PhD thesis

The use of instrumented gait analysis in interdisciplinary interventions for children with cerebral palsy

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1. Preface

The idea to complete the studies that constitute this thesis originated from a proposal by orthopaedic surgeon Niels Wisbech Pedersen to develop a stronger collaboration between the Motion Analysis Laboratory at Odense University Hospital and the Danish Cerebral Palsy follow-Up Program (CPUP), with the purpose of implementing three-dimensional instrumented gait analysis children with cerebral palsy followed in CPUP.

His initiative led to my first meeting with Anders Holsgaard-Larsen, head of research in the Motion Analysis Laboratory at Odense University Hospital, and subsequently to our drafting of a project protocol entitled "The effect of a specific treatment plan based on clinical gait analysis in the cerebral palsy follow-up program" in early March 2011. After many challenges, and meetings, methodological discussions with Søren Overgaard and others, and a huge effort by Anders Holsgaard Larsen, the project "Individually defined multidisciplinary interventions for children with cerebral palsy – The impact of three-dimensional gait analysis on gait and functional mobility" was approved as the basis for a PhD study in late summer 2012.

The thesis is based on work carried out in the Orthopaedic Research Unit at the Department of Orthopaedic Surgery and Traumatology, Odense University Hospital, and at the Department of Clinical Research, University of Southern Denmark. It is based on three clinical studies described in four scientific papers, of which two have been published and two have been submitted to peer-reviewed journals.

Acknowledgements

First of all, a very big thank you goes to the children and their families who kindly participated in the research. I am truly indebted and grateful for their involvement and for making the process so enjoyable. Their courage, strength and stories are truly inspiring and motivate me to hopefully make a difference in this challenging but incredibly satisfying field. Also, a very big thank you to all of the participating paediatricians, orthopaedic surgeons and physiotherapists who have helped with the recruiting of participants and who have been involved in the interdisciplinary interventions with the participants.

I thank my main supervisor Associate Professor Anders Holsgaard Larsen for always knowing how to motivate me to work harder and learn more, and my co-supervisors Clinical Associate Professor Niels Wisbech Pedersen MD for believing in me and trusting me to meet the challenges of the world of clinical gait analysis and Professor Søren Overgaard MD for welcoming me into his research unit and letting me learn that clinical research can be very diverse.

To all of my colleagues, fellow students and the staff in the Gait Analysis Laboratory at Odense University Hospital and the Orthopaedic Research Unit, I thank them for their support, advice and encouragement. Furthermore, I give a special thanks to Dennis Brandborg Nielsen, Lotte Slot Jensen, Rasmus Sørensen, Maria Thorning, Line Kiilerich and Christina Fonvig for their help in the data collection.

I also give a very special thanks to Maria Thorning and Anders Holsgaard Larsen for taking excellent care of the projects and participants during my maternity leave. They made it possible for me to be introduced to the challenge of balancing work life and family life in a very safe and caring way.

I acknowledge the support of the University of Southern Denmark, an Odense University Hospital Research grant, a Region of Southern Denmark Research grant and a PhD grant, the Physiotherapy Practice Foundation, the Ludvig and Sara Elsass Foundation, the Linex Foundation and the Danish Physiotherapy Research Fund. None of the supporters played a role in the study designs, collection, analysis or interpretation of data; nor in the writing or decision to submit the manuscripts for publication.

Finally, a deep and warm thanks to my son Jonas and my partner Anders, as well as extended family and friends, for reminding me that life is much more than a research education.

Abbreviations

The following abbreviations are used in text or legends in the thesis.

BL	Bilateral spastic cerebral palsy
CI	Confidence Interval
CP	Cerebral palsy
CPUP	Cerebral Palsy follow-Up Program
FMS	Functional Mobility Scale
Gait analysis	Three-dimensional instrumented gait analysis
GDI	Gait Deviation Index
GMFCS	Gross Motor Function Classification System
GMFM	Gross Motor Function Measure
GPS	Gait Profile Score
GVS	Gait Variable Score
ICC	Intra-class Correlation Coefficient
ICF	International Classification of Function
IQR	Interquartile range
PEDI	Pediatric Evaluation of Disability Inventory
PedsQl	The Pediatric Quality of Life Inventory
PODCI	Pediatric Outcome Data Collection Instrument
SD	Standard Deviation
UL	Unilateral spastic cerebral palsy

List of papers

The thesis is based on the following three studies and four papers. They will be referred to in the text by their Roman numerals and, where relevant, the letters, as indicated below.

Study / paper	Name and reference
I	Test-retest Rasmussen HM, Nielsen DB, Pedersen NW, Overgaard S, Holsgaard-Larsen A. Gait Deviation Index, Gait Profile Score and Gait Variable Score in children with spastic cerebral palsy: Intra-rater reliability and agreement across two repeated sessions. Gait & Posture. 2015;42(2):133-7.
IIa	Randomised controlled trial protocol Rasmussen HM, Pedersen NW, Overgaard S, Hansen LK, Dunkhase-Heinl U, Petkov Y, Engell V, Baker R, and Holsgaard-Larsen A. The use of instrumented gait analysis for individually tailored interdisciplinary interventions in children with cerebral palsy: a randomised controlled trial protocol. BMC Pediatrics. 2015;15(1):202.
IIb	Randomised controlled trial Rasmussen HM, Pedersen NW, Overgaard S, Hansen LK, Dunkhase-Heinl U, Petkov Y, Engell V and Holsgaard-Larsen A. The use of instrumented gait analysis for individually tailored interdisciplinary interventions in children with cerebral palsy: a randomised controlled trial. [Submitted to Development Medicine & Child Neurology, October 2017].
III	Cross-sectional study Rasmussen HM, Svensson J, Christensen MT, Pedersen NW, Overgaard S, Holsgaard-Larsen A. Threshold values of ankle dorsiflexion and gross motor function in children with cerebral palsy – a cross-sectional study [Re-submitted to Acta Orthopedica, November 2017].

2. Introduction

This thesis focuses on younger children with spastic cerebral palsy who walk unaided. They comprise more than half of all children with cerebral palsy. The vast majority of the ambulatory children with cerebral palsy experience an altered gait pattern or other walking difficulties and are dependent on healthcare interventions throughout their childhood.

The idea to explore the use of three-dimensional instrumented gait analysis (gait analysis) in individually defined interdisciplinary interventions for gross motor function emerged from experience in clinical practice and a critical appraisal of the scientific literature, which showed that evidence for the effectiveness of gait analysis was lacking for the patient group of interest.

In this introduction, the diagnosis and clinical characteristics of ambulant children with cerebral palsy are presented in terms of its effect on body functions and structures as well as activity and participation. Furthermore, a thorough description of the current healthcare and interdisciplinary interventions and gait analysis are outlined.

2.1. Cerebral palsy: The clinical signs and their impact on walking

Cerebral palsy is a diagnosis that includes a range of conditions caused by a non-progressive brain injury occurring in the developing foetal or infant brain. Although the brain injury is non-progressive, the neuro-musculoskeletal and movement-related functions may deteriorate and cause activity limitation [1].

According to the Surveillance of Cerebral Palsy in Europe the definition of cerebral palsy must include the following five key elements:

> *"Cerebral palsy is a group of disorders;*
> *- It is permanent but not unchanging;*
> *- It involves a disorder of movement and/or posture and of motor function;*
> *- It is due to a non-progressive interference/lesion/abnormality;*
> *- This interference/lesion/abnormality is in the developing/immature brain"* [1a]

Cerebral palsy is the most common congenital motor disability in childhood with a prevalence of 1.5-3.0/1000 live births (95% CI: 1.32 – 1.68 and 2.69 – 3.31) in Europe [1]. The latest published prevalence for a Danish cohort is 2.4 per 1000 live births (95% CI: 1.8 – 3.2) for children born from 2003 to 2008 in the Region of Southern Denmark [2].

The diagnosis of cerebral palsy can be categorised into four subtypes: spastic (unilateral or bilateral), dyskinetic, ataxia, and mixed form [1]. The subtype is supplemented with a classification of gross motor function using the Gross Motor Function Classification System (GMFCS) [3]. The GMFCS is an ordinal scale with five levels of function, representing clinically meaningful distinctions in motor function. Children at level I are the least disabled, although they may have limitations in advanced motor skills. Children at level V have the most severe motor disability. Approximately 65% of all children with cerebral palsy walk independently without aids and are consequently classified at GMFCS level I or II [4].

The clinical signs of cerebral palsy gradually develop during the first years of life and become visible as the child grows and the central nervous system matures. The first signs of cerebral palsy may be early development of hand dominance in grasping, around 3 to 6 months of age or delayed development of unsupported walking, around 18 to 24 months of age [5]. The most common clinical signs of spastic cerebral palsy are muscle weakness and muscle imbalance across joints, altered muscle tone, reduced passive range of motion, and deformity of bones and joints [1, 6, 7], which often lead to an altered gait pattern, such as stiffness of the knee in the swing phase of gait, excessive hip and knee flexion (crouch gait), intoeing and equinus [8]. Furthermore, the children experience activity limitations (e.g. in dressing, feeding and functional mobility) and restricted participation (e.g. when playing or participating in social, school and community activities), compared with their typical peers [9].

The development of gross motor function is often delayed and some functions may never be achieved. The children walk independently later than their peers, they walk at a slower pace and with an increased energy consumption [10]. According to the GMFCS, walking performance in children at GFMCS levels I and II after 6 years of age can be described as walking without limitation (GMFCS level I) and walking with limitation (GMFCS level II) [3]. Most children at GMFCS level I walk independently on all surfaces at 5, 50 and 500 meters, corresponding to walking at home, at school and in the community, according to the Functional Mobility Scale (FMS). However, some children can only walk independently on even surfaces and a few use sticks at 500 meters. The degree of independence in mobility is more diverse among children at GMFCS level II. The majority are independent on even surfaces, some use sticks, a walking frame (5, 50 and 500 meters) or a wheel chair (500 meters) for independent mobility [4].

When the children and their parents are asked to identify factors that adversely affect health-related quality of life, the amount of gait pathology has been shown to play an important role [11]. Furthermore, children, parents and healthcare professionals identify impairments in body function and structure as well as gross motor skills as domains they would like to see impacted by interventions [12].

2.2. Healthcare and interdisciplinary interventions

People in Denmark have universal and free access to health care. The responsibility for healthcare is shared between regions and municipalities. The municipalities are responsible for interventions by orthotists, physiotherapists and occupational therapists. The regions are responsible for the hospitals and thus, interventions such as spasticity management and orthopaedic surgery handled by orthopaedic surgeons and paediatricians [13]. Guided by the problems faced by each child, interventions are individually planned

to help the child and family to achieve their goals [14].

The healthcare professionals offer standardised clinical examinations throughout childhood using the Cerebral Palsy follow-Up Program (CPUP) developed in Sweden more than 20 years ago [13]. The use of the surveillance program and the associated national clinical quality database is designed to lead to early detection of complications, such as hip dislocation, scoliosis, and muscle contracture as well as to improvements in the quality of healthcare [13, 15]. The CPUP uses threshold values and three categories inspired by traffic light signals on passive range of motion and migration percentage of the hip joint to guide clinical decisions. For children on GMFCS levels I to III, the threshold values of passive range of motion are set to ensure that the patient is able to dorsiflex adequately in the stance and swing of walking [16]. The CPUP uses the following interpretation for the three categories of passive range of motion:

> *"Green means "clear" and that no indication of deterioration was noted during assessment, yellow indicates that vigilant observation or potentially treatment is recommended, and red indicated "alert" and that treatment is urgently needed (assuming no specific contra-indications)" [17a].*

The current interdisciplinary interventions offered by the municipal and regional healthcare providers to children with cerebral palsy at GMFCS levels I and II, are described below. The interventions have been offered to participants in the experimental and the control group in Study II.

Municipal healthcare
In the municipalities, physiotherapists responsible for interventions are affiliated with a range of different institutions, such as rehabilitation centres, nurseries, special needs schools, and independent clinics [13]. The physiotherapeutic interventions aim to prevent deterioration in, or to improve, body functions and structures and enhance the child's ability to perform activities and participate in social roles. A large variety of interventions are used depending on the problems faced by the individual child, and the clinical expertise and facilities available. An experience-based list of the interventions used within the framework of the International Classification of Function (ICF) is shown Table 1.

Orthopaedic surgeons and paediatricians prescribe orthoses that subsequently are financed by the municipalities under social legislation. Private companies provide the orthoses, based on the defined aims, the described impairments and the family's wishes. The orthotics are primarily aimed at the joints in the ankle and foot to support stability or mobility of the joints, or to support muscle function [18]. The most commonly used orthoses are the ankle/foot orthoses, insoles/foot orthoses and the dictus band/ankle strap.

The organisation of healthcare in Denmark, and the diverse geographic location across 23 municipalities of the 60 participants in Study II, has led to 58 physiotherapists and a large number of prosthetics being involved in the interventions offered to the participants.

Regional healthcare
The paediatric departments offer interdisciplinary consultations, where children, parents, and the local healthcare team consisting of professionals from the municipal and regional healthcare systems meet and agree on future surveillance, coordinate common goals and plan interdisciplinary interventions for the child [13].

Paediatricians and orthopaedic surgeons are responsible for spasticity management. The most frequently used intervention is injection of Botulinum toxin type A in hyperactive muscles in the lower extremities, most often the Gastrosoleus muscle [19].

Treatment in the form of orthopaedic surgery is performed at highly specialised centres.

Table 1. The most common interventions used by physiotherapists in Denmark

ICF dimensions	Name of intervention	Description
Body functions and structures	Fitness training	Planned structured activities involving repeated movement of skeletal muscles that result in energy expenditure.
	Strength training	Training with the use of progressively more challenging resistance to movements to improve muscle function.
	Stretching	Use of an external passive force exerted upon the limb to move it into a new and lengthened position.
Activity (Motor activities)	Functional training	Task-specific practice of functional tasks.
	Goal-directed training	Specific practice of child-set goal-based tasks.
	Hippo-therapy	Therapeutic horse riding to practise postural control, balance and symmetry.
	Home programs	Practice of tasks by the child, led by the parent or other adult and supported by the therapist, in the home or school environment.
	Hydrotherapy	Aquatic-based exercises.
	Neurodevelopmental therapy (NDT, Bobath)	Direct, passive handling and guidance to improve performance.
Participation	Assistive technology	Equipment or devices to improve independence e.g. walking frames and wheelchairs.

Abbreviations: ICF: International Classification of Function.

Some of the most common surgeries are tendon transfers, muscle tendon lengthening, rotational osteotomy and stabilisation of joints. The surgeries aim to restore joint mobility, muscle function, stability and lever arm function [20].

In total, six paediatric departments and two departments of paediatric orthopaedic surgery were involved in the healthcare of children with cerebral palsy in Study II.

2.3. Gait analysis

The purpose of gait analysis is to record biomechanical data on the movements and forces on the body segments during gait [21]. Since the introduction of gait analysis laboratories in the early 1980s, the objective biomechanical measurements during gait have played a major role in the development of surgical interventions used in the treatment of children with cerebral palsy [22]. Today, gait analysis has developed into an essential part of research in, and clinical practice for, ambulant children with cerebral palsy [21].

Referral to gait analysis is dependent on institutional guidelines or the clinical reasoning of the individual paediatrician or orthopaedic surgeon [21], as there is no international consensus on referral criteria.

In clinical practice, gait analysis is used for the diagnosis between disease entities, the assessment of severity, the extent or nature of the disease, the monitoring of progress and the prediction of outcomes of the intervention [21].

Studies have shown that gait analysis affects the decisions regarding orthopaedic surgical interventions [23-25], and that good agreement can be obtained between recommendations based on gait analysis and the surgery performed [25-28]. Furthermore, gait analysis has been used in research to evaluate interventions, such as selective dorsal rhizotomy [29, 30], orthopaedic surgery [31], botulinum toxin [32] and different types of physiotherapy [33-35].

Data collection in clinical practise

The methods currently used to perform gait analysis in children with cerebral palsy at GMFCS levels I and II at the Gait Analysis Laboratory at Odense University Hospital are described below. Some of the methods have been applied to participants in Study II, as outlined in detail in chapter 4 in section 4.3 Outcome measures and 4.4 Interventions.

Typically, the examination of a child consists of functional tests, measurement of body segments, recording and processing of gait, and a physical examination [21]. The individual parts of the examination are often adapted to the individual child, based on a weighing up of the possible gains relative to the expected time consumption in an extensive examination [36].

To support the interpretation of the biomechanical data, functional tests are used to establish the gross motor capacity of the child [37]. Non-standardised tasks, such as standing on one leg, toe walking or different kinds of jumping; and standardised measures of gross motor capacity, such as the Gross Motor Function Measure [38] and 1-minute walk test [39] are used in the interpretation of the examination.

Measurement of the child's height, leg length, joint width and body weight are taken [36].

Data are typically collected while the child walks the length of an approximately 10-meter walkway a minimum of 10 times during the examination [21]. The central measurement in gait analysis is the recording of data on the movement of the body segments in three dimensions with an optoelectronic tracking system using reflective markers placed on the skin over bony landmarks. The data allows the quantification of joint movement (joint kinematics). The joint kinematics are supplemented with data from multicomponent force plates recording the position of the ground reaction forces, as the child walks. The recordings are used to calculate the moments that the muscles and other soft tissues are exerting at the joint (kinetics). Besides kinematic and kinetic data, temporal-spatial data are collected, mainly walking velocity, steps per minute, step and stride length and step width [21].

A thorough physical examination is conducted for comparison with the biomechanical data [36]. Muscle weakness, altered muscle tone, reduced passive range of motion and deformities are the common clinical manifestations of cerebral palsy and are measured using standardised methods [37].

Interpretation, recommendations and dissemination
Although data from gait analyses are objective, the interpretation of data, recommendations of interdisciplinary interventions and dissemination of recommendations are, to some extent, subjective. Studies have documented large discrepancies in physicians' interpretations of data when identifying soft-tissue problems and bone deformities of the lower limb [40], poor agreement between specific surgical recommendations across surgeons and institutions [41] and large variation in the compliance between guideline recommended surgery and performed surgeries [26, 27, 42].

The approach called Impairment-Focused Interpretation is based on the principles that the process and the resulting report should be relevant, succinct, evidence-based, transparent, within the competence of the authors and time-efficient [36]. The overall aim is to identify and report the impairments that are affecting an individual's gait. The method does not consider or report on other factors, such as institutional resources or preferences of the child and family, which might influence clinical decisions about interventions [43]. The clinimetric properties of the method have not been reported.

In the report, the impairments that are affecting the child's gait pattern are described by body part (such as bone or muscle) and what is wrong with it (such as altered muscle tone, contracture, deformity or weakness). Furthermore, the underlying features in the gait data displayed in the graphs and supplementary data (e.g. physical examination and gross motor function performance), that identify the impairments are well documented [36]. The method is carried out in four parts: 1) orientation, 2) mark-up, 3) grouping and 4) reporting, as displayed in Table 2 [36].

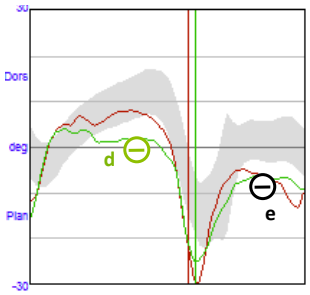
Textbooks on clinical interpretation of gait analysis have proposed guidance on the choice of treatment recommendation [37, 44]. Miller (2007) presents a description of segments and joint compensations and proposes the use of gait treatment algorithms based on the cerebral palsy subtype, the child's age and the movement features affecting

Table 2. Impairment focused interpretation
Description of the four parts of the Impairment-Focused Interpretation and examples of how the information is disseminated in the report.

1) Orientation

Review information about	*Example: Informations in the report*
• Background and diagnosis	• *Spastic unilateral cerebral palsy*
• Classification of gross motor function and performance	• *GMFCS level II - FMS 6 – 6 – 1. 1-min walk: 82.5 meter*
• Patient-reported function	• *PODCI Global Functioning Scale: 72*
• Current and past interventions	• *Past interventions: Physiotherapy*
Walking pattern and gait data	
• Visual observation of gait (video)	• *Overall Gait Deviation Index: 90.6*
• Summary scores of gait	• *Walking speed 1.18 m/s (96% of normal)*
• Temporal-spatial parameters	
• Check consistency of gait data	
• Selection of one representative trial	

2) Mark-up

Marking features	*Example: Gait Data - ankle dorsiflexion*
• Marking features on gait graphs using symbols, colours (side) and letters. See example of dorsiflexion	
List the features	*d Too little right dorsiflexion in stance*
• Type of symbol, side, variable (graph) and timing	*e too little dorsiflexion in swing.*

3) Grouping

Group and describe	*Example: Impairment*
• Group features and supplementary data	*Impairment: Left plantar flexor spasticity Documented with feature d and e; and spasticity and normal passive range of motion in the physical examination.*
• Describe: evidence (Clear, Probable, Possible), effect on walking (minor, moderate, major) and features not grouped.	*Evidence: Clear - Effect: Moderate.*

4) Reporting

Finish the report	
• Write other comments to the interpretation, if relevant (e.g. warnings, uncertainty).	

Abbreviations: Gross Motor Function Classification System (GMFCS), Pediatric Outcomes Data Collection Instrument (PODCI), Functional Mobility Scale (FMS),

the child's gait [37]. It is recommended that the formal treatment recommendations are made by healthcare professionals with relevant specific backgrounds, i.e. only an orthopaedic surgeon should make recommendations about orthopaedic surgery [36].

The results and recommendations for interventions are typically presented in a report that is distributed to the referring physician [27], but discussion of the recommendations with the surgeon who will perform the operation has also been proposed [25].

2.4. Summary – Motivation for the studies

Gait analysis has become an important and reliable method of clinical assessment of gait in ambulant children with cerebral palsy [22, 45, 46]. Nevertheless, the referral to gait analysis is dependent on institutional guidelines or the clinical reasoning of the individual paediatrician or orthopaedic surgeon[21]. The CPUP ensures continuous surveillance of all children with cerebral palsy with the same standardised assessments throughout childhood and, thus, is a common basis for decisions about interdisciplinary interventions. In CPUP, overall gross motor function and functional mobility are evaluated by standardised classification systems and measures [13]. However, the gait pattern, i.e. the manner of walking used by the child is not evaluated. Hence, the idea of combining the CPUP with the use of gait analysis in the interdisciplinary interventions for children with cerebral palsy emerged when the implementation of CPUP in Denmark was initiated.

A literature search showed that gait analysis has primarily been investigated as a measurement method. Furthermore, a few studies reported its effectiveness for evaluating outcomes of the types of orthopaedic surgical interventions used [23-25], of orthopaedic surgery of the lower limb [42] and of individualised physiotherapy [34, 35].

Thus, the research question for this thesis emerged from experience in clinical practice and a critical appraisal of the scientific literature, revealing unknown effectiveness of the use of gait analysis in interdisciplinary interventions for children with cerebral palsy.

In the planning of Study II, we became aware that the clinimetric properties of the Gait Deviation Index, a summary measure of overall gait, had only partly been described in the literature, which is the motivation for carrying out Study I.

The interpretation of the gait analysis from the baseline assessment revealed some children with severely reduced passive range of motion (corresponding to the red values in the traffic light signal used by the CPUP) were walking with only minor deviation in their gait measured with the Gait Deviation Index, which encouraged the completion of Study III.

3. Study aims and hypotheses

The overall aim of the thesis was therefore to investigate the use of gait analysis in individually defined interdisciplinary interventions for children with cerebral palsy. The specific study aims are listed below.

3.1. Study I. Test-retest

The aim of this study was to investigate the intra-rater reliability and agreement of the most common gait summary measures: the Gait Deviation Index, the Gait Profile Score and the Gait Variable Score in children with cerebral palsy across two repeated sessions.

3.2. Study II. Randomised controlled trial

This study aimed to determine if individually tailored interdisciplinary interventions with gait analysis lead to greater improvements than individually tailored interdisciplinary intervention without gait analysis in overall gait pathology, walking performance and patient-reported outcome measures of function, disability and health-related quality of life.

The predefined hypotheses were:

H1) The use of gait analysis in the planning of individually tailored interdisciplinary interventions would be superior in improving overall gait pathology (evaluated by the Gait Deviation Index (primary outcome)) compared with 'usual care' in children with cerebral palsy at GMFCS levels I and II.

H2) The use of gait analysis in the planning of individually tailored interdisciplinary interventions would be superior compared with 'usual care' in improving walking performance (1-min walk test) and patient-reported outcomes of functional mobility (Pediatric Evaluation of Disability Inventory), overall health, pain and participation in normal daily activities (Pediatric Outcomes Data Collection Instrument) as well as health-related quality of life (Pediatric Quality of Life Inventory Cerebral Palsy Module) in children with cerebral palsy at GMFCS levels I and II.

3.3. Study III. Cross-sectional study

The aim of this study was to investigate the threshold values used by the CPUP by testing the hypothesis that passive range of motion in ankle dorsiflexion is associated with gross motor function and that gross motor function differs between the groups of participants in each category. Gross motor function is measured by various methods describing the overall gross motor capacity, the ankle-specific gait capacity, and the use of gross motor skills in everyday life.

4. Methods

4.1. Study outline, registration and ethics

The thesis is based on the above three studies with the following methodological design:
Study I Intra-rater reliability and agreement study
Study II Randomised controlled trial
Study III Cross-sectional study

Study registration
The studies have been reported to the Danish Data Protection Agency (2008-58-0035). ClinicalTrials.gov have been used for study registration (NCT:02160457, Registered 09.06.2014) and the information on the site has been updated throughout the study (Updated 17.07.2015, 17.07.2016 and 20.07.2017), including the statistical analysis plan (Uploaded 25.07.2017).

