Adults with spastic cerebral palsy

Studies on effects of botulinum toxin A, walking function and gait analysis outcomes

Doctoral thesis
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(Maria 10 år)

LIST OF PAPERS

I Walking ability and predictors of performance on the 6-minute walk test in adults with spastic cerebral palsy. Maanum G, Jahnsen R, Frøslie KF, Larsen KL, Keller A. *Developmental Medicine and Child Neurology 2010, 52: e126–e132.*

II Effects of botulinum toxin A in ambulant adults with spastic cerebral palsy: A randomized double-blind placebo controlled trial. Maanum G, Jahnsen R, Stanghelle JK, Sandvik L, Keller A. *Journal of Rehabilitation Medicine 2011, 43: 338-347.*

III Face- and construct validity of the Gait Deviation Index in adults with spastic cerebral palsy. Maanum G, Jahnsen R, Stanghelle JK, Sandvik L, Larsen KL, Keller A. *Journal of Rehabilitation Medicine 2011 Dec 21 [Epub ahead of print]*.

IV Ambulant adults with spastic cerebral palsy: The validity of lower limb joint angle measurements from sagittal video recordings. Larsen KL, Maanum G, Frøslie KF, Jahnsen R. *Gait and Posture 2011 Oct 4 [Epub ahead of print]*.

SUMMARY

Background: Several studies have shown that adults with cerebral palsy (CP) are in risk of a premature walking deterioration. Adults with CP who experience reduced walking ability may benefit from clinical programs aimed to prevent deterioration and to maintain or improve function.

Overall a**im:** The overall purpose was to investigate the effects of lower limb botulinum toxin A (BoNT-A) injections in a selected population of ambulant adults with spastic CP, to study their walking ability and capacity, and to study the validity of two gait analysis outcomes, in order to contribute to clinically relevant knowledge about this group.

Designs: The studies presented in *Papers I*, *III* and *IV* were cross-sectional. The study presented in Paper *II* was a 16-week single centre, randomized double-blind placebo-controlled trial (RCT).

Material: Participants were recruited through advertisements. Inclusion criteria were: uni- or bilateral spastic CP, age between 18 to 65 years, Gross Motor Function Classification System (GMFCS) levels I-III, reduced walking ability compared to that of adolescence as confirmed by a semi-structured interview, and no intellectual disability. For *Paper IV*, 10 assessors were recruited from the clinic.

Methods: The International Classification of Functioning, Disability and Health (ICF) was used as a framework. *Paper I:* Walking function and factors predicting functional walking capacity were studied. Data included: Demographics, GMFCS, Functional Mobility Scale (FMS), questionnaire concerning walking ability, interview data, 6-minute walk test (6MWT), Borg scale, muscle tone, muscle strength, popliteal angle, Timed Up and Go (TUG) test, pain, fatigue, type of CP, and the presence of foot deformity. Statistical analyses: Bivariate analyses, including Kruskal-Wallis test and one-way analysis of variance (ANOVA), univariate- and multiple linear regression analyses. *Paper II:* The effects of BoNT-A were studied using predefined events from Three-dimensional gait analysis (3DGA) sagittal kinematics and the Short Form 36 (SF-36) as primary outcomes, and the Visual Analogue Scale (VAS) of perceived muscle-stiffness/spasticity, 6MWT, TUG test, and overall self-reported therapy effects (Global Scale) as secondary outcomes. 66 individuals received injections of either BoNT-A (n=33) or placebo (n =33). Statistical analyses: Paired sample t-test, analysis of covariance (ANCOVA), Fischer's exact test with relative risk and risk difference. *Paper III:* The validity of GDI was studied relative to the GMFCS, TUG test, 6MWT, and the Physiological Cost Index (PCI). Statistical analyses: ANOVA, and Pearson's or Spearman's correlation coefficients (r). *Paper IV:* The concurrent validity of measuring joint angles from video recordings was studied by comparing joint angles measured from sagittal video recordings with simultaneously recorded 3DGA sagittal kinematics. Statistical analyses: Agreement was assessed by Bland-Altman plots with mean differences and 95% limits of agreement (LoA). Scatter plots with Pearson's r were used supplementary.

Results: *Paper I:* The advertisement resulted in 201 responders, 126 of whom fulfilled the eligibility criteria and agreed to participate. This study included 53 men and 73 women, mean age (standard deviation (SD)) 39 (12) years; 59 with unilateral and 67 with bilateral spastic CP. GMFCS level I, n=12; level II, n=94; level III, n=20. The mean (SD) distance on the 6MWT was 485 (95) meters. FMS scores reflected independent walking performance in daily life; however 39% of the participants had reduced one GMFCS level since adolescence.

Multiple regression analyses identified gender, type of CP, popliteal angle, pain, and TUG test as significant predictors for 6MWT distance.
Papers II and *III*: The study sample was 30 men and 36 women, mean age (SD) 37 (11) years); 30 with unilateral and 36 with bilateral spastic CP. GMFCS level I, *n*=9; level II, *n*=48; level III, *n*=9. *Paper II:* No significant differences were found between the groups for the primary outcomes. BoNT-A injections demonstrated effects superior to the placebo on VAS muscle stiffness/spasticity and the Global Scale, but no differences between groups were found for 6MWT and TUG test. No serious adverse events occurred. *Paper III:* GDI had a similar distribution as shown for comparable study populations of children (mean (SD) =74.3 (11.6) in the 66 adults with CP and 101.1 (8.8) in the reference population of 50 healthy adults). A statistically significant difference in GDI was found between the reference population and GMFCS level I ($p<0.001$), between level I and II ($p<0.001$), but not between level II and III ($p=0.633$). The correlation coefficient (*r*) between GDI and 6MWT, TUG test and PCI were 0.30, -0.30, and -0.56, respectively.
Paper IV: The overall mean differences in degrees between joint angles measured by 3DGA and video recordings (3º, 5º and 7º for the hip, knee and ankle respectively) and corresponding LoA (18º, 10º and 15º for the hip, knee and ankle, respectively) demonstrated substantial discrepancies between the two methods. The correlations (*r*) ranged from low (0.39) to moderate (0.68).

Conclusions and implications:
Self-reported walking ability in adolescence compared with current GMFCS classification indicated a shift in GMFCS level for 39% of the participants. CP-related neuromuscular deficits, pain and gender were identified as factors predicting functional walking capacity. The results indicated that walking disability in high-functioning adults with spastic CP includes several factors that may be modified by systematic care and specific rehabilitation programs.

No short-term effects of BoNT-A treatment were found, compared with the placebo for any of the objective outcomes, but treatment effects were shown in favour of BoNT-A on the subjective outcomes. As part of a multidisciplinary treatment program, BoNT-A may be a potential management strategy in selected adults with spastic CP.

The GDI seemed to be a valid measure of overall gait in adults with spastic CP, thus demonstrating its potential as a research tool in this group. Low associations between GDI and TUG or 6MWT indicated the importance of using supplementary outcomes.

Quantifying lower limb joint angles from sagittal video recordings in ambulant adults with spastic CP differed from concurrent 3DGA kinematics and as such did not reflect the real sagittal joint position. This has implications for selecting the gait evaluation method.

Overall, these studies may contribute to new knowledge useful for developing and establishing mobility care and rehabilitation programs for adults with spastic CP and increasing walking difficulties. Hopefully, these studies have enlightened the complexity involved in studying walking disability in adults with spastic CP and the need for further studies to develop evidence-based general and specific health services for this population.

ABBREVIATIONS AND DEFINITIONS

BP	Bodily pain (SF-36)
BoNT-A	Botulinum toxin A
CI	Confidence interval
CP	Cerebral palsy
CONSORT	Consolidated Standards of Reporting Trials
EVGS	Edinburgh Visual Gait Score
EMG	Electromyography
GDI	Gait Deviation Index derived from 3DGA kinematics
FMS	Functional Mobility Scale
FSS	Fatigue Severity Scale
GMFCS	Gross Motor Functional Classification System
GMFM	Gross motor function measure
HRQOL	Health-related quality of life
ICF	International Classification of Functioning, Disability and Health
KLL	Kerstin L. Larsen
LoA	Limits of Agreement
m or mm.	Musculus or musculi
MAS	Modifed Ashworth Scale
MCID	Minimal clinical important difference
p	Page or pages
PCI	Physiological Cost Index
r	Pearson's or Spearman's correlation coefficient
RCT	Randomized controlled trial
ROM	Range of motion
SCPE	Surveillance of Cerebral Palsy in Europe
SD	Standard deviation
SF-GT	Salford Gait Tool
SF-36	Medical Outcome Study Short Form 36
6MWD	6-minute walk test distance
6MWT	6-minute walk test
SunRH	Sunnaas Rehabilitation Hospital
3DGA	Three-dimensional gait analysis
TUG	Timed Up and Go
U	Allergan unit
VAS	Visual Analogue Scale
VGA	Video gait analysis
WHO	World Health Organization

Gait: The manner or style of walking [19 (p. 43)].

Gait event: Points of the gait cycle, such as initial contact, which occurs when first contact is made between the foot and ground; peak stance, which occurs during the stance phase with maximum ankle dorsal flexion or knee extension; and peak swing which occurs during the swing phase with maximum ankle dorsal flexion or knee flexion [15 (p. 42-3)].

International classification of functioning, disability and health (ICF) [16, 17]:
Body function and structures: The physiological functions of body systems (including psychological functions) or anatomical elements such as organs, limbs, and their components. Impairments are problems in body structure or functions like essential deviation or loss.
Activity: The execution of a task or action by an individual. Activity limitations are the difficulties an individual may have in executing activities.
Participation: The involvement in a life situation. Participation restrictions are the problems an individual may experience in involvement in life situations.
Personal factors: The background of an individual's life and living. They comprise features of the individual that are not components of a health condition or a state of health, e.g. gender, age, lifestyle, coping styles, personality characteristics and overall behavioural patterns.
Environmental factors: The physical, social and attitudinal environments in which people live and conduct their lives (including health care systems).

Mobility: How individuals move within their multiple environments of home, school, work, and community [180].

Kinematics: The branch of mechanics that studies motion without taking into account the forces that produce a motion (e.g. the movement of joints and segments of the body through space) [46 (p. 319)].

Spasticity: "A motor disorder characterized by a velocity-dependent increase in tonic stretch reflexes ('muscle tone') with exaggerated tendon jerks, resulting from hyperexitability of the stretch reflex, as one component of the upper motor neuron syndrome" [37 (p. 485)].

Symptom of muscle stiffness/spasticity: The individual's perception of muscle stiffness. In this thesis, it was understood as the symptom of muscle stiffness experienced during walking.

Walking: The execution of gait with or without canes, crutches, a rollator, or a similar walking device [1].

Walking function was understood in this thesis to cover the constructs of *capacity*, *capability* and *performance* [58]. While *walking capacity* may be defined as the individual's ability to execute walking "in a standardised, controlled environment," *walking capability* may be defined as the individual's ability to execute walking "in his/her daily environment, taking into account the physical environment," and more or less personal factors. *Walking performance* may be defined as what the individual "actually does do in his/her daily environment", taking into account both physical environmental-, social environmental-, as well as personal factors [58].

Walking ability/capability was understood in this thesis to cover the construct of walking *performance* [58].

1. INTRODUCTION

Why study adults with cerebral palsy (CP) and walking deterioration?

Studies have shown that several adults with CP experience prematurely reduced walking ability [1-5]. This might have implications for employment, independence, and quality of life. Adults with CP who experience reduced walking ability may benefit from clinical programs aimed to prevent deterioration and to maintain or improve function [2, 4-6].

This study was inspired by Jahnsen's doctoral thesis on adults with CP [6], and by limited knowledge concerning best clinical practice for adults with spastic CP reporting increasing stiffness and difficulties in walking. Jahnsen emphasised that although CP is a condition which spans a lifetime, there is no systematic follow-up after the age of 18 years. She also stated that her findings of a premature decline in walking function needed to be investigated in clinical studies. Clinical experiences with well functioning adults with spastic CP led to a curiosity concerning their reports of reduced walking ability and perceived increasing stiffness, and to which degree this "stiffness" was related to dynamic increased muscle tone.

Knowledge from other patient groups may be used in issues concerning "activity" and "participation". However, we need specific knowledge about adults with CP concerning impairments, the effects of interventions, and valid assessment tools for gait and walking in order to establish evidence-based specific clinical programs for this group [7, 8]. The studies included in this thesis investigated walking ability, walking capacity, and the effects of lower limb BoNT-A injections in a selected population of adults with spastic CP (Papers I-II). The validity of two gait analysis outcomes was also studied (Papers III-IV).

Selected study population and conceptualisation of spastic CP

CP implies a motor dysfunction resulting from an early onset brain lesion [9-11]. One of the striking features of the CP diagnosis is its variability in clinical manifestations and aetiologies [10, 12]. This study included adults with spastic CP experiencing reduced walking ability. Perceived increase in walking difficulty as compared to adolescence, and no intellectual impairment (normal schooling), were essential inclusion criteria. Considering the musculoskeletal impairments involved in spastic CP, this thesis conceptualised spastic CP as a spastic paresis health condition [13 (p.353-6), 14 (p.215-6), 15 (p. 89-98)].

International Classification of Functioning, Disability and Health (ICF)

The ICF was published by the World Health Organization in 2001 [16]. In addition to providing a classification system, the ICF offers a conceptual framework for understanding functioning and disability as caused by a health condition involving a) body functions and -structures, b) the ability to do an activity, and c) participation in society [17, 18]. As Figure 1 indicates, the ICF views functioning and disability as outcomes of the interactions between the domains of body functions and -structures, activity and participation; personal and environmental factors are seen as modifying factors [17]. Thus, functioning is an umbrella term encompassing all *body functions*, *activities* and *participation*. Similarly, disability serves as an umbrella term for *impairments* of body functions/body structures, *activity limitations* and *participation restrictions*.

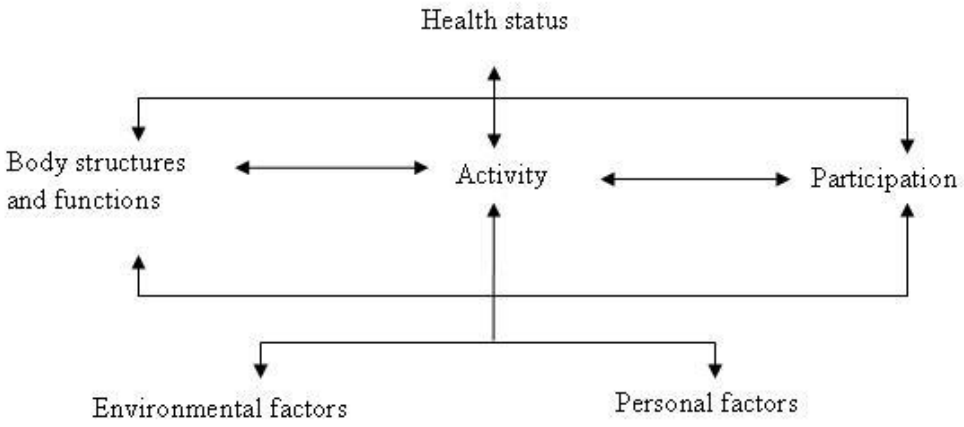

Figure 1. The International Classification of Functioning, Disability and Health (ICF)

This thesis used the ICF framework to categorise the investigated constructs and to understand and discuss the results [17, 18]. Gait was defined as the manner or style of walking ("body function") [19 (p.43)], and walking as the execution of gait ("activity and participation").

2. BACKGROUND

2.1. Cerebral palsy (CP)

Definition, causes, classification, and epidemiology

Cerebral palsy (CP)

CP refers to a clinical description rather than an aetiological diagnosis [9, 11, 20]. As a diagnostic term, CP is used to describe a group of motor syndromes resulting from disorders of early brain development [9-11].

In 2000, a working group from 14 collaborating centres in the Surveillance of Cerebral Palsy in Europe (SCPE) provided a consensus definition of CP, a decision tree for the diagnostic procedure, and a classification tree (Figure 2) for CP sub-types [11]. The SCPE definition of CP includes the following five key elements: i*) CP is a group of disorders, i.e. it is an umbrella term; ii) it is permanent but not unchanging; iii) it involves a disorder of movement and/or posture and of motor function; iv) it is due to a non-progressive interference/ lesion/abnormality; v) this interference/lesion/abnormality is in the developing/ immature brain.* Since it was published, this SCPE's definition of CP has been implemented among paediatricians in Norway and used when registering children in the Cerebral Palsy Registry of Norway [12]. This was also the definition of CP used in this thesis.

CP implicates heterogeneous conditions with regards to aetiology, pathophysiology, impairment types and severity [9, 10]. The aetiologies of CP ' are still inadequately understood, but the most frequently seen pathophysiologies are periventricular white matter lesions, cortical lesions, deep grey matter lesions and maldevelopments [9-11, 15 (p.67-83)]. The clinical manifestations depend on the extent and type of brain damage, the location, the time and the ability of the central nervous system to adapt or reorganise after the insult [10, 12, 15 (p.67-83)].

Classification

Categorisation or classification of CP subtypes has traditionally been based on the primary type of tone disorder and the distribution of the motor involvement [9, 11]. In this study, the CP subtypes were defined according to the SCPE's hierarchical classification tree, which classifies CP into three main subtypes: spastic, dyskinetic and ataxic (Figure 2) [11]. The subtype studied here was spastic CP. According to SCPE, s*pastic uni- and bilateral CP* are determined by the clinical manifestation of at least two of the following: i) abnormal pattern

of posture and/or movement; ii) increased muscle tone; iii) pathological reflexes [11]. In spastic unilateral CP, the limbs on one side of the body are involved, while the spastic bilateral CP subtype includes both the group with all four limbs involved and no walking function, and those with mainly bilateral lower limb impairment and walking function. In this study, the included individuals were those with spastic uni- or bilateral CP with walking function.

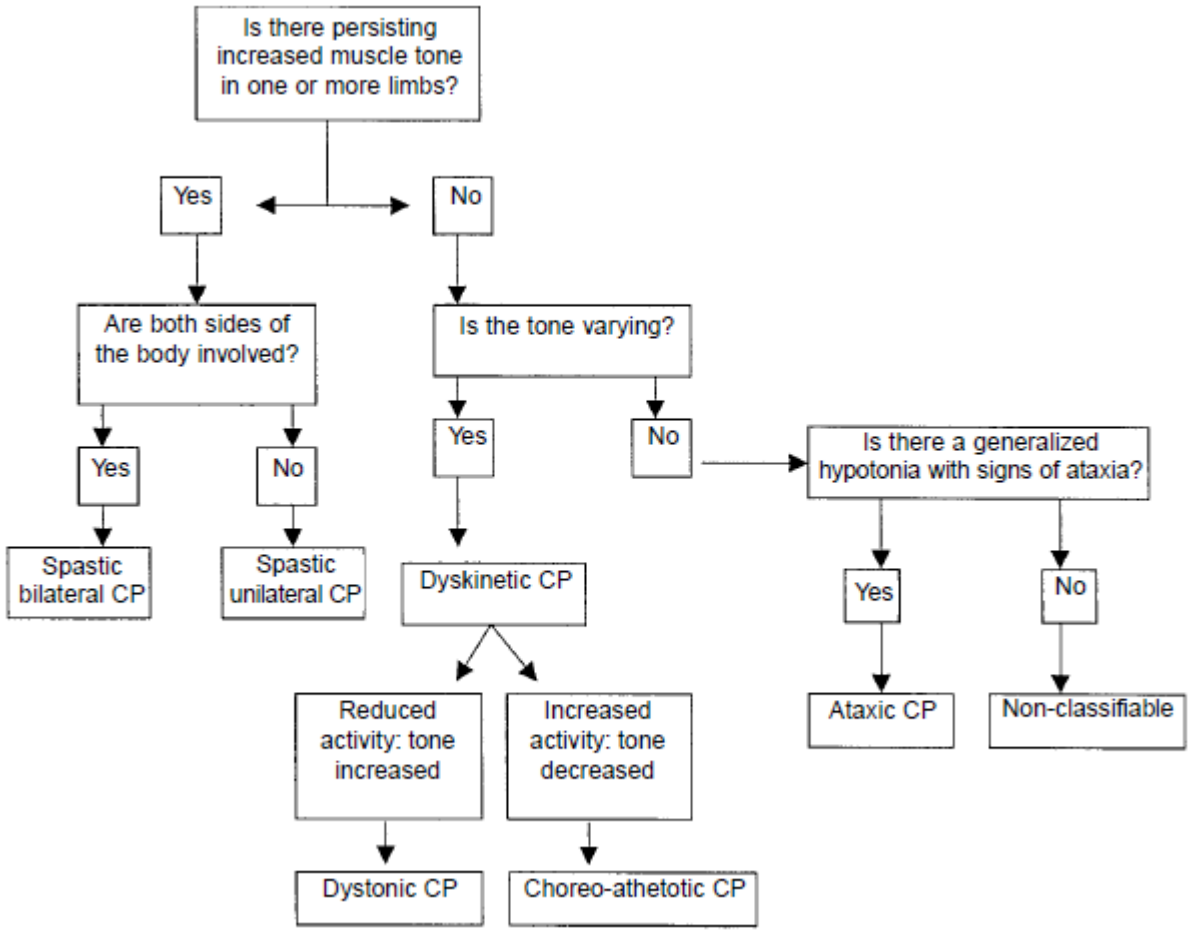

Figure 2. Hierarchical classification tree for subtypes of cerebral palsy. [The figure is reprinted with permission from Surveillance of Cerebral Palsy in Europe (SCPE)]

The Gross Motor Functional Classification System (GMFCS) [21], developed to provide a system for classifying gross motor function in children with CP, was used to classify the participants' walking performance (Table I). With established reliability and validity [21, 22], the GMFCS has been extensively used as a descriptive classification system to explore a wide range of issues in children with CP, such as assisting in the prognosis for and control of severity (e.g. the risk of hip migration) and the distribution of function in population-based registers [12, 23].

Table I:	Description of GMFCS levels (6-12 year of age) [21]
I	Walks and climb stairs without restrictions, limitations in more advanced motor skills
II	Walks without assistive devices; climb stairs holding onto a railing, limitations walking outdoors and in the community
III	Walks with assistive mobility devices; may climb stairs holding onto a railing, limitations walking outdoors and in the community
IV	Self-mobility by wheelchair
V	Self-mobility is severely limited even with the use of assistive technology

GMFCS, Gross Motor Function Classification System

Concerning adults with CP, the validity and reliability of using the original GMFCS' band descriptors for the 6-12 year age group have been investigated by Sandström et al. [24], Jahnsen et al. [25], and McCormick et al. [26]. These studies demonstrated, in general, a high interrater reliability and that the GMFCS level at the age of 12 years is highly predictive of adult motor functioning. The revised and expanded version of GMFCS (GMFCS-E&R) [27], which also includes the 12-18 years age group, was not published when this study started.

