**ABSTRACT**

**Background**: Dieticians of 18 French and Belgian hospitals tested a new device “Phé Tout®” designed to help phenylketonuria patients maintain adequate dietary control and control intake of phenylalanine (phe).

**Methods**: Phé Tout® is a double-sided, dynamic disk that covers numerous commercially-available foods mainly of the fruit and vegetable type which can be given to patients depending on their protein tolerance and which contain less than 2.5 g of protein per 100 g. The disk uses the nutritional information printed on product packaging, giving patients access to a much wider selection of foods.

**Results**: We present the results of a survey questionnaire completed by 102 children (mean age 4 years, standard deviation 3.4, range 0.5 to 13 years), 5 adults and 22 dieticians: 57% of the families did not report any particular problems, 88% stated that they would like to continue using the disk. Both health care professionals and caregivers reported very high levels of satisfaction with the device: Families appreciated its practical nature and user-friendliness, dieticians applauded the additional independence it gave families in their daily lives. The use of the device did not impact negatively the metabolic equilibrium of users.

**Conclusions**: The Phé Tout® device make it easier for patients to calculate their phe intake with an easy-to-use, pocket-sized and practical device suitable for use by all patients or their caregivers. It gives patients access to a wider range of commercially-available foods, contributing to additional independence to families in their daily lives.

**INTRODUCTION**

Since the launch of national screening programs (Guthrie test), phenylketonuria (PKU) is diagnosed extremely early, on the third day of life. It is a genetic disorder caused by a deficiency in the production of the hepatic enzyme phenylalanine hydroxylase which is required to break down the amino acid phenylalanine. Phenylalanine (phe) is essential for normal development and growth but becomes toxic for the brain at concentrations above 5 mg/dL (300 µmol/L) in children up to the age of 10 and in pregnant women, from 15 mg in teenagers and from 20 mg in adults ([HAS, 2010](#_ENREF_8)). Treatment, particularly dietary control, must be initiated early ([MacDonald et al., 2011](#_ENREF_12)). Strict control of the intake of this amino acid, which is ubiquitously present in all natural proteins, is essential. Tolerance is defined as the amount of phe an individual can ingest without any incidence on the metabolic equilibrium. It varies from patient to patient, but is generally < 350 mg/d, and must be closely controlled by weighing all foods containing proteins and excluding those high in animal proteins (meat, fish and eggs, etc.) from the diet ([Pimentel et al., 2014](#_ENREF_15), [Van Rijn, 2008](#_ENREF_19)). Dietary formulas containing a mixture of amino acids but no phe provide the patient with an age-appropriate source of protein, minerals and trace elements. Special low-protein foods (bread, pasta, flours, egg and cheese substitutes, etc.) are used to provide needed energy through carbohydrates and fats.

The biggest daily challenge faced by families living with the dietary restrictions of PKU is controlling intake of phe which is found in varying quantities in different types of protein. In France, metabolic dieticians use protein equivalence tables in which foods, mainly fruit and vegetables, are listed as servings and can be combined to create menus adapted to the individual's daily phe tolerance. One serving corresponds to the amount of the food to be weighed (g) to provide 20 mg of phe. In other countries, serving sizes are expressed as a volume, for example, in cups in the USA.

In 2009, members of the SFEIM (French Society for the Study of Inborn Metabolic Errors) in France and Belgium harmonised the various sources of information on the amino acid content of foods on which the equivalence tables given to patients were based to issue a national consensus. However, the wide variety of industrial protein substitutes available and the constant influx of new products on the market make it virtually impossible to keep these tables accurate and up to date, with the result that patients are limited in their choice of foods and continue to be reliant on their dietician's advice. This consumes precious time during appointments with the healthcare provider and is a source of disempowerment, potentially detracting from patients' compliance with dietary restrictions and their knowledge and understanding of their condition.

In developing this simple, practical and fun tool, our aim was to make it easier for patients to calculate their phe intake, give them access to a wider range of commercially-available foods, increase their independence and enhance their quality of life ([Simon et al., 2008](#_ENREF_16), [ten Hoedt et al., 2011](#_ENREF_18), [Bernstein et al., 2014](#_ENREF_2)).

**PRIMARY STUDY ENDPOINT**

Over and above giving them access to information, our aim was to get patients actively involved in the learning process and in the treatment of their disease by creating a mutual bond of trust between patient and healthcare provider. In so doing ([Golay et al., 2010](#_ENREF_6)), we hoped to enhance compliance ([Wendel and Langenbeck, 1996](#_ENREF_21), [MacDonald et al., 2010](#_ENREF_11), [Mosnier-Pudar, 2012](#_ENREF_13)) and improve the quality of life of our patients. Our device was part of a global treatment strategy focussed on patients, their dietary habits and personal resources ([Walter et al., 2002](#_ENREF_20), [Olsson et al., 2007](#_ENREF_14), [Levers-Landis et al., 2005](#_ENREF_10)).

