

**Supplement:**

**1. Standard diagnostic workup performed for every patient:**

- Blood workup: differential blood count, TPZ, INR, aPTT, thrombin time, fibrinogen, antithrombin-III, d-dimer, electrolytes, potassium, phosphate, creatinine, cystatin-C, urea, CK, CK-MB, troponin T, myoglobin, NT-pro BNP, transaminases, LDH, CRP, triglycerides, C3, C4, haptoglobin, IgA/M/G/E, blood sedimentation, blood gas analysis, Cortisol, TSH, ft4, SARS-CoV-2-IgG, 25-OH-vitamin D, vitamins B1, B6, and B12, folate and sprue diagnostics, ferritin, ANA, ANCA, Serotonine, Urinalysis: Status and Microscopy, 24-hour Cortisol levels in the Urin. - The laboratory diagnostics were expanded in a symptom-oriented manner.
- Standardized Apparative Diagnostics: Echocardiography, 12-Lead ECG, Long-term ECG, Long-term Blood Pressure Monitoring, Pulmonary Function Testing, Abdominal Ultrasound, Thyroid Ultrasound, EEG (Electroencephalography) if necessary: Nerve Conduction Velocity Testing, MRI of the Brain, Spine, or Heart, etc.
- And depending on symptoms consils with child and adolescent psychiatrist, ENT, gynecology etc. were made

**2. Questionnaires (all evaluated in studies before; those shown here are examples for age 7-12 years)**

**2.1 PedsQL (<https://www.pedsql.org>)**

**PARENT VERSION - Questionnaire on QUALITY OF LIFE AND FATIGUE -**

**PedsQLTM PedsQL (Visits 1-3) Version 4.0 - Short Form (SF15) – German (Germany)**

**Has your child had the following problems or difficulties in the PAST 4 WEEKS?**

**PROBLEMS WITH HEALTH AND ACTIVITIES**

My child...

never Rarely sometimes often Almost always ...

had trouble walking more than 100 meters. 0 1 2 3 4 ...

had trouble running. 0 1 2 3 4 ...

had trouble participating in sports activities. 0 1 2 3 4 ...

had trouble lifting something heavy. 0 1 2 3 4 ...

had trouble doing household chores. 0 1 2 3 4

### **PROBLEMS WITH MOOD/EMOTIONS**

My child...

never Rarely sometimes often Almost always ...

felt afraid. 0 1 2 3 4 ...

was sad. 0 1 2 3 4 ...

was angry. 0 1 2 3 4 ...

worried about what would happen to him/her. 0 1 2 3 4

### **PROBLEMS IN INTERACTIONS WITH OTHER YOUTH**

never Rarely sometimes often Almost always ...

had trouble getting along with other children. 0 1 2 3 4 ...

had problems because other children did not want to be friends with him/her 0 1 2 3 4 ...

was teased by other children. 0 1 2 3 4

### **PROBLEMS AT SCHOOL**

never Rarely sometimes often Almost always ...

had trouble paying attention in class. 0 1 2 3 4 ...

forgot things. 0 1 2 3 4 ...

had trouble completing schoolwork and tasks. 0 1 2 3 4

### **PROBLEMS WITH GENERAL FATIGUE**

My child...

never Rarely sometimes often Almost always ...

felt tired. 0 1 2 3 4 ...

felt physically weak (not strong). 0 1 2 3 4 ...

felt too tired to do things they like. 0 1 2 3 4 ...

felt too tired to spend time with friends. 0 1 2 3 4 ...

had trouble finishing things they started. 0 1 2 3 4 ...

had trouble starting things. 0 1 2 3 4

### **PROBLEMS WITH FATIGUE / NEED FOR REST**

My child...

never Rarely sometimes often Almost always ...

slept a lot. 0 1 2 3 4 ...

had trouble sleeping through the night. 0 1 2 3 4 ...

felt tired when they woke up in the morning. 0 1 2 3 4 ...

rested a lot. 0 1 2 3 4 ...

took many naps. 0 1 2 3 4 ...

spent a lot of time in bed. 0 1 2 3 4

### **PROBLEMS WITH MENTAL FATIGUE**

My child...

never Rarely sometimes often Almost always ...

had trouble focusing on things. 0 1 2 3 4 ...

had trouble remembering what people told them. 0 1 2 3 4 ...

had trouble remembering things they just heard. 0 1 2 3 4 ...

had trouble thinking quickly. 0 1 2 3 4 ...

had trouble remembering what they just thought. 0 1 2 3 4 ...

