wasn't going to go away and I needed to get on with it really. This is something we can control and just… think about what we've been taught at the hospital. And it was a case of just having to get on and do it. Yeah that was it."*

Once parents accepted the management regimen, and that blood levels were not always completely within their control (e.g., when the child was ill or teething, or would not eat), they were able to adopt a flexible approach to the dietary management of PKU which reduced the stress they felt when their child was not eating. Conversely, high levels of stress were maintained in parents who were less accepting.

Lack of knowledge, understanding and information

All parents reported a lack knowledge and understanding about PKU from midwives, other healthcare professionals (GPs, chemists) and the general public. Lack of knowledge from midwives was deemed to have contributed to more intense reactions of fear and shock at the diagnosis, as all parents reported a false sense of security at the heel prick test either by midwives who stated that results were unlikely to come

back as abnormal or because they had other children whose tests had come back clear.

Lucy: ***"****This one midwife came round when he'd just come out of hospital... and... she said to me, it can be really hard when your child's diagnosed with a life threatening condition... and... thankfully at that point I knew it wasn't a life threatening condition... but., that was kind of like... it's hard when you know, when professionals don't obviously know anything about it... and when they say things like that… that... that... at the time was just kind of like... I didn't really know what to say..."*

Friends, family members and the general public were reported to frequently misunderstand PKU; parents were often asked if it was like an allergy or if their child would grow out of it. A lack of knowledge was viewed as having potentially threatening consequences (e.g., someone giving their child something with protein by accident).

Nina: ***"****(talking about having a conversation with family about what food the child can eat)**...** when we give him chips you know like... [they say] Chips?! I didn't know he could eat chips! And you go, yeah it is part of an exchange... and I feel like I have this conversation like on a loop with people... it's like... I just wish people would learn about their exchanges but... we've tried to educate our friends and family... cos we did a video like... we did a little PKU awareness thing... cos this is our next big thing... we can't change it... but it... I think probably our biggest gripe with the whole situation... the whole PKU thing, is that nobody knows about it... it's just not known..."*

Ben: *"So without doubt the diagnosis of PKU was the worst part... and we envisage it being the worst part as well... cos for us... there wasn't someone on the phone to say, look this is what she's got this is what it, this is how it's going to affect you.. by*

the way, don't worry it's manageable... we didn't have that. We didn't have that point. We were just told that this is something that is very very rare, that's all we can tell you"

Some parents felt the 'mixed messages' about PKU (treatable but serious, child is 'ill' but 'not ill') was a barrier to acceptance, contributing to feelings of uncertainty and an ever present threat of symptoms, and preventing them from resolving their feelings about the diagnosis.

Jemima *"we're treated as parents with PKU... is because of the lack of knowledge of the condition we're kind of dismissed a lot... erm... as it being not a serious condition... this is what I find frustrating as a parent.. is that people don't take the condition seriously... it is very confusing, like... you're being told how you should feel... a lot of the time."*

However, some parents felt this was a positive and hopeful as PKU could be treated to ensure 'illness' did not occur. Some parents reported that a perception of PKU as not serious meant their concerns were dismissed, leading to anxiety and frustration. Some parents felt 'it could be worse' but other parents felt that PKU was a terrible disorder to have and this attitude left them feeling invalidated, or that their negative feelings about PKU were unjustified.

Support from others

Parents described how they mitigated the lack of information and awareness from others through contact with and support from other parents of children with PKU (mostly accessed via Facebook).

Lucy: "*... I joined a Facebook group, which has been amazing... just... got so much support from other people which is really good... because I think... because it's so rare you don't ever get chance to really see other people and see what they're going through... so that way, through Facebook... I'm just really grateful for that support... so I joined that group and all then... suddenly you don't feel quite so alone when you get speaking to people…"*

Social networking sites were considered by all parents to be a valuable source of support for getting timely, practical advice about food and recipes, sharing experiences and getting emotional support they felt was lacking from professionals, although every parent interviewed praised the practical advice and support they received from professionals. All parents accessed support through social networking at the point of diagnosis and were immediately contacted by parents of children with PKU who were able to offer 'proof' that PKU had a minimal impact on child development and life prospects, and that challenges could be overcome.

Ben: "…*in terms of professional support... has been second to none."*

Nina: "*That's when you go to your PKU mums and say... I'm panicking, they've been up for this many week... what's causing it, what can I do... you know... is it going to do him any harm... and they all tell you the same thing, don't panic."*

Emma: "*If I'm out and about and I'm in a restaurant and there's something I don't know, I'll put a question on Facebook, and whoever's there, out of the thousand people, because they're from America, and everywhere, they'll jump in and answer my question for me. So I've got constant, 24 hour support."*

Parents valued family and friends doing their own research which enabled parents to accept help and support for their child from wider systems and created a 'normal' life outside the immediate family environment which reinforced a wider support and acceptance of PKU (acceptance beyond parents).

Alice: "*My mum and dad it's just the like going off and doing their own research and you know… and just… just… I think like they were very positive, you know… like they weren't going "oh my god, what has she got oh no!" they weren't like that, they were like... "look, this is what she's got, we'll deal with it, we'll be here for you, anything you need, we'll help you" erm... you know when she gets bigger they'll help with cooking and stuff."*

Amy: "*So I found it reassuring that way... but when the people that did lots of research, I appreciated that as well... just to show that you've got that support there. I did appreciate that, it made me feel… just cared for and heard."*

Becoming the expert

Parents described a process of acquiring knowledge and becoming 'PKU experts'. Many felt that raising awareness of PKU and educate others was the best way to help their child, could promote future advances (for example, supermarkets and restaurants supplying low-protein foods). Some parents became 'activists' for example organising events and raising money for charity, whereas other parents raised awareness by helping people understand PKU.

Nina: "*I mean I've kind of lived and breathed it since he was... since we found out... and you know, the dieticians said that, they said you'll probably become more knowledgeable about it than us, because... you know... he's your son and you'll do everything you can."*

Some parents were reluctant to discuss PKU with others; reasons were a wish not to make a big deal about PKU, finding it emotionally draining or wanting the child to have the opportunity to tell people themselves when they were old enough. Parents experienced conflict between wanting to spread awareness and not wanting PKU to dominate their child's narrative. Parents saw themselves in an expert role, and suggested that they could be useful points of contact for other parents at the diagnosis stage.

Emma: *"I've been into the doctors to talk about it because they didn't know anything about it... talked to the receptionist, the two doctors... and the trainee nurse to explain to them what it is... because none of them have heard about it... and they look to me to help them... and they're actually quite grateful that we've stayed with them because they've never had anyone with PKU and for them it's training."*

Gratitude

Parents who were more accepting of the diagnosis of PKU reflected more on the positives aspects of PKU. Many parents felt lucky that PKU is screened for, identified and treated early and that neurological damage can be prevented by diet. Their child's achievements were described as more special, because their child's developmental trajectory could have been radically different if PKU had not been identified and treated early.

Amy: "*I think well I'm just grateful that we got the diagnosis, that we know what we're dealing with, and that she will just be a normal little girl... if we do what we can and stick to it... so we do... think ourselves lucky. Despite everything. It could be worse, you know."*

Jemima: *"Everything is so much more special when [child] does it…... because of everything that was put against him you know... you can't help but think, 60 years ago... how different my little boy would be.. only 60 years ago."*

Some parents reflected on experiences of seeing other ill children which made them think how much worse things could have been had their child had a different, progressive, untreatable or life limiting disorder.

Nina: "*I hate the self-pity thing, I hate it... there's a lot of people worse off... in that genetics department, when we go for his appointments, that kind of brings it all into perspective cos there's some really really poorly kids in that department… and you think... gosh we're really lucky because it's just dietary, you know..."*

Not all parents felt lucky; some felt that this attitude minimised the significant physical and emotional struggles they faced daily to manage the demands of providing the special diet for their child, whilst at the same time managing the emotional aspects of the potential threat of brain damage.

Emma: "*So... you know... it's really hard.. and then you've got loads of people saying that you're really lucky, but on the other hand, you're not that lucky."*

Jemima: "*Kinda like you don't know how you're meant to feel about it... people are always saying it could have been a lot worse... I know it could have been but sometimes....that's not what I want to hear because what we've got to deal with it... has got it's own challenges and is really hard... and I feel like a lot of the time I can be dismissed by.. you know... "there's worse out there" "at least he's not dying…you're not going to lose him early" you know... obviously I'm so thankful for*

all that but sometimes I want to scream at the person saying that to me cos I just think "you just do not get it, nobody gets it unless you are living with it."

DISCUSSION

This study explored the experience of parenting a child under the age of two with PKU. The parents' lived experience highlighted three processes. Firstly, parents were required to gain control over their child's blood-phe levels from the moment their child had been diagnosed. Irrespective of parental feelings and emotional reactions, all parents were aware that their child's future development depended on their ability to manage PKU appropriately. Despite anxiety about these challenges, parents soon adjusted to the requirements of maintaining the treatment for PKU and created family routines to facilitate this. Following this, parents moved into a process of minimising the impact of PKU on their child which required considerable effort from parents as they strived to make things as normal as possible for their by changing the situation. Following successfully gaining control of PKU and witnessing their child living a normal life, most parents accepted PKU as part of their and their child's lives and adopted a 'new normal'. This is similar to the experiences of parents of children with diabetes and ASD, who reported positive experiences with their child's disorder (Kayfitz, Gragg and Orr 2010; Sullivan-Bolyai et al 2006).

Not all parents were accepting of the diagnosis of PKU; some longed to remove PKU from their child, and these parents experienced more intense negative emotions which could be comparable to grief reactions, in particular denial, anger and depression which come before acceptance (Kubler-Ross 2003). This is similar to findings of parents and children with Huntington's disease, who either 'accept' or 'compartmentalise' their feelings about the disease (Maxted, Simpson and Weatherhead 2014) and parents of children with IMDs whose greater wish is for

their child to be normal and not have an IMD (Zeltner et al 2015). It should be noted that of the three mothers with these experiences, two had experienced traumatic birth experiences, which made their experiences difficult to attribute solely to their experiences with PKU. Trauma in the perinatal period could contribute to perceptions as the child as vulnerable, the parent as unable to cope and events as uncontrollable, which is exacerbated by the diagnosis of PKU which may be perceived as a 'threat' to the development of their child (Vetrone et al 1989). This is consistent with findings that parents with high trauma scores appeared to be constantly aware of PKU as a threat to their child, or that trauma could disrupt normal process of adjusting to or resolving the diagnosis (Lord, Wastell and Ungerer 2005) and thus is something health care professionals working with parents should be aware of.

Parents of children with other disorders including PKU have reported grief reactions to the diagnosis of chronic illness or disability (Awiszus and Unger 1990; George et al 2007; Lowes and Lyne 2000). Parents interviewed reported grief-like reactions to the diagnosis: denial, anger, depression and acceptance. Parents appeared to have had had little time to address these feelings (which might not even be understood as grief due to their child being alive and healthy), as they must begin immediate care. The dual model of grief (Stroebe and Schut 1999, 2010) can be applied to the parents' experiences, because they are immediately forced into primarily 'restorative' coping (what had to be dealt with and how to deal with it) rather than the healthy oscillation between restorative and loss-oriented coping (focus on aspects of the loss itself) which ultimately contributed to resolution of grief. However, in the parents of children with chronic illness or disability, grief can be ongoing in response to continued losses or triggered by transitions in the illness (Bowes et al 2009; Collings 2008; Lowes et al 2004, 2005), which is consistent with

findings of parental acceptance as a 'continuum'. Parents of children with diabetes reported managing the treatment demands in a 'robot-like fashion' (Hatton et al 1995), suggesting restorative coping. Parents who allowed themselves healthy oscillation between loss and restorative coping early on were better able to resolve their grief and appeared to have adjusted to and reached an acceptance of PKU as opposed to parents still experiencing impaired movement between restorative or loss oriented coping. The adaptive management of PKU may necessitate more restorative coping strategies, but importance should be placed on acknowledging and validating parental feelings at diagnosis to facilitate loss oriented coping and promote healthy adjustment and an awareness that acceptance is a continuum that parents can move along in response to their experiences. It is important to note that parents of children who received positive results at newborn screening can experience the healthcare professionals as insensitive if they focus purely on medical management and neglect the parents' emotional needs (DeLuca et al 2011). Thus it is important that health care professionals are able to acknowledge and validate parents' emotional needs as part of the care they provide.

Pianta and Marvin (1992) described resolution as a well balanced view of challenges and positives, with a focus on the present and future which contributes to a more positive perception of caring for a child with an illness or disability, which enables parents to move on with their life. Unresolved parents show negative biases regarding the illness or disorder and their child, are preoccupied with the illness and may be detached or confused about their feelings towards the diagnosis (Pianta and Marvin 1992) which has implications for both their mental health and parenting.

Appraisals of threat or stress may influence parental acceptance of PKU. According to the Stress-Coping Model (Lazarus and Folkman 1984), event-specific appraisals determine coping. Unresolved parents might have appraisals of their child

as vulnerable (commonly found in chronic illness), themselves us unable to cope and the threat (in this case PKU) as out of their control. Although this might lead to 'adaptive' coping strategies such as strict control, it may maintain anxiety or trauma reactions which can increase stress for parents and lead them to utilise disproportion strategies to minimise threat, which could result in the use of overprotective or restrictive parenting strategies which restrict the child's emotional or social development. This is consistent with findings from Jusiene and Kucinkas (2004) who observed more maladaptive parenting strategies in parents reacting to the diagnosis of PKU with anger or guilt and is similarly observed in parents of children with nut allergies who reduce risk and anxiety by avoiding any potentially threatening situation (Bollinger et al 2006). This is consistent with findings of Awiszus and Unger (1990) who describe coping as an attitude, not a behaviour.

Parents' experiences and appraisals seem to be affected by the communication of the diagnosis, which occurs at a time when parents have just had a new baby and may feel vulnerable and inexperienced. A lack of information and dissatisfaction with communication of abnormal screening results at the point of diagnosis increased parental distress and improved information helped mitigate uncertainty and shock (Buchbinder and Timmermans 2012).

Strengths and limitations

This is the first qualitative study to explore the experience of parenting a child with PKU from a clinical psychology perspective in the UK. However, there are some limitations to this study. All parents interviewed reported good treatment adherence so there was no representation from parents who struggled to control blood-phe levels. Parents were all married, financially stable and educated, with high levels of

family support, although these are typical samples of parents of children with IMDs who volunteer to participate in research (Cederbaum et al 2001; Packman et al 2007). Despite these characteristic, difficulties in terms of acceptance and coping still emerged and provided insight into the experiences of parenting for this population. Only one father participated, so limited conclusions can be drawn about how paternal and maternal experiences might differ, although research with parents of children with IMDs has suggested that mothers and fathers have different psychological experiences (Lord, Wastell and Ungerer 2005; Lord, Ungerer and Wastell 2008; Vetrone et al 1989).

Practical implications

Healthcare professionals can find it difficult to deliver bad news and often feel they have insufficient knowledge and training regarding this (Fallowfield and Jenkins 2004; Finan et al 2015; Warnock et al 2010) which may affect the quality of information imparted when communicating positive results at newborn screening. There may also be a lack of understanding about how people cope with receiving positive screening results, which represents a role for clinical psychology input into training professionals delivering results. Given the influence of the information received on subsequent parental appraisal of PKU, it would be beneficial for this information initially to be communicated by someone with a comprehensive understanding of PKU who can provide parents with balanced and accurate information, has a good understanding of the emotional processes involved and is skilled in sensitive communication to reduce the emotional impact of the diagnosis. Parents have requested that professionals relaying information about newborn screening have adequate information, avoid jargon, listen carefully, encourage

questions, acknowledge and validate parental distress, offer realistic reassurance and refer to specialists (Salm, Yetter and Tluczek 2012). Good quality information has been shown to provide a buffer against negative emotional reactions and facilitate better adjustment (Waisbren et al 2003).

Parents should be given time to discuss and process their feelings about the diagnosis with a trained professional (e.g. clinical psychologist, mental health professional or genetic counsellor) or expert by experience, as acknowledgement and validation of parental feelings can promote healthy adjustment. It is important that parental emotional wellbeing is considered alongside providing practical or medical advice about the management of PKU and that parents' feelings are validated and normalised to help facilitate adjustment. Health care professionals should be aware of any experiences ante or perinatally that could disrupt emotional processing of the diagnosis (e.g., traumatic birth) (Lord 2008).

Acceptance of the diagnosis should be explored with parents, given the high association with parent stress, anxiety and depression (Lloyd and Hastings 2008). Cognitions about the disorder (level of threat, controllability) could usefully be modified using cognitive therapy to help parents develop a more balanced view of PKU and its prognosis. Parents who have not accepted the diagnosis are more likely to perceive PKU as a threat, and when in 'threat neutralisation' mode may be less available to meet their child's emotional needs, which could affect the attachment relationship (Jarvis and Creasey 1991) and parenting styles (Fehrenbach and Peterson 1989; MacDonald et al 1997). Resolved parents may have more positive or realistic appraisals of risk, the controllability of PKU and their ability to cope, which enables them to use more adaptive and flexible coping strategies. Acceptance based therapeutic interventions have been shown to reduce depression and anxiety and

facilitated better adjustment in parents of children with autism (Blackledge and Hayes 2006) which could be beneficial for parents of children with PKU.

All parents interviewed desired more contact with other parents of children with PKU and valued input from health care professionals to facilitate this. It would be beneficial for health care professionals to facilitate such meetings to allow parents to see that PKU can have a minimal impact on other children (promoting a more balanced view of PKU) and to meet other parents and share experiences and expertise. Social support groups have been found to improve sense of agency and control, give a sense of belonging to a community and promote self-change (Solomon, Pistrang and Barker 2001). Specialist health care professionals could provide support and training to family members and other professionals involved in the child's care (Packman et al 2007). This would reduce parents' anxiety about entrusting the competent care of their child to others, which would reduce the burden on parents, increase support networks and improve parental wellbeing as social support has been identified as a strong mediator of stress, distress and quality of life in parents of children with PKU (Fidika et al 2013, Hatzmann et al 2009).

The research indicates a need for clearly defined post-diagnostic pathways that offer comprehensive support for parents throughout the process outlined in the results. Firstly, parents would benefit from receiving correct and complete information about PKU to provide a balanced view of PKU and reduce likelihood of negative cognitive appraisals. Secondly, support in the emotional processing of parental reaction to diagnosis through normalising and validating and extra support where indicated (e.g. counselling). Thirdly, support with the practical management of PKU (e.g. cooking, problem solving skills, support interacting with other professionals) to reduce parent stress and improve self-efficacy. Alongside this, parents should have the chance to meet other parents, children and adults with PKU

to promote acceptance and a positive attitude towards PKU. Lastly, there should be regular screening for parental mental health problems, coping and emotional wellbeing alongside medical and practical support.

Research recommendations

It would be beneficial to extend this research with a more representative sample; for example, parents of different socio-economic status, single parents or parents who are struggling to adhere and with a wider age range to explore whether the processes reported by this sample are similarly experienced in parents of children of different ages to verify if this model is applicable to parents more generally. Investigation into the impact of parental acceptance and attitude on child's attitude towards PKU and its management would be beneficial to extend this model. Further examination of the role of acceptance in parental wellbeing could be usefully explored in parents of children with PKU using quantitative methods. The development and evaluation of interventions with parents as outlined above could be investigated to see if they have a positive effect on parental wellbeing. It would be beneficial to explore health care professionals' experience and views on support for parents and the impact of PKU on their parenting to supplement the findings of this research. Given the importance of communication of the suspected diagnosis at the heel prick test, gathering the perspective of midwives who have communicated suspected PKU results to parents would be beneficial to see how this could be improved from their perspective.

Conclusion

The current study has presented parents' experiences of the processes they engage in when parenting their child with PKU. Establishing control over the treatment

requirement and minimising the impact of the disorder on the child may be independent of parental acceptance of the diagnosis. It has emphasised the importance of the goal of 'normality' and role of acceptance and how this influences parental perceptions, motivations and behaviour. The point of diagnosis has been acknowledged as a key experience in parents' lives which sets the context for the later process of control, striving for normality and acceptance, which has implications for improving the diagnostic process to promote better parental adjustment.

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Paper 3

Critical Appraisal

This paper is not intended for publication and thus no particular journal guidelines have been followed.

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INTRODUCTION

The following paper presents a critical appraisal of the research conducted as part of this thesis. It offers a critical reflection on the development, planning, implementation of the research processes of both the literature review and empirical papers. The strengths and limitations will be discussed along with reflections on the research process as whole and other issues that arose during the course of this research.

PAPER 1: SYSTEMATIC REVIEW

Rationale for topic and developing the research question

The decision for the topic of the literature review was guided by the developing aims of the empirical paper. Through discussion with supervisors and clinicians, it was decided that both projects would focus on the experience and psychological wellbeing of parents of children with PKU (with relation to treatment adherence and parenting), and initial scoping exercises suggest that there was a dearth of research in this area. The role of parents had been highlighted as very important in the management of inherited metabolic disorders (IMDs), and there is an increasing recognition of the impact of psychosocial variables on physical wellbeing and management in health conditions (McLeod 2003, De Ridder et al 2008). The psychological impact of both the diagnosis and care process on parents has been well documented in other childhood conditions (e.g. Besier et al 2011; Stewart et al 2016). The National Society for Phenylketonuria (NSPKU) highlights the importance and inclusion of the role of psychologists in providing multidisciplinary care to people with PKU and their families that addresses psychosocial factors along

with medical management, with specific acknowledgement of the role of psychosocial factors in dietary adherence (NSPKU 2014). Through clinical discussion with field supervisors, it transpired that there are few psychologists in the UK who specialise in IMDs; the British Inherited Metabolic Disorder Group for Psychologists has only 11 members and the services that we visited had varied levels of psychological input.

Initial searches of the literature revealed that there was a small evidence base of psychological research with parents of children with PKU, thus the search was expanded into other IMDs (discussed in the next section). Most existing research was medical or genetic, and concerned with treatment advances and adherence. A smaller subset of psychological research focused on patients or family functioning. There had recently been an increase in research conducted into quality of life of both parents and children (including a recent review) and psychological research with parents, of which a very small proportion was qualitative, thus the decision was made to exclude this from the search as they did not fit the research question.

Prior to arriving at the final topic, a number of other options were considered, including parenting in IMDs, parent experiences of caring for a child with an IMD and parents' experiences of the diagnosis following newborn screening, however none of these searches yielded enough results to conduct a meaningful review. Thus, it was decided in conjunction with supervisors to focus on the psychological impact of caring for a child with an IMD, as this would encompass both the impact of the diagnosis and the ongoing impact of the care process.

Development of search terms, inclusion criteria and searching the evidence

Although PKU was the most researched IMD, there was not enough data to conduct a systematic review on PKU alone. Thus search terms were expanded to include other IMDs. This posed a challenge as there are hundreds of IMDs, and no definitive list of all IMDs is available. To maintain links with empirical paper, it was decided to focus on IMDs that are diagnosed either by newborn screening or soon after birth, which can be treated with diet/supplements to prevent most neurological or physical damage (Saudubray, Sedel and Walter 2006; van Karnebeek and Stockler 2012). This again posed problems, as there are wide variations internationally regarding what disorders are screened for in newborn screening. A core set of disorders, routinely screened for internationally, specific categories of IMDs and all possible permutations of IMDs were chosen as search terms (see Appendix 2) to overcome the challenges of articles using specific IMDs as key words rather than generic terms for IMDs and the variability terms used to describe IMDs. This more inclusive criteria, combined with thorough searches of reference lists was considered beneficial to prevent relevant papers being missed, and this was evidenced by the addition of a paper on Glycogen Storage Disorder Type I, which is not routinely identified by newborn screening, but is generally diagnosed soon after birth and is deemed treatable.