Ethics
Ethics approval was obtained from the Committee for Medical Research Ethics in the Region of Southern Denmark (S-20120162) and the studies were conducted in accordance with the Declaration of Helsinki.

Children and parents were given verbal and written information about the study, experimental procedure and potential risks, such as discomfort when the patches with the reflective markers were removed and fatigue during the examinations. Furthermore, children and parents were informed that participation was voluntary and that, at any stage in the study, they could decide to discontinue participation without giving any reason and without it having consequences for their further treatment. Informed consent to participate was obtained verbally from the children, and in writing from the parents.

4.2. Participants and sample size
The number of participants, age, sex, cerebral palsy subtype and gross motor function of the participants are outlined in Table 3.

Reference group
The three studies investigated gait in children with cerebral palsy using gait summary measures that calculated the deviation from the gait of a reference group of typically developing children, preferably collected in the same gait analysis laboratory.
The Gait Deviation Index and Gait Profile Score are speed-dependent [47, 48], which can be managed by using a reference group with a walking speed similar to the study group.

The existing reference data used at our centre were from 15 children aged 7 to14 years. To mimic the age and thereby also the height and walking speed of the participants in the three studies, we supplemented the existing reference group with gait data from an additional 15 children aged 5 to 10 years without gait impairment. Thus, a reference group of 30 typically developing children aged 5 to 14 years was used to calculate the gait summary measures in the three studies.

Participants for the reference group were recruited from September 2012 to February 2013 by the research unit and through personal networks.

Study I. Test-retest
Through e-mail and an oral presentation at a national conference, the principal investigator (HMR) invited physiotherapists and medical doctors affiliated with our institution to participate in the recruitment of participants. The healthcare professionals encouraged children and their parents to participate in the study by contacting the principal investigator (HMR). Children were enrolled after screening for eligibility, and were tested and retested from March to October 2013. Eligibility criteria were age of 5 to 12 years, a diagnosis of spastic cerebral palsy at GMFCS levels I or II and could coorporate to complete the gait analysis. Exclusion criteria were: orthopaedic surgery or injection with botulinum toxin type A within 6 or 3 months prior to baseline assessment, respectively.

To mimic clinical practice and the sampling of data for the planned RCT study (Study II), three teams of two assessors conducted the data collection at the Motion Analysis Laboratory at Odense University Hospital.

Sample size
The sample size of the study was determined with an expected Intra-class Correlation Coefficient (ICC) of 0.89 for the Gait Deviation Index (primary outcome of the RCT), as reported by Miller et al. [49] and a 95% confidence interval (CI) of ± 0.1, resulting in a sample of 18 children.

Study II. Randomised controlled trial
Children registered in the CPUP in the Region of Southern Denmark and the North Denmark Region were screened for eligibility and invited to participate in Study II. Eligibility criteria were age of 5 to 8 years and a diagnosis of spastic cerebral palsy at GMFCS levels I or II. Exclusion criteria were: orthopaedic surgery or injection with botulinum toxin type A within 52 or 12 weeks prior to baseline assessment, respectively. Furthermore, the children schould to be able to participate in the examination and their parents needed to speak and understand Danish. Participants were recruited from June 2014 until June 2016 and data were collected from August 2014 to July 2017. Questionnaires were mailed to the parents prior to the examination at the Motion Analysis Laboratory at Odense University Hospital.

Sample size
The sample size for this study was based upon the Gait Deviation Index (primary outcome), collected in Study I, which included a comparable group of children with cerebral palsy (mean Gait Deviation Index 79.3, SD 12.0). A minimum clinically important difference in the Gait Deviation Index has been defined as 7.9 points by the current group of

Table 3. Participants in the studies

	Reference		Study I		Study II-III	
Number, n	15		18		60	
Age, mean (SD)	6 y 10 m	(1 y 8 m)	8 y 0 m	(2 y 1 m)	6 y 10 m	(1 y 3 m)
Sex, boys/girls, n (%)	7/8	(47/53)	12/6	(67/33)	21/39	(35/65)
CP subtype, UL/BL, n (%)		-	10/8	(56/44)	43/17	(72/28)
GMFCS I / II, n (%)		-	9/9	(50/50)	42/18	(70/30)

Abbreviations: BL: Bilateral spastic cerebral palsy; CP: Cerebral palsy; GMFCS: Gross Motor Function Classification System; SD: Standard deviation; UL: Unilateral spastic cerebral palsy (UL).

authors a priori, which is equivalent to an improvement of 10%, as suggested by Swartz et al. [30]. A minimum of 29 subjects in each group (n = 58) was required with alpha = 0.05 and 80% power. Following these estimations, it was decided to include 60 children in total (30 participants in each group), allowing for a dropout rate of 5%.

Study III. Cross-sectional study
We performed a cross-sectional study based on selected data from the baseline assessment in Study II, the randomised controlled trial.

4.3. Outcome measures

In this section, the outcome measures used in this PhD thesis are presented together with their clinimetric properties. The outcome measures are selected to cover the three individual dimensions of body function and body structures, activities and participation, and the two contextual dimensions of environmental factors and personal factors of the International Classification of Functioning, Disability and Health, version for Children and Youth (also called ICF-CY). The outcome measures, the ICF Domain they are affiliated with and their use in the studies are described in Table 4.

Diagnosis, subtype and classification of function
Date of birth and diagnosis were collected from the child's paediatrician at the initial screening for eligibility. Subtype and classification of function are used to describe participant characteristics (Studies I-III) and are used in the clinical interpretation of the gait analysis (Study II).

The GMFCS was used to classify the child's ability to perform self-initiated movements related to sitting and walking [50]. The GMFCS has strong construct validity with the Gross Motor Function Measure [51] and good inter-observer and test-retest reliability [52].

Table 4. Outcome measures

	ICF-CY Domain					Study		
	Bodyfunction and structure	Activity	Participation	Environmental factors	Personal factors	Study I Test-retest	Study II - Randomised controlled trial	Study III - Cross-sectional
Diagnosis, subtype and function								
Age and diagnosis					x	x	x	x
GMFCS		x				x	x	x
Functional Mobility Scale		x				x	x	
Instrumented gait analysis								
GMFM 66 items version		x						x
1-minute walk		x					x	x
Gait Deviation Index	x					x	x	x
Gait Profile Score	x					x		
Gait Variable Score	x					x		x
Physical examination	x							x
Patient reported outcome measures								
PEDI mobility scale		x	x	x			x	
PODCI	x	x	x				x	x
PedsQl Cerebral Palsy Module		x	x	x	x		x	x

Abbreviations: GMFCS: Gross Motor Function Classification System; GMFM: Gross Motor Function Measure; PEDI: Pediatric Evaluation of Disability Inventory; PODCI: Pediatric Outcome Data Collection Instrument; PedsQl: The Pediatric Quality of Life Inventory.

The Functional Mobility Scale was used to quantify the child's independent mobility according to the need for assistive devices in different environmental surroundings [53]. Evidence of construct validity [54], inter-rater reliability with ICCs of 0.94 to 0.95 [53] and inter-observer reliability with weighted kappa coefficients of 0.86 to 0.92 [55] have been documented.

Three-dimensional instrumented gait analysis
The gait analysis consisted of the following elements:

- Recording and processing of the gait,
- Calculation of the gait summary measures,
- Assessment of gross motor function and walking, and
- Physical examination.

All described in the following sections. The data collected during the examination were used as outcome measures in the studies and/or for clinical interpretation in Study II.

Recording and processing of the gait
As part of the gait analysis, height (centimetres), leg length (centimetres) and body weight (kilograms) were measured.

Gait analysis with three-dimensional kinematics and kinetics was performed using a 6-camera Vicon MX03 system (Study I) or an 8-camera Vicon T40 system (Study II) (Vicon, Oxford, UK) operating at 100Hz. Ground reaction forces were recorded using two force plates (AMTI, OR6-7-1000, Watertown, MA, USA), sampling at 1000Hz.

The children walked barefoot and, if relevant, also with orthotics and shoes, at a self-selected speed along a 10-m walkway until at least five acceptable trials (Study I) or ten acceptable trials (Study II) were collected for each child. Furthermore, if possible, five trials with walking speed matched to that of the baseline examination were collected (Study II). Subsequently, the parents were asked to confirm that the performance was representative of the regular gait function of their child. If not, additional trials were performed until confirmation was achieved.

The Helen Hayes marker set and corresponding Plug-in-Gait model were used to generate the kinematic data [60]. Vicon Nexus software (version 1.7.1 - 1.8.5) and Vicon Polygon software (version 3.5.2 - 4.3) were used for data processing to define gait cycles of the trials from each participant. Five trials of self-selected speed from each session were selected (Study I and Study II). Furthermore, if possible, five trials with a consistent velocity (±15%) with walking speed matched to that at baseline were also selected (Study II).

Both kinematic and kinetic data were used for the clinical interpretation (Study II) and the kinematic data were used to calculate the gait summary measures (Gait Deviation Index, Gait Profile Score and Gait Variable Score) as outcome measures (Studies I-II).

Calculation of gait summary measures
An overview of the use of gait summary measures in the studies and manuscripts is outlined in Table 5. In study III, the most affected leg was defined as the leg with the most serverly reduced range of motion in the ankle joint, i.e. the leg where one or both

measurements were classified into the red or yellow category and, if similar in range of motion, the leg with the lowest Gait Deviation Index was chosen.

Gait Deviation Index

The Gait Deviation Index is an overall quantitative index that summarises the gait pathology for each participant by comparison with a non-pathological gait. A Gait Deviation Index of 100 represents the absence of gait pathology, and each 10-point decrement below 100 indicates approximately one standard deviation from normal gait kinematics [61]. Satisfactory concurrent and construct validity of the Gait Deviation Index in children with cerebral palsy have been shown [61, 62]. Responsiveness of the Gait Deviation Index has been shown by comparing the Gait Deviation Index before and after surgical lengthening of the Gastrocnemius in children with cerebral palsy [63].

Table 5. The use of gait summary measures

	Study I	Study II	Study III
Gait Deviation Index			
Each leg	x		
Most affected leg			x
Average of both legs	x	x	
Gait Profile Score			
Each leg	x		
Overall Gait Profile Score	x		
Gait Variable Score			
Each leg	x		
Most affected leg			x

The Gait Deviation Index has been reported as a reliable measure within a single session for children with cerebral palsy [64]. Intra-tester reliability and agreement across two separate sessions have been investigated for typically developing children, demonstrating limits of agreement of ±10 points and a non-significant difference between the two sessions [64], but have not previously been investigated in children with cerebral palsy. As described in the results section of this thesis, excellent intra-rater reliability and acceptable agreement across two repeated sessions in a group of children with cerebral palsy were documented for the Gait Deviation Index in Study I [65].

Gait Profile Score

The Gait Profile Score is another overall quantitative index that, as the Gait Deviation Index, summarises the gait pathology for each participant by comparison with a non-pathological gait. It is obtained from the same gait kinematics as the Gait Deviation Index and is calculated on all gait features representing the root mean square difference between the participant's data and the average from the reference dataset [47]. Satisfactory face and criterion validity of the Gait Profile Score in children with cerebral palsy have been shown [66] and responsiveness has been documented by comparing the Gait Profile score before and after surgical lengthening of the Gastrocnemius [67].

Intra-tester reliability and agreement across two separate sessions have not previously been investigated in children with cerebral palsy. As described in the results section of this thesis, excellent intra-rater reliability and acceptable agreement across two repeated sessions in children with cerebral palsy were documented for the Gait Profile Score in Study I [65].

Gait Variable Score

The Gait Variable Score is a quantitative index in relation to Gait Profile socre, which summarises the gait pathology for each joint and is obtained from each of the gait kinematics used by the Gait Deviation Index and Gait Profile Score. It is calculated for each gait feature and represents the root mean squared difference between the participant's data and the average from the reference dataset [47]. The Gait Variable Score is illustrated by the Movement Analysis Profile (Figure 1).

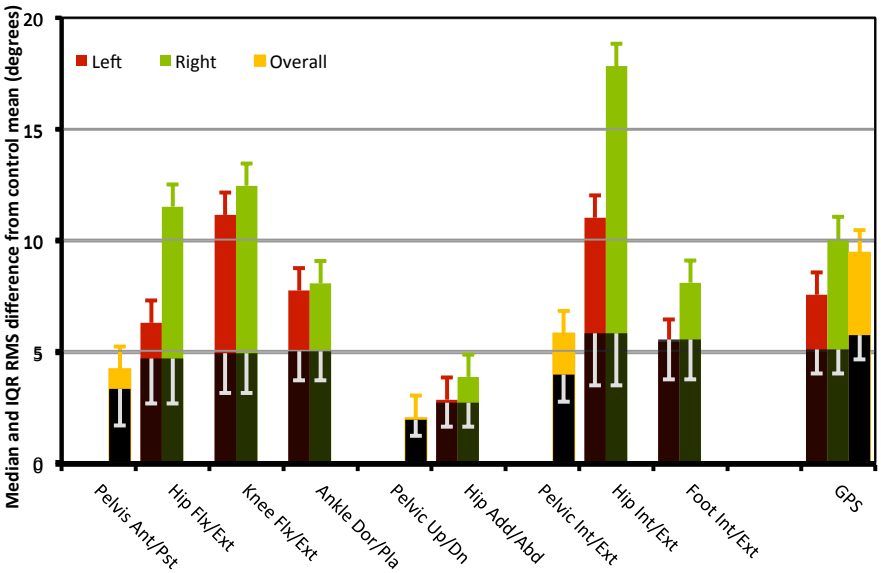


Figure 1. The Movement Analysis Profile
An example of the Movement Analysis Profile which is a graphical presentation of the scores of the 15 kinematic variables of the Gait Variable Score that together form the basis for calculation of the Gait Profile Score. The black areas are based on data from the reference group, and thus represent non-pathological gait kinematics, while the coloured areas representent the left limb, right limb and overall data from the patients being examined.

Abbreviations: Gait Profile Score: GPS, Interquartile range: IQR.

Satisfactory face validity and criterion validity of the Gait Variable Score in children with cerebral palsy have been shown [66]. Investigation of intra-session variability has suggested that the Gait Variable Score is a reliable measure within a single session [47].

Intra-tester reliability and agreement across two separate sessions have not previously been investigated in children with cerebral palsy. As described in the results section of this thesis, fair to good intra-rater reliability and acceptable agreement across two repeated sessions have been shown for the Gait Variable Score in children with cerebral palsy and were documented in Study I [65].

Assessesment of gross motor function and walking

Gross motor capacity was assessed using an experience-based selection of a minimum of 17 items from the 66-item Gross Motor Function Measure and subsequent calculation of the GMFM-66 score using the Gross Motor Function Measure Estimator software [38]. The Gross Motor Function Measure is an evaluative measure of motor function designed to document motor change in children with cerebral palsy [56]. The clinimetric properties of the measure and selected items of the measure have been extensively investigated. Excellent levels of reliability and high construct, criterion and content validity have been reported [57, 58].

Table 6. Physical examination

	Muscle function *Kendall 0-5*	**Muscle tone** *Modified Ashworth Tardieu*	**Range of motion** *Goniometer*	**Deformities** *Goniometer Observation*
Hip	Hip flexion Hip extension		Extension Abduction Intermal rotation External rotation	
Knee and tibia	Knee extension Knee flexion Quadriceps lag	Hamstring Rectus femoris	Popliteal angle Hamstring shift Knee extension Quadriceps lag Rectus femoris length	Tibial torsion Knee (valgus / varus)
Ankle and feet	Plantar flexion Dorsiflexion Inversion Eversion Confusion test	Plantar flexor	Dorsiflexion (knee 90° and 0°)	Posture of feet

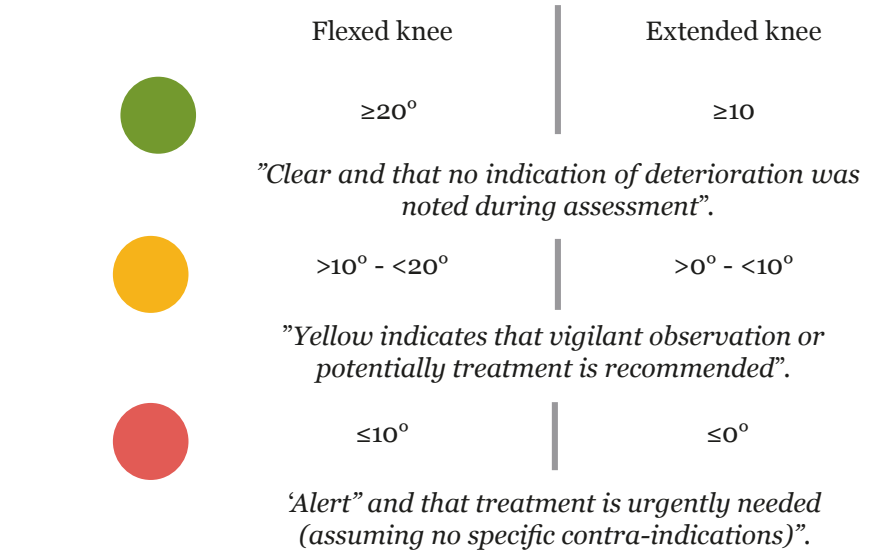


Figure 2. Ankle dorsiflexion
Clinical cut-off points, clinical interpretation for the three categories of passive range of motion and illustration of the examination of passive range of motion in ankle dorsiflexion with flexed and extended knee [16a, 17a].
Photograph used with permission from the Cerebral Palsy follow-Up Program in the Capital Region of Denmark.

Walking performance was measured with the 1-minute walk test as described by McDowell et al. [39]. Children were asked to walk as fast as possible without running on a 20-metre track for 1 minute. The test has demonstrated a high correlation with gross motor function [59] and good test-retest reliability with ICC values of 0.94 for children with cerebral palsy [39].

Physical examination

A thorough physical examination was completed after the data collection with gait analysis (Study II). The examinations were conducted as described by the CPUP [68] and Baker et al. [36] and consisted of the measures described in Table 6. The clinical examinations were used for clinical interpretation of the gait analysis, except passive range of motion in the ankle joint, which was also used in Study III.

The clinical cut-off points and clinical interpretation for the three categories of passive range of motion in ankle dorsiflexion with flexed and extended knee used in Study III, are described in Figure 2.

Patient-reported outcome measures

Pediatric Evaluation of Disability Inventory

The Mobility Scale of the original Pediatric Evaluation of Disability Inventory evaluates the child's functional mobility in everyday activities with regard to functional skills and amount of caregiver assistance [69]. A Danish version was applied as a parental questionnaire and its content and discriminative validity have been established in children with cerebral palsy [70, 71].

Pediatric Outcomes Data Collection Instrument

The Pediatric Outcomes Data Collection Instrument assesses overall health, pain and participation in normal daily activities. Concurrent and discriminant validity have been assessed by comparing the Pediatric Outcomes Data Collection Instrument with other measures of health and well-being, gross motor function and diagnostic subgroups in children with cerebral palsy [72]. Moderate to good test-retest reliability with ICC values of 0.71 to 0.97 have been reported in children with orthopaedic or musculoskeletal disorders [73].

The Pediatric Quality of Life Inventory Cerebral Palsy Module

The Pediatric Quality of Life Inventory Cerebral Palsy Module is a measure of health-related quality of life, specifically designed for children with cerebral palsy. It is based upon the parents' report and measures physical, emotional, social and school functioning. Construct validity and discriminative validity of the original version have been supported by comparing the scores from children with cerebral palsy with a generic measure of the same construct with those from children without disability. Satisfactory reliability with ICC values of 0.42 to 0.84 were demonstrated in the same study [74]. A linguistically validated Danish version was used [75].

Recommended and applied interventions

Records of the recommended and parent-reported applied interventions were used to explore the type and number of interventions in the two intervention groups with regard to the four categories: orthopaedic surgery, spasticity management, physical therapy and orthotics [14, 20]. Information about the recommended interventions was collected at the release of the gait analysis report. The applied interventions and the participants' perceived responses to the interventions were collected with a short questionnaire to the parents at 52 weeks follow-up.

Participant-perceived responses to the interventions

The parents were asked about their perception of the responses to the interventions with three clinical anchor questions by means of a 5-point Likert scale as response categories.

The question and answer categories for the anchor questions were:

> *1) "How would you describe the results of the interventions your child has participated in?"*
> *Answer categories: excellent, very good, good, fair, and poor.*
>
> *2) "In general, how would you say your child's walking ability is today compared with one year ago?"*
> *Answers categories: much better, a little better, about the same, a little worse, and much worse.*
>
> *3) "In general, how would you say your child's overall health is today compared with one year ago?" Answers categories: much better, a little better, about the same, a little worse, and much worse.*

The answers were used to determine between-group differences in the responses to the interventions and potentially also as anchor questions to determine the minimal clinically important difference [76]. Similar approaches have been used to evaluate spasticity management [77, 78] and orthopaedic surgery [79] in children and adults with cerebral palsy.

4.4. Interventions

In Study II, interventions were carried out in two study groups:
- Experimental group: Individually tailored interdisciplinary intervention based on measures performed as part of the CPUP, other clinical examinations AND gait analysis.
- Control group: Individually tailored interdisciplinary intervention based on measures performed as part of the CPUP and other clinical examinations BUT NOT gait analysis.

The two models of individually tailored interdisciplinary intervention are outlined in Figure 3.

For both the experimental and control groups, the interdisciplinary interventions addressing impairments that affect the gait are described in four categories [14, 20]: orthopaedic surgery, spasticity management, physical therapy and orthotics. The current pragmatic study design did not involve standardisation of the interdisciplinary interventions and did not provide training of the healthcare professionals in the interventions provided by the participating hospitals and municipalities.

All participants in the study continued the healthcare interventions provided by the municipalities and regions, including the yearly examinations by physiotherapists and interdisciplinary consultations.

Experimental
The experimental intervention included an individually tailored interdisciplinary intervention based on measures performed as part of the CPUP, other clinical examinations, standardised measurements of walking and recommendations from the gait analysis.

An interdisciplinary team provided recommendations for the interventions based on impairment-focused interpretation and reporting according to Baker 2013 [36]. The

data collection, interpretation, development of recommendations and dissemination of recommendations were carried out in four steps:

- Step 1: Data collection (gait analyses)
Data collection, as described in the section: gait analysis.

- Step 2 Impairment-focused interpretation
The approach 'Impairment-Focused Interpretation' [36] refers to the interpretation of the gait analysis. The principal investigator (HMR) identified and described the impairments that affected the child's gait and subsequently validated the findings with the head of the motion laboratory (AHL).

- Step 3: Recommendations for interdisciplinary interventions
The recommendations were developed to address the impairments found in the impairment-focused interpretation (Step 2) and were provided by the gait analysis team, which consisted of a neuro-paediatrician (LKH), a paediatric orthopaedic surgeon (NWP or VE), a physiotherapist (HMR) and a biomechanist (AHL).

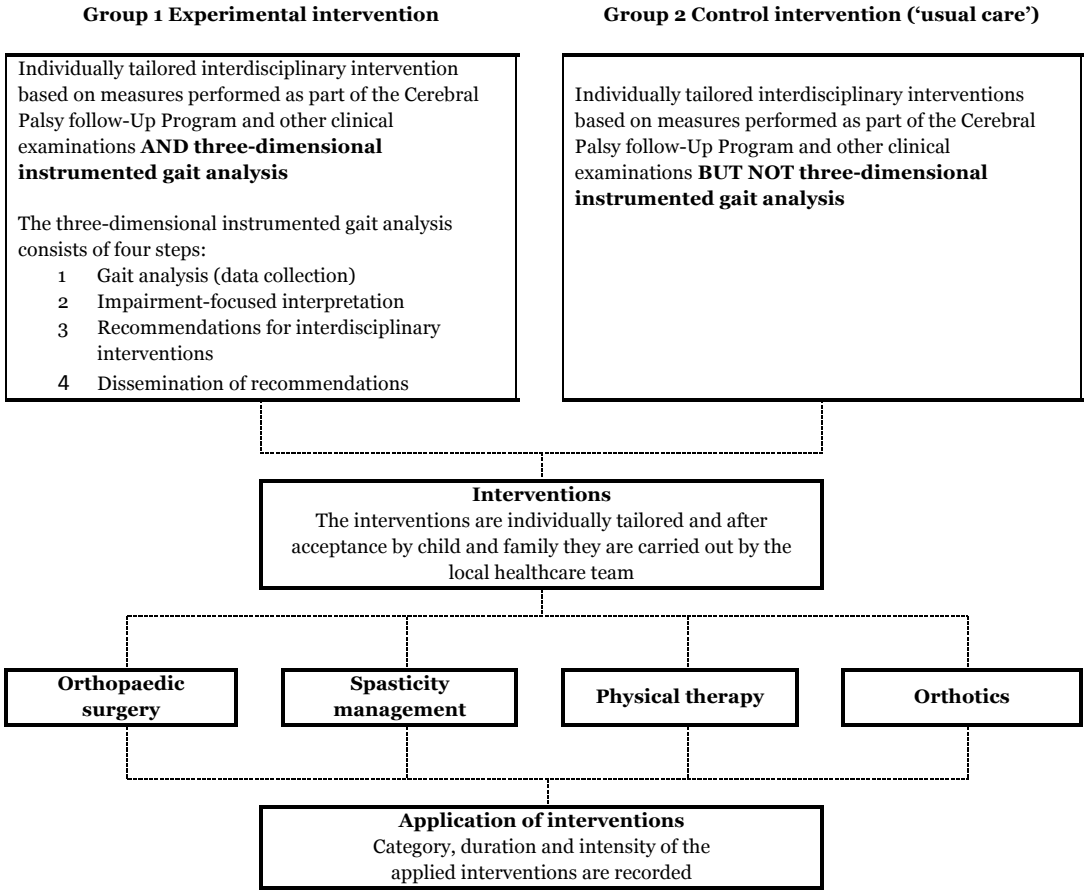


Figure 3. Interdisciplinary interventions

To facilitate an objective recommendation for treatment selection, we created a treatment algorithm, inspired by Miller 2007 [80], of the most common underlying neuro-musculoskeletal impairments of the movement features we measured. Finally, each of the recommendations for interdisciplinary interventions was based upon consensus. Otherwise, the specific interventions were not recommended.

