

**Supplementary Table S7.** Data on metabolic control of patients with PKU in the included studies.

Reference	Centres' practice/protocol for monitoring and data reported	Target blood Phe ranges for age	Blood Phe levels for age Mean $\pm$ SD [Median, range]
Acosta et al., 1998	<p><b>Protocol:</b> Blood was drawn monthly by venipuncture for analysis of plasma amino acids.</p> <p><b>Data:</b> Blood Phe levels taken after 2 to 4 h of eating.</p>	120 to 360 $\mu\text{mol/L}$	<p><b>1 mo:</b> 147<math>\pm</math>20 <math>\mu\text{mol/L}</math> (N=20)</p> <p><b>2 mo:</b> 267<math>\pm</math>46 <math>\mu\text{mol/L}</math> (N=33)</p> <p><b>3 mo:</b> 349<math>\pm</math>46 <math>\mu\text{mol/L}</math> (N=31)</p> <p><b>4 mo:</b> 356<math>\pm</math>44 <math>\mu\text{mol/L}</math> (N=34)</p> <p><b>5 mo:</b> 297<math>\pm</math>35 <math>\mu\text{mol/L}</math> (N=33)</p> <p><b>6 mo:</b> 308<math>\pm</math>38 <math>\mu\text{mol/L}</math> (N=32)</p> <p><b>During the study:</b> 297<math>\pm</math>41 <math>\mu\text{mol/L}</math> (N=35)</p>
Aldámiz-Echevarría et al., 2014	<p><b>Protocol:</b> Blood Phe concentrations were regularly measured in dried blood spots;</p> <p><b>0 to 6 mo:</b> Weekly, <b>6 mo – 2 y:</b> Every other week, <b>2 y:</b> <math>\leq</math> Monthly; More frequent check-ups during intercurrent illnesses, patients failing to adhere to the diet, etc.</p>	<p><b>&lt;6 y:</b> &lt; 360 <math>\mu\text{mol/L}</math>,</p> <p><b>6-10 y:</b> &lt; 480 <math>\mu\text{mol/L}</math>,</p> <p><b>&gt;10y:</b> &lt; 600 <math>\mu\text{mol/L}</math></p>	Data not shown
Aldámiz-Echevarría et al., 2013	<p><b>Protocol:</b> Blood Phe concentrations were regularly measured in dried blood spots;</p> <p><b>0 to 6 mo:</b> Weekly, <b>6 mo – 2 y:</b> Every other week, <b>2 y:</b> <math>\leq</math> Monthly; More frequent check-ups during intercurrent illnesses, patients failing to adhere to the diet, etc.</p> <p><b>Data:</b> Mean values reported at baseline, and every 6 mo until the end of 2y or 5y follow-up.</p>	<p><b>&lt;6 y:</b> &lt; 360 <math>\mu\text{mol/L}</math>,</p> <p><b>6-10 y:</b> &lt; 480 <math>\mu\text{mol/L}</math>,</p> <p><b>&gt;10y:</b> &lt; 600 <math>\mu\text{mol/L}</math></p>	<p><b>BH4 group (baseline):</b></p> <p><b>2y FU:</b> 255.2 <math>\pm</math> 146.8 <math>\mu\text{mol/L}</math> (N=36)</p> <p><b>5y FU:</b> 204.0 <math>\pm</math> 143.9 <math>\mu\text{mol/L}</math> (N=10)</p> <p><b>Diet-only treated group (with 2y FU; N=72):</b></p> <p><b>Baseline:</b> 418.4 <math>\pm</math> 339.6 <math>\mu\text{mol/L}</math></p> <p><b>6 mo:</b> 396.9 <math>\pm</math> 285.0 <math>\mu\text{mol/L}</math></p> <p><b>1y:</b> 384.9 <math>\pm</math> 258.6 <math>\mu\text{mol/L}</math></p> <p><b>1.5y FU:</b> 430.5 <math>\pm</math> 304.0 <math>\mu\text{mol/L}</math></p> <p><b>2y FU:</b> 468.6 <math>\pm</math> 334.4 <math>\mu\text{mol/L}</math></p> <p><b>Diet-only treated group (with 5y FU; N=20)</b></p> <p><b>Baseline:</b> 391.8 <math>\pm</math> 233.5 <math>\mu\text{mol/L}</math></p> <p><b>6 mo:</b> 466.7 <math>\pm</math> 295.5 <math>\mu\text{mol/L}</math></p> <p><b>1y:</b> 352.8 <math>\pm</math> 210.6 <math>\mu\text{mol/L}</math></p> <p><b>1.5y:</b> 533.5 <math>\pm</math> 282.2 <math>\mu\text{mol/L}</math></p> <p><b>2y:</b> 345.2 <math>\pm</math> 163.4 <math>\mu\text{mol/L}</math></p> <p><b>2.5y:</b> 395.3 <math>\pm</math> 216.2 <math>\mu\text{mol/L}</math></p> <p><b>3y:</b> 439.0 <math>\pm</math> 313.4 <math>\mu\text{mol/L}</math></p> <p><b>3.5y:</b> 484.9 <math>\pm</math> 272.5 <math>\mu\text{mol/L}</math></p> <p><b>4y:</b> 287.1 <math>\pm</math> 165.0 <math>\mu\text{mol/L}</math></p> <p><b>4.5y:</b> 401.1 <math>\pm</math> 235.2 <math>\mu\text{mol/L}</math></p> <p><b>5y:</b> 440.6 <math>\pm</math> 298.4 <math>\mu\text{mol/L}</math></p>