Another challenge was the studies conceptualisation of psychological impact, which was inconsistent across the literature. To overcome this, comprehensive search terms were used that had been identified in similar previous reviews and papers were cross-referenced with the trainee working on the linked project, which ensured that no papers and terms were missed. However search terms were perhaps over inclusive as they produced large numbers of irrelevant papers due

to terminology that could be applied to psychological and genetic/medical constructs (e.g. maternal, adaptation). If this review were to be done again, it would be beneficial to refine the search terms to reduce the amount of screening by hand, which would strike the balance of breadth of search whilst minimising number of irrelevant papers (Smith, Devane, Begley and Clark 2011). Although this process took longer, the trainee was confident that all relevant papers were identified. Non-English studies were excluded due to limitations in resources for translation. The exclusion of grey literature (doctoral theses, conference presentations etc.) was considered, as its inclusion may have mitigated against the widely recognised publication bias, however it would have been difficult to include many of these sources of information due to incomplete information (e.g. limited information or only abstract presented), quality and accessibility issues (Conn, Valentine, Cooper and Rantz 2003, Hopewell, Clarke and Askie 2006, Sacks, Reitman, Pagano and Kipelnick 1996). With regards to data extraction, it would have been beneficial for a proportion of this to be cross-checked by an independent researcher, however time constraints prevented this.

Quality assessment

Quality assessment tools are usually concerned with studies of similar designs. This posed a challenge due to the diverse designs of the studies that were included to answer the research question. Different tools were considered in discussions with supervisors and peers, and the decision made to use Quality Assessment Tool for Studies with Diverse Designs (QATSDD; Sirreyeh et al 2012) used in the linked project due to good fit with the included studies and familiarity with the tool. This was beneficial as both researchers were conducting inter-rater reliability checks for each other's ratings, which yielded similar scores (k=0.71 and 0.70 respectively).

This was a helpful tool to use, both in quality assessment and considering the quality of the empirical paper and the trainee found it straightforward to use, given her lack of experience in quality assessing studies. It has been used in a number of systematic review studies although it is not without limitations including the need for more explicit guidance for item ratings (Fenton, Lauckner and Gilbert 2015)

Write up

Meta-analysis was not deemed suitable for this review, due to the disparity between how psychological impact was conceptualised and measured in the literature which meant it was impossible to statistically pool the result. Thus a systematic review was conducted of the quantitative literature. It was interesting to note the different emphasis, approaches and language used by professionals from different disciplines and this was an important factor to consider in choosing an appropriate journal for submission. This process was difficult, as the trainee had to ensure she clarified the terms used whilst still writing in a concise manner.

Strengths, limitations and future research

It could have been beneficial to focus just on PKU because this does not come with a threat of metabolic crisis. However, there are still serious consequences if left untreated and this is similar to the other IMDs that are included in the review so it was deemed to be beneficial that the review covered a range of disorders. Only a small proportion gave an indication of either the severity of the disorder, or impact on child functioning, which would have strengthened findings. Another limitation is the quality of the studies included in this review. Due to a paucity of literature in this area the decision was made to include all studies in the review irrespective of quality scores; however despite lower ratings (which were often related to low scores with regards to sampling) these studies still added valuable information and there was no

link between poor quality of studies and anomalous results. Another limitation was that limited cause and effect could be established due to the inclusion of mainly cross sectional studies with no longer term follow up. The exclusion of qualitative literature was considered, as one paper was relevant to the research question. On reflection, it may have been beneficial to include this, as the findings were in line with the quantitative findings, however for the purpose of the review, it was difficult to compared themes elicited to quantitative reports in a way that added meaning to the review.

Future research could include qualitative research, as the 'voice' of the parents is missing in this area, which would further add explanation about how this psychological impact is experienced by parents. Qualitative and quantitative research both have a place in exploring factors that influence the role of psychological impact, and more longitudinal studies are required to examine this over time. The literature identifies a clear need for interventions for parents to be developed and evaluated.

PAPER 2: EMPIRICAL PAPER

Development of the question

The choice of age range was consistent with the one paper that explored qualitatively the experience of parents of children with PKU (Awiszus and Unger 1990). Clinicians noted that between 6 and 9 months parents have good control over the blood phe-levels of their infant, although no papers reported on blood-phe levels of very young children. Between 6 and 12 months weaning begins in children with and without PKU (MacDonald et al 2012; WHO 2001) and parents begin to introduce formula and supplements alongside phe-free foods. At around 12 months old in the UK primary caregivers are generally returning to work and entrusting their childcare to another person, a challenge identified in the literature in other chronic condition. The choice to expand the age range up to two years was made for practical recruitment reasons, as well as wanting to encompass the parents' experience of these processes, not just at the start of them. A number of developmental theories highlight this age range as important for children. From a psychoanalytic perspective, between 9-24 months the child is beginning to realise psychic separation from the mother, developing its identity and cognitive abilities and beginning to explore the world (Mahler 1972). Erikson's (1959) theory of psychosocial development identified this time period as spanning the stages between a child being reliant on and trusting its primary care givers to provide food, comfort and affection, to developing motor skills, exploring the world, becoming more independent, wanting to meet its own needs, assert its independence and 'rebel' against the authority of its parents which could cause conflict with parents. According to Piaget's theory of cognitive development (1953), the child is in the sensorimotor stage of development, in which is constructing knowledge of the world through physical interaction with it, including

taste. These normal developmental stages could cause anxieties for parents of children with PKU, where control over the infant and prevention of the consumption of food are high priorities. In the UK, all children with PKU are entitled to 15 hours a week of free nursery care at the age of two so this is something that parents might be beginning to consider. This time period was selected due to the challenges that are beginning to arise; however, it is noted that two years of age is an arbitrary cut off point. It is well known that childhood illness or disability can make the task of parenting more challenging, and this is a particular challenge in PKU as illness or disability has not yet occurred, nor might it if treatment is adequately managed. Because of this, treatment adherence is a priority for clinicians working with children and families, but psychosocial factors are an important influence on parental management and wellbeing. Thus their experience and how they make sense of this is an essential part of being able to provide better care and the broad 'experience of parenting' within a specific age range was considered an appropriate research question.

Methodology

Experience is based on the subjective experience of the person experience of the phenomenon in question, thus qualitative methods were deemed appropriate to investigate the research question, as they allow access to rich descriptions not offered by quantitative designs.

Different methodologies were considered. Thematic analysis was considered too broad and would miss the rich understanding of how participants make sense of their experiences. Grounded theory was considered, although the aim of the study was not to create a theoretical understanding, but to understand parents' experiences. Interpretative Phenomenological Analysis (IPA; Smith, 1999) was

deemed the ‘best fit’ for the research question, the aim was to capture the way a phenomenon is experienced in the context in which it takes place (Giorgio and Giorgio 2008), in this case the experience of parenting a child with PKU under the age of 2, not just to describe experiences, but making conceptual sense of their accounts (Smith and Osborne 2008). IPA has been widely used to explore experiences of parents in other health conditions (Smith et al 2006; Schweitzer et al 2012). IPA is inductive, and attempts to understand experiences and the meanings ascribed to them without prior assumptions being made (Reid, Flowers and Larkin 2005). This was beneficial because the trainee did not have exhaustive knowledge about PKU and had few preconceptions about the experiences of parents.

Developing the interview schedule

Parenting was defined as “the process of promoting and supporting the physical, emotional, social, financial, and intellectual development of a child from infancy to adulthood... the aspects of raising a child aside from the biological relationship” (p245, Davies 2000). This definition informed the development of the interview schedule, as it was acknowledged that parents are more than the enforcers of medical management of their children (reference when parenting becomes caregiving). The interview schedule was informed by the literature and developed in conjunction with clinicians. It was approved by the university Community Liaison Group and the National Society for Phenylketonuria (NSPKU). It was loosely structured, without being directive and designed to be flexible, to ensure that participants were talking about the experiences that were important to them, rather than areas deemed important by clinicians. According to Smith (2009), qualitative research requires flexible data collection tools, which allow researchers and participants to engage in a dialogue where questions can be modified and followed up as participants respond

and probe interesting and important areas as they arise. These were not restrictive, and allowed for parents to speak freely about their experiences. Four main areas were identified experience of diagnosis, demands of parenting, challenges and support. It was challenging to produce questions that were specific to the area without being too directive. Parents were given the prompts about any positive experiences, as the literature identified that parents can draw positives from their experiences and this is an essential part of the sense-making process.

Patient and Public Involvement

The importance of public involvement is endorsed by the Health Research Authority who stated that "involving patients and the public in health research will improve it by ensuring it is relevant to the needs of patients and more likely to have an impact on their health and wellbeing" (Tarpey and Bite 2014) Both linked studies were approved by the University's Community Liaison Group and the NSPKU Committee of Management who approved the studies as it fitted in with their recent investigations into quality of life of people with PKU and their families. Ideally it would have been better to include stakeholders in the development of the research, but time constraints prevented this.

Setting up the research

This research project was linked to another trainee's project. Although these were different studies, this allowed a joint ethic application to be submitted and recruitment to be shared. Working with another trainee was beneficial as it enabled sharing of the workloads of liaising with and engaging three separate sites. Positive relationships were built up with teams at the three sites through meetings and presentations, which provided a chance for clinicians to have input into the research to maximise its clinical relevance and utility. As a new researcher, the trainee was

surprised at how much work was involved liaising with REC committees and R&D departments, but enjoyed meeting with clinicians and learning about services, and developing clinically relevant research with experts in the field.

Challenges of recruitment

Parents were recruited from three sites, at which they were required to attend regular appointments with their child. As per approved protocol parents were first introduced to the study by letter and clinicians from the clinic, who agreed to promote the study. Although this was beneficial, this input was sensitive to fluctuations in dietitians' workload, as would be expected in a busy NHS clinic. Recruitment was, as anticipated, reliant on postal invitations.

Significant attempts to boost recruitment were devised in consultation with clinicians at the three sites. The trainees attended clinics to speak to parents, put up posters, and advertised on social media. Liaison with the NSPKU and moderators of active PKU support groups on social media allowed engagement of a wider audience through promotion of the study in newsletters and social media, which further legitimised the studies for parents as they were coming from trusted sources. The trainees were invited to a Christmas party run by clinicians for parents and families to promote the study, which was a good way to boost recruitment, meet families and children and network with other professionals in the area.

Additionally, two parents consented to participate but were unable to be contacted. Although not stated in the research protocol approved by the Research Ethics Committee, the decision was made to contact the participants three times by phone, with a text message, answer phone message or email to give them a choice about participation. Participants were also reminded of their right not to participate and if they expressed this wish they would not be contacted again. Despite

challenges, recruitment was successful, with seven parents recruited, in line with Smith, Flowers and Larkin's (2009) recommendation of recruitment of between four and ten participants for doctoral level studies utilising IPA. Small sample sizes are appropriate for IPA studies as generalisability to wider population is not the aim. Reid et al (2005) noted that 'less is more' with recruitment, emphasising richness of data as opposed to numbers; however, it has been noted that there is often a pressure from supervisors and ethics committees more familiar with quantitative methods to increase recruitment (Hefferon and Gil-Rodriguez 2011).

This method of recruitment has its limitations. Participants could have been recruited from support groups, but the link study was tied to clinics as it required access to medical data and further challenges could have been presented with regards to distance to travel for interviews. The pros and cons of telephone interviews were considered as this has been shown to be a good way to access hard to reach participants but also limits the amount of important ethnographic and contextual information that can be gathered (; Holt 2010; Irvine, Drew and Sainsbury 2013; Sturges and Hanrahan 2004). It was the personal preference of the trainee to conduct face-to-face interviews with parents.

Interviews

Parents preferred to be interviewed in their own home, despite being given a choice of location; this may have been motivated by child-care issues as all parents had young children. Research suggests that the location of the interview holds significance for the data collected (Herzog 2012). The home felt an appropriate location, as it was not at the clinic which could pose fears of information being passed to care-providers, and emphasises the separateness of the research from clinical care. It allowed access to invaluable contextual factors, with opportunities to

meet children with PKU and sample PKU food. This was not without difficulties. The home environment was full of disruptions and distractions due to the presence of children and other family members, however this was overcome by noting the line of discussion prior to the interruption to ensure a smooth flow of the interview and was reflected on in analytic diary. One interview was particularly difficult as the participant's mother was present, however the transcript was coded without the mother's input to minimise contamination. Researcher safety was considered when conducting interviews in the home environment. To protect anonymity clinicians were asked about any risk issues regarding home visits for all invited participants prior to any parents consenting to participate. The University of Manchester lone working policy was followed for each home visit (see appendix 16), however the trainee did not feel in any danger at any point during the research process.

There are a number of ethical considerations in conducting interviews. It has been noted that qualitative interviews often access 'sensitive' phenomena, which require clear management protocols to protect the wellbeing of participants and researchers (McCosker, Barnard and Gerber 2001). There was a further considerations of the multiple role played by the researcher. Thomson and Russo (2012) stated that clinical psychologists need to reflect on the difference between gathering information for research and building therapeutic relationships that facilitate change. It was important to manage this by being clear about the role of the researcher, which was facilitated by the by the trainees identity as a 'student' unaffiliated with the clinics. Brinkman and Kvale (2008) noted that clinical psychologists undertaking research have the unintentional opportunity to misuse their skills to access information that people are unwilling to share. The importance of doing no harm to participants was paramount. Robust distress protocols, thorough

post-interview debriefs and good supervision ensured ethical practice and the wellbeing of participants. During interviews, some parents were emotional but not distressed to a point which concerned the trainee. Parents were given control over their participation, the information they shared and their well-being was placed above the collection of interesting data (Charmaz 2014).

During interviews the trainee aimed to adopt a stance of not knowing which included openness, active attention and suspension of a preconceptions (Finlay et al 2008). Interview techniques were practiced prior to interviewing parents and reviewed with the supervisor which allowed for interview techniques to be refined. A prepared statement (appendix 13) was read at the start of the interview and parents were provided with a copy of the interview schedule. The trainee aimed to enter each interview as a 'blank slate' although acknowledged it is not possible to attain this. Despite this the training tried to approach each interview with curiosity and gain specific information about the parent's experience and what it meant to them. Sensitive topics arose such as disrupted bonds with their children following diagnosis. The trainee was inquisitive but respectful and sensitive to non-verbal cues and aware of times where she did not ask questions for fear of how they would be perceived by the parents. This was noted in the analytic diary and taken to supervision to reflect upon. The trainee ensured she had a full day to conduct interview which enabled adequate time for reflection.

Analysis

IPA is flexible, and it is noted that there are variations in the analytic process due to IPA being considered a 'perspective' or 'approach' rather than a method' (Larkin 2006). The trainee transcribed all of the interviews, which was laborious but allowed full immersion in the data which aided subsequent analysis. Recording were listened

to several times which allowed identification of meaningful data which had not been noted at the time of interview. In discussion with the supervisor the trainee chose to do the analysis by hand which she felt kept her closer to the data but made it harder to replicate. Analysis was done in conjunction with the supervisor who undertook independent concurrent analysis. This allowed the identification and verification of key themes and conceptual links, and discussion of influences on the analytic process. During interpretation, the trainee drew on psychological theories and approaches she had encountered on placements, such as Acceptance and Commitment therapy. It was valuable to be able to conduct this research with a supervisor experience in qualitative research, and it enabled coherent and plausible narratives to be developed, and increased the credibility of the findings with this additional verification. The supervisor was from a different professional background (health psychology) which brought a different but valuable perspective to the data.

Supervision

Supervision was a useful place to discuss influences on and interpretations of the data to ensure that these remained grounded in the data. Supervision was also a space to reflect differences between clinical and research interviews and provided a space to review transcripts for evidence of this. The trainee was surprised at how she was able to suspend 'therapist mode' but was aware of the influence of theoretical models and clinical approaches during analysis and was able to reflect on these in supervision.

Strengths, limitations and future directions

This thesis has good clinical relevance as field supervisors were in the process of piloting a support group for parents, with an aim that the findings of this both linked

projects would inform the content and structure of the group. However it should be noted that there are limitations with sampling. Although IPA requires homogeneous samples, due to wanting to explore the experience of a particular group of people, the sample itself was made up of mainly white, married mothers in the teaching profession (four out of six) who maintain good treatment adherence. The implications of generalising these findings to other parents of children with PKU under the age of 2 must be considered. Although there were good clinical and theoretical reasons for using an age cut off, the specific age of two could still be viewed as an arbitrary cut-off point.

The results of the empirical paper (Paper 2) extended the findings of the review (Paper 1). This paper highlighted the diagnosis of PKU as a critical time for parents which has an influence on the attitudes towards PKU as their child grows and how they maintain treatment adherence. Healthcare professionals need to be aware of parental appraisals of PKU, which maybe formed at the point of diagnosis, and offer appropriate support. Lack of information was considered a barrier for parents in accepting and integrating PKU into their lives and a source of stress. It also emphasised the role of acceptance in parental well-being and the importance of emotional support alongside practical support. The findings complemented the findings of the linked project which indicated that treatment adherence was not related to parental well-being and that parents who experience high levels of psychological distress still maintain adequate treatment adherence. Future research could usefully include expanded age ranges to see if the findings with parents of children over two yield similar results and it would be valuable to develop and evaluate interventions to improve psychological wellbeing in parents.

Dissemination

Alongside being prepared for publication, summaries of this research are being provided to the NSPKU, clinicians at all three of the recruitment sites, interested parents and on Facebook support groups to ensure that the research findings are as accessible as possible. Publication in journals does not ensure that everyone who could benefit from the research has access to it, including participants who are interested in the results. Often results are not fed back to participants which represents an ethical shortcoming (MacNeil & Fernandez 2006). The trainee was mindful of how communicating the findings to participants may be different from writing for publication, both in the amount of information, tone and presentation.

OVERALL REFLECTIONS

Although the trainee has been involved in short pieces of research previously, this was the first experience of being involved in a research project from conception to end. The trainee had ongoing reservations about her research competence which oscillated with the changing demands of the research, from feeling excited and enthused to anxious and incompetent. Prior experience conducting doctoral standard research may have better equipped the trainee to manage the challenges more confidently however this was mitigated against by supportive supervisors. A positive of this experience was working alongside another trainee which enabled the sharing of ideas and workload and provided a considerable source of support. As the research process was not consistent in terms of demand (i.e. meeting participants) it was sometimes difficult to balance the demands of the research with being on a clinical placement and maintaining a good work life balance. However, this has been an important learning process with regards to time management skills and organisation.

Paper 1 was the trainee's first experience of conducting a systematic review. Prior to undertaking this review, the trainee did not fully appreciate how rigorous and time consuming this process was and how many stages were required. This was the paper that most made the trainee question her competence, although it was a relief to find that colleagues have similar experiences. Through the attempts at finding a suitable topic, the trainee was able to familiarise herself with a vast amount of literature regarding the overall thesis topic area and how different studies have been designed and conducted and how quality appraisal work which was useful when considering the empirical paper.

Paper 2, although not the first experience with qualitative research, was the first time the trainee had used IPA. The trainee enjoyed exploring the philosophical underpinnings of this approach and the relevance of the approach to clinical practice. The trainee also considered how qualitative research was viewed in the wider scientific community given the medicalised nature of the thesis topic area.

This process provided a realistic expectation about conducting research alongside other significant clinical responsibilities. Although the trainee recognises the important of contributing to the research base, she also considered the feasibility of conducting research in a qualified post. Trainees have the luxury of dedicated research time, however in qualified posts less time is ring fenced for research and services often struggle to release clinicians from their clinical commitments for research. This is a particularly pertinent issue in a time of economic austerity in the NHS, where demand for services is high and resources are low, which may explain the low rates of research output from qualified clinical psychologists (Eke 2012) however Elphinston and Pager (2015) noted that psychologists have better workload capacity for conducting research and that tapping this potential is important to

improve health-care delivery. The trainee considered that if she were given the opportunity to be involved in research in the future she would need to make appropriate arrangements to ensure it could be adequately completed alongside clinical work.

The trainee is aware of the importance of research findings and examples of good clinical practice being properly disseminated. During this process, and on clinical placement, the trainee has seen that often valuable clinical innovations are often not written up for publication, which means they cannot reach a wider audience and contribute to the evidence base. This is essential to ensure that the best standard of care can be provided to service users, through implementation of identified and evaluated best practice based on a methologically sound base of research.

The trainee has reflected on how this process has contributed to her current clinical work specifically with regards to paying close attention to how people construct their stories, the language they use, the subtleties of what people say and mean and our propensity to fill in that gap with our own preconceptions. Through using IPA and being increasingly aware of the influence of her own preconceptions when interpreting experiences, the trainee feels she has enhanced her clinical work. The importance of service user involvement is something that the trainee feels strongly about as parents she encountered were motivated advocates of their child and were committed to patient led care; this is something she will continue to consider in future clinical and research endeavours. Overall, the trainee feels a sense of achievement regarding this process, and although it has been challenging, it has been a valuable learning opportunity.

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Appendices

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Appendix 1: Guidelines for authors submitting to Journal of Child and Family Studies

Journal of Child and Family Studies

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ISSN: 1062-1024 (print version)
ISSN: 1573-2843 (electronic version)
Journal no. 10826

Instructions for Authors

Journal of Child and Family Studies

GENERAL

In general, the journal follows the recommendations of the 2010 Publication Manual of the American Psychological Association (Sixth Edition), and it is suggested that contributors refer to this publication. The research described in the manuscripts should be consistent with generally accepted standards of ethical practice. The anonymity of subjects and participants must be protected and identifying information omitted from the manuscript.

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A title page is to be provided and should include: (1) the title (maximum of 15 words); (2) full names of the authors (without degree), with a bullet between the names of the authors; (3) brief running head; and, at the bottom of the title page, (4) the corresponding author’s initials and last name (without degree), affiliation, mailing address, and e-mail address. The initials and last name of all authors should be listed as well. All authors from the same institution should be listed together, with a bullet separating the names. For all, but the corresponding author, list the affiliation, city and state only.

Abstract

The abstract should be between 200 and 250 words. It should be concise and complete in itself without reference to the body of the paper. In addition to a general statement about the field of research as the first sentence, abstracts of experimental/research papers should contain a brief summary of the paper's purpose, method (design of the study, main outcome measures, and age range of subjects), results (major findings), and clinical significance. Abstracts of review papers should include a general statement about research area being reviewed as the first sentence, it should contain a brief summary of the review's purpose, method (data sources, study selection process), results (methods of data synthesis and key findings), and conclusions (summary statement of what is known, including potential applications and research needs). Do not use sub-headings and do not cite data or references in the abstract.

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Cite references in alphabetical order within the text.

References

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• last names and initials of all authors,

year published (in brackets)

title of article

name of publication

volume number

and inclusive pages

Do not include issue numbers of journals unless each issue begins with page 1. For book chapters, include volume number (if applicable) and page numbers, as shown below.

Consult the Publication Manual of the American Psychological Association, 6th Edition (Chapter 7) for formatting references. The style and punctuation of the references should conform to strict APA style – illustrated by the following examples:

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Roelofs, J., Meesters, C., & Muris, P. (2008). Correlates of self-reported attachment (in)security in children: The role of parental romantic attachment status and rearing behaviors. Journal of Child and Family Studies, 17, 555-566.