Epidemiology

A 2006 survey of CP registers across developing countries in Europe, North America and Asia revealed a fairly steady incidence rate of between 1.5 and 2.5 cases of CP per 1000 live births per year from the 1950s [20]. This is comparable with the findings in a recent Norwegian study [12] describing the CP rate to be 2.1 per 1000 live births. Assuming an incidence of 120 per year [12], the entire CP population in Norway may be estimated to about 8000 individuals. According to publications from the SCPE database, spastic CP occurs in 88% of all individuals with CP, with 58% bilateral (individuals with walking ability 34%) and 30% unilateral [10, 28]. An SCPE publication reported that 76% of children who walked unaided had no intellectual impairment (mainstream schooling) [28]. Thus, a rough estimate of the adult population in Norway with spastic uni-or bilateral CP, no intellectual impairment and present or previous walking ability could be about 2700 individuals [29].

2.2. Spastic CP as a spastic paresis health condition

Considering the musculoskeletal impairments involved in spastic CP, the condition may be conceptualised as an upper motor neuron syndrome or a spastic paresis health condition [13 (p.353-6), 14 (p. 215-16), 15 (p. 89-98]. Spastic paresis or upper motor neuron syndrome is defined by several researchers as the health condition that occurs following any lesion affecting certain motor pathways in the brain or spinal cord [13, 14, 30-34].

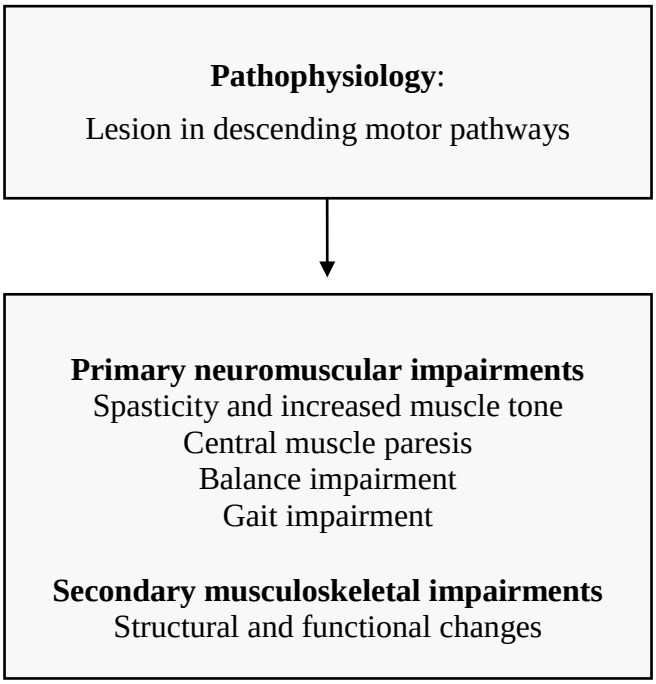

Figure 3. Pathophysiology within the central nervous system causing a spastic paresis health condition results in both primary and secondary impairments.

Common to spastic CP and other spastic paresis health conditions is the activity-dependent plastic rearrangement causing adaptive neurological changes within the brain, the spinal cord, and periphery, as well as non-neurological changes in the musculoskeletal system (Figure 3) [13, 14, 33, 34]. The functional consequences of spastic paresis range from those severely affected, unable to perform many motor activities – to the less affected, presenting a more limited motor disability. The target population in this study was well-functioning adults with spastic CP who experience increasing walking difficulties. In the following section, the spastic paresis impairments considered relevant to this study will be introduced (Figure 3).

Spasticity and increased muscle tone (hypertonia)

Muscle tone may be defined as the resistance to passive stretching while the individual attempts to relax, while increased muscle tone or hypertonia may be defined as greater-than-expected resistance to the stretching of a muscle group [13 (p. 326-9), 35]. Resistance to the passive movement of a joint represents the summation of the mechanical compliance in muscles and joints, and compensatory responses to resist the passive stretching of muscles [13, 35]. The increased muscle tone or hypertonia seen in spastic paresis health conditions may be caused by i) increased proprioceptive stretch reflex action (spasticity), ii) increased muscle fibre activity, and iii) changed mechanical compliance causing increased muscle stiffness [13, 14 (p. 9-54), 33, 34, 36].

1) Stretch reflex action; spasticity

A reflex may be defined as a typical involuntary motor response of afferent excitation [13 (p. 309, 318-19)]. In considering the stretch reflex, its components are the receptor (e.g. muscle spindles) and its primary afferent fibers (Ia and II), and the motorneuron, with its efferent fibers innervating the same synergistic and/or antagonistic muscle [13 (p. 309, 321-3)].

Most spinal stretch reflex pathways are polysynaptic, where one or more interneurons are interposed between the sensory and motor neurons [13 (p. 321-7), 14 (p. 9-54), 15 (p. 89-98]. These circuits have three main levels of control: i) control of individual muscles, ii) coordination of muscle action around a joint, and iii) the coordination of muscles at several joints [13 (p. 324-6)]. Types of interneurons are the Ia group of inhibitory interneurons, which coordinates the agonist/ antagonist by contracting one and relaxing the other (reciprocal innervation), and the Renshaw cells that are activated by a collateral of the alpha motoneurone axon, inhibiting the homologous motoneurone (recurrent inhibition) as well as its paired gamma motoneurone and the I a group of inhibitory interneurons [13 (p. 323-24, 356)].

In 1980, Lance described the clinical characteristics of spasticity 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 neurone syndrome"* [37 (p. 485)].

Lance's definition is among the most commonly cited definitions of spasticity [13, 14, 38], and was the definition used in this thesis. However, it is worth mentioning that different definitions of spasticity are proposed and in use, demonstrating that both clinicians and researchers use the term spasticity to describe a variety of clinical signs [38-40]. According to Lance, and also according to the definition of Sanger et al., spasticity is abnormal specific motor signs obtained during a clinical examination when the individual attempts to relax [37, 39]. As such, the isolated signs of spasticity may be less important for active motions such as walking [13 (p. 326-7, 356-8), 14 (p. 9-54), 41-44].

2) Active muscle fibres and co-contractions

In individuals with spasticity, an increased muscle tone at rest, which is sensitive to the degree of the stretch (e.g. positioning of the limb), is commonly apparent and is described by some as spastic dystonia [32, 34, 39]. The pathophysiology of this increased tone at rest is unclear, but probably involves influences from the brainstem on the alpha motoneuron [13 (p. 354)].

The stability of normal limb movement is dependent upon an appropriate level of antagonist muscle co-contraction [13 (p. 323-24), 45, 46 (p. 107, 396)]. The muscle spindles are in general activated more intensely when the speed and difficulty of movement increase [13 (p.325), 14 (p.34-5)]. An increased level of co-contraction is normally seen in developing children, in elderly people, and in individuals learning new motor tasks [46 (p. 107)]. A common finding in individuals with spastic CP is an increased amount of antagonistic muscle activation (co-contraction) during active motion, such as walking, as compared with healthy individuals [15 (p. 97-8), 34, 44, 45, 47].

Co-contraction may be considered dysfunctional when it is excessive and impairs the agonist function, and the functional impact from co-contractions on active movement in patients with spastic paresis is studied or described by many authors, e.g. [14 (p. 34-5), 30, 32, 34, 41-45, 48]. Gracies has described spastic co-contraction as the result of a hyperactive stretch reflex in the antagonist muscle [34]. However, Barnes and Johnson have suggested that excessive amount of co-contraction should be distinguished from a hyperactive stretch reflex in the antagonist muscle, and that it is caused by inappropriate corticospinal projections, resulting in a reduced selectivity in motor output [14]. In individuals with a spastic paresis health condition, such as adults with spastic CP, both mechanisms may be involved, and a shared pathway may be reduced presynaptic inhibition by Ia inhibitory interneurons [13 (p. 323-4, 356), 14, 30, 34, 42]. Impaired modulation of the Ib afferents from Golgi tendon organs have also been suggested to contribute to spastic co-contraction [49].

As controlled co-contraction is an important aspect of normal motor function, providing postural stability, the finding of increased level of co-activation in individuals with spastic CP may also be viewed as a strategy to cope with deficient gait and postural control [43, 46 (p. 107, 366)]. A recent study by Hägglund and Wagner on the development of passive measured muscle tone in a population of children with CP found that muscle tone increased up to four years of age and then decreased up to 12 years of age [50]. Whether this reduction of muscle tone from four years of age is related to the establishment of motor strategies and reduced co-contraction strategies during activity is not known. Neither is the further development of muscle tone and spastic co-contraction patterns into adolescence and adulthood for individuals with CP.

3) Soft tissue stiffness (biomechanical hypertonia)
The occurrence of altered soft tissue morphology and loss of extensibility where increased stiffness and less compliance manifest as increased tone is commonly seen with spasticity [14 (p. 25-8), 33, 36]. Studies have shown that children with spastic CP have reduced muscle belly length and muscle volume, increased extra-cellular matrix material and increased stiffness compared with their typically developing peers [51]. Studies on adults with spastic CP are lacking. However, recognising that muscle hypertonia in adults with spastic CP has both fixed and modifiable components may be useful in the search for effective interventions towards increasing disability associated with perceived troublesome muscle stiffness. The effects of BoNT-A were investigated in the study presented in Paper II.

Central muscle paresis
Muscle strength may be defined as the maximum force generated by a muscle or muscle group [13 (p. 317)]. A central muscle paresis may be defined as decreased voluntary motor unit recruitment, i.e. the inability to or difficulty in voluntarily recruiting skeletal motor units to generate power [13 (p. 353), 33]. Clinical manifestations may be reduced muscle strength, reduced selective motor control, and increased fatigability [33].

Different degrees of muscle weakness are common in children with spastic CP [47, 52]. Various neural mechanisms are probably involved, such as a reduced ability to activate the muscle selectively and maximally, and increased co-contractions [45, 47, 53]. In addition to neural factors, the ability of a muscle to generate force depends on its morphological and structural properties, as well as the moment (length of skeletal lever) [15, 36, 51, 53].

Balance impairment
Human balance or stability may be understood as the ability to not fall [54]. Maintenance of a specific posture (e.g. standing), voluntary movement between postures, and the reactions to an external disturbance (e.g. trip or push) requires the complex integration of higher level premotor systems, vestibular, proprioceptive and visual inputs [13 (p. 279-90), 46 (p. 165-91)]. The primary causes of impaired balance reactions in individuals with spastic CP are the lesion in the brain, which in varying degrees affects information processing, integration of sensory input, and the motor pathways leading to inadequate motor responses and probably also secondary conditions that affect posture [15, 46 (p. 263-4)]. As anticipatory adjustments are related to adequate regulation of muscle tone [13 (p. 279-90)], a possible contributing mechanism of worsened balance in adults with spastic CP may be increased levels of

antagonistic co-contractions, giving the individual an experience of stiffness and slowness [15 (p. 175), 46 (p 269)].

Gait impairment and secondary musculoskeletal impairments

Normal gait appears coordinated, efficient and effortless in meeting the goals of the individual and the demands of the environment [13, 15 (p. 31-64), 46 (p. 316-38)]. The underlying factors behind the gait impairment in CP have been divided into primary, secondary and tertiary abnormalities [15 (p. 107-28)].

The characteristics of gait in individuals with spastic CP are primarily caused by the brain lesion which influences the descending motor pathways, causing different impairments of varying degrees, such as muscle overactivity, muscle paresis, and impaired balance reactions [13-15, 31, 44]. These features, occurring as a direct result of the brain lesion, are usually referred to as "primary abnormalities" (primary impairments). The "primary abnormalities" and altered gait adversely affect musculoskeletal structures, leading to "secondary abnormalities" (secondary impairments), such as contractures and bony deformities. Contractures (e.g. unable to bring a joint in its zero-position [13 (p. 354)]) are well known secondary impairments in spastic CP [14, 15, 55, 56]. In contrast to an adult onset spastic paresis health condition, individuals with spastic CP have the risk of developing bone torsions (femur/tibia), and hip-joint and foot deformities [15, 55, 57]. Gait abnormalities caused by primary and secondary impairments may lead to compensatory gait strategies, commonly referred to as "tertiary abnormalities" [15 (p. 107-28)].

2.3. Walking function in individuals with CP

Belonging to the ICF dimension of "activity", the term *walking function* may be differentiated into three constructs of walking: -capacity ("can do in a standardised, controlled environment"), -capability ("can do in daily environment"), and -performance ("does do in daily environment"), respectively [17, 58]. In this doctoral thesis, *walking ability/capability* was considered to cover the construct of performance.

Walking function in children and adolescents with CP

A recent Norwegian study of 294 children with CP found that independent walking function was achieved at a mean of 22 months (range 10-77) for those not dependent on assistive devices, and 36 months (range 18-80) for those dependent on assistive devices [12], reflecting a later achievement than in typically developing children who walk at 10-15 months of age and are commonly able to run at 18 months [15 (p. 169)]. As the brain injury underlying

motor impairment is considered static [9], changes in established walking function in children and adolescents with spastic CP are commonly attributed to growth, maturation, the development of secondary deformities, and the influences of various treatments [15, 21, 31, 55, 59, 60].

Studies have shown that the majority of children with CP reach their maximum level of gross motor skills by approximately seven years of age [59-61]. Hanna et al. [60] studied individuals with CP aged up to 21 years and showed that those classified at GMFCS levels III to V have their peak gross motor function in childhood, whereas individuals at levels I or II have a stable gross motor function (Figure 4). A recent population-based study from Sweden of 562 children with CP, of whom 66% were spastic, found that the proportion of children who were able to walk independently on uneven surfaces was higher in each age group up to 18 years of age [62].

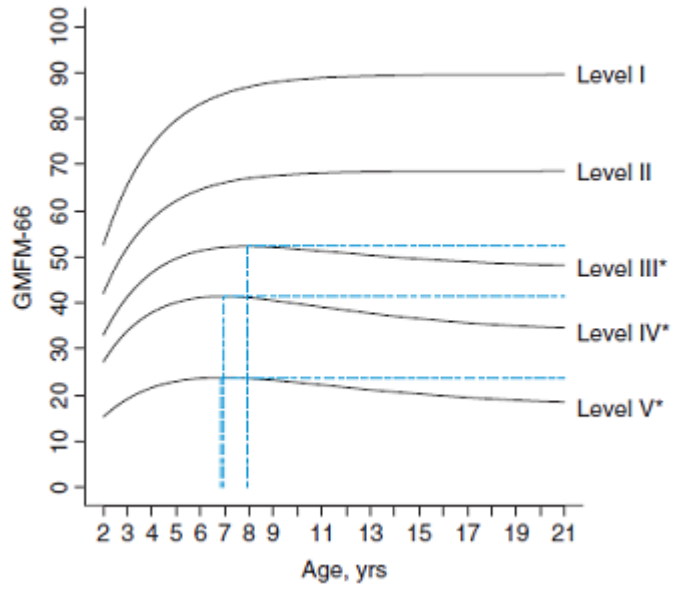

Figure 4. Predicted Gross Motor Function Measure (GMFM-66) motor scores as a function of age by Gross Motor Function Classification System (GMFCS) level. *GMFCS levels with significant average peak and decline. Dashed lines illustrate age and score at peak GMFM-66. [Copyright 2009 Wiley. Used with permission from Hanna et al. Stability and decline in gross motor function among children and youth with cerebral palsy aged 2 to 21 years. Dev Med Child Neurol. 2009; 51:295-302. Mac Keith Press]

Day et al. performed a large retrospective study of two age groups of individuals with CP, one group at 10 years of age (n = 7550) and one group at 25 years of age (n = 5721) [63]. Their study created four groups with different ambulatory abilities where group I and II are relevant for this study. Group I walked well and moved up and down stairs without the need of a

handrail, whereas group II walked well but used a handrail to walk up and down stairs. Among the children in group I, who were seen initially when they were 10 years of age and then at 25 years, all could still walk, but 23% had lost some skill. In group II from 10 to 25 years of age, all could still walk, while 23% had improved, and 22% had lost some skill [63].

Walking function in adults with CP

Walking ability and capacity

The authors of several surveys, including one seven-year follow-up study, have shown that 20-50% of individuals with CP report deteriorating walking ability in early adulthood [1-5]. The previously mentioned retrospective study by Day et al. [63], found that among 5771 adults with CP who initially walked well, but were in need of a handrail when ascending stairs at 25 years of age, about 30% had declined in walking ability by the age of 40. Sandström et al. [24] studied 48 adults with CP and found that 16 had deteriorated in GMFCS level since their adolescence. The study by McCormick [26] on 103 individuals with CP between 17-38 years of age (75% being < 25 years), found that the GMFCS levels of 24 individuals had deteriorated and nine had improved in comparison with the classification when they were 12 years of age. Although several authors have reported results on reduced walking ability in adults with CP, no studies have investigated walking ability, walking capacity and predictors for walking capacity in adults with spastic CP who report reduced walking ability. This was investigated in the study presented in Paper I.

Symptoms and signs; self-report and clinical findings

The most frequent self-reported causes of deteriorating walking ability in adults with CP are musculoskeletal pain, fatigue, contractures, increased stiffness/spasticity and reduced balance [1, 3-5, 24, 64-67].

In a Swedish survey by Andersson et al. 79% of the participants reported musculoskeletal pain [1]. The Norwegian survey by Jahnsen et al. reported similar results (82%), equal to the general population [65, 68]. However, 28% of the participants had chronic pain, which was twice as many as that in the general population, and with an impact on physical role function, life satisfaction and functional skills. Results from the study by Jahnsen et al. also showed that the impact from pain started at a lower age than in the general population [65, 68]. Other studies have demonstrated similar results [1, 5, 24, 66]. The same survey by Jahnsen et al. found that adults with CP suffered from fatigue at a rate more than twice that of the general

population [64, 69]. The 7-year follow-up study by Opheim et al. did not show increased prevalence or level of fatigue, probably because of an already high level of fatigue [5]. The previously mentioned survey by Andersson et al. found that approximately 80% of the participants reported contractures [1]. Similar results were reported in the survey by Jahnsen et al. [65]. The survey by Andersson indicated increased spasticity, balance problems, knee problems and a lack of physical training as causes of reduced walking ability [1]. A Norwegian study (Sintef report) included 37 adults with CP between 25-64 years of age [67]. Twenty-nine of the participants had spastic CP, and 23 were able to walk. Increased muscle "stiffness," often resulting in reduced balance, was reported by two out of three participants in the qualitative part of this study (n = 24) [67]. Reduced balance was also a frequently reported symptom in the survey by Jahnsen et al. (63%) and the seven-year follow up by Opheim et al. (65%) [3, 5].

Although several publications have shown that adults with CP report increased levels of CP-related impairments and reduced walking ability, there are few publications on clinical findings and/or interventional studies related to walking. The authors of a clinical descriptive study of 256 individuals with CP aged 17-83 years reported increased muscle tone and musculoskeletal deformities as the most prominent clinical findings [70]. In addition they found that daily activities were affected by the topography of motor deficits (e.g. uni- or bilateral CP), the level of muscle strength, muscle tone, and deformities. As low correlation was found between the level of muscle weakness and tone, the authors recommended that muscle weakness and muscle tone should be managed independently. It should be noted that a majority of their study population (80%) had mental retardation and severe motor impairments (quadriplegia).

The previous mentioned study on 48 adults with CP by Sandström et al. found limited joint range of motion (ROM) in 45 of the participants [24]. Of the joints assessed (shoulder, elbow, wrist, hip, knee and ankle), limited ROM was found to occur most frequently in the ankle joint. Part of the previously mentioned Sintef report [67] was published as an article on the need for lower limb orthopaedic surgery [71]. The majority had reduced joint ROM, more prevalent in individuals at a lower functional level. The investigators concluded that there were indications for lower limb orthopaedic surgery in eight of the 37 participants. Similar types of orthopaedic surgery (e.g. lengthening procedures of achilles tendon, hamstring, hip muscles and triple arthrodesis for foot) were reported in a publication on orthopaedic issues in the musculoskeletal care of adults with CP [72]. A recent clinical study investigating balance

function in 16 adults with bilateral spastic CP found problems of balance predominantly related to inadequate postural responses and anticipatory adjustments [73].

Andersson et al. found that progressive whole body strength training improved functional walking capacity (6-minute walk test (6MWT)) and mobility (gross motor function measure (GMFM) and the Timed-Up and Go (TUG) test) in 10 adults with bilateral spastic CP [74], while the study by Maeland et al. on 12 adults with bilateral spastic CP randomized to a progressive seated leg press exercise program, or to their usual training regimes, found improved strength but no effects on 6MWT [75]. Ahlborg et al. [76] investigated the effects of whole-body vibration training compared with resistance training in 14 adults with spastic bilateral CP and found that the vibration training group improved more than the resistance training group on muscle strength, when tested at a rapid angle speed (90º/seconds).

Long-term follow-up studies of the selective dorsal rhizotomy (SDR) procedure (e.g. selectively ablation of afferent nerves that return the stretch reflex arc to the spinal cord [14]) have been published [78-80]. After 20 years, compared with the preoperative assessments, several of the adults with spastic bilateral CP, aged 22-33 years, had improved in GMFCS level and demonstrated reduced muscle tone [79]. Also gait seemed to demonstrate long term functional benefits into adulthood [78, 80]. However, since those who undergo the SDR procedure are strictly selected [80, 81], the benefit of reducing stretch reflex actions is difficult to generalise to all individuals with spastic CP.

Personal- and environmental factors

The impaired gait seen in individuals with spastic CP includes changed biomechanics with increased muscular effort, energy expenditure and risk for degenerative joint conditions [15, 82, 83], and it has been suggested that adults with CP show musculoskeletal or performance changes typical of aging earlier than their healthy peers [3, 4, 84]. In general, aging may be associated with sensory deficits, muscle weakness, changed muscle activation patterns, and reduced balance and walking function [46 (p. 363-75), 85].

Regarding coping styles and personality characteristics, both “too much” and “too little” have been described as aggravating factors in respect of fatigue and/or a deteriorating function in adults with CP. Jahnsen et al. [64] found that those with moderate impairment were at the highest risk of overuse conditions, while those at lower functional levels were at greater risk of inactivity. A theory of “physiological burn-out” caused by continuously high energy consumption has been hypothesised as one potential cause of premature functional

deterioration [86]. In a qualitative study on 22 adults with CP aged 35-68 years Sandström studied "lived experiences" [66]. The author described that stubbornness and "fighting spirit" were typical parts of individuals' strategies for managing the disability, and that increasing impairments or functional deterioration first revealed themselves by affecting daily activities.