had trouble remembering more than one thing at a time. 0 1 2 3 4

### **PATIENT VERSION – Quality of Life and Fatigue Questionnaire - PedsQL™ PedsQL**

Version 4.0 - Short Form (SF15) – German (Germany) QUESTIONNAIRE for

ADOLESCENTS

**In the past 4 WEEKS, did you experience the following problems or difficulties?**

**HEALTH AND ACTIVITY PROBLEMS**

Never Almost Never Sometimes Often Almost Always

It was hard for me to walk more than 100 meters. 0 1 2 3 4

It was hard for me to run. 0 1 2 3 4

It was hard for me to participate in sports activities. 0 1 2 3 4

It was hard for me to lift something heavy. 0 1 2 3 4

It was hard for me to do household chores. 0 1 2 3 4

**MOOD/FEELING PROBLEMS**

Never Almost Never Sometimes Often Almost Always

I felt afraid. 0 1 2 3 4

I was sad. 0 1 2 3 4

I was angry. 0 1 2 3 4

I worried about what would happen to me. 0 1 2 3 4

**PROBLEMS WITH OTHER ADOLESCENTS**

Never Almost Never Sometimes Often Almost Always

I had trouble getting along with other kids. 0 1 2 3 4

Other kids didn't want to be friends with me. 0 1 2 3 4

Other kids teased me. 0 1 2 3 4

**PROBLEMS AT SCHOOL**

Never Almost Never Sometimes Often Almost Always

I had trouble paying attention in class. 0 1 2 3 4

I forgot things. 0 1 2 3 4

I had trouble completing schoolwork and tasks. 0 1 2 3 4

**GENERAL EXHAUSTION PROBLEMS**

Never Almost Never Sometimes Often Almost Always

I feel tired. 0 1 2 3 4

I feel physically weak (not strong). 0 1 2 3 4

I feel too tired to do things I like. 0 1 2 3 4

I feel too tired to spend time with friends. 0 1 2 3 4

I have trouble finishing things I start. 0 1 2 3 4

I have trouble starting things. 0 1 2 3 4

### **FATIGUE/NEED FOR REST PROBLEMS**

Never Almost Never Sometimes Often Almost Always

I sleep a lot. 0 1 2 3 4

I have trouble sleeping through the night. 0 1 2 3 4

I feel tired when I wake up in the morning. 0 1 2 3 4

I rest a lot. 0 1 2 3 4

I take a lot of naps. 0 1 2 3 4

I spend a lot of time in bed. 0 1 2 3 4

### **MENTAL FATIGUE PROBLEMS**

Never Almost Never Sometimes Often Almost Always

I have trouble keeping my attention focused. 0 1 2 3 4

I have trouble remembering what people tell me. 0 1 2 3 4

I have trouble remembering things I just heard. 0 1 2 3 4

I have trouble thinking quickly. 0 1 2 3 4

I have trouble remembering what I was just thinking. 0 1 2 3 4

I have trouble remembering more than one thing at a time. 0 1 2 3 4

### **3. Therapy Effect**

#### **PARENT VERSION – Questions on Therapy Effects (GEEE Current Effects)**

Rief W, Nestoriuc Y, Mueller EM. Generic rating scale for previous treatment experiences, treatment expectations, and treatment effects (GEEE). PsychArchives 2021.doi:10.23668/psycharchives.4717)

In the following section, please describe any changes your child has experienced since participating in this study, based on your perception:

1. How much improvement in symptoms has your child experienced since then?

No improvement 0 1 2 3 4 5 6 7 8 9 10 Maximum imaginable improvement

2. How much worsening of symptoms has your child experienced since then?

No worsening 0 1 2 3 4 5 6 7 8 9 10 Maximum imaginable worsening

3. How many complaints/side effects from the treatment has your child experienced since then?

No complaints 0 1 2 3 4 5 6 7 8 9 10 Maximum imaginable complaints

### **PATIENT VERSION – Questions on Therapy Effects (GEEE Current Effects)**

Rief W, Nestoriuc Y, Mueller EM. Generic rating scale for previous treatment experiences, treatment expectations, and treatment effects (GEEE). PsychArchives 2021.doi:10.23668/psycharchives.4717

In the following section, please describe any changes you have experienced since participating in this study:

1. How much improvement in symptoms have you experienced since then?

No improvement 0 1 2 3 4 5 6 7 8 9 10 Maximum imaginable improvement

2. How much worsening of symptoms have you experienced since then?

No worsening 0 1 2 3 4 5 6 7 8 9 10 Maximum imaginable worsening

3. How many complaints/side effects from the treatment have you experienced since then?

No complaints 0 1 2 3 4 5 6 7 8 9 10 Maximum imaginable complaints

#### **4. Daily online Diary**

To help us understand how you are feeling during the study, we ask you to fill out the first part daily and the second part after your training sessions.

##### **Quality of Life and Resilience**

Never Almost Never Sometimes Often Almost Always

It was hard for me to walk more than 100 meters. 0 1 2 3 4

I feel physically weak (not strong). 0 1 2 3 4

I need to rest a lot. 0 1 2 3 4

I have trouble concentrating. 0 1 2 3 4

If you felt good today, you don't need to answer this question. If you didn't feel well, list your top 3 symptoms. Please name the symptom that bothered you the most first.

##### **Free text:**

##### **Other**

I went to school today: Yes, No

How long did you go to school in hours:

Other (e.g., I was sick today): Free text

I had was physical active today: Yes No

What did you do: Free text

Do you want to tell us something: Free text

**The flowering were only answered on exercise therapy days:**

What did you like about the training session, and did you enjoy it? What didn't you like: Free text:

Do you feel that your symptoms have improved compared to the last training session: Free text:

Do you have any wishes for the next training session: Free text

Did you exercise independently between training sessions: Free text

If yes, how often and for how long? What did you do: Free text

Did you use an activity tracker: Yes, No

If No – Why: Free text

**Entry by physical therapist on days of exercise therapy:**

Were there any technical problems?

Was everyone on time?

Break times?

Unplanned events/incidents?