Book:

McBee, L. (2008). Mindfulness-based elder care: A CAM model for frail elders and their caregivers. New York: Springer.

Book Chapter:

Singh, N.N., Winton, A.S.W., Singh, J., McAleavey, K., Wahler, R.G., & Sabaawi, M. (2006). Mindfulness-based caregiving and support. In J.K. Luiselli (Ed.), Antecedent assessment and intervention: Supporting children and adults with developmental disabilities in community settings (pp. 269-290). Baltimore, MD: Paul H. Brookes.

Tables

Tables follow the Reference section. Create tables using the table creation and editing feature of your word processing software (e.g., Word) instead of spreadsheet programs. Tables that are a single column are actually lists and should be included in the text as such. Number tables consecutively using Arabic numerals in order of appearance in the text. Cite each table in the text and note approximately where it should be placed. Type each table on a separate page with the title and legend included. Double-space the table and any footnotes to it. Set each separate entry in a single table cell. Do not use underlining. Properly align numbers, both horizontally and vertically. Use brief headings for columns. If abbreviations are necessary, define them in a key at the bottom of the table. Keep footnotes to a minimum; if necessary, use superscript letters to denote them.

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Figures follow the tables. Figures must be submitted in electronic form. Figures and illustrations (photographs, drawings, diagrams, and charts) are to be numbered in one consecutive series of Arabic numerals.

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Informed consent: “Informed consent was obtained from all individual participants included in the study.”

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Appendix 2: Search terms used in systematic review

	Search terms used
P (Population)	Parent$ or father$ or mother$ or caregiv$ or famil$
I (Intervention)	(Phenylketonuria or (maple and syrup and urine and disease) or (isovaleric and acidemia) or (isovaleric and acidemia) or (isovaleric and aciduria) or (acyl-CoA and dehydrogenase) or (very and long and acyl-CoA and dehydrogenase and deficien$$) or (medium and chain and acyl-CoA and dehydrogenase and deficien$$) or (glutaric and aciduria) or homocystinuria or (inherited and metabolic and disorder) or (inborn and error$ and metabolism) or (intoxication-type and inborn and errors and metabolism) or (urea and cycle) or (organic and aciduria) or (organic and acidemia) or (Inborn and errors and amino and acid and metabolism) or (fatty and oxidisation) or (amino and acid and metabolism))
C (Comparison)	-
O (Outcome)	(wellbeing or (well and being) or well-being or adjustment or adaptation or adaption or adaptive or psycholog* or psychosocial or psychiatr* or social or emotional or (mental and health) or (mental and disorder) or stress or depression or depressive or anxiety or coping)

(entered as ‘P AND I AND O’)

Appendix 3: Quality rating criteria for Quality Assessment Tool for Studies with Diverse Designs

Criteria	0 = Not at all	1 = Very slightly	2 = Moderately	3 = Complete
Explicit theoretical framework	No mention at all.	Reference to broad theoretical basis.	Reference to a specific theoretical basis.	Explicit statement of theoretical framework and/or constructs applied to the research.
Statement of aims/objectives in main body of report	No mention at all.	General reference to aim/objective at some point in the report including abstract.	Reference to broad aims/objectives in main body of report.	Explicit statement of aims/objectives in main body of report.
Clear description of research setting	No mention at all.	General description of research area and background, e.g. 'in primary care'.	General description of research problem in the target population, e.g. 'among GPs in primary care'.	Specific description of the research problem and target population in the context of the study, e.g. nurses and doctors from GP practices in the east midlands.
Evidence of sample size considered in terms of analysis	No mention at all.	Basic explanation for choice of sample size. Evidence that size of the sample has been considered in study design.	Evidence of consideration of sample size in terms of saturation/information redundancy or to fit generic analytical requirements.	Explicit statement of data being gathered until information redundancy/saturation was reached or to fit exact calculations for analytical requirements.
Representative sample of target	No statement	Sample is limited but	Sample is somewhat diverse but not entirely	Sample includes individuals to represent

Criteria	0 = Not at all	1 = Very slightly	2 = Moderately	3 = Complete
group of a reasonable size	of target group.	represents some of the target group or representative but very small.	representative, e.g. inclusive of all age groups, experience but only one workplace. Requires discussion of target population to determine what sample is required to be representative.	a cross section of the target population, considering factors such as experience, age and workplace.
Description of procedure for data collection	No mention at all.	Very basic and brief outline of data collection procedure, e.g. 'using a questionnaire distributed to staff'.	States each stage of data collection procedure but with limited detail, or states some stages in details but omits others.	Detailed description of each stage of the data collection procedure, including when, where and how data were gathered.
Rationale for choice of data collection tool(s)	No mention at all.	Very limited explanation for choice of data collection tool(s).	Basic explanation of rationale for choice of data collection tool(s), e.g. based on use in a prior similar study.	Detailed explanation of rationale for choice of data collection tool(s), e.g. relevance to the study aims and assessments of tool quality either statistically, e.g. for reliability & validity, or relevant qualitative assessment.
Detailed recruitment data	No mention at all.	Minimal recruitment data, e.g. no. of questionnaire sent and no. returned.	Some recruitment information but not complete account of the recruitment process, e.g. recruitment figures but no information on strategy used.	Complete data regarding no. approached, no. recruited, attrition data where relevant, method of recruitment.
Statistical	No	Reliability and	Some attempt to assess	Suitable and thorough

Criteria	0 = Not at all	1 = Very slightly	2 = Moderately	3 = Complete
assessment of reliability and validity of measurement tool(s) (Quantitative only)	mention at all.	validity of measurement tool(s) discussed, but not statistically assessed.	reliability and validity of measurement tool(s) but insufficient, e.g. attempt to establish test–retest reliability is unsuccessful but no action is taken.	statistical assessment of reliability and validity of measurement tool(s) with reference to the quality of evidence as a result of the measures used.
Fit between stated research question and method of data collection (Quantitative)	No research question stated.	Method of data collection can only address some aspects of the research question.	Method of data collection can address the research question but there is a more suitable alternative that could have been used or used in addition.	Method of data collection selected is the most suitable approach to attempt answer the research question
Fit between stated research question and format and content of data collection tool e.g. interview schedule (Qualitative)	No research question stated.	Structure and/or content only suitable to address the research question in some aspects or superficially.	Structure & content allows for data to be gathered broadly addressing the stated research question(s) but could benefit from greater detail.	Structure & content allows for detailed data to be gathered around all relevant issues required to address the stated research question(s).
Fit between research question and method of analysis	No mention at all.	Method of analysis can only address the research question basically or broadly.	Method of analysis can address the research question but there is a more suitable alternative that could have been used or used in addition to offer greater detail.	Method of analysis selected is the most suitable approach to attempt answer the research question in detail, e.g. for qualitative IPA preferable for experiences vs. content analysis to elicit frequency of occurrence of events, etc.
Good justification for	No	Basic	Fairly detailed explanation of	Detailed explanation

Criteria	0 = Not at all	1 = Very slightly	2 = Moderately	3 = Complete
analytical method selected	mention at all.	explanation for choice of analytical method	choice of analytical method.	for choice of analytical method based on nature of research question(s).
Assessment of reliability of analytical process (Qualitative only)	No mention at all.	More than one researcher involved in the analytical process but no further reliability assessment.	Limited attempt to assess reliability, e.g. reliance on one method.	Use of a range of methods to assess reliability, e.g. triangulation, multiple researchers, varying research backgrounds.
Evidence of user involvement in design	No mention at all.	Use of pilot study but no involvement in planning stages of study design.	Pilot study with feedback from users informing changes to the design.	Explicit consultation with steering group or statement or formal consultation with users in planning of study design.
Strengths and limitations critically discussed	No mention at all.	Very limited mention of strengths and limitations with omissions of many key issues.	Discussion of some of the key strengths and weaknesses of the study but not complete.	Discussion of strengths and limitations of all aspects of study including design, measures, procedure, sample & analysis.

Appendix 4: Glossary of inherited metabolic **disorders**

All content acquired from http://www.newbornscreening.info/Parents/facts.html unless otherwise stated.

Contents

3MCC DEFICIENCY

3MCC deficiency is one type of organic acid disorder. Some children with this condition have problems breaking down an amino acid called leucine from the food they eat.

IF 3MCC DEFICIENCY IS NOT TREATED, WHAT PROBLEMS OCCUR?

Each child with 3MCC deficiency may have somewhat different effects. In fact, some children with this condition never have symptoms and may not ever need treatment.

Babies with 3MCC deficiency are healthy at birth. If symptoms occur, they often start after 3 months of age. Some babies do not have their first symptoms until 6 months to 3 years of age. Others do not have symptoms until adulthood. Some people will never develop symptoms.

3MCC deficiency can cause episodes of illness called metabolic crises. Some of the first symptoms of a metabolic crisis are:

- poor appetite
- extreme sleepiness or lack of energy
- behaviour changes
- irritable mood
- muscle weakness
- nausea
- vomiting

Common blood and urine findings are:

- low blood sugar, called hypoglycaemia
- increased levels of acidic substances in the blood, called metabolic acidosis
- high levels of ammonia in the blood
- low levels of carnitine in the blood
- increased ketones in the urine
- liver problems

If a metabolic crisis is not treated, a child with 3MCC deficiency can develop:

- breathing problems
- seizures
- liver failure
- coma, sometimes leading to death

If a metabolic crisis is not treated, it could result in death. In surviving babies and children, repeated episodes of metabolic crisis can cause brain damage. This can lead to life-long learning problems or intellectual disabilities.

Episodes of metabolic crisis can be triggered by:

- illness or infection
- going without food for long periods of time
- eating large amounts of protein

When a child is ill or goes without food for too long, the body breaks down its own protein and fat to use for energy. In some people with 3MCC deficiency, this can trigger a metabolic crisis.

Between episodes of metabolic crisis, children with 3MCC deficiency are usually healthy.

Some children do not ever have metabolic crises. However, they may have other symptoms. These can include:

- poor growth and development
- either low muscle tone or spasticity

Some people do not have any symptoms until adulthood. Some of the symptoms seen in adults are:

- weakness
- fatigue

Some people with 3MCC deficiency never have symptoms and are only found to be affected after a brother or sister is diagnosed, or they may be diagnosed through newborn screening.

WHAT IS THE TREATMENT FOR 3MCC DEFICIENCY?

In some children, prompt treatment is needed to prevent metabolic crises and the health effects that follow. Certain treatments may be advised for some children but not others. Children who do not show symptoms may not need treatment.

The following are treatments that are used for some babies and children with 3MCC deficiency:

1. Low-leucine diet, including medical foods and formula
A food plan low in leucine with limited amounts of protein is sometimes needed. Most food in the diet will be carbohydrates (bread, cereal, pasta, fruit, vegetables, etc.). Carbohydrates give the body many types of sugar that can be used as energy. Eating a diet high in carbohydrates and low in protein can help prevent hypoglycaemia and metabolic crises.

Foods high in protein that may need to be avoided or limited include:

- milk and dairy products, meat and poultry, fish, eggs, dried beans and legumes, nuts and peanut butter

Many vegetables and fruits have only small amounts of protein and can be eaten in carefully measured amounts. Do not remove all protein from the diet. Children with 3MCC deficiency need small amounts of protein to grow properly.

If needed, your dietician will create a food plan that contains the right amount of protein, nutrients and energy for your child. Some children may be on a special food plan throughout life.

Medical foods and formula
There are medical foods such as special low-protein flours, pastas, and rice that are made especially for people with organic acid disorders. If necessary for your child, your dietician will tell you how to use these foods.

In addition to a low-protein diet, some children are given a special leucine-free medical formula. Your metabolic doctor and dietician will decide whether your child needs this formula. Some states offer help with payment, or require private insurance to pay for the formula and other special medical foods.

2. Medications
Some children may benefit by taking L-carnitine. This is a safe and natural substance that helps body cells make energy. It also helps the body get rid of harmful wastes. Your doctor will decide whether or not your child needs L-carnitine. Unless you are advised otherwise, use only L-carnitine prescribed by your doctor.

Your doctor may suggest other medications or supplements that may be helpful in preventing some of the symptoms of 3MCC deficiency. Do not use any medication without checking with your doctor.

WHAT HAPPENS WHEN 3MCC DEFICIENCY IS TREATED?

Many children found to have 3MCC during newborn screening will never need treatment.

With prompt and careful treatment, children who have shown symptoms of 3MCC deficiency have a good chance to live healthy lives with typical growth and development.

Even with treatment, some children still have repeated bouts of metabolic crisis. This can cause brain damage and may lead to life-long learning problems or intellectual disabilities.

ARGINASE DEFICIENCY

Arginase deficiency is one type of **amino acid disorder**. People with this condition have problems removing ammonia from the body. Ammonia is a harmful substance. It is made when protein and its building blocks, amino acids, are broken down for use by the body.

IF ARGINASE DEFICIENCY IS NOT TREATED, WHAT PROBLEMS OCCUR?

The effects of this condition vary from person to person. Symptoms can start in infancy or not until later in childhood. Many children have their first symptoms around one year to three years of age. Effects in infants can include:

- poor growth
- learning delays
- spasticity
- poor coordination and balance problems
- fussiness or illness when fed high protein food

Episodes of illness caused by high levels of ammonia in the blood can sometimes occur but are not common. Some of the first symptoms of high blood ammonia are:

- poor appetite
- excess sleepiness or lack of energy
- irritability
- vomiting

If untreated, other symptoms can follow:

- muscle weakness
- decreased or increased muscle tone
- breathing problems
- problems staying warm
- seizures
- swelling of the brain
- coma, and sometimes death

Often, symptoms of arginase deficiency do not begin until later in infancy or childhood. Common effects in older infants and children include:

- poor growth
- spasticity
- small head size
- hyperactivity
- behaviour problems
- learning delays

- avoidance of meat or other high protein foods
- occasional bouts of vomiting and excessive sleepiness

Episodes of high blood ammonia, described above, happen rarely. If they occur, they are more likely to happen:

- after going without food for long periods
- during illness or infection
- after high-protein meals

WHAT IS THE TREATMENT FOR ARGINASE DEFICIENCY?

Your baby's primary doctor will work with a metabolic doctor and a dietician to care for your child.

Prompt treatment is needed to prevent the build-up of arginine and ammonia. You should start treatment as soon as you know your child has the condition.

The following are treatments often recommended for babies and children with arginase deficiency:

1. Low-protein diet and/or special medical foods and formula
Most children need to eat a diet made up of very low-protein foods and special medical foods. Your dietician will create a food plan that contains the right amount of protein, nutrients, and energy to keep your child healthy. The food plan should be continued throughout your child's life.

Low-protein diet
One of the main treatments is a low-protein diet. Foods that need to be avoided or limited include:

- milk, cheese and other dairy products
- meat and poultry
- fish
- eggs
- dried beans and legumes
- nuts and peanut butter

Eating these foods can cause ammonia and arginine to build up, resulting in the symptoms described above. Many vegetables and fruits have only small amounts of protein and can be eaten in carefully measured amounts.

Do not remove all protein from the diet. Your child still needs a certain amount of protein for normal growth and development. Any changes in the diet should be made under the guidance of a dietician.

Medical foods and formula
There are medical foods such as special low-protein flours, pastas, and rice that are made especially for people with amino acid disorders.

Your child may be given a special formula that contains the correct amount of nutrients and amino acids. Your metabolic doctor and dietician will tell you whether your child should use this formula and how much to use. Some states offer help with payment, or require private insurance to pay for the formula and other special medical foods.

Your child's exact food plan will depend on many things such as his or her age, weight, and general health. Your dietician will fine-tune your child's diet over time.

2. Medication

There are certain medications that can help the body get rid of excess arginine and ammonia. Your metabolic doctor will decide which medications your child should take.

3. Blood tests

Your child will need to have regular blood tests to measure ammonia and amino acid levels. Your child's diet and medication may need to be adjusted based on blood test results.

WHAT HAPPENS WHEN ARGINASE DEFICIENCY IS TREATED?

With prompt and lifelong treatment, children with arginase deficiency may be able to live healthy lives with typical growth and learning.

Even with treatment, some children still have effects from high blood levels of arginine and ammonia. This can result permanent learning problems, intellectual disability or spasticity.

ARGININOSUCCINIC ACIDEMIA

From Wikipedia, the free encyclopaedia

Argininosuccinic aciduria, also called **argininosuccinic acidemia**, is an inherited disorder that causes the accumulation of argininosuccinic acid (also known as "ASA") in the blood and urine. Some patients may also have an elevation of ammonia, a toxic chemical, which can affect the nervous system. Argininosuccinic aciduria may become evident in the first few days of life because of high blood ammonia, or later in life presenting with "sparse" or "brittle" hair, developmental delay, and tremors.

An infant with argininosuccinic aciduria may seem lethargic or be unwilling to eat, have poorly controlled breathing rate or body temperature, experience seizures or unusual body movements, or go into a coma. Complications from argininosuccinic aciduria may include developmental delay and mental retardation. Progressive liver damage, skin lesions, and brittle hair may also be seen. Immediate treatment and lifelong management (following a strict diet and using appropriate supplements) may prevent many of these complications.

CITRULLINEMIA

Citrullinemia is one type of amino acid disorder. People with this condition cannot remove ammonia from the body. Ammonia is a harmful substance. It is made when protein and its building blocks, amino acids, are broken down for use by the body. This causes brain damage. If not treated, excess ammonia in the blood can cause death.

IF CITRULLINEMIA IS NOT TREATED, WHAT PROBLEMS OCCUR?

Normally, the body changes ammonia into a substance called “urea”. Urea is then safely removed in the urine. If ammonia is not changed to urea, high levels build up in the blood. This can be very harmful. If ammonia levels stay high for too long, severe brain damage can occur.

The symptoms, and the age they start, vary from person to person. There are two main forms of this condition. The most common is called “classic”. It usually starts in infancy. There are also milder forms that start later in infancy or childhood. There is also a rare adult form more common in people from Japan. Some women only have symptoms during or after pregnancy.

Classic citrullinemia

Infants seem healthy at birth but quickly develop symptoms. Within a few days of life, babies will have high levels of ammonia in their blood. Some of the first symptoms of high blood ammonia are:

- poor appetite, extreme sleepiness or lack of energy, irritability, vomiting

If not treated, high ammonia levels cause:

- muscle weakness
- decreased or increased muscle tone
- breathing problems
- problems staying warm

- seizures
- swelling of the brain
- coma, and sometimes death

Other effects of citrullinemia can include:

- poor growth
- enlarged liver
- learning delays or intellectual disabilities

Without treatment, most babies die within the first few weeks of life.

Milder forms
In the milder forms, symptoms start later in infancy or childhood. Symptoms in untreated children can include:

- poor growth
- dry, brittle hair
- hyperactivity
- behaviour problems
- learning problems or intellectual disabilities
- avoidance of meat and other high-protein foods
- spasticity
- Stroke
- episodes of high levels of ammonia in the blood
- liver failure

Episodes of high blood ammonia often happen:

- after going without food for long periods of time, during illness or infection, after high-protein meals

Some of the first symptoms of high blood ammonia in children are:

- poor appetite, severe headache, vomiting, extreme sleepiness or lack of energy, slurred speech, poor coordination or balance problems

If not treated, children with high blood ammonia levels may develop:

- breathing problems
- swelling of the brain
- seizures
- coma, sometimes leading to death

A rare form of citrullinemia occurs during and after pregnancy. Women may experience:

- vomiting
- lethargy
- seizures
- confusion and hallucinations
- changes in behaviour including manic episodes and psychosis
- swelling of the brain

Some people have very mild or no symptoms and are only found to be affected after a brother or sister is diagnosed.

WHAT IS THE TREATMENT FOR CITRULLINEMIA?

Prompt treatment is needed to prevent the build-up of ammonia. You should start treatment as soon as you know your child has the condition.

The following are treatments often recommended for babies and children with citrullinemia:

1. Low-protein diet and/or special medical foods and formula

Most children need to eat a diet made up of very low-protein foods, special medical foods, and, sometimes, a special formula. Your dietician will create a food plan that contains the right amount of protein, nutrients, and energy to keep your child healthy. A special food plan should be continued throughout your child's life.

Low-protein diet

The most effective treatment for citrullinemia is a low-protein diet. Foods that need to be avoided or strictly limited include:

- milk, cheese, and other dairy products, meat and poultry, fish, eggs, dried beans and legumes, nuts and peanut butter

Eating foods high in protein can cause ammonia to build up, causing severe illness. Many vegetables and fruits have only small amounts of protein and can be eaten in carefully measured amounts. Do not remove all protein from the diet. Your child still needs a certain amount of protein for normal growth and development. Any changes in the diet should be made under the guidance of a dietician.

Medical foods and formula

There are medical foods such as special low-protein flours, pastas, and rice that are made especially for people with amino acid disorders.

Your baby may need to drink a special medical formula that contains the correct amount of amino acids and nutrients. Your metabolic doctor and dietician will decide whether your child needs this treatment. Some states offer help with payment, or require private insurance to pay for the formula and other special medical foods.

Your child's exact food plan will depend on many things such as his or her age, weight, and general health. Your dietician will fine-tune your child's diet over time. Any diet changes should be made under the guidance of a dietician.

2. Medication

There are certain medications that can help the body get rid of ammonia. These are taken by mouth or by tube feeding to prevent high ammonia levels. Your doctor will decide whether your child needs these medications, which ones, and how much to use.

During episodes of high ammonia, children need to be treated in the hospital. Medications to remove ammonia are often given by IV. Dialysis is sometimes needed to remove ammonia from the blood.

An amino acid called arginine is often given by mouth to help prevent ammonia build-up. Your doctor will tell you whether your child needs arginine and how much to use. Do not use any supplements or medications without checking with your doctor.

3. Blood tests

Your child will have regular blood tests to measure ammonia and amino acid levels. Your child's diet and medication may need to be adjusted based on blood test results.

5. Liver transplantation

Liver transplant surgery is an optional treatment for people with citrullinemia. The ASAS enzyme that causes citrullinemia is located in the liver. Because of this, some children with citrullinemia have had liver transplantation surgery (removal of their liver and replacement with a donor liver) to treat their citrullinemia symptoms.

This major surgical procedure is associated with risks, and individuals who have had a liver transplant must take medication for the rest of their lives to prevent their body from rejecting the donor liver.

However, successful liver transplantation has been reported to improve quality of life and prolong survival in some cases.

Many factors must be considered before surgery and this option should be discussed very thoroughly with your child's physicians.

WHAT HAPPENS WHEN CITRULLINEMIA IS TREATED?

With prompt and lifelong treatment, children with citrullinemia can often live healthy lives with typical growth and learning. Early treatment can help prevent high ammonia levels.

Even with treatment, some children still have episodes of high ammonia. This can result in brain damage. This can cause lifelong learning problems, intellectual disabilities or spasticity.

DISORDERS OF INTRACELLULAR COBALAMIN METABOISM (COBAL C DEFICIENCY)

(ADAPTED FROM Nuria Carrillo-Carrasco, MD, David Adams, MD, PhD, and Charles P Venditti, MD, PhD.)

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Clinical characteristics.