Health care services may be viewed as an environmental factor for individuals with CP [18, 57]. Similar to the physical and social environment and personal factors (e.g. age, lifestyle, coping styles, personality characteristics, and overall behavioural patterns); this may aggravate or modify the individual's walking disability in a lifespan [6, 17]. Considering physical impairments in individuals with CP, several publications have emphasised the contrast between well-organised multidisciplinary health care programs available during childhood and the less specialised and systematic preventive and/or interventional health care in adulthood [2, 4-6, 82].

2.4. Care and rehabilitation of musculoskeletal impairments in spastic CP

There are publications about the need for orthopaedic surgery directed towards both residual and acquired musculoskeletal deformities in adults with CP [71, 72, 82]. However, with the exception of some general expert opinion reports (e.g. [57, 82, 87]), the literature is scarce regarding the benefits of systematic multidisciplinary management programs, including lower limb BoNT-A therapy or the use of 3DGA in ambulant adults with spastic CP.

Multidisciplinary management programs for children with spastic CP

A common goal of the multidisciplinary gait management programs for ambulant children with spastic CP is to optimise gait and minimise secondary impairments [15, 57]. These programs commonly consist of regularly physiotherapy, with interplay between the use of orthotics, pharmacologic hypertonia management as well as SDR and/or orthopaedic surgery procedures [14, 15, 31, 57, 81].

Pharmacological hypertonia therapy may be systemic, using oral or intrathecal medication, or local peripheral injection procedures, including intramuscular chemical denervation by BoNT-A [14 (p. 131-93), 57, 87]. Treatment with BoNT- A has been used for children with CP internationally since 1988 [31, 88], and in Norway and Sweden since the late 1990s [89, 90]. A Swedish population-based study published in 2005 reported that one of three children with spastic CP had received BoNT-A treatment before the age of eight years [55]. Several publications support that a systematic prevention program including muscle tone management results in less hip luxations and a reduced and/or delayed need for surgery [55, 91, 92]. Thus,

in children with spastic CP, BoNT-A therapy may have a disease modifying effect [55, 88, 92-95]. A study has also demonstrated the benefit of using BoNT-A in the decision process for lower limb muscle lengthening surgery [96]. In general, lower limb orthopaedic surgery is typically indicated when major secondary impairments are recognised and there is an insufficient response to non-operative management strategies [15, 31, 55, 81, 92].

3DGA may be considered as the criterion standard assessment tool of gait in children with CP [15, 91, 97, 98]. Although there is a cost/benefit controversy over the clinical usefulness of 3DGA for ambulant children with CP [57, 99], it appears as a useful tool to gain insight into complex gait mechanisms [15, 55, 57, 81, 91-93, 98].

Botulinum toxin A (BoNT-A), mechanism of effect and expert opinions

The bacterium Clostridium Botulinum produces seven antigenically distinct protein neurotoxins labelled A-G: two of them, serotype A (BoNT-A) and B, are used in clinical practice [14 (p. 165-7), 100-102]. After intramuscular injection BoNT-A acts in the cytosol of nerve endings to block the mechanism that governs exocytose of acetylcholine [100]. This resulting block of acetylcholine release at neuromuscular junctions produces a dose dependent chemical denervation, resulting in reduced muscular activity [103]. The therapeutic effect usually lasts between two to six months [100, 104].

Muscle weakening with BoNT-A in adults with spastic CP, what is the rationale?

The BoNT-A procedure may be conceptualised as a treatment approach for focal hypertonia, where the main advantage is its focal, selective and reversible effect with no major adverse effects [31, 101, 102, 105, 106]. One clinical finding in spastic paresis may be an imbalance between mildly hyperactive agonists and severely hyperactive antagonists [104, 107]. Such antagonistic focal muscle overactivity may contribute to impaired functioning [104, 107, 108]. By its mechanism of blocking the transfer of acetylcholine for muscle contractions BoNT-A may have the potential to balance agonist – antagonist action during activities [14, 92, 93, 104, 109]. This may have implications for gait, walking function, and perceived stiffness during walking [31, 32, 87, 95, 104, 105, 107].

Dosages and injection techniques

This study used the BoNT-A Botox® (Allergan Inc., Irvine, Ca, USA). Several experts recommend 50 Allergan Units (U) as the maximum dose per injection site, a maximum total dose ranging from 400 to 600 U Botox®, and suggest dosing for the various muscles [87, 104, 105, 110, 111]. Several studies injecting musculi (mm) gastrosoleus for spastic equines in

children with CP may support that higher doses give the best result, e.g. [112]. However, one study found conflicting results regarding this [113]. Publications on adults have discussed the possibility that high dose BoNT-A treatment may result in excessive muscle weakening, thereby leading to deterioration in limb function for those having functional improvement as a goal [107, 114, 115]. Injection guidance in targeting the muscles selected for injection has been recommended by several authors [104, 105, 116]. The two methods used in the present study are further described. With the *auditive EMG injection technique,* the injection needle is used to detect motor unit activity [116]. As it may be difficult to distinguish contractures from muscle overactivity, this technique have been considered useful in confirming the existence of muscle activity [106, 108, 116-118]. In *the nerve/muscle stimulation technique*, repetitive electrical stimulation with the injection needle cause contraction of the target muscle. By producing a visually apparent 'twitch' in the target muscle, this technique may be useful to confirm placement of the needle [116].

2.5. Research on spastic paresis walking disability and lower limb BoNT-A

BoNT-A and spastic paresis walking disability – review of literature

In 2005, 2010 and 2011 the author of this thesis carried out a literature review by searching Medline via PubMed, Embase, Cochrane Central Register of Clinical Trials, Swe+, ISI Web of Science and Google Scholar, in order to identify relevant literature in Norwegian, Swedish, Danish or English on spastic paresis and effects from lower limb intramuscular botulinum toxin injections on gait impairment/reduced walking function in i) children/ adolescents with spastic CP, ii) adults with spastic CP, and iii) individuals with adult onset spastic paresis. A combination of text words and MeSH terms was used and searched for in the title and abstract fields. The titles and abstracts of the studies from the search were screened, and the full texts of the relevant studies were collected. The studies further described were selected according to their relevance for this study in respect to aim and methods (design, population, intervention, outcomes), with the American Academy of Neurology (AAN) classification of evidence for interventions (Table II), the ICF domains as well as the principles of evidence-based medicine as a framework [7, 17, 102, 119 (p. 13-19, 49)].

Table II: Classification of evidence for interventions

I	Randomized controlled trial (RCT) with masked or objective outcome assessment in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences. The following are required: a) concealed allocation, b) primary outcome(s) clearly defined, c) exclusion/inclusion criteria clearly defined, and d) adequate accounting for drop-outs (with at least 80% of enrolled subjects completing the study) and cross over with numbers sufficiently low to have minimal potential for bias.
II	Prospective matched group cohort study in a representative population with masked outcome assessment that meet b-d above, or an RCT in a representative population that lacks one criteria a-d.
III	All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement.
IV	Not meeting Class I, II or III criteria including consensus, expert opinion or a case report

Several classification systems have been developed to score the methodological quality of interventional studies. The American Academy of Neurology classification of evidence for interventions is one such classification system [102, 119 (p. 49)].

Evidence level

Before the study began, the only study found on lower limb BoNT-A injections in adults with spastic CP and gait impairment/reduced walking function was the pilot study by Ward in 1999 [120], who studied the effects of lower limb BoNT-A injections in five individuals with spastic bilateral CP (Table III). Ward suggested that BoNT-A had the potential to improve ROM, reduce muscle tone, and reduce the time taken to perform a 10-meter walk test. On the subjective score, four reported their experience as "better" and one as "unchanged." Four other studies, a randomized controlled trial (RCT) in 2000 [118] and three open-labelled trials [108, 121, 122] may suggest positive results regarding lower limb function, ROM and self-reported effects in adults with CP. However, as shown in Table III, none of these studies were performed in adults with spastic CP only. As well, the study by Wissel et al. found greater benefit from BoNT-A on muscle tone and gait in younger children (seven year or less) compared to the group of participants older than seven years [112].

Table III: Studies on lower limb BoNT-A injections in adults with spastic CP

Citation and design	Participants	Intervention	AAN
Dunne et al. [108][1]. Prospective case series.	Miscellaneous, *n* =40: Stroke (19), hereditary spastic paraparesis (6), multiple sclerosis (4), Friedrich's ataxia (3), CP (2), motor neuron disease (2), traumatic brain injury (3), spinal cord injury (1). N = 27 treated in lower limb. Mean age 50 (range 12-82) years.	BoNT-A: hip adductors, hamstrings, toe muscles and mm. iliopsoas, soleus, gastrocnemius, tibialis posterior and anterior. Continuation of ongoing rehabilitation program.	IV
Wissel et al. [112]. Double blind, dose-ranging RCT	Spastic CP, *n* = 33: Bilateral (diplegia) (23), unilateral (10). Mean age 10 (range 3-21) years	BoNT-A: mm. gastrocnemius, soleus, semitendinosus, gracilis, rectus femoris	II
Ward [120]. Prospective pilot study.	Spastic bilateral CP, *n* = 5. All participants had hip flexion deformities of 15-40 degrees. Age range 16- 21 years.	BoNT-A: toe muscles, mm. psoas, soleus. Physiotherapy twice a week and daily stretching.	IV
Richardson et al. [118][1]. Double blind, placebo-controlled RCT.	Miscellaneous, *n* =52: Stroke (23), brain injury (15), spinal cord injury (6), tumour (5), CP (3). N = 20 treated in lower limb. Mean age 40 (range 16-79) years.	BoNT-A: toe muscles and mm gastrocnemoius, tibialis posterior. Continuation of ongoing rehabilitation program.	I
Papadonikolakis et al. [121]. Prospective case series.	Spastic CP, *n* = 49: Bilateral (41) (diplegia 33, quadriplegia 8), unilateral (8). Mean age 11 (range 2- 23) years.	BoNT-A: mm. tensor fascia lata, rectus femoris, hip adductors, hamstrings, gastrocnemius. Physiotherapy 4-5 times weekly after the injection	IV
Bergfeldt et al. [122][1]. Retrospective study of an out-patient cohort.	Miscellaneous, *n* =100: stroke (39), traumatic brain injury (17), Rett syndrome (1), brain tumor (1), paraplegia (1), Spastic CP (41; 31 bilateral (16 diplegia, 15 quadriplegia), 6 unilateral.) N = 58 treated in lower limb. Mean age CP group 33 (Standard Deviation (SD) = 12) years.	BoNT-A: adductors, hamstrings, toe muscles and mm. psoas, gastrocnemius, soleus, tibialis posterior and anterior. Individualised multidisciplinary management approach.	IV

BoNT-A, botulinum toxin A. CP, cerebral palsy. AAN, American Academy of Neurology classification of evidence for interventions (Table II, page 18). RCT, randomized controlled trial. [1]Upper limb not reported.

Also the open labelled study by Bergfeldt et al. published in 2009 [123], who reported benefits for BoNT-A on several domains of the Medical Outcome Study Short Form-36 (SF-

36), had a study population with miscellaneous diagnoses. Viewing the literature, no larger studies were found which investigated the effects from BoNT-A in a population of adults with spastic CP only.

This search result was in contrast to the numerous publications on children with spastic CP and lower limb BoNT-A intervention for gait impairment as shown in recent systematic reviews [91, 124]. However, few high quality RCTs considered relevant for this thesis were found. A Cochrane review published in 2000, which focused on outcomes measuring disability and function, included only three RCTs [94, 95, 125, 126]. These studies were all limited in quality (e.g. small sample sizes and several bias issues). The authors of this review concluded that if the aim of treatment was to improve function, there was no strong controlled evidence to support or refute the use of BoNT-A for the treatment of lower limb spasticity in children with CP. It was suggested that future research should be pragmatic in its approach to the dose and distribution of the toxin, and that outcome should be measured on function and disability. Since then several studies have been published. In 2000, Ubhi et al. [127] published a 12-week RCT to investigate the effect of BoNT-A on gait and walking function in 40 children with spastic CP. The investigators injected individualised doses of BoNT-A or placebo (saline) into mm. gastrocnemii or soleus (for three of the participants, it was also injected into the hamstrings). They found improvement in favour of BoNT-A on gait (initial foot contact) and GMFM, but did not find significant changes in the ankle's ROM and physiological cost index (PCI). Koman et al. [128] published an RCT using standardised doses into the m. gastrocnemius to investigate the effects on hypertonic m. gastrocnemius and ankle function in 114 children with spastic CP. The authors suggested effects from BoNT-A, with improved gait. However, both the study of Ubhi et al. and Koman et al. revealed improvements on only 50% and 61% respectively of those receiving BoNT-A.

The study by Love et al. in 2001 on children with spastic unilateral CP used a six month matched pair design and an individualised dosing of the injected muscles (mm. gastrocnemius, soleus and for several tibialis posterior) [129]. The authors suggested effects from BoNT-A on muscle tone as measured with a Modified Ashworth scale (MAS), increased ROM, and improved gross motor function (GMFM). Baker et al. [113] investigated the efficacy and safety of three different BoNT-A doses in an RCT on 125 children with spastic bilateral CP. They found effects in favour BoNT-A for muscle length and the subjective treatment response, however, in contrast to the study by Love et al., they found no effects on gross motor function (GMFM).

Despite possible limitations of using a cross-over design for BoNT intervention, Reddighough et al. [130] published a clinically relevant study on 49 children with spastic bilateral CP. The injections were based on clinician decision making, where all children were injected in at least two muscle groups and most were injected in four sites (hamstrings, calf-muscles, adductors). They found no or only limited effects from BoNT-A on functional or impairment outcomes, but the parental reports came out in favour of BoNT-A. The authors suggested that isolated reduction of spasticity was limited in respect of its ability to give functional improvements, but that such treatment may provide a window of opportunity for a therapy program.

In 2006, Scholtes et al. [131] published a 48-week RCT investigating the effects of multilevel BoNT-A (hamstrings, hip adductors, mm. psoas, rectus femoris, gastrcnemius, soleus and tibialis posterior) and comprehensive rehabilitation, compared with usual therapy carried out on 46 children with spastic CP with a flexed knee gait. They found effects in favour of BoNT-A and comprehensive rehabilitation for gross motor function (GMFM) and problem score (e.g. improved balance, reduced tripping, better walking ability), but not for energy cost. This result was in contrast to the results found by Reddighough et al. [130]. However, the participants in the study by Scholtes et al. were assessed six times, and the design did not separate between the effects of the comprehensive rehabilitation program and the BoNT-A injections [131].

Compared with children with spastic CP, there were also considerably fewer studies on lower limb BoNT-A therapy in adults with gait impairments/reduced walking ability caused by an adult onset spastic paresis health condition. In 1996, Burbaud et al. [117] used an RCT with cross-over design to study the effects of BoNT-A on 23 patients with spasticity of ankle muscles secondary to stroke or traumatic brain injury. The results were improvements in favour of BoNT-A on MAS, subjective treatment effect, and the video score of gait. The authors considered that simultaneous negative features, such as muscle paresis, could affect the results of gait, but also emphasised that decreased ankle muscle tone may have modified the balance of segmental tonic influences and improved control of antagonist muscles. In 2003, a 12-week double blind placebo-controlled RCT on 234 individuals with gait impairment after stroke was published [114]. The authors used three standardised doses for mm. gastrosoleus, and 2-minute walking distance was the primary outcome. There were no differences between BoNT-A and placebo on walking distance, but effects in favour of BoNT-A were found for calf muscle tone (MAS), limb pain and reduced need for walking aids. While the study by Burbaud et al. found that the duration of spasticity influenced the

effects of BoNT-A, the study by Pittock et al. had contrary findings [114, 117]. A double-blind dose-ranging RCT on 45 ambulant individuals with post-stroke spasticity, found that a medium sized dose offered the best total effect, e.g. both on muscle tone and the visual analogue scale (VAS) for walking function and pain [115].

General considerations

Bias and transparency

A noticeable result of the performed literature review was the extensive number of low quality articles (not described further here) and guideline papers (e.g. [101, 104, 107]). As it is only during the last few years that clinical studies have been required to be registered in web-based databases, such as ClinicalTrial.gov (http://clinicaltrials.gov/), publication bias may be important to consider [132]. Also relatively new is the request for "Interest of conflict statements," and that clinical trials should be reported according to the Consolidated Standards of Reporting Trials (CONSORT) [133].

Safety and research challenges

BoNT-A treatment is considered safe [105, 110, 134]. Serious adverse effects are rare, but mild and transient adverse effects can occur, such as excessive weakening of the treated muscles, or self-limiting fatigue, nausea and headaches. Occasionally, more serious adverse effects may occur, such as breathing, swallowing, or speech difficulty. Thus individuals receiving BoNT-A therapy should always be informed to contact their doctor if such symptoms occur [105].

Several publications have discussed the difficulties of measuring the effects from BoNT-A on active functioning, such as walking, and have emphasised various methodological challenges in respect to study design, enrolment criteria, and clinically relevant outcomes that measure motor functioning that have yet to be resolved [105, 110, 135].

Recently published reviews

Since the beginning of this study, several reviews have been published, using a systematic search approach and/or different tools to grade the quality of studies included and/or level of evidence (e.g. items from the PEDro Scale, CONSORT and The Cochrane Library [124], the guideline set from the American Academy of Cerebral Palsy and Developmental Medicine (AACPDM) [136], or the grading system developed by the American Academy of Neurology) [91, 110].

The authors of a systematic review stated that the outcomes in BoNT-A studies on children with CP have traditionally been in the ICF's domain of "body-function/structure" (e.g. muscle tone or range of motion) rather than in the domain of "activity" [137]. This trend becomes even stronger if 3DGA kinematics, time/distance parameters and kinetics are categorised to the ICF domain of "body function." This may have influenced the results of two systematic reviews which found only moderate evidence for effects from BoNT-A on functional improvements in children with spastic CP [124, 136].

Another review using a meta-analytic technique, investigated whether the treatment of spastic equinovarus deformity following stroke resulted in increased walking velocity [138]. The authors concluded that the use of BoNT-A was associated with a statistically significant increase in walking velocity, but questioned the clinical significance of this result [138]. They also discussed the limitations of using velocity as an outcome in the light of capturing possible treatment effects on gait, stability, satisfaction with treatment, and the discontinued need for walking aids.

Despite limited evidence in children with CP, stroke survivors and patients with multiple sclerosis, there has been a strong expert opinion regarding the use of BoNT-A in a multidisciplinary integrated approach [91, 105, 110, 139]. The 2010 international consensus statements by Love et al. on BoNT-A for lower limb spasticity in children with CP stated that BoNT-A was the adjunctive intervention [91]. This was in contrast to the parallel consensus publication BoNT-A for lower limb disorders of movement and muscle tone in adults by Olver et al., stating that the optimal combination of adjunctive treatments to augment the effect of intramuscular BoNT-A therapy has not yet been established [110].

These two 2010 international consensus statements by Love et al. and Olver et al. reviewed the scientific evidence and need for further studies of lower limb BoNT-A therapy by using the American Academy of Neurology grading system [91, 102, 110]. Their results are summarised in Table IV. It may be worth mentioning that while experts in the field commonly recommend a multilevel approach (e.g. [87, 92, 105]), there is still only limited scientific evidence for its effectiveness (Table IV) [91, 110].

Table IV: The 2010 scientific evidence of lower limb BoNT-A injections

Treatment outcomes	**Adults**	**Children**
Reduce spastic muscle overactivity	Established effective	Established effective
Increase range of motion	Inconclusive	Probably effective
Increase gross motor function	Inconclusive	Probably effective
Increase goal achievement	Probably effective	Probably effective
Reduce pain	Inconclusive	Inconclusive
Effect on spastic equines to improve gait	-	Established effective
Injections to multiple lower limb muscles in respect of improving gait, goal attainment and function	-	Inconclusive

"Established effective" = at least two consistent Class I studies. "Probably effective" = at least one Class I study or two consistent Class II studies. "Inconclusive" = inadequate or conflicting data [91, 102, 110, 119 (p.49)]

Additionally, the authors of these two publications suggested that evaluation of BoNT-A treatment should involve goal attainment, measures of symptoms or impairments, measures of function, and that it may be relevant to assess whether there has been an improvement at the level of participation (e.g. quality of life) [91, 110]. While the authors of the publication on lower limb BoNT-A in children with spastic CP emphasised 3DGA as the "cornerstone outcome measure" [91], outcomes assessing treatment effects from the patient perspective were emphasised as important outcomes in the adult population [110].

2.6. Assessment tools in ICF framework

This study used the ICF framework to guide the selection of assessment tools [17]. Included were gait analysis, energy cost of walking and physical examination ("body functions/-structures"), functional assessments of walking and mobility ("activity" and "participation"), as well as self-reports covering both "body functions/-structures," "activity" and "participation." The following sections will introduce relevant methodology concerning the studies presented in Papers III and IV, as well as the selected assessment tools for the studies presented in Papers I-IV.

Important properties for assessment tools are reliability and validity [8]. Very few studies have specifically investigated assessment tools for adults with spastic CP. Therefore, a number of the selected assessment tools in this study were based on the results from clinical and/or methodological studies on comparable patient populations.

Validity of assessment tools

While the reliability of an assessment tool refers to the extent to which a score is free of random error, such as the natural variation in the subject, variation in the measurement tool, or the tester, validity is the capacity of an assessment tool to assess what it is intended and presumed to assess [140 (p. 255, 259)].

Many types of outcome validity are referred to in the literature, such as face validity, construct validity, and criterion validity [8, 140 (p. 259-61)]. Face validity relates to whether a measurement appears to assess what it is supposed to [8], while the construct validity addresses the question for which the constructs are measured [8, 140]. Three aspects may be considered when investigating construct validity. These are "known group validity," which assumes that a different group of patients are expected to yield different scores, and "convergent" and "discriminant" validity, which are tested by investigating the strength of association between assessment tools measuring related and unrelated constructs [140]. The study presented in Paper III investigated the face- and construct validity of the Gait Deviation Index (GDI) in adults with spastic CP. Criterion validity refers to the performance of an assessment tool against a so-called "gold standard," or criterion standard [8, 140]. The study presented in Paper IV investigated the concurrent criterion validity of assessing lower limb joint angles from a video gait recording.

Gait analysis (body functions)

Gait analysis by visual observation is the simplest and most common gait analysis method. Using this method to analyse a video gait recording has several advantages, such as being a permanent qualitative description of the individual's gait, as well as giving the clinician more time to observe an individual's gait by reassessing the walk repeatedly, without the effect of patient fatigue [15, 141]. The most comprehensive gait analysis is 3DGA [15, 141].

