Faculteit Revalidatiewetenschappen
master in de revalidatiewetenschappen en de kinesitherapie

Masterthesis

Early Motor Development in Children with Duchenne Muscular Dystrophy

Rosanne Loos
Marieke Vandecruys
Scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesitherapie, afstudeerrichting revalidatiewetenschappen en kinesitherapie bij kinderen

PROMOTOR :
Prof. dr. Katrijn KLINGELS

COPROMOTOR :
Mevrouw Jasmine HOSKENS
Faculteit Revalidatiewetenschappen
master in de revalidatiewetenschappen en de kinesitherapie

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We also want to thank our promoter, Prof. dr. K. Klingels, for the useful advice and feedback on our master’s thesis.

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Finally, we are grateful to both our families, partners and friends for their continuous support, pre-reading this master’s thesis, their patience and encouraging words during this project.

KASTERLEE, 3 June 2019
R.L.
GEEL, 3 June 2019
M.V.
CONTEXT OF THE MASTER’S THESIS

This master’s thesis, elaborated by Rosanne Loos and Marieke Vandecruys, is part of a five-year program at the Faculty of Rehabilitation Science and Physiotherapy of UHasselt. The thesis can be classified in the research domain of paediatric rehabilitation, more specifically in the category of “motor development within muscular dystrophies”. This master’s thesis belongs to a broader research project on the evaluation of early motor development in infants and young children with DMD, performed under the supervision of Prof. dr. K. Klingels and J. Hoskens in collaboration with KULeuven (Prof. dr. H. Feys) and UZ Leuven (Prof. dr. N. Goemans, M. Van den Hauwe).

Duchenne Muscular Dystrophy (DMD) is a severe, X-linked, neuromuscular disease that affects approximately 1/3300-6000 live males worldwide (Deconinck & Dan, 2007; Ellis, Vroom, & Muntoni, 2013). Patients with DMD experience progressive muscle weakness, due to mutations in the dystrophin gene. These mutations cause an absent or insufficient functional dystrophin, a cytoskeletal protein that enables the strength, stability and functionality of myofibers (Birnkrant et al., 2018).

Signs and symptoms of DMD begin at a mean age of 2.5 years due to progressive muscle weakness of the lower limbs. However, diagnosis is often made at a mean age of 4.9 years (Ciafaloni et al., 2009). This means that there is a delay of about 2.5 years between onset of DMD symptoms and the time of definitive diagnosis. This delay results in lost opportunities for timely genetic counselling, early interventions, initiation of mutation-specific therapies and other treatments. There are two important factors which are responsible for the late diagnosis: 1) the lack of information about the early motor development of young DMD children and 2) the absence of an appropriate motor evaluation scale for young children with DMD.

For this reason, investigating early motor signs in children with DMD would have a great added value. By doing so, the signs might be recognized sooner and the rehabilitation started on time.
Based on this information, the aim of this study was to investigate the early gross and fine motor development in young infants and children with DMD between 0-5 years, on the basis of different motor evaluation scales. In addition, this study also aimed to compare the development of DMD children with typically developing (TD) children of the same age.

For this purpose, thirteen children who were diagnosed with DMD were recruited from the Neuromuscular Reference Centre UZ Leuven. Alongside, thirteen aged matched TD children were randomly recruited via family and acquaintances of the investigators. The insights into the early motor development of children with DMD could contribute to diagnosing the disease, optimizing the treatment of the children and the guidance of the parents.

During the second year of this master’s thesis the research protocol was tested on young children with DMD. The protocol had already been implemented in children with DMD, tests were performed in the NMRC UZ Leuven. In the scope of this master’s thesis, we only made a limited contribution to the testings of children with DMD. On the other hand, the TD children were recruited and tested independently by ourselves and later on checked by our supervisors through video recording. We also performed the complete data processing, statistical analysis and the academic writing process under supervision of our (co-)promotor.
REFERENCES


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<table>
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<th>Description</th>
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<tbody>
<tr>
<td>3MWT</td>
<td>3-Minute Walk Test</td>
</tr>
<tr>
<td>Bayley-III</td>
<td>Bayley Scales of Infant and Toddler Development, Third Edition</td>
</tr>
<tr>
<td>DMD</td>
<td>Duchenne Muscular Dystrophy</td>
</tr>
<tr>
<td>MFM-20</td>
<td>Motor Function Measures for Neuromuscular Diseases</td>
</tr>
<tr>
<td>NMRC</td>
<td>Neuromuscular Reference Centre</td>
</tr>
<tr>
<td>NSAA</td>
<td>North Star Ambulatory Assessment</td>
</tr>
<tr>
<td>PDMS-II</td>
<td>Peabody Developmental Motor Scale, Second Edition</td>
</tr>
<tr>
<td>PUL-2</td>
<td>Performance of Upper Limb, Second Edition</td>
</tr>
<tr>
<td>RFF</td>
<td>Rise From Floor</td>
</tr>
<tr>
<td>(R-)NSAA</td>
<td>(Revised) North Star Ambulatory Assessment</td>
</tr>
<tr>
<td>TD</td>
<td>Typically developing</td>
</tr>
<tr>
<td>TFTs</td>
<td>Timed Function Tests</td>
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<td>UZ Leuven</td>
<td>University Hospital Leuven</td>
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1. Abstract

**Background:** The main feature of Duchenne Muscular Dystrophy is progressive muscle weakness, which already starts early in life and leads to various motor problems.

**Objectives:** The study aim was to describe and evaluate early gross and fine motor development in young DMD children (0-5 years) in comparison with TD children, using different motor evaluation scales.

**Participants:** Thirteen DMD and age matched TD children, between 11m-5y11m old, were tested with different motor evaluation scales.


**Results:** Significant differences were found between scores of DMD and TD children on both gross and fine motor subdomains of Bayley-III (p = 0.0027) and PDMS-II (p = 0.0001). Both evaluation scales show lower scores on the gross motor subdomain in comparison with the fine motor subdomain. Another significant difference was found on the (Revised)NSAA (p = 0.0004) and MFM-20 (p = 0.001). For the TFTs only a significant difference was found in the subdomain “Rise From Floor” (p = 0.0006). No significant difference between DMD and TD children was found on the 3MWT (p = 0.06). Results of PUL-2 show significant differences between DMD and TD children on “PUL Shoulder” (p = 0.01) and “PUL Wrist” (p = 0.005). However, no significant difference was found on “PUL Elbow” (p = 0.10).

**Conclusion:** Young DMD children score lower on both gross and fine motor skills compared with TD children. These early motor symptoms of DMD children should be recognized early in life, so diagnosis can be made earlier and treatment can be started on time.
2. Introduction

Duchenne Muscular Dystrophy (DMD) is the second most prevalent neuromuscular disorder (Emery & Muntoni, 2003), affecting up to 1/3300-6000 live males worldwide (Deconinck & Dan, 2007). It is an X-linked inherited neuromuscular disorder causing mutations in the dystrophin gene. Due to this mutation, the main feature is progressive muscle weakness, which starts in the lower limbs and can lead to gait problems. At a later stage, the muscles of the upper limbs also become affected. Finally, the heart and respiratory muscles will degenerate as well (Worton et al., 2001). In addition to motor disorders, DMD is also accompanied by cognitive, behavioural and language disorders (Ciafaloni et al., 2009; Connolly et al., 2013; Cyrulnik et al., 2007, 2008).

Notable clinical features of DMD include symptom onset early in life, usually at 2 or 3 years of age. Gait disturbances and delayed motor development are early presenting symptoms. A “honeymoon” period, between ages 3 and 6 years, during which there may be transient improvements, may occur. However, following the honeymoon period, clinical deterioration is noted, and by the age of 13 the patient is usually wheelchair-bound (Desai & Gerard, 2013).

An accurate and early diagnosis of DMD plays a crucial role in the effective management of patients: it has the potential to lead to earlier intervention, appropriate genetic counselling, treatment with mutation-specific therapies (where applicable) and appropriate assignment to clinical trials (Aartsma-Rus et al., 2019). However, reports indicate that significant delays in diagnosis of DMD persist (Birnkrant et al., 2018; Ciafaloni et al., 2009). For instance, Ciafaloni et al. (2009), noted that the first signs and symptoms of DMD occur at a mean age of 2.5 years but that definitive diagnosis is only made at the mean age of 4.9 years.