## 5. Further Results

**Table 1: Impact of exercise therapy on quality of life and overall treatment effect, as well as physical testing**

|                                 |           | Group 1 - 12 weeks intervention group |          |    |    |     |     |    | Group 2 - 6 weeks intervention group |                  |                  |     |     |     |     |    |           |                   |                   |
|---------------------------------|-----------|---------------------------------------|----------|----|----|-----|-----|----|--------------------------------------|------------------|------------------|-----|-----|-----|-----|----|-----------|-------------------|-------------------|
|                                 |           | 1                                     | 2        | 3  | 4  | 5   | 6   | 7  | Mean (CI)                            | 1                | 2                | 3   | 4   | 5   | 6   | 7  | Mean (CI) |                   |                   |
| quality of life (score)*        |           |                                       |          |    |    |     |     |    |                                      |                  |                  |     |     |     |     |    |           |                   |                   |
| Visit I                         |           | parent                                | 40       | 30 | 35 | 85  | 60  | 30 | 70                                   | 50 (31.3-68.7)   | 55               | 25  | 35  | 45  | 100 | 35 | 70        | 52.1 (28.3-76.0)  |                   |
|                                 |           | patient                               | 40       | 30 | 25 | 55  | 60  | 25 | 75                                   | 44.3 (27.1-61.5) | 50               | 95  | 65  | 38  | 100 | 21 | 54        | 60.4 (33.8-87.1)  |                   |
| Problems with Visit II          |           | parents                               | 70       | 55 | 45 | 100 | 80  | 40 | 60                                   | 64.3 (45.5-83.1) | 60               | 90  | 45  | 50  | 85  | 35 | -         | 60.8 (37.5-84.2)  |                   |
| health and activities           |           | patients                              | 75       | 50 | 45 | 90  | 95  | 50 | 85                                   | 70.0 (51.7-88.3) | 63               | 100 | 42  | 56  | 54  | 17 | -         | 55.3 (26.8-83.9)  |                   |
| (5 items)                       | Visit III |                                       | parents  | 80 | 35 | 65  | 100 | 90 | 65                                   | 80               | 73.6 (55.3-91.9) | 85  | 100 | 100 | 50  | 85 | 60        | 90                | 81.4 (63.6-99.3)  |
|                                 |           |                                       | patient  | 75 | 60 | 70  | 100 | 90 | 60                                   | 100              | 79.3 (61.3-97.3) | 100 | 100 | 100 | 58  | 79 | 50        | 100               | 83.9 (63.6-104.1) |
| Visit IV                        |           | parent                                | 75       | 50 | 60 | 85  | 100 | 75 | -                                    | 74.2 (55.8-92.3) | 50               | 100 | 85  | 30  | 100 | 55 | 100       | 74.3 (47.5-101.0) |                   |
|                                 |           | patient                               | 75       | 40 | 35 | 90  | 95  | 60 | -                                    | 65.8 (41.2-90.5) | 42               | 100 | 71  | 25  | 75  | 42 | 100       | 65.0 (37.7-92.3)  |                   |
| Visit I                         |           | parent                                | 69       | 50 | 44 | 88  | 44  | 25 | 62                                   | 54.6 (35.2-74.0) | 100              | 38  | 75  | 19  | 81  | 44 | 44        | 57.3 (30.9-83.7)  |                   |
| problems with mood and feelings |           | patient                               | 56       | 50 | 50 | 69  | 25  | 25 | 69                                   | 49.1 (33.8-64.5) | 50               | 31  | 63  | 38  | 63  | 19 | 75        | 48.4 (29.9-67.0)  |                   |
| (4 items)                       | Visit II  |                                       | parents  | 50 | 50 | 56  | 100 | 81 | 75                                   | 94               | 72.3 (55.1-89.5) | 94  | 50  | 94  | 25  | 75 | 44        | -                 | 63.7 (33.9-93.5)  |
|                                 |           |                                       | patients | 69 | 88 | 56  | 75  | 38 | 75                                   | 81               | 68.9 (53.2-84.6) | 94  | 38  | 94  | 50  | 56 | 19        | -                 | 58.5 (26.7-90.3)  |
| Visit III                       |           | parents                               | 100      | 69 | 69 | 100 | 94  | 63 | 75                                   | 81.4 (67.3-95.6) | 100              | 100 | 100 | 44  | 81  | 31 | 81        | 76.7 (50.5-103.0) |                   |
|                                 |           | patient                               | 94       | 63 | 56 | 75  | 38  | 75 | 94                                   | 70.7 (52.0-89.5) | 100              | 100 | 100 | 75  | 88  | 38 | 100       | 85.9 (64.5-107.3) |                   |
| Visit IV                        |           | parent                                | 69       | 69 | 63 | 75  | 100 | 56 | -                                    | 72.0 (56.1-87.9) | 63               | 100 | 100 | 44  | 75  | 44 | 75        | 71.6 (50.1-93.0)  |                   |