- Newborns, who can have intrauterine growth retardation (IUGR) and microcephaly;
- Infants, who can have poor feeding, failure to thrive, pallor, and neurologic signs, and occasionally haemolytic uremic syndrome (HUS) and/or seizures including infantile spasms;
- Toddlers, who can have failure to thrive, poor head growth, cytopenias (including megaloblastic anaemia), global developmental delay, encephalopathy, and neurologic signs such as hypotonia and seizures; and
- Adolescents and adults, who can have neuropsychiatric symptoms, progressive cognitive decline, and/or subacute combined degeneration of the spinal cord.

Management.

No therapy completely mitigates all disease manifestations.

Prevention of primary manifestations: Early institution of therapy may reduce but not completely prevent primary manifestations. To prevent metabolic decompensations, patients are advised to avoid situations that result in catabolism, such as prolonged fasting and dehydration.

Agents/circumstances to avoid: Prolonged fasting (longer than overnight without dextrose-containing intravenous fluids); dietary protein intake below the recommended dietary allowance (RDA) for age or more than that prescribed by a metabolic specialist; methionine restriction; and the anaesthetic nitrous oxide.

GALACTOSEMIA

https://www.nlm.nih.gov/medlineplus/ency/article/000366.htm

Galactosemia is a condition in which the body is unable to use (metabolize) the simple sugar galactose.

People with galactosemia are unable to fully break down the simple sugar galactose. Galactose makes up half of lactose, the sugar found in milk.

If an infant with galactosemia is given milk, substances made from galactose build up in the infant's system. These substances damage the liver, brain, kidneys, and eyes.

People with galactosemia cannot tolerate any form of milk (human or animal). They must be careful about eating other foods containing galactose.

Symptoms

Infants with galactosemia can develop symptoms in the first few days of life if they eat formula or breast milk that contains lactose. The symptoms may be due to a serious blood infection with the bacteria *E coli*.

Symptoms of galactosemia are:

Convulsions, Irritability, Lethargy, Poor feeding -- baby refuses to eat formula containing milk, Poor weight gain, Yellow skin and whites of the eyes (jaundice), Vomiting

Treatment

People with this condition must avoid all milk, products that contain milk (including dry milk), and other foods that contain galactose, for life. Read product labels to make sure you or your child with the condition are not eating foods that contain galactose.

Outlook (Prognosis)

People who are diagnosed early and strictly avoid milk products can live a relatively normal life. However, mild mental impairment may develop, even in people who avoid galactose.

Possible Complications

These complications can develop:

- Cataracts
- Cirrhosis of the liver
- Delayed speech development
- Irregular menstrual periods, reduced function of ovaries leading to ovarian failure
- Mental disability
- Severe infection with bacteria (*E coli sepsis*)
- Tremors (shaking) and uncontrollable motor functions
- Death (if there is galactose in the diet)

GLUTARIC ACIDEMIA TYPE I (GA-1)

GA-1 stands for “glutaric acidemia, type 1”. It is one type of organic acid disorder. People with GA-1 have problems breaking down the amino acids lysine, and tryptophan from the food they eat.

IF GA-1 IS NOT TREATED, WHAT PROBLEMS OCCUR?

Babies with GA-1 are usually healthy at birth, although many are born with a larger than average head size. Other symptoms usually start between two months and four years of age.

GA-1 causes episodes of severe illness called metabolic crises. Some of the first symptoms of a metabolic crisis are:

- poor appetite, extreme sleepiness or lack of energy, irritability, jitteriness, nausea, vomiting, low muscle tone (floppy muscles and joints), muscle weakness
-

If untreated, other symptoms then follow:

- tics or spasms of the muscles, rigid muscle contractions called spasticity, involuntary jerking movements of the arms and legs, called dystonia, poor coordination and balance problems, increased levels of acidic substances in the blood called metabolic acidosis, seizures, swelling of the brain or blood in the brain, coma, sometimes leading to death

Episodes of metabolic crisis are often triggered by:

- illness or infection, fever, going without food for long periods of time

Other effects of GA-1 that can happen even without a metabolic crisis are:

- poor growth, enlarged liver, low muscle tone, progressive spasticity, dystonia, repeated episodes of fever, excessive sweating, delays in walking and other motor skills, learning delays and intellectual disabilities, speech problems, brain damage

Some people have very mild or no symptoms and are only found to be affected after a brother or sister is diagnosed.

WHAT IS THE TREATMENT FOR GA-1?

Prompt treatment is needed to prevent episodes of metabolic crisis. You need to start treatment as soon as you know your child has GA-1. Certain treatments may be advised for some children but not others. Treatment is usually needed throughout life.

The following are treatments often recommended for babies and children with GA-1:

1. Medication

Riboflavin is a vitamin that helps the body process protein. It may also help lessen the amount of glutaric acid made by the body. Your doctor may recommend that your child take riboflavin supplements by mouth.

Some children may be helped by L-carnitine. This is a safe and natural substance that helps body cells make energy. It also helps the body get rid of harmful wastes. Your doctor will decide whether or not your child needs L-carnitine supplements. Unless you are advised otherwise, use only L-carnitine prescribed by your doctor.

Children with symptoms of a metabolic crisis need medical treatment right away. They often need to be treated in the hospital. During a metabolic crisis, children may be given fluids, glucose, insulin, carnitine and other medications by IV to help get rid of harmful substances in the blood. Ask your metabolic doctor if you should carry a special travel letter with medical instructions for your child’s care.

2. Avoid going a long time without food
Infants and young children with GA-1 need to eat frequently to prevent a metabolic crisis. In general, it is often suggested that infants be fed every four to six hours. Some babies need to eat even more frequently than this. It is important that infants be fed during the night. They may need to be woken up to eat if they do not wake up on their own. Your metabolic doctor and dietician will give you an appropriate feeding plan for your infant. Your doctor will also give you a 'sick day' plan, tailored to your child's needs, for you to follow during illnesses or other times when your child will not eat.

Your metabolic doctor will continue to advise you on how often your child should eat as he or she gets older. When they are well, many older children and adults with GA-1 can go without food for up to 12 hours without problems. They may need to continue the other treatments throughout life.

3. Food plan, including medical foods and formula
Most children need to eat a diet made up of foods low in lysine and tryptophan. Special medical foods and a special formula are usually part of the diet. Your dietician will create a food plan that has the right amount of protein, nutrients, and energy for your child.

Low-protein (lysine and tryptophan) diet
Foods that will need to be avoided or strictly limited include:

- milk, cheese, and other dairy products
- meat and poultry
- fish
- eggs
- dried beans and legumes
- nuts and peanut butter

Many vegetables and fruits have only small amounts of lysine and tryptophan and can be eaten in carefully measured amounts.

Do not remove all protein from the diet. Your child still needs a certain amount of protein for normal growth and development. Any changes in the diet should be made under the guidance of a dietician familiar with GA-1.

Medical foods and formula
There are medical foods such as special low-protein flours, pastas, and rice that are made especially for people with organic acid disorders.

A special medical formula that contains the right level of amino acids and nutrients for your child may be recommended. Your metabolic doctor and dietician will tell you whether your child should be on this formula and how much to use. Some states offer help with payment, or require private insurance to pay for the formula and other special medical foods.

Your child's exact food plan will depend on many things such as his or her age, weight, general health, and blood test results. Your dietician will fine-tune your child's diet over time.

The long-term benefits of the special diet and medical foods are not yet known. However, it is important to follow the food plan as long as your doctor advises.

4. Regular blood tests
Your child will have regular blood tests to measure his or her amino acid levels. Urine tests may also be done. Your child's diet and medication may need to be adjusted based on blood and urine test results.

WHAT HAPPENS WHEN GA-1 IS TREATED?

With prompt and lifelong treatment, children with GA-1 can often live healthy lives with typical growth and learning. Early treatment can help prevent episodes of metabolic crisis and the resulting health effects.

Even with treatment, some children continue to have episodes of metabolic crisis. This can lead to brain damage and long-term problems with involuntary movements and spasticity. After age six, metabolic crises are less common.

GLUTARIC ACIDEMIA TYPE II (GA-2)

GA-2 stands for “glutaric acidemia, type 2”. People with GA-2 have problems breaking down fat and protein into energy for the body. GA-2 has symptoms that are part of two different groups of disorders: fatty acid oxidation disorders and organic acid disorders.

IF GA-2 IS NOT TREATED, WHAT PROBLEMS OCCUR?

GA-2 can cause bouts of illness called metabolic crises. Some of the first symptoms of a metabolic crisis are:

- extreme sleepiness, behaviour changes, irritable mood, muscle weakness, poor appetite

Other symptoms then follow:

- fever, nausea, diarrhoea, vomiting, hypoglycaemia, increased levels of acidic substances in the blood, called metabolic acidosis

If a metabolic crisis is not treated, a child with GA-2 can develop:

- breathing problems, seizures, coma, sometimes leading to death

Symptoms can first show up in the newborn period or later in childhood or sometimes even adulthood.

GA-2 in newborns

Some babies have their first symptoms shortly after birth. Rapid breathing and weak tone often happen one to two days after birth. Episodes of metabolic crisis often show up at this time, too.

Many babies with GA-2 have an odour that smells like “sweaty feet”. In addition, they often have serious heart and liver problems.

Without treatment, most babies die within the first few weeks of life. Even with treatment, many babies with GA-2 die of severe heart problems within a few months.

Some newborns with GA-2 also have birth defects. If this is the case, treatment is usually not helpful. Babies with GA-2 and birth defects usually die within the first weeks of life.

GA-2 in childhood

The symptoms of GA-2 can be very different from person to person. If symptoms do not happen in the newborn period, they may begin anytime from early childhood through adulthood.

Symptoms in childhood can include:

- nausea
- vomiting
- muscle weakness
- periods of hypoglycaemia (after exercise, after eating too much protein, after going too long without food, during illness or infection)
- full metabolic crisis (described above)

Some people with GA-2 never have symptoms and are only found to be affected after a brother or sister is diagnosed.

WHAT IS THE TREATMENT FOR GA-2?

Certain treatments may be advised for some children but not others. When necessary, treatment is usually needed throughout life. The following are treatments often recommended for children with GA-2:

1. Avoid going a long time without food

Infants and young children with GA-2 need to eat frequently to prevent hypoglycaemia or a metabolic

crisis. Your metabolic doctor will tell you how often your child needs to be fed. In general, it is often suggested that infants be fed every four to six hours. Some babies need to eat even more frequently than this. It is important that infants be fed during the night. They may need to be woken up to eat if they do not wake up on their own. Your metabolic doctor and dietician will give you an appropriate feeding plan for your infant. Your doctor will also give you a 'sick day' plan, tailored to your child's needs, for you to follow during illnesses or other times when your child will not eat.

Your metabolic doctor will continue to advise you on how often your child should eat as he or she gets older. When they are well, many teens and adults with GA-2 can go without food for up to 12 hours without problems. They may need to continue the other treatments throughout life.

2. Diet

A low-fat, low-protein, high-carbohydrate diet is often advised. Carbohydrates give the body many types of sugar that can be used as energy. In fact, for children needing this treatment, most food in the diet should be carbohydrates (bread, cereal, pasta, fruit, vegetables, etc.). Do not remove all fat and protein from the diet. Children with GA-2 need a certain amount of each to grow properly.

Your dietician can help you create a food plan that meets your child's needs. Any diet changes should be made under the guidance of a dietician experienced with GA-2.

3. Riboflavin, L-carnitine and glycine supplements

Some children and adults with GA-2 are helped by taking daily riboflavin supplements. Check with your doctor to see whether your child should take riboflavin.

Some children may be helped by taking L-carnitine. This is a safe and natural substance that helps body cells make energy. It also helps the body get rid of harmful wastes. Your doctor will decide whether or not your child needs L-carnitine supplements. Unless you are advised otherwise, use only L-carnitine prescribed by your doctor.

Some people with GA-2 are helped by taking glycine supplements. Ask your doctor whether your child should take glycine.

Do not use any of these supplements without checking with your doctor.

WHAT HAPPENS WHEN GA-2 IS TREATED?

GA-2 in newborns

A small number of newborns with symptoms of GA-2 have shown benefit from treatment. But, in most cases, treatment has not been helpful. Many newborns with GA-2 die from heart problems within the first few months of life.

GA-2 in children

With prompt and careful treatment, children and adults with GA-2 usually live healthy lives with normal growth and development.

The goal of treatment is to prevent long-term problems. However, children who have repeated metabolic crises may develop life-long learning problems.

GLYCOGEN STORAGE DISORDER (Type I)

https://www.nlm.nih.gov/medlineplus/ency/article/000338.htm

GSD type I is a condition in which the body cannot break down glycogen. Glycogen is a form of sugar (glucose) that is stored in the liver and muscles. It is normally broken down into glucose to give you more energy when you need it.

Causes

GSD I occurs when the body lacks the protein (enzyme) that releases glucose from glycogen. This causes abnormal amounts of glycogen to build up in certain tissues. When glycogen is not broken down properly, it leads to low blood sugar.

Symptoms

- Generally diagnosed before the age of 2 following symptomatic presentation of seizures or other manifestations of severe fasting hypoglycaemia,hyperventilation and apparent respiratory distress due to metabolic acidosis; episodes of vomiting due to metabolic acidosis, often precipitated by minor illness and accompanied by hypoglycemia. Other symptoms include constant hunger and need to eat often, easy bruising and nosebleeds, fatigue, Irritability, puffy cheeks, thin chest and limbs, and swollen belly.

Possible future complications

- Delayed puberty, Enlarged liver, Gout, Inflammatory bowel disease, Liver tumours, Severe low blood sugar, Stunted growth or failure to grow

Children with this condition are usually diagnosed before age 1.

Treatment

The goal of treatment is to avoid low blood sugar. Eat frequently during the day, especially foods that contain carbohydrates (starches). Older children and adults may take corn-starch by mouth to increase their carbohydrate intake. In some children, a feeding tube is placed through their nose into the stomach to provide sugars or uncooked corn-starch throughout the night. The tube can be taken out each morning. A medicine to lower uric acid in the blood and decrease the risk for gout may be prescribed. Your provider may also prescribe medicines to treat kidney disease, high lipids, and to increase the cells that fight infection. People with GSD I cannot properly break down fruit or milk sugar. It is best to avoid these products.

Outlook (Prognosis)

With treatment, growth, puberty, and quality of life have improved for people with GSD I. Those who are identified and carefully treated at a young age can live into adulthood.

Early treatment also decreases the rate of severe problems such as:

- Gout, Kidney failure, Life-threatening low blood sugar, Liver tumours,

Possible Complications can occur:

Frequent infection, Gout, Kidney failure, Liver tumours, Osteoporosis (thinning bones), Seizures, lethargy, confusion due to low blood sugar, Short height, Underdeveloped secondary sexual characteristics (breasts, pubic hair), Ulcers of the mouth or bowel.

ISOVALERIC ACIDEMIA (IVA)

IVA stands for “isovaleric acidemia”. It is one type of organic acid disorder. People with IVA have problems breaking down an amino acid called leucine from the food they eat.

IF IVA IS NOT TREATED, WHAT PROBLEMS OCCUR?

The effects of IVA vary from person to person. There are two main forms of the condition. About half of all babies start showing symptoms shortly after birth. The other form, called “chronic-intermittent”, starts later in infancy or childhood.

IVA in babies

Babies with IVA seem healthy at birth. Often, the first symptoms start between one day and two weeks of age.

IVA causes episodes of illness called metabolic crises. Some of the first symptoms of a metabolic crisis are:

- poor appetite
- extreme sleepiness or lack of energy
- vomiting
- problems staying warm
- an odour similar to “sweaty feet”

Other symptoms can then follow:

- increased levels of acidic substances in the blood, called metabolic acidosis
- high levels of ammonia in the blood
- ketones in the urine
- low platelets
- low level of white blood cells
- seizures
- swelling of the brain
- bleeding in the brain
- coma, sometimes leading to death

If not treated, many babies die during their first metabolic crisis. In those who survive, repeated episodes of metabolic crisis can cause brain damage. This can result in life-long learning problems or intellectual disabilities.

Chronic/intermittent IVA

Symptoms often start around one year of age. Some children, though, do not have symptoms until later in childhood.

Episodes of metabolic crisis can be brought on by illness, infection, or by eating large amounts of protein. When a child is ill, body protein is broken down for energy. In a child with IVA, this can cause high levels of isovaleric acid and results in a metabolic crisis.

Between episodes of metabolic crisis, children with IVA are usually healthy.

Some people have very mild or no symptoms and are only found to be affected after a brother or sister is diagnosed. Newborn screening also identifies infants that may never develop serious symptoms.

WHAT IS THE TREATMENT FOR IVA?

Your baby’s primary doctor will work with a metabolic doctor and a dietician experienced with IVA to care for your child.

Prompt treatment is needed to prevent metabolic crises and the health effects that follow. You should start treatment as soon as you know your child has IVA. Certain treatments may be advised for some children but not others. Treatment is usually needed throughout life.

The following are treatments often recommended for babies and children with IVA:

1. Low-leucine diet, medical foods and formula

Most children need to eat a diet made up of foods low in leucine. Special medical foods and a leucine-free formula are usually part of the diet. Your dietician will create a food plan that contains the right amount of protein, nutrients, and energy to keep your child healthy. A special food plan should be continued throughout life.

Low-leucine / low-protein diet

Foods high in protein (and leucine) that may need to be avoided or limited include:

- milk and dairy products, meat and poultry, fish, eggs, dried beans and legumes, nuts and peanut butter

Eating large amounts of these foods can cause isovaleric acid levels to rise, causing illness.

Many vegetables and fruits have only small amounts of protein and can be eaten in carefully measured amounts.

Do not remove all protein from the diet. Children with IVA need a certain amount to grow properly. Any diet changes should be under the guidance of a dietician.

Medical foods and formula

There are medical foods such as special low-protein flours, pastas, and rice that are made especially for people with organic acid disorders. Your dietician will tell you how to use these foods to supplement your child's diet.

In addition to a low-protein diet, many children are given a special leucine-free medical formula. Your metabolic doctor and dietician will decide whether your child needs this formula. Some states offer help with payment, or require private insurance to pay for the formula and other special medical foods.

2. Medications

Glycine is an amino acid that helps the body get rid of isovaleric acid. It is often given as a supplement to children with IVA. It may help prevent metabolic crises. Your doctor will tell you whether your child needs glycine and how much to use.

Some children may benefit by taking L-carnitine. This is a safe and natural substance that helps body cells make energy. It also helps the body get rid of isovaleric acid and other harmful wastes. Your doctor will decide whether or not your child needs L-carnitine. Unless you are advised otherwise, use only L-carnitine prescribed by your doctor.

Do not use any medication or supplement without checking with your metabolic doctor.

Children with symptoms of a metabolic crisis need medical treatment right away. During a metabolic crisis, children may be given bicarbonate, glucose, and other medications by IV to help reduce the acid levels in the blood.

WHAT HAPPENS WHEN IVA IS TREATED?

With prompt and careful treatment, children with IVA have a good chance to live healthy lives with typical growth and development.

Even when treated, some children still have repeated bouts of metabolic crisis. This can lead to life-long learning problems or intellectual disabilities. As they get older, children tend to have fewer metabolic crises

LONG CHAIN 3-HYDROXYACYL-COA DEHYDROGENASE DEFICIENCY (LCHADD)

LCHADD stands for “long chain 3-hydroxyacyl-CoA dehydrogenase deficiency”. It is one type of fatty. People with LCHADD have problems breaking down fat into energy for the body.

IF LCHADD IS NOT TREATED, WHAT PROBLEMS OCCUR?

LCHADD can cause mild effects in some people and more serious health problems in others. Babies and children with LCHADD usually begin to show symptoms sometime from birth through age two. LCHADD causes episodes of hypoglycaemia.

If hypoglycaemia is not treated, a child with LCHADD can develop:

- breathing problems, swelling of the brain, seizures, coma, sometimes leading to death

Symptoms often happen after having nothing to eat for more than a few hours. Symptoms are also more likely to occur when a person with LCHADD gets sick or has an infection.

Between episodes of hypoglycaemia, people with LCHADD are usually healthy. However, repeated episodes can cause brain damage. This can result in learning disabilities or intellectual disabilities.

Babies and children who are not treated may have:, enlarged liver and other liver problems, enlarged heart and other heart problems, vision loss due to build-up of pigment in the retina, anaemia, nerve problems, bouts of muscle weakness and pain, especially after heavy exercise or illness

WHAT IS THE TREATMENT FOR LCHADD?

Treatment is usually needed throughout life. The following are treatments often recommended for children with LCHADD:

1. Avoid going a long time without food

Infants and young children with LCHADD need to eat frequently to prevent a metabolic crisis. In general, it is often suggested that infants be fed every four to six hours. Some babies need to eat even more frequently than this. It is important that infants be fed during the night. They may need to be woken up to eat if they do not wake up on their own. When they are well, many teens and adults with LCHADD can go without food for up to 12 hours without problems. The other treatments usually need to be continued throughout life.

2. Diet

Sometimes a low fat, high carbohydrate food plan is recommended. Carbohydrates give the body many types of sugar that can be used as energy. In fact, for children needing this treatment, most food in the diet should be carbohydrates (bread, pasta, fruit, vegetables, etc.) and protein (lean meat and low-fat dairy foods). Any diet changes should be made under the guidance of a dietician familiar with LCHADD.

3. MCT oil, L-carnitine and other supplements

5. Avoid prolonged exercise or exertion.

Long periods of heavy exercise can also trigger symptoms.

WHAT HAPPENS WHEN LCHADD IS TREATED?

With prompt and careful treatment, children with LCHADD can often live healthy lives with typical growth and development. Even with treatment, some people with LCHADD continue to have episodes of hypoglycaemia. This can lead to learning problems or intellectual disabilities. And, even with treatment, some people still develop vision, muscle, liver or heart problems.

MAPLE SYRUP URINE DISEASE (MSUD)

MSUD is an amino acid disorder. People with MSUD have problems breaking down certain amino acids found in protein.

IF MSUD IS NOT TREATED, WHAT PROBLEMS OCCUR?

There are a number of different forms of MSUD. The most common form, “classic MSUD”, can be life-threatening and must be treated promptly to prevent serious health problems. Other forms, including ‘intermediate’ and ‘intermittent’ forms of MSUD, are less severe. These milder forms are less common. This fact sheet contains information on classic MSUD.

Classic MSUD
Symptoms start as soon as a baby is fed protein, usually shortly after birth. Some of the first symptoms are:

- poor appetite, weak suck, weight loss, high pitched cry, urine that smells like maple syrup or burnt sugar

Babies with MSUD have episodes of illness called metabolic crisis. Some of the first symptoms of a metabolic crisis are:

- extreme sleepiness, sluggishness, irritable mood, vomiting,

If not treated, other symptoms can follow:

- episodes where muscles tone alternates between being rigid and floppy, swelling of the brain, seizures, high levels of acidic substances in the blood, called metabolic acidosis, coma, sometimes leading to death

Symptoms of a metabolic crisis often happen:

- after going too long without food, during illness or infection, during stressful events such as surgery

Without treatment, brain damage can occur. This can cause intellectual disabilities or spasticity. Some babies become blind. If not treated, most babies die within a few months.

WHAT IS THE TREATMENT FOR MSUD?

Prompt treatment is needed to prevent intellectual disabilities and serious medical problems. Most children need to eat a very low-protein diet and drink a special medical formula. You should start the diet and the formula as soon as you know your child has MSUD.

The following are treatments often recommended for children with MSUD:

1. Medical Formula
In addition to a low-protein diet, children are often given a special medical formula as a substitute for milk. This formula gives them the nutrients and protein they need while helping keep their BCAA levels in a safe range.

