Summary
Most children with spastic cerebral palsy (CP) have a deviating gait pattern, and one of the typical patterns is a flexed knee gait. Children who walk with a flexed knee gait are specifically at risk of deteriorating in mobility. To prevent this (potential) deterioration, treatment is indicated at an early stage. It is postulated that the cause of this gait pattern is attributable to a combination of abnormal involuntary muscle activity (such as spasticity), muscle weakness and/or reduced muscle length. In this, spasticity is defined as ‘a motor disorder characterized by a velocity-dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex, as one component of the upper motor neuron syndrome’. This is clinically recognisable as a velocity-dependent increase in muscle tone in response to muscle stretch, demonstrated at a certain angle in the range of motion (ROM).

The presence and severity of spasticity and other impaired muscle functions vary per patient. Nonetheless, characteristic for all patients with CP is that the impairments are not equally spread throughout their muscles. This results in a muscle imbalance, for instance in an agonist-antagonist couple (such as flexor-extensor) there is generally more spasticity and/or shortening in one muscle than in the other. Treatment of this muscle imbalance is considered to be the main prerequisite for a potential improvement in mobility. The treatment rationale is therefore to aim at decreasing the muscle activity in spastic (usually flexor) muscles, stretching the shortened (usually flexor) muscles, and strengthening the weakened (usually extensor) muscles at the same time. To decrease spasticity, botulinum toxin type A (BTX-A) can be injected in the muscle, and a comprehensive rehabilitation treatment, consisting of intensive physical therapy, orthosis and serial casting, can be used to train the weaker extensor muscles, stretch the shorter flexor muscles and increase mobility.

In this thesis it was hypothized that treatment with multilevel BTX-A and comprehensive rehabilitation will improve spasticity, muscle length and the flexed knee gait pattern, which in turn is hypothized to improve activities in the domain
Summary

of mobility. Multilevel BTX-A treatment refers to the injection of multiple muscles (around the hip, knee and ankle) within one treatment session, and is particularly indicated for children with a gait which is characterized by flexion of the knee in midstance. For the evaluation of spasticity, an appropriate measurement instrument was needed. Since the characteristics of patients with CP differ widely, it is likely that certain patients will benefit more than others from multilevel BTX-A and comprehensive rehabilitation.

This thesis therefore evaluates:

1. the available instruments for the clinical assessment of spasticity in children with CP, and their compliance with the velocity-dependent concept of spasticity (Chapter 2)
2. the reliability of a new instrument for the clinical assessment of spasticity in children with CP (Chapter 3)
3. the effects of multilevel BTX-A and comprehensive rehabilitation on spasticity, muscle length and gait pattern in children with CP who walk with a flexed knee gait (Chapter 4)
4. the effect of multilevel BTX-A and comprehensive rehabilitation on mobility in children with CP who walk with a flexed knee gait (Chapter 5)
5. the predictors of multilevel BTX-A and comprehensive rehabilitation on gait pattern and mobility in children with CP who walk with a flexed knee gait (Chapter 6)

The most widely accepted definition of spasticity was formulated by Lance in 1980. In this definition, he defined spasticity as the clinical symptom of a velocity-dependent increase in muscle tone at passive stretch. Elaborating on this definition to include a clinical assessment of spasticity implies grading the intensity of the muscle tone and comparing it at different passive velocity stretches. Although ignored in Lance’s definition, the patient’s testing posture and
the initial length from which the muscle is stretched are both of significant influence on spasticity.

Chapter 2 presents the results of a critical review of the various clinical instruments that are used to evaluate spasticity in children with CP. The purpose of this study was to evaluate whether these clinical instruments assess spasticity in accordance with the velocity-dependency as defined by Lance, and whether these assessments are properly standardized. The various clinical instruments were identified through systematic literature searches, and evaluated on: 1) whether the assessment was made at different standardized velocities of passive stretch, 2) whether a standardized testing posture was defined, and 3) how spasticity was quantified.