|                                      |           |          |            |           |           |            |           |           |           |                         |            |            |            |           |            |           |            |                          |
|--------------------------------------|-----------|----------|------------|-----------|-----------|------------|-----------|-----------|-----------|-------------------------|------------|------------|------------|-----------|------------|-----------|------------|--------------------------|
|                                      |           | patient  | <b>88</b>  | <b>75</b> | <b>56</b> | <b>75</b>  | <b>56</b> | <b>50</b> | -         | <b>66.7</b> (51.1-82.2) | <b>75</b>  | <b>100</b> | <b>100</b> | <b>18</b> | <b>100</b> | <b>38</b> | <b>88</b>  | <b>74.1</b> (43.3-105.0) |
| Visit I                              |           | parent   | 17         | 25        | 17        | 100        | 25        | 22        | 58        | <b>37.7</b> (9.2-66.3)  | 25         | 25         | 33         | 17        | 58         | 25        | 42         | 32.1 (19.4-45.0)         |
|                                      |           | patient  | 42         | 8         | 17        | 100        | 17        | 17        | 58        | <b>37.0</b> (6.6-67.4)  | 25         | 33         | 33         | 8         | 50         | 8         | 58         | 30.7 (13.0-48.4)         |
| Visit II                             |           | parents  | <b>42</b>  | <b>42</b> | <b>50</b> | <b>100</b> | <b>42</b> | <b>42</b> | <b>33</b> | <b>50.1</b> (29.3-71.0) | 25         | 42         | 33         | 17        | 67         | 0         | -          | 30.7 (6.7-54.7)          |
|                                      |           | patients | <b>67</b>  | <b>50</b> | <b>50</b> | <b>100</b> | <b>33</b> | <b>67</b> | <b>67</b> | <b>62.0</b> (42.6-81.4) | 25         | 25         | 33         | 17        | 52         | 0         | -          | 25.3 (7.3-43.4)          |
| Problems with<br>peers               | Visit III | parents  | <b>100</b> | <b>33</b> | <b>42</b> | <b>100</b> | <b>42</b> | <b>75</b> | <b>67</b> | <b>65.6</b> (39.9-91.3) | <b>100</b> | <b>100</b> | <b>100</b> | <b>50</b> | <b>50</b>  | <b>17</b> | <b>100</b> | <b>73.9</b> (42.0-105.7) |
|                                      |           | patient  | <b>100</b> | <b>42</b> | <b>58</b> | <b>100</b> | <b>50</b> | <b>67</b> | <b>75</b> | <b>70.3</b> (49.1-91.5) | <b>100</b> | <b>100</b> | <b>83</b>  | <b>67</b> | <b>83</b>  | <b>17</b> | <b>100</b> | <b>78.6</b> (51.0-106.2) |
|                                      | Visit IV  | parent   | <b>67</b>  | <b>50</b> | <b>42</b> | <b>100</b> | <b>75</b> | <b>58</b> | -         | <b>65.3</b> (43.7-87.0) | <b>42</b>  | <b>100</b> | <b>100</b> | <b>25</b> | <b>67</b>  | <b>17</b> | <b>100</b> | <b>64.4</b> (30.4-98.4)  |
|                                      |           | patient  | <b>67</b>  | <b>33</b> | <b>42</b> | <b>100</b> | <b>67</b> | <b>58</b> | -         | <b>61.2</b> (36.6-85.8) | <b>42</b>  | <b>100</b> | <b>100</b> | <b>17</b> | <b>100</b> | <b>33</b> | <b>92</b>  | <b>69.1</b> (35.1-103.2) |
|                                      | Visit I   | parent   | 17         | 25        | 17        | 100        | 25        | 33        | 58        | <b>39.3</b> (11.3-67.2) | 25         | 25         | 33         | 17        | 58         | 25        | 42         | 48.4 (29.9-67.0)         |
|                                      |           | patient  | 42         | 8         | 17        | 100        | 17        | 17        | 58        | <b>37.0</b> (6.6-67.4)  | 25         | 33         | 33         | 8         | 50         | 8         | 58         | 63.7 (33.9-93.5)         |
|                                      | Visit II  | parents  | <b>42</b>  | <b>42</b> | <b>50</b> | <b>100</b> | <b>42</b> | <b>42</b> | <b>33</b> | <b>50.1</b> (29.3-71.0) | 25         | 42         | 33         | 17        | 67         | 0         | -          | 58.5 (26.7-90.3)         |
|                                      |           | patients | <b>67</b>  | <b>50</b> | <b>50</b> | <b>100</b> | <b>33</b> | <b>67</b> | <b>67</b> | <b>62.0</b> (42.6-81.4) | 25         | 25         | 33         | 17        | 52         | 0         | -          | 25.3 (7.3-43.4)          |
| Problems with<br>school (3<br>items) | Visit III | parents  | <b>100</b> | <b>33</b> | <b>42</b> | <b>100</b> | <b>42</b> | <b>75</b> | <b>67</b> | <b>65.6</b> (39.9-91.3) | <b>100</b> | <b>100</b> | <b>100</b> | <b>50</b> | <b>50</b>  | <b>17</b> | <b>100</b> | <b>73.9</b> (42.0-105.7) |
|                                      |           | patient  | <b>100</b> | <b>42</b> | <b>58</b> | <b>100</b> | <b>50</b> | <b>67</b> | <b>75</b> | <b>70.3</b> (49.1-91.5) | <b>100</b> | <b>100</b> | <b>83</b>  | <b>67</b> | <b>83</b>  | <b>17</b> | <b>100</b> | <b>78.6</b> (51.0-106.2) |
|                                      | Visit IV  | Parent   | <b>67</b>  | <b>50</b> | <b>42</b> | <b>100</b> | <b>75</b> | <b>58</b> | -         | <b>65.3</b> (43.7-87.0) | <b>42</b>  | <b>100</b> | <b>100</b> | <b>25</b> | <b>67</b>  | <b>17</b> | <b>100</b> | <b>64.4</b> (30.4-98.4)  |
|                                      |           | Patient  | <b>67</b>  | <b>33</b> | <b>42</b> | <b>100</b> | <b>67</b> | <b>58</b> | -         | <b>61.2</b> (36.6-85.8) | <b>42</b>  | <b>100</b> | <b>100</b> | <b>17</b> | <b>100</b> | <b>33</b> | <b>92</b>  | <b>69.1</b> (35.1-103.2) |
|                                      | Visit I   | Parent   | 21         | 33        | 21        | 96         | 17        | 33        | 50        | 38.7 (13.2-64.3)        | 75         | 29         | 50         | 25        | 83         | 29        | 21         | 44.6 (21.1-68.0)         |
|                                      |           | Patients | 42         | 42        | 29        | 83         | 42        | 21        | 63        | 46.0 (26.7-65.3)        | 83         | 46         | 42         | 42        | 58         | 13        | 71         | 50.7 (29.7-71.6)         |
| Problems with<br>Visit II            |           | parent   | <b>67</b>  | <b>46</b> | <b>38</b> | <b>92</b>  | <b>67</b> | <b>50</b> | <b>50</b> | <b>58.6</b> (41.7-75.4) | <b>79</b>  | <b>67</b>  | <b>42</b>  | <b>25</b> | <b>67</b>  | <b>21</b> | -          | 50.1 (24.7-75.7)         |
|                                      |           | patient  | <b>58</b>  | <b>54</b> | <b>42</b> | <b>92</b>  | <b>46</b> | <b>63</b> | <b>71</b> | <b>60.9</b> (45.3-76.5) | <b>79</b>  | <b>38</b>  | <b>38</b>  | <b>21</b> | <b>60</b>  | <b>13</b> | -          | 41.5 (15.8-67.2)         |
| general<br>fatigue                   | Visit III | parents  | <b>83</b>  | <b>46</b> | <b>58</b> | <b>96</b>  | <b>50</b> | <b>67</b> | <b>63</b> | <b>66.1</b> (49.6-82.7) | <b>88</b>  | <b>96</b>  | <b>67</b>  | <b>50</b> | <b>96</b>  | <b>25</b> | <b>83</b>  | <b>72.1</b> (47.5-96.8)  |
|                                      |           | patients | <b>83</b>  | <b>67</b> | <b>46</b> | <b>100</b> | <b>54</b> | <b>71</b> | <b>75</b> | <b>70.9</b> (54.3-87.5) | <b>88</b>  | <b>96</b>  | <b>83</b>  | <b>50</b> | <b>91</b>  | <b>25</b> | <b>100</b> | <b>76.1</b> (50.3-102.0) |
|                                      | Visit IV  | parent   | <b>67</b>  | <b>50</b> | <b>50</b> | <b>92</b>  | <b>67</b> | <b>50</b> | -         | <b>62.7</b> (45.2-80.1) | <b>46</b>  | <b>100</b> | <b>71</b>  | <b>25</b> | <b>83</b>  | <b>25</b> | <b>83</b>  | <b>61.9</b> (34.1-89.6)  |