**MAIN STAGES IN THE STUDY**

June 2009 – June 2010: Calculation algorithm and device prototype design phase carried out by dieticians at the Bordeaux university hospital (CHU).

October 2010 – July 2011: Design improved and a professionally-made mock-up proposed by Merck-Serono.

July 2010: Meeting between the innovation unit, Aquitaine Science Transfert® and the dieticians to present the tool, assess its potential applications and the design protection strategy. The decision was taken to register a trademark and sign a partnership contract with the pharmaceutical company.

September 2011: Agreement for the plan of action received from the Bordeaux CHU after verification of the SFEIM's position and request for a clinical validation study on the device.

November 2011: Start of the validation study.

February 2012: "phé tout" brand name registered by Aquitaine Science Transfert® on behalf of the Bordeaux CHU.

June 2012: Oral presentation of the study results at the SFEIM plenary session.

July 2012 – February 2013: Signature of the partnership contract Between Bordeaux CHU and Merck-Serono.

March 2013: Oral presentation at the SSIF in Istanbul.

September 2013: Poster presented at the SSEIM meeting in Barcelona.

October 2013: Device distributed to French dieticians.

**MATERIALS AND METHODS**

**1- Development of the device: constraints and aims**

Our aim was to produce an easy-to-use, pocket-sized and practical device suitable for use by all patients or their caregivers. The consensual method used to calculate the percentage of phe per 100 g of protein depending on the food was as follows: potato, cereal, flour, semolina, pasta (5%), corn (4.7%), mean of green vegetables + potato (3.8%), Fruit (3.2%), peas (3%) ([Souci et al., 2008](#_ENREF_17), [FCEN, 2008](#_ENREF_4)).

Most of the industrial products targeted were vegetable- or fruit-based and some contained cereals or milk. These included jars of baby food and children's ready meals without meat or fish, frozen meals and canned goods, etc. The diversity of our selection, which included some products with a high phe content, meant that we had to use two calculation formulas: one for preparations containing fruit and vegetables alone, and another to calculate the additional phe (Figure 1: Algorithm).

We also had to make sure that the device could not be used incorrectly and therefore compromise the patient's metabolic equilibrium, and that increase in independence ensuing from its use would not encourage them to relax their dietary control, again with untoward metabolic consequences.

The double-sided disk divides commercially available foodstuffs into 2 groups depending on the nutrients they contain: the green side is used for pure green vegetable/potato or fruit preparations and the red side, products which also contain cereals or milk (Figure 2: The disk).

It provides three types of information, which reflect individual preferences and habits:

* The amount of food to be weighed to obtain a 20 mg portion of phe.
* The amount of phe (mg) in a whole jar (most widely consumed size = 130 g) of a baby food. A whole jar can therefore be given at a single meal without having to worry about using up left-overs at the next meal. This method presupposes that the patient's daily phe tolerance, in mg, is known.
* The number of portions of phe contained in 100 g of product presented in graph form, which is easier to read than fractions or decimals.

Packaged in a sleeve decorated with fresh fruit and vegetables, the disk is supplied with instructions for use which also provide guidelines and recommendations to assist with food diversification in young children (Table 1: Advice for use).

**2- Test phase:**

*Methodology*

Dieticians at 17 French hospitals and one Belgian hospital agreed to test the device for a minimum of one month between January and the end of April 2012, on 102 children (mean age 4.5 years, standard deviation 3.4, range 0.5 to 13 years) and 5 adults (18 to 34 years) with PKU whose low phe tolerance meant they had to weigh all foods containing protein.

The caregivers' questionnaire was designed to establish the following: the system generally used to calculate phe portions, the number of times the disk was used, the reasons for using the disk infrequently or not at all, the meals bought, levels of satisfaction with the way they were taught to use the disk and with its subsequent use (9 specific items + 1 overall score on a scale of 1 to 5), the problems encountered and the impact on family quality of life.

A second questionnaire to be completed by dieticians indicated whether the tool was offered to all the children seen (and if not, why), recorded their feelings about it (6 specific items + 1 overall score on a scale of 1 to 5), assessed the advantages and disadvantages of the device and collected their suggestions for possible changes/improvements.

The impact of using the device on the metabolic balance of patients was measured by recording the last five serum phe levels before the test, the last of which was taken at time 0 (baseline), then for one month during the test (mandatory) then at 3 and 4 months if possible.