An important key factor for the delayed diagnosis is the lack of information on the natural history of young DMD children. As already mentioned above, many DMD children show early signs and symptoms of developmental delay and inability to develop certain motor abilities, such as running fast or jumping. However, due to the “honeymoon period” between 3 and 6 years, these early symptoms are often underestimated or overlooked by families and physicians. A second important factor for the delayed diagnosis is the absence of an appropriate motor evaluation.
scale for young children with DMD. There are several evaluation scales to assess the early gross and fine motor development in typically developing (TD) infants and young children.

A widely used instrument is the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III). Another tool used to map gross and fine motor development is the Peabody Developmental Motor Scale, Second Edition (PDMS-II). These generic tools are based on normal development. However, a previous pilot study has shown that the hierarchy of the motor items is not always applicable in children with DMD who often achieve milestones later or in a different order than TD children. Therefore, a number of condition-specific motor evaluation scales have specifically been developed for children with DMD, in particular the North Star Ambulatory Assessment (NSAA) and the Performance of Upper Limb Measure for DMD (PUL-2). Other frequently used scales in DMD children are walking tests (3MWT) and Timed Function Tests (TFTs) (Mazzone et al., 2010). The Motor Function Measure for Neuromuscular Disease (MFM-20) was specifically developed for younger children, with a focus on neuromuscular functioning. However, all above mentioned condition specific tests often used in DMD are only applicable from the ages of 3-4. None of these scales chart the different developmental domains of DMD children from the ages 0-5.

In conclusion, still little is known about the early motor development of DMD children between the age of 0 and 5 years old. Signs and symptoms are often not recognized by parents, caregivers and medical professionals. Alongside, treatment forms are most effective early in development. This warrants the need for therapeutic clinical trials in younger DMD children, i.e. when the disease is still in the early phase. As a first step, it is important to gain more insights in the specific problems in gross and fine motor development at very early ages to enhance the recognition of these problems by parents, caregivers and medical professionals and to delineate early treatment interventions.

Therefore, the aim of this study was to describe and evaluate early gross and fine motor development in infants and young children with DMD aged between 0 and 5 years, in comparison with TD children using different available motor evaluation scales.
3. Method

3.1. Participants

Participants were recruited from the Neuromuscular Reference Center of the University Hospital Leuven (NMRC UZ Leuven), between the period of January 2018 – January 2019. The children had to meet the following inclusion criteria: age between 0 and 5.99 years, diagnosed with DMD and the ability to perform the test procedure. If the parents were interested to cooperate, they received an informed consent with further information. If they agreed to participate, the researcher contacted the parents to make specific agreements about the planning and organization.

In addition, a healthy control group was randomly recruited with the help of friends, family and acquaintances. These TD children were selected based on age, matching the already recruited children with DMD. These children were recruited in April 2019. Children with a cognitive, motor or language delay were excluded. If the parents and the child agreed to participate, an informed consent was signed by the parents.

For both groups, a written informed consent (appendix 1) in accordance with the Declaration of Helsinki, was signed prior to participation. The study was approved by the local ethics committee (Commissie Medische Ethiek UZ - KU Leuven - SS59068) (appendix 2).
3.2. Test procedure

The children with DMD were tested by two examiners, i.e.: 1) physiotherapist, M. Van den Hauwe, of the NMRC UZ Leuven who carried out the tests during standard evaluations at the consultation and 2) physiotherapist, J. Hoskens, with support of R. Loos and M. Vandecruys who performed the tests at the children’s home. Depending on the age of the children, the appropriate motor evaluation scales were used (Table 1). The average duration of testing per child was 2 hours.

The testing of the TD children was performed by R. Loos and M. Vandecruys at the children’s home during a 2-hour session. Each testing was recorded by video so that our supervisors could control the quality.

3.3. Outcome measures

3.3.1. Primary outcome measures

Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III): The Bayley-III aims to map the development of infants and children from 16 days to 42 months old and consists of five different ordinal scales. The five domains that are evaluated are: cognition (91 items); language, subdivided into receptive communication (49 items) and expressive communication (46 items); motor skills, subdivided into fine (66 items) and gross motor skills (72 items); social-emotional development (35 items) and adaptive behaviour (241 items). The last two domains are evaluated via parent questionnaires. The scale has been proven to be reliable and valid (Bayley et al., 2006; Deroma et al., 2013; Pearson, 2015).

In the scope of this study the focus was on the Bayley-III motor assessment, including scaled scores (median: 10; IQR: 5-15) for gross and fine motor development as well as a composite score (median percentile: 50) (Connolly et al., 2013). The gross motor part contained items which measured movements of the limbs and torso and static positioning. The fine motor skills’ subtests consisted of items that assessed comprehension and visual perceptual-motor integration.
Peabody Developmental Motor Scales, Second Edition (PDMS-II): This ordinal scale evaluates gross and fine motor skills in infants and young children from 0 to 6 years. In total, the scale contains 98 items (Chien et al., 2009; Tavasoli et al., 2014). There are six subdomains, namely: reflex, static, locomotion, object manipulation, grasping and visuomotor integration. Raw scores on the different subdomains were calculated into scaled scores (median: 10; IQR: 5-15) and by doing so converted to percentile scores (median percentile: 50). The scale has been proven to be reliable and valid (Folio et al., 2000).

3.3.2. Secondary outcome measures

Motor Function Measure for Neuromuscular Diseases (<7 years) (MFM-20): The MFM-20, for children aged 2 to 6 years, consists of 20 gross motor items about: standing, transfers, axial and proximal motor functioning and more distal motor skills. These items are scored on an ordinal scale ranging from a minimum of 1 to a maximum of 3. High inter- and intra-rater reliability and good discriminant validity were found for the MFM-20 (De Lattre et al., 2013).

(Revised) North Star Ambulatory Assessment (NSAA): The NSAA is a functional scale about gross motor skills developed especially for ambulatory DMD children older than 5 years. Seventeen different items are assessed, each item being scored on an ordinal scale of 0-2. There is a modified version for children aged 3 to 5 years (Mercuri et al., 2016). The scale has been proven to be reliable and valid (De Sanctis et al., 2014; Eagle et al., 2007; Mazzone et al., 2009).

Timed Function Tests (TFTs): The Timed Function Tests are four timed tasks: Rise From Floor (RFF), 10-meter run, Climbing four stairs (“Stairs up”), and Descending four stairs (“Stairs down”). The children must perform these tasks as quickly as possible. The speed and quality of the execution of the tasks is assessed (Mazzone et al., 2010). For this test norm values were collected in Flemish TD children between 2.5 and 6 years old. However, Nagy et al. (2019) proved TFTs to have a lower test-retest reliability than 3MWT.
3-Minute Walk Test (3MWT): This is a shortened version of the 6-Minute Walk Test (6MWT). It is mainly used in young children for whom the 6MWT is too difficult, due to the long distance. The 3MWT measures the distance the child can walk in three minutes at a normal pace and on a flat surface. This test provides more information about the submaximal functional mobility and endurance in ambulatory DMD children. The 3MWT has been found reliable (Goemans et al., 2013). For the 3MWT test norm values were also collected in Flemish TD children between 2.5 and 6 years old.

Performance of Upper Limb Measure for DMD 2.0 (PUL-2): The PUL-2 is specifically developed for DMD children from 3 years and older. The test examines upper limb function on three levels: shoulder (12 items), elbow (17 items) and wrist (13 items), with each item being scored on an ordinal scale of 0-2. The PUL-2 has a very good reliability (Duong, T., 2016).

3.3.3. Overview tests per age

Depending on the age of the child, different tests were used. Table 1 gives an overview of the different tests based on age.