|                                      |          |          |    |    |    |     |    |    |    |                  |     |     |    |     |     |    |     |                   |
|--------------------------------------|----------|----------|----|----|----|-----|----|----|----|------------------|-----|-----|----|-----|-----|----|-----|-------------------|
|                                      |          | Patients | 71 | 50 | 25 | 88  | 79 | 42 | -  | 59.2 (33.9-84.5) | 54  | 100 | 67 | 25  | 79  | 42 | 100 | 66.7 (40.3-93.1)  |
| Visit I                              | Parent   |          | 42 | 58 | 25 | 92  | 46 | 38 | 33 | 47.7 (27.3-68.2) | 67  | 33  | 63 | 50  | 38  | 25 | 25  | 43.0 (27.0-59.0)  |
|                                      | Patients |          | 29 | 25 | 33 | 75  | 71 | 29 | 42 | 43.4 (24.1-62.8) | 58  | 29  | 71 | 54  | 42  | 29 | 38  | 45.9 (31.3-60.4)  |
| Visit II                             | parent   |          | 46 | 54 | 38 | 92  | 83 | 67 | 46 | 60.9 (42.0-79.8) | 58  | 33  | 75 | 46  | 50  | 33 | -   | 49.2 (32.4-66.0)  |
| Problems with fatigue / need to rest | patient  |          | 71 | 42 | 21 | 88  | 79 | 33 | 79 | 59.0 (34.6-83.5) | 58  | 33  | 71 | 38  | 38  | 21 | -   | 43.2 (24.1-62.2)  |
| Visit III                            | parents  |          | 75 | 33 | 54 | 83  | 83 | 75 | 63 | 66.6 (49.8-83.4) | 79  | 67  | 92 | 50  | 50  | 38 | 75  | 25.3 (7.3-43.4)   |
| (6 items)                            | patients |          | 75 | 50 | 54 | 96  | 79 | 50 | 88 | 70.3 (52.7-87.8) | 79  | 67  | 92 | 67  | 63  | 67 | 71  | 73.9 (42.0-105.7) |
| Visit IV                             | parent   |          | 58 | 50 | 38 | 71  | 75 | 54 | -  | 57.7 (43.3-72.0) | 54  | 100 | 79 | 46  | 38  | 42 | 88  | 78.6 (51.0-106.2) |
|                                      | Patients |          | 54 | 33 | 25 | 83  | 92 | 25 | -  | 52.0 (20.9-83.1) | 58  | 100 | 67 | 29  | 38  | 67 | 83  | 64.4 (30.4-98.4)  |
| Visit I                              | Parent   |          | 42 | 50 | 21 | 100 | 17 | 50 | 54 | 47.7 (22.5-73.0) | 38  | 33  | 67 | 38  | 88  | 13 | 54  | 69.1 (35.1-103.2) |
|                                      | Patients |          | 33 | 38 | 38 | 100 | 54 | 33 | 63 | 51.3 (28.8-73.8) | 46  | 29  | 50 | 50  | 83  | 0  | 50  | 44.6 (21.1-68.0)  |
| Visit II                             | parent   |          | 46 | 79 | 50 | 100 | 50 | 63 | 63 | 64.4 (46.6-82.3) | 63  | 75  | 63 | 50  | 63  | 33 | -   | 50.7 (29.7-71.8)  |
|                                      | patient  |          | 75 | 38 | 38 | 100 | 54 | 42 | 75 | 60.3 (38.3-82.2) | 79  | 38  | 71 | 67  | 88  | 0  | -   | 50.2 (24.7-75.7)  |
| Problems with mental fatigue         | parents  |          | 67 | 46 | 63 | 100 | 63 | 67 | 75 | 68.7 (53.6-83.8) | 100 | 79  | 75 | 54  | 96  | 29 | 100 | 41.5 (15.8-67.2)  |
| (6 items)                            | patients |          | 63 | 88 | 71 | 100 | 75 | 50 | 75 | 74.6 (59.6-89.6) | 100 | 92  | 88 | 100 | 100 | 33 | 96  | 72.1 (47.5-96.8)  |
| Visit IV                             | parent   |          | 67 | 63 | 50 | 100 | 96 | 63 | -  | 73.2 (52.1-94.3) | 96  | 100 | 96 | 50  | 96  | 29 | 100 | 76.1 (50.3-102.0) |
|                                      | Patients |          | 71 | 33 | 38 | 100 | 96 | 42 | -  | 63.3 (31.9-94.8) | 63  | 100 | 92 | 50  | 83  | 17 | 100 | 61.9 (34.1-89.6)  |