- Step 4: Dissemination of recommendations
The parents of the child and the local healthcare team, which consisted of a paediatrician, a paediatric orthopaedic surgeon, a physiotherapist and/or an orthotist, were informed by mail about the recommendations for interventions based on knowledge from the gait analysis. The family and local healthcare teams were encouraged to contact the principal investigator (HMR) if they had any queries or uncertainties.

Adherence to the recommended interventions was not a prerequisite for participation in the current pragmatic study. As in daily clinical practice, the child, his/her family and the local healthcare team had the option to follow or to reject the recommended intervention or to choose interventions other than those recommended by the gait analysis team.

Control
The control intervention (‘usual care’) included individually tailored interdisciplinary interventions based on measures performed as part of the CPUP and other clinical examinations, but not gait analysis.

4.5. Statistical methods

An overview of the statistical methods used in each of the studies is shown in Table 7 and described briefly for each of the studies in the following sections.

Study I. Test-retest

Participant characteristics were presented with descriptive statistics. The distribution of the data was investigated using normal probability plots and the Shapiro-Wilk test [81]. Not normally distributed data were logarithmically transformed. Investigation of systematic differences was performed using the Students paired t-test and the Wilcoxon signed Ranks Test. Bland-Altman plots with 95% limits of agreement, were used to explore agreement between the two sessions [82, 83]. Reliability of each variable was quantified using ICC (two-way random effect model) and 95% CIs [82]. Agreement was assessed with the Standard Error of Measurement and absolute reliability with the Smallest Detectable Change [82].

Study II. Randomised controlled trial

The data associated with baseline characteristics were checked for completeness and their distribution was investigated using normal probability plots and the Shapiro–Wilk test [81]. Descriptive statistics were calculated with mean and standard deviation (SD), median and interquartile range (iqr) or number of patients.
Main comparative analyses between groups were performed on the full analysis set with missing data imputed using last observation carried forward. A multiple regression model with group and baseline value of the relevant variable as covariate was used to analyse between-group mean changes. The model assumptions were checked for relationship, homoscedasticity, outliers and normality of residuals. Since minor violations of the assumptions were present, the analysis was done with robust estimation.

Differences between the interventions applied and participant-perceived responses to the interventions were investigated with descriptive statistics, Pearson's chi-squared and Wilcoxon's rank-sum test.

Study III. Cross-sectional study

Participant characteristics were presented with descriptive statistics. The statistical distribution of data was investigated using normal probability plots and the Shapiro–Wilk test [81]. Scatterplots with fitted values were prepared to provide an overview of the data. Correlations were investigated with Pearson correlation coefficients or the Spearman's rank correlation coefficient.

Differences were investigated with one-way ANOVA or the Kruskal-Wallis test and, if relevant, pairwise comparisons with Wilcoxon rank sum test (Mann-Whitney).

Table 7. Overview over statistical methods

	Study I	Study II	Study III
Participant characteristics			
Descriptive statistics	x	x	x
Statistical distribution			
Normal probability plots	x	x	x
Shapiro-Wilk test	x	x	x
Transformation			
Logarithmically transformation	x		
Analysis			
Student paired t-test	x		
Wilcoxon signed ranks test	x		
Interclass correlation coefficient	x		
Standard error of measurement	x		
Smallest detectable change	x		
Multiple regression analysis		x	
Pearson's chi-squared test		x	
Wilcoxon rank sum test		x	x
Pearson correlation coefficients			x
Spearman’s rank correlation coefficient			x
One-way Analysis of variance			x
Kruskal-Wallis test			x
Graphics			
Bland-Altman plots	x		
Scatterplots with fitted values	x		x

5. Summary of results

5.1. Study I. Test-retest

Three teams of two assessors conducted the data collection from the 18 children, aged 5 to 12 years, with spastic cerebral palsy, at two sessions separated by 1 to 9 days.

No systematic bias was observed between the sessions and no heteroscedasticity was observed in Bland-Altman plots (Figure 4).

For the Gait Deviation Index and Gait Profile Score, excellent reliability with ICC values of 0.8 to 0.9 were found, while the Gait Variable Score was found to have fair to good reliability with ICCs of 0.4 to 0.7.
The agreement for the Gait Deviation Index and the logarithmically transformed Gait Profile Score, in terms of Standard Error of the Mean as a percentage, varied from 4.1% to 6.7%, whilst the smallest detectable change ranged from 11.3% to 18.5%.

For the logarithmically transformed Gait Variable Score, we found a fair to large variation in Standard Error of the Mean as a percentage, which ranged from 7% to 29% and in the smallest detectable change from 18% to 81%.

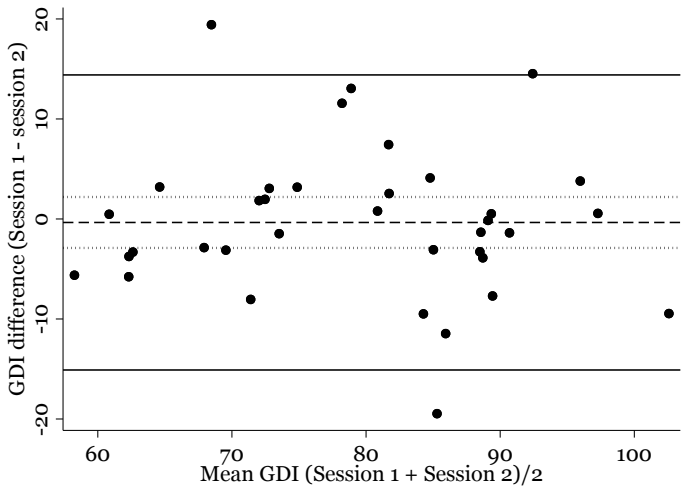


Figure 4. Example of Bland–Altman plot of Gait Deviation Index (GDI) with 95% limits of agreement (blacklines), mean difference (black dash line) and 95% CI (black dotted line).

5.2. Study II. Randomised controlled trial

In total, 160 children were invited to participate in the study. Of these, 83 children were screened for eligibility and 60 participants were randomised to either the experimental intervention (n=30) or the control intervention ('usual care') (n=30) groups. Recruitment of participants and data collection were carried out between June 2014 and July 2017. Complete assessments were available from 57 participants at baseline, 48 participants at 26 weeks follow up, and 55 participants at the primary endpoint at 52 weeks. All children received their allocated intervention of interdisciplinary interventions with or without gait analysis.

The 60 participating children had a median age of 6 years and 11 months. The full list of patient characteristics is presented in Table 1 in Paper IIb. The cerebral palsy subtype and GMFCS levels for the participants were 43 children with unilateral (experimental group / control group, n=21/n=22), 17 with bilateral (n=9 / n=8) spastic cerebral palsy, 42 children at GMFCS level I (experimental group / control group, n=20/n=22) and 18 at GMFCS level II (n=10 / n=8).

Primary outcome

At 52 weeks follow up, the mean change scores in the Gait Deviation Index for self-selected walking speed did not differ significantly between the groups (difference in Gait Deviation Index: -0.59, 95% CI; -3.9 - 2.8, Eta2 < 0.01), (Figure 5). In total, 11 participants improved more than the a priori-defined minimum clinically important difference of 7.9 on the Gait Deviation Index (experimental group / control group, n=5/n=6), resulting in a non-significant risk difference of -0.03 (95% CI; -0.23 – 0.16, Z=0.33, p=0.738).

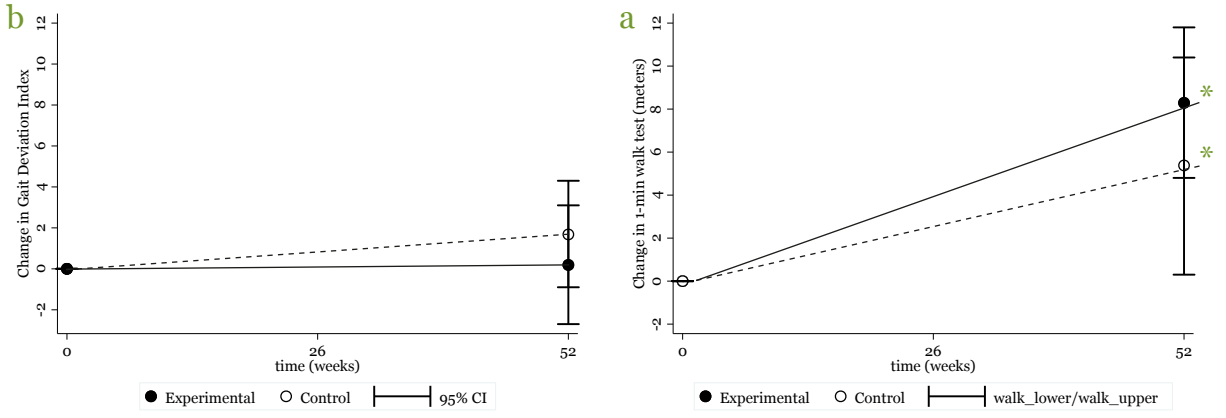


Figure 5. Within-group change from baseline in Gait Deviation Index (a) and 1-minute walk test (b)from baseline to 52 weeks.

* Statistically significant within-group change.

Secondary outcomes

No statistical significant between-group differences in change scores were observed in the 1-minute walk test (3.02 meter (-2.9 - 9.0), Eta2 = 0.02) at 52 weeks or in the patient-reported outcome measures at 26 or 52 weeks. Statistical significant and potential clinically relevant within-group improvements were seen in some of the secondary outcome measures at 26 and 52 weeks. Examples of the within-group changes are outlined in Figure 5 and Figure 6. The complete table of the within-group and between-group differences is outlined in Table 2 in Paper IIb.

Additional/tertiary outcomes

No significant difference was observed between the groups in participant-perceived responses to the interventions (p=0.19) or changes in walking (p=0.38). However, a difference between the groups was seen in overall health in favour of the experimental group (p=0.03) (Figure 7).

Interventions

The compliance with the recommended types of interventions was 24 of 28 participants for physiotherapy (% (95% CI), 86% (67 – 96), 6 of 10 participants for orthotics (60% (26 – 88)), 5 of 14 for spasticity management (36% (13 - 65)) and 0 out of 1 for orthopaedic surgery (0% (no 95% CI calculated)).

Adverse events

The participants (children and parents) did not report any serious adverse events during the study period. However, during the testing, the assessors experienced one child who did not want to wear the adhesive reflective markers at the post examination, and five children (three at baseline and two at follow-up) were too tired to complete the 1-minute walk test after the collection of gait data was completed.

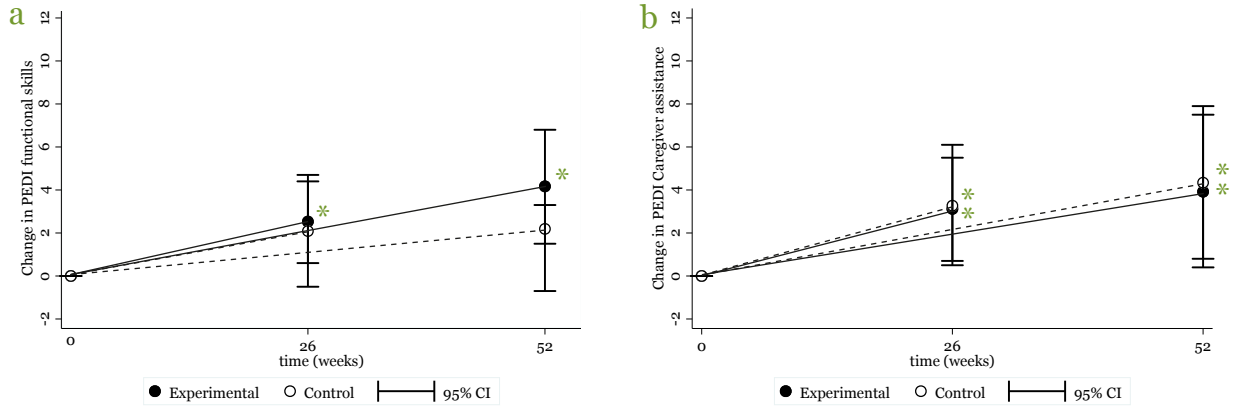


Figure 6. Within-group change from baseline in Functional skills (a) and Caregiver assistance (b) of the Mobility scale of the Pediatric Evaluation of Disability Inventory (PEDI) from baseline to 26 weeks and from baseline to 52 weeks.
* Statistically significant within-group change.

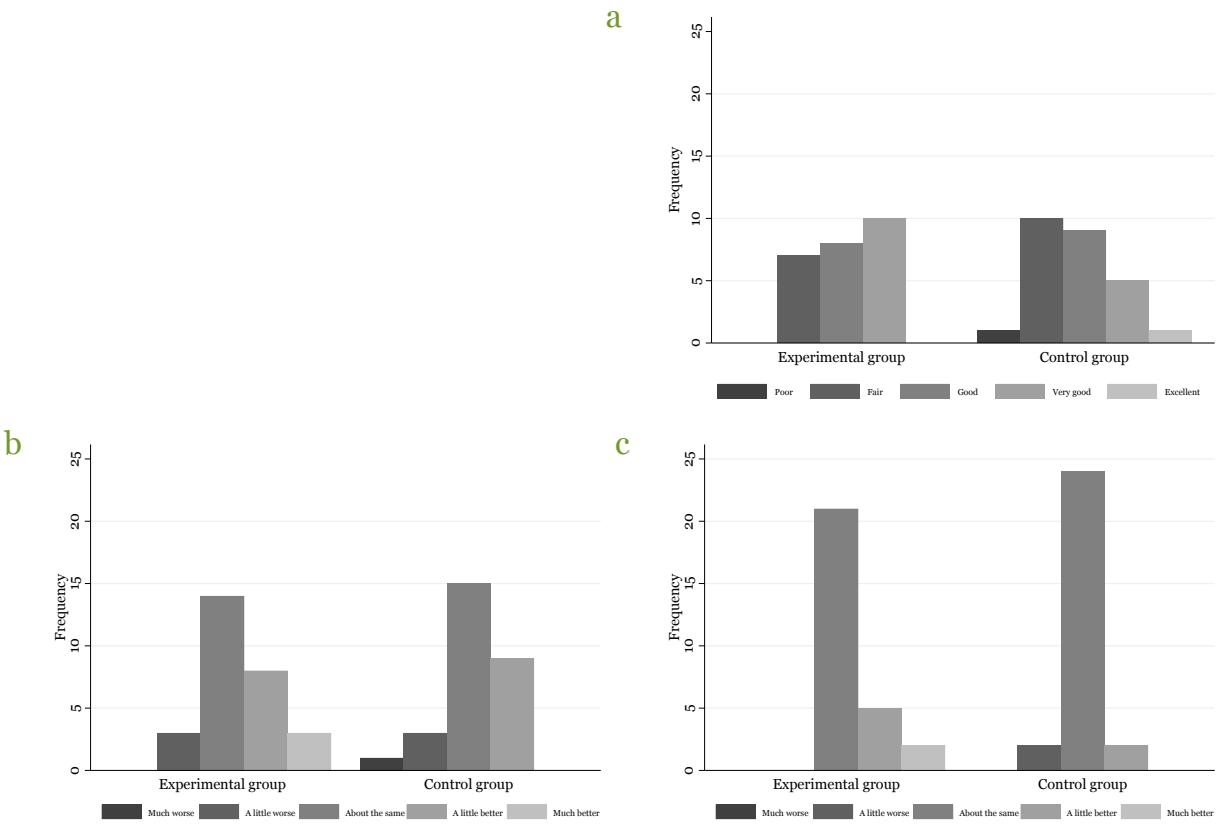


Figure 7. Bar charts illustrating the frequency of answers in each of the five categories for the participant-perceived responses to the interventions (a), changes in walking (b) and in overall health (c).

5.3. Study III. Cross-sectional

A total of 60 children with cerebral palsy participated in this study, and of these a full dataset was available for 57 participants at baseline.

Statistically significant moderate correlations were observed between the Gait Variable Score of the ankle and DF with flexed knee ($r = -0.37$, [95% CI:-0.57 - -0.13], $p<0.05$) and extended knee ($r = -0.37$, [95% CI: -0.57 - -0.13], $p<0.05$) and peak dorsiflexion and DF with flexed knee ($r = 0.49$, [95%CI: 0.26 – 0.67], $p < 0.001$) and extended knee ($r = 0.55$, [95% CI: 0.35 – 0.71], $p < 0.001$). No significant correlations between the other measures of gross motor function and passive dorsiflexion were observed. Examples of scatterplots of the correlations are outlined in Figure 8.

There were statistically significant differences in the Gait Variable Score of the ankle and peak dorsiflexion between the three groups of participants based on the categories with flexed and extended knee (Table 2 in paper III) .

For ankle dorsiflexion with flexed knee, the median Gait Variable Scores of the ankle for the red and green categories were 13.74° and 7.58°; the distributions in the two groups differed significantly ((z-score, p-value), $z = -2.63$ $p = 0.009$) and with extended knee, the median Gait Variable Score of the ankle for the red and green categories were 16.79° and 7.62°; the distributions in the two groups differed significantly ((z-score, p-value), $z = -2.43$ $p = 0.015$).

For Peak dorsiflexion, we observed a difference in red versus green and red versus yellow passive range of motion categories with flexed knee ((mean (95% CI) -9.6° (-14.4 to -4.7) and -7.9° (-13.1 to -2.6), respectively) and between red versus green and yellow versus green passive range of motion categories with extended knee (-9.57° (-15.4 to -3.8) and -7.9° (-14.2 to -1.5), respectively).

No statistically significant group-mean differences were observed between the participants classified into each of the passive range of motioncategories of passive ankle range of motion on the variables of Gait Deviation Index, 1-minute walk, Gross Motor Function Measure, the Pediatric Quality of Life Inventory Cerebral Palsy Module and Pediatric Outcomes Data Collection Instrument transfer and basic mobility scores.

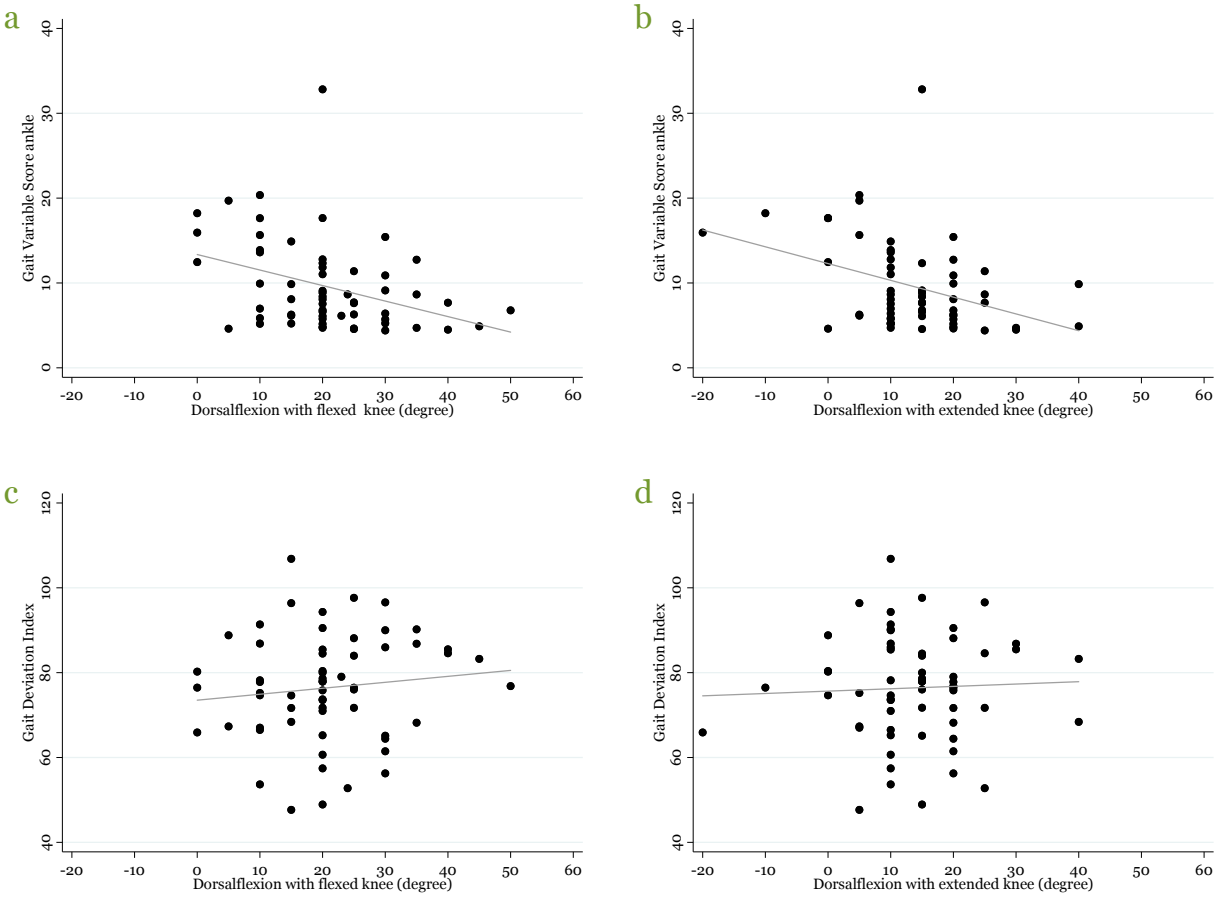


Figure 8. Examples of scatterplot of the correlation of Gait Variable Score of the ankle (a - b) and Gait Deviation Index (c - d) versus passive range of motion in dorsiflexion with flexed (a - c) and extended knee (b - d).

6. Discussion

In the following sections the methods and results are discussed and the ethical considerations are presented.

6.1. Applied methods

The overall topic of the thesis is the use of gait analysis in children with spastic cerebral palsy. The participants were not assessed by a paediatrician to evaluate and confirm the diagnosis of spastic cerebral palsy at the time of inclusion in the studies. However, the participants were recruited on the basis of their participation in the Cerebral Palsy follow-Up Program, and at all baseline assessments an experienced physiotherapist participated and confirmed the clinical signs of spastic cerebral palsy.

In the use of gait analysis, as for most outcome measures used in clinical science, one must be aware that uncertainties associated with the techniques used might lead to problems regarding the accuracy of the data collected. The Helen Hayes marker set and corresponding Plug-in-Gait model [60] used was derived from normal adults and the relationship between bones, joint centres and muscles might be different in children with cerebral palsy. Furthermore, the models depend on consistent marker placement on the participant, which sometimes is difficult due to the need for the child to stand still for long periods of time. The potential problems with marker placements was minimized by having well-trained teams of two people conducting the gait analysis and by adapting the marker placement situation to the wishes of the individual child. Furthermore, test-retest reliability in our laboratory was established on a similar patient group in study I. Thus, intrinsic and extrinsic variations of outcome measures were provided before initiation of study II.

Summary measures of gait

Summary measures of gait (Gait Deviation Index, Gait Profile Score and Gait Variable Score) were used as outcome measures in the studies. An advantage of the summary measures is that they use the gait pattern across the most important joints and movements in the lower extremities through the entire gait cycle to calculate a single score. For patients, parents, clinicians and other non-experts, a single score is more easily interpreted compared with a comprehensive report, describing all the detailed information collected during the gait analysis. However, the absolute reliability with the smallest detectable change reported in Study I meant that to accurately claim a true change in the individual child, relatively large changes in gait were necessary. Furthermore, the usability of the summary measures in the interpretation of the results of a gait analysis was limited, since the measures could not be used to identify the impairments causing the features affecting the score.

The use of a single score to evaluate changes in gait may be preferable in studies of patients, where the features impacting gait can be seen in a range of different joints and movements. This is the case in children with cerebral palsy, compared with the use of selected features from the gait cycle, such as maximal ankle dorsiflexion in stance or knee extension in initial contact. A few disadvantages in the use of summary measures as outcome measures has been reported: the lack of direction specificity which might lead to underestimation of change [84] , the distribution of the Gait Profile Score and Gait Variable Score data that is generally not considered normal [47] and the impact of gait speed [47, 48]. The disadvantages can to some extent be addressed during planning of the study, especially the impact of gait speed, which can be minimised using a speed-matched reference group. Furthermore, matching the walking speed of the participants during data collection at follow-up has been used [85]. In Study II, we planned to use this approach, but it proved impossible to instruct the children to walk at a certain walking speed.

There is growing evidence for the use of the Gait Deviation Index in children with cerebral palsy [65, 86]. However, this measure has been criticised because responsiveness has only been documented in relation to orthopaedic surgery [86]. Furthermore, a strong correlation between baseline scores and the change scores has been reported, in patient undergoing total hip artrplasty which supports a theory of a risk of ceiling effect [87].

Study I. Test-retest

Before using summary measures of gait to evaluate effectiveness in a randomised controlled trial, we documented the intra-rater reliability and agreement across two repeated sessions for the Gait Deviation Index, Gait Profile Score and Gait Variable Score. To reflect the inclusion and exclusion criteria in the intervention study, we decided on relatively narrow inclusion criteria, which might have affected the results of the study. This decision has limited the external validity of the study and might have constrained the reliability results, since the study sample was a selected group of children with cerebral palsy who were relatively homogeneous. However, the decision might have improved the possibility of achieving reasonable agreement and absolute reliability [82].