2. Diet low in branched-chain amino acids
The diet is made up of foods that are very low in the BCAAs. This means your child will need to avoid foods such as cow’s milk, regular formula, meat, fish, cheese and eggs. Regular flour, dried beans, nuts, and peanut butter must be avoided or strictly limited. Many vegetables and fruits have only small amounts of the BCAAs and can be eaten in carefully measured amounts. There are other medical foods such as special low-protein flours, pastas, and rice that are made especially for people with MSUD. Lifelong treatment with the MSUD diet is necessary. Children are at risk for episodes of metabolic crisis when they don’t follow the diet.

3. Supplements

Children with a rare form of MSUD, called “thiamine-responsive MSUD”, can often be helped by thiamine supplements. Some children with classic MSUD may also benefit from thiamine. Ask your doctor whether your child should take thiamine supplements. Do not use any supplements without checking with your doctor.

4. Tracking BCAA levels

Your child will have regular blood tests to measure amino acid levels. The diet and formula may need to be adjusted based on blood test results.

Children with MSUD need to eat more carbohydrates and drink more fluids during any illness – even if they’re not hungry – or they could have a metabolic crisis. Children who are sick may not want to eat. If they can’t eat, or if they show signs of a metabolic crisis, they may need to be treated in the hospital.

5. Liver transplantation

Liver transplant surgery is an optional treatment for people with MSUD. The BCKAD enzyme that causes MSUD is located in the liver. Because of this, some children with MSUD have had liver transplantation surgery (removal of their liver and replacement with a donor liver) to treat their MSUD symptoms.

This major surgical procedure is associated with risks, and individuals who have had a liver transplant must take medication for the rest of their lives to prevent their body from rejecting the donor liver. However, successful liver transplantation cures people of their MSUD symptoms.

Many factors must be considered before surgery and this option should be discussed very thoroughly with your child’s physicians.

WHAT HAPPENS WHEN MSUD IS TREATED?

With prompt and lifelong treatment, children with MSUD often have healthy lives with typical growth and development. Early treatment can help prevent brain damage and intellectual disabilities.

However, children with MSUD are at increased risk to have attention deficit hyperactivity disorder (ADHD), anxiety and depression even if they have had a liver transplant. The reasons for this are not well understood at this time.

Even with treatment, some children still develop swelling of the brain or have episodes of metabolic crisis. Children who have repeated metabolic crises may develop permanent brain damage. This can cause lifelong learning problems, intellectual disabilities or spasticity.

MEDIUM CHAIN ACYL-COA DEHYDROGENASE DEFICIENCY (MCADD)

MCADD stands for “medium chain acyl-CoA dehydrogenase deficiency”. It is one type of fatty acid oxidation disorder. People with MCADD have problems breaking down fat into energy for the body.

IF MCADD IS NOT TREATED, WHAT PROBLEMS OCCUR?

MCADD can cause bouts of illness called metabolic crises. Children with MCADD often show effects for the first time between three months and three years of age. Some of the first symptoms of a metabolic crisis are: extreme sleepiness, behaviour changes, irritable mood, poor appetite

Some of these other symptoms may also follow: fever, diarrhoea, vomiting, hypoglycaemia

If a metabolic crisis is not treated, a child with MCADD can develop: breathing problems, seizures, coma, sometimes leading to death

Between episodes of metabolic crisis, people with MCADD are usually healthy. However, repeated episodes can cause permanent brain damage. This may result in learning problems, intellectual disabilities or spasticity.

Symptoms often happen after having nothing to eat for more than a few hours. Hypoglycaemia and metabolic crises are also more likely to occur when a person with MCADD gets sick or has an infection.

Some children with MCADD have very mild symptoms or no symptoms at all.

WHAT IS THE TREATMENT FOR MCADD?

When necessary, treatment is usually needed throughout life. The following are treatments often recommended for children with MCADD:

1. Avoid going a long time without food

Infants and young children with MCADD need to eat frequently to prevent hypoglycaemia or a metabolic crisis. Your metabolic doctor will tell you how often your child needs to be fed. In general, it is often suggested that infants be fed every four to six hours. Some babies need to eat even more frequently than this. It is important that infants be fed during the night. They may need to be woken up to eat if they do not wake up on their own. When they are well, many teens and adults with MCADD can go without food for up to 12 hours without problems. Most children do not have metabolic crises past the age of ten. However, some may need to continue treatment throughout life.

2. Diet

Sometimes a low fat, high carbohydrate food plan is recommended. Carbohydrates give the body many types of sugar that can be used as energy. In fact, for children needing this treatment, most food in the diet should be carbohydrates (bread, pasta, fruit, vegetables, etc.) and protein (lean meat and low-fat dairy foods).

3. L-carnitine supplements

Some children may be helped by taking L-carnitine. This is a safe and natural substance that helps body cells make energy. It also helps the body get rid of harmful wastes.

WHAT HAPPENS WHEN MCADD IS TREATED?

With prompt and careful treatment, children with MCADD usually live healthy lives with typical growth and development. The goal of treatment is to prevent long-term problems. However, children who have repeated metabolic crises may have life-long learning disabilities, spasticity, chronic muscle weakness or other effects.

METHYLMALONIC ACIDEMIA (MMA)

MMA stands for “methylmalonic acidemia”. It is one type of organic acid disorder. People with MMA have problems breaking down and using certain amino acids and fatty acids from the food they eat.

IF MMA IS NOT TREATED, WHAT PROBLEMS OCCUR?

Each child with MMA is likely to have somewhat different effects. Many babies with MMA start having symptoms in the first few days of life. Others begin to show symptoms sometime in infancy or childhood. Some people with MMA may never develop symptoms.

MMA causes episodes of illness called metabolic crises. Some of the first symptoms of a metabolic crisis are:

- poor appetite, vomiting, extreme sleepiness or lack of energy, low muscle tone (floppy muscles and joints)

Common blood and urine findings are:

- ketones in the urine
- high levels of acidic substances in the blood, called metabolic acidosis
- high blood ammonia levels
- high blood and urine levels of glycine
- high blood and urine levels of methylmalonic acid and propionic acid
- high levels of other harmful substances
- low platelets
- low white blood cells
- anaemia

If a metabolic crisis is not treated, a child with MMA can develop:

- breathing problems
- seizures
- stroke
- coma, sometimes leading to death

A metabolic crisis can be triggered by:

- eating large amounts of protein
- illness or infection
- going too long without food
- stressful events such as surgery

Between episodes of metabolic crisis, children with MMA may be healthy. However, some continue to have problems with health and development. Some children have long-term problems even if they have never had a metabolic crisis. These can include:

- learning disabilities or intellectual disabilities
- delays in walking and motor skills
- abnormal involuntary movements (dystonia and chorea)
- rigid muscle tone, called spasticity
- poor growth with short stature
- skin rashes and infections
- osteoporosis
- enlarged liver
- kidney disease or failure
- vision loss due to problems with the nerves in the eye

Without treatment, brain and nerve damage can occur. This can cause intellectual disabilities and problems with involuntary movements. Death is common in untreated babies and children.

A small number of people with MMA never show symptoms.

WHAT IS THE TREATMENT FOR MMA?

Your baby's primary doctor will work with a metabolic doctor and a dietician familiar with MMA to care for your child.

Prompt treatment is needed to reduce the chance for intellectual disabilities and serious medical problems. Children with 'vitamin B12 responsive' MMA are given vitamin B12. In addition, most children need to be on a low-protein diet and drink a special medical formula. You should start the treatments as soon as you know your child has MMA.

The following are treatments often recommended for children with MMA:

1. Medication

The main treatment for 'vitamin B12 responsive' MMA is vitamin B12 injections in the form of hydroxocobalamin (OH-cbl) or cyanocobalamin (CN-cbl). Vitamin B12 injections can prevent symptoms in children with this form of MMA.

Over 90% of children with CblA deficiency respond to vitamin B12 injections. About 40% of children with CblB deficiency are helped by this treatment. Your doctors may need to treat your child with vitamin B12 for short period of time to determine whether this treatment is useful.

Children with MMA may benefit by taking L-carnitine. This is a safe and natural substance that helps the body make energy. It also helps get rid of harmful wastes. Your doctor will decide whether or not your child needs L-carnitine. Unless you are advised otherwise, use only L-carnitine prescribed by your doctor.

Antibiotics taken by mouth can help lower the amount of methylmalonic acid made in the intestines. Your doctor will decide if your child needs antibiotics and, if so, what type.

Children who are having symptoms of a metabolic crisis should be treated in the hospital. During a metabolic crisis, your child may be given medications such as bicarbonate through an IV to help reduce the acid levels in the blood. Glucose is given by IV to prevent the breakdown of protein and fat stored in the body.

Do not use any medication without checking with your doctor.

2. Low-protein diet, medical foods and medical formula

Low-protein diet

A food plan low in the amino acids leucine, valine, methionine, and threonine with limited amounts of protein is often recommended. Most food in the diet will be carbohydrates (bread, cereal, pasta, fruit, vegetables, etc.). Carbohydrates give the body many types of sugar that can be used as energy. Eating a diet high in carbohydrates and low in protein and fat can help prevent metabolic crises.

Foods high in protein that may need to be avoided or limited include:

- milk and dairy products
- meat and poultry
- fish
- eggs
- dried beans and legumes
- nuts and peanut butter

Many vegetables and fruits have only small amounts of protein and can be eaten in carefully measured amounts. Do not remove all protein from the diet. Children with MMA need a certain amount to grow properly.

Your dietician can create a food plan that contains the right amount of protein, nutrients, and energy to keep your child healthy. It is likely your child will need to be on a special food plan throughout life.

Medical formula and foods
In addition to a low-protein diet, your child may be given a special medical formula. This formula contains the correct amount of protein and nutrients your child needs for normal growth and development. Your metabolic doctor and dietician will tell you what type of formula is best and how much to use.

There are also medical foods such as special low-protein flours, pastas, and rice that are made especially for people with organic acid disorders. Your dietician will tell you how to use these foods as part of your child's diet.

Some states offer help with payment or require private insurance to pay for the formula and other special medical foods.

3. Avoid going a long time without food
Infants and young children with MMA need to eat frequently to prevent a metabolic crisis. Your metabolic doctor will tell you how often your child needs to be fed. In general, it is often suggested that infants be fed every four to six hours. Some babies need to eat even more frequently than this. It is important that infants be fed during the night. They may need to be woken up to eat if they do not wake up on their own. Your metabolic doctor and dietician will give you an appropriate feeding plan for your infant. Your doctor will also give you a 'sick day' plan, tailored to your child's needs, for you to follow during illnesses or other times when your child will not eat.

Your metabolic doctor will continue to advise you on how often your child should eat as he or she gets older.

4. Regular blood and urine tests
Tracking of ketones
Periodic urine tests to check the level of ketones can be done at home or at the doctor's office. Ketones are substances formed when body fat is broken down for energy. This happens after going without food for long periods of time, during illness, and during periods of heavy exercise. Too many ketones in the urine may signal the start of a metabolic crisis.

Blood tests
Your child will have regular blood tests to measure the level of amino acids. Urine tests may also be done. Your child's diet and medication may need to be adjusted based on the results of these tests.

6. Organ transplantation
Some children with MMA are given liver or kidney transplants, or both. This may reduce some of the symptoms. However, transplant surgery has serious risks and may or may not be right for your child. Talk with your doctor or metabolic specialist if you have questions about the risks and benefits of transplantation.

WHAT HAPPENS WHEN MMA IS TREATED?

Babies and children who have prompt and ongoing treatment may be able to live healthy lives with normal growth and development. In general, the earlier treatment is started, the better the outcome.

Children who respond to vitamin B12 treatment tend to do very well as long as treatment is continued. Children who are not treated until after they have symptoms may have lasting health and learning problems.

Even with treatment, some children develop life-long learning disabilities or intellectual disabilities. In addition, despite treatment, seizures, involuntary movement disorder

ORNITHINE TRANSCARBAMYLASE DEFICIENCY

(https://ghr.nlm.nih.gov/condition/ornithine-transcarbamylase-deficiency)

http://www.babysfirsttest.org/newborn-screening/conditions/ornithine-transcarbamylase-deficiency#sthash.lyRF0MOC.dpuf

Ornithine transcarbamylase deficiency is an inherited disorder that causes ammonia to accumulate in the blood. Ammonia, which is formed when proteins are broken down in the body, is toxic if the levels become too high. The nervous system is especially sensitive to the effects of excess ammonia.

An infant with ornithine transcarbamylase deficiency may be lacking in energy (lethargic) or unwilling to eat, and have poorly-controlled breathing rate or body temperature. Some babies with this disorder may experience seizures or unusual body movements, or go into a coma. Complications from ornithine transcarbamylase deficiency may include developmental delay and intellectual disability. Progressive liver damage, skin lesions, and brittle hair may also be seen.

Dietary Treatments: Your baby may need to be on a low-protein diet in order to avoid the proteins that his or her body cannot break down. Your baby's doctor might also recommend special formulas and foods for children with ornithine transcarbamylase deficiency (OTC). These formulas will likely need to continue through adulthood.

Supplements and Medications: Your baby's health care provider may prescribe supplements to help your baby's body get rid of excess ammonia in the blood. Everyone has some ammonia in his or her blood, but high levels can be toxic.

Dialysis: Some babies with OTC may require dialysis to lower the levels of ammonia in their bodies. Dialysis is a treatment that uses a special machine to filter harmful wastes, salt, and excess fluid from the blood.

Prognosis: When ornithine transcarbamylase deficiency (OTC) is detected early and proper treatment is started immediately, many babies with the condition are able to live longer lives with improved growth and development. Unfortunately, even with treatment, some children may experience learning disabilities, intellectual disabilities, or tight muscles (spasticity), which are commonly associated with OTC. Children who do not receive treatment for OTC are at risk for severe intellectual disability, seizures, coma, or even death.

PHENYLKETONURIA (PKU)

WHAT IS PKU?

PKU stands for “phenylketonuria”. It is one type of **amino acid disorder**. People with PKU have problems breaking down an amino acid called phenylalanine from the food they eat.

IF PKU IS NOT TREATED, WHAT PROBLEMS OCCUR?

Babies with PKU seem perfectly normal at birth. The first effects are usually seen around 6 months of age. Untreated infants may be late in learning to sit, crawl and stand. They may pay less attention to things around them. Without treatment, a child with PKU will have intellectual disabilities.

Some of the effects of untreated PKU include:

intellectual disabilities, behaviour problems, hyperactivity, restlessness or irritability, seizures, a skin condition called eczema, a “musty” or “mousy” body odour, fair hair and skin

WHAT IS THE TREATMENT FOR PKU?

Prompt treatment is needed to prevent intellectual disabilities. Newborns need to drink a special medical formula. It is still possible to breastfeed your baby as long as you get help from your dietician. Babies who are breastfed usually need the medical formula as well.

Most children need to eat a special diet made up of very low-protein foods, special medical foods, and the special formula. You must start the low-Phe diet as soon as you know your child has PKU. Your dietician will create a food plan that contains the right amount of protein, nutrients, and energy to keep your child healthy. The diet should be continued throughout life.

The following are treatments often advised for children with PKU:

1**. Medical formula**
Even though they need less Phe, children with PKU still need a certain amount of protein. The medical formula gives babies and children with PKU the nutrients and protein they need while helping keep their Phe levels within a safe range.

2. Low-Phe food plan
The low-Phe food plan is made up of foods that are very low in Phe. This means your child must avoid or strictly limit the following foods:

- milk and all dairy products including cheese, yogurt, ice cream, regular formula, meat and poultry, fish, eggs, nuts and peanut butter, dried beans, regular flour

It is very important that your child avoid the sugar substitute aspartame. Aspartame contains high amounts of Phe. It can quickly raise the blood levels of Phe in people with PKU. Your child must not have any diet foods or drinks that contain aspartame. Some medicines and vitamins also contain aspartame.

Many vegetables and fruits have only small amounts of Phe and can be eaten in carefully measured amounts. In addition, there are other medical foods such as low-Phe flours, baking mixes, breads, and pastas that are made especially for people with PKU.

3. Tracking Phe levels

Babies and young children with PKU need to have regular blood tests to measure their Phe levels. If there is too much or too little Phe in the blood, the diet and formula may need to be adjusted.

WHAT HAPPENS WHEN PKU IS TREATED?

Children with PKU who start treatment soon after birth and keep their Phe levels within the suggested range usually have normal growth and intelligence. Some children, even when treated, have problems with school work and may need extra help. If treatment is not started until several weeks after birth, delays or learning problems may occur. The level of delay varies from child to child. Children who start treatment after 6 months of age often have intellectual disabilities. Treatment is still important, even if started late, because it can help control behaviour and mood problems and can prevent further damage to the brain.

PROPIONIC ACIDEMIA (PA)

PA stands for “propionic acidemia”. It is one type of organic acid disorder. People with PA have problems breaking down and using certain amino acids from the food they eat.

IF PA IS NOT TREATED, WHAT PROBLEMS OCCUR?

Each child with PA is likely to have somewhat different effects. Many babies with PA start having symptoms in the first few days of life. Others have their first symptoms sometime in infancy. There are also some people who have mild or no symptoms.

PA causes episodes of illness called metabolic crises. Some of the first symptoms of a metabolic crisis are:

- poor appetite, vomiting, irritable mood, extreme sleepiness or lack of energy, low muscle tone (floppy muscles and joints), heart problems

If a metabolic crisis is not treated, a child with PA can develop:

- breathing problems, seizures, swelling of the brain, stroke, coma, sometimes leading to death.

A metabolic crisis can be triggered by:

- eating large amounts of protein, illness or infection, going too long without food, stressful events such as surgery

Between episodes of metabolic crisis, children with PA are often healthy.

Long-term effects are seen in some children and adults with PA. These can include:

- learning disabilities or intellectual disabilities
- delays in walking and motor skills
- abnormal involuntary movements (dystonia or choreoathetosis)
- rigid muscle tone, called spasticity
- poor growth with short stature
- seizures
- osteoporosis
- inflammation of the pancreas, called pancreatitis
- vision loss due to problems with the nerves in the eye
- premature ovarian failure
- kidney problems

Without treatment, brain damage can occur. This can result in intellectual disabilities. If not treated, many babies with PA die within the first year of life.

A small number of people with PA never show symptoms and are only found to be affected after a brother or sister is diagnosed.

WHAT IS THE TREATMENT FOR PA?

Your baby’s primary doctor will work with a metabolic doctor and a dietician to provide care for your child.

Prompt treatment is needed to prevent intellectual disabilities and serious medical problems. Most children need to be on a low-protein diet and drink a special medical formula. You should start the diet and formula as soon as you know your child has PA.

The following are treatments often recommended for children with PA:

1. Low-protein diet, medical foods and medical formula

Low-protein diet

A food plan low in the amino acids leucine, valine, methionine, and threonine, with limited amounts protein is often recommended. Most food in the diet will be carbohydrates (bread, cereal, pasta, fruit, vegetables, etc.). Carbohydrates give the body many types of sugar that can be used as energy. Eating a diet high in carbohydrates and low in protein can help prevent metabolic crises.

Foods high in protein that may need to be avoided or limited include:

- milk and dairy products, meat and poultry, fish, eggs, dried beans and legumes, nuts and peanut butter

Many vegetables and fruits have only small amounts of protein and can be eaten in carefully measured amounts. Do not remove all protein from the diet. Children with PA need a certain amount of protein to grow properly.

Your dietician will create a food plan that contains the right amount of protein, nutrients, and energy to keep your child healthy. Your child will need to be on a special food plan throughout his or her life.

Medical formula and foods

In addition to a low-protein diet, your child may be given a special medical formula. This formula contains the correct amount of protein and nutrients needed for normal growth and development. Your metabolic doctor and dietician will tell you what type of formula is best and how much to use.

There are also medical foods such as special low protein flours, pastas, and rice that are made especially for people with organic acid disorders. Your dietician will tell you how to use these foods as part of your child's diet.

Some states offer help with payment, or require private insurance to pay for the formula and other special medical foods.

2. Avoid going a long time without food

Infants and young children with PA need to eat frequently to prevent a metabolic crisis. Your metabolic doctor will tell you how often your child needs to be fed. In general, it is often suggested that infants be fed every four to six hours. Some babies need to eat even more frequently than this. It is important that infants be fed during the night. They may need to be woken up to eat if they do not wake up on their own. Your metabolic doctor and dietician will give you an appropriate feeding plan for your infant. Your doctor will also give you a 'sick day' plan, tailored to your child's needs, for you to follow during illnesses or other times when your child will not eat.

Your metabolic doctor will continue to advise you on how often your child should eat as he or she gets older.

3. Medication

Children with PA may benefit by taking L-carnitine. This is a safe and natural substance that helps the body make energy. It also helps get rid of harmful wastes. L-carnitine is part of the usual treatment for PA. Your doctor will tell you how much your child needs. Unless you are advised otherwise, use only L-carnitine prescribed by your doctor.

Certain antibiotics, taken by mouth, can help reduce the amount of propionic acid in the intestines. Your doctor will decide if your child needs antibiotics and, if so, what type.

Some children may be given biotin supplements by mouth. Biotin is a type of B vitamin that helps the body make energy from food. Biotin has not been proven to help in PA. But, your doctor may talk with you about trying this supplement to see if it is of benefit to your child.

Children who are having symptoms of a metabolic crisis should be treated in the hospital. During a metabolic crisis, your child may be given medications such as bicarbonate by IV to help reduce the

acid levels in the blood. Glucose is often given by IV to prevent the breakdown of protein and fat stored in the body.

Do not use any medication or supplement without first checking with your doctor or metabolic doctor.

4. Regular blood and urine tests

Tracking of ketones
Your child will have periodic urine tests to check the level of ketones. These can be done at home or at the doctor's office. Ketones are substances formed when body fat is broken down for energy. This can happen after going without food for long periods of time, as the result of an illness, or during periods of heavy exercise. Ketones in the urine may signal the start of a metabolic crisis.

Blood tests
Your child will have regular blood tests to measure the levels of amino acids. Urine tests may also be done. Your child's diet and medication may need to be adjusted based on the results of these tests.

6. Liver transplant
Liver transplant surgery is an optional treatment for people with PA. The PCC enzyme that causes PA is located in the liver. Because of this, some children with PA have had liver transplantation surgery (removal of their liver and replacement with a donor liver) to treat their PA symptoms.

This major surgical procedure is associated with risks, and individuals who have had a liver transplant must take medication for the rest of their lives to prevent their body from rejecting the donor liver. However, even with a successful liver transplantation people with PA may still need to have a restricted diet.

Many factors must be considered before surgery and this option should be discussed very thoroughly with your child's physicians.

WHAT HAPPENS WHEN PA IS TREATED?

Babies who have prompt and ongoing treatment before they have a metabolic crisis may have normal growth and development. In general, the earlier treatment is started, the better the outcome.

Even with treatment, some children have life-long learning problems or intellectual disabilities. Seizures or problems with involuntary movements also occur in some children, despite treatment. Children with PA often have more infections than usual. These need to be treated promptly to avoid a metabolic crisis.

SHORT CHAIN ACYL-COA DEHYDROGENASE DEFICIENCY (SCADD)

SCADD stands for “short chain acyl-CoA dehydrogenase deficiency”. It is one type of fatty acid oxidation disorder. Some people with SCADD cannot break down fat into energy for the body. However, most babies with newborn screening results showing SCADD never have symptoms.