#### Physical testing

##### 6-Minute-Walking-Test

|           |     |     |     |     |     |     |     |                     |     |     |     |     |     |     |     |                     |
|-----------|-----|-----|-----|-----|-----|-----|-----|---------------------|-----|-----|-----|-----|-----|-----|-----|---------------------|
| Visit I   | 500 | 242 | 404 | 357 | 599 | 334 | 336 | 396.0 (286.1-505.9) | 392 | 635 | 397 | 482 | 432 | 285 | 380 | 429.0 (328.6-529.5) |
| Visit II  | 714 | 200 | 481 | 443 | 730 | 745 | 534 | 549.6 (366.0-733.1) | 392 | 587 | 383 | 586 | 570 | 386 | 480 | 483.4 (393.5-573.3) |
| Visit III | 894 | 423 | 585 | 587 | 763 | 369 | 878 | 642.7 (449.2-836.2) | 922 | 844 | 459 | 867 | 653 | 534 | 997 | 753.7 (563.5-943.9) |
| Visit IV  | 632 | 216 | 383 | 979 | 661 | 623 | 820 | 616.3 (380.5-852.1) | 401 | 800 | 765 | 516 | 570 | 500 | 659 | 601.6 (466.4-736.8) |

##### Sit-to-Stand

|           |             |             |             |             |            |             |             |                            |             |             |             |             |             |             |             |                           |
|-----------|-------------|-------------|-------------|-------------|------------|-------------|-------------|----------------------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|---------------------------|
| Visit I   | 21          | 22          | 15          | 50          | 27         | 21          | 22          | 25.43 (14.9–35.96)         | 17          | 34          | 30          | 25          | 15          | 9           | 21          | 21.6 (13.5–29.7)          |
| Visit II  | <b>24</b>   | <b>24</b>   | <b>20</b>   | <b>63</b>   | <b>33</b>  | <b>33</b>   | <b>34</b>   | <b>33.0 (19.8–46.3)</b>    | 17          | 37          | 34          | 24          | 17          | 11          | 20          | 22.9 (14.1–31.6)          |
| Visit III | <b>32</b>   | <b>28</b>   | <b>20</b>   | <b>116</b>  | <b>28</b>  | <b>31</b>   | <b>34</b>   | <b>41.3 (10.5–72.0)</b>    | <b>23</b>   | <b>48</b>   | <b>44</b>   | <b>34</b>   | <b>32</b>   | <b>32</b>   | <b>49</b>   | <b>37.4 (28.4–46.4)</b>   |
| Visit IV  | <b>24</b>   | <b>24</b>   | <b>14</b>   | <b>76</b>   | <b>34</b>  | <b>22</b>   | <b>34</b>   | <b>32.6 (13.7–51.4)</b>    | <b>21</b>   | <b>43</b>   | <b>33</b>   | -           | <b>30</b>   | <b>30</b>   | <b>33</b>   | <b>31.7 (24.2–39.1)</b>   |
| Hand-Grip |             |             |             |             |            |             |             |                            |             |             |             |             |             |             |             |                           |
| Visit I   | 13          | 8           | 15          | 22          | 31         | 11          | 16          | 16.6 (9.4–23.7)            | 15          | 29          | 18          | 18          | 22          | 10          | 9           | 17.3 (10.9–23.7)          |
| Visit II  | <b>31</b>   | <b>13</b>   | <b>31</b>   | <b>22</b>   | <b>37</b>  | <b>17</b>   | <b>26</b>   | <b>25.3 (17.4–33.2)</b>    | 15          | 30          | 16          | 23          | 20          | 10          | 9           | 17.6 (10.7–24.4)          |
| Visit III | <b>43</b>   | <b>16</b>   | <b>31</b>   | <b>24</b>   | <b>32</b>  | <b>21</b>   | <b>29</b>   | <b>28.0 (19.9–36.1)</b>    | <b>20</b>   | <b>36</b>   | <b>19</b>   | <b>28</b>   | <b>33</b>   | <b>18</b>   | <b>12</b>   | <b>23.7 (15.6–31.8)</b>   |
| Visit IV  | <b>38</b>   | <b>12</b>   | <b>28</b>   | <b>34</b>   | <b>30</b>  | <b>20</b>   | <b>28</b>   | <b>27.1 (19.1–35.2)</b>    | <b>19</b>   | <b>34</b>   | <b>19</b>   | <b>23</b>   | <b>28</b>   | <b>17</b>   | <b>15</b>   | <b>22.1 (15.9–28.4)</b>   |
| VC (%)    |             |             |             |             |            |             |             |                            |             |             |             |             |             |             |             |                           |
| Visit I   | 4,26        | 2,66        | 2,24        | 2,98        | 2,24       | 2,78        | 3,67        | 3.0 (2.3–3.7)              | 3,04        | 2,72        | 3,94        | 2,81        | 2,39        | 2,61        | 1,65        | 2.7 (2.1–3.4)             |
| Visit II  | <b>4,3</b>  | <b>3,29</b> | <b>3,89</b> | <b>2,98</b> | <b>3,2</b> | <b>2,29</b> | <b>3,54</b> | <b>3.4 (2.8–4.0)</b>       | 3,54        | 3,44        | 3,33        | 2,93        | 2,16        | 2,83        | -           | 3.0 (2.5–3.6)             |