The sample size in studies of clinimetric properties of outcome measures is debated. The Guidelines for Reporting Reliability and Agreement Studies (GRAAS) [88], which we used in our planning of the study, acknowledge that the decision on sample size is not a simple one. These guidelines state that articles should explain how the sample size was chosen and state the number and characteristics of raters, subjects and replicated observations. Based on a sample size calculation, we included 18 participants and a total of 36 legs and used three assessor teams and two repeated measures of the same subject, which in the context of other studies in the field seems to be acceptable. A recent systematic review of clinimetric properties on measures of gait and walking refers to the original criteria described by Consensus-bases Standards for the selection of health status Measurement Instruments (COSMIN), that all studies with a sample size below 30 are given the methodological rating ‘Poor’ [89, 90]. The systematic review documents that only half of the studies on the subject include more than 30 participants and include studies with as few as four participants with cerebral palsy [90].

The methodologically optimal timing of the repeated sessions of gait analysis was expected to be at the same time and on the same weekday, where the child's activity levels during the days before the examination were comparable. However, to include the participants within an acceptable period of time, this was not possible. Consequently, the planning was balanced between the family's preferences, logistical constraints and the optimal timing, and the only absolute rule in the planning of the sessions was a maximum period between the sessions of 10 days.

Study II. Randomised controlled trial
The randomised controlled trial design is considered the 'gold standard' for clinical studies, and provides the most reliable evidence on the effectiveness or efficacy of healthcare interventions [91]. Study II was registered at ClinicalTrials.gov before enrolment of the first participants, the study protocol was published in an international peer-reviewed journal, the statistical analysis plan was published at ClinicalTrials.gov before unblinding of the data, and the results reported according to the CONSORT statement. Furthermore, only five participants were lost to follow-up on the primary outcome at 52 weeks, and only two participants did not complete any of the patient-reported outcome questionnaires, and thus, were completely lost at 52 weeks follow-up. These are all important requirements for a trial being rated as a high quality randomised controlled trial.

The total population of children with spastic cerebral palsy in the Region of Southern Denmark and the North Denmark Region were invited to participate in the study by their local healthcare teams in the CPUP. Together with few exclusion criteria, this strengthens the external validity and generalisability of the results from Studies II and III. Since it has been reported that the CPUP reduces the secondary consequences of cerebral palsy [92-94], the use of the surveillance program in the areas of recruitment may have reduced the proportion of children who are likely to experience severe secondary consequences of their cerebral palsy, such as reduced passive range of motion, compared with areas that do not offer a prevention program.

The relatively young age group was chosen for the study to ensure inclusion of participants at an age before the development of extensive and fixed deformities that might cause severe impairments and associated gait pathology [7]. Furthermore, the young age group was chosen for pragmatic reasons to avoid children being excluded because of earlier interventions in the form of orthopaedic surgery and to reduce the risk of participants dropping out or crossing over as part of clinical practice ('usual care'). However, this methodological decision restricts the relevance of the current findings to a relatively young age group and consequently reduces the generalisability of the results.

The decision to include children at GMFCS levels I and II was made to ensure valid data from the gait analysis to be used as the primary outcome measure. However, this may have limited the generalisability of the study results.

The sample size calculation was based on a minimum clinically important difference of 7.9 in the Gait Deviation Index, corresponding to a change of 10% as suggested by Schwartz et al. [30]. The minimum clinically important difference of 10% was used by Schwartz et al. to evaluate outcomes of orthopaedic surgery and selective dorsal rhizotomy. However, that degree of change might have been too optimistic for our study

sample and the interventions used. Furthermore, the Gait Deviation Index has recently been criticised since responsiveness has only been established in patients with cerebral palsy undergoing orthopaedic surgery [90]. The findings of the current study do not show that the experimental intervention has superior impact on the change score of the primary outcome, Gait Deviation Index - a finding that is supported by the secondary outcomes. Thus, it cannot be assumed that the missing difference on the primary outcome, Gait Deviation Index, is due to lack of responsiveness.

In the study, we used a pragmatic approach to reflect common clinical practice and ensure high external validity and generalisability of the results. This is in contrast to studies emphasising internal validity that are carried out in an 'ideal setting' with highly selected participants, practitioners and hospitals [95]. The pragmatic approach can be seen as a limitation, since reduced adherence to the recommended interventions and inconsistency in the delivery of the interdisciplinary interventions may have affected the results. One could argue that formal training in the use of the results from the gait analysis and the interventions recommended could have had an impact on the study results. A more detailed explanatory approach could have counteracted these issues but would have risked a conclusion of less value for current clinical practice, with reduced external validity and generalisability.

The use of the Impairment-Focused Interpretation approach in the interpretation of the data from the gait analysis was chosen to ensure a structured and transparent method to prepare the report. It would have been preferable if the method could have been tested in clinical practice and investigated for its ability to identify features and underlying impairments before its use in the study. However, this was not possible for our study.

A limitation in the design and outcome measures used is the lack of a standardised and detailed description of the specific interventions offered to the families, the specific applied intervention and reasons for not offering or applying interventions. This challenge is broader than the design of our study, as there are also numerous different interventions provided by medical practitioners or allied health professionals in the community and a pronounced lack of consensus about the naming of these interventions [14].

The primary follow-up period of 52 weeks was chosen to balance the desire for (i) a short follow-up for the interventions' spasticity management and physiotherapy and (ii) sufficient time for the effects of orthopaedic surgery and orthotics to be measureable, which might take as long as 24 months to emerge [96]. Based on the reported interventions applied in the study, one can speculate that a shorter follow-up (i.e. 16 weeks post release of the report) would have been more sensitive. Our study was designed to evaluate long-lasting effectiveness however, and extra follow-up at 16 or 20 weeks post start of the interventions would have been methodologically preferable but difficult to implement and not feasible for the study's sample. In addition, it could have been relevant to plan the timing of the gait analysis and the release of the report to coincide with the examinations and interdisciplinary consultations offered by the local healthcare teams. In the planning of the study, this was not considered possible, which means that for some participants, there may have been a longer period of time from the release of the report to their local healthcare team having an opportunity to discuss the recommended

interventions.

The study included a wide range of outcome measures that covered all dimensions of the International Classification of Functioning, Disability and Health [97] that seemed relevant to the participants, their parents and the healthcare professionals. As the primary outcome, we used the summary measure, the Gait Deviation Index. The properties of the measure were discussed previously in section 6.1.1. Summary measures of gait. Measures used to document the effectiveness of interventions should ideally be relevant to participants, such as survival or health-related quality of life [91]. Although it has been documented that gait plays an important role for children and their parents [11], the Gait Deviation Index must be considered as a surrogate outcome and may not be directly relevant for the participants.

6.1.4. Study II.I Cross-sectional

To investigate potential associations between outcomes of different constructs at a specific moment in time, the cross-sectional design was used. However, the study design does not allow conclusions about causality nor the extent to which the traffic light categories are able to identify children who are at risk of developing secondary consequences, such as deformities of the foot. Furthermore, the strength of our results is limited by the relatively small sample size.

The study sample of relatively young children with cerebral palsy may have reduced the number of participants with yellow and red threshold values in passive range of motion in ankle dorsiflexion, and thereby limited the strength of the results based on the groups formed by the three traffic light categories in Study III.

The rationale for the focus on the ankle joint is that reduced passive range of motion, at this specific joint, is quite common in our study sample of relatively young and well-functioning children with spastic cerebral palsy [7]. Despite the focus on joint mobility in the patients, it is well known that there is a large variability of goniometric measurements of passive range of motion [98].

6.2. Study findings and current evidence

Study I. Test-retest

The study provides evidence of the Gait Deviation Index and Gait Profile Score having excellent reliability and acceptable agreement in a group of children with cerebral palsy. However, the study also revealed a large variability in some of the Gait Variable Scores, which highlights the need for careful consideration in research and clinical practice. The study supports the use of gait summary measures in children with spastic cerebral palsy at GMFCS levels I and II at a relatively early age (8.0 ±1.2 years). The results observed in the study are comparable with the reported reliability of other outcomes retrieved from gait analysis [49, 90, 99].

Study II. Randomised controlled trial

Study II investigated the effectiveness of using gait analysis in the interdisciplinary interventions for 60 participants with cerebral palsy at GMFCS levels I or II, (median age 6 years 11months), who were randomised to the experimental or control group. No superior effectiveness in the change scores of the experimental compared with the con-

trol group were documented at 26 weeks or 52 weeks follow-up for measures of gait, health, pain, participation in normal daily activities or health-related quality of life. Thus, the study did not provide evidence for the use of gait analysis in the interdisciplinary interventions in a case-mix of children with cerebral palsy at GMFCS levels I and II, at an early age.

Our results agree with a previous randomised controlled trial on the outcome of lower extremity orthopaedic surgery with and without gait analysis [42]. The study reported lack of compliance between the recommended interventions and the interventions applied, as in our study. Several studies have reported the degree of compliance [25-28], but only a few have documented the reasons for the lack of compliance [8]. These reasons included a decision by the surgeon, a request from the patient/family and a change in patient status. The lack of compliance may also be caused by the absence of consensus about the interpretation and reporting of data, and the fact that even though the data from the gait analysis are objective, the interpretation and recommendations are to some extent subjective [40]. Lofterod et al. (2007) suggest that discussion of the recommendations with the surgeon who will perform the operation might improve the compliance [25].

In our study, the timing of the gait analysis and release of the report and recommendation to the interdisciplinary consultations offered by the paediatric departments might have improved the compliance. In practice, this could mean that the gait analysis, interpretation, recommendation and dissemination should be completed within a pre-defined time period and that the participants meet with their local healthcare team immediately after the report is available, to discuss the recommendations and decide on treatment.

An explanation for the lack of difference in the change scores between the groups may be the interventions recommended and applied. During the study, some of the healthcare professionals involved in the local teams expressed uncertainty about the recommended interventions and how they should be used in clinical practice (i.e. how the progressive resistance should be applied to improve muscle strength in the Tibialis Anterior or how often the training should be applied to be effective). This suggests that there might be a lack of common use and understanding of interventions across sectors and interdisciplinary professional groups. Furthermore, only a few studies of high quality have investigated the effectiveness of interventions to improve the impairments identified by gait analysis, making it uncertain as to what extent the applied intervention has the potential to affect the impairments [14].

Study III. Cross-sectional

This study showed that threshold values (traffic light categories) on passive range of motion in ankle dorsiflexion used by the CPUP were moderately associated with measures of gait that are specific to movement in the ankle (the Gait Variable Score ankle and peak dorsiflexion) in this sample, but not with measures of overall gait function, walking or gross motor capacity or performance. The study questions the clinical value of the categories for assessing overall gross motor function, but emphasises their value to identify isolated deviation of ankle movement during gait.

Our findings accord with the relationship between changes in passive range of motion and gait function reported in a study investigating the effects of gastrocnemius fascia lengthening in 19 children with cerebral palsy [31]. They establish a stronger association between the changes in passive range of motion in ankle dorsiflexion after surgical Gastrocnemius fascia lengthening and ankle specific gait function measured with the Gait Variable Score ankle, compared with overall gait function measured with the Gait Deviation Index [31, 63, 67].

To our knowledge, the threshold values on passive range of motion used by the CPUP have not previously been investigated as to whether they:

> *"ensure that the patient has enough passive range of motion to perform adequate dorsiflexion in walking"* [16a].

6.3. Ethical considerations

The children were included in the studies after they and their parents had given their informed consent. Their participantion were based on interest and not on a referral from their paediatrician or a paediatric orthopaedic surgeon. All participants received the results from their examinations either after their baseline assessment (Study I and the experimental group in Study II) or after their follow-up assessment (the control group in Study II). This was done since the effectiveness of gait analysis in the interdisciplinary interventions was unknown.

Very few children experienced discomfort during the assessments, but some children felt too tired to complete the entire assessment. When this happened, the child was asked if they wanted to continue the assessment, and if not, the child's choice was accepted and the healthcare team focussed on the participation in the parts of the assessment that the child had completed.

In Study II, some parents expressed that parts of the questionnaires were difficult to answer or generated reflections and thoughts about their situations. In these cases, the team explained the purpose of the questionnaires, answered any queries that had arisen or referred the parents to their local healthcare team for further discussion.

From an ethical point of view, the experiences and efforts of the participants are considered acceptable, given the purpose of the studies.

7. Conclusion

Study I. Test-retest
The Gait Deviation Index and Gait Profile Score demonstrated excellent reliability and acceptable agreement, proving that they can both be used in research and clinical practice. However, the observed large variability in some of the Gait Variable Scores requires cautious consideration when selecting outcome measures for children aged 5 to 12 years with cerebral palsy at GMFCS levels I and II.

Study II. Randomised controlled trial
This study could not confirm the hypothesis that improvement in the overall gait pathology, walking performance and patient-reported outcomes following individually tailored interventions when gait analysis is used are superior to those following 'usual care' in a case-mix of all children with cerebral palsy at GMFCS levels I and II, at an early age.

Study III. Cross-sectional
Passive range of motion in ankle dorsiflexion is moderately associated with ankle-specific measures of gross motor function (Gait Variable Score ankle and peak dorsiflexion), and the mean scores of the ankle-specific measures were different in the three categorical groups. In contrast to our hypothesis, we did not find an important relationship between pas¬sive range of motion in ankle dorsiflexion or the three related categories and overall measures of gross motor capacity or the use of gross motor skills in everyday life.

8. Perspectives

Gait analysis using the Gait Deviation Index has been used as a 'gold standard' measure of gait in children with cerebral palsy [90]. However, it is important to keep in mind that there are areas of the clinimetric properties of the Gait Deviation Index still to be investigated, such as the responsiveness of the measure and also the risk of a ceiling effect when the gait pattern is close to normal (which results in the Gait Deviation Index scoring close to 100).

The randomised controlled trial did not provide the expected evidence for the use of gait analysis in clinical practice in a case-mix of children with cerebral palsy at GMFCS levels I and II, at an early age. The highly specialised examination may still be relevant in many situations, for example, if a functional diagnosis of impairments affecting gait or documentation of changes after interventions are needed. Knowledge and evidence about which specific children with cerebral palsy may benefit from the use of gait analysis in clinical practice is lacking.

Exploratory data collected during Study II calls for further investigations that are beyond the scope of this thesis. One could have investigated differences in the change scores in the explorative outcome measures, characteristics of the responders and non-responders and to what extent the clinical examination or the patient-reported outcome measures could be used to detect children who have extensive deviations in gait who could potentially benefit from gait analysis. Furthermore, there is an obvious need to focus research on interpretation, reporting and dissemination of results and recommendations from gait analysis and on the process, where healthcare professionals incorporate the results and recommendations into clinical decision-making and thus comply with those recommendations.

The study of the clinical value of measures of passive range of motion and the three traffic light categories of dorsiflexion for indicating gross motor function in children with cerebral palsy did not have the casaulity to change clinical practice, but the study does highlight the need for further research to ensure valid tools to support clinical decision-making. Extensive validation of the follow-up program to reduce development of hip dislocation has been performed, including documentation that passive range of motion is a poor indicator of the risk of hip displacement [100]. The large amount of information in the clinical databases of the CPUP in Sweden, Norway and Denmark could be used to investigate the extent to which the measurement of passive range of motion and the three traffic light categories could be used as indicators of the development of secondary consequences, such as decreasing use of walking / standing functions or deformities in bones and joints.

9. Summary

English summary

The majority of ambulatory children with cerebral palsy experience an altered gait pattern or other walking difficulties and are dependent on healthcare interventions throughout their childhood. In the Nordic countries, a surveillance program and associated database, called the Cerebral Palsy follow-Up Program (CPUP) are used to ensure timely and consistent examinations. The interventions offered to children with cerebral palsy are based upon clinical examinations and standardised measures of overall gross motor function and functional mobility. However, the gait pattern, i.e. the manner of walking used by the child is not evaluated. This can be done with 3-dimensional instrumented gait analysis (gait analysis).

Gait analysis has been used in clinical practice and research for more than thirty years and is widely recognised as the 'gold standard' measure of gait in children with cerebral palsy. However, the potential added benefits of using gait analysis on gait, walking and patient-reported outcomes in the decision-making associated with interdisciplinary interventions to address impairments in gait have not been investigated. Thus, the overall aim of this thesis was to study the use of gait analysis in individually defined interdisciplinary interventions on gait, walking and patient-reported outcomes in children with cerebral palsy.

The starting point for the thesis was the investigation of intra-rater reliability and agreement of gait summary measures across two repeated sessions (later to be used in the randomised controlled trial). The study showed that the summary measures: the Gait Deviation Index and Gait Profile Score have excellent reliability and acceptable agreement. However, a large variability in some of the Gait Variable Scores was documented.

Having established documentation for the reliability and agreement of the Gait Deviation Index (primary outcome measure), a randomised controlled trial investigating the effectiveness of interdisciplinary interventions based on the use of gait analysis versus 'usual care' was conducted. A total of 60 children aged 5 to 8 years with spastic cerebral palsy at Gross Motor Function Classification System (GMFCS) levels I or II were randomised to the experimental or control group. No significant or clinically relevant between-group differences in the change scores of the primary outcome (Gait Deviation Index) or secondary outcome measures (1-min walk test, Pediatric Evaluation of Disability Inventory, The Pediatric Quality of Life Inventory Cerebral Palsy Module and The Pediatric Outcome Data Collection Instrument) were found at 26 weeks or 52 weeks follow-up. Showing that the addition of gait analysis in a case-mix of children with cerebral palsy at GMFCS levels I and II at an early age does not improve gait function, gross motor function and patient-reported outcome measures of disability and quality of life more than 'usual care' (without gait analysis).

Lastly, using a mechanistic approach to the data from the baseline assessment of the participants in the randomised controlled trial, we investigated the potential relationship between passive range of motion and passive traffic light categories used by the CPUP versus gait summary measures from the instruments' gait analysis, gross motor function and patient-reported outcome measures. We found that in our study sample, the range of motion in ankle dorsiflexion and the traffic light categories were correlated with measures of gait that are specific to movement in the ankle and not with measures of overall gait function, walking or gross motor capacity or performance.

In conclusion, the results of this thesis do not support the use of gait analysis in the decision-making of interdisciplinary intervention in a case-mix of children with cerebral palsy at GMFCS levels I and II, at an early age. Studies investigating which children with cerebral palsy could benefit from the use of gait analysis in clinical practice are warranted.

Danish summary - Dansk resume

De fleste gående børn med cerebral parese oplever at de bevæger anderledes and andre børn, og de vil ofte være afhængige af sundheds tilbud gennem hele deres barndom. I Danmark og de øvrige nordiske lande anvendes et opfølgningsprogram og en tilhørende database, kaldet CPOP – Opfølgningsprogram for Cerebral Parese (CPUP på svensk).

De overordnede mål med CPOP er at forbedre kvaliteten af sundhedstilbuddene til børn og unge med cerebral parese og begrænse udviklingen af sekundære følger hos det enkelte barn. Dette sker bl.a. ved at alle børn med cerebral parese tilbydes ensartede undersøgelser gennem hele barndommen. De tværfaglige indsatser til børn med cerebral parese, planlægges på baggrund af kliniske undersøgelser og standardiserede målemetoder til at vurdere grovmotorik og gang. Men barnets gangmønster evalueres ikke, hvilket kan gøres med 3-dimensionel klinisk ganganalyse.

Ganganalyse har været anvendt i klinisk praksis og forskning til børn med cerebral parese i mere end tredive år og er anerkendt som et 'guld standard' til vurdering af bevægelser under gang (gangmønstret) hos børn med cerebral parese. De mulige fordele ved at bruge ganganalyse i beslutninger om tværfaglige indsatser er ikke tidligere undersøgt. Det overordnede formål med afhandlingen er at undersøge effekterne af at anvende ganganalyse i individuelt tilpassede tværfaglige indsatser på ændringer i gangfunktionen hos børn med cerebral parese.

Første studie undersøgte pålidelighed og overensstemmelse for tre målemetoder, der beregner en samlet score for afvigelser i barnets bevægelserne under gang (Gait deviation Index, Gait Profile Score og Gait Variable Score). Resultaterne viste at de to overordnede score (Gait Deviation Index og Gait Profile Score) har en god pålidelighed og acceptabel overensstemmelse, mens en stor variation for nogle af Gait Variable Scores blev dokumenteret.

Herefter blev der gennemført et lodtrækningsstudie, hvor anvendelse ganganalyse i de tværfaglige tilbud til børn og unge med cerebral parese blev sammenlignet med det nuværende tilbud, hvor ganganalyse ikke tilbydes rutinemæssigt til alle børn. I studiet blev 60 børn med spastisk cerebral parese og gangfunktion uden hjælpemidler (GMFCS niveau I eller II) i alderen 5 til 8 år, tilfældigt fordelt mellem de to grupper. Ingen signifikante eller kliniske relevante forskelle blev dokumenteret imellem ændringerne i de to grupper ved 26 uger eller 52 ugers opfølgning. Resultaterne viser at brugen af ganganalyse til alle børn med cerebral parese og gangfunktion uden hjælpemidler (GMFCS niveau I og II) i en tidlig alder, ikke forbedrer gangmønstret eller deltagernes oplevelse af funktionsnedsættelen og livskvalitet.

Resultaterne i afhandlingen understøtter ikke brugen af ganganalyse i beslutninger om tværfaglige indsatser til alle børn med cerebral parese på GMFCS niveau I og II i en tidlig alder. Der er behov for forskningsprojekter, der fokuserer på hvilke grupper af børn med cerebral parese, der kan drage fordel af at ganganalyse anvendes.

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11. Papers

Paper I

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Gait Deviation Index, Gait Profile Score and Gait Variable Score in children with spastic cerebral palsy: Intra-rater reliability and agreement across two repeated sessions

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ABSTRACT

The Gait Deviation Index (GDI) and Gait Profile Score (GPS) are the most used summary measures of gait in children with cerebral palsy (CP). However, the reliability and agreement of these indices have not been investigated, limiting their clinimetric quality for research and clinical practice. The aim of this study was to investigate the intra-rater reliability and agreement of summary measures of gait (GDI; GPS; and the Gait Variable Score (GVS) derived from the GPS).

The intra-rater reliability and agreement were investigated across two repeated sessions in 18 children aged 5–12 years diagnosed with spastic CP. No systematic bias was observed between the sessions and no heteroscedasticity was observed in Bland–Altman plots. For the GDI and GPS, excellent reliability with intraclass correlation coefficient (ICC) values of 0.8–0.9 was found, while the GVS was found to have fair to good reliability with ICCs of 0.4–0.7. The agreement for the GDI and the logarithmically transformed GPS, in terms of the standard error of measurement as a percentage of the grand mean (SEM%) varied from 4.1 to 6.7%, whilst the smallest detectable change in percent (SDC%) ranged from 11.3 to 18.5%. For the logarithmically transformed GVS, we found a fair to large variation in SEM% from 7 to 29% and in SDC% from 18 to 81%.

The GDI and GPS demonstrated excellent reliability and acceptable agreement proving that they can both be used in research and clinical practice. However, the observed large variability for some of the GVS requires cautious consideration when selecting outcome measures.

1. Introduction

Three-dimensional instrumented gait analysis (3DGA) has become an important examination in children with cerebral palsy (CP) in both research and clinical practice [1]. Healthcare professionals such as physiotherapists and biomedical engineers perform 3DGA. The examination provides a large amount of complex and interdependent data, which have led to the development of indices that can describe the quality of the gait pattern in a single score [2]. The summary measures most commonly used are the Gait Deviation Index (GDI) [3] and the Gait Profile Score (GPS) [4], which both provide a single score of the quality of the patient's kinematics during gait.

The GDI is based on the calculation of the distance between the patient's data and the average from the reference dataset on 15 gait features of gait kinematics of the pelvis, hip, knee and ankle [3]. The GPS is obtained from the same gait kinematics as the GDI and is calculated on all gait features representing the root mean square difference between the patient's data and the average from the reference dataset [4].

The Gait Variable Score (GVS), which consists of nine gait variables for each side of the body, can be derived from the GPS

Abbreviations: 3DGA, three-dimensional instrumented gait analysis; CP, cerebral palsy; FMS, Functional Mobility Scale; GDI, Gait Deviation Index; GMFCS, Gross Motor Function Classification System; GPS, Gait Profile Score; GVS, Gait Variable Score; ICC, intraclass correlations coefficient; SDC, smallest detectable change; SEM, standard error of measurement; SEM%, standard error of the mean as a percentage of the grand mean.

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score. An overall GVS for the pelvis is used and by convention the left side value is taken [4].

The GDI and GPS are different ways of scaling the same underlying construct and therefore there is little point in using both outcome measures [4]. There is debate about the use of the GDI and GPS in clinical practice and research. At present, there are pros and cons for both indices and choosing one over the other is often based on personal preference [2].

Despite being frequently used in research, the clinimetric properties of the GDI and GPS have only partly been described in the literature. Studies of children with CP have shown that the GDI and GPS demonstrate satisfactory concurrent validity when compared with gold standard measures of gait and gross motor function [3–6]. They have also shown responsiveness to surgical lengthening of the gastrocnemius muscle [7,8], and the GDI has been reported as a reliable measure within a single session [9]. However, intra-tester reliability and agreement across two separate sessions have, to our knowledge, only been investigated for the GDI in typically developing children, demonstrating limits of agreement of ±10 points and a non-significant difference between the two sessions [9]. The variability between two separate sessions can be described as 'intrinsic variation', which reflect biological variation within individuals under investigation and 'extrinsic errors', such as inconsistent marker placement, anthropometric measures, data sampling and processing [1].

In addition, only a few studies have investigated the reliability and agreement of 3DGA on children with CP. A systematic review found three studies reporting reliability and agreement of 3DGA [1]. Two of the papers used a recently criticized method, coefficient of multiple correlation [10], to investigate reliability in gait and reported values between sessions above 0.7 [11,12]. The third paper reported intraclass correlation coefficient (ICC) above 0.6 [13]. The above mentioned three studies compare differences in the joint movement between sessions, in contrast to the present study, where variations from reference dataset between sessions are compared.