Thirteen clinical spasticity assessment instruments were identified and evaluated. Most of these instruments, including the mostly frequently used Ashworth Scale (AS) and the Modified Ashworth Scale (MAS), do not comply with the concept of spasticity, as defined by Lance. They grade muscle tone only at one (often non-specified) velocity of passive stretch. Only the Tardieu Scale (TS) measures the velocity-dependent increase in muscle tone and compares the intensity and the angle of appearance of the increased muscle tone at (three) different velocities. However, these velocities have not been fully standardized. With respect to the standardised posture, the TS assesses patients in two positions: sitting and lying. With respect to quantification, the TS produces separate scores for both tone intensity and ROM at different velocities. However, these are used ambiguously by different users.

In conclusion, only the original TS is a suitable instrument for the assessment of spasticity, since it grades muscle tone intensity and ROM at three different velocities. However, the original testing protocol has a comprehensive and time-consuming clinical scoring system.
Although the velocity-dependent characteristic of spasticity can only be studied by stretching the muscle at two different velocities, e.g. slow and fast, it is especially important to test spasticity with a fast passive stretch. This makes it possible to detect the dominant phenomenon of spasticity: the ‘catch’, a sudden appearance of increased resistance in response to a fast passive stretch at a certain angle before the end ROM, which stops the movement immediately. Based on this rationale, a new spasticity assessment instrument was developed, the Spasticity Test (SPAT), which was based on the TS.

Chapter 3 describes the feasibility and reliability of the SPAT in five leg muscles. With this instrument, the muscle is first passively stretched at a slow velocity (≥ 3 seconds) to measure the maximum ROM. Spasticity is then assessed during a passive stretch at a fast velocity (< 1 second) to measure the joint angle of the catch (AOC) and to grade the intensity of the muscle resistance on a 4-point (0,1,2,3) spasticity scale. The SPAT has a standardized testing protocol describing the patient and observer position for each muscle tested, as well as describing the ROM and AOC measurement, using hand-held goniometry.

Twenty children with a diagnosis of spastic paresis were included in this study. They were all tested three times on one day by two different observers. In each session, the ROMs of five leg muscles were assessed (hamstrings, short adductors, soleus, gastrocnemius and rectus femoris muscles), after which spasticity was assessed with the spasticity scale and the AOCs. In all the tests the goniometry was performed by a third observer. Reliability was expressed in absolute agreement (AA) (only for the spasticity scale), and in Intraclass Correlation Coefficients (ICCs) and Standard Errors of Measurement (SEMs).

The SPAT was easy to administer, and the assessment was performed in 5 to 8 minutes. The intra-rater reliability was good for the hamstrings, soleus and gastrocnemius muscles (ROM: SEM range 2.9’ - 5.1’, spasticity scale: AA 70% - 95%, AOC: SEM 4.8’ - 6.4’). When the spasticity scale was simplified to a 2-point (0,1) scale rating the absence or presence of a catch, the intra-rater reliability was
also good for the adductor muscle, but not for the rectus femoris muscle. The inter-rater reliability was only good for the gastrocnemius muscle (ROM: SEM 4.0°, spasticity scale: AA 65%, AOC: SEM 3.6°). These results show that repeated SPAT measurements should be performed by the same trained examiner. In conclusion, when applied by one examiner, the new SPAT is a feasible and reliable clinical instrument to measure spasticity for all of the leg muscles studied, except for the rectus femoris muscle. To improve inter-rater reliability, we suggest that a special training programme for examiners should be developed, and that the velocity of the stretch should be further standardized by means of a measurement device.