| Visit III | <b>4,42</b> | <b>3,29</b> | <b>3,89</b> | <b>2,98</b> | -          | <b>2,39</b> | <b>3,44</b> | <b>3.4 (2.7–4.1)</b>       | <b>3,44</b> | -           | <b>3,26</b> | <b>2,74</b> | <b>2,16</b> | <b>2,83</b> | <b>0,61</b> | <b>2.5 (1.4–3.6)</b>      |
| Visit IV  | <b>4,95</b> | <b>3,75</b> | <b>4,17</b> | <b>2,44</b> | -          | <b>2,73</b> | <b>3,67</b> | <b>3.6 (2.7–4.6)</b>       | <b>3,44</b> | <b>4,78</b> | <b>2,88</b> | <b>2,93</b> | -           | -           | <b>1,61</b> | <b>3.1 (1.7–4.6)</b>      |
| CK (U/l)  |             |             |             |             |            |             |             |                            |             |             |             |             |             |             |             |                           |
| Visit I   | 186         | 101         | 136         | 119         | 89         | 146         | 112         | 127.0 (97.0–157.0)         | 129         | 80          | 93          | 66          | 49          | 108         | 108         | 90.4 (65.0–115.9)         |
| Visit II  | <b>214</b>  | <b>132</b>  | <b>133</b>  | <b>284</b>  | <b>103</b> | <b>222</b>  | <b>152</b>  | <b>177.1 (117.6–236.7)</b> | 129         | 80          | 78          | 70          | 68          | 108         | 129         | 94.6 (69.7–119.5)         |
| Visit III | <b>175</b>  | <b>198</b>  | <b>160</b>  | <b>107</b>  | 92         | <b>114</b>  | <b>111</b>  | <b>136.7 (99.3–174.1)</b>  | <b>169</b>  | <b>75</b>   | <b>105</b>  | <b>77</b>   | <b>75</b>   | <b>150</b>  | <b>177</b>  | <b>118.3 (75.8–160.8)</b> |
| Visit IV  | <b>169</b>  | <b>120</b>  | <b>214</b>  | <b>182</b>  | <b>85</b>  | <b>121</b>  | <b>80</b>   | <b>138.7 (91.8–185.7)</b>  | <b>124</b>  | <b>75</b>   | <b>93</b>   | <b>55</b>   | <b>60</b>   | <b>43</b>   | <b>101</b>  | <b>78.7 (52.1–105.3)</b>  |

\* mean value of visits from PedsQL (higher scores (100 the highest) indicate better HRQoL / health related quality of life); all values are

rounded to a whole number, CI rounded to one numer after the point; bold vales are taken after exercise therapy

**Table 2 Groups characteristics, impact of exercise therapy on participation in daily life and treatment effect**

|                           |         | Group 1 - 12 weeks intervention group |   |   |   |    |   |    | Group 2 - 6 weeks intervention group                |    |   |   |   |    |    |
|---------------------------|---------|---------------------------------------|---|---|---|----|---|----|---|----|---|---|---|----|----|
|                           |         | 1                                     | 2 | 3 | 4 | 5  | 6 | 7  | 1   | 2  | 3 | 4 | 5 | 6  | 7  |
| <b>Treatment effect*</b>  |         |                                       |   |   |   |    |   |    |   |    |   |   |   |    |    |
| Improve-ment* Visit II    | parent  | <b>4</b>                              | 4 | 3 | 0 | 5  | 5 | 6  | no values as there had been no intervention so far. |    |   |   |   |    |    |
|                           | patient | <b>6</b>                              | 2 | 6 | 1 | 3  | 7 | 6  |   |    |   |   |   |    |    |
| Visit III                 | parent  | <b>8</b>                              | 6 | 5 | 4 | 5  | 7 | 5  | <b>8</b>  | 8  | 5 | 8 | 0 | 7  | 7  |
|                           | patient | <b>8</b>                              | 8 | 7 | 8 | 7  | 9 | 9  | <b>9</b>  | 10 | 8 | 6 | 5 | 8  | 10 |
| Visit IV                  | parent  | <b>8</b>                              | 6 | 6 | 1 | 10 | 7 | 10 | <b>6</b>  | 10 | 8 | 2 | 1 | 10 | 9  |
|                           | patient | <b>8</b>                              | 5 | 8 | 8 | 10 | 7 | 10 | <b>9</b>  | 10 | 4 | 2 | 2 | 10 | 9  |
| Deterio-ration * Visit II | parent  | <b>0</b>                              | 0 | 0 | 0 | 0  | 0 | 2  | no values as there had been no intervention so far. |    |   |   |   |    |    |
|                           | patient | <b>1</b>                              | 0 | 2 | 0 | 0  | 3 | 0  |   |    |   |   |   |    |    |
| Visit III                 | parent  | <b>0</b>                              | 0 | 0 | 0 | 0  | 1 | 1  | <b>0</b>  | 0  | 0 | 2 | 0 | 0  | 1  |
|                           | patient | <b>0</b>                              | 0 | 2 | 0 | 0  | 2 | 1  | <b>0</b>  | 0  | 0 | 4 | 0 | 0  | 1  |
| Visit IV                  | parent  | <b>0</b>                              | 0 | 6 | 0 | 0  | 0 | 0  | <b>0</b>  | 0  | 3 | 0 | 0 | 0  | 0  |
|                           | patient | <b>0</b>                              | 0 | 0 | 5 | 0  | 4 | 0  | <b>0</b>  | 0  | 0 | 1 | 0 | 0  | 0  |