Supplementary Table 7. *Cont.*

Reference	Centres' practice/protocol for monitoring and data reported	Target blood Phe ranges for age	Blood Phe levels for age Mean $\pm$ SD [Median, range]
Aldámiz-Echevarría et al., 2015	<p><b>Protocol:</b> Blood Phe concentrations were regularly measured in dried blood spots;  <b>0 to 6 mo:</b> Weekly, <b>6 mo – 2 y:</b> Every other week, <b>2 y:</b> <math>\leq</math> Monthly;  More frequent check-ups during intercurrent illnesses, patients failing to adhere to the diet, etc.</p> <p><b>Data:</b> Mean values reported at study baseline, at 6 mo, and 1 y follow-up</p>	<p>&lt;6 y: &lt; 360 <math>\mu\text{mol/L}</math>,  6-10 y: &lt; 480 <math>\mu\text{mol/L}</math>,  &gt;10y: &lt; 600 <math>\mu\text{mol/L}</math></p>	<p><b>BH4 group (baseline)</b>  286.9 <math>\pm</math> 153.7 <math>\mu\text{mol/L}</math> (N=22)</p> <p><b>Diet-only treated group:</b>  <b>Baseline:</b> 306.8 <math>\pm</math> 167.8 <math>\mu\text{mol/L}</math> (N=44)  <b>6 mo:</b> 358.2 <math>\pm</math> 232.6 <math>\mu\text{mol/L}</math> (N=44)  <b>1y:</b> 353.7 <math>\pm</math> 236.4 <math>\mu\text{mol/L}</math> (N=44)</p>
Alm et al., 1986	<p><b>Protocol:</b> Blood Phe samples were collected at home by the parents or the patients.  <b>0-3 y:</b> 2-4 times per month  <b>&gt;3y:</b> 1-2 times per month</p> <p><b>Data:</b> % Phe levels within target range or a period of 8 to 18y</p>	<p><b>0-8 y:</b> 0.24-0.72 <math>\mu\text{mol/L}</math>  <b>&gt;8y:</b> 0.24-1.0 <math>\mu\text{mol/L}</math></p>	<p><b>Good compliance in N=11;</b>  &gt;75% of Phe levels were within target range  <b>Fair compliance in N=5;</b>  50-75% of Phe levels were within target  <b>Poor compliance in N=5;</b>  &lt;50% of Phe levels were within target  <b>Unknown in N=2 (Normal IQ)</b></p>
Daly et al., 2017	<p><b>Protocol:</b> Weekly; overnight fasting morning blood spots were collected on filter cards by trained caregivers at home.</p> <p><b>Data:</b> Median of blood Phe collected during 6 mo compared with median from previous 12 mo entering the study.</p>	<p><b>5-10y:</b> 120–360 <math>\mu\text{mol/L}</math>  <b>11-16y:</b> 120–600 <math>\mu\text{mol/L}</math></p>	<p><b>GMP group - 12 mo pre-GMP:</b>  [275 <math>\mu\text{mol/L}</math>; N=12]  <b>GMP group - 6 mo during GMP:</b>  [317 <math>\mu\text{mol/L}</math>; N=12]  <b>AAM group - 12 mo AAM (pre-study):</b>  [325 <math>\mu\text{mol/L}</math>; N=9]  <b>AAM group - 6 mo during study:</b>  [280 <math>\mu\text{mol/L}</math>; N=9]</p>
Daly et al., 2019	<p><b>Protocol:</b> Weekly overnight fasting morning blood spots were collected by trained caregivers at home. During the last 48h of each study period (days 13 and 14), trained caregivers collected four hourly blood spots on filter cards at home.</p> <p><b>Data:</b> 70% of blood Phe concentrations within the Phe target range for age, for 6 mo before starting the study, and median Phe over the 24h in each study period (on days 13-14) at: 08.00, 12:00, 16:00, 20:00 and 24:00.</p>	<p><b>5-10y:</b> 120–360 <math>\mu\text{mol/L}</math>  <b>11-16y:</b> 120–600 <math>\mu\text{mol/L}</math></p>	<p><b>R1:</b> [290 <math>\mu\text{mol/L}</math>; 30–580 <math>\mu\text{mol/L}</math>; N=19]  <b>R2:</b> [220 <math>\mu\text{mol/L}</math>; 10–670 <math>\mu\text{mol/L}</math>; N=19]  <b>R3:</b> [165 <math>\mu\text{mol/L}</math>; 10–640 <math>\mu\text{mol/L}</math>; N=19]</p>