3DGA (Papers II-IV)

A 3DGA is performed in a specially equipped motion analysis laboratory, which provides information about three dimensional kinematics (joint angles) and kinetics (moment and powers), gait quality (video) and, in several laboratories, muscle activity (surface-EMG) and energy expenditure during walking [81, 97, 99]. This study used the Vicon Motion Systems consisting of six infrared MX13 100 Hz cameras (Vicon Motion Systems, Oxford, UK), two AMTI OR6-7 force plates (Advanced Mechanical Technology, Inc., Watertown, USA), and two digital video cameras (sagittal and frontal plane; recording at a frequency of 25 Hz).

Both kinematics and spatio-temporal measures, such as step length, cadence (steps/minute), walking velocity and stance phase/swing phase ratios, are good indicators of overall gait and descriptors of an end product [15, 81, 141]. They do not provide information about underlying mechanisms, such as the forces and timing of the muscle agonist-antagonist that interact to produce these measures (kinetics and surface EMG-measures).

The kinematic output from 3DGA data typically results in a huge amount of data. Common points (gait events) chosen in the gait cycle for research purposes are the sagittal plane ankle and knee initial contact, peak stance and peak swing [80, 93, 94]. Based on the assumption that these gait events could possibly be affected by abnormal muscle activation [15, 43, 46 (p. 389-94), 142], these were also the chosen gait events in the study presented in Paper II. In addition, sagittal hip range of motion was included as a measure of dynamic ROM.

When using kinematics from 3DGA as an outcome it is a challenge to choose only one single parameter, and several summary scores have been developed [81, 143, 144]. The Gait Deviation Index (GDI) utilises pattern recognition to determine the extent of gait pathology using just one score [143]. The GDI is based on 3DGA kinematics from the pelvis and hip in three planes, from the knee and ankle in the sagittal plane, and from foot progression, providing a total of 459 data points. By the use of singular value decomposition, 15 "gait features" are extracted. Applied to a control group, these "gait features" define an average,

non-pathological gait. The absolute distance between an individual exhibiting gait pathology and the control group is then calculated, providing a measure with good statistical properties from which the extent of gait pathology can be determined [143, 144]. Two publications on healthy children and children with CP have demonstrated good face validity, showing that healthy children had a GDI score of approximately 100 with a standard deviation (SD) of 10, while the study populations of ambulant children with CP had a mean score (SD) of 72 (10) and 77 (13), respectively [143, 145]. There were no publications on adults with CP and GDI, and this was investigated in the study presented in Paper III.

Video gait analysis (VGA) (Paper IV)

Expensive technology, complexity, and the level of time consumed are factors that all result in restricted access to 3DGA in ordinary clinical practice [99]. Therefore analysis of video gait recordings is a widely used technique [15, 146-149]. It may be used both as a primary method, and in conjunction with more sophisticated computerised systems such as 3DGA or Gait Rite [15, 150].

Different video gait analysis (VGA) tools have been developed to assist the observer in organising the analysis as well as for reporting the observations [125, 127, 146-149, 151]. One major limitation of observational or VGA is the lack of objective measures for specific gait descriptors, such as joint angles [15]. In the development of a clinical program for adults with CP and decreased walking ability, there was a need to investigate the validity of measuring lower limb joint angles from sagittal video recordings of walking, and this was investigated in the study presented in Paper IV.

Energy cost of walking (body functions)

Several methods may be used to assess energy cost during walking. They range from simple indirect methods to tools with complex technology requiring expertise to manage [152, 153]. Two indirect methods, one subjective and one objective, used in the studies presented in Paper I and Paper III are described below.

Perceived exertion (Paper I)

The perception of physical exertion may be defined as the "subjective intensity of effort, strain, and/or discomfort that is experienced during exercise" [154]. The Borg 6-20 ratings of the perceived exertion scale (Borg scale) [155] has been used in both research and clinical practice [154, 156]. This scale may be considered as a measure of the individual's experienced exercise intensity, with reported correlations of Borg scale ratings and levels of

oxygen uptake or heart rates of r >0.80 [154, 156]. A study on adults with CP reported a test-retest reliability of intra class correlation coefficient (ICC) = 0.72 [157].

The Physiological Cost Index (PCI) (Paper III)

PCI is considered to be an easily applicable assessment tool requiring minimal equipment and expertise, which objectively and indirectly indicate the energy expenditure, physiological costs or effort of walking [158, 159]. The formula is:

$$\text{PCI} = \frac{\text{Heart rate (walking)} - \text{Heart rate (rest)}}{\text{Walking speed (meter/minute)}} \quad [158]$$

Despite the recognised limitations of this equation [152, 160], the correlation between heart rate measurement and the volume of oxygen uptake during walking has shown high agreement in children with CP [153], and the equation is considered to be reliable [152].

Lower limb physical examination (body structures/-functions)

Common assessments of lower limb impairments related to gait impairment in individuals with spastic CP are ROM, muscle tone, muscle strength, selective motor control, and the evaluation of foot and bone alignments [15 (p. 181-220)]. Assessments of standing balance and equilibrium responses are also recommended [15]. Several physical examination charts have been developed by experienced motion analysis laboratories. The physical examination chart used in this study (Attachment 1) was developed by the principal investigator based on viewing the literature (e.g. [15, 161]), participation in the European Society of Motion Analysis in Adults and Children (ESMAC) gait courses and meetings. The assessment tools related to variables used in the studies presented in Papers I-II are further described.

Range of motion (ROM) (Papers I- II)

The joint range of motion may refer to the number of degrees of motion that are present in a joint. The range of muscle length may refer to the length of the muscle (also commonly expressed in terms of degrees of joint motion) [15]. In individuals with spastic CP and GMFCS levels I-III, the popliteal angle is a frequently used "muscle length" hamstring test [15 (p. 192-4)]. The uni- and bilateral popliteal angle assess the degree of limited knee-extension when the hip(s) is (are) flexed 90º. Unilateral popliteal angle may be defined as the degrees lacking from full knee-extension when the ipsilateral hip is flexed to 90º and the contralateral hip is in full extension. The bilateral popliteal angle is measured when both hips are flexed until the anterior and posterior spina iliaca superior are aligned vertically. A notably smaller bilateral popliteal angle may be referred to as a hamstring shift and a measure

of the true hamstring length [15]. The unilateral popliteal angle may be considered to not discriminate regarding whether the measured muscle length is due to real shortened hamstrings or to functionally shortened hamstrings resulting from short hip flexors [15]. The unilateral popliteal angle was used in this study. Intrarater reliability of unilateral popliteal angle has been reported for children with CP [162].

Muscle tone (Papers I-II)

Common clinical methods of assessing muscle hypertonia in spastic paresis are rating scales such as the Ashworth Scales to grade the resistance to passive movements, the Tardieu-method to assess "catch," and tendon-tap methods to assess abnormal reflexes [163]. The Ashworth scales were developed to detect the reflexive component (spasticity) of muscle hypertonia [164, 165]. However, it is now established that they assess passive resistance to motion that include both the reflexive and non-reflexive components of muscle hypertonia [163, 166]. An Ashworth Scale was considered to be a clinically relevant measure to describe muscle tone in lower limbs in adults with spastic CP.

Table V: The modified Ashworth Scale used in this study

Østensjø et al. [167][a]	**Score**	**Ghobti et al. [168][a]**	**Score**
Hypotonic: less than normal tone, floppy	0	No increase in muscle tone	0
Normal, no increase in muscle tone	1	Slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of the range of motion	1
Mild: slight increase in tone, 'catch' in limb movement or minimal resistance to movement through less than half of the range	2	Marked increase in muscle tone, manifested by a catch in the middle range and resistance throughout the remainder of the range of motion, bur affected part easily moved	2
Moderate: more marked increase in tone through most of the range of motion but affected part is easily moved	3	Considerable increase in muscle tone, passive movement difficult	3
Severe: considerable increase in tone, passive movement difficult	4	Affected part(s) rigid in flexion or extension	4
Extreme: affected part rigid in flexion and extension	5		-

[a]Since none of the participants were scored as 0, the scale used by Østensjø et al. was adapted to that by Ghobti et al.

The modified Ashworth Scale (MAS) as published by Østensjø et al, adapted to the scale of Ghobti et al. was used (Table V) [167, 168]. Interrater reliability has been reported for individuals with multiple sclerosis or sequels after a stroke [168].

Muscle strength (Papers I-II)
Technological advancement has led to the development of objective assessment tools to assess the muscles' ability to generate force (muscle strength) [15 (p.185)]. As the equipment is expensive and the procedures more time consuming, the manual method is still commonly used [15, 169]. The 0-5 grade manual muscle test scale described by Hislop was considered to be a clinically relevant lower limb muscle strength assessment tool [169]. The manual muscle test scale has demonstrated validity with dynamometer testing [170]. Because manual muscle testing is prone to examiner bias, all the tests were performed by the same assessor [169, 170].

Foot deformity (Paper I)
Foot anatomy and biomechanics are complex, and evaluation should be performed in both the non-weight bearing and weight bearing position [15 (p. 205-20)]. In this study, a visual examination was carried out for foot-deformities on the weight-bearing foot.

Assessments of walking and mobility (activity, participation)

Walking and mobility in controlled environments (capacity) (Papers I-III)
Outcomes in the domain of "activity" are frequently based on the assessment of an individual's completion of specific tasks in controlled environments. *The 6MWT* [171], assessing functional walking capacity and the *TUG test* [172], assessing functional mobility, are two such tests and were used in this study.

The 6MWT, which assesses the maximum distance a person can walk within six minutes, was originally developed as an endurance measure in chronic heart failure [173], but has later been used to assess functional walking capacity in several patient groups [171]. Due to its ease of application and similarity to daily activities, 6MWT has been considered to be a useful clinical tool when improvement in walking function is a goal e.g. [74-76, 171]. Regarding the validity of 6MWT for elderly and neurological populations, the 6MWT is considered a general measure of overall functional walking capacity, involving the integrated response of multiple body systems (respiratory, cardiovascular, skeletal, nervous and muscular systems) [171, 174, 175]. In older adults 6MWT has been found to be associated with functional measures, but not with aerobic capacity [176]. Known factors influencing the 6MWT are

height, age, increased body weight, female gender, shorter walking corridor (more turns), heart- and lung conditions, arthritis in lower limb joints, and muscle wasting [171].

The reliability of 6MWT has been investigated in adults with CP [157]. The authors studied the test-retest reliability of 6MWT, with two weeks between the tests on 25 adults with spastic or athetotic CP and a mean age of 36 years, where 12 subjects walked with walking aids and 13 without. They found (for the group with walking aids/and not walking aids, respectively) and average walking distance of 211/414 (first test), intra class correlation coefficients (ICCs) of 0.94/0.96, and 65/53 meters as the minimal detectable change.

The *TUG test* was originally developed as a functional balance test for the elderly [177]. By assessing, in time, the ability to stand up from a chair, walk a distance of three meters, turn around, walk back and sit down, the TUG test captures the complex interaction between balance and movement, including planning, initiating, executing, and completing a series of linked movements that are common in daily activities [46 (p. 273-75), 172]. As the TUG test involves several tasks that are potentially destabilising, it may be considered to test anticipatory aspects of postural control [46]. The TUG test has demonstrated test–retest reliability with ICC=0.99 in children with CP [178], and a study on individuals with multiple sclerosis has reported changes of 21% improvement or 27% deterioration to be clinically meaningful [179].

Walking and mobility in daily environments (ability) (Paper I)

Mobility may be defined as the way people move within multiple environments of home, school, work, and community [180]. In children with CP, the *Functional Mobility Scale (FMS)* has been found to be a valid and reliable assessment tool to classify mobility [180, 181]. The FMS rates the performance of mobility on a 1-6 scale at three different distances: 5, 50 and 500 meters. The six point scale separates the use of assistive devices and mobility aids on a spectrum ranging from a wheelchair (a score of 1) to walking with no aid of any kind (a score of 6). No studies have specifically investigated the use of FMS in adults with CP. However, its items and classification system also seems relevant for the adult population with CP, and the FMS was used to describe walking ability in the study presented in Paper I. Other assessment tools related to walking ability and participation may be self-reports, such as questionnaires developed for the "purpose of the actual study" e.g. [1, 3], and/or health related quality of life (HRQOL) assessment tools.

Self-reports (body functions, activity, participation)

Perceived walking ability (Paper I)

The questionnaire concerning present walking ability (Paper I, Appendix SI), was developed by studying other questionnaires used in adult CP research [1, 3], and through workshops. No formal reliability or validity testing was performed. However, applicability was explored in the ordinary clinic at SunHF before the start of the study.

Health related quality of life (HRQOL) (Paper II)

Quality of life represents the widest range of human experience, and usually refers to overall well-being or life-satisfaction [182, 183]. The term HRQOL distinguishes itself from quality of life by being a narrower concept primarily concerned with factors that are influenced by health conditions or services [182, 183]. Although there is no agreement about a single definition, there seems to be consensus that HRQOL encompasses the domains of physical and mental health as well as social interaction [183-185].

The questionnaires assessing HRQOL may be generic or disease-specific. The HRQOL instrument Medical Outcome Study Short Form 36 (SF-36) was designed as a generic tool to measure eight health domains on the basis of the individual's perceived burden of his or her illness on a 0-100 scale [186, 187]. It has been shown to be valid and reliable for different health conditions [188, 189], and SF-36 has been translated into many languages, including Norwegian [189].

SF-36 was considered to measure important aspects related to the research question in the study presented in Paper II [184, 185]. SF-36 has been used in a survey on adults with CP comparing the relative burden of diseases with the general population [65, 190]. For individuals with rheumatoid arthritis, it has been frequently used in interventional studies investigating health benefits by means of different treatments [191]. Individuals with rheumatoid arthritis have pain, deficits in physical function and fatigue [191, 192], and may be comparable with high-functioning adults with spastic CP. This population's estimated minimal clinical important difference (MCID) of 5–10 points [191, 192] was used to interpret the SF-36 results in the study presented in Paper II.

SF-36 domain of bodily pain (Papers I and II)

Pain may be defined as "an unpleasant sensory and affective experience associated with actual or potential tissue damage, or described in terms of such damage" [193]. The SF-36 domain of "bodily pain" (BP) covers both the degree of pain as well as the impact of pain on

daily functioning [187, 189], and was used to assess pain in this study. The SF-36 BP domain has been shown to be valid and reliable in individuals with rheumatoid arthritis [192, 194].

Perceived muscle stiffness/spasticity (Paper II)

Spasticity is a clinical sign with associated symptoms [195, 196]. Perceived muscle stiffness in adults with spastic CP may be symptoms from increased muscle activity and changed muscle properties. The study presented in Paper II assessed the perceived impact from muscle-stiffness/spasticity during walking by using a 0-100 millimeter VAS scale [195]. A 0–10 point spasticity numeric rating scale has been demonstrated to be a valid and reliable tool in the assessment of muscle-stiffness/spasticity in persons with multiple sclerosis, and a 30% change has been reported to be clinically meaningful [196].

Fatigue (Paper I)

Fatigue may be defined as a sense of physical tiredness and lack of energy that is distinct from tiredness and sadness [197]. This study assessed fatigue with the Fatigue Severity Scale (FSS) [198], which was originally developed to assess fatigue in individuals with multiple sclerosis and systemic lupus erythematosus. In FSS nine statements are rated on a Likert scale ranging from 1 (strong disagreement) to 7 (strong agreement) according to the experience during the last month. The FSS has been validated for the Norwegian population [199], and has demonstrated test–retest reliability in individuals with systemic lupus erythematosus [200].

2.7. Rationale

Walking ability and functional walking capacity in adults with spastic CP (Paper I)
Studies report that several adults with CP experience increasing difficulties with walking in early adulthood [1-5]. Musculoskeletal pain, fatigue, contractures, increased stiffness/ spasticity and reduced balance are commonly reported related complaints [1, 3-5, 24, 64-67]. To the best of my knowledge, walking ability and functional walking capacity in those who report increasing walking difficulties are less thoroughly investigated.

Effects of BoNT-A (Paper II)
Publications and clinical experience have shown that several adults with spastic CP report increasing stiffness relating to reduced balance and walking abilities [1, 15 (p. 75), 67]. Muscle hypertonia in adults with spastic CP may be considered to have both fixed and modifiable components [13, 14, 33, 34, 36]. To the best of my knowledge, no larger studies have investigated the effects from BoNT-A on increasing walking difficulties in adults with spastic CP.

Challenges of using 3DGA in research and clinical practice (Papers III-IV)
Despite its objectivity, when selecting kinematics from 3DGA as an outcome, it is a challenge to choose a single parameter [143]. The GDI determines the extent of gait pathology using only one score [143]. To the best of my knowledge no studies on GDI exist on adults with CP.

Expensive technology, complexity, and the amount of time consumed result in restricted access to 3DGA in ordinary clinical practice [99]. In the development of a clinical program for ambulant adults with CP, there was a need to investigate the validity of lower limb joint angles measured from sagittal video recordings of walking.

3. AIMS

The overall purpose was to investigate the effects of lower limb BoNT-A injections in a selected population of ambulant adults with spastic CP, to study their walking ability and capacity, and to study the validity of two gait analysis outcomes, in order to contribute to clinically relevant knowledge about this group.

The research questions were:

Paper I

- What are the levels of walking performance and walking capacity in a group of adults with spastic CP who report reduced walking ability?
- Which clinical and demographic factors predict walking capacity?

Paper II

- What are the effects of BoNT-A on gait?
- What are the effects of BoNT-A on different HRQOL domains?
- What are the effects of BoNT-A on mobility and walking capacity?
- What are the effects of BoNT-A on perceived muscle stiffness/spasticity?
- What are the overall perceived treatment effects of BoNT-A?

Paper III

- How is the face validity of GDI in adults with spastic CP?
- Does GDI discriminate between different GMFCS-levels?
- What is the association between GDI and walking capacity, mobility, and energy cost of walking?

Paper IV

- What is the concurrent criterion validity of joint angle measurements from sagittal gait video recordings?

4. METHODS

4.1. Setting

This research was performed at Sunnaas Rehabilitation Hospital (SunRH), Norway.

4.2. Designs

Three prospective studies were included in this thesis. Study I (Paper I) used a cross sectional design with one of the variables (GMFCS) based on retrospective self-reporting. Study II included two papers → Paper II: A single centre double blind, placebo-controlled RCT with parallel group design, and Paper III: An explorative cross sectional face- and construct validity study using data from the baseline assessment in Paper II. Study III (Paper IV) was a cross sectional concurrent criterion validity study.

4.3. Study populations

Adults with spastic CP were recruited through one advertisement in Norway's leading newspapers (VG and Aftenposten) in January 2007, on the web-pages of the CP-association and SunRH, and on the SunRH information board from November 2006 to August 2008. The observers in Study III were recruited from the clinic at SunRH through information on e-mail.

Recruitment procedures

Each response to the advertisement was followed up by the principal investigator. When the SunRH reception desk, secretary at the outpatient clinic, or nurse at the inpatient clinic received the first contact, they sent an e-mail to the principal investigator with the respondent's name and phone number.

Eligibility criteria

The studied participants were selected based on the eligibility criteria given in Table VI. In a semi-structured phone interview, perceived present walking ability compared with the walking ability in late adolescence (defined as 18 years of age for most of the participants, and 15 years of age for those who were currently 18 years of age) was explored. Walking ability was considered as decreased if reduced walking distance, and/or increased muscle-stiffness/ spasticity, and/or pain, and/or balance difficulties interfering with walking ability were reported.

Table VI: Inclusion and exclusion criteria

	Inclusion criteria	Exclusion criteria
Shared eligibility criteria **Papers I & II**	Diagnosis of CP[1]	Cognitive impairment[2]
	Spastic unilateral or bilateral CP[3]	Other conditions that may affect the level of physical function (rheumatoid, neurological, psychological)
	Age between 18 and 65 years	Orthopaedic surgery within the past 18 months
	GMFCS levels I-III[4]	Intramuscular injections of BoNT-A within the preceding three months
	Self-reported decreased walking ability compared with adolescence[5]	Pregnancy
	Ability to walk independently with or without handheld mobility device continuously for six minutes	
Additional eligibility criteria **Paper II**	Increased muscle tone in lower-extremity muscle group(s)[6]	Planning pregnancy
	Independent walking without need of support from walking aids for minimum 20 m	Musculoskeletal pathology with no indication for BoNT-A treatment[7]
	Gait characterised by functional equines[8] and/or pathological knee extension or –flexion strategy	New treatment the past four weeks which affect the musculoskeletal system (pain-killers, acupuncture, physical therapy, fitness training)
	No changes in other treatments during the study period	

[1]Medical records. [2]No cognitive impairment defined as attendance of regular school without support. [3]Clinical findings of enhanced excitability of tendon tap reflexes (hyperreflexia) and/or exaggerated stretch reflexes. [4]Walking ability. [5]Semistructured interview. [6]Modified Ashworth scale score of at least "2" for one muscle group or "1" for several muscle groups. [7]for example fixed flexion contractures > 20° hip and/or knee, and/or ankle. [8]Toe-toe or toe-heel initial contact strategy.

4.4. Study procedures and intervention

Study procedures

Prior to the beginning of the study a thorough study manual was developed. Sessions for general information and details about study procedures, as well as specific lectures for involved SunHF staff, were carried out by the principal investigator (Table VII).

Table VII: Sessions and lectures with involved SunRH staff

- Personell at the SunRH reception desk, two secretaries at the outpatient clinic, and two nurses at the inpatient clinic involved in the recruitment procedures:
    - Lectures and schemes

- The SunRH pharmacist and two nurses involved in the procedures of randomization, blinding and intervention:
    - Lectures and schemes

- Principal investigator and three involved physiotherapists from the SunRH motion analysis laboratory:
    - Participation at ESMAC[1] basic and advanced gait courses, training sessions and consensus on 3DGA
    - Lectures, training sessions and consensus on clinical examination procedures

SunRH, Sunnaas Rehabilitation Hospital. [1]European Society of Motion Analysis in Adults and Children.

Papers I and II

The different study steps (inclusion, assessments, and intervention) were performed by the principal investigator (the author of this thesis) for all the participants. All assessments in the study were carried out in the same order. The clinical assessments, including 3DGA, were performed by the principal investigator together with one of three physiotherapists. When there were scoring uncertainties, these were discussed, and the principal investigator made the final conclusion. In order to limit the influence of activity-based measures on self-reported measures, the questionnaires were administered first, then functional tests, then clinical assessments, and then 3DGA for all the participants.