To be clinically and scientifically useful, measurements must be both valid and reliable [1,14]. Thus, to provide complete clinimetric properties of the GDI, GPS and GVS, there is a need to investigate their reliability and agreement to inform a decision about which indices to use in future research investigating the quality of gait kinematics. Therefore, the aim of this study was to investigate the intra-rater reliability and agreement of the GDI, GPS and GVS in children with CP across two repeated sessions.

2. Methods

A test–retest trial was conducted to evaluate the intra-rater reliability and agreement across two repeated sessions of the GDI, GPS and GVS in children diagnosed with CP. Ethics approval was obtained from the Committee for Medical Research Ethics in the Region of Southern Denmark (S-20120162) and the Danish Data Protection Agency (12/25588). The current study conforms to the format described in the article 'Guidelines for Reporting Reliability and Agreement Studies' (GRRAS) [14].

2.1. Assessors and participants

Three assessor teams were each formed by two of three assessors as illustrated in Fig. 1. This was done to replicate daily clinical practice and the research design of a planned randomized controlled trial (NTC02160457). To ensure the intra-rater design, one of the three assessor teams performed both tests. The reflective markers were applied by the primary assessor and approved by the secondary assessor.

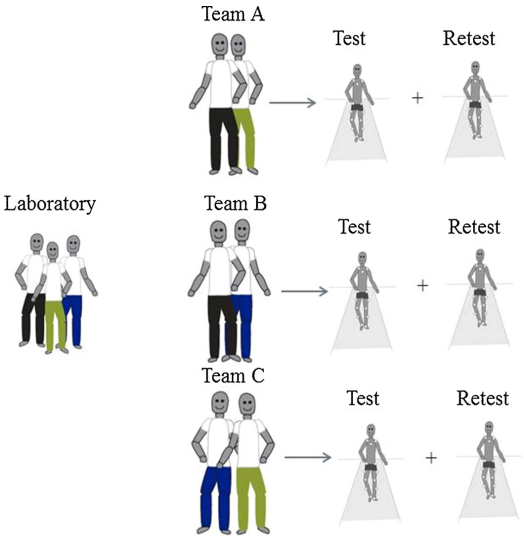


Fig. 1. The three assessors (Laboratory); the three assessor teams (Team A; B and C); test and retest for three participants.

Two 3DGA sessions on separate days were scheduled according to the family's preferences and logistical constraints. To minimize fatigue or memory bias, the sessions were, if possible, scheduled at the same time of the day within one week or within a period of maximum ten days. On the second test day, the assessors where blinded to the data obtained during the first assessment. A convenient sample of children was included if they were aged 5–12 years; diagnosed with spastic CP; classified at Gross Motor Function Classification System (GMFCS) level I or II; and could cooperate to complete the 3DGA. Children were excluded if they had been treated with Botulinum toxin within the previous 3 months or orthopedic surgery within the last 6 months.

Children were recruited by physiotherapists and medical doctors affiliated with our institution. Children were enrolled from March to October 2013.

The sample size was determined with an expected ICC of 0.89, as reported by Miller et al. [13] as the average ICC for hip rotation, hip adduction, knee flexion, and ankle plantar flexion in children with CP. With two repeated measurements, an expected ICC value of 0.89 and a 95% confidence interval (CI) of ±0.1, a sample of 18 children was required.

Before enrolment in the study, the parents of the children were contacted and the children screened for eligibility by the principal investigator (HMR). Written and oral information about the study aim and procedures was given and written informed consent was obtained from the parents.

2.2. Apparatus

3DGA was performed using a six-camera motion capture system (Vicon MX03, Oxford, UK), the Helen Hayes marker set and the Plug-in-Gait model to generate the kinematic data [15]. Vicon Nexus software (version 1.7.1) and Vicon Polygon software (version 3.5.2) was used for data processing to define gait cycles and to generate kinematic parameters. Subsequently, the GDI, GPS and GVS were calculated according to the methods provided by Schwartz and Rozumalski [3] and Baker et al. [4] using our own reference dataset of 30 typically developing children.

The statistical analysis was done using Stata/IC 13.1 (Stata Corp., College Station. TX, USA).

2.3. Data collection and processing

The children walked barefoot at a self-selected speed back and forth along a 10 m walkway until at least five acceptable trials, with a consistent velocity (±15%), were collected for each child. The parents subjectively confirmed that the gait performance was representative of the regular gait pattern of their child. Five trials from each session were processed and gait summary indices were calculated. The GDI and GPS were calculated separately for each leg and as an overall score for each individual using the method provided by Schwartz and Rozumalski [3] and Baker et al. [4], respectively. The nine GVS (pelvic tilt, hip flexion, knee flexion, ankle dorsal flexion, pelvic obliquity, hip abduction, pelvic rotation, hip rotation, foot progression) were calculated for each leg. In the statistical analysis, the median scores of the GDI, GPS and GVS were used. The median scores were chosen based on unpublished results from our institution to minimize possible effect of outliers.

2.4. Statistical analysis

Descriptive statistics were calculated for age, gender, CP subtype, GMFCS, Functional Mobility Scale and days between sessions. A conservative approach to describe outliers as more than 3 standard deviations (SD) of the mean was chosen and outliers were subsequently omitted from further analysis [16].

The statistical distribution of the GDI, GPS and GVS was investigated using normal probability plots and the Shapiro–Wilk test [17]. Since the GPS and GVS were not normally distributed, the parameters were logarithmically transformed, as recommended by Baker et al. [4]. Following this, the distribution of the logarithmically transformed GPS and GVS was re-examined by using normal probability plots and the Shapiro–Wilk test again. The logarithmically transformed GPS and GVS of pelvic tilt, hip flexion, pelvic obliquity, hip abduction, pelvic rotation, hip rotation and foot progression were normally distributed. However, the logarithmically transformed GVS of knee flexion, ankle dorsal flexion and hip rotation were not normally distributed according to the Shapiro–Wilk test. Based upon the normal probability plots, we decided to apply the same statistical procedures for all GVS. Investigation of systematic differences between the two sessions was performed using the Student's paired *t*-test and the Wilcoxon signed Ranks Test for the GDI and GPS/GVS, respectively.

Bland–Altman plots with 95% limits of agreement as the mean difference ± 1.96 × SD, mean and 95% CIs of the difference of the mean, was used to explore agreement between the two sessions [18,19]. Reliability of each variable was quantified using ICC (two-way random effect model) and 95% CIs [18]. The ICC was interpreted by the Fleiss' classification using the following thresholds: below 0.40 indicated poor reliability; between 0.40 and 0.75, fair to good reliability; and above 0.75, excellent reliability [20].

Furthermore, agreement was assessed with the standard error of measurement (SEM) and absolute reliability with the smallest detectable change (SDC) specified as an absolute value and as a percentage of the mean that is independent of the unit of measurement [18].

The SEM was calculated as $SD \times \sqrt{(1 - ICC)}$, where SD is the standard deviation of the grand mean (mean of session 1 and session 2) from all participants. The SEM is presented in the unit of measurement (SEM) and percentage of the grand mean (SEM%).

The SDC was calculated at a 95% confidence level as $SEM \times 1.96 \times \sqrt{2}$. The SDC is presented in the unit of measurement (SDC) and percentage of the grand mean (SDC%). Since the logarithmically transformed data are used for the calculations of SEM and SDC of the GPS and GVS, the unit of measurement is the logarithmically transformed score. Furthermore, the inverse functions of the logarithmically transformed data are presented.

Data are presented as mean and SD, median and interquartile range or as number of patients and percentage, as appropriate. The level of significance was set at $p < 0.05$.

Table 1
Characteristics of the study group.

Age	Mean (SD), range
Age, years	8.0 (2.1), 5.3–12.7
Gender, CP Subtype and function	*n* (%)
Gender, men/women	12/6 (67/33)
CP spastic subtype, UL/BL	10/8 (56/44)
GMFCS, I/II	9/9 (50/50)
FMS 5 meters; level 5/6	9/9 (50/50)
FMS 50 meters, level 5/6	9/9 (50/50)
FMS 500 meters, level 1/5/6	2/7/9 (11/39/50)

Cerebral palsy (CP) spastic subtype, unilateral (UL)/bilateral (BL), Gross Motor Function Classification System (GMFCS), Functional Mobility Scale (FMS).

3. Results

Three teams of two assessors conducted the data collection. Two assessors had a background as physiotherapists and one was a biomedical engineer. The assessors had 6–18 months of experience at our gait laboratory, and they all underwent a training period before the sampling began. In total, 18 children volunteered to participate. The characteristics of the participants are presented in Table 1. The two 3DGA sessions were separated by 1–9 days (mean 4.4 days, SD 2.9). The data include the scores of 18 left and 18 right legs, 36 legs in total. After selection of the median scores, eight outliers from a total of 648 GVS were identified and omitted from the statistical analysis. No outliers were identified for the GDI or GPS. In the studied population the GDI scores ranged from 55 to 107 and the GPS scores ranged from 4.8 to 14.9.

No systematic bias was observed between test and retest sessions since no significant differences between the sessions were demonstrated (Table 2). No tendency toward a greater difference, the larger mean 'trumpet shape', heteroscedasticity, was observed on the Bland–Altman plots (Fig. 2). The results of the ICC, SEM and SDC for GDI, GPS and GVS are listed in Table 3.

The reliability of the GDI and GPS was found to be excellent (ICC (range); 0.81–0.88). For the GVS, the reliability was fair to good (ICC; 0.43–0.72) with the exception of the GVS knee flexion that demonstrated excellent reliability (ICC; 0.78) and the GVS hip rotation showed poor reliability (ICC; 0.22) (Table 2).

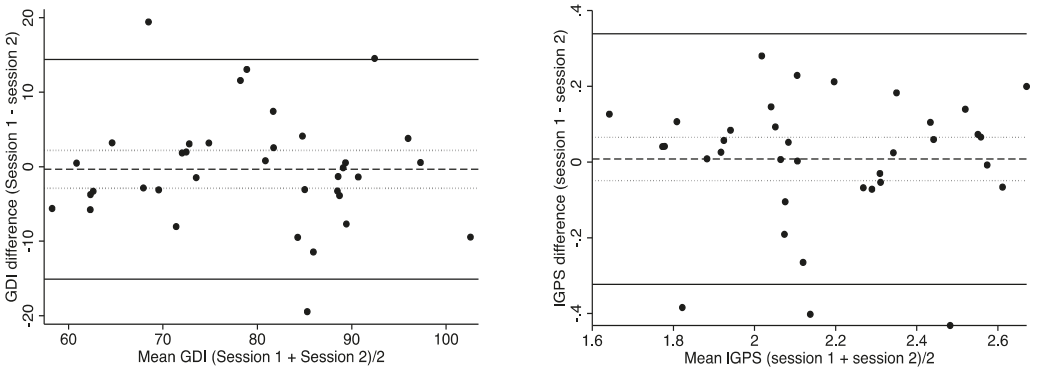
For agreement, the GDI and the logarithmically transformed GPS demonstrated SEM% values ranging from 4.1 to 6.7% and SDC% from 11.3 to 18.5% (Table 3).

Furthermore, the agreement of the logarithmically transformed GVS demonstrated a large variation SEM%, ranging from 7.21 to 28.91% and SDC% from 18.33 to

Table 2
Summary of Gait Deviation Index, Gait Profile Score and Gait Variable Score and level of significance.

Measure	*N*	Session 1	Session 2	*p*-Value*
Gait Deviation Index		**Mean (SD)**	**Mean (SD)**	
Left or right	36	79.08 (11.86)	79.43 (12.42)	0.78
Overall	18	79.08 (11.14)	79.43 (11.30)	0.79
Gait Profile Score		**Median (IQR)**	**Median (IQR)**	
Left or right	36	8.47 (3.87)	8.58 (3.66)	0.07
Overall	18	8.69 (3.67)	9.48 (4.00)	0.24
Gait Variable Scores		**Median (IQR)**	**Median (IQR)**	
Pelvic tilt	18	5.27 (5.29)	5.24 (7.79)	0.48
Hip flexion	35	8.35 (5.32)	7.80 (5.04)	1.00
Knee flexion	36	11.83 (7.52)	13.56 (7.89)	0.24
Ankle dorsal flexion	34	9.17 (2.24)	8.34 (2.30)	0.23
Pelvic obliquity	18	3.49 (1.95)	2.51 (2.43)	0.10
Hip abduction	33	4.67 (1.61)	4.61 (2.70)	0.49
Pelvic rotation	17	5.87 (1.85)	6.68 (2.11)	0.63
Hip rotation	35	7.58 (8.04)	6.97 (6.96)	0.74
Foot progression	36	7.78 (4.00)	7.88 (4.00)	0.62

Gait Deviation Index is presented as mean and standard deviation (SD); Gait Profile Score and Gait Variable Score as median and interquartile range (IRQ).
* *p*-Value: Difference between the two sessions.



A Gait Deviation Index B Logarithmic transformed Gait Profile Score

Fig. 2. Examples of Bland–Altman plots of (A) Gait Deviation Index (GDI) and (B) the logarithmically transformed Gait Profile Score (IGPS) with 95% limits of agreement (black lines), mean difference (black dash line) and 95% CI (black dotted line).

80.53% (Table 3). For the logarithmically transformed GVS, we found a large variation in SEM%, from 7.21 to 28.91% and in SDC% from 18.33 to 80.53%.

4. Discussion

Despite the wide use of summary measures of gait (GDI, GPS and GVS) in research and clinical practice for, their reliability and agreement have not previously been demonstrated.

Given that the GDI and GPS are different ways of scaling the same underlying construct, it might seem redundant to investigate both of the indices [2]. However, despite the similarity in the underlying approach, different mathematical methodologies are used and consequently, the reliability of each kinematic variable might not be comparable.

GPS and GVS are generally not considered to be normally distributed [4,7,21], as was also seen in our data, and the logarithmically transformation of the scores before performing statistical tests is needed. The logarithmically transformation increases the homogeneity of the data, which might affects the obtained ICC values and thereby reduced the clinimetric quality. Furthermore, the transformation hampers the interpretation of the results, such as the logarithmically transformed SEM% and SDC%.

Based upon numeric comparison, no difference in reliability and agreement for the GDI and the logarithmically transformed GPS were observed. The difference in scaling of the two measures makes it difficult to interpret the small differences found in SDC%.

4.1. Practical relevance of our results

The study did not reveal any systematic difference between the sessions and showed that the systematic error does not change with increasing mean values. The limits of agreement for the GDI were found to be within 15 points, which as expected is larger than the 10 points found in typically developing children [9].

The excellent reliability observed for both the GDI and GPS (ICC: 0.81–0.88) are comparable with the average between-visit ICC values of 0.85 of seven kinematic variables reported by Miller et al. [13]. Similar to our results with large variation in reliability for the GVS (ICC; 0.22–0.78), several studies have reported large variation in reliability indices of kinematics in different study populations [1].

In general, the kinematics of the sagittal plane are more reliable than the frontal plane, which is more reliable than the transverse plane, with values for reliability indices typically >0.80, >0.70 and <0.70 for each respective plane [1]. Reduced values of reliability

Table 3
Clinimetric properties for Gait Deviation Index, Gait Profile Score and Gait Variable Score.

Measure	*N*	ICC	Standard error of measurement			Smallest detectable change		
Gait Deviation Index		**ICC (95% CI)**	**SEM**		**SEM %**	**SDC**		**SDC %**
Left or right	36	0.81 (0.73–0.89)	5.28		6.67	14.65		18.48
Overall	18	0.88 (0.80–0.95)	3.90		4.92	10.80		13.63
Gait Profile Score		**ICC (95% CI)**	**SEM**	**SEM[1]**	**SEM %**	**SDC**	**SDC[1]**	**SDC %**
Left or right	36	0.82 (0.75–0.90)	0.12	1.13	5.45	0.33	1.39	15.11
Overall	18	0.88 (0.80–0.95)	0.09	1.09	4.06	0.25	1.29	11.25
Gait Variable Scores		**ICC (95% CI)**	**SEM**	**SEM[1]**	**SEM %**	**SDC**	**SDC[1]**	**SDC %**
Pelvic tilt	18	0.67 (0.49–0.85)	0.46	1.58	28.91	1.27	3.55	80.53
Hip flexion	35	0.69 (0.57–0.82)	0.24	1.27	11.34	0.67	1.95	30.91
Knee flexion	36	0.78 (0.69–0.87)	0.18	1.20	7.21	0.50	1.65	19.97
Ankle dorsal flexion	34	0.53 (0.36–0.71)	0.15	1.16	6.86	0.41	1.51	18.33
Pelvic obliquity	18	0.43 (0.14–0.72)	0.31	1.36	26.25	0.85	2.33	79.81
Hip abduction	33	0.44 (0.24–0.65)	0.25	1.28	16.25	0.69	1.99	45.72
Pelvic rotation	17	0.72 (0.55–0.88)	0.22	1.25	11.96	0.61	1.85	29.03
Hip rotation	35	0.22 (0.00–0.48)	0.45	1.57	22.11	1.25	3.50	60.68
Foot progression	36	0.60 (0.44–0.75)	0.26	1.30	12.61	0.72	2.05	34.96

Intraclass correlation coefficients (ICC); standard error of measurement (SEM); standard error of measurement in percent (SEM %); smallest detectable change (SDC); smallest detectable change in percent (SDC %). The logarithmically transformed data for Gait Profile Score and Gait Variable Score are used, except for SEM[1] and SDC[1] that are the inverse function of the logarithmically transformed results.

indices were expected in our study population. However, our results show the same variation between the planes as generally reported except for the GVS ankle dorsal flexion (ICC: 0.53) and pelvic rotation (ICC 0.72), which differs from the other GVS of the sagittal and transverse plane, respectively.

In direct comparison of ankle movement, Miller et al. [13] reported a between-visit ICC value of 0.94 in ankle movement in which are somewhat better than our results. The discrepancy might be explained by differences in the study populations and the logarithmic transformation.

General guidelines for acceptable values of agreement do not exist, but the reported agreement between sessions in SEM% for both the GDI and the logarithmically transformed GPS (7 and 4%, respectively) seems acceptable for both research and clinical practice. In contrast, the SEM% for the GVS was as high as 29%, which makes measurement error an important consideration regarding the use of the GVS.

Studies investigating the effects of gastrocnemius fascia lengthening have found improvements larger than the SDC observed in our study [7,8]. Therefore, the current results hold promise for the use of the GDI and GPS in both research and clinical practice. In contrast, other studies investigating the validity of gait summary measures showed differences in the GDI and GPS between GMFCS level I and GMFCS level II (10.2° and 2.3° for overall mean GDI and overall median GPS, respectively) [4,6]. The current SDC of 10.8° and 1.3° for the overall GDI and overall GPS, respectively, indicates that the GDI might only be useful at an individual level when significant progress above SDC is expected.

A minimal clinically important difference of 1.7° has been proposed for the GPS [21]. The difference of 1.7° is larger than the current SDC of 1.3° for the overall GPS. Therefore, the GPS seems to be a sensitive measure to detect clinically important changes in gait deviation.

The GDI, GPS and GVS measure the distance (positive or negative) from the kinematic curves of normally developing children. If the gait pattern in the two repeated sessions mirror the curves of the reference group, i.e. from increased knee flexion to increased knee extension, the indices will not show any change. Consequently, changes between the two sessions might be underestimated or even overlooked by the GDI, GPS and GVS [22]. Despite this potential limitation, the GDI and GPS have shown responsiveness to orthopedic surgery [7,8].

4.2. Limitations

Compared with other reliability studies on the topic, the current study has a similar sample size [11,13]. However, a sample size of 18 children might be considered relatively low and this may impact the results. The relatively narrow inclusion criteria for our study, might have limited the results of reliability and the external validity of our study, but improved the possibility to achieve a reasonable agreement and absolute reliability.

5. Conclusion

Excellent reliability and acceptable agreement and no systematic bias between test sessions were found for the Gait Deviation Index (GDI) and Gait Profile Score (GPS), the GDI and GPS can be used to document changes in deviations from normal gait in children with spastic cerebral palsy. Furthermore, our study showed large variability in both reliability and agreement for the Gait Variable Score, which might be important information in the interpretation of gait analysis in clinical practice and in the selection of outcome measures.

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Conflict of interest statement

All the authors of this manuscript declare that they have no conflicts of interest related to the current study.

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Paper IIa

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STUDY PROTOCOL Open Access

The use of instrumented gait analysis for individually tailored interdisciplinary interventions in children with cerebral palsy: a randomised controlled trial protocol

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Abstract

Background: Children with cerebral palsy (CP) often have an altered gait. Orthopaedic surgery, spasticity management, physical therapy and orthotics are used to improve the gait. Interventions are individually tailored and are planned on the basis of clinical examinations and standardised measurements to assess walking ('care as usual'). However, these measurements do not describe features in the gait that reflect underlying neuro-musculoskeletal impairments. This can be done with 3-dimensional instrumented gait analysis (IGA). The aim of this study is to test the hypothesis that improvements in gait following individually tailored interventions when IGA is used are superior to those following 'care as usual'.

Methods/Design: A prospective, single blind, randomised, parallel group study will be conducted. Children aged 5 to 8 years with spastic CP, classified at Gross Motor Function Classification System levels I or II, will be included. The interventions under investigation are: 1) individually tailored interdisciplinary interventions based on the use of IGA, and 2) 'care as usual'. The *primary* outcome is gait measured by the Gait Deviation Index. *Secondary* outcome measures are: walking performance (1-min walk test) and patient-reported outcomes of functional mobility (Pediatric Evaluation of Disability Inventory), health-related quality of life (The Pediatric Quality of Life Inventory Cerebral Palsy Module) and overall health, pain and participation (The Pediatric Outcome Data Collection Instrument). The primary endpoint for assessing the outcome of the two interventions will be 52 weeks after start of intervention. A follow up will also be performed at 26 weeks; however, exclusively for the patient-reported outcomes.

Discussion: To our knowledge, this is the first randomised controlled trial comparing the effects of an individually tailored interdisciplinary intervention based on the use of IGA versus 'care as usual' in children with CP. Consequently, the study will provide novel evidence for the use of IGA.

Trial registration: Trial registration: ClinicalTrials.gov NCT02160457. Registered June 2, 2014.

Keywords: Gait analysis, Cerebral Palsy, Gait Deviation Index, Study protocol

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Background

Cerebral palsy (CP) is a diagnosis that includes a range of conditions caused by a non-progressive brain injury occurring in the developing foetal or infant brain. Although the brain injury is non-progressive, the neuro-musculoskeletal and movement-related functions may deteriorate and cause activity limitation [1]. Most children with CP exhibit an altered gait such as stiff knee gait, crouch gait, excessive hip flexion, intoeing or equinus [2]. Thirty-eight to sixty-five per cent of all children with CP walk independently and are consequently classified on the Gross Motor Function Classification System (GMFCS) at level I or II [3, 4].

The interdisciplinary interventions addressing impairments that affect the patients' gait can be described in four categories: orthopaedic surgery, spasticity management, physical therapy and orthotics [5, 6]. Guided by the problems faced by each child with CP, interventions should be individually planned to help the child and family to achieve their goals [6].

In Denmark, a patient-centred and evidence-based approach is pursued. An adapted version of the Swedish Cerebral Palsy follow-Up Program is used, where the healthcare professionals use standardised examinations of the child throughout childhood [7]. A local team, which usually consists of a paediatrician, a paediatric orthopaedic surgeon and a physiotherapist, is responsible for the follow up and individually tailored interdisciplinary interventions for each child with CP. The local team meets with the child and family once or twice a year to examine the child's development and to plan and coordinate common goals and interventions for the child. As part of the Cerebral Palsy follow-Up Program, the overall gross motor function and walking performance are evaluated by standardised measures such as the GMFCS, the Functional Mobility Scale and sometimes the Gross Motor Function Measure (GMFM) [8–10]. However, objective features in the gait that reflect underlying neuro-musculoskeletal impairments are not described. This can be done with 3-dimensional instrumented gait analysis (IGA).

The purpose of IGA is to provide objective and valid measures of gait in three planes [11]. With the use of infrared camera technology and force plates embedded in the floor, it is possible to determine joint movement (kinematics), joint torque and power (kinetics) and tempo-spatial parameters. IGA thus provides a large amount of interdependent data and variables corresponding to different gait pathologies.

The quantity and complexity of data have led to the description of different indices that quantify a part of, or the overall, gait pathology into a single score. For example, the Gait Deviation Index (GDI) [12], and Gait Profile Score [13] summarise the overall gait into a single score for each patient, whereas the Gait Variable Score is an index for a single gait variable rather than a single score for all variables [13].

The use of IGA in combination with clinical examinations and standardised measures provide quantifiable information for clinical decisions regarding individually tailored interventions, in contrast to the current practice ('care as usual') where only clinical examinations and standardised measures are used. In the last two decades, pre-operative IGA has developed to the point where it has become an important investigation in ambulant children with CP [11, 14, 15]. Studies have shown that IGA can significantly affect the decisions regarding orthopaedic surgical interventions [16–18], and that there is good agreement between recommendations based on IGA and the surgery performed [19]. The effects of individually defined physiotherapy in children with CP based on clinical examinations and IGA have been investigated in a prospective double blind cross-over study [20]. The authors observed a superior effect of individually defined physiotherapy on achievement of treatment goals, gross motor function and some selected gait parameters compared with a generic training program. The use of IGA *per se* has only been investigated in relation to decision-making in orthopaedic surgery and effects of individually defined physical therapy.