Table 1: overview test per age

<table>
<thead>
<tr>
<th>Age</th>
<th>Gross motor</th>
<th>Fine motor</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3.5 years</td>
<td>Bayley-III</td>
<td>Bayley-III</td>
</tr>
<tr>
<td>0-6 years</td>
<td>PDMS-II</td>
<td>PDMS-II</td>
</tr>
<tr>
<td>2-6 years</td>
<td>MFM-20</td>
<td></td>
</tr>
<tr>
<td>2.5-6 years</td>
<td>3MWT TFTs</td>
<td></td>
</tr>
<tr>
<td>3-3.5/4 years</td>
<td>(R)NSAA</td>
<td></td>
</tr>
<tr>
<td>3-6 years</td>
<td>PUL-2</td>
<td></td>
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</table>
3.4. **Statistical analysis**

Descriptive statistics were used to document subject characteristics. Data distribution was checked by the Shapiro-Wilk test and visual inspection of the data. Because of the normal distribution for age, length and weight, independent sample T-tests (two paired) were used to compare both samples. Based on the Shapiro Wilk test, data distribution and the sample size (n < 30), non-parametric statistics were chosen for the motor outcome measures. For the Bayley-III and PDMS-II scaled scores were used based on reference values. These scaled scores were converted to percentile scores. Therefore, we had the possibility to categorize every child based on standard deviations. Following categorization was used: children who deviated more than 1 SD, which corresponds with a percentile score <16, were categorized “at risk”; and children who deviated more than 2SD, which corresponds with a percentile score <5, were categorized in the category “deviant development”. For the MFM-20, NSAA, TFTs, 3MWT and PUL-2 raw scores were used. These scaled and raw scores of the children with DMD were compared with the control group of TD children via the Mann-Whitney U test.

Statistical analysis was performed in SPSS 25 and the significance level of 0.05 was applied.
4. Results

4.1. Participants

This study included thirteen DMD children between 0 and 5 years old (mean age: 3.69y; ± Std: 1.54).

The mean length was 97.78 centimeters (± 11.86 cm) and mean weight was 16.20 kilograms (± 4.79 kg). There were three types of mutations reported within the DMD group: 80% was diagnosed with a deletion, 10% with a duplication and another 10% with a frameshift. Furthermore, thirteen age matched TD children between 0 and 5 years (mean age: 3.66y; ± Std 1.51) were included as a control group. The mean length was 102 centimeters (± 12 cm) and mean weight was 16.47 kilograms (± 3.95). No significant differences were found between the DMD and TD group regarding age, height and weight.

Table 2 in appendices gives an overview of the participant characteristics.

All the children of the DMD and TD group (n = 26) were evaluated by the PDMS-II. Alongside, the younger children (<42 months) also completed the Bayley-III (n = 13). Twenty-four children were evaluated by the MFM-20, twenty children by the NSAA, nineteen children by the TFTs, twenty by the PUL-2 and nineteen by the 3MWT.
4.2. **Comparison DMD and TD children**

4.2.1. **Bayley-III**

The six DMD children younger than 42 months scored significantly lower than the seven TD children, both on gross motor ($p = 0.0027$) and fine ($p = 0.0027$) Bayley-III subdomains. In the DMD group, lowest scaled scores were achieved in the gross motor subdomain (median: 4; IQR: 2.75-5.25), in comparison to the fine motor subdomain (median: 5; IQR: 2.75-8.25). All six DMD children scored below percentile score 5 in both subdomains, and thus can be categorized as “deviant development”. On the other hand, all seven TD children scored better than expected on the Bayley-III, with a median percentile score of 89.

Figure 1 illustrates the Bayley-III scaled scores per subdomain per group, based on median of the scaled scores and IQR (P25-75).
4.2.2. PDMS-II

Thirteen DMD children were tested with the PDMS-II; again DMD children scored significantly lower than TD children on all five subdomains ($p=0.0001$). Lowest scaled scores were achieved in the subdomain “Locomotion” (median: 4; IQR: 4.00-4.50). Regarding the individual scores in this subdomain, two children scored “at risk” with a percentile score lower than 16. All other children ($n=11$) scored below percentile 5 and therefore can be categorized as “deviant developing”. The subdomain “Object Manipulation” (median: 6; IQR: 5.00-6.75) achieved the second lowest scaled scores with seven children scoring below percentile 16 and the other four children scoring below percentile 5. The third lowest subdomain was “Stationary” (median: 7; IQR: 6.00-8.00); In this subdomain six children scored below percentile 16 and two children achieved a percentile score lower than 5. The fine motor subdomains “Grasping” (median: 8; IQR: 6.00-10.00) and “VMI” (median: 8; IQR: 6.00-9.50) had the best scaled scores. In the subdomain “Grasping”, only two children scored below percentile 16 and three children scored below percentile 5. In the category “VMI” only one child scored below percentile 16 and two children scored below percentile 5.

The thirteen TD children, tested by the PDMS-II, scored all above average on all five subdomains. Highest scores were achieved in the subdomain “VMI” (median: 13; IQR: 10.25-14.00) with all TD children scoring a percentile score $>50$.

Figure 2 provides a visualization of the PDMS-II scaled scores per group, based on median of the scaled scores and IQR (P25-75).
4.2.3. MFM-20, (R-)NSAA, TFTs, 3MWT and PUL-2.0

Regarding the MFM-20 scores of the twelve DMD children and twelve TD children, significant differences were found between both groups (p = 0.001), with a disadvantage for the DMD group (median: 52; IQR: 48.50-56.50). None of the DMD children scored a maximal score on the MFM-20. In the control group (median: 60; IQR: 57.50-60.00), eight out of twelve children achieved a maximal score.

Another significant difference (p = 0.0004) was noticed in the scores in the (R-)NSAA, collected from ten DMD children (median: 21; IQR: 17.50-25.00) and ten TD children (median: 34; IQR: 31.00-34.00). None of the DMD children achieved a maximal score, however, eight out of ten TD children did.

Regarding the scores of the TFTs, no significant differences were found between the seven DMD children and the ten TD children when performing the “Climbing four stairs” (p = 0.08) and “Descending four stairs” (p = 0.14). Despite the non-significant difference, DMD children were slower on the “Climbing four stairs” (median: 2.96; IQR: 2.43-5.21) compared with the TD children (median: 2.29; IQR: 1.99-3.33). Only seven out of thirteen DMD children were able to perform this subtest.

Alongside, no significant difference was found between the scores of the nine DMD children and the ten TD children on the “10-meter run” (p = 0.05). However, a trend toward significant difference was seen, with DMD children (median: 5.71; IQR: 4.40-6.93) clearly needing more time to run 10 meters than the TD children (median: 3.81; IQR: 3.38-5.02) did. Again on this subtest, one DMD child was not able to perform this test.

In the item “Rise From Floor”, a significant difference was seen between the DMD group (n = 9) and control group (n = 10) (p = 0.0006).
On the 3MWT, no significant difference was found between the walking distance of DMD children (n = 7) and TD children (n = 12) (p = 0.06). Regarding the scores of the DMD group (median: 158.00; IQR: 135.00-187.00) the maximum distance, achieved by the oldest child, was 200 meters. In comparison, the maximal distance achieved by the oldest child in the TD group (median: 185.70; IQR: 166.50-263.25) was 300 meters.

Results on the PUL-2 scale varied given the different subtests. A significant difference between the eight DMD children and twelve TD children was found on the “PUL Shoulder” and “PUL Wrist” (p = 0.01 and p = 0.005). However, there was no significant difference for the “PUL Elbow” (p = 0.10), only a negative tendency for the DMD group. Regarding individual scores, only a DMD child achieved maximal scores on the “PUL Shoulder” (median: 9; IQR: 8.00-11.00), “PUL Elbow” (median: 15; IQR: 14.00-16.75) and “PUL Wrist” (median: 11; IQR: 7.50-12.00). These results are in strong contrast with the control group, in which nine out of twelve children achieved maximal scores on the “PUL Shoulder” (median: 12; IQR: 10.50-12.00) and “PUL Elbow” (median: 17; IQR: 15.50-17.00) and ten children achieved a maximal score on the “PUL Wrist” (median: 13; IQR: 13.00-13.00). Four DMD children did not complete the PUL-2 because of age < 3 years and a DMD child was not able to perform the test due to fatigue and a lack of motivation.