Supplementary Table 7. *Cont.*

Reference	Centres' practice/protocol for monitoring and data reported	Target blood Phe ranges for age	Blood Phe levels for age Mean $\pm$ SD [Median, range]
Dobbelaere et al., 2003	<i>Protocol:</i> Fasting blood Phe levels by measurement on Guthrie card (dried blood spot) on a regular basis (at least monthly)  <i>Data:</i> Mean, median and range of serum Phe levels.	<480 $\mu\text{mol/L}$ (8 mg/dl)	457.3 $\pm$ 313.8 $\mu\text{mol/L}$ (N=19) [347 $\mu\text{mol/L}$ ; 25-1172 $\mu\text{mol/L}$ ]
Evans et al., 2017	Not reported	Not reported	Not reported
Evans et al., 2018	<i>Protocol:</i> Weekly fasting levels  <i>Data:</i> Median and range of serum Phe levels during the first 2 years of life.	120–360 $\mu\text{mol/L}$	<b>From weaning to 12 mo of age:</b> [175 $\mu\text{mol/L}$ ; 90–310 $\mu\text{mol/L}$ ; N=31]; <b>12-24 mo of age:</b> [180 $\mu\text{mol/L}$ ; 100–400 $\mu\text{mol/L}$ ; N=31]
Evans et al., 2019	Not reported	Not reported	Not reported
Evers et al., 2018	<i>Protocol:</i> Blood Phe was measured in plasma or dried bloodspot; at least 5 samples per period  <i>Data:</i> In BH4 group, median Phe concentration at baseline was calculated from data on a period of 12 mo before the start of BH4 testing. Median, IQR was reported at baseline and 5y follow-up.	$\leq 12$ years: 120–360 $\mu\text{mol/L}$ >12 years: 120–600 $\mu\text{mol/L}$	<b>BH4 group (baseline):</b> [322 $\mu\text{mol/L}$ ; IQR: 239-470 $\mu\text{mol/L}$ ; range: 178-605 $\mu\text{mol/L}$ ; N=18]  <b>Diet-only group (baseline):</b> [395 $\mu\text{mol/L}$ ; IQR: 275-652 $\mu\text{mol/L}$ ; range: 201-800 $\mu\text{mol/L}$ ; N=21] <b>Diet-only group (5y follow-up):</b> [354 $\mu\text{mol/L}$ ; IQR: 222-690 $\mu\text{mol/L}$ ; range: 137-1084 $\mu\text{mol/L}$ ; N=21]
Ferguson et al., 1996	<i>Protocol:</i> During study weekend; <b>Friday:</b> 1h after lunch (baseline), <b>Saturday:</b> 1 h after each meal (breakfast, lunch, dinner, supper) - representing maximum post-meal blood Phe, <b>Sunday:</b> In the morning (after fasting).  <i>Data:</i> Mean, median, range of serum Phe levels.	120-700 $\mu\text{mol/L}$	395 $\pm$ 71.8 $\mu\text{mol/L}$ (N=12) [384.1 $\mu\text{mol/L}$ ; 330-472 $\mu\text{mol/L}$ ]  <b>Serum Phe over 24h:</b> <b>Group A:</b> [329.6 $\mu\text{mol/L}$ ; 187-574; N=4] <b>Group B:</b> [384.1 $\mu\text{mol/L}$ ; 267-534; N=3] <b>Group C:</b> [472 $\mu\text{mol/L}$ ; 240-656; n=5]