In the RCT (Paper II), intramuscular injections were administered within one week after the baseline assessment. Two of the participants were assessed three and six weeks prior to the intervention, respectively. The follow-up assessment was made exactly eight weeks after the injections. The participants also answered a postal/mailed questionnaire after four months (week 16). None of the participants participated in a specific follow-up program, but were allowed to continue their pre-study, individual, ongoing treatment or training regimes [113, 129].

Paper IV

Physiotherapist Kerstin Lundberg Larsen (KLL) was the principal investigator. A subset of 10 participants was drawn randomly from the RCT study population. Ten observers (nine physiotherapists and one certified prosthetic/orthotist) were recruited from SunRH. Before the assessments, the observers attended a lecture on gait, gait parameters, and gait assessment

methods, in addition to instruction in the use of Salford Gait Tool (SF-GT) and goniometry measurement on a screen.

Randomization and blinding in Study II (Paper II)

The Department of Biostatistics, University of Oslo, independently produced the computer generated randomization list for trial drug allocation with the SunRH pharmacist undertaking masking, dispensing and labelling. Blocks of 10 were used to ensure fairly even-numbered treatment groups. Each eligible participant was assigned an identification number by the time of inclusion, which corresponded to the treatment allocation schedule stored by the hospital pharmacist.

To conceal the identity of interventions for investigators and participants, a pharmacist and a nurse not otherwise involved in the study prepared the BoNT-A or saline vials. The syringes were labelled with stickers which made them appear identical. All investigators (the involved physiotherapists and the authors of Paper II including), were blinded with regard to the individuals' group assignment during the study and the explorative statistical analyses. The participants were instructed not to discuss their treatment experience with the assessors. To ensure the blinding, a statistician not previously involved in the study received the study-data and performed the statistical analyses before the randomization list was delivered.

Intervention in Study II (Paper II)

Drug treatment was 50 U/ml of Botox® (Allergan Inc., Irvine, Ca, USA) (BoNT-A). One of three nurses and the SunRH pharmacist prepared the syringes of either BoNT-A 100U/2ml 0.9% saline or a 2-ml placebo dose of saline 0.9% solution according to the randomization list. The nurses involved in this preparation of study syringes were otherwise not involved in the project, while the pharmacist was also the individual keeping the randomization list in the deepest confidentiality from the beginning of the study until the statistical analyses for the study presented in Paper II were determined and performed.

Local anaesthesia was offered and achieved by the application of EMLA® 5% cream (AstraZeneca) to the injection sites 1 hour before injection. The injections were performed with a hollow monopolar Teflon-coated EMG needle connected to a "switch shifter," nerve-stimulator (RDG Medical NL 500 0587) and an auditive EMG electromyography (Injection Amplifier Medical Equipment 86z8). The muscles were located and injected according to the guidance described by Perotto [201]. The decision process of which muscles to inject was based on information obtained through observation of gait, the presence of increased muscle

tone during the clinical examination as well as a positive response from auditive EMG [108, 116-118] (Table VIII).

Table VIII: Target muscle identification for injections[a]

Target muscles	Criteria during gait analysis[b]	Criteria during clinical examination[c]	Criteria during intervention
Medial hamstrings[d] and biceps femoris	Increased flexion of the knee during initial contact and stance phase	Increased muscle tone Increased popliteal angle, but not >90°	Positive response from auditive EMG and electrical stimulation of motor point
Rectus Femoris	Decreased progression to flexion of the knee joint during initial swing phase	Increase muscle tone Patella alta	Positive response from auditive EMG and electrical stimulation of motor point
Adductors[e]	Adduction of the hip interfering with stability during gait cycle	Increased muscle tone	Positive response from auditive EMG
Gastrocnemius	Increased knee flexion during stance and/or pathological plantar flexion of the ankle during gait cycle	Increased muscle tone Reduced maximum ankle dorsiflexion with knee extended, but not less than -20°	Positive response from auditive EMG
Soleus	Plantar flexion of the ankle during stance phase	Increased muscle tone Reduced maximum ankle dorsiflexion with knee 90°flexed but not less than -10°	Positive response from auditive EMG and electrical stimulation of motor point
Tibialis posterior	Varus/adduction/supination of the forefoot during gait cycle	Callus (signs of overload) on the lateral border of the foot	Positive response from auditive EMG and electrical stimulation of motor point
Flexor digitorum[f]	Toe flexion during stance phase	Callus (signs of overload) of the toes	Positive response from auditive EMG and electrical stimulation of motor point

[a]Botulinum toxin type A (Botox ®) 50U/ml or placebo (0.9% saline). [b]Visual observation of a) gait in the 6-minute walk test, and b) sagittal and frontal plane video-assessments from three dimensional gait analysis . [c]Increased muscle tone as judged by a score on modified Ashworth Scale ≥ 1 . [d]Semitendinosus and semimebranosus. [e]Adductor longus and – magnus. [f]Longus and brevis; brevis identified with EMG only.

Following the intramuscular injections, the participants remained in the investigator's office for a minimum of 30 minutes. The intervention was uni- or bilateral, and the dose for each muscle was flexible within a certain accepted range [111] (Table IX).

Table IX: Pre-specified injection doses [111]

Muscle	Pre specified injection dose
Rectus femoris	1.5-2 ml (75-100 units Botox ®)
Hamstrings[1]	2 –7 ml (100-350 units Botox ®)
Gastrocnemius	3-4 ml (150-200 units Botox®)
Soleus	2ml (100 units Botox®)
Tibialis posterior	1.5 ml (75 units Botox ®)
Flexor digitorum[2]	0.5 ml–1.5 ml (25–75 units Botox®)

[1]Semitendinosus 1-1.5 ml (50-75 units Botox®), semimembranosus 1-1.5 ml (50-75 units Botox ®), biceps femoris 1-2 ml (50-100 units Botox ®). [2]Flexor digitorum brevis 0.5 ml (25 units Botox ®), flexor digitorum longus 1.5 ml (75 units Botox®). Maximum dose 8ml (400 U Botox®), 1ml per injection site.

4.5. Outcomes

The ICF framework was used to classify the constructs contained in the selected outcome variables. The outcomes were specified before study start for the studies presented in *Papers I, II,* and *IV*. The study presented in *Paper III* was a secondary explorative short report with research questions based on two recent publications on children with CP [143, 145], as well as limitations revealed of predefined 3DGA outcomes in the BoNT-A interventional study presented in Paper II. Table X lists the outcome variables used in Papers I-IV.

Table X: Outcome variables

Variable	Assessment tool	Specific outcome	ICF	Paper			
				I	II	III	IV
Gait	3DGA	Ankle and knee IC, PkSt, PSw, Hip ROM (°)	BF		X		
Gait	3DGA	GDI	BF			X	
Gait	Sagittal video recording	Goniometric SF-GT[1] gait events (°)	BF				X
Gait	3DGA	Sagittal kinematic SF-GT gait events	BF				X
Joint range of motion lower limb	Goniometer	Averaged unilateral popliteal angle lower limb (°)	BS	X	X[2]		
Muscle tone lower limb	MAS	Averaged MAS scores lower limb	BF	X	X[2]		
Muscle strength lower limb	Manual muscle test scale	Averaged muscle test scores lower limb	BF	X	X[2]		
Foot deformity	Visual assessment	The presence of foot deformity (yes/no)	BS	X			
Walking capacity	6MWT	Distance in meters	A	X	X		
Mobility	TUG test	Time in seconds	A	X	X		
Perceived effort of exertion	Borg scale	The scoring from the 6-20 scale	BF	X			
Energy cost	Polar heart rate monitor and 6MWT	The results of : $HR_{walking}$ - HR_{rest} / walking speed (meter/minute)	BF			X	
HRQOL	SF-36	0-100 score of: BP, GH, MH, PF, RE, RP, SF and VT	BF A/P	X[3]	X		
Perceived muscle stiffness/ spasticity	0-100 mm VAS muscle stiffness/spasticity	The VAS score	BF		X		
Fatigue	FSS	Average score	BF	X			
Perceived therapy effect	Global Scale	Worse – unchanged – improved	-		X		
	Adverse events	Yes/no	-				

BF, body function; BS, body structure; A, activity; P, participation. 3DGA, three-dimensional gait analysis;. IC, initial contact; PkSt, peak stance; PSw, peak swing; ROM, range of motion. GDI, Gait Deviation Index. SF-GT, Salford Gait Tool .MAS, modified Ashworth Scale. 6MWT, 6-minute walk test. TUG, Timed-Up and Go test. PCI, physiological cost index. HRQOL, health related quality of life: SF-36, Short Form 36; BP, bodily pain; GH, general health; MH, mental health; PF, physical functioning; RE, role emotional; RP, role physical; SF, social functioning; VT, vitality. VAS, visual analogue scale. FSS, fatigue severity scale. [1] SF-GT, Salford Gait Tool; Appendix 1 in Paper IV. [2]Not as outcome variables, but as descriptive variables to describe the study population. [3]Only BP.
[15, 93, 94, 112, 122, 142, 143, 149, 155, 158, 167-169, 171, 172, 187, 189, 195, 198, 199]

In Paper II the primary outcomes were gait as measured with 3DGA sagittal kinematics (ankle and knee initial contact, peak stance and peak swing as selected points from the gait cycle, and hip ROM during a gait cycle) [43, 93, 94, 142], and HRQOL (the eight domains of SF-36 [187, 189]). Secondary outcomes were walking capacity and mobility (6MWT [171] and TUG test [172]), perceived effects on muscle-stiffness/spasticity (VAS muscle-stiffness/spasticity [195], and overall treatment effect (Global Scale [112, 122]). In the next sections, the procedures regarding outcome variables and variables used to describe the study population will be presented.

4.6. Assessments and data processing

Gait analysis (Papers II-IV)

3DGA

Gait was evaluated by kinematics and video data from the 3DGA Vicon motion analysis system. Anthropometric measurements, placement of retro reflective passive markers according to the VICON Plug-in Gait® model (Figure 5) (Vicon Motions Systems, Oxford, UK), and the gait captures for all the participants were performed by the principal investigator assisted by one of the test-assistants (primarily KLL) at the SunRH motion analysis laboratory. Each gait capture session consisted of i) static capture for calibration, ii) warm-up walking trial(s) to familiarise the participant with the study protocol, which required the participants to walk barefoot at comfortable walking speed, and iii) capture of walking trials on a 10 m walkway until a minimum of three walking trials of valid kinematic data had been captured.

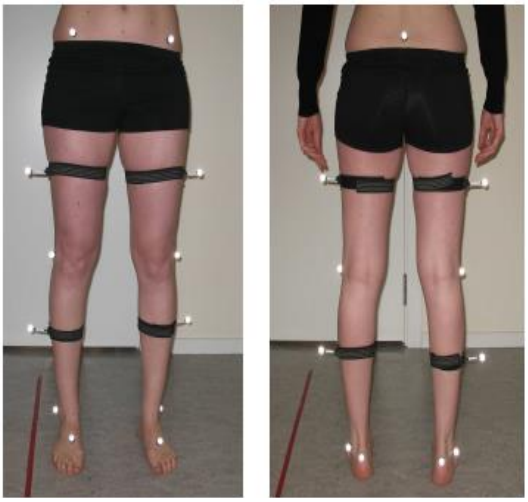

Figure 5. Marker set 3DGA [Used with permission from Linda Rennie. Reliability in three dimensional gait analysis. Master thesis. University of Bergen 2008]

The data processing procedures were performed with Workstation software (Oxford Metrics, Oxford, UK) and presented in the Polygon software (Vicon, Oxford, UK). One gait cycle on the right and left side was extracted from each walking trial. Three walking trials from the baseline and three walking trials from week 8 with the median most similar gait speed were selected for further analyses. One person (KLL) performed all the data processing. In Paper II

and Paper IV the Pipeline External Communication Server (PECS, Vicon, Oxford, UK) exported the selected kinematic parameters from Polygon to Microsoft Excel 2003. Data from one leg was selected for the statistical analyses in Paper II and IV. In Paper II this was the affected side for unilateral spastic CP and the randomly chosen right leg for bilateral spastic CP; in Paper IV, the right leg was chosen.

To calculate the GDI, relevant gait data were exported from Polygon into an Excel template designed to correctly format the data. These data were then imported into a custom-made Access database and written and calculated in the Excel template provided by the authors [143]. At first, the GDI scores for a previously collected reference population at the SunHF motion analysis laboratory (n = 50, mean age 39.7 years SD 11.7) [202] were calculated relative to the control data by Schwartz and Rozumalski [143]. Following this, the GDI scores for the present study population were calculated using our own reference data. One randomly chosen gait trial with individually calculated right and left GDI scores was used to obtain the descriptive GDI scores for the reference population (n=100 limbs) and the participants with CP (n=132 limbs). For subsequent analyses, the GDI scores of the left and right leg were averaged and described as the mean GDI (mGDI) [145]; for the participants with CP, the mean of three left and three right gait trials were used. Similar procedures as for the mGDI presented in Paper III were used to obtain GDI data from the week 8 assessment (presented as secondary analyses in Table XVII at p. 75 in the Discussion part of the thesis).

Video recordings

During the 3DGA captures simultaneously frontal and sagittal video tape recordings were made. These video data had two purposes: i) Paper II: Video data were systematically investigated before the final decision of which muscle(s) to inject. ii) Paper IV: 10 randomly chosen sagittal video-recordings were used to investigate the validity of lower limb joint angle measurements from video recordings. The observers played the videos using PCs with 17 inch flat screens. The joint angles of the hip, knee, and ankle from the right limb were measured according to a modified Salford Gait Tool (SF-GT) sheet (Appendix 1 of Paper IV). It was possible to play the video recordings back and forth one frame at a time, and to freeze the picture when performing the measurements. A 30 cm long goniometer with each degree marked was used. The observers worked independently, with no collaboration with each other.

Reliability of 3DGA

3DGA is considered as a reliable gait assessment tool [203]. However, competence within each gait laboratory is a recognised threat to 3DGA reliability. Therefore, a reliability study of 12 adults with spastic bilateral CP was carried out at the SunHF motion analysis laboratory. As this reliability study will be presented elsewhere, only preliminary analyses are presented (see chapter 4.7. Statistical issues, p. 52).

Physical examination (Papers I and II)

Unilateral popliteal angle [15, 162], measured bilaterally with a goniometer was the chosen lower limb ROM measure. The assessment procedures are described in Appendix SII of Paper I. The average of the two unilateral popliteal angles were calculated and presented [167, 204].

The *modified Ashworth scale (MAS)* [167, 168] was used to assess muscle tone of the ankle plantar flexors, knee flexors, knee extensors and hip adductors bilaterally. The assessment procedures are described in Appendix SII of Paper I. The measures of muscle tone were transformed into a summary measure calculated as the mean of the measurements [167, 204].

The *manual muscle test scale* according to Hislop was used as an indicator of muscle strength in hip flexors, extensors and abductors, knee flexor and extensors and ankle plantar and dorsal flexors bilaterally [169]. The assessment procedures are described in Appendix SII of Paper I. The measures on muscle strength were transformed into a summary measure calculated as the mean of the measurements [167, 204].

The feet were visually examined with the participants in a standing position [205]. *Foot deformity* was decided when tibiocalcaneal angle was estimated to be greater than 5° varus/ valgus (yes/no). For 66 of the participants this procedure was documented by posterior/anterior and medial/lateral photos. These photos were used in a secondary evaluation of right and/or left foot deformity during the data processing procedures.

Timed-Up and Go and 6-minute walk test (Papers I-III)

All the participants performed the TUG test and underwent the 6MWT in a quiet corridor with a marked starting point, subsequent small marks for each meter, and a long mark at the 30 meter point that was the turning point for the 6MWT (Figure 6). A digital stopwatch with an accuracy of one decimal figure in units of one second was used to measure the time in both the TUG test and the 6MWT. As performance on the TUG test is shown to be related to chair type [206], this study used an armchair according to the recommendations. In the 6MWT, chairs were used as turning points to support turning if needed.

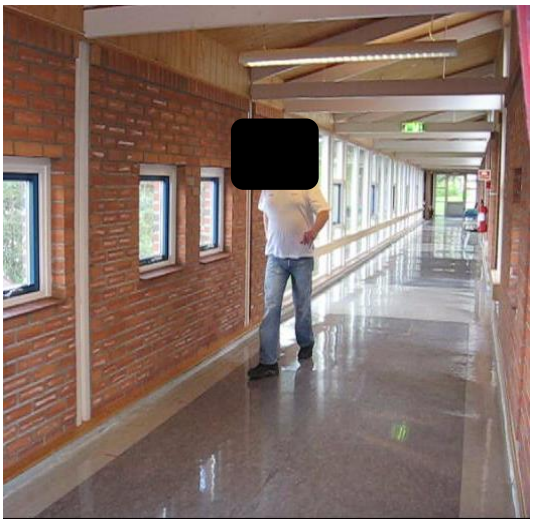

Figure 6 *The "6MWT corridor"*

Before the tests, a Polar heart rate monitor (Polar Electro Oy Finland) was attached to the participants, and the participants relaxed for at least 5 minutes, or until their heart rate reached a steady state (resting heart rate). The resting heart rate was attained when heart rate readings taken one minute apart were within five beats of one another. The last value was chosen and controlled by a 15-second palpation of the radial pulse.

The *TUG test* was performed: Sitting on the chair with their backs touching the back of the chair, the participants were instructed to rise, walk as fast and safely as possible to a marker on the floor 3 meters away, turn around, walk back to the chair, and sit down on set cues. Timing started on the word "start" and finished once the participant's back touched the back of the chair [172]. Participants performed the test three times; the fastest time measured in seconds with one decimal place was used.

Necessary rest and the instructions for the *6MWT* were then given. The participants were instructed to walk as fast, as safely and as long as possible for six minutes. The investigator repeated set phrases every minute during the walk [171]. The total distance recorded to the nearest meter, 6MWT distance (6MWD), was the variable used.

Energy cost of walking (Paper I and Paper III)

Immediately after the 6MWT was completed, and while the subject was still standing, the individual's heart rate was assessed from the heart rate monitor and his or her perceived exertion was judged on the *Borg scale* [155, 156].

Physiological cost or effort of walking was estimated by calculating the *PCI* by data obtained during the 6MWT procedure [153, 158]. (The formula has been presented at p.28).

Self-report (Papers I and II)

Health related quality of life

HRQOL was assessed using the Norwegian SF-36 (version 1.2, chronic) [187, 189]. The SF-36 measures eight health domains using a multi-item scale. The content of these eight domains are summarised in Table XI.

Table XI: The eight health domains of Short Form 36 (SF-36) version 1.2 [187, 189]

Health domains	**Content**
Bodily pain (BP)	Two questions concerning the severity of pain perception and the impact from pain on social functioning.
Physical functioning (PF)	Ten questions concerning limitation of physical functioning because of health problems
Role physical (RP)	Four questions concerning limitation in usual activities because of physical health problems
General health (GH)	Five questions concerning general health perception
Vitality (VT)	Four questions on vitality (energy and fatigue)
Social functioning (SF)	Two questions concerning limitation on social functioning because of physical or emotional problems
Role emotional (RE)	Three questions on limitation in usual activities because of emotional problems
Mental health (MH)	Five questions concerning general mental health (psychological distress and well-being)

The raw scores were coded and recalibrated, then added and transformed into eight health domains scored on a 0-100 scale, with higher number representing better health [187].

VAS muscle stiffness/spasticity
A 100 mm VAS scale was used to assess the perceived impact from muscle-stiffness/ spasticity during walking [195, 196]. The rating instruction was "rate your muscle stiffness/spasticity during walking with the text "no muscle-stiffness/spasticity" placed to the left of the 100 mm VAS scale and "highest imaginable muscle stiffness/spasticity" to the right.

Fatigue Severity Scale
The level of fatigue was assessed using the FSS [198, 199]. The mean of all statement scores was the FSS score used.

Global Scale
A Global Scale was used to document the overall perceived effect of the therapy. This scale consisted of a 3-point verbal rating scale (worse – the same – better) [112, 122].

CP specific classification items and descriptive variables (Papers I-IV)
A standard scheme was used by the principal investigator for relevant anamnesis (Attachment 2). These data were used to supplement the information from medical records.

CP type
The classification of CP type was based on medical records and clinical examination (Attachment 1) according to the SCPE criteria of spastic CP [11].

GMFCS
The GMFCS was used to rate the participants walking performance (Table 1 p. 5) [21]. The present *GMFCS* level was rated based on observation and information from the participants. The need for a railing to descend stairs was used to discriminate between GMFCS level I and II (e.g. by discreetly observing how they ascended and descended stairs during the study visit, and by asking them about the way they walked up or down stairs in familiar environments). The GMFCS level at late adolescence (18 years of age for most of the participants, and 15 years of age for those who were 18 years of age), was rated based on information from the participants [25].

FMS
The *FMS* was rated based on information from the participants about their usual method of mobility in three different environments representing 5, 50 and 500 meters [180].

Questionnaire concerning present walking ability

The questionnaire concerning present walking ability included a "checklist" on the causes of changes in walking ability, walking performance in different contexts, and on limiting symptom(s) related to walking. In addition, the participants could add their own comments (Paper I, Appendix SI).

Adverse events

Registration of adverse events was performed by the participants by marking "No adverse events/unwanted effects" or "Yes, adverse events/unwanted effects." This last statement was supplemented by a "describe" section and space to give more detailed comments.

4.7. Statistical issues

Sample sizes

Based on the research question and the best available literature, an a priori power calculation was carried out for the RCT. A mean difference of 6° was considered clinically relevant, and a SD of 8° for ankle dorsiflexion in stance was assumed [93]. Sample size was calculated using the formula: $n = 2 \times (\sigma / \Delta)^2 * C$. ($\sigma$ = SD, Δ = mean difference, and C = Constant according to a significance level of 0.05 and a power at 80%; here C = 7.9) [207]. This resulted in a sample size of 28 in each group. Five individuals were added to each group in case of drop- outs.

As a result the sample size was estimated at 66 participants for the RCT (Paper II). This was desiccative for the number of participants in the studies presented in Paper I and Paper III. The sample size of 10 CP-participants and 10 observers in the study presented in Paper IV was based on similar studies [147, 149]. The different sample sizes are presented in Figure 7.

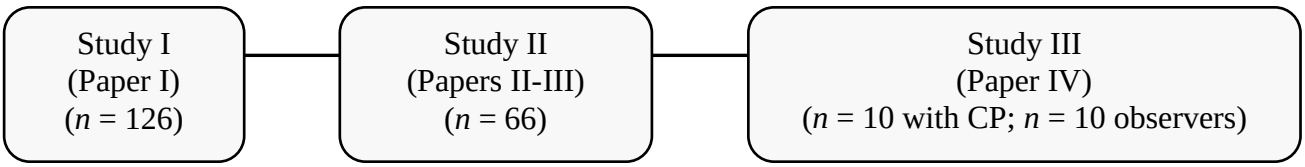

Figure 7. The sample sizes for the studies presented in Papers I-IV.