IF SCADD IS NOT TREATED, WHAT PROBLEMS OCCUR?

SCADD is a highly variable and not well understood. Most babies found to have SCADD through newborn screening never have symptoms. Things that cause stress, such as lack of sleep, going without food for too long, illness, or infection are thought to trigger episodes of illness called metabolic in some children but not others.

For the small number of people with SCADD who show effects, the condition occurs in two different forms: one found in infants, the other found in adults.

SCADD in infants
This type of SCADD is found in newborns and infants. Symptoms, when they happen, often start between the first week and 3 months of life.

Some of the first symptoms of a metabolic crisis are:

- extreme sleepiness, behaviour changes, irritable mood, poor appetite

Other symptoms then follow:

- fever, diarrhoea, vomiting, increased levels of acidic substances in the blood, called metabolic acidosis

If a metabolic crisis is not treated, a child with SCADD can develop:

- breathing problems, seizures, coma, sometimes leading to death,

Other effects of SCADD seen in some infants and children:

- poor weight gain, delays in learning, delays in walking and other motor skills, hyperactivity, decreased or increased muscle tone, muscle weakness, enlarged liver, enlarged spleen

Symptoms of a metabolic crisis often happen after having nothing to eat for more than a few hours. Symptoms are also more likely when a child with SCADD gets sick or has an infection.

Many children with this condition have never had any effects and may only be found to have SCADD after a brother or sister has been diagnosed. Most children diagnosed through newborn screening never develop any symptoms related to SCADD.

WHAT IS THE TREATMENT FOR SCADD?

Certain treatments may be advised for some children but not others. Babies found to have SCADD on newborn screening, but who have not shown any effects, may not need treatment. When necessary, treatment is usually needed throughout life. The following are treatments recommended for some, but not all, children with SCADD:

1. Avoid going a long time without food

Some babies and young children with SCADD may need to eat often to avoid a metabolic crisis. These children should not go without food for more than four to six hours. In fact, some babies may need to eat even more often than this. They may also need to be fed during the night. When they are well, most

teens and adults with SCADD can go without food for up to 12 hours. People who have had symptoms may need to continue the other treatments throughout life.

2. Diet

A low fat, high carbohydrate food plan may be advised for some children with SCADD. Carbohydrates give the body many types of sugar that can be used as energy. In fact, for children needing this treatment, most food in the diet should be carbohydrates (bread, pasta, fruit, vegetables, etc.) and protein (lean meat and low-fat dairy foods). Any diet changes should be made under the guidance of a dietician familiar with SCADD.

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3. L-Carnitine and Riboflavin supplements

WHAT HAPPENS WHEN SCADD IS TREATED?

It is not known how effective treatment is in preventing problems. Treatment may help prevent or control symptoms in some children. Children who need treatment and are treated early may be able to live healthy lives with typical growth and development. Some children, though, may continue to have learning delays, muscle weakness and other health problems despite treatment.

TYROSINEMIA I

This condition is one type of **amino acid disorder**. People with tyrosinemia 1 have problems breaking down an amino acid called tyrosine from the food they eat. If not treated, the condition causes severe liver disease and other serious health problems.

IF TYROSINEMIA 1 IS NOT TREATED, WHAT PROBLEMS OCCUR?

The symptoms can vary a great deal from person to person. There are two types of tyrosinemia 1. The more common form happens in infants. The less common form is seen in older children and adults.

Tyrosinemia 1 in infants:
Babies usually show effects of the condition within the first few months of life. Some of the first symptoms may be:

- diarrhoea and bloody stools, vomiting, poor weight gain, extreme sleepiness, irritability, “cabbage-like” odour to the skin or urine

Liver problems are common. They can lead to:

- enlarged liver, yellowing of the skin, tendency to bleed and bruise easily, swelling of the legs and abdomen

Kidney problems also happen and can lead to:

- rickets, a bone thinning condition, delays in walking

Without prompt and careful treatment, babies with severe liver and kidney problems usually die.

Some babies also have episodes that include:

- pain or weakness, especially in the legs, breathing problems, rapid heartbeat, seizures, coma, sometimes leading to death

Tyrosinemia 1 in children (“chronic” form):
Children with the chronic form usually start having symptoms after two months of age. Some of the first signs may be trouble gaining weight and episodes of vomiting and diarrhoea. Over time, the condition can cause liver, kidney and nerve problems.

- *Liver*: If the condition is not treated, a rare type of liver scarring called nodular cirrhosis can happen. This gets worse over time and can lead to liver failure. If not treated, many children develop liver failure or liver cancer before the age of 10. Medication, when started early, can prevent liver failure in most children.

- *Kidneys*: Serious kidney problems can occur in untreated children. When the kidneys are not working properly, episodes of vomiting, weakness and fever can happen. Rickets, a bone thinning condition, may happen in children with kidney damage. Medication can prevent kidney problems in most children.

- *Neurologic crises:* Some children have episodes of weakness, pain or numbness in their arms, legs or other parts of the body. Breathing problems and rapid heartbeat may also

happen. Some children have seizures that can lead to coma. Medication can stop episodes of neurologic crisis in most children.

- *Other:* A small number of children have had heart problems. Some have had high blood pressure.

WHAT IS THE TREATMENT FOR TYROSINEMIA 1?

Your baby's doctor will work with a metabolic doctor and dietician to care for your child. Lifelong treatment is usually needed to prevent liver and kidney problems.

Treatment consists of medication and a diet low in tyrosine and another amino acid called phenylalanine (phe). The low-tyrosine/phenylalanine diet is made up of a special medical formula and carefully chosen foods. You must start the treatment as soon as you know your child has the condition.

The following treatments are often recommended for children with tyrosinemia 1:

1. Medication

A medication called nitisinone (Orfadin®), also known as NTBC, is used to prevent liver and kidney damage. It also stops the neurologic crises. The medication lessens the risk for liver cancer. Your child should start taking Nitisinone as soon as possible. Your doctor will need to write a prescription for this medication.

Nitisinone will increase the level of tyrosine in your child's blood. So, a low-tyrosine diet is a very important part of treatment.

Vitamin D is sometimes used to treat children who have rickets.

Do not take any medication without talking with your doctor.

2. Medical Formula

The special medical formula gives babies and children the nutrients and protein they need while helping keep their tyrosine levels within a safe range. Your metabolic doctor and dietician will tell you what type of formula is best and how much to use.

3. Low-tyrosine / phenylalanine diet:

The diet is made up of foods that are very low in tyrosine and phenylalanine. This means your child will need to limit foods such as cow's milk and regular formula. He or she will need to avoid meat, eggs and cheese. Regular flour, dried beans, nuts and peanut butter contain these amino acids and must also be limited.

Many vegetables and fruits have only small amounts of phenylalanine and tyrosine and can be eaten regularly in carefully measured amounts.

There are other medical foods such as special flours, pastas, and rice that are made especially for people with tyrosinemia 1. Some states offer help with payment, or require private insurance coverage for formula and other special medical foods.

Your metabolic doctor and dietician will decide on the best food plan for your child. The exact plan will depend on many things such as your child's age, weight, general health, and how well the medication is working. Your dietician will fine-tune your child's diet over time.

4. Blood, urine and other tests

Your child will have regular blood and urine tests to check:

- amino acid levels
- the amount of succinylacetone
- nitisinone level
- liver and kidney function

These tests help your doctor and dietician figure out whether any changes to the medication or diet are needed.

Some experts suggest that children with tyrosinemia 1 have a CT or MRI scan of their liver once a year to check for scarring or cancer.

5. Liver transplantation

Before nitisinone was available, liver transplantation was one of the main treatments for tyrosinemia 1. Now, nitisinone can prevent or reverse many of the liver problems and decreases the risk of developing liver cancer. For most children, nitisinone will delay, and hopefully prevent, the need for liver transplant.

Liver transplantation is still an option for those children that show signs of liver cancer or liver failure. If you have questions, talk to your metabolic doctor or doctor about the benefits and risks of transplantation.

WHAT HAPPENS WHEN TYROSINEMIA 1 IS TREATED?

When treatment is started early, severe liver, kidney, and neurologic symptoms can be prevented. Children who are treated usually have normal growth and intelligence.

If treatment is not started right away, children may have some liver or kidney damage. Rickets may already be present and need to be treated. Delays in growth and development may also be present. The effects of delayed treatment vary from child to child.

VERY LONG CHAIN ACYL-COA DEHYDROGENASE DEFICIENCY (VLCADD)

VLCADD stands for "very long chain acyl-CoA dehydrogenase deficiency." It is one type of fatty acid oxidation disorder. People with VLCADD have problems breaking down certain types of fat into energy for the body.

IF VLCADD IS NOT TREATED, WHAT PROBLEMS OCCUR?

VLCADD is variable and can cause mild effects in some people and more serious health problems in others. Symptoms may start in infancy or not until adulthood. There are three forms of VLCADD: “Early”, “Childhood” and “Adult”.

It is common for babies and children with the early and childhood types of VLCADD to have episodes of illness called metabolic crises. If a metabolic crisis is not treated, a child with VLCADD can develop:

- breathing problems, seizures, coma, sometimes leading to death

Periods of hypoglycaemia can happen with or without the other symptoms. Hypoglycaemia can cause a child to feel weak, shaky or dizzy with clammy, cold skin. If not treated, it can lead to coma, and possibly death.

Either hypoglycaemia or a full metabolic crisis can occur:

- after going too long without food, during illness or infection , after heavy exercise

Symptoms of early and childhood VLCADD often happen after a period of having nothing to eat for more than a few hours. Symptoms are also more likely when a child with VLCADD gets sick or has an infection.

Early VLCADD
About half of babies diagnosed with VLCADD have the "early" type. They usually start to show effects between birth and 4 months. In addition to metabolic crises, babies can also have:

- enlarged heart, irregular heartbeat and other heart problems, enlarged liver and other liver problems, muscle problems

If not treated, babies with early VLCADD usually die young.

Childhood VLCADD
About one third of people with VLCADD have the childhood type. They usually show symptoms in late infancy or early childhood. Episodes of hypoglycaemia or full metabolic crisis happen during illness or after long periods of not eating. Other effects can include:

- enlarged liver, other liver problems, muscle weakness, especially after exercise, heart problems are usually not seen in childhood VLCADD.

Some children with VLCADD have never had symptoms and are only found to be affected after a brother or sister has been diagnosed.

WHAT IS THE TREATMENT FOR VLCADD?

When necessary, treatment is usually needed throughout life. The following are treatments often recommended for children with VLCADD:

1. Avoid going a long time without food

Infants and young children with VLCADD need to eat frequently to prevent a metabolic crisis. In general, it is often suggested that infants be fed every four to six hours. Some babies need to eat even more frequently than this. It is important that infants be fed during the night. They may need to be woken up to eat if they do not wake up on their own. Your metabolic doctor and dietician will give you an appropriate feeding plan for your infant. Your doctor will also give you a 'sick day' plan tailored to your child's needs for you to follow during illnesses or other times when your child will not eat. When they are well, many teens and adults with VLCADD can go without food for up to 12 hours without problems. The other treatments usually need to be continued throughout life.

2. Diet

Sometimes a low fat, high carbohydrate diet is recommended. Carbohydrates give the body may types of sugar that can be used as energy. In fact, for children needing this treatment, most food in the diet should be carbohydrates (bread, pasta, fruit, etc.) and protein (lean meat and low-fat dairy foods). Any diet changes should be made under the guidance of an experienced dietician.

People with VLCADD cannot use certain building blocks of fat called "long chain fatty acids". Your dietician can help create a food plan low in these fats. Much of the rest of fat in the diet may be in the form of medium chain fatty acids.

3. MCT oil and L-carnitine supplements

5. Avoid prolonged exercise or exertion.
Long periods of exercise can also trigger symptoms.

WHAT HAPPENS WHEN VLCADD IS TREATED?

With prompt and careful treatment, people with the childhood and adult forms of VLCADD can often live healthy lives with typical growth and development. Before diagnosis through newborn screening was available, the early form of VLCADD was fatal. Now, with immediate and ongoing treatment, many infants with VLCADD are surviving.

Appendix 5: Author guidelines for Journal of Genetic Counselling

Journal of Genetic Counseling

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Journal no. 10897

Instructions for Authors

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4. Key words: A list of 3-10 key words is to be provided directly below the abstract. Key words should express the precise content of the manuscript, as they are used for indexing purposes.

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List references alphabetically at the end of the paper. References should include (in this order): last name and initials of authors, year published, title of article, name of publication, volume number, and inclusive pages. Where there are seven or more authors, abbreviate the seventh and subsequent authors as et al.

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Bennett, R. L. , Steinhaus, K. A., Uhrich, S. B., O' Sullivan, C. K., Resta, R. G. , Lochner-Doyle, D., Markel, D. S., Vincent, V., & Hamanishi, J. (1995). Recommendations for Standardized Human Pedigree Nomenclature. Journal of Genetic Counseling, 4, 267-279.

Bennett, R. L., Steinhaus French, K., Resta, R. G., & Lochner Doyle, D. (2008). Standardized Human Pedigree Nomenclature: Update and Assessment of the Recommendations of the National Society of Genetic Counselors. Journal of Genetic Counseling, 17, 424-433.

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Authors should refrain from misrepresenting research results which could damage the trust in the journal, the professionalism of scientific authorship, and ultimately the entire scientific endeavour. Maintaining integrity of the research and its presentation can be achieved by following the rules of good scientific practice, which include:

- The manuscript has not been submitted to more than one journal for simultaneous consideration.
- The manuscript has not been published previously (partly or in full), unless the new work concerns an expansion of previous work (please provide transparency on the re-use of material to avoid the hint of text-recycling ("self-plagiarism")).
- A single study is not split up into several parts to increase the quantity of submissions and submitted to various journals or to one journal over time (e.g. "salami-publishing").
- No data have been fabricated or manipulated (including images) to support your conclusions
- No data, text, or theories by others are presented as if they were the author's own ("plagiarism"). Proper acknowledgements to other works must be given (this includes material that is closely copied (near verbatim), summarized and/or paraphrased), quotation marks are used for verbatim copying of material, and permissions are secured for material that is copyrighted.

  Important note: the journal may use software to screen for plagiarism.
- Consent to submit has been received explicitly from all co-authors, as well as from the responsible authorities - tacitly or explicitly - at the institute/organization where the work has been carried out, **before** the work is submitted.
- Authors whose names appear on the submission have contributed sufficiently to the scientific work and therefore share collective responsibility and accountability for the results.

In addition:

- Changes of authorship or in the order of authors are not accepted **after** acceptance of a manuscript.
- Requesting to add or delete authors at revision stage, proof stage, or after publication is a serious matter and may be considered when justifiably warranted. Justification for changes in authorship must be compelling and may be considered only after receipt of written approval from all authors and a convincing, detailed explanation about the role/deletion of the new/deleted author. In case of changes at revision stage, a letter must accompany the revised manuscript. In case of changes after acceptance or publication, the request and documentation must be sent via the Publisher to the Editor-in-Chief. In all cases, further documentation may be required to support your request. The decision on accepting the

change rests with the Editor-in-Chief of the journal and may be turned down. Therefore authors are strongly advised to ensure the correct author group, corresponding author, and order of authors at submission.

- Upon request authors should be prepared to send relevant documentation or data in order to verify the validity of the results. This could be in the form of raw data, samples, records, etc.
  If there is a suspicion of misconduct, the journal will carry out an investigation following the COPE guidelines. If, after investigation, the allegation seems to raise valid concerns, the accused author will be contacted and given an opportunity to address the issue. If misconduct has been established beyond reasonable doubt, this may result in the Editor-in-Chief's implementation of the following measures, including, but not limited to:

- If the article is still under consideration, it may be rejected and returned to the author.
- If the article has already been published online, depending on the nature and severity of the infraction, either an erratum will be placed with the article or in severe cases complete retraction of the article will occur. The reason must be given in the published erratum or retraction note.
- The author's institution may be informed.

COMPLIANCE WITH ETHICAL STANDARDS

To ensure objectivity and transparency in research and to ensure that accepted principles of ethical and professional conduct have been followed, authors should include information regarding sources of funding, potential conflicts of interest (financial or non-financial), informed consent if the research involved human participants, and a statement on welfare of animals if the research involved animals.

Authors should include the following statements (if applicable) in a separate section entitled "Compliance with Ethical Standards" when submitting a paper:

- Disclosure of potential conflicts of interest
- Research involving Human Participants and/or Animals
- Informed consent

Please note that standards could vary slightly per journal dependent on their peer review policies (i.e. single or double blind peer review) as well as per journal subject discipline. Before submitting your article check the instructions following this section carefully.

The corresponding author should be prepared to collect documentation of compliance with ethical standards and send if requested during peer review or after publication.

The Editors reserve the right to reject manuscripts that do not comply with the above-mentioned guidelines. The author will be held responsible for false statements or failure to fulfill the above-mentioned guidelines.

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

Authors must disclose all relationships or interests that could have direct or potential influence or impart bias on the work. Although an author may not feel there is any conflict, disclosure of relationships and interests provides a more complete and transparent process, leading to an accurate and objective assessment of the work. Awareness of a real or perceived conflicts of interest is a perspective to which the readers are entitled. This is not meant to imply that a financial relationship with an organization that sponsored the research or compensation received for consultancy work is inappropriate. Examples of potential conflicts of interests **that are directly or indirectly related to the research** may include but are not limited to the following:

- Research grants from funding agencies (please give the research funder and the grant number)
- Honoraria for speaking at symposia
- Financial support for attending symposia
- Financial support for educational programs
- Employment or consultation
- Support from a project sponsor
- Position on advisory board or board of directors or other type of management relationships

- Multiple affiliations
- Financial relationships, for example equity ownership or investment interest
- Intellectual property rights (e.g. patents, copyrights and royalties from such rights)
- Holdings of spouse and/or children that may have financial interest in the work

In addition, interests that go beyond financial interests and compensation (non-financial interests) that may be important to readers should be disclosed. These may include but are not limited to personal relationships or competing interests directly or indirectly tied to this research, or professional interests or personal beliefs that may influence your research.
The corresponding author collects the conflict of interest disclosure forms from all authors. In author collaborations where formal agreements for representation allow it, it is sufficient for the corresponding author to sign the disclosure form on behalf of all authors. Examples of forms can be found

- here:

The corresponding author will include a summary statement in the text of the manuscript in a separate section before the reference list, that reflects what is recorded in the potential conflict of interest disclosure form(s).

See below examples of disclosures:

Funding: This study was funded by X (grant number X).

Conflict of Interest: Author A has received research grants from Company A. Author B has received a speaker honorarium from Company X and owns stock in Company Y. Author C is a member of committee Z.

If no conflict exists, the authors should state:

Conflict of Interest: The authors declare that they have no conflict of interest.

RESEARCH INVOLVING HUMAN PARTICIPANTS AND/OR ANIMALS

1) Statement of human rights

When reporting studies that involve human participants, authors should include a statement that the studies have been approved by the appropriate institutional and/or national research ethics committee and have been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

If doubt exists whether the research was conducted in accordance with the 1964 Helsinki Declaration or comparable standards, the authors must explain the reasons for their approach, and demonstrate that the independent ethics committee or institutional review board explicitly approved the doubtful aspects of the study.

The following statements should be included in the text before the References section:

Ethical approval: "All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards."

For retrospective studies, please add the following sentence:

"For this type of study formal consent is not required."

2) Statement on the welfare of animals

The welfare of animals used for research must be respected. When reporting experiments on animals, authors should indicate whether the international, national, and/or institutional guidelines for the care and use of animals have been followed, and that the studies have been approved by a research ethics committee at the institution or practice at which the studies were conducted (where such a committee exists).

For studies with animals, the following statement should be included in the text before the References section:

Ethical approval: "All applicable international, national, and/or institutional guidelines for the care and use of animals were followed."

If applicable (where such a committee exists): "All procedures performed in studies involving animals were in accordance with the ethical standards of the institution or practice at which the studies were conducted."

If articles do not contain studies with human participants or animals by any of the authors, please select one of the following statements:

"This article does not contain any studies with human participants performed by any of the authors."

"This article does not contain any studies with animals performed by any of the authors."

"This article does not contain any studies with human participants or animals performed by any of the authors."

INFORMED CONSENT

All individuals have individual rights that are not to be infringed. Individual participants in studies have, for example, the right to decide what happens to the (identifiable) personal data gathered, to what they have said during a study or an interview, as well as to any photograph that was taken. Hence it is important that all participants gave their informed consent in writing prior to inclusion in the study. Identifying details (names, dates of birth, identity numbers and other information) of the participants that were studied should not be published in written descriptions, photographs, and genetic profiles unless the information is essential for scientific purposes and the participant (or parent or guardian if the participant is incapable) gave written informed consent for publication. Complete anonymity is difficult to achieve in some cases, and informed consent should be obtained if there is any doubt. For example, masking the eye region in photographs of participants is inadequate protection of anonymity. If identifying characteristics are altered to protect anonymity, such as in genetic profiles, authors should provide assurance that alterations do not distort scientific meaning.

The following statement should be included:

Informed consent: "Informed consent was obtained from all individual participants included in the study."

If identifying information about participants is available in the article, the following statement should be included:

"Additional informed consent was obtained from all individual participants for whom identifying information is included in this article."

Appendix 6: Approval letter from university research subcommittee

Dear Katie

Research Subcommittee - 17th November 2014

Thank you for attending the Research Sub-Committee meeting on 17th November 2014. The committee were satisfied that the revisions made were appropriate and in accordance with the feedback from the meeting of 6th October 2014 and you may now proceed with your research as set out in your revised proposal. Given that the arrangements for the specialist IPS supervision are still to be finalised, we require that these should be reviewed in **three months** time by Dr Anja Wittkowski in her capacity as your academic tutor/research advisor

For the purposes of ethical scrutiny by relevant NHS and/or University bodies, this letter may be taken as confirmation that your research proposal has been independently reviewed and that it is considered to meet necessary scientific and methodological standards.

On behalf of the Research Subcommittee, we wish you good luck with your research work.

Yours sincerely
Dr Dougal Julian Hare
Senior Lecturer in Clinical Psychology
Chair of Research Sub-Committee

A hard copy of this letter will be posted to you today.