Chapters 4 and 5 present the results of a multi-centre randomized controlled trial on the effect of multilevel BTX-A injections and comprehensive rehabilitation in children with CP who walk with a flexion pattern. Forty-six children were included in this study. The inclusion criteria were: diagnosis of CP; ability to walk (with or without a walking aid or an ankle-foot orthoses); gait characterized by persistent flexion of the knee in midstance; age between 4 and 12 years; spasticity in two or more leg muscles interfering with mobility; with an indication for multilevel BTX-A. The children were randomly assigned to the intervention or the control group. The intervention group was treated with multilevel BTX-A injections and comprehensive rehabilitation. The comprehensive rehabilitation consisted of a 12-week period of intensive physical therapy according to a standardized protocol, orthoses and, if necessary (i.e. if the ROM of the gastrocnemius muscle was less than 0° dorsiflexion), serial casting. Children in the intervention group were assessed twice during a 6-week baseline period, and there were 4 follow-up measurements at 6, 12, 24 and 48 weeks after the injections. The control group continued to receive usual care (low intensity physical therapy, some used orthoses) for a period of 18 to 30 weeks. They were assessed every 6 weeks. After this baseline period, the children in the control group were also treated with
multilevel BTX-A and comprehensive rehabilitation, with a follow up at 6, 12, 24 and 48 weeks after treatment.

Chapter 4 first evaluates the effect of multilevel BTX-A and comprehensive rehabilitation on gait pattern, muscle length and spasticity, as opposed to usual care. For the purpose of this study, the effect in the intervention group (n=23) up to 24 weeks after treatment was compared with the effect of usual care in the control group (n=23).

The gait pattern was evaluated with the Edinburgh Visual Gait Analysis Interval Testing (GAIT) scale. Knee angle at midstance, ankle angle at midstance, knee angle at terminal stance, and hip rotation at terminal swing were also measured. Muscle length and spasticity were assessed with two components of the SPAT; the ROM during a slow passive stretch (>3 sec) and the AOC during a fast (<1 sec) passive stretch, respectively.

After 6 weeks there was a significant improvement in the quality of the gait pattern (1.7 points improvement on the GAIT score, \( p < 0.01 \)) and in the gait kinematics during mid stance (7° improved knee extension, \( p < 0.01 \)) and terminal swing (5° improved knee extension, \( p < 0.01 \), and 4° improved hip rotation, \( p = 0.02 \)). The 7° improvement in knee extension at mid stance, in particular, was found to be clinically relevant. No effect was found at 24 weeks, but it is likely that this second assessment was too late to demonstrate sustained improvement, because no gait assessment was performed at 12 weeks. A significant effect in muscle length was found at 6 weeks: muscle length improved in the hamstrings (9°, \( p < 0.01 \)) and in the gastrocnemius muscles (5°, \( p < 0.01 \)), and both improvements were maintained up to 24 week after treatment. These changes were found to be clinically relevant. No change was found in the length of the rectus femoris and adductor muscles, but since these muscle lengths were both normal at baseline this was to be expected. A reduction in spasticity was found at 6 and 12 weeks in the injected hamstrings (11°, \( p < 0.01 \)) and gastrocnemius muscles (6°, \( p = 0.01 \)).
could be expected because of the pharmacological mechanism of BTX-A, which is known to be only temporary. An additional effect was found in the uninjected soleus muscles (5°, \( p = 0.02 \)), which could be due to diffusion of BTX-A from the injected gastrocnemius muscle.

Based on the results of this study, multilevel BTX-A and comprehensive rehabilitation (as opposed to usual care) is effective in improving gait pattern, increasing the muscle length of shortened muscles and decreasing spasticity in injected muscles in children who walk with flexed knees. Of these effects, only the effect on muscle length was still present after 24 weeks.

Subsequently, Chapter 5 evaluates the effectiveness of multilevel BTX-A injections and comprehensive rehabilitation on mobility. For the purpose of this study, the effect in the intervention group (n=23) up to 24 weeks after treatment was compared with the effect of usual care in the control group (n=23) (e.g. trial analysis). The uncontrolled long-term effect at 48 weeks after treatment was also evaluated within the total group (n=46) (e.g. before-after analysis). Finally, subgroup analysis for the level of Gross Motor Function Classification System (GMFCS) and age were performed to detect differences in treatment effect between the groups.

The primary outcome for mobility was the Gross Motor Function Measure-66 (GMFM66). The secondary outcomes were the energy cost of walking (measured in a sub-group of 21 children) and a parent self-reported problem score (0-10 scale).