Supplementary Table 7. *Cont.*

Reference	Centres' practice/protocol for monitoring and data reported	Target blood Phe ranges for age	Blood Phe levels for age Mean $\pm$ SD [Median, range]
Giovaninni et al., 2014	<p><b>Protocol:</b> Fasting plasma Phe levels taken at 9 a.m. <math>\pm</math> 1h on the day of recruitment and at the end of trial.</p> <p><b>Data:</b> Mean and median plasma Phe levels.</p>	2–6 mg/dL	<p><b>Test PS group: N=27</b>  <b>Baseline:</b> 6.22<math>\pm</math>5.4 mg/dl [5.43 mg/dl]  <b>At the end of trial:</b> 4.47<math>\pm</math>4.08 mg/dl [3.7 mg/dl]</p> <p><b>PKU conventional PS group: N=28</b>  <b>Baseline:</b> 5.96<math>\pm</math>5.02 mg/dl [5.52 mg/dl]  <b>At the end of trial:</b> 5.56<math>\pm</math>4.92 mg/dl [4.93 mg/dl]</p>
Gökmen-Özel et al., 2011	<p><b>Protocol:</b> Once daily finger prick blood samples (fasting pre-breakfast at standardised times) were taken on day 5–7 of the pre-study period and on days 12–14 in part A (subjects took control PS) and B (subjects took trial PS). These daily bloods were collected over 3 days for each trial period to allow for any variability in daily plasma Phe concentrations.</p> <p><b>Data:</b> Median plasma Phe levels;  <b>Pre-study:</b> On days 5-7 (1st wk)  <b>Part A:</b> On days 12-14 (2-3rd wk)  <b>Part B:</b> On days 12-14 (4-5th wk)</p>	120-360 $\mu$ mol/L	<p><b>Pre-study (0-7 d):</b>  [240 <math>\mu</math>mol/L; 150-420 <math>\mu</math>mol/L; N=14]</p> <p><b>Part A (patients took Control PS for 14d):</b>  [275 <math>\mu</math>mol/L; 150-590 <math>\mu</math>mol/L; N=14]</p> <p><b>Part B (patients took Trial PS for 14d):</b>  [230 <math>\mu</math>mol/L; 41-710 <math>\mu</math>mol/L; N=14]</p>
Green et al; 2019	<p><b>Protocol:</b> Dried blood spots following an overnight fast by fingertip puncture was collected.</p> <p><b>Data:</b> Mean blood Phe from past 3 historical blood Phe tests prior to recruitment.</p>	120-700 $\mu$ mol/L at time of recruitment	<p><b>Historical blood Phe (from records):</b>  618<math>\pm</math>292 <math>\mu</math>mol/L (N=16)</p> <p><b>During study:</b> 464 <math>\pm</math> 196 <math>\mu</math>mol/L (N=16)</p>
Hoeksma et al., 2005	Not reported	Not reported	Not reported
Huemer et al., 2007	<p><b>Protocol:</b> Blood Phe was measured at baseline and after 6 and 12 mo from dried blood spots using ion-exchange chromatography (for clinical follow-up, not for study purposes).</p> <p><b>Data:</b> Mean, median and range of blood Phe was measured at baseline and after 6 and 12 mo.</p>	<p><b>&lt;10y:</b> 40-240 <math>\mu</math>mol/L (0.7–4 mg/dl)</p> <p><b>10-15y:</b> 40-900 <math>\mu</math>mol/L (0.7–15 mg/dl)</p>	<p><b>Mean Phe level was elevated, median was normal;</b>  456<math>\pm</math>432 <math>\mu</math>mol/L (N=34) [204 <math>\mu</math>mol/L; 24-1386 <math>\mu</math>mol/L]  <b>&lt;10 years:</b> 8/17 (47%) had Phe concentrations exceeding therapeutic levels;  <b>10-15y of age:</b> Within therapeutic levels, 534<math>\pm</math>324 <math>\mu</math>mol/L [408 <math>\mu</math>mol/L; 174-1188 <math>\mu</math>mol/L]  <b>&gt;15y of age:</b> Within therapeutic levels, 444<math>\pm</math>228 <math>\mu</math>mol/L [483 <math>\mu</math>mol/L; 150-714 <math>\mu</math>mol/L]</p>