Median and IQR (P25-75) scores of the MFM-20 (A), NSAA (B), TFTs (C), 3MWT (D) and PUL-2 (E) are provided in boxplots in figure 2.

Table 3 in appendices gives an overview of amount of DMD children who completed the test, median scores, IQR (P25-75), p-value and amount of DMD children who scored below percentile 16 or percentile 5 for: Bayley-III, PDMS-II, NSAA, MFM-20, PUL-2, 3MWT and TFTs.
Figure 1: Boxplots with t-bars of the scaled scores Bayley-III gross (in red) and fine (in blue) motor (in red) subdomain (shows median and IQR)
* BaFMSgs: Bayley fine motor scaled scores, BaGMgs: Bayley gross motor scaled scores, DMD: DMD group, NORM: norm group

Figure 2: Boxplots with t-bars of the scaled scores of PDMS-II subdomains: Stationary (in blue), Locomotion (in red), Object Manipulation (in green), Grasping (in orange) and Visual Motor Integration (in yellow) (shows median and IQR)
*PeSTss: PDMS-II Stationary scaled scores, PeLOss: PDMS-II Locomotion scaled scores, PeOMss: PDMS-II Object Manipulation scaled scores, PeGRss: PDMS-II Grasping scaled scores, PeVMIss: PDMS-II Visual Motor Integration scaled scores *dotted line: scale score 10
A. MFM-20 raw scores per group with red dotted line as maximal score

B. NSAA raw scores per group with red dotted line as maximum score
C. TFTs raw scores per group with subdomains: Rise From Floor (in blue), Climbing four stairs (in red) and Descending four stairs (in green) in seconds and 10-meter run test (in orange) in meters

D. 3MWT raw scores in meters per group
E. PUL-2 raw scores with subdomains: PUL Shoulder (in blue), PUL Elbow (in red) and PUL Wrist (in green)

Figure 3: Boxplots with t-bars of the raw scores of MFM-20 (A), NSAA (B), TFTs (C), 3MWT (D) and PUL-2 (E) (shows median and IQR)
5. Discussion

The aim of this study was to gain insights in the early gross and fine motor development in young children (0-5 years) with DMD. Based on a comprehensive protocol of motor evaluation scales, in comparison with age matched TD children.

Specific problems in gross and fine motor development of young DMD children could play an important clinical role to enhance the recognition of the disease by parents, caregivers and medical professionals and to delineate early treatment interventions. The age of diagnosis has an important influence on the course of the disease, this because of treatments being most effective early in development. This fact warrants the need for therapeutic clinical trials in younger DMD children, i.e. when the disease is still in its early phase.

The most important outcome of this study was that all children diagnosed with DMD scored significantly lower on both gross and fine motor subdomains compared with TD children. In contrast, all TD children scored above average on all tests. This result is consistent with the findings of Connolly et al. (2013), who earlier found that DMD children, in comparison with TD children, showed less maturational improvements with age in gross and fine motor skills. Also Pane et al. (2013) found that motor skills of pre-school DMD children improved on a slower rate than those of TD children.

Within the gross and fine motor skills of the DMD children, we found that the scores on the gross motor subdomain were lower in comparison with the scores on the fine motor subdomain. This discrepancy between gross and fine motor development was in concordance with findings of Connolly et al. (2014), who concluded that DMD children scored significantly lower than TD children on the Bayley-III gross motor skills, whereas fine motor skills revealed a trend towards increase after one-year follow-up. This can be explained by the muscle degeneration starting in the lower limbs and causing difficulties with gross motor skills, e.g. walking and running (Worton et al., 2001). It is interesting to speculate that for this reason young DMD children prefer spending more time on activities that do not involve gross motor skills. Despite the fact that DMD children score higher on fine motor skills, in comparison with gross motor skills, their scores are not age
adequate. Yet, little is known about the fine motor development in young DMD children. However, Janssen, Bergsma, Geurts and De Groot (2014) confirm our findings that upper extremity activity limitations already occur early in the ambulatory phase. Limitations in the upper extremity are mainly expressed in: stiffness, pain and activity limitations, which cause difficulties in fine motor tasks. Therefore, upper extremity limitations are an important issue to be aware of. Caregivers should not only pay attention to the lower extremity, but also be attentive to upper limb activity (Janssen, Bergsma, Geurts, & De Groot, 2014).

The Bayley-III is the most widely used standardized measure in the clinical research and early intervention setting for children with developmental delay. A recent study of Miller et al. (2018) concluded that the Bayley-III scaled scores were lower in children with DMD compared with published controls. Also other previous studies investigated the use of the Bayley-III in children with DMD (Connolly et al., 2013, 2014). The findings of our study are similar to those of the above-mentioned literature. More specifically, we found that all DMD children who performed the Bayley-III scored below percentile score 5, meaning that all DMD children deviated more than 2 SD and can be categorized as “deviant development”. These low percentile scores were achieved both in gross and fine motor development. A possible explanation for these findings could be the fact that the Bayley-III is developed for TD children. Moreover, we found that DMD children fell out on specific items such as jumping, running and ball activities. Also Connolly et al. (2013) cited that DMD children gain gross motor skills and function over the first 7 years. However, the pace and the way of how they reach these motor milestones differ in comparison with TD children. Additionally, the Bayley-III can only be taken in children up to 42 months. DMD children will not achieve maximum scores at this age, resulting in lower scores than TD children. We believe that if it was capable to score beyond the “stop rule”, the DMD children could reach other items and thus obtain higher scores on the Bayley-III. Hence, a modified Bayley-III scale with an adjusted item order should be developed for this young DMD population.
Unlike the Bayley-III, the PDMS-II has not often been used with DMD children. Yet, we ascertained the same differences in gross and fine motor skills on the PDMS-II as found on the Bayley-III. First of all, an important note has to be made regarding the organization of the PDMS-II item orders. The item orders include very large steps, especially in the subdomain “Locomotion”. These large steps between the different items may be too difficult for all children and therefore cause an immediate stop in scoring. This might explain the fact that both DMD and TD children achieved lower scores on the “Locomotion” subdomain in comparison to the “VMI” subdomain, wherein highest scores were achieved in both groups.

Secondly, a remarkable finding was that TD children scored above average on all five subdomains. Therefore, we suggest that the reference values of the PDMS-II are not representative for our Flemish control group of TD children.

Despite the fact that the Bayley-III and PDMS-II are developed for TD children, an important advantage is that both tests can be performed in children younger than 3 years. This is not possible with the condition-specific motor evaluation scales, such as (R-)NSAA.

Regarding this (R-)NSAA, De Sanctis et al. (2014) and Mercuri et al. (2016) concluded that DMD children scored significantly lower in comparison with age matched TD children. These findings were confirmed by our study. Furthermore, we found that none of the DMD children achieved maximal scores. This lack of achieving maximal scores was confirmed by De Sanctis et al. (2014), who concluded that DMD children could never achieve full scores on the NSAA. A possible reason for this was that some items were not possible to perform at the age of 3 years but could be achieved at a later age, while other items were rarely achieved, irrespective of the age (De Sanctis et al., 2014). Despite the fact that the (R-)NSAA contains only DMD relevant items in motor development, which represents possible muscle weakness, DMD children will not achieve full scores compared to TD children. We might explain this discrepancy in the different scoring criteria, whereby DMD children use compensatory strategies, which is not consistent with a full score.
According to our findings on the TFTs, we stated that there were no significant differences between the scores of the DMD children and the TD children on following subtests of the TFTs: “Climbing four stairs” (p = 0.08), “Descending four stairs” (p = 0.14) and “10-meter run” (p= 0.05). These findings are in contrast with Martini et al. (2014), who found significant differences between DMD and TD children on the subtests “Climbing four stairs” and “Descending four stairs”. Also Mazzone et al. (2010, 2011 & 2013) found lower scores on the four different subtests of the TFTs with an increasing age. However, there is a trend towards significance in our study on the subdomains “Climbing four stairs” and “10-meter run”.