\* all values are rounded to a whole number, bold values are taken after exercise therapy – one being the lowest and 10 the highest score for improvement or deterioration

**Table 3 Detailed Results of the Linear Mixed Effects Model**

| Fixed Effects  | 6MWT          |            |                |       | Handgrip      |           |              |       | Sit-to-Stand  |           |               |       | CK            |           |               |        |
|--|---------------|------------|----------------|-------|---------------|-----------|--------------|-------|---------------|-----------|---------------|-------|---------------|-----------|---------------|--------|
|  | Estimates     | std. Error | CI             | p     | Estimate      | std.<br>r | CI           | p     | Estimate      | std.<br>r | CI            | p     | Estimates     | std.<br>r | CI            | p      |
| Group I (12 Weeks – Intercept)                       | 396.13        | 66.44      | 262.39 – 529.8 | <0.00 | 16.41         | 3.00      | 10.38 – 22.4 | <0.00 | 25.43         | 6.24      | 12.86 – 37.9  | <0.00 | 127.00        | 15.72     | 95.36 – 158.6 | <0.001 |
| Visit 2  | 153.37        | 76.05      | 0.29 – 306.45  | 0.050 | 8.73          | 1.89      | 4.93 – 12.53 | <0.00 | 7.57          | 4.36      | -1.20 – 16.35 | 0.089 | 50.14         | 16.95     | 16.02 – 84.27 | 0.005  |
| Visit 3  | 246.66        | 76.05      | 93.58 – 399.74 | 0.002 | 11.41         | 1.89      | 7.62 – 15.21 | <0.00 | 15.86         | 4.36      | 7.08 – 24.63  | 0.001 | 9.71          | 16.95     | -             | 0.569  |
| Visit 4  | 220.13        | 76.05      | 67.05 – 373.21 | 0.006 | 9.27          | 1.89      | 5.47 – 13.07 | <0.00 | 7.14          | 4.36      | -1.63 – 15.92 | 0.108 | 11.71         | 16.95     | -             | 0.493  |
| Group II (6 Weeks - Reference)                       | 32.87         | 93.96      | -              | 0.728 | 0.94          | 4.24      | -7.59 – 9.48 | 0.825 | -3.86         | 8.83      | -             | 0.664 | -36.57        | 22.23     | -81.31 – 8.17 | 0.107  |
| Visit 2 * Group (Reference: 6)                       | -99.10        | 107.55     | -              | 0.362 | -8.51         | 2.67      | -13.89 – -   | 0.003 | -6.29         | 6.16      | -18.69 – 6.12 | 0.313 | -46.00        | 23.98     | -94.26 – 2.26 | 0.061  |
| Visit 3 * Group (Reference: 6)                       | 78.06         | 107.55     | -              | 0.472 | -5.09         | 2.67      | -            | 0.063 | 0.00          | 6.16      | -             | 1.000 | 18.14         | 23.98     | -             | 0.453  |
| Visit 4 * Group (Reference: 6)                       | -47.66        | 107.55     | -              | 0.660 | -4.61         | 2.67      | -9.99 – 0.76 | 0.090 | 4.75          | 6.16      | -7.66 – 17.16 | 0.445 | -23.43        | 23.98     | -             | 0.334  |
| <b>Random Effects</b>                                |               |            |                |       |               |           |              |       |               |           |               |       |               |           |               |        |
| $\sigma^2$   | 20241.92      |            |                |       | 12.46         |           |              |       | 66.50         |           |               |       | 1006.00       |           |               |        |
| $\tau_{00}$  | 10657.85      |            |                |       | 50.49         |           |              |       | 206.30        |           |               |       | 723.25        |           |               |        |
| ICC  | 0.34          |            |                |       | 0.80          |           |              |       | 0.76          |           |               |       | 0.42          |           |               |        |
| <b>Model-level summary statistics</b>                |               |            |                |       |               |           |              |       |               |           |               |       |               |           |               |        |
| Marginal R <sup>2</sup> / Conditional R <sup>2</sup> | 0.290 / 0.535 |            |                |       | 0.211 / 0.844 |           |              |       | 0.139 / 0.790 |           |               |       | 0.345 / 0.619 |           |               |        |

$\sigma^2$  = residual (within-group) variance,  $\tau_{00}$  = random intercept (between-group) variance, Intraclass Correllation Coefficient (between Group difference), N = number of patients,;

Marginal R<sup>2</sup> = variance explained by fixed effects only, Conditional R<sup>2</sup> = variance explained by fixed effects only