**RESULTS**

1. **Distribution of the 107 patients per centre:**

A total of 107 patients were included in the following 18 centres: Amiens (3), Angers (9), Bordeaux (7), Brest (1), Bruxelles (2), Caen (5), Clermont-Ferrand (2), Grenoble (5), Lille (3), Limoges (2), Lyon (1), Marseille (17), Nancy (4), Paris Necker hospital (22), Paris R Debré hospital (7), Rouen (10), Strasbourg (1), Toulouse (6).

1. **Family's responses: 107**

Overall, approximately two third of the families (N = 72) used the tool several times a week, and 103 recorded their impressions and made suggestions, all of which were included in the analysis.

Three-quarters of the families were using the French lists of food servings (1 serving contains 20 mg of phe) and one quarter used calculation formulae based on the mean phe content in foods; 16.8% used the disk every day and 49.5%, i.e. 2/3 of the families (N = 72), several times a day: their results were used to calculate the impact of using the disk on serum phe levels. The remainder of the families used the disk as follows: 24.3%, once a month; 7.5%, never; and 1.9%, an unknown number of times.

Regarding the nature of food, 83 % of the families (n = 95) bought ready-made vegetable dishes, 60% potato-based preparations, 59% stewed fruit, 38 % baby foods (mainly children < 2 years old) and 37% vegetable sauces (average age 5.2 years).

Overall, 103 families recorded their impressions and made suggestions, all of which were taken into account in the analysis.

The following scores were obtained: Tool learning: 4.2; tool handing: 4.4; visual aspect: 4.7; practical aspect of the format: 4.5; purchasing time saving: 3.6; meal time saving: 4; larger range of products purchased: 4; autonomy: 4; interest of consensual tool: 4.6; global assessment: 4.4.

**The 6 specific items achieved scores of more than 3.6, and the global score for the disk was 4.4 out of 5.**

The answers to the open questions were as follows:

* The most common reason cited for seldom/not using the disk was the level of expertise already acquired by caregivers and patients over the years (mean age of patients was 7 ½ years) which made them reluctant to change their calculation system (Table 2: Tool seldom or not used).
* 57% did not report any specific problems encountered with the disk
* 88% stated they would like to continue using it
* Most often appreciated was its pragmatic, easy-to-use design. Three responders found it to be less practical and 2 reported they had difficulties using it.

The difficulties experienced in using the disk and suggestions for improvement were as follows:

* 18 families would like to have access to products with a protein content in excess of the 2.5 g/100 g limit on the red side of the disk; this was particularly the case for older children and adults whose tolerance allows them occasional consumption of certain milk products.

(See Table 3: Difficulties expressed by families)

* Comparison of the mean of the five serum phe results obtained before the test with at least one result measured during the test in the 72 patients using the disk several times a week did not show any significant differences. Phe levels had returned to normal or were still in the normal range for 88% of the patients, 7% remained above the normal range and 6% had risen to outside the normal range.
1. **Dieticians' responses: 22**

The assessments performed by dieticians on the 1 to 5 scale were as follows: Tool learning: 4.1; quality of relations with caregiver: 4.1; follow-up time saving: 4; autonomy of families: 4.6; interest/lists: 4.4; consensus interest: 4.5; global assessment: 4.4

The 6 specific items achieved scores in excess of 4/5, with overall scores of 4.3. The item garnering the highest scores was independence of families (4.6/5), whose importance was stressed in the open comments section of half these questionnaires.

1/3 noted that the families using the disk subsequently purchased a broader range of products and brands, including new arrivals on the market.

* Two limitations of the disk were pointed out:
	+ One in three dieticians felt that the tool was not suitable for everyone since some caregivers may find it hard to use.
	+ One dietician in two would have liked the protein scale on the red side of the disk to go beyond 2.5 g/100 g of product (this was also suggested by caregivers).
1. **Assessing the impact on serum phenylalanine levels**

The mean of the last 5 serum phe level measurements taken before the test was compared with at least one value obtained during the study in the 72 patients using the disk several times a week: during the time they used the disk, 43.1 % of the patients had their level measured once, 23.6% twice, 19.4%, three times and 13.9%, four times. The results showed that mean serum levels were the same before and after the test (3.59 *vs*. 3.55).

**DISCUSSION AND CONCLUSION**

The number of patients enrolled over the four months of this survey was limited because the interval between appointments with the specialist gets longer as children get older.

Both healthcare providers and caregivers appreciated the disk particularly for its practicality and the increased independence it allows patients. The use of the device did not have a negative impact on the metabolic equilibrium of patients; 88% of families stated that they would like to continue using it.