Regarding the subtest “Climbing four stairs”, a first possible reason for our conflicting findings could be the fact that children first develop the skill of descending a stair before climbing one. A second explanation may be that only seven DMD children performed this subtest which is a difference of three TD children (n = 10). This way, the limited number of children who performed this subtest might have influenced the results. Additionally, it is also important to note that children can use compensation strategies (e.g. using the handrail) and by doing so achieve higher scores on the “Climbing four stairs”.

Also for the trend towards significant findings on the “10-meter run test” we assume a number of possible reasons. Multiple previous studies, e.g. Dolgjo et al. (2011) and Goudriaan et al. (2018), investigated gait deviations in children with DMD. However, the minimum age of the included DMD children in most studies was 5 years. There is an important lack of research on gait deviations in young children with DMD. It might thus be possible that the gait of young DMD children does not show large differences with the gait of TD children. These assumptions correspond to earlier findings of Martini et al. (2014) which showed no significant differences between DMD and TD children on the “10-meter run” test at the initial assessment, whereas the results became significant on the 6- and 12-months follow-up testings. The older the DMD children were, the longer the time and the more compensatory movements they needed while walking. In addition, also here possible compensations might play an influencing role. Mazzone et al. (2010) noted the importance of individual differences in the progression of several variables (e.g. contractures, muscle imbalance, weight or height) as influencing factors for affecting specific aspects of function in these TFTs.
The only significant difference found in the TFTs was on the “Rise From Floor” subtest (p = 0.0006). The so called “Gower sign”, which implements that the child will go from lying to standing by the use of the upper extremity, is an important characteristic of the disease. Therefore, we hypothesized to find a significant difference between both groups.

The trend toward significant, seen in “Climbing four stairs” and “10-meter run”, was also found in the 3MWT (p = 0.06). Regarding maximal scores, there was a difference of 100 meters between both groups. A reason for the non-significant findings might be the small sample size (seven DMD children and ten TD children) that could have influenced the results.

Previous literature, such as Henricson et al. (2012) and McDonald et al. (2010), examined the scores of DMD children (4-12 years) on the 6MWT. These two studies found lower mean scores in DMD children than in healthy controls. However, in both studies no significant differences were found between both groups. During our study, we experienced that the 6MWT was rather long and intensive, causing loss of motivation and interest. Thus, we believe that a shorter version of this test, i.e. 3MWT, would be better to get a realistic picture of time parameters of a young DMD child.

The PUL-2 showed significantly differences between DMD and TD children on the subdomains “PUL Shoulder” and “PUL Wrist”. However, no significant differences were found in the “PUL Elbow”. Artilheiro et al. (2017) had already cited the proximal-to-distal degradation of upper limb strength. This proximal-to-distal degradation could be an explanation for the significant lower scores on the “PUL Shoulder” subdomain. In this subdomain, all items focus on shoulder strength, which is the first muscle group of the upper extremity that will lose strength. Contradictory to this fact, also significant differences were found on the “PUL Wrist”. However, it is important to notice that the subdomain “PUL Wrist” contains more items that require cognitive skills (e.g. pincer grasp, tracing path, writing, etc.). Previous literature has already examined that not only motor skills are affected in DMD children, but also cognitive, behaviourial and language problems can be present in the pathology (Ciafaloni et al., 2009; Connolly et al., 2013; Cyrulnik et al., 2007, 2008).
As already mentioned, the “PUL Elbow” shows a non-significant result. A possible explanation could be that the items of this subdomain are easier to perform and require less cognitive capacity.

In our study, we unfortunately had to deal with some insuperable limitations. First of all, one of the most important limitations of this study was the small sample size \((n = 13\) DMD; \(n = 13\) TD). We experienced that the comparison of one DMD child with one age matched TD child was both a strength and a limitation. Therefore, we recommend the comparison of one DMD child with more TD children of the same age in future research. This way, possible above average scores of TD children could be bypassed.

A second limitation that we encountered during our testings was the duration of the test moments. The average duration of testing per child was 2 hours. Especially for young children this is a long time to concentrate and be motivated. Therefore, children could lose interest and motivation. Besides this, also the environment was a possible disturbing factor, especially during the tests of the TD children at home. In some cases, there was not enough room for testing items or the parents/siblings distracted the child. In future studies, standardized test settings would be recommended in order to prevent possible environmental influences on test results. Alongside, we advise multiple test moments to eliminate fatigue or a lack of motivation due to long test durations.

A following limitation was that the received therapy or medication was not taken into account in our study. Physiotherapy, specific medication and other treatments may have had an influence on our test results. A reason for not taking this data into account was 1) a lack of information about this data and 2) the young age of the included DMD children, this with the background information that medical therapy often starts at an average age of 7 years old (Bushby et al., 2010). However, we assume that some children did receive therapy or other treatments. We want to emphasize that further research on the possible influence of early interventions, such as treatment and medication, on early motor development in DMD children is advisable.
The last important limitation concerned the comparison of the number of the conducted testings between both groups. We can state that TD children took more different testings in comparison to the DMD group. More specifically, we completed every possible testing based on the age of the child in TD children. However, this was not possible in the DMD children, this because of fatigue, lack of motivation, lack of understanding, inability of the child, muscle strength, etc. De Sanctis et al., 2014 also concluded that the assessments couldn’t always be completed because of cognitive delay or behavioural signs (attention deficit and hyperactivity disorder) that are present in a proportion of DMD children. Therefore an important recommendation for further research is that cognition and behaviour testing should also be included during the evaluation of motor development in young DMD children.
6. Conclusion

In conclusion, this study shows that all diagnosed DMD children scored lower on different motor evaluation scales compared to age matched TD children. Moreover, both gross and fine motor skills achieved lower scores in DMD children, whereas TD children scored above average on all motor evaluation scales. Despite the fact that the average age of diagnosis of DMD is around 4.9 years, gross and fine motor symptoms are already seen earlier in life but are often not recognized by parents, caregivers and medical professionals. Alongside, much attention is paid to problems in gross motor skills. However, we also found significant lower scores on fine motor skills. Therefore, we believe that more attention should be paid to fine motor development in young children with DMD. Furthermore, there is a need for large scaled clarification of the specific gross and fine motor problems in young DMD children, especially early in life. To detect these specific motor problems, adapted motor evaluation scales for young children with DMD should be developed.
7. List of references


8. Appendices

Table 2: Overview characteristics DMD group
Table 3: Overview results DMD group
Appendix 1: Informed consent
Appendix 2: Ethics committee
Appendix 3: Author guidelines
Appendix 4: Progress form
Appendix 5: Evaluation reports
Table 2: Overview characteristics DMD group

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<th>Mutation Place</th>
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Table 3: Overview results DMD group

Overview results DMD group (amount of DMD children who completed the test, median scores, IQR (P 25-75), p-value and amount of DMD children who scored below percentile 16 or percentile 5) for Bayley-III, PDMS-II, NSAA, MFM-20, PUL-2, 3MWT and TFTs.

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<th>IQR (P 25-75)</th>
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Appendix 1: Informed Consent

INFORMATIE- EN TOESTEMMINGSFORMULIER

Beste ouders,

Prof. Dr. Nathalie Geemans, Prof. Dr. Liesbeth De Waele, kinesitherapeute Marleen Van den Hauwe en psycholoog Joaana Willen van het Neuromusculair Referentiecentrum (NMRC) van het Universitair Ziekenhuis Gasthuisberg in Leuven, in samenwerking met Dr. Katrijn Klingels en kinesitherapeute Jasmine Hoskins van de Faculteit Bewegings- en Revalidatiewetenschappen van de KU Leuven, trachten een beter inzicht te verwerven in de vroege ontwikkeling van baby’s en jonge kinderen met ziekte van Duchenne, Duchenne Spierdystrofie is een ernstige erfelijke ziekte die de spieren langzaam aantast en verzwakt. De periode voor de leeftijd van 5 jaar wordt de presymptomatische fase genoemd, nochtans hebben verschillende studies aangetoond dat de eerste tekenen en symptomen van Duchenne Spierdystrofie optreden voor de leeftijd van 8 maanden. Duchenne spierdystrofie is vooral bekend vanwege de impact op het motorische domein, maar deze stoornis wordt ook geassocieerd met cognitieve, taal- en gedragsstoornissen. Er is echter nog maar heel weinig onderzoek gedaan omtrent de ontwikkeling van de jonge populatie jongens met Duchenne Spierdystrofie. Vervolgens is aangemoedigd dat verschillende therapien en thera pijlen te bekijken.