Supplementary Table 7. *Cont.*

Reference	Centres' practice/protocol for monitoring and data reported	Target blood Phe ranges for age	Blood Phe levels for age Mean $\pm$ SD [Median, range]
Kindt et al., 1983	<p><b>Protocol:</b> Plasma Phe was determined by the fluorimetric method; samples were usually drawn after an overnight fast, in some cases 4 h after the last meal, and sent to the hospital every week for the 1<sup>st</sup> year of life, every 2 week for the 2<sup>nd</sup> year and once every 1 or 2 month thereafter. Minor colds and any diseases were noted.</p> <p><b>Data:</b> Range of means.</p>	<p>182-667 <math>\mu\text{mol/L}</math></p> <p><i>Phe deficit:</i> &lt;121 <math>\mu\text{mol/L}</math>; <i>Catabolic state/Too high Phe intake:</i> Phe&gt;970 <math>\mu\text{mol/L}</math></p>	<p>Metabolic control was equally well in both groups: <b>RDA group:</b> N=8 <b>0-12 mo:</b> 303-752 <math>\mu\text{mol/L}</math> <b>12-24 mo:</b> 273-642 <math>\mu\text{mol/L}</math> <b>FAO group:</b> N=8 <b>0-12 mo:</b> 376-673 <math>\mu\text{mol/L}</math> <b>12-24 mo:</b> 436-545 <math>\mu\text{mol/L}</math></p>
MacDonald et al., 2006	<p><b>Protocol:</b> Twice daily finger prick blood samples (fasting pre-breakfast and pre-evening meal at standard times) were taken on day 8–14 of each trial period by parents/carers. Twice daily blood samples were collected for 3 days during a baseline and washout period. Frequency of monitoring: <b>0-5y:</b> Weekly; <b>&gt;5y:</b> Fortnightly</p> <p><b>Data:</b> Mean, median, range of Phe concentrations were estimated from morning and evening blood samples for each subject.</p>	<p><b>0-5y:</b> 120- 360 <math>\mu\text{mol/L}</math>;</p> <p><b>School age:</b> 120-480 <math>\mu\text{mol/L}</math></p>	<p><b>Low dose PS period:</b> 505<math>\pm</math>206.8 <math>\mu\text{mol/L}</math> (N=25) [530 mmol/L; 140-910 <math>\mu\text{mol/L}</math>];</p> <p><b>High dose PS period:</b> 214.8<math>\pm</math>74.9 <math>\mu\text{mol/L}</math> (N=25) [200 <math>\mu\text{mol/L}</math>; 100-390 <math>\mu\text{mol/L}</math>]</p>
MacDonald et al; 2003	<p><b>Protocol:</b> Four-hourly skin puncture blood specimens were collected for 48 h in each study protocol. Frequency of monitoring: <b>0-5y:</b> Weekly; <b>&gt;5y:</b> Fortnightly</p>	<p><b>0-5y:</b> 120- 360 <math>\mu\text{mol/L}</math>;</p> <p><b>School age:</b> 120-480 <math>\mu\text{mol/L}</math></p>	<p>None of the blood Phe concentrations exceeded the MRC (1993) upper recommended limits in any protocol (n=16).</p>
MacDonald et al., 1996	<p><b>Protocol:</b> Twice daily, 4 days a week (same days as diet diaries) during the 21 days study period.</p> <p><b>Data:</b> Mean, median, range of Phe concentrations taken twice daily.</p>	<p><b>0-4y:</b> 120-360 <math>\mu\text{mol/L}</math> <b>5-10 y:</b> 120-480 <math>\mu\text{mol/L}</math> <b>11y&lt;:</b> 120-700 <math>\mu\text{mol/L}</math></p>	<p><b>Morning:</b> 282<math>\pm</math>162 <math>\mu\text{mol/L}</math> (N=19) [230 <math>\mu\text{mol/L}</math>; 127-660 <math>\mu\text{mol/L}</math>]</p> <p><b>Evening:</b> 243<math>\pm</math>184 <math>\mu\text{mol/L}</math> (N=19) [176 <math>\mu\text{mol/L}</math>; range= 68-659 <math>\mu\text{mol/L}</math>]</p> <p>There was a significant difference between mean early morning and late afternoon plasma Phe and a widespread variation in the change between early morning and late afternoon concentrations: mean plasma Phe change -40<math>\pm</math>62 <math>\mu\text{mol/L}</math>.</p>