To our best knowledge, the potential added benefit of using IGA in the decision-making of interdisciplinary interventions directed towards impairments in gait has not been investigated in children with CP. Thus, a study investigating potential difference in improvements in overall gait pathology following individually tailored interdisciplinary intervention with or without IGA is needed. The aim of this study is to determine which of two modalities (i.e. individually tailored interdisciplinary intervention with or without IGA) leads to greater improvements in the overall gait pathology, walking performance and patient-reported outcomes of functional mobility, overall health, pain and participation in normal daily activities and health-related quality of life after 52 weeks. However, it is important to note that the study is not intended to document the effect of IGA alone, but to document the difference in the effects of the interdisciplinary interventions, when IGA is implemented in the experimental group.

The primary hypothesis to be tested is:

H^1) The use of IGA in the planning of individually tailored interdisciplinary interventions will be more effective in improving overall gait pathology (evaluated by GDI (primary outcome)) compared with 'care as usual' in children with CP at GMFCS levels I and II.

The secondary hypotheses are:

H^2) The use of IGA in the planning of individually tailored interdisciplinary interventions will be more effective

compared with 'care as usual' in improving walking performance (1-min walk test) and patient-reported outcomes of functional mobility (Pediatric Evaluation of Disability Inventory), overall health, pain and participation in normal daily activities (Pediatric Outcomes Data Collection Instrument) as well as health-related quality of life (Pediatric Quality of Life Inventory Cerebral Palsy Module) in children with CP at GMFCS levels I and II.

Furthermore, a number of hypothesis-generating analyses will be performed on the effects of the two modalities on the following explorative outcomes: gait, walking performance and the family-centred behaviour of health care providers.

Methods/Design

Study design

A prospective, single blind, parallel group, balanced randomisation [1:1] study will be conducted in accordance with guidelines of the CONSORT statement [21, 22]. The experimental design and outcome measures are depicted in Fig. 1 and design considerations are outlined in Table 1.

The current study complies with the principles of the Declaration of Helsinki. Ethics approval has been obtained from the Committee for Medical Research Ethics in the Region of Southern Denmark (S-20120162) and the Danish Data Protection Agency (2008-58-0035). Trial registration: ClinicalTrials.gov NCT02160457. Registered June 2, 2014, Update June 6, 2014.

Participants and study setting

Participants in the Cerebral Palsy follow-Up Program in the Region of Southern Denmark and the North Denmark Region will be screened for eligibility according to inclusion and exclusion criteria described below. Written information about the study will be provided to parents and physiotherapists of eligible children by the principal investigator (HMR). Subsequently, oral information will be given to the parents of eligible children, and for those who are interested, an appointment will be scheduled for questions and

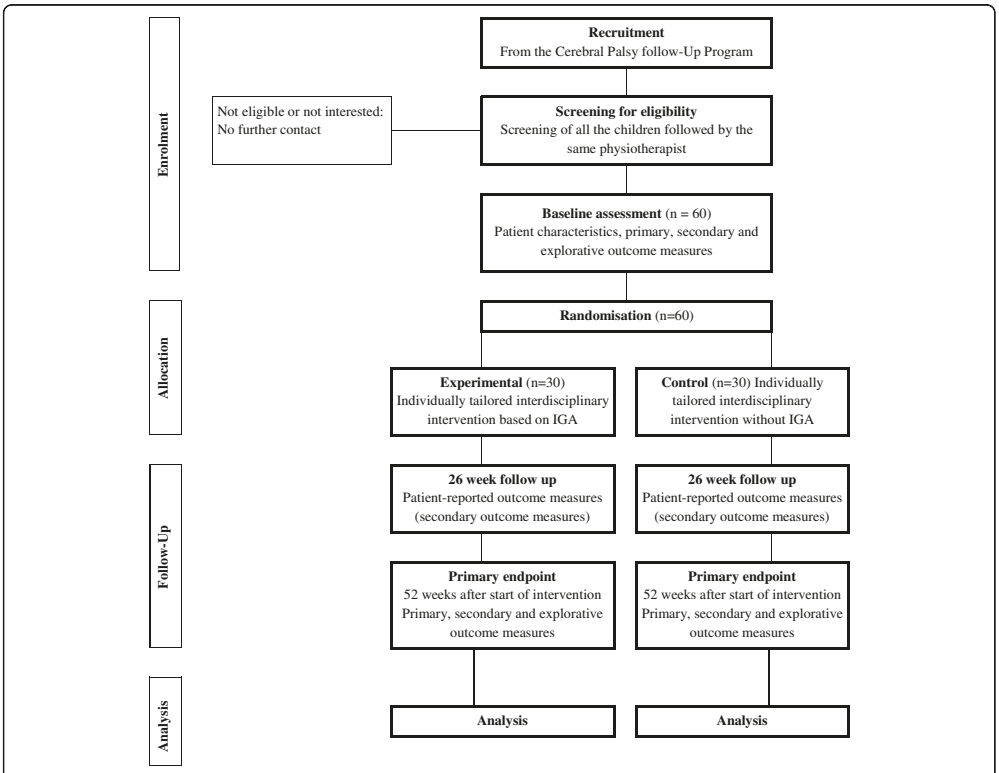

Fig. 1 Flow diagram for the trial. The flow diagram presents an overview of the progress through the phases of the trial

Table 1 Design considerations. Considerations regarding the design of the study and the participants/children

Issue of consideration	Impact on study design
Compliance by patients, families and practitioners for the recommended interdisciplinary interventions	*Patients and families* Parents and the local team will receive the gait analysis report where the impairments are outlined and the recommendations are explained. *Practitioners* The local team will be contacted and given the opportunity to ask questions about the report and recommendations.
Risk of noncompliance with intervention amongst practitioners who are responsible for healthcare for two or more participants.	*Physical therapy* First randomised patient will undergo randomisation as described. The remaining patients followed by the same physiotherapist will be given the same allocation. *Orthopaedic surgery, spasticity management, orthotics* Relatively few practitioners carry out these interventions; therefore it is not possible to take into account the risk of noncompliance with the intervention amongst practitioners.
Synchronisation of interventions	Gradually, it could be assumed that methods/knowledge/attention introduced by the IGA will influence the control group. This will be evaluated post-hoc via a comparison of interventions used in the control group in the first 6 months of the study with the interventions used in the last 6 months of the study.

further information about the study. Written consent to participate will be obtained prior to the baseline test.

Eligible participants are children aged 5 to 8 years diagnosed with spastic CP, classified at Gross Motor Function Classification System levels I or II. Exclusion criteria are: earlier interventions in the form of orthopaedic surgery within the past 52 weeks, injection with botulinum toxin type A in the 12 weeks prior to baseline assessments, and relocation to another region during the trial. Furthermore, a child will be excluded if he/she is not able to demonstrate sufficient co-operation and cognitive understanding to participate in the IGA.

This study involves six hospital units in the two regions, and the Orthopaedic Research Unit at the University of Southern Denmark. The results from the initial examination, IGA and outcome measures will be collected at the Motion Analysis Laboratory at Odense University Hospital. Patient-reported outcome questionnaires will be mailed to the parents of the participants. Interdisciplinary interventions in both groups will be conducted by the local teams at the six hospital units (paediatricians and paediatric orthopaedic surgeons) and in the 33 municipality units (physiotherapists) in the two regions. During the study period, all participants will remain in the Cerebral Palsy follow-Up Program and will receive individually tailored interdisciplinary interventions as part of the public health care system.

Intervention

The study interventions will be carried out in two study groups:

- Experimental: Individually tailored interdisciplinary intervention based on measures performed as part of the Cerebral Palsy follow-Up Program, other clinical examinations AND IGA.
- Control: Individually tailored interdisciplinary intervention based on measures performed as part of the Cerebral Palsy follow-Up Program and other clinical examinations BUT NOT IGA ('care as usual').

The two models of individually tailored interdisciplinary intervention are outlined in Fig. 2. The trial is not designed to distinguish between the different elements in the two intervention groups.

For both the experimental and control groups, the interdisciplinary interventions addressing impairments that affect the patients' gait, can be described in four categories [5, 6]:

- *Orthopaedic surgery*, such as tendon transfer, muscle tendon lengthening, rotational osteotomy and stabilisation of joints that aim to restore joint mobility, muscle function, stability and lever arm dysfunction [23].
- *Spasticity management*, where the most frequently used intervention is injection of botulinum toxin type A in muscles with increased muscle tone in the lower extremities [24].
- *Physical therapy* such as goal-directed training or functional training of specific elements of the gait or walking [6].
- *Orthotics*, such as ankle-foot orthoses that provide stability and/or mobility of the joints and/or support muscle function [25].

The study will not involve standardisation of the interdisciplinary intervention and will not provide training in

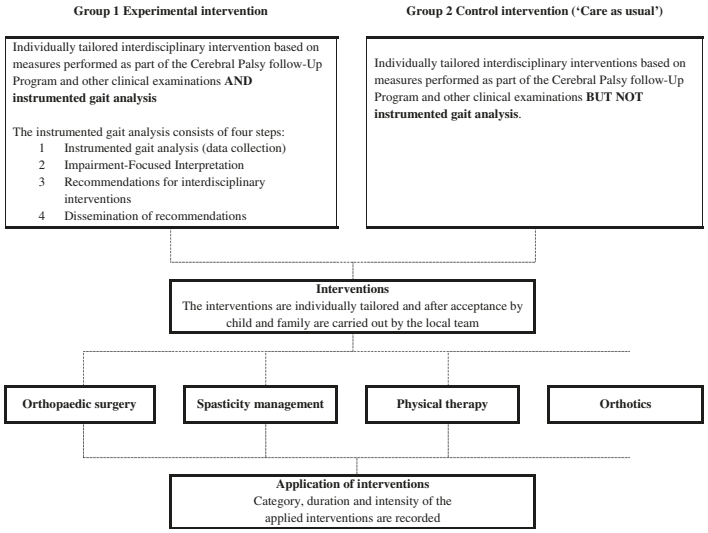

Fig. 2 Models of individually tailored interdisciplinary interventions. This figure gives an overview of the two models of individually tailored interdisciplinary interventions that are under investigation in the study

the interventions provided by the participating hospitals and municipalities. This is to ensure a pragmatic approach to reflect common practice and ensure high external validity of the study.

Experimental

The experimental intervention will include an individually tailored interdisciplinary intervention based on clinical examinations, standardised measurements of walking and recommendations for interventions based on knowledge about the impairments that affects the gait from IGA. An interdisciplinary team will provide recommendations for interventions based on impairment-focused interpretation and reporting according to Baker 2013 [26]. The data collection, interpretation, development of recommendations and dissemination of recommendations will be carried out in four steps:

Step 1: Instrumented gait analyses (data collection) Instrumented gait analysis including clinical examination, sagittal and coronal plane video recording and 3-dimensional kinematics and kinetics will be carried out. An 8-camera Vicon T40 system (Vicon, Oxford, UK) operating at 100Hz will be used for data collection. Ground reaction forces will be recorded using two force plates (AMTI, OR6-7-1000, Watertown, MA, USA), sampling at 1000Hz. The Plug-in Gait model, Vicon Nexus Software (version 1.7.1 or later) and Vicon Polygon software (version 3.5.2 or later) will be used for data processing, to define gait cycles, spatio-temporal parameters, kinematic and kinetic data [27]. The children will walk barefoot and, if relevant, also with orthotics and shoes, at a self-selected speed along a 10-m walkway until at least five acceptable trials are collected for each child. To validate the gait performance, parents will be asked if the gait is representative of their child's normal walking.

Step 2 Impairment-focused interpretation The approach 'Impairment-Focused Interpretation' [26] refers to the interpretation of the gait analysis. The principal investigator (HMR) will identify and describe the impairments that are affecting the child's gait in a standardised report and subsequently validate findings with the head of the motion laboratory (AHL).

Step 3: Recommendations for interdisciplinary interventions addressing impairments from IGA The recommendations will address the impairments found in the impairment-focused interpretation (*Step 2*) and will be provided by the gait analysis team, which will consist of a neuro-paediatrician (LKH), a paediatric orthopaedic surgeon (NWP or VE), a physiotherapist (HMR) and a biomechanist (AHL). To facilitate an objective recommendation for treatment selection based on treatment algorithms described by

Miller 2007 [28], we created a list of the most common underlying neuro-musculoskeletal impairments of the primary movement features found in IGA (see Table 2). Finally, each of the recommendations for interdisciplinary interventions will be based upon consensus. Otherwise, the specific interventions will not be recommended.

Table 2 Considerations before recommending interdisciplinary interventions. To facilitate an objective recommendation for treatment selection, we created a list of the most common underlying neuro-musculoskeletal impairments of the primary movement features found in IGA. The table describes the primary segment of movement feature (column 1), underlying neuro-musculoskeletal impairment (column 2–3) and the interdisciplinary interventions under consideration (column 4–7)

Primary segment of movement featureand underlying neuro-musculoskeletal impairment	Interdisciplinary interventions under consideration			
	Orthopaedic surgery	Spasticity management	Physical therapy	Orthotics
Pelvic				
Altered range of movement in anterior/posterior tilt, caused by impairments in:				
Body structures	x			
Muscle tone function		x		
Muscle power or endurance function			x	
Altered range of movement in pelvic obliquity, caused by impairments in:				
Body structures (Limb length discrepancies)	x			x
Compensation for reduced control of movements			x	
Hip				
Altered range of movement in flexion/extension, caused by impairments in:				
Body structures	x		x	
Muscle tone function		x		
Muscle power or endurance function			x	x
Altered range of movement in abduction/adduction, caused by impairments in:				
Body structures	x		x	
Muscle tone function		x		
Muscle power or endurance function			x	x
Altered range of movement in rotation, caused by impairments in:				
Body structures	x			
Muscle tone function		x		
Muscle power or endurance function			x	x
Compensation for reduced control of movements			x	
Knee				
Altered range of movement in flexion/extension, caused by impairments in:				
Body structures	x		x	
Muscle tone function		x		
Muscle power or endurance function			x	x
Compensation for reduced control of movements			x	x
Ankle and foot progression				
Altered range of movement in dorsi- or plantarflexion, caused by impairments in:				
Body structures	x		x	x
Muscle tone function		x		
Muscle power or endurance function			x	x
Altered range of movement in foot progression, caused by impairments in:				
Body structures and/or function (Tibial torsion, Planovalgus, Equinovarus))	x			x
Compensation for reduced control of movements			x	x

Step 4: Dissemination of recommendations to the child, family and local team The parents of the child and the local team, which consists of a paediatrician, a paediatric orthopaedic surgeon, a physiotherapists and/or an orthotist, will be informed about the recommendations for interventions based on knowledge from IGA. To promote the application of the recommended intervention from IGA, members of the local team will be asked if they have any questions about the results of the report and whether they will follow the recommendations. Furthermore, they will be asked which specific goals they have set for the applied interventions.

Adherence to the recommended interventions is not a prerequisite for participation in the study. As in daily clinical practice, the child, his/her family and the local team will have the option to follow or to reject the recommended intervention or to choose other interventions than those recommended by the gait analysis team.

Control

The control intervention ('care as usual') will include individually tailored interdisciplinary interventions based on measures performed as part of the Cerebral Palsy follow-Up Program and other clinical examinations, but not the IGA.

Measurements

All patient characteristics and outcomes are listed in Table 3. Patient characteristics, IGA and 1-min walk will be performed at baseline and at 52 weeks post start of intervention (primary endpoint). The patient-reported outcome measures will be conducted at baseline, 26 weeks, and 52 weeks post start of intervention. The time point 'start of intervention' is defined as the week where the report is released. The data collection in the control group will be adjusted according to the planned time points in the experimental group. Furthermore, to acknowledge that surgery might be influenced by a long planning phase (i.e. consideration of surgery, involvement of patient and family and planning) and rehabilitation, a second post intervention examination will be performed at 52 weeks post operation and included in a per protocol analysis.

In addition to the baseline data and classification, primary and secondary outcome measures, a range of exploratory outcome measures will be collected. The primary and the secondary outcome measures will be used to confirm or reject the described hypotheses, while the explorative outcome measures will be used for hypothesis generation, and to report other potential beneficial or harmful effects of the interventions.

Baseline data and classification of function

The Gross Motor Function Classification System (GMFCS) will be used to classify the child's ability to carry out self-initiated movements related to sitting and walking [9]. The GMFCS has strong construct validity with the Gross Motor Function Measure (GMFM) [29] and good inter-observer and test-retest reliability with generalisability coefficient values of 0.93 and 0.79 [30]. Furthermore, the Functional Mobility Scale will be used to quantify the child's mobility according to the need for assistive devices in different environmental settings [10]. Construct validity has been investigated and inter-observer reliability with agreement values of 0.86 to 0.92 with weighted kappa coefficients have been shown [31, 32].

Primary outcome measure

Overall gait pathology IGA will be conducted as described in *Step 1: Instrumented gait analyses.* Data from five representative trials will be analysed. Both at baseline and post intervention, the data collection will be done at a self-selected walking speed. If the self-selected walking speed on the two occasions differs more than 15 %, the data collection will also be conducted at a walking speed matched to that at baseline. A trained lab technician will perform the data collection and data processing.

The primary outcome measure is the GDI, which is based upon kinematic data from the IGA, and is an overall quantitative index that summarises the overall gait pathology into a single score for each patient by comparison with non-pathological gait. A GDI value of 100 represents the absence of gait pathology, and each 10-point decrement below 100 indicates one standard deviation from normal gait kinematics [12]. For the primary outcome measure, the median of the five trials for each leg will be used to calculate the average of both legs to provide a single index for each child. Since gait speed *per se* might affect GDI, the primary outcome analysis will be based upon matched walking speed, as described above.

Satisfactory concurrent and construct validity of the GDI in children with CP have been shown [12, 33]. The GDI has demonstrated excellent intra-rater reliability and acceptable agreement across two repeated sessions in children with CP [34]. The responsiveness of GDI has been shown by comparing the GDI score before and after surgical lengthening of the gastrocnemius in children with CP [35].

Secondary outcome measures

Walking performance Walking performance will be measured by using the 1-min walk test and will be performed as described by McDowell et al. [36]. It has demonstrated high correlation with gross motor function [37] and good test-retest reliability with ICC values of 0.94 for children with CP [36].

Functional mobility The Mobility Scale of the original Pediatric Evaluation of Disability Inventory evaluates the

Table 3 Summary of measures to be collected. All patient characteristics and outcomes to be collected at baseline, 26 weeks and at primary endpoint (52 weeks) are listed in the table

	Instrument	Baseline	26 weeks	Primary endpoint
Baseline data and classification of function				
Age (years)		x		
Ability to carry out self-initiated movements	GMFCS	x		x
Functional mobility	FMS	x		x
Height (cm)		x		x
Leg length (cm)		x		x
Primary outcome measure: Gait				
Overall gait pathology	GDI	x		x
Secondary outcome measures				
Walking performance (metre)	1-min walk	x		x
Functional mobility	PEDI	x	x	x
Health-related quality of life	PedsQL	x	x	x
Overall health, pain and participation	PODCI	x	x	x
Explorative outcome measures Walking performance, gait pathology, spatio-temporal parameters, and behaviour of health care providers				
Gait pathology	GVS	x		x
Step length and timeStride length and cadenceTime of single support for each leg and double supportWalking speed	IGA	x		x
Family-centred behaviour of health care providers	MPOC-20	x	x	x
Recommended and applied interventions				
Categories of recommended interventions		x		
Categories of applied interventions			x	x

Abbreviations: GMFCS Gross Motor Function Classification System, *FMS* Functional Mobility Scale, *IGA* Instrumented gait analysis, *GDI* Gait Deviation Index, *1-min walk* 1 min Walk Test, *PEDI* Pediatric Evaluation of Disability Inventory, *PedsQL* Pediatric Quality of Life Inventory Cerebral Palsy Module™, *PODCI* Pediatric Outcome Data Collection Instrument, *GVS* Gait Variable Score, *MPOC-20* Measure of Processes of Care, *CPUP* Cerebral Palsy follow-Up Program

child's functional mobility in everyday activities with regard to functional skills and amount of caregiver assistance [38]. A Danish version will be applied as a parental questionnaire: The content and discriminative validity have been established in children with CP [39, 40].

Health-related quality of life The Pediatric Quality of Life Inventory Cerebral Palsy Module is a measure of health-related quality of life, specifically designed for children with CP. It is based upon the parents' report and measures physical, emotional, social and school functioning. Construct and discriminative validity of the original version have been supported by comparing the scores from children with CP with a generic measure of the same construct with those from children without disability. Satisfactory reliability with ICC values of 0.42 to 0.84 was demonstrated in the same study [41]. A linguistically validated Danish version will be used [42].

Overall health, pain and participation The Pediatric Outcomes Data Collection Instrument assesses overall health, pain and participation in normal daily activities. Concurrent and discriminant validity have been assessed by comparing the Pediatric Outcomes Data Collection Instrument with other measures of health and well-being, gross motor function and diagnostic subgroups in children with CP [43]. Moderate to good test-retest reliability with ICC values of 0.71 to 0.97 has been reported in children with orthopaedic or musculoskeletal disorders [44]. The Pediatric Outcomes Data Collection Instrument is currently being translated into Danish.

Exploratory outcome measures

Gait pathology Data from the IGA will be used to calculate the median Gait Variable Score of the first five trials for each leg at a self-selected walking speed and at matched (pre and post) walking speed, to identify changes in gait pathology at joint levels. The explorative outcome measures based upon the Gait Variable Score will be used for hypothesis-generation purposes.

Satisfactory face and criterion validity of the Gait Variable Score in children with CP have been shown [45]. Investigation of intra-session variability has suggested that the Gait Variable Score is a reliable measure within a single session [13]. Fair to good intra-rater reliability and acceptable agreement across two repeated sessions

have been shown for the Gait Variable Score in children with CP [34].

Walking performance The following spatio-temporal parameters from the IGA will be used:

1) Step length and time, and limb-to-limb asymmetry index,
2) Stride length and cadence,
3) Time of single support for each leg and double support, and limb-to-limb asymmetry index, and
4) Walking speed.

Intra-subject reliability of gait analysis in normal and spastic children has been investigated. The study reported acceptable coefficients of variation of 3.4 to 9.7 % on spatio-temporal parameters in children with spastic CP [46].

Family-centred behaviour of health care providers Measure of Processes of Care is a self-report measure of parents' perception of the extent to which the health services that their child receives are family-centred. Concurrent validity has been investigated by comparison with measures of satisfaction and stress. Discriminative validity has been demonstrated by comparing Measure of Processes of Care scores between different programs of service delivery and acceptable reliability with Cronbach's alpha of 0.83 to 0.90 has been documented [47]. A Danish version will be used [48].

Recommended and applied interventions Records of the recommended and applied interventions will be used to explore the type and number of interventions in the two groups with regard to category (Orthopaedic surgery, Spasticity management, Physical Therapy and Orthotics).

Adverse events

Any adverse events that occur in the experimental and control groups will be registered and reported in accordance with the standards of the Danish Health and Medicines Authority. Information about adverse events will be gathered from parents of the participants, from the local teams and from the gait laboratory staff. Adverse events may occur as a direct result of the study activities, such as a fall during the IGA or indirectly as a result of the interdisciplinary interventions, such as pressure sores after casting. Any detected adverse advents or unintended effects will be reviewed by the principal study investigator (HMR) and by a neuro-paediatrician (LKH). The events will be listed and defined, with reference to standardised criteria where appropriate.

Sample size

The sample size for this study is calculated to create power for the primary hypothesis. The sample size calculation is based upon the GDI (primary outcome), collected as part of another study in our laboratory on a comparable group of children with CP (mean GDI 79.3, SD 12.0). A minimum clinically important difference in GDI has been defined as 7.9 points by the current group of authors a priori, which is equivalent to an improvement of 10 %, as suggested by Swartz et al. [49] . A minimum of 29 subjects in each group ($n = 58$) is required with alpha = 0.05 and 80 % power. Following these estimations, it was decided to include 60 children in total (30 patients in each group), allowing for a drop-out rate of 5 %.

Randomisation

After baseline assessment, children will be randomised to either the 'Experimental' or the 'Control' group. The randomisation will be stratified according to the physiotherapist to whom the child is appointed. For children who are followed by a physiotherapist, who is responsible for two or more children, the first child randomised will determine how the following children will be allocated.

Randomisation will be computer-generated by a researcher with no other involvement in the study. Participants will be allocated by a sequence of numbers: 0 – referring to 'Experimental', and 1 – referring 'Control'. The allocation sequence will be concealed in sequentially numbered opaque, sealed envelopes. When all participants followed by the same physiotherapist have completed the baseline assessment the principal investigator (HMR) will open the envelope and inform the child's parents and the local team about the allocation.

Blinding

Participants and the local team will not be blinded. Data collectors and data analysts will be blinded.

Data and statistical analysis

Main comparative analyses between groups will be performed using an intention-to-treat analysis (all cases with available baseline data carried forward). Between-group mean differences and 95 % confidence intervals will be estimated with a linear model in which baseline scores are entered as the only covariate [50, 51]. Model specifications will depend on evaluation of distributional properties of collected data and appropriate adaptation of point estimate and variation indicators. Data analysis will be performed on the groups of children randomised first and for the whole group of children to explore any differences with regard to whether a child was randomly assigned to the intervention or followed another child in the randomisation.

Secondly, a per protocol analysis will be performed. Proportional odds models will compare the difference between the two groups based on the participant-perceived response to treatment.

Discussion

To our knowledge, this is the first randomised controlled trial investigating the effectiveness of an individually tailored interdisciplinary intervention addressing impairments identified by IGA compared with 'care as usual' in children diagnosed with CP. Such a trial is warranted because IGA is widely used for orthopaedic surgical planning [11, 14, 15] and has been shown to affect the decision-making in the planning of orthopaedic surgery [18]. However, its effectiveness regarding gait pathology, walking performance and patient-reported outcomes of functional mobility, overall health, pain and participation in normal daily activities as well as health-related quality of life have never been investigated.