Binnen dit onderzoek zullen we daarom deze jonge groep jongens mee opvolgen en de verschillende ontwikkelingsdomeinen evalueren met verschillende leeftijdspecifieke evaluatieschalen per domein. Er bestaan reeds verschillende evaluatie-instrumenten om de vroege ontwikkeling van baby’s en jonge kinderen te evalueren, een veelgebruikt instrument zijn de Bayley Scales of Toddler and Infant Development, third edition (Bayley-III). Dit is een schaal voor kinderen van 15 dagen tot 42 maand en 15 dagen oud, die de ontwikkeling op 5 domeinen evalueren, namelijk cognitie, taal, motoriek, sociaal emotionele en adaptieve gedragsvaardigheden. Er bestaan tevens een aantal specifieke motorische meetschalen, die speciaal voor kinderen met DMD ontwikkeld zijn. Dit zijn onder meer de North Star Ambulatory Assessment (NSAA), Timed Function tests (TFTs), 3-min walk test (3MWLT), PUL-2.

Aangezien er voor de verschillende motorische meetschalen geen uniforme referentiewaarden bestaan, zijn we ook op zoek naar een groep typisch ontwikkelende jongens tussen 0 tot 6 jaar oud, die we rechtstreeks kunnen vergelijken met de jongens met Duchenne Spierdystrofie. Zo kunnen we nog beter het verschil in ontwikkeling en bereiken van mijlpalen in kaart brengen. We zouden deze jongens 1 keer evalueren. Op basis van de geboortedatum van uw zoon zal bekeken worden of hij in aanmerking komt om deel te nemen aan de studie en zullen de onderzoekers verder contact met u opnemen.

Amendement, december 2018
UZ Leuven—“Evaluatie van de vroege ontwikkeling bij baby’s en jonge kinderen met Duchenne Spierdystrofie.”

De evaluaties kunnen bij u thuis, in het kinderdagverblijf of indien van toepassing op de school van uw zoon plaatsvinden en zullen 1 tot 2u in beslag nemen. Indien nodig kunnen deze opgesplitst worden. Om kwaliteit van de testgegevens te garanderen zullen de evaluaties gefilmd worden en achteraf door 1 onderzoeker gescroord worden. De videofragmenten zullen na scoring meteen vernietigd worden. Tijdens deze evaluaties zal uw kind op een speelse manier uitgedaagd worden om te laten zien wat hij allemaal kan. Uit ervaring blijkt dat de meeste kinderen de speeltjes leuk vinden. Hieronder kan u een overzicht vinden met de mogelijke evaluatieschalen die gebruikt zullen worden tijdens dit onderzoeksproject. De meeste schalen zijn leeftijdgebonden en zullen ook niet allemaal elke zes maanden afgenomen worden. Op het einde zal uw kind een kleine attentie krijgen voor zijn medewerking.

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<td>PUL-2</td>
<td>NSAA</td>
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Amendement, december 2018
Implicaties deelname

Met dit schrijven wordt uw zoon gevraagd om deel te nemen aan de studie. Als u hierin toestemt, zullen wij verder contact met u opnemen om de evaluaties van uw zoon in te plannen.

Aan de deelname aan het project zijn geen risico's voor uw zoon verbonden. Het afnemen van de schalen is volledig niet-invasief en zal geen ongemakken veroorzaken. Elk kind heeft tevens het recht om elk ogenblik vragen te stellen over de tests en de testafname kan op elk moment gestopt of onderbroken worden. Hiervoor is geen geldige reden noodzakelijk en dit zal nooit in het nadeel van uw kind spelen. Deelname aan dit onderzoek volledig kosteloos.

Tot de leeftijd van 18 jaar hebben wij voor alle onderzoeksprojecten de toestemming van de ouders nodig om een kind vrijwillig te laten deelnemen aan dit project. Zonder uw expliciete instemming kan uw zoon niet deelnemen. U heeft het recht om de deelname te weigeren, en tevens om u te allen tijde terug te trekken.

Conform de EU Verordening 2016/679 (Algemene Verordening Gegevensbescherming) en de Belgische Wetgeving betreffende de bescherming van natuurlijke personen met betrekking tot de verwerking van persoonsgegevens, zal uw persoonlijke levenssfeer en deze van uw kind gerespecteerd worden. De hoofdonderzoeker, Prof. Dr. Goemans en mede-onderzoekers verzekeren dat de gegevens, gebruikt in het kader van dit onderzoek, gecodeerd zullen worden verwerkt zodat de privacy van u en uw kind ten allen tijde wordt gerespecteerd en gegarandeerd. Indien gewenst kan u de testgegevens van uw kind bij de onderzoekers opvragen. De resultaten van dit onderzoek worden minstens tot 5 jaar na publicatie bewaard zodat andere onderzoekers juistheid van de gegevens en verwerking kunnen controleren. De lokale Data Protection Officer kan gecontacteerd worden via gdr.research@uzleuven.be.

U heeft het recht om een klacht in te dienen over hoe uw informatie wordt behandeld, bij de Belgische toezichthoudende instantie die verantwoordelijk is voor het handhaven van de wetgeving inzake gegevensbescherming: Gegevensbeschermingsautoriteit (GBA)

Drukersstraat 35,
1000 Brussel
Tel. +32 2 274 48 00
e-mail: contact@apd-gba.be
Website: www.gegevensbeschermingsautoriteit.be

Deze studie werd geëvalueerd door de commissie medische ethiek van UZ Leuven die een gunstig advies heeft uitgebracht.

Amendement, december 2018
Conform de Belgische wet inzake experimenten op de menselijke persoon van 7 mei 2004, is de opdrachtgever foutloos aansprakelijk voor alle schade die de deelnemende patiënt en/of zijn rechthebbenden oplopen en die rechtstreeks dan wel onrechtstreeks verband houdt met de proef. De opdrachtgever van deze studie (KU Leuven) heeft een verzekering afgesloten die deze aansprakelijkheid dekt.

Indien we beroep mogen doen op uw medewerking, gelieve dan bijgevoegd toestemmingsformulier in te vullen en terug te bezorgen aan de klasleerkracht of rechtstreeks door te sturen naar Jasmine Hoskens:

Departement Revalidatiewetenschappen
t.a.v. Jasmine Hoskens
O&N IV Herestraat 49, bus 1510
3000 Leuven

Indien u nog vragen heeft, mag u ook steeds contact met ons opnemen via e-mail of telefonisch op 016/32.91.75.

Dank bij voorbaat voor uw bereidwillige medewerking.
Toestemmingsformulier voor het deelnemen aan wetenschappelijk onderzoek

Titel onderzoek:
‘Evaluatie van de vroege ontwikkeling bij baby’s en jonge kinderen met Duchenne Spierdystrofe’

Ik, ondergetekende, moeder/vader/voogd/wettelijke vertegenwoordiger (schrap wat niet past)

_________________________________________ (voornaam, naam), van
_________________________________________ (voornaam, naam kind)
_________________________________________ (geboortedatum kind)

verklaar hierbij in de mogelijkheid gesteld te zijn de informatie in dit formulier te lezen en vrij te kiezen om
mijn kind wel of niet te laten deelnemen aan dit onderzoek. Ik heb van deze informatie ook een eigen kopie
ontvangen en ga akkoord met de inhoud hiervan.

Ik ben geïnformeerd dat ik vrij ben om mijn medewerking aan het project in te trekken op gelijk welk ogenblik.
Ik begrijp dat alle gegevens strikt en vertrouwelijk behandeld zullen worden. De gecodeerde gegevens kunnen
deel uitmaken van wetenschappelijk publicaties of voorstellingen zonder evenwel de identiteit van mijn kind
keren te maken.