Supplementary Table 7. *Cont.*

Reference	Centres' practice/protocol for monitoring and data reported	Target blood Phe ranges for age	Blood Phe levels for age Mean $\pm$ SD [Median, range]
Pinto et al., 2019	<p><b>Protocol:</b> Median blood Phe levels were measured by fasting blood spots performed at home. Phe levels were collected for a median of 6 mo before the first and second dietary assessment, with a median of 6 (range 2–20) (assessment period 1) vs. 11 (range 2–23) blood spots (assessment period 2). Frequency of recommended monitoring: &lt;1y: Once weekly; 1-12y: Once every 2 weeks; <math>\geq</math>12 y: Once monthly</p> <p><b>Data:</b> Median and IQR of Phe levels</p>	<p><b>0-12 y:</b> 120- 360 <math>\mu</math>mol/L; <b>School age (12y&lt;):</b> 120-480 <math>\mu</math>mol/L</p> <p><b>Tyr levels:</b> &lt;480 <math>\mu</math>mol/L</p>	[279 $\mu$ mol/L; IQR: 203-360 $\mu$ mol/L] n=40
Ponzone et al; 2008	<p><b>Protocol:</b> Monitoring of plasma Phe concentration was performed by amino acid chromatography: <b>0-1y:</b> Weekly; &gt;1y: Every 2 months.</p>	<600 $\mu$ mol/L (10 mg/dl)	Not reported
Rocha et al., 2012 & 2013	<p><b>Protocol:</b> Frequency of recommended monitoring: &lt;1y: Once weekly; 1-12y: Once every 2 weeks; &gt;12 y: Once monthly</p> <p><b>Data:</b> Median of Phe concentrations during the year before the evaluation was used to assess the metabolic control.</p>	<p><b>Good control:</b> &lt;12y: Median Phe &lt;6 mg/dL (360 <math>\mu</math>mol/L)</p> <p>&gt;12y: Median Phe&lt;8 mg/dL (480 <math>\mu</math>mol/L)</p>	<p>Globally, 68.5% of patients had a good metabolic control n=89;</p> <p><b>Good metabolic control range:</b> &lt;12y: 93.2% were within this range; &gt;12y: 50% were within this range.</p>
Rohde et al., 2012 & 2014a	<p><b>Protocol (2014a):</b> Phe concentration was determined bi- to four-weekly. Dried blood Phe was recorded over a 3-day period after 6 (study phase 3) and 12 mo (study phase 4)</p> <p><b>Protocol (2012):</b> During the study samples of capillary whole blood were taken on filter paper daily between 07:00 and 09:00 hours after an overnight fast. Twice a week, they mailed the filter paper cards to the hospital.</p>	40–240 $\mu$ mol/L	<p><b>2014a:</b> Throughout the study, mean dried blood Phe concentrations remained within the recommended range</p> <p><b>2012:</b> Average dried-blood Phe concentrations remained stable and were within the recommended range throughout the study;</p> <p><b>At baseline:</b> 230 <math>\pm</math> 63 <math>\mu</math>mol/L [N=14; 121-306 <math>\mu</math>mol/L] <b>Restricted fruits-vegetables intake:</b> 246<math>\pm</math>140 <math>\mu</math>mol/L <b>Unrestricted intake:</b> 243<math>\pm</math>137 <math>\mu</math>mol/L</p>

Supplementary Table 7. *Cont.*

Reference	Centres' practice/protocol for monitoring and data reported	Target blood Phe ranges for age	Blood Phe levels for age Mean $\pm$ SD [Median, range]
Rohde et al., 2015	<p><b>Protocol:</b> Last 6 Phe-concentrations in dried blood prior to study entry.</p> <p><b>Data:</b> Median, range of last 6 Phe concentrations</p>	<p>Upper therapeutic limit of Phe:</p> <p>&lt;10y: 240 <math>\mu</math>mol/L</p> <p>&gt;10y: 900 <math>\mu</math>mol/L</p>	<p><b>1-9y:</b> Good to acceptable metabolic control;</p> <p><b>Diet 1:</b> [161 <math>\mu</math>mol/L; 77-829 <math>\mu</math>mol/L; N=22]</p> <p><b>Diet 2:</b> [229 <math>\mu</math>mol/L; 92-554 <math>\mu</math>mol/L; N=25]</p> <p><b>Diet 3:</b> [236 <math>\mu</math>mol/L; 75-744 <math>\mu</math>mol/L; N=30]</p> <p><b>Diet 4:</b> [249 <math>\mu</math>mol/L; 78-531 <math>\mu</math>mol/L; N=25]</p> <p><b>Diet 5:</b> [288 <math>\mu</math>mol/L; 156-529 <math>\mu</math>mol/L; N=6]</p> <p><b>Total:</b> [236 <math>\mu</math>mol/L; 75-829 <math>\mu</math>mol/L; N=108]</p> <p><b>10-15y:</b> Good to acceptable metabolic control;</p> <p><b>Diet 1:</b> [361 <math>\mu</math>mol/L; 119-810 <math>\mu</math>mol/L; N=5]</p> <p><b>Diet 2:</b> [565 <math>\mu</math>mol/L 170-1157 <math>\mu</math>mol/L; N=10]</p> <p><b>Diet 3:</b> [532 <math>\mu</math>mol/L 119-844 <math>\mu</math>mol/L; N=13]</p> <p><b>Diet 4:</b> [627 <math>\mu</math>mol/L 184-812 <math>\mu</math>mol/L; N=10]</p> <p><b>Diet 5:</b> [629 <math>\mu</math>mol/L 584-802 <math>\mu</math>mol/L; N=3]</p> <p><b>Total:</b> [565 <math>\mu</math>mol/L; 119-1157 <math>\mu</math>mol/L; N=41]</p>
Rohde et al., 2014b	Not reported	Not reported	Almost all included patients show Phe concentrations within their age-specific target ranges, according to the German guidelines.
Schulpis et al., 2013	<p><b>Protocol:</b> Blood was taken after 9-10 h fasting for the evaluation of Phe (Phe instant Phe blood level at the moment of sampling). Phe was measured with a standardized enzymatic assay in dried blood samples on filter paper.</p> <p><b>Data:</b> Mean, SD of blood Phe levels.</p>	Not reported	<b>Blood Phe; Group B (strictly adherent to the diet)</b> 492.0 $\pm$ 100.0 $\mu$ mol/L; N=30
Stockler-Ipsiroglu et al., 2015	<p><b>Protocol:</b> Blood samples were collected after a 3–6 h fasting for children &lt;2 y and after a 6–10 h overnight fast in older children. Dried blood spots were obtained during regular home-based monitoring, or in plasma from blood samples obtained during a clinic visit.</p> <p>Minimum frequency;</p> <p><b>&lt;6 mo:</b> Twice weekly; <b>6-18 mo:</b> Once weekly;</p> <p><b>18 mo-12y:</b> Every 2 weeks; <b>&gt;12 y:</b> Monthly</p> <p><b>Data:</b> Mean, median, range of blood Phe at baseline (1 mo pretreatment)</p>	<p>2–6 mg/dl (120–360 <math>\mu</math>mol/l)</p> <p><b>In patients &gt;12y:</b> &lt; 10 mg/dl (&lt;600 <math>\mu</math>mol/l)</p>	<p><b>Baseline:</b> 4.53<math>\pm</math>1.23 mg/dl [4.61 mg/dl; 3.13-6.59 mg/dl; N=11]</p>