Handling of drop-out and missing data

All the studies were prospective, and an effort was made to avoid missing data during the data collection phase. In Paper II, the results presented were based on per-protocol analysis (n = 65) at week 8 and the last results carried forward at week 16 (n = 65).

Statistical methods

Descriptive data were presented as mean (SD), medians and quartiles, or by frequency distributions. All statistical tests were two-sided, and a 5% significance level was used. In order to identify significant changes and support interpretation of the results, 95% confidence intervals (CIs) were presented [208]. The Statistical Product and Service Solutions (SPSS Inc., Chicago, Illinois, USA) versions 15.0 and 18.0 were used in most calculations. However, the principal component analysis, ridge modelling, and the bootstrap routines to model the multiple linear regression in the study presented in Paper I were performed in the R statistic software, version R.2.9.1 (http://www.r-project.org/). R was also used in calculating the bootstrap CIs of the eight SF-36 domains in the RCT presented in Paper II.

Paper I

There were no missing data. Differences in TUG scores and 6MWD between the GMFCS levels were analysed using the Kruskal–Wallis test for comparison of groups with Mann-Whitney U test as post hoc tests for non-normally distributed data (TUG scores), and the one-way analysis of variance (ANOVA) with Tukey's post hoc tests for normally distributed data (6MWD).

Relevant literature was considered to identify possible predictors of 6MWD, reflecting both patient characteristics and the different ICF domains. As the TUG scores displayed a skewed distribution, it was log transformed. Bivariate relations between selected variables were explored in cross tables, box plots, and scatter plots, with corresponding Pearson's and Spearman's correlation coefficients. These plots were also visually checked for linearity with the 6MWD. The regression model building included univariate regression analyses, analyses of several custom models considered to be of importance, and stepwise procedures. Every step of the analysis involved statistical diagnostics, and discussions of the clinical importance of the finding.

Paper II

There were no missing data. A paired sample t-test was used to analyse changes in continuous variables from the baseline in each group. This approach was chosen due to the demonstrated robustness of parametric statistics for moderately skewed data [209], and because analyses with non-parametric statistics and bootstrap CIs (bootstrap methods with 10 000 replicates) (SF-36) gave similar results. As the residual check was found to be satisfactory, the analysis of covariance (ANCOVA) was used to compare differences between the groups in primary

and secondary outcomes at week 8 and 16, with the week 8 or 16 score as the dependent variable and the baseline score and treatment group as independent variables [210]. The Fischer's exact test with relative risk (RR) and risk difference were applied to compare the Global Scale scores between the two groups [133]. These statistical methods were also used in secondary exploratory analyses of the proportions of participants, achieving what was considered a clinically relevant improvement for the SF-36 scales and VAS-muscle-stiffness/spasticity.

Paper III

A one-way analysis of variance (ANOVA) with Tukey's post hoc tests was used to determine significant differences in mGDI scores between the reference population and different GMFCS levels. Pearson's or Spearman's correlation (*r*) was used to estimate the association between mGDI and TUG, 6MWT, and PCI. The magnitude of the *r* was evaluated as *little* (0-0.25), *low* (0.26-0.49), *moderate* (0.50-0.69), *high* (0.70-0.89) and *very high* (0.90-1.0) [140 (p. 358)].

Paper IV

There was one missing data from the SF-GT measurements, resulting in 1799 joint angles. Agreement between actual measurements in degrees was calculated using Bland-Altman plots with mean differences and 95% limits of agreement (LoA), i.e. 2 standard deviations of the differences (2*SDdiff) [211]. Scatter plots with Pearson's *r* were used supplementary, and the magnitudes of the *r* were evaluated as described above [140]. To explore whether increased movements in the transverse plane could explain the differences between measurements in 3DGA and SF-GT, the transverse plane 3DGA curves for pelvis, hip and foot-progression were visually compared with scatter plots of the initial contact knee joint angle from the SF-GT measurements and the sagittal plane 3DGA.

Preliminary analysis of 3DGA reproducibility

The test-retest reproducibility of 3DGA data presented in Paper II underwent preliminary investigation (and will be published elsewhere), using a sample of 12 adults with spastic bilateral CP, GMFCS levels I-III assessed by the same investigators on two different days (median one day between the tests). The standard error of measurement (SEM) was calculated using the formula $SD_{diff}/\sqrt{2}$ [8, 212]. The results are presented in Table XII.

Table XII: Preliminary results on reproducibility of 3DGA sagittal kinematics

Outcomes from 3DGA sagittal kinematic	**Standard error of measurement (SEM) [212]**
Ankle initial contact	3.1°
Ankle peak stance	3.1°
Ankle peak swing	2.6
Knee initial contact	3.4°
Knee peak stance	3.4°
Knee peak swing	3.2°
Hip range of motion	1.5°

3DGA, three dimensional gait analysis.

4.8. Ethics, regulatory requirements, and funding

The fundamental principles of medical ethics were taken into account, including respect for the individual's autonomy, a minimum of burden to the individual, and balancing the risks, costs and benefits, following the guidelines for Good Clinical Practice [213].

It was recognised that adults with spastic CP could have unsatisfied needs, that several of the respondents would not be eligible for participating in this project, and that several would have having expectations about automatic follow-up when participating in this study. Efforts were made to give detailed spoken and written information about practical issues relevant to the study, and the close cooperation with the SunRH clinical department was essential in handling this ethical concern.

Before the project began, all the studies, including the reliability study of 3DGA, received approval to be carried out from the Regional Ethical Committee and permission from the Data Protection Officer.

The ethical approval of the BoNT-A interventional study, included the approval from the Norwegian Medicines Agency (EudraCT.no 2006-001427-19, project no. 206 24 503). As a pharmacological study, it had to fulfil several requirements considering unexpected adverse events and unexpected serious adverse events (SUSAR's) (e.g., "obligatory" reports and "change" – or "status" reports, and specific insurances). This study was registered at ClinicalTrials.gov ((http://clinicaltrials.gov/; ClinicalTrials.gov identifier: NCT00432055) at the beginning of the study.

All participants were given spoken and written information about the aims of the three studies, testing procedures and intervention when relevant, and the data protection procedures. The participants gave a written informed consent concerning each study separately before they were included. In Study III (Paper IV), both participants with CP and the observers recruited from the SunRH clinic gave written informed consent.

The entire project was supported by The East Regional Health Administration and SunRH (grant number 206 24 503), and had no link or cooperation with the pharmaceutical industry.

5. SUMMARY OF PAPERS – MAIN RESULTS

5.1. Study participants

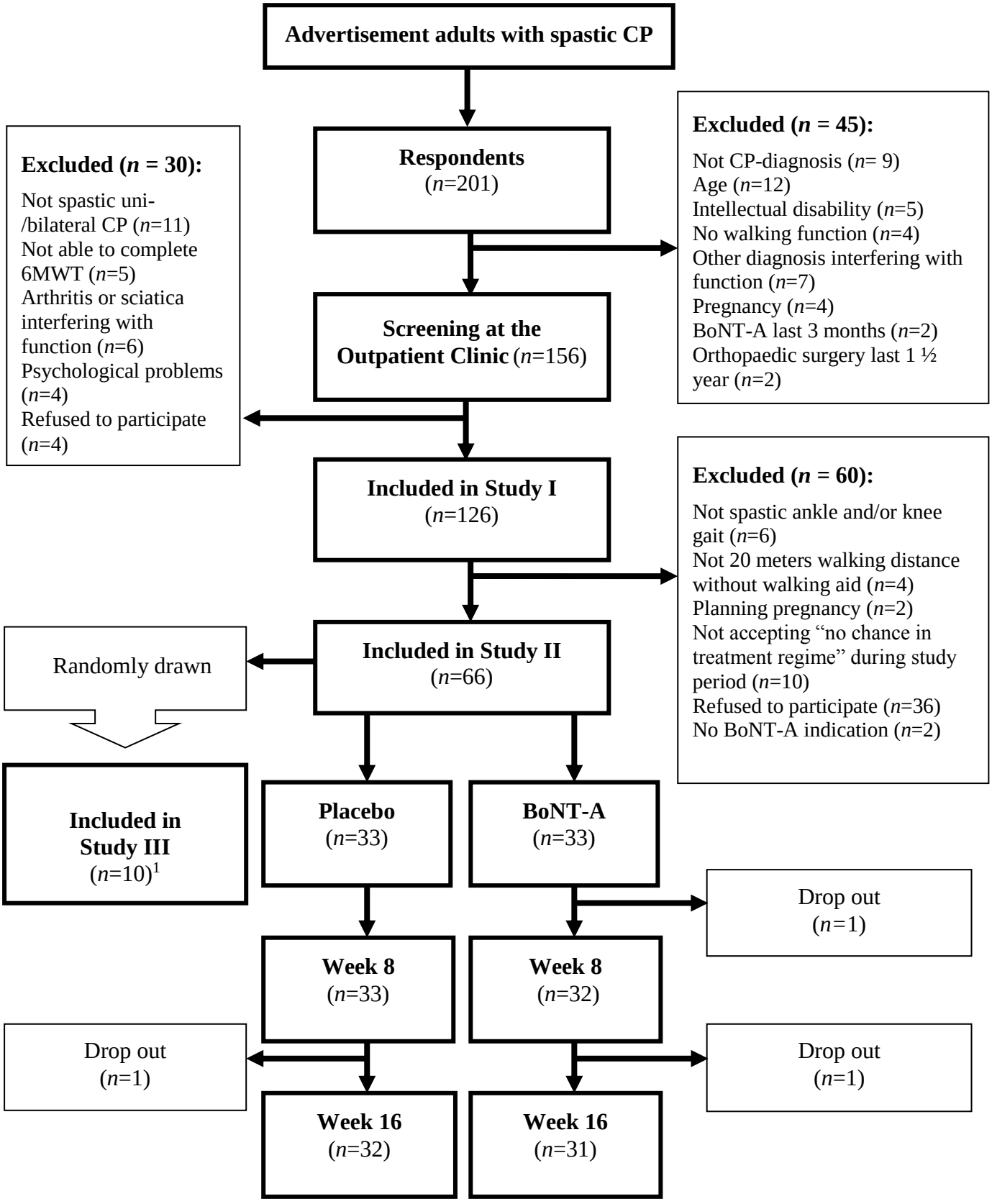

Figure 8. Flowchart study participants. [1]In additions 10 observers recruited from the clinic at SunRH

Of the 201 respondents to the advertisement, 156 met the inclusion criteria and were enrolled for further testing (Figure 8). After clinical examination, another 26 individuals were excluded, four refused to participate, and 126 individuals were included to Study I which is presented in Paper I (Figure 8). From this population another 24 individuals were excluded and 36 refused to participate in Study II which is presented in Paper II. The participants in Study III (Paper IV) were 10 observers and 10 randomly drawn participants from the study population of Study II.

Table XIII: Demographics, type of CP and functional level of participants in Study I and II

	Study I (Paper I)	**Study II (Papers II-III)**		
	All	**All**	**BoNT-A**	**Placebo**
	***(n* =126)**	***(n* = 66)**	***(n* = 33)**	***(n* = 33)**
Demographics				
Gender, *n*				
Women	73	36	19	17
Men	53	30	14	16
Age, years, mean (SD)	39 (12)	37 (11)	36 (11)	38 (12)
Education (duration), *n*				
First level (9 years)	25	13	6	7
Second level (12 years)	49	26	15	11
Third level (>12 years)	52	27	12	15
Income[1], *n*				
Paid work ≥ 20% or student	97	51	25	26
Disablement benefit/unemployed	51	21	13	15
Diagnosis and functional level, *n*				
Spastic CP				
Unilateral	59	30	16	14
Bilateral	67	36	17	19
GMFCS				
Level I	12	9	5	4
Level II	94	48	24	24
Level III	20	9	4	5

CP, cerebral palsy. GMFCS, Gross Motor Functional Classification System. [1]For several with less than 100% paid work and some of the students the income was combined with with disablement benefit, so the number add up to more than the number of participants.

The study populations in Study I and II were comparable (Table XIII and Table XIV).
All the participants had the diagnosis of spastic unilateral (hemiplegia) or bilateral (diplegia) CP in their medical record, were ethnically Norwegians, had attended mainstream education, were GMFCS levels I-III, and perceived reduced walking ability compared with adolescence.

Approximately half of the participants had undergone some kind of lower limb orthopaedic surgery Table XIV). Lengthening procedures of mm.gastrocnemius/soleus muscles (tendo-achilles lengthening and/or isolated muscle lengthening procedures) were the most common (*n* = 47 (37%) in Study I, and *n* = 29 (44%) in Study II.

Table XIV: Clinical characteristics of participants in Study I and -II

	Study I (Paper I)	**Study II (Papers II-III)**		
	All ***(n* =126)**	**All** ***(n* = 66)**	**BoNT-A** ***(n* =33)**	**Placebo** ***(n* = 33)**
Medical history[1], *n*				
Medication	52	29	17	12
Other diagnosis	63	30	16	14
Previous lower limb BoNT-A	4	4	2	2
Previous lower limb surgery	62	38	19	19
Lower limb impairment				
Muscle tone, median (IQR)	1 (0.5-1.6)	1.1 (0.6-1.7	1.3 (0.8-1.9)	1.6 (0.9-2.7)
Muscle strength, median (IQR)	4.4 (4.1-4.7)	4.5 (4.2-4.6)	4.5 (4.2-4.6)	4.6 (4.3-4.8)
Popliteal angle, mean (SD)	51 (13)	52 (12)	54 (11)	51 (11)
Training, *n*				
Never	7	6	2	4
Every month	35	14	7	7
Every week	37	17	10	7
Several times a week	47	29	14	15
Physiotherapy, *n*				
Never	24	14	6	8
Every month	27	13	5	8
Every week	45	30	17	13
Several times a week	22	9	5	4
Orthotics/orthopaedic shoes, *n*	34	17	9	8

[1]From medical records, information from the participants, and by inspection for scars (lower limb surgery). Several participants had more than one medication and/or other diagnosis and/or previous surgery procedures.

5.2. Paper I

This study aimed to describe walking function in a population of adults with spastic CP experiencing reduced walking ability, and to identify clinical and demographic factors predicting their functional walking capacity as measured with the 6MWD.

Of the study population of 126, the majority 75% (*n* = 94) were classified at GMFCS level II. According to GMFCS level at adolescence, 39% (*n* = 50) had declined one GMFCS level. FMS scores showed that 93% (*n* = 117) walked without aids at home (FMS 6 or 5), 84% (*n* = 105) at school/workplace, and 70% (*n* = 88) in the community setting. Increased stiffness was the most frequently reported cause of reduced walking ability.

The mean (SD) 6MWD was 485 (95) meters. TUG values and 6MWD varied significantly across the GMFCS levels ($p<0.001$).

In multiple linear regression analyses, gender, type of CP, popliteal angle, SF-36 BP, and TUG values were identified as significant predictors for 6MWD (Table IV in Paper I), explaining 67% of the total variance of 6MWD.

Females had a shorter 6MWD than males, as did participants with bilateral CP compared to those with unilateral CP. An increase of 1° in the popliteal angle resulted in a 2.6 meter shorter 6MWD; transferring this result to clinical practice, a 10° increase in popliteal angle would have resulted in a 6MWD that was shorter by 26 meters. The regression coefficient for BP reflected a 6MWD 1.3 meters longer, with a score that was one point higher on the 0 to 100 BP scale, indicating less pain. The regression coefficient for a log-transformed TUG of -377 reflects a shorter 6MWD with increasing TUG values (in seconds). Participants with a TUG value at the lower quartile for the group (5.9 seconds) walked on average 100 meters further than those at the upper quartile for the groups (9.6 seconds).

In short, self-reported walking ability in adolescence compared with current GMFCS classification indicated a shift in GMFCS level for 39% of the participants. CP-related neuromuscular deficits, pain, and gender were identified as factors predicting functional walking capacity, explaining 67% of the variations in 6MWD.

5.3. Paper II

This RCT aimed to investigate the short term effects of BoNT-A compared to placebo in adults with spastic CP experiencing reduced walking ability. A flowchart for this study is presented in Paper II.

The outcomes at baseline were comparable between the treatment groups (Table XV).

Table XV: Outcomes at baseline

	Placebo (*n* = 33) Mean (SD)	**BoNT-A (*n* = 32)[a] Mean (SD)**
Primary outcomes		
Kinematics (degrees, (°))		
Ankle initial contact	-6.2 (7.1)	-7.2 (6.0)
Ankle peak stance	14.6 (4.7)	10.7 (4.7)
Ankle peak swing	-0.2 (4.9)	-1.8 (6.2)
Knee initial contact	17.2 (8.8)	17.4 (7.6)
Knee peak stance	7.6 (8.6)	6.0 (8.6)
Knee peak swing	53.2 (8.6)	53.7 (6.9)
Hip range of motion	41.1 (7.5)	43.4 (6.8)
SF-36 (0-100)		
Mental health	77.7 (16.8)	74.4 (14.6)
Vitality	51.5 (22.8)	45.2 (15.5)
Bodily pain	64.8 (22.1)	54.4 (24.7)
General health	63.5 (18.9)	59.8 (22.9)
Social function	83.3 (17.9)	80.1 (18.7)
Physical function	64.9 (17.8)	67.8 (20.7)
Role physical	54.6 (42.1)	43.8 (39.1)
Role emotional	77.8 (36.0)	69.8 (39.1)
Secondary outcomes		
6MWT distance (meter)	493 (74.7)	495 (92.1)
TUG test (seconds)	7.4 (2.6)	7.3 (1.9)
VAS muscle-stiffness/spasticity (0-100)	45.8 (22.7)	41.5 (24.9)

SF-36, Medical Outcome Study Short Form 36. 6MWT, 6-minute walk test. TUG, Timed Up and Go. VAS, visual analogue scale.

The muscles selected for injection did not differ between the groups. The median dose injected was 6ml (300 Allergan Units Botox®) (range 3-8 ml). The number of muscles injected and total doses is presented in Table XVI.

Table XVI: Number of muscles injected

Muscle(s) injected	BoNT-A (*n*)	Placebo (*n*)
Gastrocnemius	5	6
Gastrocnemius, soleus	6	4
Gastrocnemius, tibialis posterior	5	3
Gastrocnemius, soleus, tibialis posterior	3	5
Gastrocnemius, soleus, flexor digitorum	0	1
Gastrocnemius, tibialis posterior, flexor digitorum	1	1
Gastrocnemius, semimembranosus, semitendinosus	2	2
Gastrocnemius, semimembranosus, semitendinosus,soleus	2	0
Gastrocnemius, semimembranosus, semitendinosus, tibialis posterior	0	1
Gastrocnemius, semimembranosus, semitendinosus, rectus femoris	1	2
Gastrocnemius, rectus femoris	1	1
Gastrocnemius, rectus femoris, tibialis posterior	1	0
Semimembranosus, semitendinosus	1	1
Semimembranosus, semitendinosus, biceps femoris	2	1
Semimembranosus, semitendinosus, rectus femoris	3	5
Total number of injected muscles[a]	101	104
Total (ml) injected	201.0	205.5

[a]for several of the participants there were bilateral treatment.

There were no statistically significant or clinically relevant benefits of BoNT-A compared with the placebo on the kinematic variables (Paper II Table V). No statistically significant differences were found between the groups in SF-36 for either of the domains at week 8 (Paper II Table V) or week 16 (data not shown). Both groups demonstrated significant improvement for BP, and the BoNT-A group also showed significant improvement for vitality (VT). Several of the SF-36 domains showed the upper limits of CIs exceeding the predefined MCID on the group level as well as between the groups. Exploratory analyses investigating the number of participants who had improved according to the predefined MCID for SF-36 showed a statistically significant difference in favour of the BoNT-A group for mental health at week 8 (Paper II Fig. 2), and for mental health and social functioning at week 16 (data not shown).

At week 8, both groups demonstrated reduced VAS muscle-stiffness/spasticity with a statistically significant difference between the groups in favour of BoNT-A (Paper II Table VI). Using a 30% improvement from baseline as clinically relevant improvement for VAS muscle-stiffness/spasticity, this was observed for 16 individuals in the BoNT-A group and nine in the placebo group (relative risk (RR) 1.83, 95% CI 0.95, 3.53). Improvement on the Global Scale ("better") was reported by 19 respondents in the BoNT-A group versus nine in the placebo group (Paper II Table VI). At week 16 there was no significant differences between the groups for either the VAS muscle-stiffness/spasticity or Global Scale (data not shown). Mild intervention related adverse events were similar between the groups.

In short, there were no differences between the groups for the primary outcomes (3DGA kinematics and SF-36), but significant differences in favour of the BoNT-A group for the self-reported secondary outcomes VAS-muscle-stiffness/spasticity and Global Scale. The treatment with BoNT-A was safe.

5.4. Paper III

This study aimed to study the face and construct validity of the GDI for adults with spastic CP. Face validity was studied by investigating if the GDI had similar distributional properties to those previously demonstrated in child populations. Construct validity was studied by investigating whether GDI differed between GMFCS levels and by the association between the GDI and activity measures for mobility (TUG) and walking capacity (6MWT), as well as energy cost during walking as measured with the PCI.

The GDI mean (SD) of 101.1 (8.8) for the reference population, and the lower GDI scores in adults with CP (mean 74.3, SD 11.6) were similar to previous publications on GDI's distributional properties in healthy children and children with CP [143, 145].

The distributions of mGDI scores for the reference population and the adults with CP at different GMFCS levels are illustrated in Fig. 1 in Paper III, showing statistically significant differences between the reference population and the groups with CP ($p < 0.001$). There were statistically significant differences in mGDI between participants at GMFCS level I and level II (mean difference 13.5, 95% CI 5.7, 21.2), and also between level I and level III (mean difference 17.0, 95% CI 7.0, 27.1). However, there were no significant differences in mGDI between participants at level II and level III (mean difference 3.5, 95% CI -4.2, 11.3). The associations between mGDI and functional walking capacity (6MWT), and basic mobility

(TUG), were low (6MWT: *r* 0.30, 95% CI 0.09, 0.49; TUG: *r* -0.30, 95% CI -0.52, -0.05). A moderate association was found between mGDI and PCI (*r* -0.56; 95% CI -0.69, -0.38).

In short, GDI demonstrated similar results in distributional properties (mean (SD) and GMFCS levels) as those reported in studies on healthy children and children with CP. Thus, GDI appeared to show the extent of gait pathology, also indicating good validity for healthy adults and adults with spastic CP. Low associations between GDI and the results of 6MWT and TUG suggested that gait and walking/mobility are two different constructs.