Gelieve ook uw persoonlijke contactgegevens hieronder aan te vullen, zodat wij u ten allen tijden kunnen
contacteren.

Tel: __________________________________________

E-mail: _______________________________________

Datum en handtekening ouder(s)/voogd/wettelijke vertegenwoordiger:

Datum en handtekening onderzoeker:

Ik, ondergetekende _____________________________ (naam onderzoeker), bevestig dat ik de nodige informatie in verband met
dit onderwerp heb verschaffen aan de verschillende partijen. Zij kregen een tevens persoonlijk een kopie van het informatieformulier en het
toestemmingsformulier werd ondertekend door de verschillende partijen. Ik ben steeds bereid om zo nodig aansluitende informatie te
geven en/ of vragen te beantwoorden. Er zal geen druk op het kind uitgeoefend worden om aan de studie deel te nemen. Ik verklaar dat ik
werk volgens de ethische principes beschreven in de verklaring van Helsinki en de Belgische wet van 7/5/2004 over proeven op mensen.

Amendement, december 2018
Toestemmingsformulier voor het deelnemen aan wetenschappelijk onderzoek

Titel onderzoek:
‘Evaluatie van de vroege ontwikkeling bij baby’s en jonge kinderen met Duchenne Spierdystrofie’

Ik, ondergetekende, moeder/ vader/ voogd/ wettelijke vertegenwoordiger (schrap wat niet past)

__________________________________________________________ (voornaam, naam), van
__________________________________________________________ (voornaam, naam kind)
__________________________________________________________ (geboortedatum kind)

verklaar hierbij in de mogelijkheid gesteld te zijn de informatie in dit formulier te lezen en vrij te kiezen om
mijn kind wel of niet te laten deelnemen aan dit onderzoek. Ik heb van deze informatie ook een eigen kopij
ontvangen en ga akkoord met de inhoud hiervan.
Ik ben geïnformeerd dat ik vrij ben om mijn medewerking aan het project in te trekken op gelijk welk ogenblik.
Ik begrijp dat alle gegevens strikt en vertrouwelijk behandeld zullen worden. De gecodeerde gegevens kunnen
deel uitmaken van wetenschappelijk publicaties of voorstellingen zonder evenwel de identiteit van mijn kind
kenbaar te maken.

Gelieve ook uw persoonlijke contactgegevens hieronder aan te vullen, zodat wij u ten allen tijden kunnen
contacteren.

Tel: ______________________________________________________

E-mail: ______________________________________________________

Datum en handtekening ouder(s)/ voogd/ wettelijke vertegenwoordiger:

Datum en handtekening onderzoeker:

Ik, ondergetekende ____________________________ (naam onderzoeker), bevestig dat ik de nodige informatie in verband met
deze studie heb verschaft aan de verschillende partijen. Zij kregen een tevens persoonlijk een kopij van het informatieformulier en het
toestemmingsformulier werd ondertekend door de verschillende partijen.
Ik ben steeds bereid om zo nodig aanvullende informatie te geven en/ of vragen te beantwoorden. Er zal geen druk op het kind
uitgeoefend worden om aan de studie deel te nemen. Ik verklaar dat ik werk volgens de ethische principes beschreven in de verklaring
van Helsinki en de Belgische wet van 7/5/2004 over proeven op mensen.

Amendement, december 2018
Appendix 2: Ethics committee

'Evaluation van de vroege ontwikkeling bij baby’s en jonge kinderen met Duchenne Sjouderatrofië.'

Betreft: Amendement studie: SS9068: 'Evaluation van de vroege ontwikkeling bij baby’s en jonge kinderen met Duchenne Sjouderatrofië'

Geachte,

Hieronder kan u de antwoorden op de opmerkingen betreffende het amendement van onze studie SS9068: 'Evaluation van de vroege ontwikkeling bij baby’s en jonge kinderen met Duchenne Sjouderatrofië' vinden. In bijlage werden ook de aangepaste, geamendeerde documenten toegevoegd. De extra wijzigingen op basis van onderstaande opmerkingen werden in het grijs gemaakt.

Protocol amendement versie oktober 2018

1) Graag hadden we toelichting ontvangen omtrent de rekrutering van deze 20 controle-deelnemers (age matched).

TOELICHTING: We zullen hiervoor kinderdagverblijven en kleuterscholen aanschrijven met de vraag informatie- en toestemmingssformulieren uit te delen. Uit de groep kinderen wiens ouders toestemming verlenen zullen we op basis van de geboortedata kinderen selecteren. De matching op leeftijd gebeurt met max. drie maanden rond de kalenderleeftijd van de jongen met Duchenne. We zullen 3 gezonde kinderen selecteren per Duchenne jongen. We opteren voor meerdere subjecten per Duchenne jongen om selectie bias te voorkomen. Een extra document ter informatie en toestemming voor de directie van kinderdagverblijven en scholen werd aangemaakt en toegevoegd in bijlage.

Tevens zullen de evaluaties van de typisch ontwikkelende jongens gebeuren door meerdere onderzoekers. Om de kwaliteit van de data te garanderen, opteren we daarom om de evaluaties van deze kinderen te filmen en achteraf door 1 persoon te laten controleren en scoren. De videofragmenten zullen na scoring meteen vernietigd worden.

Deze informatie werd ook toegevoegd aan het protocol en het ICF document voor de ouders.

ICF ouders versie oktober 2018:

1) De versienummering doorheen de verschillende pagina’s is niet correct. Gelieve dit aan te passen.

ANTWOORD: De versienummering werd aangepast in het bijgevoegde ICF document.

2) Wordt er een vergoeding voorzien voor de deelnemer en gespendeerde tijd en die van hun ouders? Gelieve dit te vermelden in het ICF.

ANTWOORD: Er wordt geen vergoeding voorzien voor de deelnemers en hun ouders, daar we niemand hiermee onder druk willen zetten. De kinderen krijgen wel een kleine attentie voor hun medewerking. Dit laatste werd toegevoegd in bijgevoegde ICF document.

3) In het kader van de GDPR adviseren we om de volgende aanpassingen te implementeren in het informatie- en toestemmingsformulier:

a. De verwijzing naar de wet van 8 december 1992 dient vervangen te worden door de verwijzing naar de EU Verordening 2016/679 (Algemene Verordening
Gegevensbescherming) en de Belgische Wetgeving betreffende de bescherming van
natuurlijke personen met betrekking tot de verwerking van persoonsgegevens.

**ANTWOORD:** Dit werd toegevoegd in het bijgevoegde ICF document.

b. De contactgegevens van de lokale Data Protection Officer dienen vermeld te worden
(voor UZ Leuven is dit: gdpr.research@uzleuven.be).

**ANTWOORD:** Deze contactgegevens werden toegevoegd in bijgevoegde ICF document.

c. Onderstaande paragraaf omtrent de GBA dient toegevoegd te worden:

"U heeft het recht om een klacht in te dienen over hoe uw informatie wordt
behandeld, bij de Belgische toezichthoudende instantie die verantwoordelijk is voor
het handhaven van de wetgeving inzake gegevensbescherming:

Gegevensbeschermingsautoriteit (GBA)
Drukkersstraat 35,
1000 Brussel
Tel. +32 2 274 48 00
E-mail: contact@opd-gba.be
Website: www.gegevensbeschermingsautoriteit.be"

**ANTWOORD:** Deze gegevens werden toegevoegd in het bijgevoegde ICF document.

d. Graag ook de opdrachtgever identificeren/lokaliseren als verwerkings-
verantwoordelijke.

**ANTWOORD:** In bijgevoegd ICF document werd toegevoegd dat de
hoofdonderzoeker, Prof. Dr. Goemans en mede-onderzoekers verzekeren dat de
gegevens, gebruikt in het kader van dit onderzoek, gecodeerd zullen worden verwerkt
zodat de privacy van de kinderen ten allen tijde gegrondereerd blijft.