Supplementary Table 7. Cont.

Reference	Centres' practice/protocol for monitoring and data reported	Target blood Phe ranges for age	Blood Phe levels for age Mean $\pm$ SD [Median, range]
Sweeney et al., 2012	<p><b>Protocol:</b> Blood Phe levels were measured using a weekly home-collected filter paper blood spot at a regular time that suited the family, continued as usual, and measured by tandem mass spectrometry. Dietary management aimed for blood Phe levels within the range recommended by the Medical Research Council Working Party on Phenylketonuria (1993).</p> <p><b>Data:</b> Mean, median and range of blood Phe levels at baseline and at 6 mo follow-up.</p>	120-360 $\mu$ mol/L	<p><b>Phase I-total; baseline:</b> 407<math>\pm</math>145 <math>\mu</math>mol/L [450 <math>\mu</math>mol/L; 202-723 <math>\mu</math>mol/L; N=17]  <b>Phase I-total; 6 mo:</b> 431<math>\pm</math>179 <math>\mu</math>mol/L [425 <math>\mu</math>mol/L; 119-737 <math>\mu</math>mol/L; N=10]</p> <p><b>Phase I-Control; before new exchange system:</b> 352<math>\pm</math>175 <math>\mu</math>mol/L [334 <math>\mu</math>mol/L; 67-609 <math>\mu</math>mol/L; N=8]  <b>Phase I-Control; 6 mo after new exchange system:</b> 306<math>\pm</math>165 <math>\mu</math>mol/L [256 <math>\mu</math>mol/L; 81-553 <math>\mu</math>mol/L; N=8]</p> <p><b>Phase II-baseline:</b> 442<math>\pm</math>137 <math>\mu</math>mol/L [456 <math>\mu</math>mol/L; 274-657 <math>\mu</math>mol/L; N=18]  <b>Phase II-6 mo:</b> 399<math>\pm</math>149 <math>\mu</math>mol/L [359 <math>\mu</math>mol/L; 185-663 <math>\mu</math>mol/L; N=18]</p>
Thiele et al., 2017	<p><b>Protocol:</b> To evaluate patients' lifetime metabolic control, their individual mean Phe concentration per year from birth onward to the age of 18 years was calculated retrospectively from medical records. Phe concentrations were measured in dried blood by liquid chromatography/tandem mass spectrometry or by fluorometry.</p> <p><b>Data:</b> Individual mean, SD Phe concentration per year from birth to 18 y of age.</p>	<p><b>1-10 y:</b> 42-240 <math>\mu</math>mol/l (0.7-4 mg/dl)  <b>11-16 y:</b> 42-900 <math>\mu</math>mol/l (0.7-15 mg/dl)  <b>&gt; 16y:</b> 42-1200 <math>\mu</math>mol/l (0.7-20 mg/dl)</p>	<p>Mean dried blood Phe concentrations remained in the age-specific recommended range during the evaluation period;  <b>0-1 y:</b> 301<math>\pm</math>153 <math>\mu</math>mol/L; <b>1-2 y:</b> 290<math>\pm</math>151 <math>\mu</math>mol/L  <b>2-3 y:</b> 307<math>\pm</math>170 <math>\mu</math>mol/L; <b>3-4 y:</b> 320<math>\pm</math>168 <math>\mu</math>mol/L  <b>4-5 y:</b> 341<math>\pm</math>189 <math>\mu</math>mol/L; <b>5-6 y:</b> 332<math>\pm</math>197 <math>\mu</math>mol/L  <b>6-7 y:</b> 335<math>\pm</math>191 <math>\mu</math>mol/L; <b>7-8 y:</b> 331<math>\pm</math>170 <math>\mu</math>mol/L  <b>8-9 y:</b> 333<math>\pm</math>165 <math>\mu</math>mol/L; <b>9-10 y:</b> 361<math>\pm</math>197 <math>\mu</math>mol/L  <b>10-11 y:</b> 367<math>\pm</math>174 <math>\mu</math>mol/L; <b>11-12 y:</b> 423<math>\pm</math>89 <math>\mu</math>mol/L  <b>12-13 y:</b> 456<math>\pm</math>224 <math>\mu</math>mol/L; <b>13-14 y:</b> 468<math>\pm</math>226 <math>\mu</math>mol/L  <b>14-15 y:</b> 506<math>\pm</math>256 <math>\mu</math>mol/L; <b>15-16 y:</b> 541<math>\pm</math>503 <math>\mu</math>mol/L  <b>16-17 y:</b> 579<math>\pm</math>275 <math>\mu</math>mol/L; <b>17-18 y:</b> 637<math>\pm</math>270 <math>\mu</math>mol/L</p>
Trefz et al., 2009	<p><b>Protocol:</b> Different protocols at each 15 centers.</p> <p><b>Data:</b> Mean, SD of blood Phe levels over prior 6 months (baseline)</p>	$\leq$ 360 $\mu$ mol/L	<p><b>Over prior 6 mo to BH4 therapy:</b>  <b>BH4 group:</b> 314<math>\pm</math>107 <math>\mu</math>mol/L [112-474 <math>\mu</math>mol/L; N=33]  <b>Placebo:</b> 303<math>\pm</math>74 <math>\mu</math>mol/L [176-447 <math>\mu</math>mol/L; N=12]  <b>Total:</b> 309 <math>\mu</math>mol/L (N=45)</p> <p><b>Final Phe level at 10-wk:</b>  <b>Placebo:</b> 461<math>\pm</math>235 <math>\mu</math>mol/L (N=12)</p>