The trial analysis showed a significant treatment effect on mobility (GMFM66) in favour of the intervention group at 12 and 24 weeks (2.1, \( p = 0.02 \) and 3.5 points, \( p < 0.01 \) respectively). This was also found on the problem score (-1.8 and -1.7 points, \( p < 0.01 \) respectively). The effect on both outcomes were considered to be clinically relevant. No treatment effect was found on energy cost. The before-after analysis also showed long-term (i.e. 48 weeks after treatment) effects on these outcomes (GMFM-66 2.3 points, \( p < 0.01 \); PS -1.4 points, \( p < 0.01 \)), and there was also a long-
term significant effect on energy cost (-1.8 J/kg/m, \( p < 0.01 \)). However, these long-term findings should be confirmed in a randomized controlled study. With respect to the effect on energy cost 48 weeks after treatment, it was found that children who used walking aids (GMFCS level III) improved significantly more than children walking without aids (GMFCS levels I and II). A possible explanation for this is that children in the latter group seem to be non-responsive to change in energy cost because their energy cost is already low, although it is higher than that of healthy children.

Based on the results of this study, multilevel BTX-A and comprehensive rehabilitation (as opposed to usual care) is an effective method of treatment that leads to clinically relevant improvements in mobility, in terms of GMFM-66 score and parent-perceived mobility problems, in children who walk with flexed knees. Conversely, it does not effect the energy cost of walking.

Patients with spastic CP are very heterogeneous with respect to the severity of impaired muscle functions, localisation of the motor disorder, and the severity of motor involvement. Therefore, it is likely that certain patients will benefit more than others from multilevel BTX-A and comprehensive rehabilitation. Chapter 6 describes a study in which an attempt was made to identify predictors for a favourable outcome of multilevel BTX-A injections and comprehensive rehabilitation on gross motor function (measured with the Gross Motor Function Measure (GMFM66)) and gait pattern (assessed according to the knee angle at midstance) in children who walk with a flexed knee gait. For this purpose, we used follow-up data (6, 12, 24 and 48 weeks after treatment) from the total group (n=46) in the randomized controlled trial as described in chapters 4 and 5. All in the literature suggested factors were considered to be possible predictors of outcome: age, gender, severity of motor involvement, localisation of the motor disorder, level of motor function, muscle strength, ROM, spasticity, and gait kinematics.
Of all the potential predictors, only age and ankle angle at midstance were found to be predictive of an improvement in gross motor function and gait pattern, respectively. Age was associated in such a way that the treatment had a better medium-term (12 weeks) effect on older children, increasing with 0.4 points on the GMFM66 per year of the child’s age (on condition that other factors remain unchanged). This finding was considered to be clinically relevant. Ankle angle at midstance was associated with gait pattern in such a way that the best long-term (48 weeks) effect was found in children with increased ankle dorsal flexion. However, the 0.21° increase towards knee extension, which results from a 1° increase in ankle dorsiflexion, was not clinically relevant. The predictive power of the different models was weak, explaining less than 20-40% of the total variance. Moreover, none of the potential predictors gender, severity of motor involvement, localisation of the motor disorder, ROM, and spasticity were found predictive for any outcome at any of the different follow-up points.

Based on these results, the only relevant significant predictor for a favourable response of multilevel BTX-A injections and comprehensive rehabilitation in this patient group, with regard to gross motor function, is older age.

In Chapter 7 provides the general discussion. Several methodological considerations and aspects of outcome assessment were discussed and the effectiveness of the multilevel BTX-A injections and comprehensive rehabilitation was evaluated. It was concluded that a combined treatment package of multilevel BTX-A and comprehensive rehabilitation is effective in obtaining improvements in mobility in children with CP who walk with a flexed knee gait. With regard to the clinical assessment of spasticity, it was concluded that the velocity-dependent increased resistance to passive stretch should always be assessed by measuring the muscle response at two different velocities of muscle stretch. Furthermore, chapter 7 discussed the clinical implications, and formulated recommendations for future research.