De hoofdonderzoeker heeft kennis genomen van de geamendeerde documenten en heeft geen
wetenschappelijke noch ethische bezwaren. Tevens zullen er geen onderzoekskosten ten laste gelegd
worden van de patiënt, de ziekteverzekering of het ziekenhuis.

Met de meeste hoogachting,

[Signature]

Prof. Dr. N Goemans (hoofdonderzoeker)

Volgende aangepaste documenten werden in bijlage toegevoegd:
- Informatie- en toestemmingsformulier voor de ouders (typisch ontwikkelende kinderen)
- Onderzoeksprotocol
- Informatiebrief voor directie van kinderdagverblijven en scholen
Appendix 3: Author guidelines

https://www.elsevier.com/journals/neuromuscular-disorders/09608966/guide-for-authors
### Appendix 4: Progress form

<table>
<thead>
<tr>
<th>DATUM</th>
<th>INHOUD OVERLEG</th>
<th>HANDTEKENINGEN</th>
</tr>
</thead>
</table>
| 23/01/18 | Weer productie | Promotor:  
Cpromotor/Begeleider:  
Student(e):  |
| 27/01/18 | Initiatief | Promotor:  
Cpromotor/Begeleider:  
Student(e):  |
| 12/02/18 | Oorsprong materiaal | Promotor:  
Cpromotor/Begeleider:  
Student(e):  |
| 28/02/18 | Onderzoeks metingen | Promotor:  
Cpromotor/Begeleider:  
Student(e):  |
| 02/03/18 | Onderzoeks metingen | Promotor:  
Cpromotor/Begeleider:  
Student(e):  |
| 09/03/18 | Onderzoeks werking | Promotor:  
Cpromotor/Begeleider:  
Student(e):  |
|         |               | Promotor:  
Cpromotor/Begeleider:  
Student(e):  |
|         |               | Promotor:  
Cpromotor/Begeleider:  
Student(e):  |
|         |               | Promotor:  
Cpromotor/Begeleider:  
Student(e):  |
In te vullen door de promotor(en) en eventuele copromotor aan het einde van MP2:

<table>
<thead>
<tr>
<th>Naam Student(e):</th>
<th>Datum:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Titel Masterproef:</td>
<td></td>
</tr>
</tbody>
</table>

1) Geef aan in hoeverre de student(e) onderstaande competenties zelfstandig uitvoerde:
   - NVT: De student(e) levert hierin geen bijdrage, aangezien hij/zij in een reeds lopende studie meewerkt.
   - 1: De student(e) was niet zelfstandig en sterk afhankelijk van meestudent(e) of promotor en teamleden bij de uitwerking en uitvoering.
   - 2: De student(e) had veel hulp en ondersteuning nodig bij de uitwerking en uitvoering.
   - 3: De student(e) was redelijk zelfstandig bij de uitwerking en uitvoering.
   - 4: De student(e) had weinig tot geringe hulp nodig bij de uitwerking en uitvoering.
   - 5: De student(e) werkte zeer zelfstandig en had slechts zeer sporadisch hulp en bijsturing nodig van de promotor of zijn team bij de uitwerking en uitvoering.

<table>
<thead>
<tr>
<th>Competenties</th>
<th>NVT</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opstelling onderzoeksvraag</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Methodologische uitwerking</td>
<td></td>
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</tr>
<tr>
<td>Data-acquisitie</td>
<td></td>
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<tr>
<td>Data management</td>
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<tr>
<td>Dataverwerking/Statistiek</td>
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<tr>
<td>Rapportage</td>
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</tr>
</tbody>
</table>

2) Niet-bindend advies: Student(e) krijgt toelating/geen toelating (schrappen wat niet past) om bovenvermelde Wetenschappelijke stage/masterproef deel 2 te verdedigen in bovenvermelde periode. Deze eventuele toelating houdt geen garantie in dat de student geslaagd is voor dit opleidingsonderdeel.

3) Deze wetenschappelijke stage/masterproef deel 2 mag wel/niet (schrappen wat niet past) openbaar verdedigd worden.

4) Deze wetenschappelijke stage/masterproef deel 2 mag wel/niet (schrappen wat niet past) opgenomen worden in de bibliotheek en docserver van de UAntwerpen.

Datum en handtekening Student(e) 28/05/19

Datum en handtekening promotor(en) 29/05/19

Datum en handtekening Co-promotor(en) 28/05/19
In te vullen door de promotor(en) en eventuele copromotor aan het einde van MP2:

<table>
<thead>
<tr>
<th>Naam Student(e):</th>
<th>Datum:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taal:</td>
<td>Nederlands</td>
</tr>
<tr>
<td>Titel Masterproef:</td>
<td>Early motor development in children with Achondroplasia muscular dystrophy</td>
</tr>
</tbody>
</table>

1) Geef aan in hoeverre de student(e) onderstaande competenties zelfstandig uitvoerde:
   - NVT: De student(e) leverde hierin geen bijdrage, aangezien hij/zij in een reeds lopende studie meewerkte.
   - 1: De student(e) was niet zelfstandig en sterk afhankelijk van medestudent(e) of promotor en teamleden bij de uitwerking en uitvoering.
   - 2: De student(e) had veel hulp en ondersteuning nodig bij de uitwerking en uitvoering.
   - 3: De student(e) was redelijk zelfstandig bij de uitwerking en uitvoering.
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<table>
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<th>Competenties</th>
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<th>5</th>
</tr>
</thead>
<tbody>
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<tr>
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<tr>
<td>Rapportage</td>
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<td></td>
</tr>
</tbody>
</table>

2) Niet-binderend advies: Student(e) krijgt toelating/geen toelating (schrappen wat niet past) om bovenvermelde Wetenschappelijke stage/masterproef deel 2 te verdedigen in bovenvermelde periode. Deze eventuele toelating houdt geen garantie in dat de student geslaagd is voor dit opleidingsonderdeel.

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4) Deze wetenschappelijke stage/masterproef deel 2 mag wel/niet (schrappen wat niet past) opgenomen worden in de bibliotheek en docserver van de UHasselt.

<table>
<thead>
<tr>
<th>Datum en handtekening Student(e)</th>
<th>Datum en handtekening promotor(en)</th>
<th>Datum en handtekening Co-promotor(en)</th>
</tr>
</thead>
<tbody>
<tr>
<td>28/05/19</td>
<td>29/05/19</td>
<td>28/05/19</td>
</tr>
</tbody>
</table>
Auteursrechtelijke overeenkomst

Ik/wij verlenen het wereldwijde auteursrecht voor de ingediende eindverhandeling:
**Early Motor Development in Children with Duchenne Muscular Dystrophy**

**Richting:** master in de revalidatiewetenschappen en de kinesitherapie-revalidatiewetenschappen en kinesitherapie bij kinderen

Jaar: **2019**

in alle mogelijke mediaformaten, - bestaande en in de toekomst te ontwikkelen - , aan de Universiteit Hasselt.

Niet tegenstaand deze toekenning van het auteursrecht aan de Universiteit Hasselt behoud ik als auteur het recht om de eindverhandeling, - in zijn geheel of gedeeltelijk -, vrij te reproduceren, (her)publiceren of distribueren zonder de toelating te moeten verkrijgen van de Universiteit Hasselt.

Ik bevestig dat de eindverhandeling mijn origineel werk is, en dat ik het recht heb om de rechten te verlenen die in deze overeenkomst worden beschreven. Ik verklaar tevens dat de eindverhandeling, naar mijn weten, het auteursrecht van anderen niet overtredt.

Ik verklaar tevens dat ik voor het materiaal in de eindverhandeling dat beschermd wordt door het auteursrecht, de nodige toelatingen heb verkregen zodat ik deze ook aan de Universiteit Hasselt kan overdragen en dat dit duidelijk in de tekst en inhoud van de eindverhandeling werd genotificeerd.

Universiteit Hasselt zal mij als auteur(s) van de eindverhandeling identificeren en zal geen wijzigingen aanbrengen aan de eindverhandeling, uitgezonderd deze toegelaten door deze overeenkomst.

Voor akkoord,

Loos, Rosanne  Vandecruys, Marieke

Datum: **11/06/2019**