Supplementary Table 7. *Cont.*

Reference	Centres' practice/protocol for monitoring and data reported	Target blood Phe ranges for age	Blood Phe levels for age Mean $\pm$ SD [Median, range]
van Spronsen et al., 2009	<p><b>Protocol:</b> The means of Phe concentrations of blood samples collected at the 1 mo, 6 mo, 1, 2, 3, 5, 10 y of age were subsequently used to decide on metabolic control and to include or exclude data on tolerance of the individual patient at that point. Data that were not within the target range of the Phe concentrations were excluded when calculating Phe tolerance.</p> <p><b>Data:</b> Mean Phe tolerance at the seven time points (1 mo, 6 mo, 1, 2, 3, 5, 10 y of age) was used.</p>	200–500 $\mu$ mol/L	<p>Fluctuations in plasma Phe concentrations were observed in almost all patients under the same prescribed Phe intake n=213.</p> <p>The decrease in the number of patients with Phe concentration within target limits was in line with data of other studies showing that from the ages of 5 to 10 years progressively fewer plasma concentrations are within range.</p>
Wendel et al., 1990	<p><b>Protocol:</b> Blood specimens were drawn and mailed to laboratory for analysis;</p> <p><b>0-1y:</b> At least one estimation every 2 weeks;</p> <p><b>&gt;1y:</b> One estimation every 4 weeks; at least one quantitative estimation (by fluorometry or automated amino acid analysis) every 2 months;</p> <p><b>Data:</b> Mean, median, range of blood Phe were calculated over each 6-month period.</p>	2-6 mg/dl	<p><b>In low Phe plasma level group:</b> 5.9<math>\pm</math>0.9 mg/dL [6.1 mg/dL; 5.6-9.4 mg/dL, N=112]</p> <p>Plotting the data of the high-level subgroup separately, it became apparent that the means of the median plasma Phe levels of the great majority of the PKU patients were maintained quite well at the designated upper limit of 6 mg/dl.</p>

Abbreviations; PKU, phenylketonuria; Phe, phenylalanine; mo, months; y, year; h, hour; SD, standard deviation; BH4, tetrahydrobiopterin; FU: follow-up; N, number of patients; GMP: glycomacropeptide; AAM: amino acid mixture; IQR: interquartile range; PS, protein substitute; RDA, recommended dietary allowance; FAO, Food and Agriculture Organization of the United Nations; MRC, Medical Research Council; Tyr, tyrosine.