The IGA has been investigated for quality as a measurement tool [12, 33, 35, 46, 52]. The current trial seeks to investigate the effectiveness of the IGA when applied in a clinical practice involving multiple steps such as interdisciplinary interventions in regard to changes in the overall gait pathology, walking performance and patient-reported outcomes of functional mobility, overall health, pain and participation in normal daily activities and health-related quality of life after 52 weeks. Consequently, the current trial uses a pragmatic approach and is accordingly not designed to distinguish between the different elements in the two intervention groups but rather to reflect common practice and ensure high external validity. This is in contrast to studies emphasising internal validity that are carried out in an 'ideal setting' with highly selected participants, practitioners and hospitals [21].

The randomised controlled trial design will be used to assess potential benefits associated with the use of the IGA in interdisciplinary interventions, and thereby, provide novel evidence. The randomised controlled trial design is considered the gold standard for a clinical trial, and provides the most reliable evidence on the efficacy of healthcare interventions [22]. The study can be used to support the decision-making as to whether IGA should be applied in routine daily practice to all children with spastic CP at GMFCS levels I and II. Thus, the purpose of the study warrants a pragmatic approach as opposed to a more explanatory design. The key differences in the two approaches can be described in terms of purpose, setting, participants, intervention and outcomes [21], which will be incorporated in the following sections of the discussion.

The study will be carried out in the Region of Southern Denmark and the North Denmark Region. Participants will be recruited through the local teams in the Cerebral Palsy follow-Up Program, and will encourage attendance among eligible children. The Cerebral Palsy follow-Up Program makes it possible to gain information to make a thorough description of the 'reach' of recruitment of participants into the population of interest and to document potential study composition differences across the stages of the trial [22]. The relatively young age group has been chosen to ensure inclusion of children at an early age, before the development of extensive and fixed deformities that cause impairments and associated gait pathology [53]. To ensure good data quality from IGA, participants at GMFCS levels I and II have been chosen. However, this may impact the generalisability of findings.

To reflect the current clinical procedures in Denmark and to emphasise external validity, the experimental intervention will be carried out in five steps. Selected practitioners, who are highly trained, are responsible for the first three steps (*Step 1: IGA, Step 2: Impairment-focused interpretation, and Step 3: Recommendations for interdisciplinary interventions*). Both the selected practitioners and the local team will be involved in the remaining step (*Step 4: Dissemination of recommendations*) and planning of individually tailored interdisciplinary interventions. Paediatric orthopaedic surgeons will perform the orthopaedic surgical procedures while the local teams will carry out other interventions in terms of spasticity management, physical therapy and orthotics. Consequently, only parts of the experimental intervention (*Steps 1,2 and 3*) will be standardised and strictly enforced by researchers responsible for the study, whereas the remaining parts of the experimental interventions will be performed through the collaboration of local teams, the selected practitioners and the researchers. The local teams, regardless of treatment group, will use their standard procedures in the interdisciplinary interventions.

There is a risk of poor adherence to the recommended interventions by participants and local teams. This has previously been reported in a randomised controlled trial that investigated the impact of gait analysis on surgical outcomes in ambulatory children with CP, where less than half (42 %) of the IGA recommendations were followed [54]. To improve understanding of the recommended interventions from the IGA, members of the local team will be asked if they have any questions about the results of the report and whether they will follow the recommendations. The identification of individually tailored treatment goals has previously been used in studies concerning physical therapy [55, 56] and orthopaedic surgery [57] for children with CP. Studies have shown that the approach can promote improvement in everyday activities and gross motor function [55], and that the approach resulted in goals that were more frequently and smoothly implemented [56].

As for the majority of studies that involve interventions that cannot be blinded, the current study design

has a potential risk of non-compliance of participants with the intervention they are randomised to. In this study, there is a risk that participants randomised to the control intervention ('care as usual') will benefit from knowledge obtained by practitioners from participants in the experimental intervention. However, since IGA is only performed in our institution, no one will gain access to the examination without our knowledge. Thus, the risk of non-compliance is primarily believed to be at the physiotherapist level. Consequently, as described above, in cases where physiotherapists are responsible for the interventions for two or more participants, the first randomised patient will determine the allocation of the following patients. The interventions performed at the level of orthopaedic surgery, spasticity management and orthotics will be carried out by relatively few practitioners. Thus, it will be easier to contain this risk and practitioners will simply be requested to continue with their standard care for the 'care as usual' group. These professionals have taken part in the IGA interpretations for a number of years. A consequence of this set-up might be that the interventions in the 'care as usual' group could be influenced by the professional experience gained from previous interpretations of the IGA.

We have chosen a follow-up period of 52 weeks. This is done to balance the desire for a short follow up for the interventions' spasticity management and physical therapy, while the effects of orthopaedic surgery and orthotics might take as long as 24 months to emerge [58].

A wide range of outcome measures has been used to document the effectiveness of interventions in children with CP [43, 44]. For this study, we have decided to include assessments of body function and structure, activity and participation levels from the International Classification of Functioning, Disability and Health [59]. The primary outcome measure is at the level of 'body function', where we use overall gait pathology classified by the GDI as a measure of gait pattern functions that are defined as functions of movement patterns associated with walking [59] and can be used to reflect the extent to which the goal of 'better looking gait' has been reached [60]. Performance on the GDI was chosen as the primary outcome rather than on the Gait Profile Score, because it seems to be more sensitive to change in children with a relatively mildly affected gait [13], as expected with the study population of children at GMFCS levels I and II. The gait pattern function has been found to be one of the important domains for youth with CP, parents and medical professionals, when considering treatment outcomes [60].

The secondary outcome measures are a range of measures on the level of 'activity and participation'. The measures have been chosen to be relevant to the particular group of children participating in the study. The Gait Variable Score will be calculated to document changes in the nine kinematic variables and will be used to document explorative changes at the joint level. Thus, we have chosen a wide range of outcome measures that covers all levels of the International Classification of Functioning, Disability and Health and seems relevant to participants, their parents and the healthcare professionals.

One might argue that the Gross Motor Function Measure [8] could be a relevant outcome measure. However, due to the time-consuming IGA procedure, it would be difficult to motivate the children for further examination and, consequently, difficult to achieve valid output measures. Furthermore, there is a risk of a ceiling effect when the Gross Motor Function Measure is used for children at GMFCS level I after the age of five years, due to their relatively high level of functioning.

The current trial will provide novel evidence for the effects of an individually tailored interdisciplinary intervention designed to address impairments identified by IGA versus 'care as usual' in children with spastic CP. The results of the trial will be submitted to peer-reviewed journals for publication, irrespective of the outcome, in accordance with the CONSORT statement for the reporting of randomised controlled trials.

Abbreviations

CP: cerebral palsy; GDI: gait deviation index; GMFCS: gross motor function classification system; ICC: intra-class correlations coefficient; IGA: instrumented gait analysis.

Competing interests

The authors declare that they have no competing interests. The participants will receive reimbursement for the additional transportation costs they experience. Participants will not receive any payment for their participation in the study. The healthcare professionals will not receive any payment for their participation in the study.

Authors' contributions

All the authors participated in the conception and design of the study. HMR and AHL were involved in drafting the trial protocol. NWP, RB and SO revised the first draft and commented and revised the subsequent draft. All authors have read and approved the final manuscript.

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Paper IIb

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Title page

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Title
Instrumented gait analysis for individually tailored interdisciplinary interventions in children with cerebral palsy – a randomised controlled trial

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Abstract

AIM: To test the hypothesis that improvements in gait following interdisciplinary interventions using instrumented gait analysis are superior to those following 'care as usual' in children with cerebral palsy.

METHOD: A single-centre, prospective, single blind, parallel group, randomised controlled trial investigating the effectiveness of interventions based on the use of gait analysis. Primary outcome was gait (Gait Deviation Index) and secondary outcomes were: walking (1-min walk test) and patient-reported outcome measures of function, disability and health-related quality of life. Follow ups were done at 26 weeks (questionnaires) and at the primary endpoint at 52 weeks (all outcomes).

RESULTS: Sixty participants with cerebral palsy at the Gross Motor Function Classification System levels I/II, (median age 6y11m), were randomised to interdisciplinary interventions with or without instrumented gait analysis. No significant or clinically relevant between-group differences in change scores of the primary or secondary outcomes were found.

CONCLUSION: Interdisciplinary interventions using instrumented gait analysis did not improve gait or patient-reported outcomes of function, disability and health-related quality of life in a case-mix of ambulatory children with cerebral palsy, at an early age. Evidence about which specific children with cerebral palsy benefit from use of instrumented gait analysis in clinical practice is lacking.

What this paper adds

- A case-mix of children with cerebral palsy does not benefit from gait analysis
- Gait analysis should not be implemented to all ambulant children with cerebral palsy

Cerebral palsy (CP) is caused by a non-progressive brain injury in the developing brain, which influences neuro-musculoskeletal functions including gait, walking and functional mobility and, as a consequence, impacts overall health, participation in daily activities as well as health-related quality of life.
The majority of children with CP walk independently and exhibit altered gait such as stiff knee gait or equinus (1). In Denmark, impairments that affect the patient's gait are addressed by a local healthcare team (local team), which consists of a paediatrician, a paediatric orthopaedic surgeon, a physiotherapist and/or an orthotist (2, 3). Interventions are planned on the basis of clinical examinations and standardised measures such as the Gross Motor Function Classification System (GMFCS) and Gross Motor Function Measure ('care as usual').

Three-dimensional instrumented gait analysis (gait analysis) provides objective measures of gait in three planes, which can be used to identify features in gait and underlying neuro-musculoskeletal impairments, which may be of relevance in the planning of interdisciplinary interventions (4). Studies have shown that gait analysis affects the decisions regarding orthopaedic surgical interventions (5), and that good agreement can be obtained between recommendations based on gait analysis and the surgery performed (6).
The effects of orthopaedic surgery and physiotherapy with and without gait analysis, to specify impairments in gait, have been investigated in uni-disciplinary settings with varying results; the use in planning physiotherapy has been reported to be superior to clinical examinations alone (7, 8), which is not the case in orthopaedic surgery (9). Nonetheless, the effects of interdisciplinary interventions with and without gait analysis have not been investigated in children with CP.

The current study aimed to test the hypothesis that improvement in overall gait pathology, walking performance and patient-reported outcome measures of function, disability and health-related quality of life following individually tailored interventions when gait analysis is used are superior to those following 'care as usual'.

Method
A single-centre, prospective, single blind, parallel group, balanced randomisation [1:1] superiority trial approved by the Committee for Medical Research Ethics in the Region of Southern Denmark (S-20120162), the Danish Data Protection Agency (2008-58-0035) and compliant with the Declaration of Helsinki was conducted. A study protocol has been published previously (2) and the trial and the statistical analysis plan have been registered at ClinicalTrails.gov (NCT02160457). The reporting follows the recommendations from the CONSORT statement (10). After commencement of the trial, minor changes in data collection and the number of secondary analyses were made and described in the published statistical analysis plan (NCT02160457).

Participants

Patients registered in the Danish version of the Cerebral Palsy follow-Up Program in the Region of Southern Denmark and the North Denmark Region were screened for eligibility and invited to participate. Eligibility criteria have been described in detail previously (2). In brief, eligible participants were children aged 5 to 8 years, diagnosed with spastic CP at Gross Motor Function Classification System (GMFCS) levels I or II. Exclusion criteria were: orthopaedic surgery up to 52 weeks prior to baseline assessment or injection with Botulinum toxin type A 12 weeks prior to baseline assessment. Furthermore, the children were excluded if they were unable to participate in the examination or their parents could not speak and understand Danish. The participants (children and parents) were invited to the baseline assessment at the Motion Analysis Laboratory at Odense University Hospital, where the parents signed an informed consent form (2).

Randomisation

After baseline assessment, participants were randomised to either the experimental or the control group (see below). The randomisation was stratified according to the specific physiotherapist to whom the participant was appointed (i.e. the first participant randomised determined how the following participant was allocated). The allocation sequence was computer-generated by a researcher with no other involvement in the study. The allocation sequence (0 = experimental group / 1 = control group) was concealed in sequentially numbered opaque, sealed envelopes. When the participants had completed the baseline assessment, the principal investigator (HMR) opened the envelope and informed the parents and the local team about the allocation. The assessors were blinded to the assigned interventions throughout the study. Furthermore, data were masked for group allocation during statistical analysis and interpretation of results.

Interventions

Both study groups received individually tailored interdisciplinary interventions based on information from clinical examinations and standardised measurements and the experimental group was provided with an additional gait analysis report. This was prepared through four steps:
Step 1) Gait analysis was carried out as part of the baseline assessment including clinical examination, video recording and 3-dimensional kinematics and kinetics by an 8-camera Vicon T40 system (Vicon, Oxford, UK) operating at 100Hz and two force-plates (AMTI, OR6-7-1000, Watertown, MA, USA), sampling at 1000Hz. The Plug-in Gait model, Vicon Nexus Software (version 1.7.1 or later) and Vicon Polygon software (version 3.5.2 or later) were used for data processing. The children walked barefoot and, if relevant, also with orthotics and shoes, at a self-selected speed along a 10-m walkway until at least five acceptable trials were collected.
Step 2) Impairment-focused interpretation and reporting were performed according to Baker 2013 (11). This involves identification of features that reflect the impairments affecting the child's gait.
Step 3) The recommendations for interventions were based on consensus and given by the gait analysis team, which consisted of a neuro-paediatrician (LKH), a paediatric orthopaedic surgeon (NWP or VE), a physiotherapist (HMR) and a biomechanist (AHL).

Step 4) The report from the gait analysis (Step 2) and the recommendations for interdisciplinary interventions (Step 3) were, to reflect daily clinical practice, mailed to the participant and members of their local team, who were responsible for implementing the recommendations. The time point 'start of intervention' was defined as the week where the report was sent. Data collection in the control group was adjusted according to the planned time points in the experimental group.
The local teams provided the interventions in both study groups addressing impairments that affected the child's gait, which included orthopaedic surgery, spasticity management, physiotherapy and/or orthotics. The study did not involve standardisation of the intervention and adherence to the recommended interventions was not a prerequisite for this pragmatic study.

Outcome measures

At baseline, weight, height and leg length were measured. In addition, classification according to the GMFCS and Functional Mobility Scale (12, 13) were performed, and CP subtype was collected from the local teams.
All outcomes were assessed at baseline and 52 weeks post start of intervention. In addition, patient-reported outcome measures were also conducted at 26 weeks. Six assessors who remained blinded to group allocation performed data collection with gait analysis and 1-minute walk test at the Motion Analysis Laboratory at Odense University Hospital. The patient-reported outcome questionnaires were mailed to the participants and collected on the visit to the hospital or returned by mail.
The primary outcome was the between-group difference in change of Gait Deviation Index (GDI) (14), analysed by gait analysis as described in Step 1. GDI is based upon kinematic data and summarises the overall gait pathology into a single score when compared with non-pathological gait (14). GDI was calculated according to the methods provided by Schwartz & Rozumalski (2008) (14), using our own reference dataset of 30 typically developing children (15). The median of five trials for each leg was used to calculate the average of both legs to provide a single index for each child. We have previously demonstrated excellent reliability (ICC 0.81-0.88) and acceptable agreement for GDI in a similar patient group (15).
The between-group differences in change scores were evaluated for all secondary outcome measures. Walking performance was evaluated using the 1-min walk test (16) and functional mobility in everyday activities with regard to functional skills and amount of caregiver assistance was evaluated with the Danish version of the Mobility Scale of the original Pediatric Evaluation of Disability Inventory (17). The Pediatric Quality of Life Inventory Cerebral Palsy Module was used to evaluate health-related quality of life (18) and the Pediatric Outcomes Data Collection Instrument was used to evaluate overall health, pain and participation in normal daily activities (19). Information about the recommended and applied interventions were used to explore adherence to the recommended interventions and to compare the interventions used in the study groups. Furthermore, the parents were asked about their perception of the interventions with three anchor questions with a 5-point Likert scale as response categories (Table 3).

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Statistics

The statistical analysis plan has been published at ClinicalTrails.gov (NCT02160457) prior to analysis and unblinding of group allocation. The sample size was based on data from a previous study performed in our laboratory demonstrating a group-mean GDI of 79.3 (SD 12.0)(15). Furthermore, a minimum clinically important difference in GDI was a priori defined as 7.9, which is equivalent to an improvement of 10%, as suggested by Swartz et al. (20). Therefore, a minimum of 29 subjects in each group (n = 58) was required with alpha = 0.05 and 80% power. We anticipated a dropout rate of 5% and aimed to include 60 children (randomisation 1:1).

Data of baseline characteristics were checked for completeness and distribution was investigated using normal probability plots and the Shapiro–Wilk test. Descriptive statistics were calculated with mean and standard deviation (SD), median and interquartile range (iqr) or number of patients. Main comparative analyses between groups were performed on the full analysis set with missing data imputed using last observation carried forward. A multiple regression model with group and baseline values of the relevant variable as covariates was used to analyse between-group mean changes. The model assumptions were checked for relationship, homoscedasticity, outliers and normality of residuals. Since minor violations of the assumptions were present, the analysis was performed with robust estimation.

Differences between the interventions applied and participant-perceived responses to the interventions were investigated with descriptive statistics, Pearson's chi-squared and Wilcoxon's rank-sum test.

Statistical analyses were performed using Stata/IC 14.2 or later for Mac (StataCorp, College Station Tx, USA). The significance level for all statistical results was $p < 0.05$.

Results

In total, 160 children were invited to participate in the study. Of these, 83 children were screened for eligibility and 60 participants were randomised to either the experimental intervention (n=30) or the control (n=30) groups (Figure 1). Recruitment of participants and data collection were carried out between June 2014 and July 2017. Complete assessments were available from 57 participants at baseline, 48 participants at 26 weeks follow up, and 55 participants at the primary endpoint at 52 weeks. All children received their allocated intervention of interdisciplinary interventions with or without gait analysis.

The 60 participating children had a median age of 6 years and 11 months. The full list of patient characteristics is presented in Table 1. The CP subtype and GMFCS levels for the participants were 43 children with unilateral (experimental group / control group, n=21/n=22), 17 with bilateral (n=9 / n=8) spastic CP, 42 children at GMFCS level I (experimental group / control group, n=20/n=22) and 18 at GMFCS level II (n=10 / n=8).

Primary outcome

At 52 weeks follow up, the mean change scores of GDI at self-selected walking speed did not differ significantly between the groups (GDI: -0.59 [-3.9 to 2.8], $Eta^2 < 0.01$) (Table 2). In total, 11 participants improved more than the a priori-defined minimum clinically important difference in GDI of 7.9 (experimental group / control group, n=5/n=6), resulting in a non-significant risk difference of -0.03 (95% CI; -0.23 – 0.16, Z=0.33, p=0.738).

Secondary outcomes

No significant between-group differences in change scores were observed in the 1-minute walk test (3.02 meter [-2.9 to 9.0], $Eta^2 = 0.02$) at 52 weeks or in the patient-reported outcome measures at 26 or 52 weeks. Significant and potential clinically relevant within-group improvements were seen in some of the secondary outcome measures at 26 and 52 weeks (Table 2).

Additional/tertiary outcomes

No significant difference was observed between the groups in participant-perceived responses to the interventions (p=0.19) or changes in walking (p=0.38). However, a difference between the groups was seen in overall health (p=0.03) (Table 3).

Interventions

The compliance with the recommended types of interventions were 24 of 28 participants for physiotherapy (% [95% CI], 86% [67-96], 6 of 10 participants for orthotics (60% [26-88]), 5 of 14 for spasticity management (36% [13-65]) and 0 out of 1 for orthopaedic surgery (0% [no 95% CI calculated] (Table 3).

Adverse events

The participants (children and parents) did not report any serious adverse events during the study period. However, during the testing, the assessors experienced one child who did not want to wear the adhesive reflective markers at the post examination, and five children (three at baseline and two at follow up) were too tired to complete the 1-minute walk test.

Discussion

In this randomised controlled clinical trial, we found that implementing gait analysis in the interdisciplinary interventions in children with CP did not have a significant impact on change scores between groups on gait, walking or patient-reported outcome with only a few, non-serious adverse events reported. Our findings are not in line with previous studies investigating the effectiveness of the use of gait analysis in individualised physiotherapy for children with CP (7, 8). However, our findings are equal to the results of a previous randomised controlled trial on the outcome of lower extremity orthopaedic surgery with and without gait analysis (9). The lack of documented between-group differences in change scores may be attributed to our study population of relatively young and well functioning children (GMFCS levels I and II), the pragmatic

implementation of the applied interventions, the timing of follow up, and the selected outcome measures.

Minimum clinically important improvements (MCII) have been proposed for the subscales of the Pediatric Outcomes Data Collection Instrument (21) and also for the primary outcome of the current study (GDI: ≥ 10% improvements) (20). However, anchor-based questions about the patient's perception of the MCII are not available for the outcome measures and, thus, it is difficult to interpret whether the observed within-group improvements are of clinical importance. In addition, one must keep in mind that although not documented by normative data, improvements can be expected over a period of 52 weeks, as part of the natural clinical course.

Also, it is important to keep in mind that we have not investigated the effects of gait analysis on gait problems reported by the participants or before and after a specific intervention, but rather as an integral part of the interdisciplinary interventions.

Despite initiatives to increase internal validity, the overall compliance with the recommended types of interventions (spasticity management, orthoses and physiotherapy) in the current trial was 66%. The reported rates of compliance with recommendations range from 42% to 97% in studies investigating outcomes of surgery with and without gait analysis (9, 22). The following reasons for non-compliance have previously been proposed: inconsistent results from different examinations, lack of knowledge about gait analysis, and preferences of the participants (9). The current pragmatic study was not designed to reveal reasons for not following the recommendations, but the issue merits further investigation.

In this study, we have used objective and patient-reported outcome measures. Furthermore, we have asked the participants about their perceived effects from the intervention. The assessments were chosen to make it possible to detect changes on a wide range of constructs, including changes important to the participants. For the primary outcome, we used GDI, an objective measure of deviation in gait. There is growing evidence that GDI is a useful objective outcome measure to quantify the degree of deviation from normality in children with CP (15, 23). However, the measure has been criticised for not being responsive in detecting changes in gait, when the movements are close to normal gait (24) and that responsiveness has only been documented in the context of orthopaedic surgery (23). Furthermore, a risk of ceiling effect has been suggested for patients with a relatively high GDI score (23, 25).

Strengths and limitations

We conducted a pragmatic randomised controlled trial following the CONSORT statement on a representative sample of patients recruited from the total population of children with spastic CP, resulting in a study with high external validity and generalisability. A limitation of the study is the fact that the participants (parents and children) and the local teams were unblinded and thus,

aware of their intervention. Nonetheless, the data collection and the statistical analysis were performed blinded.

The pragmatic approach used to reflect daily clinical practice may, on the other hand, have introduced a limitation because of potential inconsistency in the delivery of the interventions. Furthermore, the study did not aim at or was not designed to ensure a standardised implementation of the applied interventions and reasons for not offering or applying interventions. A more explanatory approach could have counteracted some of the issues described above, with the risk of a conclusion of less external validity and generalisability.

Generalisability

The participants were recruited from the total population of children with spastic CP. However, the study population was limited to young, ambulant children with spastic CP, meaning that the results may not be generalisable to older children, children with other subtypes of CP, or children with more limited function.

Interpretation

This study could not confirm the hypothesis that improvement in the overall gait pathology, walking performance and patient-reported outcomes following individually tailored interventions when gait analysis is used are superior to those following 'care as usual' to a case-mix of all children with CP at GMFCS levels I and II, at an early age. The examination may still be relevant in many situations, for example, if a functional diagnosis or documentation of changes are needed.

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Tables

Table 1 – Baseline characteristics

	Experimental (n=30)		**Control** (n=30)	
Gender and classification of diagnosis and function				
Girls / boys, n	9/21	-	12/18	-
CP spastic subtype, Unilateral / bilateral, n	21/9	-	22/8	-
GMFCS level I/II, n	20/10	-	22/8	-
FMS 5 meters; level 5/6, n	9/21	-	7/23	-
FMS 50 meters; level 2/5/6, n	0/9/21	-	1/8/21	-
FMS 500 meters; level 1/2/5/6, n	7/0/3/20	-	7/1/4/18	-
Age, height and weight and body mass index				
Age (Years, months), median (iqr)	6 y 6 m	(2 y 8 m)	6 y 11 m	(1y 10m)
Height (meters)	1.22	(0.08)	1.24	(0.11)
Weight (kg), median (iqr)	22.00	(6.00)	21.00	(11.00)
Body Mass Index, median (iqr)	15.40	(2.47)	14.88	(3.58)
Outcome measures				
Gait Deviation Index	78.20	(12.31)	75.45	(10.45)
Gait speed (meters / sec)	1.13	(0.13)	1.17	(0.18)
1-min walk test, (meters / min)[a]	79.39	(13.87)	78.77	(15.21)
Pediatric Evaluation of Disability Inventory				
Functional skills	79.65	(11.35)	82.81	(12.25)
Caregiver assistance	80.67	(14.00)	82.65	(15.55)
The Pediatric Quality of Life Inventory				
Daily Activities	62.27	(23.29)	63.68	(23.43)
School Activities, median (iqr)	75.00	(31.25)	62.50	(31.25)
Movement and Balance	78.17	(16.27)	71.13	(21.80)
Pain and Hurt[b]	67.50	(23.06)	64.22	(21.77)
Fatigue	58.75	(21.12)	57.08	(25.47)
Eating Activities, median (iqr)	80.00	(15.00)	82.50	(25.00)
Speech and Communication, median (iqr)	87.50	(27.08)	81.25	(18.75)
The Pediatric Outcomes Data Collection Instrument				
Global Functioning Scale	76.48	(11.90)	76.88	(12.84)
Upper Extremity and Physical Function, median (iqr)	79.17	(20.83)	80.95	(25.00)
Transfer and Basic Mobility, median (iqr)	91.67	(13.64)	93.94	(15.15)
Sports and Physical Functioning, median (iqr)	70.14	(36.11)	71.34	(27.95)
Pain/Comfort Scale	75.89	(20.97)	75.83	(20.04)
Happiness Scale, median (iqr)[c]	77.50	(35.00)	80.00	(35.00)

Values are presented as mean ± SD if not otherwise stated

Explanations:

[a] EXP group, n=28, CON group: n=29, [c] CON group, n= 29, and [d] EXP group, n=29.