Direct reference to the nutritional information on industrial product packaging is an undoubted advantage for more accurate calculations. The dynamic nature of the disk and its applicability to any industrial food means that patients and caregivers are no longer dependent on fixed and rapidly outdated lists. This gives patients access to a wider range of products and promotes dietary diversification.

Our tool is part of a patient-centric approach to treatment education and encourages patients to take greater responsibility for their health ([HAS, 2007](#_ENREF_7), [Lamour and Gagnayre, 2008](#_ENREF_9), [Giordan, 2010](#_ENREF_5)). However, healthcare providers ensure that this educational approach and the increased independence it brings are appropriate for their individual patients. Patients and their caregivers should be taught how to use the disk during an appointment with their dietician.

This project is the fruit of the combined input of a number of dedicated individuals. Working together and sharing experiences has been extremely enriching, both personally and professionally. Despite our seemingly different approaches, we were able to harmonise our practices. As healthcare professionals, we have a duty to develop new skills in the treatment education field to improve the way we manage our patients. This is particularly important for patients with chronic conditions. It is up to us to innovate and create ever-more appropriate and tailored materials. Families using our device learn to manage their phe intake much as they would their household budget (how much does an item cost? how much money do I have? what risks do I run if I buy it)? Patients and caregivers are thus able to make informed choices without assistance. The concept of "allowed and forbidden" foods no longer applies.

Registering a trademark for an educational tool not only ensures that the author's intellectual property rights are protected, it also – and above all - serves to control its end utilisation and distribution.

Future possible developments for our device include its extension to other metabolic disorders such as homocystinuria or maple-syrup-disease and even its use by dieticians in countries employing different portion systems (50 mg portions, for example) after modification of the calculation algorithm and pending an international dietary consensus ([Blau et al., 2010](#_ENREF_3), [Ahring et al., 2009](#_ENREF_1)).

A second disk with a scale exceeding the 2.5 g of protein per 100 g of food appears appropriate for patients with good phe tolerance (especially teenagers and adults).

The same disk concept could be used for other metabolic diseases such as homocystinuria or maple-syrup-disease.

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**TABLES:**

Table 1: **Advice for use**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Age** | **Food** | **Leaflet** | **Green Side of the Disk** | **Red Side of the Disk** |
| **> 4 months** | Infant cereals with or without gluten non dairy |  |  | **X** |
| **> 5 months** | Fresh green vegetables/potatoesCooked, fresh fruits or juice | **X** |  |  |
| Packaged green vegetables/potatoesPackaged fruit, compote or juice |  | **X** |  |
| **End of 1st year** | Potatoes alone at a meal | **X** |  | **X** |
| Packaged green vegetables/potatoesPackaged fruit, compote or juice |  | **X** |  |
| "House" green vegetables/potatoesRaw, cooked, fresh fruit or juice | **X** |  |  |
| Packaged green vegetables/potatoes(small jars, plates, frozen food)with milk, fresh cream or cerealswithout meat |  |  | **X** |
| Deserts with milk and/or cerealsWithout aspartam |  |  | **X** |

Table 2: **Tool seldom or not used**

|  |  |  |
| --- | --- | --- |
|  | **NUMBER** | **AGE (years)** |
| Used to usual system | 9 | **13** | Mean: 7.5*SD: 4.4**Min-Max: 2-13* |
| Usual system more practical | 3 |
| Prefers using a personal Excel table (tool used by grand- mother) | 1 |
| Only eats fresh fruits | 5 | **7** | 1.5 - 4 – 5.5 - 12 - 33  |
| Knows the foods, eats the same products | 1 | 3 |
| Used to quantities | 1 | 5 |
| No time to test it | 1 | **2** | 5 |
| Did not take time to test it, did not understand | 1 | 8 |
| Mother scared (used by father only) | 1 | **1** | 1 |

Table 3: **Difficulties expressed by families**

|  |  |  |
| --- | --- | --- |
|  | NUMBER | AGE (years) |
| Protein intake scale < 2.5g (wish > 2.7g/100g of food, even 5g | **15** | Mean = 7.4*SD = 4.2Min-Max = 2.5 - 18* |
| More adapted for infant dishes | 3 | 7-13-13 |
| A bit disturbed by number of information | 1 | 1.5 |
| Difficulties in understanding | 1 | 9 |
| Adaptation time (2d) to understand the visual presentationInformation "1 part =" not eye- catching enough | 1 | 34 |

**FIGURES LEGENDS:**

Figure 1: **Algorithm**

Figure 2: **The disk**

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