Appendix 7: REC approval

NHS
Health Research Authority
Research Ethics Service
RES Committee North West - Greater Manchester Central
3rd Floor
Barlow House
4 Minshull Street
Manchester
M1 3DZ

Telephone: 0161 625 7825
Fax:0161 625 7299

24 June 2015

Dr Dougal Julian Hare
Senior Lecturer in Clinical Psychology
University of Manchester
The University of Manchester
2nd Floor Zochonis Building
Brunswick Street
Manchester
M13 9PL

Dear Dr Hare

Study title:	**An investigation of parenting experiences, psychological well-being and treatment adherence for parents of children with PKU.**
REC reference:	**15/NW/0454**
IRAS project ID:	**171668**

Correspondence has been received responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact the REC Manager, Mrs Kath Osborne, nrescommittee.northwest-gmcentral@nhs.net. Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised. subject to the conditions specified below.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from NRES. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Copies of advertisement materials for research participants [Poster]	1	24 April 2015
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Insurance certificate]	1	24 April 2015
Interview schedules or topic guides for participants [Interview schedule component 2]	1	24 April 2015
Letter from sponsor [Sponsorship letter]	1	24 April 2015
Letters of invitation to participant [Reminder letter component 1]	1	24 April 2015
Letters of invitation to participant [Reminder letter component 2]	1	24 April 2015
Letters of invitation to participant [Thank you letter component 1]	1	24 April 2015
Letters of invitation to participant [Thank you letter Component 2]	1	24 April 2015
Letters of invitation to participant [Invitation Letter Component 1]	2	23 June 2015
Letters of invitation to participant [Invitation letter Component 2]	2	23 June 2015
Non-validated questionnaire [Demographics Questionnaire component 1]	1	24 April 2015
Non-validated questionnaire [Dependency Question Component 1]	1	24 April 2015
Other [CV Anja Wittkowski]	1	24 April 2015
Other [CV Debbie Smith]	1	24 April 2015
Other [CV Katie Carpenter]	1	24 April 2015
Other [CV Simon Jones]	CV Simon Jones	24 April 2015
Other [CV Stewart Rust]	1	24 April 2015
Other [Participant Debrief Sheet]	1	24 April 2015
Participant consent form [Consent form component 1]	1	24 April 2015
Participant consent form [Consent form Component 2]	1	24 April 2015
Participant information sheet (PIS) [PIS Component 1]	2	23 June 2015
Participant information sheet (PIS) [PIS Component 2]	2	23 June 2015
REC Application Form [REC_Form_15052015]		15 May 2015
Referee's report or other scientific critique report [Research Subcommittee Letter]	1	
Research protocol or project proposal [Protocol]	1	20 March 2015
Summary CV for Chief Investigator (CI) [CV Dougal Hare]	1	24 April 2015
Summary CV for student [CV Emma Medford]	1	24 April 2015
Summary CV for supervisor (student research) [CV Dougal Hare]	1	24 April 2015
Validated questionnaire [GHQ 12]	1	24 April 2015
Validated questionnaire [MSPSS]	1	24 April 2015
Validated questionnaire [PIP Page 1]	1	24 April 2015
Validated questionnaire [PIP Page 2]	1	24 April 2015
Validated questionnaire [RSA Page 1]	1	24 April 2015
Validated questionnaire [RSA Page 2]	1	24 April 2015

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at
http://www.hra.nhs.uk/hra-training/

15/NW/0454	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely

K. Osborne .

Signed on behalf of
Professor S J Mitchell
Chair

A Research Ethics Committee established by the Health Research Authority

Appendix 8: R&D Approval for recruitment sites

Central Manchester University Hospitals NHS
NHS Foundation Trust

Research Office
1st Floor, The NOWGEN Centre
29 Grafton Street
Manchester M13 9WU
Tel: 0161-276-3565

Dr Simon Jones
Willink Biochemical Genetics Unit
Laboratory Medicine
6th Floor
St Mary's Hospital
Central Manchester University Hospitals NHS Foundation Trust
Oxford Road
Manchester
M13 9WL

27th August 2015

Dear Dr Jones,

PIN: R03976
Cost Code: N/A
CSP Reference: N/A
REC Reference: 15/NW/0454
Research Study: An investigation of parenting experiences, psychological well-being and treatment adherence for parents of children with PKU.

Thank you for submitting the above study for NHS R&D permission. The University of Manchester is the Sponsor for this study which is not on the NIHR portfolio.

I am pleased to confirm that the Research Office has now received all necessary documentation, and the appropriate governance checks have been undertaken. This letter is issued subject to the research team complying with the attached conditions, Trust SOPs, the DH Research Governance Framework, and any other applicable regulatory requirements. This approval is in relation to the documentation listed.

The target for this study is

- 70 Day from Valid Submission to 1st Patient Recruited: **20th October 2015**

You are required to keep R-Peak (Research Management database) updated with recruitment figures and inform the Research Office when the status of your trial changes.

I would like to take this opportunity to wish you well with your research.

Yours sincerely

Dr Max Pilotti
Research Contracts Manager

cc. Lucy Dwyer – Divisional Research Manager; Stewart Rust - Researcher; Katie Carpenter – Researcher; Emma Medford – Researcher; Dougal Hare – Chief Investigator

Central Manchester University Hospitals NHS
NHS Foundation Trust

Research Office
1st Floor, The NOWGEN Centre
29 Grafton Street
Manchester M13 9WU
Tel: 0161-276-3565

Dr Simon Jones
Willink Biochemical Genetics Unit
Laboratory Medicine
6th Floor
St Mary's Hospital
Central Manchester University Hospitals NHS Foundation Trust
Oxford Road
Manchester
M13 9WL

27th August 2015

Dear Dr Jones,

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Cost Code: N/A
CSP Reference: N/A
REC Reference: 15/NW/0454
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I am pleased to confirm that the Research Office has now received all necessary documentation, and the appropriate governance checks have been undertaken. This letter is issued subject to the research team complying with the attached conditions, Trust SOPs, the DH Research Governance Framework, and any other applicable regulatory requirements. This approval is in relation to the documentation listed.

The target for this study is

- 70 Day from Valid Submission to 1st Patient Recruited: **20th October 2015**

You are required to keep R-Peak (Research Management database) updated with recruitment figures and inform the Research Office when the status of your trial changes.

I would like to take this opportunity to wish you well with your research.

Yours sincerely

Dr Max Pilotti
Research Contracts Manager

cc. Lucy Dwyer – Divisional Research Manager; Stewart Rust - Researcher; Katie Carpenter – Researcher; Emma Medford – Researcher; Dougal Hare – Chief Investigator

Alder Hey Children's NHS
NHS Foundation Trust

Clinical Research Business Unit
1st Floor
Eaton Road, Liverpool
L12 2AP
0151 252 5570
Matthew.Peak@alderhey.nhs.uk
Charlie.Orton@alderhey.nhs.uk
Katherine.Jopson@alderhey.nhs.uk
Lucy.Cooper@alderhey.nhs.uk
www.alderhey.com

Katie Carpenter
Trainee Clinical Psychologist
Section for Clinical and Health Psychology
School of Psychological Sciences
University of Manchester
2nd Floor Zochonis Building
Brunswick Street
Manchester
M13 9PL

25th August 2015

RE: An investigation of parenting experiences, psychological well-being and treatment adherence for parents of children with PKU
REC Ref: 15/NW/0454
R&D Ref: 15/20/RE

Dear Katie Carpenter,

Thank you for submitting the above application to the Research & Development Office. It has now been reviewed against the requirements of the Research Governance Framework for Health and Social Care and relevant legislation. I am pleased to confirm that following completion of these checks approval is now granted for the study to commence within the Alder Hey Children's NHS Foundation Trust.

All NHS Trusts are performance managed by the National Institute for Health Research (NIHR) by benchmarks which measure the time taken to recruit the first patient into a research study and the local site's recruitment to time and target. All investigators within the Trust are supported by Data Managers within the Clinical Research Business Unit who can interpret these benchmarks for you and advise you on the timing and format in which data should be submitted to the CRBU. **R&D approval is conditional upon these data being submitted in a timely fashion each month.**

It will be the responsibility of the local Principal Investigator to comply with the responsibilities laid down, in the Research Governance Framework for Health and Social Care, by the Department of Health. Please see the enclosed leaflet for further information.

A full copy of the Research Governance Framework for Health and Social Care can also be obtained from the Department of Health website at www.doh.gov.uk or the R&D Office.

Yours sincerely

pp LM Cooper

Professor Matthew Peak
Director of Research

Version 6_ 19 January 2015

Bradford Teaching Hospitals NHS
NHS Foundation Trust

Enquiries on this matter should be made to:

The Research Management & Support Office
Bradford Institute for Health Research (BIHR)
Bradford Royal Infirmary
Duckworth Lane
BRADFORD
BD9 6RJ
Email: BradfordResearch.Applications@bthft.nhs.uk
Tel: 01274 36 (6808)/(4687)
Fax: 01274 38(2640)

Research Support & Governance Manager
Mrs Jane Dennison
Email: jane.dennison@bthft.nhs.uk
Tel: 01274 382575 (Direct)

Director of Research/BIHR
Professor John Wright
Email: john.wright@bthft.nhs.uk
Tel: 01274 364279 (Direct)

14th August 2015

Mrs Inderdip Hunjan
St Luke's Hospital
Little Horton Lane
Bradford
BD5 0NA

Dear Mrs Inderdip Hunjan

NHS Permission Letter for Research conducted at Bradford Teaching Hospitals NHS Foundation Trust

Re: An investigation of parenting experiences, psychological well-being and treatment adherence for parents of children with PKU.
Sponsor: University of Manchester
R&D Ref No: 1860
REC Ref No: 15/NW/0454
CSP Reference: 171668

Following submission of your Site-Specific Information form and supporting documentation seeking permission to conduct the above study at Bradford Teaching Hospitals NHS Foundation Trust (the "Foundation Trust"), I am pleased to inform you that your application has successfully completed an internal review process appropriate for this type of study and has satisfied our research governance checks. A project record has been created on the Foundation Trust's research database. You may commence research activities at the Foundation Trust in the locations specified in your Site-Specific Information (SSI) form subject to the terms of this letter. The effective date of NHS permission for research is the date of this letter and this is the earliest commencement date for research activities at the Foundation Trust. This letter supersedes all previous letters you have received from us with regard to permission to proceed with this research at Bradford Teaching Hospitals NHS Foundation Trust. NHS permission for the above research has been granted on the basis described in the application forms, protocol and supporting documentation. The documents reviewed were:

Reviewed Documents –

SSI form 171668/821512/6/706/278892/328463
NHS R&D form 171668/806864/14/646
Protocol v1 dated 20/03/2015
Participant Information Sheet v2 dated 23/06/15
Participant Information Sheet v2 dated 23/06/15
Participant Consent Form v1 24/04/2014
Participant Consent Form v1 24/04/2014

REC Favourable Opinion letter 12/06/15

The site for which NHS permission for research is given is -

Bradford Teaching Hospitals NHS Foundation Trust

The terms referred to are:

1. You are the Principal Investigator or Local Collaborator for this Study and you are responsible for the conduct of this Study at this site and for accurate reporting on study performance and conduct.
2. NHS Indemnity applies to this Study with respect to negligent harm. However, NHS Indemnity does not provide compensation in the event of non-negligent harm.
3. This Study is a non-CTIMP (ie, not a clinical trial that involves an investigational medicinal product) and you may commence recruitment on receipt of this letter if you are ready to start.
4. Ongoing permission is subject to you adhering to the Trust's standard conditions of NHS Permission for research (attached).
5. You comply with the R&D Office's Oversight Plan as detailed below.

The approach taken for each Study shall be proportionate to the risks associated with the Study and the level of monitoring and support being undertaken by the Sponsor. The R&D Office's Oversight Plan for this study is as follows –

1 Study Tracking
Please provide the R&D Office with –

a. Updates on performance and conduct when requested in a timely manner and in the format requested. Please ensure you keep the Research Management & Support Office informed of changes to the Principal Investigator's contact details.

b. Completed Principal Investigator end of study declaration report (as defined in the protocol) (together with final recruitment figures for the Foundation Trust) available from the Downloads section of the Bradford Institute for Health Research website at www.bradfordresearch.nhs.uk

c. Copy of amendment documentation and a copy of the REC and MHRA (if applicable) approval letters prior to implementing the changes at the Foundation Trust.

2 Issue Management –

a. Managing External Agreements.
b. Managing Internal Agreements.
c. Overseeing Study Processes.
d. Managing Research Passports

If an issue arises during the Study, please ensure you have a process in place to escalate this and seek support from the R&D Office.

3 Audit -
The R&D Office performs a risk assessment prior to issuing this letter which provides the Foundation Trust with a risk-based approach to audit activities. The R&D Office undertakes to audit at least 10% of its research projects each year. Priority will be given to studies with the higher risk scores, clinical trials involving an investigational medicinal product(s) (CTIMPs), NIHR portfolio studies, and studies sponsored by the Foundation Trust. Some low risk studies may not be subject to scheduled audit at all. You will be informed by the R&D Office if a scheduled audit of this research study is planned in plenty of time (ie, at least six weeks' notice).

The R&D Office always has the option to conduct specific oversight activities at any time as the result of any exceptional activity / events identified during the Study and failure to comply with these terms may lead to suspension or termination of NHS Permission for research.

Please inform the R&D Office immediately should you have any concerns about patient safety or wellbeing with regard to research at the Foundation Trust.

If you have any queries during the conduct of your research, please do not hesitate to contact the Research Support & Governance Manager using the contact details provided at the top of this letter. May I take this opportunity to wish you well with your research Study.

Please help us to improve our service by completing the feedback form we emailed you and returning it to the R&D Office as soon as possible.

Yours sincerely

PROFESSOR JOHN WRIGHT
Director of Research/BIHR

Encs
cc CI/Sponsor/study co-ordinator

Appendix 9: Participant information sheets

MANCHESTER 1824 The University of Manchester | Central Manchester University Hospitals NHS Foundation Trust | Bradford Teaching Hospitals NHS Foundation Trust | Alder Hey Children's NHS Foundation Trust

Participant Information Sheet

V3

11.12.15

PKU: Parenting experiences and wellbeing.

Research Team: Dr Emma Medford, Miss Katie Carpenter, **Dr Anja Wittkowski (University of Manchester), Dr Dougal Hare (Cardiff University),** Dr Simon Jones & Dr Stewart Rust (Central Manchester University Hospitals NHS Foundation Trust)

We would like to invite you to take part in our research study. Joining the study is entirely up to you. Before you decide we would like you to understand why the research is being done and what it would involve for you. One of our team will answer any questions you have.

Part 1 tells you the purpose of this study and what it will involve if you take part.

Part 2 gives you more detailed information about the conduct of the study.

We recommend that you take a minimum of 24 hours to consider the information below before deciding whether to take part.

Part 1

1.1 What is the purpose of the study?

There has been little research on what it is like to look after a child with Phenylketonuria (PKU). It would be useful to gain more information about this so we can identify the most effective ways to support parents. This part of the study (Part 2) will investigate what it's like to parent a child with PKU under the age of 2 years old. Another part of the study (Part 1) will investigate parent's wellbeing, the things that might help to improve their wellbeing, and what might help parents and children stick to a low protein diet.

1.2 Why have I been invited to take part in this study?

You have been invited to take part in **Part 2** because you have a child with PKU who is under the age of 2.

1.3 Do I have to take part?

No, you do not have to take part in the study if you do not want to. Taking part in the research is voluntary; this means it is completely up to you to decide whether or not to take part. Your decision to participate in this study will not be connected to the care you and your family are receiving now or in the future. If you decide to take part and sign the consent form but change your mind later, you are free to withdraw at any point during the study without giving a reason and without any consequence to your current or future treatment.

1.4 What will participation involve?

- You will be asked to complete a consent form that enables one of the research team to contact you about participating in the research.
- You can return the consent form in the prepaid envelope, or bring it to your next appointment at the PKU clinic.
- If you decide to participate, an interview slot will be booked at a time and location that is convenient for you.
- You will be interviewed by one member of the research team. This will take about 90 minutes (15 minutes to introduce the study and ask questions, 60 minutes for the interview and 15 minutes to debrief at the end).
- This will involve asking some questions about your experiences of parenting your child and talking about the experiences that have been important to you.

1.5 What are the possible disadvantages and risks of taking part?

It is possible that the interview might raise issues which could be distressing to think about. You will be able to stop the interview at any point if it becomes too distressing and there will be time to talk about this at the end of the interview. A list of agencies and people you can contact from your PKU clinic is provided should you need any additional information/support.

1.6 What are the possible benefits of taking part?

There are no direct benefits of taking part but the information gained will help services to fully understand the needs of families and the demands of caring for a child with PKU. It will help professionals to understand what it is like to parent a child with PKU and in turn to develop appropriate support packages, which may help other families in the future. Groups for parents are currently being piloted at Manchester Children's Hospital and the results of this study will inform further development of this.

1.7 Will my taking part in the study be kept confidential?

Yes. We will handle data sensitively and in confidence, and follow legal and ethical guidelines. More details are given in Part 2.

Part 2

2.1 What will happen if I do not want to carry on with the study?

You can withdraw from the study completely at any time without giving a reason and without any consequence to your family's current or future treatment, up until the data has been analysed. When the data is analysed it will not be personally identifiable.

2.2 What if there is a problem?

It is unlikely that anything would go wrong, but if you have a concern about any aspect of the study, you should contact one of the researchers (email pku@manchester.ac.uk and phone 07555 350386) who will do their best to answer your questions. If they are unable to resolve your concern or you wish to make a complaint regarding the study, please contact a University Research Practice and Governance Co-ordinator on 0161 275 7583 or 0161 275 8093 or by email to research.complaints@manchester.ac.uk

2.3 Will my data be confidential?

- All data which is collected about you and your child will be kept strictly confidential and only viewed by members of the research team. It will be stored securely in a locked filing cabinet at the University.
- Interviews will be audio recorded. The recorder will be kept in a locked briefcase after the interview. This will then be transferred onto a password protected computer which will be stored securely in a locked cabinet when not in use.
- The interviews will be transcribed. All names and identifiable data will be omitted from the transcription. Transcriptions will be in a password protected folder on the computer. You will be given an ID number for this process, so your name will not be used.
- Only members of the research team will have access to recordings or transcripts.
- Once the analysis is complete, the audio recordings will be destroyed securely.
- We will ask for details of your GP, but will not routinely contact him/her. During the study if we have any concerns about risk of harm

to anyone, then we will have to contact the appropriate agency/person to provide support. If possible, we would speak to you first about this.

- We plan to publish the research; names of participants will not be used, although if you consent we will use direct, anonymised quotes.
- The data will be kept for 5 years, as per the University of Manchester protocol. After this, all data will be destroyed.

2.4 Will I receive any payment for taking part in the study?

No, participants will not receive any payment for taking part. However, upon completion of the interview, you will be sent a £15 shopping voucher as a thank you for taking part.

2.6 Who is organising the research?

This research is being conducted as part of the Doctorate in Clinical Psychology at the University of Manchester for Trainee Clinical Psychologists/postgraduate students Dr Emma Medford and Miss Katie Carpenter. **It will be carried out under the guidance of Dr Dougal Hare, Dr Anja Wittkowski, Dr Simon Jones and Dr Stewart Rust**. It is funded by the University.

2.7 Where will the findings be published?

- We intend to publish the results in peer-reviewed journals
- We intend to present the results at scientific conferences
- We may put a summary of the findings in an NSPKU (The National Society for Phenylketonuria) newsletter.
- We will provide participants with a summary of the findings if they would like this.

2.8 Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee who protect the rights, safety, dignity and well-being of participants. This study has been reviewed and given a favourable opinion by the North West Greater Manchester Central Research Ethics Committee.

2.9 Who can I contact for further information?

If you would like to discuss the study or have any questions or concerns, please do not hesitate to contact a member of our research team at (email pku@manchester.ac.uk and phone 07555 350386), or **Dr Anja Wittkowski, Division of Clinical Psychology, 2nd Floor, Zochonis Building, University of Manchester, Brunswick Street, Manchester, M13 9PL.**

If you would like to take part please complete the enclosed consent form and either return in the pre-paid envelope or at your next PKU clinic appointment.

You can keep this copy of the information sheet.

Appendix 10: Consent form

CONSENT FORM `V1 24.4.15

Participant ID:_____

Title of Project: PKU: Parenting experiences and wellbeing.

Name of Researcher: Dr Emma Medford & Miss Katie Carpenter

University of Manchester in collaboration with Central Manchester University Hospital

Department of Genetic Medicine.

		Please tick as appropriate
1	I confirm that I have read the information sheet dated..... (version.....) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2	I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected, up until the research data has been analysed.	
3	I understand that data collected during the study may be looked at by individuals from the University of Manchester, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my data.	
4	I consent to being contacted by a member of the research team regarding participating in this research.	
5	I give permission for direct quotes to be used in the write up of this research. I understand that these will be anonymous and no identifiable information will be used.	
6	I agree to take part in the above study.	

7	I consent to the research interview being audio recorded.	
8	I consent to the audio recordings to be transcribed.	

Name of Participant (Parent) _____ Participant Signature _____

Date _____

Please include the below details so we can contact you about the study.

Phone number: _____

Email address: _____

Participant ID:_____

Date of meeting:

I confirm that I understand what the study involves and am willing to participate. I consent to the above points.

Signed:

Name:

Date:

Researcher signature:

Researcher name:

Date:

Appendix 11: Letter of invitation

MANCHESTER 1824 The University of Manchester | Central Manchester University Hospitals NHS Foundation Trust | Bradford Teaching Hospitals NHS Foundation Trust | Alder Hey Children's NHS Foundation Trust

Template Invitation Letter **V2 23.6.15**

Dear ….

PKU: Parenting experiences and wellbeing.

We are writing to invite you to take part in a research study being conducted at the University of Manchester with parents of children with Phenylketonuria (PKU).

There has been little research on what it is like to look after a child with PKU. It would be useful to gain more information about this so we can identify the most effective ways to support parents.

There are two parts to this study. Part 1 will investigate how parent's wellbeing is affected and what might help to improve their wellbeing. It will also investigate some of the things that help parents and children stick to a low protein diet. Parents of children with PKU between the ages of 0 to 16 are invited to take part.

Part 2 will investigate what it's like to parent a child with PKU under the age of 2 years old. Parents of children with PKU up to the age of 2 are invited to take part.

As you have a child with PKU who is under 2 years old you have been invited to take part in both parts of the study. This letter is an invitation to take part in **Part 2**. You will receive a separate letter inviting you to take part in Part 1.

If you would like to find out more about this project, please read the participant information sheet. If you would like any further information, please phone us on 07555 350386 or email us at pku@manchester.ac.uk

If you would like to take part after reading the participant information sheet, please complete the enclosed consent form. Please return the Consent Form in the addressed pre-paid envelope (no stamp is required), or hand it in to your PKU clinic reception at your next appointment. When we receive your consent form we will contact you to book an interview time with you. This will be at a time and location that is convenient for you.

If you would prefer NOT to take part in this project please complete and return the attached opt-out form in the pre-paid envelope, so that we do not contact you again.

We look forward to hearing from you.

Yours sincerely,

_____
Dr Emma Medford, Trainee Clinical Psychologist

_____
Miss Katie Carpenter, Trainee Clinical Psychologist

PKU: Parenting experiences and wellbeing.

Opt out form : Part 2

I would NOT like to take part in the above study.	

You do not have to give a reason, but if you feel able to tell us why, it will help us to understand why some people choose not to take part in this type of project.

_____
_____

_____
_____

Name of child _____

Name of Parent / Carer _____

Date _____

Thank you for taking the time to complete and return this form

Appendix 12: Thank you letter for participants

Thank You Letter **V1 24.4.15**

Dear

PKU: Parenting experiences and wellbeing.

We are writing to express our thanks to you for taking part in Part 2 of the above study. Thank you very much for taking part in the interview.

Your participation is very important as it will help contribute toward our understanding of how best to support parents of children with PKU.

Please find enclosed with this letter a £15 shopping voucher as a thank you for taking part.

If you would like to receive a summary of the study findings, please phone us on 07555 350386 or email us at pku@manchester.ac.uk

Yours sincerely,

_____
Dr Emma Medford, Trainee Clinical Psychologist

_____
Miss Katie Carpenter, Trainee Clinical Psychologist

I confirm that I have received £15 vouchers as a thank you for my participation in this study.

Name:_____

Signature: _____

Date: _____

Appendix 13: Interview schedule

MANCHESTER 1824 The University of Manchester | Central Manchester University Hospitals NHS Foundation Trust | Bradford Teaching Hospitals NHS Foundation Trust | Alder Hey Children's NHS Foundation Trust

PKU: Parenting experiences and well being

Qualitative study: Topic guide for semi structured interview

Version 1, 24.04.2015

What follows is a guide:-

The order and exact content of the questions will be determined by the participant so the order and wording of the questions may vary as the interview develops.