5.5. Paper IV

This study investigated concurrent criterion validity by comparing joint angles measured from sagittal video recordings with 3DGA kinematics (joint angles). It also explored the question of whether movement deviations in the transverse plane identified with 3DGA affected the validity of sagittal video joint angle measurements.

The SF-GT measurements from the 10 observers are summarised in Paper IV Fig. 2. For each of the 18 3DGA kinematics (joint angles) and SF-GT measured joint angles, 10 Bland-Altman plots and 10 scatter plots were made; the researchers then calculated the mean differences and LoA, and Pearson's correlation coefficients, one for each of the observers' concordance with 3DGA. The summaries of these numbers are presented in Paper IV Table 1.

The best agreement between SF-GT and 3DGA was found for the knee joint with mean differences for the different gait events ranging from 0º to 17º and LoA in the range 8-15º. Clinically relevant examples of the ranges of individual observer's agreements are mean difference (LoA) of -1º (10º) and -13º (11º) for knee joint angle at initial contact, and 2º (6º) and 11º (11º) for knee joint angle in midstance. The overall mean correlations for the hip, knee and ankle were 0.39, 0.68, and 0.39 respectively (Paper IV Table 1). Paper IV Fig. 3 shows the variation of visually estimated joint angels of knee initial contact for all the 10 participants against the simultaneous 3DGA joint angles, as well as transverse plane curves for one gait cycle.

In short, substantial discrepancies and a lack of agreement between joint angles measured from sagittal video recordings and kinematics (joint angles) from 3DGA were found. Discrepancy between the 3DGA kinematics (joint angles) and the SF-GT measurements was seen both with and without deviations from the reference band in transverse 3DGA kinematics.

6. DISCUSSION

The discussion part of this thesis is twofold: *First*, methodological aspects will be discussed. *Second*, a discussion of the main results will be presented.

6.1. Methodological considerations

Research quality

The quality of the studies in this thesis relies on sufficient consideration of validity and reliability where validity may be defined as "the approximate truth of an inference" and reliability as "consistency" [214 (p. 511, 513), 215]. Considering study quality, validity judgements are not absolute, and threats to validity are not mutually exclusive, which indicates that decreasing the threat to one type of validity may increase another [215]. The following sections will attempt to consider important perspectives with regard to the validity and/or reliability of the studies included in this thesis.

Study designs

All the studies included in this thesis were prospective, thus creating an opportunity to control the data recording.

Considering resources, time available and limited knowledge regarding walking ability and functional walking capacity in well-functioning adults with spastic CP, the choice of a cross-sectional design in Study I (Paper I) was considered appropriate [216]. However, cross-sectional designs cannot reveal dynamic processes and changes, and conclusions about cause and effect relationships must be interpreted with caution [216].

In Study II (Paper II) the challenge was to organise and conduct a clinically relevant intervention study. Aiming to provide the strongest possible basis to infer that the observed results could be attributed to the effects from BoNT-A and not other factors, a double (triple) blinded placebo controlled RCT was selected. Maximising internal validity relates to both minimising bias, (e.g. structural deficiencies in a study which tends to produce results or conclusions that differ systematically from the truth) [132], and confounding factors, (e.g. when a baseline characteristic is associated with the outcome, but unevenly distributed between the treatment groups). Thus, the blinded design was intended to control bias, and the randomized procedure was intended to control any confounding factors. Potential confounders related to a BoNT-A intervention, such as age, lower limb impairments, previous

orthopaedic surgery in lower limbs, physiotherapy, training, and educational level were comparable between the two treatment groups.

However, it is recognised that an RCT design has its limitations in such a heterogeneous population, where heterogeneity makes it difficult to identify effects attributable to the intervention, thus limiting internal validity. Despite the fact that such a study design in general requires more participants than a pre- and post design, the chosen design was considered to be the best. The main reason for this was that no studies on the effects of BoNT-A in adults with CP have previously been conducted. In addition to being an effect-study we considered this first BoNT-A RCT on adults with CP to also be a safety and feasibility study.

The realistic time course and number of interventions required for a complex condition like walking disability in adults with spastic CP clearly revealed that the 16-week study period was a limitation. In reviewing the literature, week 1, week 4, week 8 and week 16 were considered as possible primary endpoints [93, 113-115, 127, 130]. It was considered that a week 1 endpoint would mainly measure body structure/function, a week 4 endpoint probably was too short to make a difference regarding activity and participation, and that a week 16 endpoint would be limited by the fact that the injection was performed only once and with no integrated specific post-treatment physiotherapy. According to the study aim, it was important to address the primary effects from BoNT-A on tone reduction and gait (body structure functions) as well as its potential effects on activity and participation. Eight weeks were a compromise regarding this issue, as the medical effect of BoNT-A effect was still present and the participants had had some time to adapt to potential effects. This evaluation point was similar to that used in more recent publications studying the effects from lower limb BoNT-A in ambulant children with spastic bilateral CP or adults with sequels after stroke [217, 218]. The chosen evaluation time at week 16 was a compromise between the ideal and the possible.

Sample representativity

The representativity of study populations is of importance concerning the external validity of a study. This study population consisted of self-selected volunteers through advertisements, thus unexplained and unexpected bias may have occurred.

Response bias, which is a type of selection bias, may have influenced the results presented in Papers I-III. It is recognised that women may respond to newspaper advertisements to a higher degree than men [219]. However, the advertisements were also on web-pages and on

the SunHF information board. Furthermore, it is possible that those with busy jobs or daily lives, or more severe impairment, and/or living at a long distance from the hospital, did not consider study participation to be feasible. In the BoNT-A study as well, we must consider both expectation and attention, the so-called popularity bias, e.g. the interest stirred up by the possible effects of BoNT-A and/or a previous history of difficulties in getting this treatment [132]. However, one advantage of the recruited study population was that a self-experienced reduction in level of walking ability, in addition to the diagnosis, was one of the inclusion criteria. This leads to a study population with a reasonable function, where perceived increased impairment was the target for the interventional procedure, and may be considered to be a strength of the study [135, 220]. On the other hand, preconceived individual preferences of the responders regarding what was considered to be reduced walking ability introduced heterogeneity [66, 73]. In addition, the advertisement text may have influenced the way in which the responders reported their experiences.

The participants recruited were characterised by a relatively high functional level. None were cognitively impaired, and except from three individuals aged 18 years, none lived with their parents. Compared with other study populations of adults with CP [1-3, 157], this study (Papers I-III) had more women, only individuals with spastic uni- or bilateral CP, a higher participation level (education and work, training and physiotherapy), and better gross motor function (GMFCS levels, 6MWD).

The comparable levels of pain and fatigue with the study population of Jahnsen et al. and Opheim et al., probably reflects the foremost occurrence of such symptoms in adults with CP [5, 64, 65]. Perceived health as measured with SF-36 was also comparable with the study population of Jahnsen et al. [65, 190]. The high attendance rate to physiotherapy and/or fitness training may be explained by the inclusion criteria.

In general, the clinical manifestations of spastic CP are very heterogeneous [9, 10, 12]. Thus, the results in this study should only be generalised to those comparable with the population investigated. Compared with a total population survey from Norway of children with CP born between 1996-1998, where 55% were classified in level I and II, and 17% in level III (28% in level IV-V) [12], 98% of this study population was classified at GMFCS level I and II in adolescence. For that reason, our study population may be considered a selected well-functioning group of individuals with spastic CP. However, as demonstrated by the results of 6MWT (range 260 meters – 730 meters) and TUG test (range 3.6 seconds – 24 seconds), this

study population (n = 126) also varied considerably in respect to walking capacity and mobility.

Study procedures

As the data collection was performed solely by the principal investigator, the possibility that the semi-structured interviews and the clinical examinations were performed differently, or that the questions were misunderstood or interpreted differently and/or resulted in missing items, was reduced. However, the semi-structured interviews may have been biased by preconceived preference or inclination that influenced the way in which the interview procedure was performed.

The importance of patient preference, placebo effects and the doctor-patient relationship should not be underestimated. In this study the principal investigator may have introduced non-specific treatment effects. In recognition of the power to define the reference point from which the participants judged their disability, the communication with the participants was carried out very carefully. Though, as the researcher considered this study to be important, it was probably easy to be enthusiastic. However, since this was a blinded study, there were no differences in the personal meetings between the placebo and the BoNT-A group. The fact that the principal investigator was responsible for and/or performed both intervention and evaluation may be considered as a limitation. However, this was considered acceptable due to the blinded design.

Intervention

The rationale of carrying out a BoNT-A intervention study was based on the possibility that reducing dynamic muscle hypertonia (muscle overactivity) could improve gait, and walking-related stiffness with implications for activity and participation. Intramuscular BoNT-A injections impacts only the dynamic component of muscle tone [221]. As muscle overactivity may be difficult to differentiate from contracture, auditive EMG was used to verify the presence of a dynamic component. Hopefully this factor assured the purpose of the intervention which was to treat muscle overactivity [118]. The muscles selected for injections were also individualised. Thus, the BoNT-A injection procedure per se may be considered valid. However, specific additional therapy was not given, the maximum dose was 400 Allergan Units of Botox®, m. iliopsoas was not injected, and the intervention was performed only once. As a result, these factors may have created a threat to the external or "ecological" validity.

As external validity concerns the extent to which the results can be generalised to treatment settings, people, times, or other variables beyond those that were studied, this study is limited when considering the integrated multidisciplinary BoNT-A treatment regime defined by experts in the field [91, 105, 110]. On the other hand, in conducting research comparing the effects of BoNT-A and physiotherapy/specific training with placebo and physiotherapy/ specific training, one must recognise that treatments of interest may differ simultaneously along multiple dimensions in possible positive and negative directions [222]. In adults with spastic CP there is limited knowledge regarding dose and tolerance of both physiotherapy and training [223]. If a physiotherapy program with the aim to improve gait, i.e. integrated stair climbing and treadmill training had been included for this population, some of the study participants could have been at risk for exhaustion and musculoskeletal pain. As well, in a multimodal intervention, it would be difficult to separate the contribution of BoNT-A in potential effects [131, 222, 224].

Validity of assessment tools and the variables analysed

The validity of a study also depends on whether assessment tools and outcomes are clinically relevant or important. The use of the ICF as a conceptual framework, as well as outcomes from self-reports, a technical objective test, and physician-performed tests may be considered as strengths in this doctoral thesis. However, scarce specific knowledge of these assessment tools' validity and reliability for the population studied is a limitation. Except for the 3DGA data, no formal reliability testing was performed. An effort was made to reduce the issue of reliability by following a strict study protocol [8].

Health-related quality of life and instrumented gait analysis

Data from SF-36 and 3DGA were selected as the primary outcome measures in the RCT. These were considered to be clinically relevant assessment tools for measuring patient perspectives related to health status and participation, and gait [15, 184]. Using HRQOL instruments such as SF-36 is considered important in comprehensive assessments of treatment effects in clinical studies [191]. A disease- specific HRQOL instrument addressing clinically important aspects of a specific health condition would probably have had greater sensitivity. However, this does not exist for adults with CP, and therefore, based on the data from Jahnsen [65, 190], SF-36 was considered to be the best HRQOL instrument available. However, SF-36 demonstrated ceiling-effects in three of the eight subscales (role emotional (RE), role physical (RP) and social functioning (SF)), revealing its limitations in respect of longitudinal validity –

or its properties to measure change over time. In addition to ceiling effects, the results of SF-36 also revealed some "paradox" scorings on the items concerning physical functioning for several of the participants (e.g. "no problem climbing stairs"). This may reflect adaptation to, or acceptance of, their health condition [225, 226], and that the disability refers to limitations and restrictions related to a health problem, while HRQOL relates more to how someone feels about their functional status [191]. These issues helped to decide to present the SF-36 data by its eight domains and not by the two component scores.

Kinematics from instrumented 3DGA was selected as an outcome because it was considered to be a clinically relevant objective outcome. Among several factors imprecise marker placement may be considered as the key factor contributing to 3DGA data variation [203], and the test-retest reproducibility underwent a preliminary investigation. Our result for the standard error of measurement (SEM) were all < 5° and thus considered to be acceptable and in keeping with those reported by others [203]. However, the predefined kinematic outcomes were limited by the heterogeneity of gait strategies and muscles selected for intervention, creating sub-populations with limited or no potential for improvement. Therefore, the validity of the GDI was studied, and then used as an outcome in secondary analyses exploring potential BoNT-A effects from baseline to week 8 (see chapter 6.2, General discussion of results p. 75).

Considering that dynamic increased muscle tone was the targeted impairment, not using surface EMG may be a limitation. Surface EMG analysis synchronised with 3DGA might have been useful in respect to objective data on co-activation patterns and/or "out of phase" activity [227]. However, at the study's start the SunHF motion analysis laboratory did not have this equipment. When not using surface-EMG, VAS muscle stiffness/spasticity during walking was considered to be clinically relevant. It was assumed that this VAS scale could assess perceived muscle responses during walking [196]. Considering the BoNT-A mechanism of action, VAS muscle stiffness/spasticity during walking might have been a more adequate primary outcome in this study. This may also be supported by the previously described consensus publication, which considered self-reports to be the most important outcomes for adults with spastic paresis health conditions [110]. However, as a general impression, the 3DGA sessions in this study resulted in data of good quality and took 60-75 minutes to perform. Thus, 3DGA is suggested as an appropriate assessment tool for gait research in adults with spastic CP, especially for descriptive purposes in longitudinal studies.

Functional assessments

The distance covered in a *6MWT* was the chosen outcome of overall functional walking capacity [171, 174, 175]. In investigating walking ability in this poorly investigated study population we regarded a "functional capacity" measure to be more robust in relation to impairment level than a measure of walking performance where personal factors such as initiative and personal choices could have distorted this relationship. No practice walk was performed due to practical and medical issues (time constraints and a fatigable study-population) and may be a limitation [157]. However, as possible learning effects are reported to subside after about eight weeks [228], this may not have affected the results.

As the *TUG* test captures the complex interaction between balance and movement, including planning, initiating, executing, and completing a series of linked movements that are common in daily activities, it was chosen as the assessment tool to measure functional mobility [46 (p. 273-5)]. In recognition of the limitations of the TUG test as a specific measure of balance and its similarities with 6MWT, it was considered important to use an assessment tool with the potential ability to catch relevant aspects of postural control. The total score of Balance Evaluation Systems Test (BESTest) would have been a more specific measure of balance [73, 229]. However, the BESTest was not published when this study started [229].

In general these two assessment tools were considered to be both clinically relevant and overall very appropriate. They required minimal equipment and were safe and easy to administer. As reported by Anderson [157], the participants in this study also found it easy to understand the instructions and to perform the 6MWT.

Self reports and physical examination

As symptoms and perceived functioning do not necessarily correlate with objective impairments, the participants' perspectives were considered to be important [191]. Therefore outcomes derived from the previously discussed SF-36 and VAS muscle-stiffness/spasticity were selected in the RCT (Paper II). Also, a three-point global rating scale was used to document overall perceived therapy effects [112, 122]. Having only three choices may be considered as strength in terms of consistency. However, reduced sensitivity is a limitation of this measure; assessment tools measuring goal achievement, such as the Goal Attainment Scaling (GAS) [110, 182, 217, 230], might have been more specific. In this study, when investigating the effects of BoNT-A, both the VAS muscle stiffness/spasticity and the Global

Scale may have reflected the individual's own experience in a more sensitive way than SF-36 [118].

The *Questionnaire concerning present walking ability* (Paper I Appendix I) had its weaknesses. First of all, it was not a standardised instrument tested on validity or reliability, and there is no documentation on its applicability. By using a "checklist" approach, the participants may have been tempted to say "yes" more easily. On the other hand, more general questionnaires may have induced recall bias. Despite recognised limitations of the questionnaire used, it might have revealed clinically relevant issues associated with the individual's own experiences of increasing walking difficulties.

The study purpose, literature review and clinical experience decided the selected variables from the physical examination. It was thought these could be important predictors for functional walking capacity as assessed by the 6MWT in Paper I, as well as for comparing the two treatment groups' lower limb impairment in the RCT. Though widespread in clinical use, these lower limb outcomes have limitations of their reliability [162, 167, 168, 170]. The use of summary scores may have further limited the selected measurements for muscle length (popliteal angle), muscle hypertonia (MAS), and muscle strength (manual muscle test). However, the purpose was to have clinically relevant scores for lower limb impairment, and therefore sum scores were judged to be sufficiently precise [167, 204].

Sample sizes

A sample size calculation was performed for the RCT, providing implications for the number of participants in the studies presented in Papers I and III. Our results on 3DGA kinematics were statistically non-significant, and the question about sample size and Type II error could be questioned. However, the SDs for the chosen kinematic data were all within the range of the SD used when estimating sample size. Considering the narrow CIs, where neither of the CIs' lower or upper limits exceeded the predefined clinically relevant change, we assumed our statistically non-significant results on 3DGA kinematics in the RCT to be true [208]. Though, considering the results of the other CIs presented, it is recognised that the RCT was challenged by the issue of statistical power.

The sample size in Paper IV is smaller than recommended in order to allow the limits of agreement to be accurately estimated [216 (p. 402)]. Yet, the results gave valuable information about the lack of validity of estimating lower limb joint angles from sagittal video

gait recordings.

Validity of statistical methods and interpretation of data

The strength of these studies include nearly no missing data and a transparent approach concerning statistical analyses. CIs were used to provide information about significance, variation and direction of effect under investigation [208].

Bootstrapping, which is recommended to estimate the CIs of variables with an unknown probability distribution [231], was considered to be the most valid approach to estimate the CIs in the final multiple regression model (Paper I), as well as to control the presented CIs for SF-36 in the RCT (Paper II). However, it is recognised that CIs reflect statistical uncertainty only, and not all the uncertainty that may be present in a study.

The regression modelling procedures in Paper I attempted to explore a wide range of different subsets of predictor variables to support the final model. Because most participants were at GMFCS level II and FMS 5, and because of colinearity in models with the TUG test and FMS, GMFCS and FMS were not included in the multiple regression analysis. The assumptions for multiple linear regression (e.g. distributional properties of residuals, multicolinearity diagnostics, and leverage values (Cook's distance)), were thoroughly checked during the model building, and all results were discussed for clinical relevance [232]. However, potential predictors are restricted to those chosen for the study. As the validity of results depends on complete knowledge of important confounders and their precise measurement, care should be taken when interpreting results such as those presented, and the model requires further validation in studies on similar samples.

In the RCT, the researchers considered whether or not to adjust the p-values due to multiple testing and the risk of Type I error. However, this was judged unnecessary due to the transparency of presenting CIs. Clinically important differences derived from the literature and preliminary analyses of 3DGA were used to interpret whether changes from baseline reflected clinically meaningful changes. However, clinically important differences were not specifically investigated for this study population and this is a limitation.

6.2. General discussion of results

The overall important findings from this study were:

- *Self-reported reduced walking ability was related to a shift in GMFCS-level for 39% of the participants.*
- *TUG test and 6MWD differed between functional levels as classified with the GMFCS.*
- *The identified predictors for 6MWD were the result of TUG test, type of CP, popliteal angle, pain and gender. The results indicated a complex interrelation between the factors investigated.*
- *BoNT-A injections demonstrated no effects superior to placebo on gait as measured with selected gait events from 3DGA kinematics or the different domains of SF-36.*
- *BoNT-A injections demonstrated effects superior to placebo on VAS muscle stiffness/spasticity and the Global Scale, but no differences between treatment groups were found for the 6MWT and TUG test.*
- *Distributional properties for GDI in a healthy adult reference population and for adults with spastic CP were similar to previous publications on the GDI's distributional properties for healthy children and children with CP.*
- *Low correlation between the GDI and the 6MWT or TUG indicated that for any given distance on 6MWT or any given time used on the TUG there could be a wide variety of kinematic patterns and vice versa, suggesting that these measurements measured different aspects of walking function.*
- *Quantifying lower limb joint angles from sagittal video recordings of gait demonstrated low concurrent criterion validity.*

In the following section, the main findings will be discussed.

Walking ability and - capacity

Walking ability

In this selected study population, the individuals' self-reported walking ability in adolescence, compared with their current GMFCS classification, showed a reduction in GMFCS level for 39% of the participants. Hanna et al. demonstrated a stability of walking ability until young adulthood [60]. However, the results of Sandström et al. [24] and McCormick et al. [26] may also reflect results similar to this study, showing that even individuals at GMFCS level I have a premature reduction in walking ability. However, not being specifically developed for use in adults with CP, it remains unanswered whether the finding of a 39% reduction in GMFCS level should be considered to be "the natural history," or being suggestive for interventional procedures [5, 9, 46 (p. 363-75)].

For the participants investigated in this study, it may be reasonable to assume that their perceived reduced walking ability compared with their experience in adolescence reflected increasing impairments, such as stiffness and pain, interfered with their functional level. As such this might be experienced as a threat to achieved social roles, including independence and usual frequency of social life/lifestyle activities. Since different social roles as well as personal factors put different demands on walking, it seems reasonable that the degree of presenting impairments related to perceived walking ability varied considerably in this population of relatively high functioning adults with spastic CP [66, 73]. Considering health services as an environmental factor, the clinical finding of foot deformity in 60% of the participants, while only 27% had orthotics and/or orthopaedic shoes may point to unmet needs [2, 4, 82].

In the ICF framework it seems reasonable to assume that several factors are involved related to experienced walking ability in adults with spastic CP. This emphasises the importance of using several assessment tools as well as further work on the validity of GMFCS into adulthood (>18 year). Based on 2632 gross motor function measure (GMFM assessments and the GMFCS levels, Rosenbaum et al. [61] created five distinct and significant different motor growth curves, which described the limits of gross motor development in children with CP. As expected, the estimated limit of development decreased as the severity of impairment increased. While the study by Hanna et al. (Figure 4, p.11) demonstrated the stability of motor function in GMFCS levels I-II up to the age of 21 years [60], Opheim et al. found a marked decline in walking ability in bilateral spastic CP at the age of 35 years [5]. This indicates the importance of longitudinal studies into adulthood on gross motor function, including its related factors for well-functioning individuals with spastic CP [84].

The assumption of a more complex link between a deviating gait and walking ability in adults, compared with children, may be supported by finding that the GDI did not discriminate between GMFCS level II and III. This is in contrast to other studies, reporting that such gait indexes could discriminate between GMFCS level II and III in children with CP [145, 226]. The issue of capacity versus performance (i.e., what a person can do, versus what he/she does do in daily life) may make the GMFCS level III more heterogeneous in adults than in children with CP, because of the element of choice as regard to their use of assistive devices [24-27, 58, 66, 84].