The following topics and prompts serve as an interview guide.

Probe and ask for examples as the time permits.

Introductions & Background

Explain purpose of interview. Reassure that the interview will not have an impact on the care they receive and that they are free to stop the interview at any time.

This statement will be read to the participants:

"As parents you are adjusting to finding out that your child has been given a diagnosis of PKU. Since that time, you might have been thinking about what that means not only for your child, but also for you as a parent. We are interested in finding out about what it is like to be a parent to a child with PKU and the parenting process. By parenting we mean promoting and supporting the physical, social and emotional development of your child. We understand that the dietary aspect of parenting is very important, however being a parent includes many more things. We are interested in finding out more about the impact a diagnosis of PKU might impact on some of these things. We have some loosely structured questions, however we want to find out what has been important to you in your experiences so far. If you have more than one child with PKU we would like to focus on the child who is under the age of 2".

Diagnosis of PKU

- Explore parent's knowledge and understanding of PKU prior to their child being diagnosed (for example if this is not their first child with PKU was this different this time).

The process of parenting

Explore experiences of parenting (child) so far
Explore what parenting (child) involves (getting an idea about the demands, how much time can be dedicated to other parenting roles alongside dietary management, thinking about emotional, social, physical development as well as bonding with child).
Description of the way the parent feels they parent their child (parental styles- strict, permissive etc.)
Explore how the diagnosis might have changed the way in which they thought they would parent their child (adaptations to parenting)
Any impact this has had on how they interact with their child
Differences in parenting other children (if they have other children who are older and have PKU, or do not have PKU)
Exploration of how parents perceive role in parenting (how they see their 'job' as parent)

Challenges

Find out if there have been times when parenting their child has been hard (specific challenges- e.g. weaning)
Asking about expected and unexpected challenges that have arisen in parenting (physical, social, emotional).
Exploring how parents have managed these (emotionally, physically?)
Exploring any positives/positive experiences to date (related to PKU or parenting more generally)
Any personal feelings or thoughts that impact on parenting

Support

Things that have helped with parenting child
Thing/experiences that have helped parent personally/ not helped (things that they do themselves)
Things that others have done that have/have not helped? (professionals, family members, friends)
Experience of the support has been provided.

Any other important topics?

- Check with participant whether there are any other important aspects that have not been covered

Following interview

Thank participant.
Ask participants how they have found the interview.
Clarify whether participant has experienced any distress above what might be expected (due to discussing sensitive issues).
Researcher to give participant contact details of support organisations and signpost participant to appropriate agencies if they are distressed.

Appendix 14: Participant debrief sheet

MANCHESTER 1824 The University of Manchester | Central Manchester University Hospitals NHS Foundation Trust | Bradford Teaching Hospitals NHS Foundation Trust | Alder Hey Children's NHS Foundation Trust

Participant Debrief Sheet V2 11.12.15

PKU: Parenting experiences and wellbeing.

Thank you for participating in this research. We hope that you have found it interesting and have not been upset by any of the topics in the questionnaires or interview.

However, if you have found any part of this experience to be distressing there are a number of people and organisations that you can contact for support.

- If you would like to speak to one of the researchers, please contact us by phone on 07555 350386 or by email at pku@manchester.ac.uk**. Alternatively, you can contact Dr. Anja Wittkowski by writing to University of Manchester, Oxford Rd, Manchester M13 9PL or emailing anja.wittkowski@manchester.ac.uk.**

- If you feel as though you are struggling to cope, or feeling low in mood, it is important that you go to your GP for support.

- You can also talk to your PKU clinician who will be able to signpost you to an appropriate support service.

There are also a number of organisations listed below that you can contact.

Organisations
National Society for Phenylkentonuria (NSPKU) 030 3040 1090 info@nspku.org www.nspku.org This NSPKU provides information and support to people with PKU and their families and carers. The NSPKU has a network of local support groups.

Climb 0800 652 3181 info.svcs@climb.org.uk www.climb.org.uk Climb offers information and support on metabolic diseases to young people, adults, families and professionals.
Contact a Family 0808 808 3555 helpline@cafamily.org.uk www.cafamily.org.uk Contact a Family offer information, support and advice for parents of children with medical conditions and disabilities. They have a range of guidance for parents online.
NHS Direct 111 Open 24 hours a day. They provide health advice and information.
Samaritans 0845 7909090 Open 24 hours a day. They offer confidential emotional support by telephone, email, text, letter and face to face.

Appendix 15: Approved advertising material

Twitter for NSPKU:

UoM are conducting research with parents of children with PKU. We want to know about your experiences and support needs. pku@manchester.ac.uk

UoM are conducting research with parents of children with PKU from Bradford, Alder Hey & Manchester PKU clinics. Look out for your packs in the post!

Are you the parent of a child with PKU (under 2yrs)? We want to hear about your experiences. Contact pku@manchester.ac.uk to find out how to take part in our research.

Are you the parent of a child with PKU (0-16yrs)? We want to hear about your experiences. Contact pku@manchester.ac.uk to find out how to take part in our research.

Information for newsletters:

The University of Manchester is collaborating with Alder Hey Children's NHS Foundation Trust, Bradford Teaching Hospitals NHS Foundation Trust and Central Manchester University Hospitals NHS Foundation Trust to carry out research with parents of children with PKU, looking at the experience of parenting and parental wellbeing. There are two parts to this research study. Part 1 looks at parental well-being and what can help with this. It will also look at things that can make it easier for parents and children to stick to a low protein diet. Part 2 looks at the experience of parenting a child with PKU.

WHY?

We are doing this because here has been little research on what it is like to look after a child with PKU. We would like to find out more about this so we can identify the most effective ways to support parents and provide evidence to help develop services.

WHO?

Parents of children with PKU who are currently seen at Alder Hey, Bradford or Manchester PKU clinics.

Part 1: Parents of children with PKU aged 0-16.

Part 2: Parents of children with PKU under the age of 2.

WHAT?

Part 1 will involve completing questionnaires. Part 2 will involve interviewing parents about their experiences. Parents will receive a shopping voucher as a thank you for taking part.

HOW?

If your child attends Bradford, Manchester or Alder Hey PKU clinics, you will have received information about both parts of the study. For Part 1 (0-16 years) you can return your questionnaires and consent form in the freepost envelopes, or hand them in at your clinic appointment. For Part 2 (under 2 years) you can return your consent form in the freepost envelopes and a member of the research team will contact you to book in a time to meet.

If you would like to find out more about the studies, please contact us on 07555 350386 or email us at pku@manchester.ac.uk.

Facebook:

The University of Manchester is conducting research with parents of children with PKU who attend Alder Hey, Manchester (St. Mary's) or Bradford (St. Luke's) PKU clinics. We want to find out what it is like for parents and how best to support them. We are looking at parental wellbeing and the experience of parenting. The study has two components.

Part 1 looks at parental well-being and what can help with this. It will also look at things that can make it easier for parents and children to stick to a low protein diet. It involves filling in questionnaires.

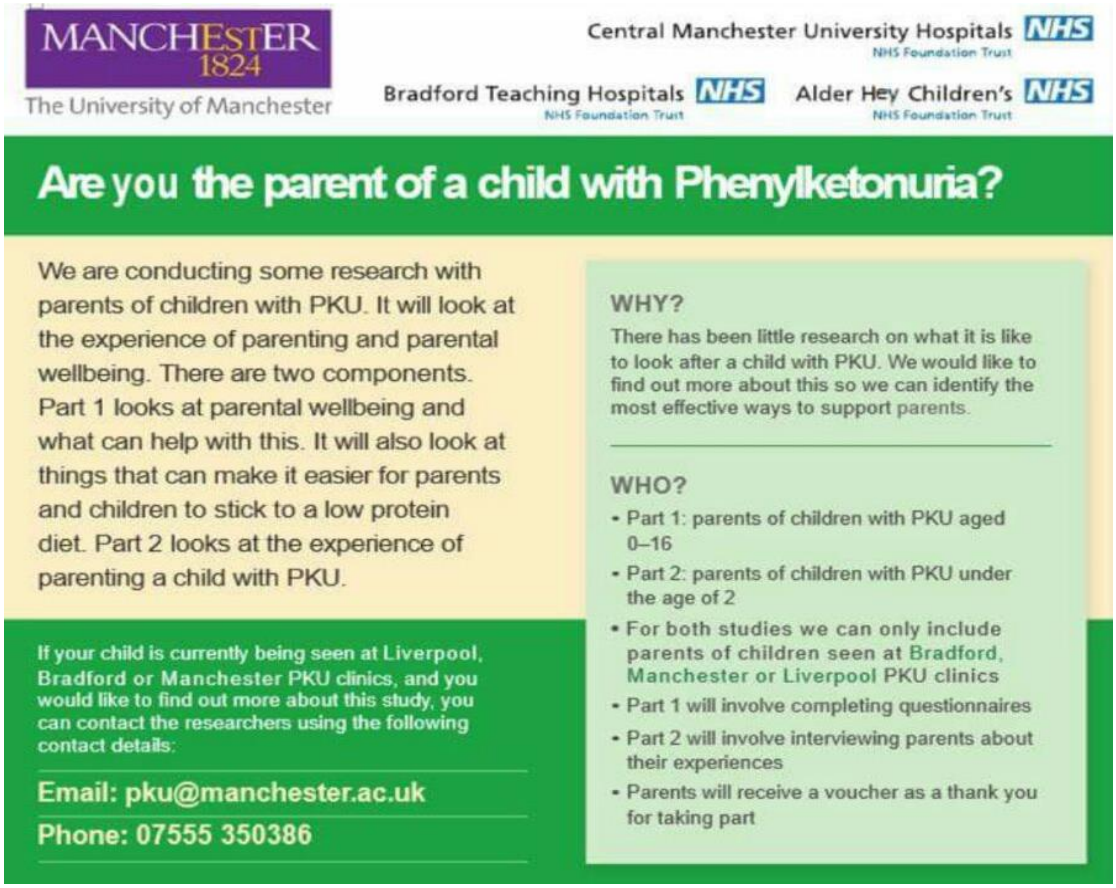
Part 2 looks at the experience of parenting a child with PKU. It involves talking to a researcher about your experiences so far.

You will receive a shopping voucher as a thank you for participating.

We are doing this because here has been little research on what it is like to look after a child with PKU. We would like to find out more about this so we can identify the most effective ways to support parents and provide evidence to help develop services.

If you would like to take part, or want more information please contact us on 07555 350386 or email us at pku@manchester.ac.uk.

(Poster attached)



[redacted] PKU (Phenylketonuria) [redacted]K & Ireland!
7 Mar at 16:17 •

Hi all, I am posting this information on here with the kind permission of site admin as I am aware that this is firstly a support group but we wanted to raise awareness of some research that is being conducted with parents of children with PKU.

The University of Manchester is conducting research with parents of children with PKU who attend Alder Hey, Manchester (St. Mary's) or Bradford (St. Luke's) PKU clinics. We want to find out what it is like for parents and how best to support them. We are looking at parental wellbeing and the experience of parenting.

The study has two components.
Part 1 looks at parental well-being and what can help with this. It will also look at things that can make it easier for parents and children to stick to a low protein diet. It involves filling in questionnaires.
Part 2 looks at the experience of parenting a child with PKU. It involves talking to a researcher about your experiences so far.

You will receive a shopping voucher as a thank you for participating.

We are doing this because here has been little research on what it is like to look after a child with PKU. We would like to find out more about this so we can identify the most effective ways to support parents and provide evidence to help develop services.
If you would like to take part, or want more information please contact us on 07555 350386 or email us at pku@manchester.ac.uk.

[redacted] Yorkshire PKU Support Group
7 Mar at 16:08 •

This is an official study that is running through the Liverpool, Manchester and Bradford PKU clinics. I received an invite through the hospital a while back and participated in the study. They are still looking for more people to join in so please do contact them if you're willing to share your views.

@kids_dietitian

@NSPKU Important #PKU research looking for volunteers @louisedietitian @MetabolicSarah

Appendix 16: University of Manchester Lone Worker Policy

MANCHESTER 1824
The University of Manchester

Safety Services Guidance

Guidance on lone working

Key word(s) :	Lone working, remote working, working without supervision
Target audience :	Anyone working beyond earshot of another person, or otherwise unable to summon assistance; managers responsible for preparing risk assessments for lone workers.

Contents

Management cycle	Useful paragraphs
Plan	1-7
Do	8-20
Monitor	
Review	21-22

Introduction

1. This Guidance should be read in conjunction with the University Arrangements Chapter 10 on Lone Working. This chapter defines lone working as; "A person working without close or direct supervision and without contact from others. It can take place both out of hours and during the normal working day." The key point is that the lone worker may not be able to summon assistance quickly in the event of an emergency.

2. This definition covers those workers who could be working in a university building or similar environment, in a community or research setting.

3. This guidance should be used to develop or revise local arrangements and systems to protect lone workers, reflecting the local needs of staff and the environments within which they work.

4. Line managers and staff who supervise students have a duty of care and responsibility to ensure that risk assessments and local procedures are developed, implemented, monitored and adhered to. Lone workers also have a responsibility to follow the procedures for their own safety.

5. In order that lone workers feel safe and secure, and perform their duties in a relatively safe environment they must be confident that there is organisational commitment and support, backed up by strong management procedures.

6. Incidents involving lone workers are very rare; however, it is important that lone workers are encouraged to report all incidents of physical and non-physical assault, using the University's incident report form. This will also ensure that any lessons learned can be fed back into risk management processes and further preventive measures can be developed. Some incidents may need to be reported to the enforcing authorities via the University Safety Office.

Objectives

7. This guidance is designed to provide lone workers and their line managers with practical advice to assist in preparing for a lone worker situation and meet legislative responsibilities under the Health and Safety at Work Act 1974 and the Management of Health and Safety at Work Regulations 1999. In particular, it can be used to :

    - raise staff awareness of safety issues relating to lone working

- ensure that lone working is risk-assessed in an appropriate way and that safe systems and methods of work are put in place to reduce the risk, so far as is reasonably practicable
- help staff recognise risks and provide practical advice on safety when working alone, including, where appropriate, how to use technological solutions
- identify the organisational structures, communication links, and those with responsibilities to support lone workers if they need assistance
- encourage full reporting and recording of any adverse incidents relating to lone working.

Managing risk

8. The University is required to implement measures to manage, control and mitigate risks to lone workers. Once an incident occurs, the level of follow-up action should be proportionate to the risk. As a minimum, the risk assessment should be reviewed. Other measures might include removing weaknesses or failures that have allowed an incident to take place (procedural, systematic or technological), and identifying further training needs of staff and students in relation to the prevention and management of verbal or physical assault, or other training such as correctly identifying and operating the relevant technology.

Risk assessment

9. Schools and Directorates should use their existing risk assessment arrangements to manage risks in relation to lone workers: to identify risks in relation to lone working to:

    - assess the risks to lone workers
    - implement measures to reduce the risks to lone workers, including appropriate information, instruction, training and supervision to minimise these risks
    - evaluate the control measures and ensure that risks to lone workers are appropriately managed.

10. A suitable and sufficient risk assessment for lone working should be based on the University's Lone Working Chapter 10, and consider the following factors, together with any specific risks associated with the work being undertaken:

    - Who is going to be working alone?
    - Where will they be working?
    - Are they competent to carry out the work?

- Does the workplace present a special risk to the lone worker in addition to risks associated with the work itself?
- Is there a safe means of access and egress from the work location?
- Can all plant, substances and materials involved in the work be safely handled by one person? (Consider whether the work involves lifting objects too large or awkward for one person or whether more than one person is needed to operate essential controls for the safe running of equipment).
- Are some individuals more at risk than others when working alone?
- Are young persons especially at risk if they work alone?
- Is the person medically fit and suitable to work alone?
- Are the fire precautions for the building fully operational and understood by the lone worker?
- Are all fire precautions available if the work takes place out-of-hours?
- Is the lone worker fully familiar with how to respond in an emergency? Eg do they know how to activate the fire alarm, phone numbers to call, who to contact?
- Are there effective communication links in the area they will be working at the time they are working?
- Is the level of supervision at other times sufficient to ensure that any problems are identified and dealt with?
- Is there a risk of accidental release of material which could cause acute injury or require extensive decontamination? e.g. gas release, explosion, spillage (Work such as this should not take place unaccompanied)
- Are any other precautions necessary?

Example risk assessments

11. To assist with the production of risk assessments, the following lone worker example risk assessments and checklists have been produced:

    - Community based lone worker risk assessment
    - Community based lone worker checklist
    - On-campus lone worker in an office setting risk assessment
    - On-campus lone worker in an office setting checklist

    The above documents can be accessed at
    http://www.healthandsafety.manchester.ac.uk/toolkits/lone_working/example_ras/

Dynamic risk assessment

12. There may be a requirement for risk assessments to be carried out by the lone worker on a dynamic basis, e.g. in response to frequent changes in circumstances. A generic risk assessment will need to explain the circumstances under which dynamic risk assessments take place, and address the competency and training needs of the individuals carrying them out.

13. See Guidance on generic and dynamic risk assessment

Lone worker movements

14. The specific controls necessary must be proportionate to the risk and will be informed by the risk assessment process but could include:

    - details of location and anticipated time of return left with a manager or colleague
    - details of vehicles used by lone workers left with a manager or colleague, for example, registration number, make, model and colour
    - regular contact with a manager or relevant colleague, particularly if they are delayed or have to cancel an appointment
    - panic buttons in isolated offices or consultation rooms
    - mobile phone solutions with text, panic, GPS, 'man down' and smartphone solutions.

15. Where there is genuine concern, for example, as a result of a lone worker failing to attend a visit or an arranged meeting within an agreed time, or to make contact as agreed, the manager should use the information provided in a log or Outlook diary to locate them and ascertain whether they turned up for previous appointments that day. Depending on the circumstances and whether contact through normal means (mobile phone) can be made, the manager or colleague should involve University Security if necessary (see escalation process para 22).

16. If it is thought that the lone worker may be at risk, it is important that matters are dealt with quickly, after considering all the available facts. Security will advise if police involvement is needed, and will need full access to information held and personnel who may hold it, if that information might help trace the lone worker and provide a fuller assessment of any risks they may be facing.

17. It is important that contact arrangements, once in place, are adhered to. Many such procedures fail simply because staff forget to make the necessary call when

they finish their shift. The result is unnecessary escalation and expense, which undermines the integrity of the process.

The buddy system

18. It is essential that lone workers keep in contact with colleagues and ensure that they make another colleague aware of their movements. This can be done by implementing management procedures such as the 'buddy system'.

19. To operate the buddy system, managers must ensure that a lone worker nominates a buddy. This is a person who is their nominated contact for the period in which they will be working alone. The nominated buddy will:

    - be fully aware of the movements of the lone worker
    - have all necessary contact details for the lone worker
    - attempt to contact the lone worker if they do not contact the buddy as agreed
    - follow the agreed local escalation procedures for alerting their senior manager and Security if the lone worker cannot be contacted or if they fail to contact their buddy within agreed and reasonable timescales.

20. The buddy must understand their role and what the procedures and requirements are. Contingency arrangements should be in place for someone else to take over the role of the buddy in case the nominated person is unavailable, for example if the lone working situation extends past the end of the nominated person's normal working day or shift, if the shift varies, or if the nominated person is away on annual leave or off sick.

Escalation process

21. It is important for School and Directorates to have a risk-based escalation process, outlining who should be notified if a lone worker cannot be contacted or if they fail to contact the relevant individual within agreed or reasonable timescales. The escalation process should provide identification of contact points at appropriate stages which may include, line manager, senior manager, security and, ultimately, the police. Any individual nominated in an escalation process should be fully aware of their role and responsibilities.

Researcher safety

22. Researcher safety is well documented by the Social Research Association (SRA), in their code of practice.

23. The University of Manchester has issued Guidance on conducting interviews and research in fieldwork. Safety Services Lone Working toolkit contains useful checklists.

Further sources of guidance

Suzy Lamplugh Trust

For information on lone worker alarms and alerting devices:
http://www.suzylamplugh.org/personal-safety-tips/lone-worker-directory/

For safety apps
http://www.suzylamplugh.org/personal-safety-tips/app-directory/

For advice on safe travelling alone
http://www.suzylamplugh.org/personal-safety-tips/free-personal-safety-tips/travelling-for-work/ and
http://www.suzylamplugh.org/personal-safety-tips/free-personal-safety-tips/transport-safety/

HSE Publication on Lone Working

Royal College of Nursing Guide to Lone Working

British Sociological Society Statement of Ethical Practice, March 2002 contains some guidance on conducting interviews.

Appendix 17: Example of annotated transcription

get through it really... I didn't really.. I couldn't really take on anyone else's.. but they were there to initially support me because.... For a long time while they're little.. they know no different.. you are their main carer and you do all the hard work as you would a normal child, so obviously.. it's M who has the PKU and will always have the PKU.. but for the first good few years of their life.. it's the parents that are working hard to keep everything within range.. and so I think it was the realisation of how hard it was going to be.... like hitting home... it was one of them.. I felt completely overwhelmed by the care all of a sudden that M needed.. but when people were offering me help.. I didn't trust anyone to look after M so I got myself in a bit of a thing where I was overwhelmed by the care he needed.. but I didn't trust anyone to take him and that is still something I struggle with now with him, turning 2. There's a small circle of people who can have M who I trust.. you know with his diet and care... giving him his formula... but I think that'll always be the way with M, whereas my eldest N, you know.. any family member he can go to... and I don't have to think twice. But with M it takes a lot more planning..

K: So you said there is sort of a circle of people. Can I just ask who's in that? Sort of who's in that circle?

P1: Yeah.. it's my mum, my husband's mum... my sister and that's probably it.. and then with N, there are so many more.. like grandads and my other sisters and (HUSBAND A's) sister.. but you know.. although they would follow it... it's just.. it's just stressful for me.. getting everything ready for M to go there.. and I'd just rather not do it. Whereas with my mum and his mum.. there is an understanding already you know.. where they kind of know what he can have and can't have...

K: Yep, so you said it's stressful. I wonder if you could talk a bit more about that...

P1: Yep, well I mean.. I'm quite stressed at the minute because we're going to New York on Monday morning which is fantastic.. once in a lifetime trip.. but.. I get all caught up in the stress of M.. you know.. being looked after by someone else.. and I do think my relatives who have him.. find it stressful as well.. erm.. so what we do is we do it in small.. stays.. so we're going away Monday to Friday.. so his mum is having them for two and a half days and erm.. my mum is having them for the other two and a half days.. cos I do think that is it too much for just one of them to have both of them.. I say both of them, I mean M. Erm.. yeah because it is such, I think.. for them.. it's easy for me because it's all I've done with him.. but I do think that for someone who's not doing it every day it is a hard diet to get your head around... it's hard counting and he's at a funny age.. a two year old can just change their mind.. "don't want". I try and plan what he is going to eat through the day so I get his exchanges and you know, his amount of protein right.. but.. he's a two year old.. so it's hard to say what he's going to eat for the day.. they often change their mind... they're you know.. fussy at two.. so I do think.. my close relatives who have M find it stressful as well, but they wouldn't say it to me because they are.. they don't want me to withdraw... because I think they know that I need the support... so.. yeah.. I mean as well this weekend..