Walking capacity

The walking capacity in this study population was better than in previously studied adults with CP [74-76, 157], but was lower compared with the general population [233]. As with samples of healthy populations, gender was a statistically significant and clinically relevant predictor for the results of 6MWT; height and body mass index are likely to contribute to this finding [233]. Although a normally distributed age range from 18 to 65 years we did not find any effect of age in the final model for 6MWD. This was surprising [3, 5, 171], but may be due to the impact of the TUG or to other CP-related impairments being more important predictors than age. Moreover, the fundamental challenge of age effects in a cross-sectional study is recognised.

The Borg scale was not a significant predictor, probably reflecting that most of the participants were more limited by neuromuscular impairment than by cardiovascular factors. This has also been demonstrated for stroke populations [175]. As expected, the type of CP was a significant predictor for 6MWD, which implies that individuals with spastic bilateral CP have more neurological impairments [9, 12]. Because there is conflicting evidence on how motor impairments relate to each other and to function for children with CP [167, 204], it seems logical that our results indicate a complex interrelation between the variables investigated.

Increased mean popliteal angle was associated with decreased 6MWD. By choosing unilateral popliteal angle instead of bilateral popliteal angle [15], the 'functional hamstring length' with the potential effect of a contra-lateral hip flexor tightness was measured, a length which was considered relevant when choosing a lower-limb range of motion measure related to walking capacity. The effect of mean muscle tone in the adjusted analyses may have been confounded by other effects, such as the mean popliteal angle. This is supported by the association between reduced range of motion and increased spasticity/more impairment in spastic CP [15, 70, 71, 167], the 'increased stiffness' as the most frequently reported cause of perceived reduction in walking ability, and the fact that the MAS does not discriminate between dynamic muscle overactivity and changed mechanical compliance causing increased muscle stiffness [163, 166].

Mean lower-limb muscle strength was not a significant predictor in the final regression model for 6MWT distance. This may reflect the narrow range of muscle strength and the clinical impression that the participants had satisfactory muscle strength for walking [234]. However,

both strict test conditions and the limitations of manual muscle testing are recognised [169, 170]. Thus, we hypothesise that muscle strength is important for maintaining functional mobility in more demanding mobility tasks than walking in a corridor [46 (p. 363-75), 235].

As the TUG is a measure of functional mobility, the interrelations between the TUG, GMFCS, FMS, and 6MWD were expected. It was considered important to use a measure with a potential ability to detect anticipatory aspects of postural control, as well as sensory and perceptual abilities required in functional mobility [46 (p. 165-91)], thus challenging the complex impairments mentioned in the definitions of CP [9, 11]. Although the 6MWT and TUG are different measures, there is some overlap in tasks, which may have overestimated the effect of the TUG on 6MWD. Further, it is recognised that the performance of the TUG is related to age, possibly because of its dependence on muscle strength as well as anticipatory postural control, both of which decrease with age [46 (p. 363-75), 235]. Thus the TUG may have confounded the effects of age and muscle strength in the final regression model for 6MWD. Pain, as a significant predictor for functional walking capacity, confirmed the earlier reported impact of pain on reduced walking ability in adults with CP [1, 5, 24, 65, 66]. In contrast, fatigue was adjusted out, reflecting that other variables were more important. However, it seems reasonable to hypothesise a greater impact from pain and fatigue if walking performance had been investigated [5, 58].

Overall, the results support the need for more studies with adequate sample sizes addressing subgroups, the use of more specific assessment tools covering balance, as well as studies with a longitudinal design exploring the effects of aging on walking.

Effects of Botulinum toxin A (BoNT-A)

After the present study started two RCTs and two open labelled studies using similar multilevel injection regimes and/or outcomes have reported effects of BoNT-A in children with spastic CP and equinus or flexed knee gait, and with stiff-knee gait due to stroke [131, 217, 218, 224, 236]. In two publications on the same study population, Scholtes et al. used an RCT design and compared the effect of multilevel BoNT-A injections and comprehensive rehabilitation with usual care [131, 224]. They found improvements in gait, mobility and self-report considering problems related to lower limb functioning. In a double-blind placebo controlled RCT, Bjornson et al. found reduced muscle tone and a trend of improved gross motor function in favour BoNT-A group, but no between group differences in perceived functional benefits (“family satisfaction”) [217]. Caty et al. injected several muscles in 20

individuals with stiff knee gait due to stroke and found improved gait as measured with 3DGA sagittal knee kinematics and mechanical work [218]. Another open labelled study on stiff knee gait after stroke found improved 3DGA sagittal kinematics after intramuscular injection of BoNT-A into m. rectus femoris, or temporary anaesthetic motor block targeting the rectus femoris [236]. However, a double blind placebo controlled BoNT-A RCT on post-stroke ankle spasticity by Kaji et al. demonstrated results similar to those of the present study with small effects on gait strategies [237].

The 3DGA results of this study probably reflect that gait strategies in adults with spastic CP are relatively fixed due to co-existing impairments, such as contractures, muscle weakness, and reduced motor control and balance. As such, reducing muscle tone alone was not enough to change joint angles during gait [15, 110, 224, 237]. However, comparable studies have shown effects on gait in children with spastic CP [127, 128]. To explore whether sub-populations with no potential of improvement on the predefined kinematic events affected the 3DGA results presented, secondary analyses were performed to investigate effects on overall gait as measured with the GDI (Table XVII). Since others have demonstrated changes in GDI after lower limb surgery in children with CP [238, 239], the narrow CIs presented in Table XVII probably support the previously reported results showing no effects on gait (Paper II).

Table XVII: GDI and spatiotemporal variables

	Placebo (*n* =33) Difference[1] Mean (95% CI)	**BoNT-A (*n* =32) Difference[1]** Mean (95% CI)	**Between-groups (*n* = 65) Difference[2]** Mean (95% CI)
GDI	-0.6 (-2.9; 1.7)	0.6 (-1.2; 2.1)	0.9 (-1.8; 3.7)

***p> 0.05. GDI: Gait Deviation Index. BoNT-A: botulinum toxin A. [1]Paired t-test, [2]Analysis of Covariance with week 8 score as the dependent variable and baseline score and treatment group as independent variables.**

In this study both groups showed statistically significant improvements in the SF-36 domain BP at week 8, indicating a placebo effect. However, it is possible that the pain relief in the control group may have occurred due to the injection procedure and/or irritation due to the injected substance in spite of no active substance being present [240]. Thus, the results may not have been a pure placebo effect. With regard to the pain-relieving effect of BoNT-A, there is increasing evidence that BoNT-A not only interferes with the release of acetylcholine at neuromuscular junctions, but also interferes with the release of excitatory neurotransmitters

associated with chronic pain [100, 241], and similar results were also found in the RCT by Pittock et al. [114]. As such, the benefit of BoNT-A treatment in this population of adults with spastic CP might have been both reduced hypertonia mediated by neural reflexes, and the modulation of pathways involved in chronic myofascial pain.

The placebo group demonstrated a trend of positive changes in the SF-36 physical domains at week 8. However, this was not supported by statistically significant differences between the groups regarding the number of participants undergoing a change from baseline to a degree defined as clinically relevant. An explanation may be that individuals with chronic physical disabilities score perceived physical functioning in different ways [225]. In contrast, explorative analysis on MCIDs revealed a statistically significant difference in favour of BoNT-A on the SF-36 mental health and social function domains. Others have demonstrated similar results on these psychological dimensions, and explained this as an indirect effect of an increase in the ability to perform and enjoy everyday activities [123], whereas another study on stroke patients did not find any improvement in these domains of SF-36 [218]. Thus, our results for mental health and social functioning in favour of BoNT-A should be interpreted with caution.

At the group level, the TUG showed a significant improvement in the BoNT-A group, but not in the placebo group. This might indicate that subgroups in this study experienced a positive effect of BoNT-A on muscular hyperactivity where a potential mechanism could have been reduced co-activation patterns [34, 76, 109, 117, 236]. The recent study by Robertson et al. also found a possible trend of improved TUG [236], and previous studies have found effects on mobility by using the Rivermead motor assessment scale or GMFM [118, 127, 129]. However, this may be speculative, and further studies are needed.

The results on VAS muscle-stiffness/spasticity may indicate that adults with spastic CP have impairments due to muscle overactivity that can improve with intramuscular BoNT-A injections. Studies on patients with multiple sclerosis have demonstrated similar results for the perceived severity of muscle-stiffness/spasticity when carrying out interventions targeted towards muscle overactivity [139, 196]. A potential positive effects of BoNT-A were also shown by the Global Scale scores, which demonstrated a 59% treatment effect and 27% placebo effect. These results were similar to previously described RCTs [112-114, 117, 118, 130]. Also the RCT by Mancini et al. demonstrated improved “VAS walking function”, especially for those who received a medium BoNT-A dose (322 units) [115]. In contrast, there

was no difference between treatment and placebo on self-reported lower limb goal attainment in two recent RCTs on post-stroke patients and children with spastic CP [217, 237]. This may reflect both the discrepancy between assessing perceived severity and goal achievement [118], as well as differences in goals, e.g. muscle stiffness and pain versus gait or functional ability [118, 122].

Overall, the results demonstrated no effects superior to placebo on objective outcomes, but effects in favour BoNT-A on overall perceived therapy effect and VAS muscle-stiffness/spasticity, and the treatment was well tolerated. This result from injection therapy *only* may indicate potential benefit of BoNT-A therapy for selected adults with spastic CP.

The Gait Deviation Index (GDI) and video gait analysis

GDI

The GDI demonstrated similar results in distributional properties (mean (SD) and between GMFCS-levels) as those reported in studies on healthy children and ambulant children with CP [143, 145]. Thus, the GDI appeared to discriminate between degrees of gait pathology, both in healthy adults and adults with spastic CP. The recent study by Langerak et al. on long term outcome after SDR, using GDI as one of the outcomes, found similar distributional properties [80].

Except for one short report on amputees [242], no publications have reported associations between the GDI and functional tests similar to daily activities. However, two studies in children with CP have investigated the associations between the GDI and functional walking ability or gross motor function derived from the Functional Assessment Questionnaire (FAQ), GMFCS, and GMFM [143, 145]. Finding that the GDI distinguished between these instruments' different levels, the authors of these two studies suggested that the GDI is related to functional walking ability and gross motor function. These results probably reflect that the gait of children with CP is closely related to their performance of gross motor activities in daily life. Our results, which show only a low association between the GDI and 6MWD, and also between the GDI and TUG test score may, as previously discussed, reflect that other issues beyond a deviating gait are important for functional walking capacity or mobility for adults with CP [3, 5, 84].

Gait impairment, as estimated by the GDI, was less associated with basic mobility (TUG) and walking distance (6MWD) than the increased heart rate required for walking (PCI) [158].

This finding of a higher association between two measures in the domain of "body functions" seems reasonable, and for children with CP a strong correlation between the energy cost of walking and the degree of impairment has been demonstrated [159]. The reason that only a moderate association was found between GDI and PCI could possibly be explained by the fact that an increased heart rate during walking does not discriminate between increased energy costs due to pathological gait or low aerobic capacity [158].

Video gait analysis

Several studies have reported the reliability of video gait analysis (VGA) to be satisfactory [127, 146-148, 151, 243]. However, reliability does not guarantee validity. Neither Scholtes et al. [224], who used joint angles measured from video recordings and the Edinburgh Visual Gait Score (EVGS) [146], nor Kim et al. [244], who used the Physician's Rating Scale [125], discussed the limitations of VGA. On the other hand, a recent publication, in which VGA was used to evaluate the effects of SDR gait in persons with CP, addressed the limitations of measuring gait in only two dimensions [245].

Our study demonstrated substantial discrepancies and lack of agreement between lower limb joint angles measured on a video-screen and sagittal plane kinematics from 3DGA. The measured knee joint angles achieved the highest agreement with the concurrent 3DGA results. Toro et al. [149], using the least significant difference (LSD) statistics, reported a fairly high mean difference between SF-GT and 3DGA for all joints (16º) and a wide range in degrees (2–63º). Even if their study demonstrated that 80–81% of the mean measurements were within the range of 16º, this indicates uncertainty about the validity. A recent study by Grunt et al. investigated the agreement between joint angles measured with 3DGA and computer-based video screen measurement [246]. Despite the use of a computer-based video screen measurement, a wide range of differences between the measurements was found. The Grunt et al. study [246], using one investigator, demonstrated the highest agreement for peak knee flexion in swing (mean difference (LoA) = 1.4º (11º)), and the lowest agreement for peak ankle dorsiflexion in swing (mean difference (LoA) = 12º (14.6º)). These results were similar to this study, where 10 investigators evaluated joint angles by using a plastic goniometer on a screen. Grunt et al. [246] concluded that computer-based video screen measurements should be used with caution and that rotational deficit could cause problems in the interpretation. However, Grunt et al. did not present data to support this. Our study did not demonstrate that increased movements in the transverse plane kinematics resulted in a higher discrepancy in

the joint angles measurements from video recordings (Fig. 3, Paper IV). However, this may be due to the limited sample size.

Thus, after exploring the issue of validity in measuring complex movements, such as gait in adults with spastic CP in only two dimensions, we suggest that VGAs are considered as subjective, qualitative measures. As such, categorical ordinal scales and not goniometric measured joint angles should be the outcome [216]. The Edinburgh Visual Gait Score (EVGS), considered the leading VGA tool, assesses joint motion in the sagittal and coronal plane by means of a very detailed ordinal scale assumed to represent overall gait in CP [146, 247]. The qualitative strength of this instrument has been shown in the studies by Grunt et al. and Hillman et al. [245, 248].

The GDI, functional tests and gait analysis in clinical practice and research

Low associations between the GDI and the results of 6MWT and TUG test suggest that gait and functional walking capacity/mobility are different constructs. While the findings of Desloovere et al. indicated that both clinical examination and 3DGA data should be considered in clinical decision-making on ambulant children with spastic CP [161], the present study may indicate the importance of considering both gait and walking in clinical decision-making on ambulant adults with spastic CP. In addition, when evaluating walking ability in adults with CP, the relation between GDI and PCI probably support the inclusion of a relevant clinical exercise test [226].

The literature is conflicted about the ability of the TUG to differentiate between the different GMFCS levels [178, 249]. This study found a significant difference in TUG values across GMFCS levels, which may indicate its usefulness as a screening tool for functional balance in adults with spastic CP. Overall, these studies suggest the appropriateness of using both technical (3DGA) and functional (6MWT/TUG) tests when examining increasing walking difficulties in adults with spastic CP. However, further study is needed to determine GDI's, 6MWT's and TUG's responsiveness in adults with spastic CP. While TUG and 6MWT seems attractive for both clinical practice and research, both the outcomes and the type of gait analysis may differ in research and clinical practice.

By its distributional properties and presenting the gait in only one score, the GDI from 3DGA may be an attractive outcome in gait research. In clinical practice, the Movement Analysis Profile, which uses the same data points from 3DGA kinematics as in the calculation of the GDI but presents them as nine distinct kinematic variables for the right and left leg, may be a

more appropriate outcome due to a higher level of details [250]. As 3DGA includes expensive technology and time-consuming processing procedures, VGA is more available both in clinical practice and research. This may demonstrate the importance of appropriate interpretation of VGAs [247].

7. CONCLUSIONS AND IMPLICATIONS

Factors predicting functional walking capacity were highly interrelated. The study results suggest that walking disability in high functioning adults with spastic CP includes several impairments, walking limitations and mobility restrictions as well as personal factors that may be modified by systematic care and specific rehabilitation programs.

BoNT-A may be an alternative to oral medication and/or irreversible surgical interventions for selected adults with spastic CP and an increasing severity of walking disability. However, the positive effects of BoNT-A alone in this study were found to be limited. The BoNT-A in combination with specific multidisciplinary post-treatment care was not studied, and still needs to be evaluated.

Self-reported reduced walking ability in high-functioning adults with spastic CP may have multiple interrelated causes, pointing to the importance of assessing walking disability using both impairment as well as capacity and performance measures, and taking personal preferences into account. Systematic follow up programs, objective outcomes, and capacity tests are probably important to detect other causes for a deteriorating walking function than primary impairments and the long term results of having CP.

As a valid one-score summary measure of overall gait pathology, GDI may be a useful outcome measure in research on adults with spastic CP. The use of 3DGA in clinical practice must consider costs versus benefits, while VGA may be incorporated in clinical programs. Quantifying lower limb joint angles from sagittal video recordings in ambulant adults with spastic CP differed from concurrent 3DGA kinematics and as such did not reflect the real sagittal joint position. Video captured gait should be analysed by ordinal scales chosen in accordance with the necessary detail level and known gait strategies for the population of interest. Other measurements, such as spatiotemporal parameters and functional tests on mobility, may generate continuous quantitative data.

To the best of my knowledge, no studies similar to those included in the present doctoral thesis have been published. Overall, these studies may contribute to new knowledge useful for developing and establishing mobility care and rehabilitation programs for adults with spastic CP and increasing walking difficulties. Hopefully, this thesis has revealed the complexity involved in studying walking disability in adults with spastic CP, and the need for further studies to develop evidence-based general and specific health services for this population.

8. SUGGESTIONS FOR THE FUTURE

Clinical programs

There is a need to establish multidisciplinary mobility care and rehabilitation programs for adults with spastic CP GMFCS levels I-III. Such programs should include assessments covering the framework of ICF and specific management strategies targeting defined treatment goals.

Proposal for further research

1. There is a lack of methodological studies investigating the validity and reliability of assessment tools considered important in both clinical programs and further research. In particular, the TUG test, 6MWT, 3DGA, and self-report assessment tools should be studied in adults with spastic CP characterised by a relative high functional level.
2. If clinical programs are to be established, a systematic approach is considered important. Clinical data on adults with CP are required for a multitude of purposes, including life planning by the adult individual with CP and health services planning.
3. Included in this thesis are 3DGA data on 66 adults with spastic CP between 18-65 years of age. In gaining knowledge about how gait and walking develop over time in adults with spastic CP, follow-up studies on this population are suggested.
4. Outcomes on gait in this study described overall gait, and not the underlying mechanisms causing this gait. Further studies to elucidate such mechanisms are needed, using surface EMG and kinetics from 3DGA as outcomes.
5. Considering the literature review on gait impairment and/or reduced walking ability in adults with a spastic paresis health condition, there is limited knowledge regarding whether a multidisciplinary treatment program with lower limb BoNT-A therapy is more beneficial than such a program without BoNT-A therapy. It is therefore suggested that a larger long-term randomized study should be conducted, including several treatment arms, several spastic paresis health conditions, and using objective and subjective outcomes covering the ICF-framework.

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ATTACHMENTS

Attachment 1

MUSKEL-/LEDDSTATUS (°)			**MUSKELTONUS**			**MUSKELSTYRKE (Hislop 0-5)**		
Hofte	*Ve*	*Hø*	**MODIFISERT ASHWORTH SKALA (0-4)**			**Hofte**	*Ve*	*Hø*
Fleksjon			**Hofte**	*Ve*	*Hø*	Hofteflektorer (ryggleie)		
Fleksjonskontr.(Thomas test)			Adduktorer			Hofteabduktorer (sideleie)		
Ekstensjon			**Kne**			Hofteekstensorer (mageleie)		
Abduksjon a) hofte 0º, kne 90º			Kneekstensorer			Trendelenburg (positiv/negativ)		
b) hofte 0º kne 0º			Kneflektorer			**Kne**		
Adduksjon			**Ankel**			Kneekstensorer (sittende)		
Utadrotasjon			Plantarflektorer			Kneflektorer (sittende)		
Innadrotasjon			**MODIFISERT TARDIEU SKALA 'catch' (°)**			**Ankel**		
Dunc. Ely test (f.bredder)			Hofte/kne:'Rectus catch'			Plantarflektorer (liggende)		
Dunc. Ely test			Kne: 'hamstring catch'			Dorsalflektorer (liggende)		
Kne			Ankel: 'triceps surae catch'			**'HEEL RISE' (>10)**		
Fleksjon			**REFLEKSER** (0, +, ++, +++, +++(+), ++++)			**OMKRETS**		
Ekstensjon						Legg (største omkrets)		
Poplitealvinkel - unilateral			Patellar refleks			Lår (10 cm over øvre kant patella)		
Poplitealvinkel – bilateral			Achillesrefleks			**SMC (1-4)** (selektiv motorisk kontroll ankel dorsalfleksjon)		
Ankel			**AKSEFORHOLD ANKEL/FOT**					
Dorsalfleksjon (kne 90°)			Thigh – foot vinkel (º)			**ANTEVERSJONSVINKEL (°)**		
Dorsalfleksjon (kne 0°)			Bimalleolær akse (º)			**BALANSE** (Standing balance 0-4)		
Plantarfleksjon			Fotform: Normal (1), Valgus (2), Varus (3)					
Kommentarer:						**Undersøkt av:**		
			Midfootbreak (ja/nei)					
			Hallux valgus (ja/nei)					

Attachment 2

Deltaker nr……. ”**0-uke” konsultasjon, dato:** ……..

Kjønn: 1 = Kvinne 2 = Mann **Kvinner:** Gravid (sett ring): 1 = Ja 2 = Nei
Planlegger graviditet: 1 = Ja 2 = Nei

Alder: ……. År

Sivil status (sett ring):
1 = ugift/aleneboende 2 = gift/samboende 3 = skilt/separert 4= enke(mann)

Høyeste utdannelse (sett ring):
1 = Folkeskole/ungdomsskole 2 = handelsskole/yrkesskole/gymnas
3 = Høyskole/universitet

Arbeid/trygd (sett ring):
1 = Betalt fulltidsarbeid 2 = Betalt deltidsarbeid 3 = Attføring
4 = Uføretrygdet fullt 5 = Uføretrygdet delt 6 = Annet
……..

Hjelpemidler (sett ring):
1 = Ortopediske sko 2 = ortose (r) 3 = krykke (r)
4 = Rullator 5 = manuell rullestol 6 = Elektrisk rullestol

Andre sykdommer:
……
……
Bruk av medisiner, ikke CP-relatert (angi hvilke):
……
……
Tidligere operasjoner, ikke CP-relatert (hva, når):
.....
.....

Tidligere Botox-behandling (hvilke muskler, når)
……

Treningsvaner:
Jeg trener utenom fysioterapi:
1 = Aldri 2 = Sjelden 3 = hver måned 4 = hver uke 5 = flere ganger i uken

Fysioterapi:
Jeg går til fysioterapi:
1 = Aldri 2 = Sjelden 3= hver måned 4 = hver uke 5 = flere ganger i uken
6 = Annet →Hva?.....

Type CP:
1 = Spastisk i høyre ben 2 = Spastisk i venstre ben 3 = Spastisk i begge ben

PAPERS I-IV