Abbreviations: Cerebral palsy (CP), Gross Motor Function Classification System (GMFCS), Functional Mobility Scale (FMS).

Table 2 – Mean difference within groups (95% CI) and difference between groups at 26 and 52 weeks follow up (95% CI)

	Within-group mean change [95% CI]								**Between-group difference** (experimental vs Control)					
	Baseline to 26 weeks				Baseline to 52 weeks				Baseline to 26 weeks		Baseline to 52 weeks			
	Experimental (n=30)		**Control** (n=30)		**Experimental** (n=30)		**Control** (n=30)						*p*	Eta^2
Gait Deviation Index (GDI)	-	-	-	-	0.19	[-2.7-3.1]	1.68	[-0.9;4.3]	-	-	-0.59	[-3.8-2.6]	0.72	<0.01
1-minute walk test[a]	-	-	-	-	*8.29	[4.8-11.8]	*5.38	[0.3;10.4]	-	-	3.02	[-2.9-8.9]	0.31	0.02
PEDI, Mobility scale														
Functional skills	*2.53	[0.6;4.4]	2.09	[-0.5;4.7]	*4.17	[1.5-6.8]	2.19	[-0.7-5.1]	0.15	[-3.0-3.3]	1.37	[-2.4-5.1]	0.47	<0.01
Caregiver assistance	*3.12	[0.7;5.5]	*3.27	[0.5;6.1]	*3.92	[0.4-7.5]	*4.34	[0.8-7.9]	-0.57	[-3.8-2.7]	-0.93	[-5.5-3.6]	0.68	<0.01
PedsQL, Cerebral Palsy Module														
Daily Activities	*6.68	[2.7;10.6]	2.75	[-0.1;5.6]	*11.12	[6.5-15.7]	*7.52	[3.7-11.3]	3.72	[-0.8-8.2]	3.26	[-1.9-8.4]	0.21	0.03
School Activities	-1.81	[-9.7;6.1]	3.13	[-3.0;9.2]	1.88	[-5.0-8.8]	1.45	[-6.1-9.0]	-4.41	[-14.3-5.5]	1.12	[-8.7-10.9]	0.82	0.06
Movement and Balance	-1.50	[8.3;5.2]	1.71	[-4.7;8.1]	2.25	[-3.5-8.0]	7.00	[-0.5-2.8]	-1.05	[-9.9-7.8]	-1.19	[-9.4-7.0]	0.77	<0.01
Pain and Hurt[b]	4.58	[-0.8;10.0]	-0.64	[-4.1;2.8]	-4.17	[-11.5-3.2]	3.88	[-2.0-9.8]	5.69	[-0.22-11.6]	-7.13	[-15.6-1.3]	0.10	0.05
Fatigue	4.58	[-1.2;10.4]	*7.29	[1.2;13.4]	1.67	[-4.6-7.9]	5.42	[-1.8-12.6]	-2.47	[-10.6-5.7]	-3.41	[-12.5-5.7]	0.46	<0.01
Eating Activities	1.17	[-3.0;5.3]	*3.67	[0.6;6.7]	1.50	[-3.6-6.6]	-0.17	[-5.7-5.3]	-1.81	[-6.9-3.3]	2.73	[-4.5-9.9]	0.44	0.01
Speech and Communication	*3.61	[0.7;6.5]	3.54	[-0.3;7.4]	2.15	[-3.7-8.0]	3.96	[-0.5-8.4]	-0.28	[-4.8-4.2]	-2.64	[-8.8-3.5]	0.40	0.01
PODCI														
Global functioning scale	*3.31	[0.8;5.8]	1.14	[-1.2;3.5]	*2.91	[0.5-5.3]	2.27	[-0.7-5.3]	2.15	[-1.2-5.5]	0.58	[-3.1-4.2]	0.75	<0.01
Upper extremity function	2.36	[-1.2;5.9]	0.83	[-3.2;4.9]	4.09	[0.9-7.3]	-0.50	[-3.2-4.9]	1.25	[-3.7-6.2]	4.31	[-0.6-9.2]	0.08	0.05
Transfer and basic mobility	2.47	[-0.2;5.1]	1.06	[-1.3;3.4]	*4.34	[1.6-7.0]	*2.52	[0.5-4.5]	1.31	[-1.9-4.6]	1.63	[-0.6-3.9]	0.15	0.04
Sports and physical functioning	*4.14	[0.6;7.7]	2.36	[-1.1;5.9]	*5.80	[1.9-9.7]	4.30	[-1.2-9.8]	1.78	[-3.1-6.7]	1.52	[-4.7-7.7]	0.62	<0.01
Pain/Comfort Scale	4.22	[-2.6;11.1]	1.02	[-4.9;6.9]	-2.63	[-9.7-4.5]	2.69	[-3.7-9.1]	3.22	[-4.8-11.2]	-5.3	[-14.0-3.4]	0.23	0.03
Happiness Scale[c]	4.48	[-1.8;10.8]	2.50	[-3.6;8.6]	0.17	[-6.6-7.0]	4.17	[-2.9-11.3]	2.11	[-5.7-9.9]	-3.89	[-13.0-5.2]	0.40	0.01

Values are presented as mean and 95% confidence intervals.

Explanations: [a] Experimental group, n=28 and Control group, n=29, [b] Control group, n= 29, [c] Experimental group, n=29, * $p < 0.05$

Abbreviations: Pediatric Evaluation of Disability Inventory (PEDI), The Pediatric Quality of Life Inventory (PedsQL) and The Pediatric Outcomes Data Collection Instrument (PODCI).

Table 3 – The recommended interventions, applied interventions, compliance and the distribution of the answers for the anchor questions.

	Experimental	Control	Chi^2 *p*-value
Recommended interventions (n=30)			
Physiotherapy	30	-	-
Orthotics	12	-	-
Spasticity management	16	-	-
Orthopaedic surgery	1	-	-
Applied interventions (n=29/28)			
Physiotherapy	24	24	0.76
Orthotics	8	12	0.31
Spasticity management	7	10	0.38
Orthopaedic surgery	0	1	0.32
Compliance (n=28)	+ Rec & + app / + Rec		
Physiotherapy	24 / 28		
Orthotics	6 / 10		
Spasticity management	5 / 14		
Orthopaedic surgery	0 / 1		
	Experimental	**Control**	**Wilcoxon** *p-value*
Anchor: Interventions (n=26/25)			
Excellent	0	1	
Very good	10	5	
Good	8	9	
Fair	7	10	
Poor	0	1	0.19
Anchor Walking (n=28 /28)			
Much better	3	0	
A little better	8	9	
About the same	14	15	
A little worse	3	3	
Much worse	0	1	0.38
Anchor: Overall health (n=28 /28)			
Much better	2	0	
A little better	5	2	
About the same	21	24	
A little worse	0	2	
Much worse	0	0	0.03

The applied interventions (reported by the participants), recommended interventions based on instrumented gait analysis, compliance (+ Rec & + app = Number of participants where the intervention was recommended AND applied, + Rec = Number of participants where the intervention was recommended) and the distribution of different answer categories for the anchor questions “How would you describe the results of the interventions your child has participated in?”, “In general, how would you say your child’s walking ability is today compared with one year ago?” and “In general, how would you say your child’s overall health is today compared with one year ago?”.

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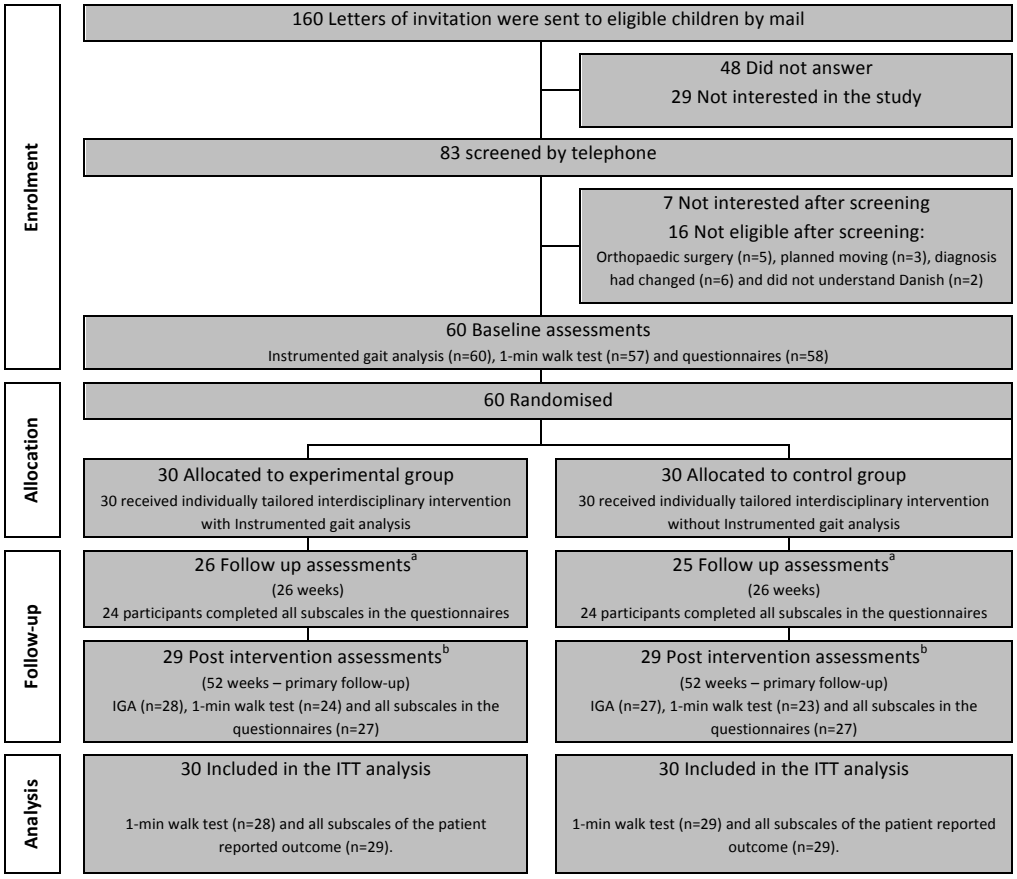
Title

Instrumented gait analysis for individually tailored interdisciplinary interventions in children with cerebral palsy – a randomised controlled trial

Figure 1 – Flow diagram of participants in the study



Explanations:

[a] Nine participants did not return the patient-reported outcome measures by mail.

[b] Five participants did not complete the 3D motion analysis (one child refused to participate and four parents reported lack of time to travel and/or participate in the examination, two participants did not answer the patient-reported outcome questionnaires.

Abbreviations: Intention to treat (ITT).

Paper III

Title

Threshold values of ankle dorsiflexion and gross motor function in children with cerebral palsy – a cross-sectional study

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III

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Abstract

Background and purpose - Threshold values defining three categories of passive range of motion are used in the Cerebral Palsy follow-Up Program to guide clinical decisions. The aim of the study was to investigate the threshold values by testing the hypothesis that passive range of motion in ankle dorsiflexion is associated with gross motor function and that function differs between the groups of participants in each category.

Patients and methods - We analyzed data from 60 ambulatory children (aged 5-9 years) with spastic Cerebral Palsy. Outcomes were passive range of motion in ankle dorsiflexion with flexed and extended knee and gross motor function (Gait Deviation Index, Gait Variable Score of the ankle, peak dorsiflexion during gait, 1-minute walk, Gross Motor Function Measure, the Pediatric Quality of Life Inventory Cerebral Palsy Module and Pediatric Outcomes Data Collection Instrument).

Results - Significant ($p<0.05$) and moderate correlations were documented for range of motion versus Gait Variable Score of the ankle ($r=-0.37$ and $r=-0.37$) and range of motion versus peak dorsiflexion ($r=0.49$ and $r=0.55$). Differences between the groups formed by the categories were shown for Gait Variable Score of the ankle and peak dorsiflexion ($p < 0.05$). No other significant correlations or differences between the categories were observed.

Interpretation - The results suggest that threshold values for ankle dorsiflexion used in the Cerebral Palsy follow-Up Program are of limited clinical value in assessing overall gross motor function, but may be used to identify deviations in ankle-specific gait function.

Introduction

Muscle contractures and joint deformities are common clinical manifestations of Cerebral Palsy (CP) (Nordmark et al. 2009). A surveillance program, entitled the Cerebral Palsy follow-Up Program (CPUP), is often used to ensure early identification and treatment of deterioration (Alriksson-Schmidt et al. 2016, Rasmussen et al. 2016). As part of the clinical evaluation, the CPUP uses threshold values inspired by traffic light signals on passive range of motion (ROM). The ROM is classified on the basis of threshold values into three categories with the following interpretation: ‘‘green’’ means ‘‘clear’’ and that no indication of deterioration is noted, ‘‘yellow’’ indicates that vigilant observation, modified treatment or initiation of treatment is necessary, and ‘‘red’’ indicates ‘‘alert’’ and that treatment is urgently needed, assuming no specific contraindications are present (Alriksson-Schmidt 2016). For ambulatory children on the Gross Motor Function Classification System (GMFCS) levels I-III, the threshold values have been set to ensure that the patient has enough ROM to perform adequate ankle dorsiflexion (DF) in the stance and swing phases of walking (2017). The categories are used in clinical practice as easy-to-understand interpretations of the measurement of ROM and are used to guide decisions about future examinations and interventions (Hagglund et al. 2011).

A study investigating the association between the three categories of ROM in DF and gross motor function measured with the Functional Mobility Scale found a significant association between the categories (Chi-square association, r_{Φ} = -0.268, p=0.01) in young adults with CP (Brantmark et al. 2015). Despite the use of the threshold values for clinical evaluation in several countries, how these thresholds were identified has never been fully explained and, to our knowledge, they are not evidence-based. Furthermore, their potential relationships with measures of gross motor function in children with CP have never been established.

Thus, the aim of the study was to investigate the threshold values used by CPUP by testing the hypothesis that ROM in DF is associated with gross motor function and that gross motor function differs between the groups of participants in each category. Gross motor function is measured by various methods describing the overall gross motor capacity, the ankle-specific gait capacity, and the use of gross motor skills in everyday life.

Patients and methods

We performed a cross-sectional study based on data from the baseline assessment in a randomized controlled trial (Rasmussen et al. 2015a) / NCT02160457. The reporting of the current study conforms to recommendations by the STROBE panel (von Elm et al. 2008).

Ethics and trial registration

The study complies with the principles of the Declaration of Helsinki. Approval of the study was obtained from the Committee for Medical Research Ethics in the Region of Southern Denmark (S-20120162) and from the Danish Data Protection Agency (2008-58-0035). Trial registration: ClinicalTrials.gov NCT02160457.

Participants and setting

Patients registered in the Danish version of the CPUP in the Region of Southern Denmark and the North Denmark Region were screened for eligibility and invited to participate. Eligibility criteria have been described in detail previously (Rasmussen 2015). In brief, eligible participants were children aged 5 to 8 years, diagnosed with spastic CP at GMFCS levels I or II. Children were not eligible if they had received earlier interventions in the form of orthopedic surgery in the previous 52 weeks or injection with botulinum toxin type A in the 12 weeks prior to the baseline assessment (exclusion criteria). Furthermore, the children were excluded if they were unable to demonstrate sufficient co-operation and cognitive understanding to participate in the examination, if they relocated to another region during the trial, or if their parents could not speak and understand Danish. Informed consent to participation was achieved prior to the study (Rasmussen 2015).

Participants were recruited and data collected from June 2014 until July 2016. Questionnaires were mailed to the parents prior to the examination at the Motion Analysis Laboratory at the Odense University Hospital. A total of six experienced physiotherapists, who performed each examination in pairs, were involved in the data collection.

Measurements

The baseline assessment methodology has previously been described and published in detail (Rasmussen 2015). In short, the assessment consisted of: patient characteristics, a thorough physical examination, 3-dimensional instrumented gait analysis, functional tests of walking and gross motor capacity, and patient-reported outcomes about the use of gross motor skills in everyday life (see below).

Patient characteristics were described with the following measures: gender (girls or boys), age (years); height (meters), weight (kilograms), CP subtype (unilateral or bilateral spastic CP) and classification according to the GMFCS.

Classification according to the three categories was obtained from measurements of maximal DF with flexed knee (DF (knee 90°)) and extended knee (DF (knee 0°)) performed by two examiners with a goniometer according to the CPUP protocol (CPUP 2017). The starting positions were supine, hip and knee in 90° of flexion when measuring DF (knee 90°) or with the hip and knee extended when measuring DF (knee 0°). While the hind foot were maintained in neutral to avoid calcaneal valgus or varus, the fixed arm of the goniometer was placed parallel to the front of the tibia and the moving arm at the lateral side of the foot (Nordmark 2009). The threshold values for DF used by the CPUP are outlined in Table 1.

The method used for data collection with 3-dimensional instrumented gait analysis has previously been described in detail (Rasmussen 2015). Briefly, we collected ten walking trials at a self-selected speed using an 8-camera motion capture system (Vicon MX03, Oxford, UK) and the Plug-in-Gait model (Davis et al.

1991). Vicon Nexus software (version 1.7.1 to 1.8.5) and Vicon Polygon software (version 3.5.2 to 4.3) were used for data processing to define gait cycles for 10 trials from each participant. Subsequently, five trials with a consistent velocity (±15%) were selected and used for the calculation of the Gait Deviation Index, Gait Variable Score of the ankle and the maximal active DF in the stance phase (Schwartz et al. 2008, Baker et al. 2009). The Gait Deviation Index and Gait Variable Score of the ankle are gait summary measures of overall gait function and ankle joint kinematics, respectively, providing information on the amount of deviation from a reference group. For reference, our own dataset of 30 typically developing children was utilized (Rasmussen et al. 2015a). A reliability study performed in our laboratory has documented excellent intra-rater reliability and acceptable agreement for the Gait deviation Index and fair to good intra-rater reliability and acceptable agreement for the Gait Variable Score of the ankle across two repeated sessions in children with CP (Rasmussen 2015a).

Gross motor capacity was assessed using the 1-minute walk test (McDowell et al. 2009) and selected items from the 66-item Gross Motor Function Measure (Russell et al. 2013). The use of gross motor skills in everyday life was assessed using a linguistically validated Danish version of the subscale movement and balance of the Pediatric Quality of Life Inventory Cerebral Palsy Module (Varni et al. 2006) and a Danish version of the subscale of transfer and basic mobility of the Pediatric Outcomes Data Collection Instrument (Daltroy et al. 1998).

Statistical methods

The current study is based upon a sample of children with CP who volunteered to participate in a randomized controlled trial. The sample size calculation for the original study was based on a between-group change score of 7.9 points on the primary outcome measure: the Gait Deviation Index (Rasmussen 2015b).

Descriptive statistics were calculated for gender, CP subtype and classification according to the GMFCS. In the statistical analysis, the median scores of the Gait Deviation Index and Gait Variable Score of the ankle from five trials were used. In the analysis of ROM, the Gait Deviation Index, Gait Variable Score of the ankle and Peak dorsiflexion, we used data from the affected side of patients with unilateral CP and for participants with bilateral CP, we used the most affected side. The most affected side was determined as the leg with the highest number of measurements in the red and/or yellow categories in DF and in cases without differences in categories, the side with the lowest Gait Deviation Index. The statistical distribution of data was investigated using normal probability plots and the Shapiro–Wilk test (S S Shapiro 1965). The Gait Variable Score of the ankle (p<0.001) and Pediatric Outcomes Data Collection Instrument transfer and basic mobility scores (p<0.001) were not normally distributed.

Scatterplots with fitted values of the outcome measures were prepared to provide an overview of the data. Correlations between ROM and the outcome variables were investigated with Pearson correlation coefficients, except for the Gait Variable Score of the ankle and Pediatric Outcomes Data Collection Instrument transfer and basic mobility scores, where the Spearman's rank correlation coefficients were used. The correlation coefficients were interpreted according to Dancey and Reidy (Dancey et al. 2011). Differences in the normally distributed outcome variables in the three ROM categories were investigated with one-way ANOVA. The Gait Variable Score of the ankle and Pediatric Outcomes Data Collection Instrument transfer and basic mobility scores were both assessed with the Kruskal-Wallis test and, if relevant, pairwise comparisons with Wilcoxon rank-sum test (Mann-Whitney).

Statistical analyses were performed using Stata/IC 14.2 for Mac (StataCorp, College Station, Texas, USA). The significance level for all statistical results was $p < 0.05$.

Results

One hundred and sixty patients were invited to participate in the randomized controlled trial. Of these, 48 patients did not answer, 36 were not interested in further information and 16 were not eligible after screening. Consequently, this cross-sectional study was based on 60 participants with spastic CP at GMFCS levels I and II (21 girls; average age 6 years and 10 months (SD: 1 year 3 months), 43 diagnosed with unilateral CP). Details of height, weight, ROM, ROM categories and gross motor function of the participants are shown in Table 1.

Statistically significant moderate correlations were observed between the Gait Variable Score of the ankle and DF with flexed knee ($r = -0.37$, [95% CI:-0.57 - -0.13], $p<0.05$) and extended knee ($r = -0.37$, [95% CI:-0.57 - -0.13], $p<0.05$) and peak dorsiflexion and DF with flexed knee ($r = 0.49$, [95%CI: 0.26 – 0.67], $p < 0.001$) and extended knee ($r = 0.55$, [95% CI: 0.35 – 0.71], $p < 0.001$) (Table 2).

There were statistically significant differences in the Gait Variable Score of the ankle and peak dorsiflexion between the three groups of participants based on the categories with flexed and extended knee (Table 2). For DF with flexed knee, the median Gait Variable Scores of the ankle for the red and green categories were 13.74° and 7.58°; the distributions in the two groups differed significantly ((z-score, p-value), $z = -2.63$ $p = 0.009$) and with extended knee, the median Gait Variable Score of the ankle for the red and green categories were 16.79° and 7.62°; the distributions in the two groups differed significantly ((z-score, p-value), $z = -2.43$ $p = 0.015$). For Peak dorsiflexion, we observed a difference in red versus green and red versus yellow ROM categories with flexed knee ((mean (95% CI) -9.6° (-14.4 to -4.7) and -7.9° (-13.1 to -2.6), respectively) and between red versus green and yellow versus green ROM categories with extended knee (-9.57° (-15.4 to -3.8) and -7.9° (-14.2 to -1.5), respectively). No statistically significant group-mean differences were observed between the participants classified into each of the ROM categories of DF on the variables of Gait Deviation Index, 1-minute walk, Gross Motor Function Measure, the Pediatric Quality of

Life Inventory Cerebral Palsy Module and Pediatric Outcomes Data Collection Instrument transfer and basic mobility scores.

Discussion

This study aimed to investigate the threshold values of ROM in DF used by the CPUP. We hypothesized that DF and gross motor function would be associated and that there would be differences in gross motor function between the three groups based on the categories. Moderate correlations between DF and deviations in ankle movement during gait in children with CP at GMFCS levels I and II were observed. Furthermore, differences were found between scores of the specific gait function in the ankle joint (Gait Variable Score of the ankle and peak dorsiflexion) and the three ROM categories but no association or differences were observed for overall measures of gross motor capacity (Gait Deviation Index, 1-minute walk and Gross Motor Function Measure) or the use of gross motor skills in everyday life (Pediatric Quality of Life Inventory Cerebral Palsy Module and Pediatric Outcomes Data Collection Instrument transfer and basic mobility) Thus, our hypotheses were only partly confirmed and the results suggest that threshold values of DF in the CPUP are of limited clinical value in assessing overall gross motor capacity and the use of gross motor skills in everyday life, but may be used to identify deviations in ankle-specific gait function. Detection of deviations in ankle-specific gait function might be useful in the identification of distal deterioration before it might progresses to a more proximal involvement.

Our findings accord with the relationship between changes in passive ROM and gait function reported in a study investigating the effects of gastrocnemius fascia lengthening in 19 children with CP (mean age: 8 years) on DF by goniometry and gait function by gait summary measures (Galli et al. 2005). The study reports improvements in DF with flexed knee (from 4.3° before to 8.6°after surgery) and extended knee (from -4.3° before to 9.4° after surgery) with accompanying improvements in overall gait function (Gait Deviation Index from 70.4 before to 82.9 after surgery) (Gait Variable Score of the ankle 22.2° before to 11.5°after surgery) (Galli 2005, Cimolin et al. 2011, Ferreira et al. 2014). These findings suggest that

improvements in DF entail improvement in gait function at the joint level (Gait Variable Score of the ankle) and, to some degree, in overall gait function (Gait Deviation Index).

The moderate correlations found in the current study suggest that factors other than ROM may explain the majority of the observed variation. This is supported by a study comparing clinical examination (passive ROM, spasticity, strength and selective motor control) with 3-dimensional instrumented gait analysis in children with CP. That study found a fair to moderate correlation between the clinical examination and data from the 3-dimensional instrumented gait analysis and concluded that both types of data provide important information about the problems faced by children with CP (Desloovere et al. 2006).

The categories used in the CPUP are set to ensure that the patient has enough ROM to perform adequate DF in walking (CPOP 2017). Our results support the complex interaction between different dimensions of function, as proposed by the International Classification of Functioning, Disability and Health (WHO 2007). However, it might be important to investigate the categories for other important issues of spastic gait, such as energy expenditure or the risk of developing deformities (Hagglund et al. 2005, Nordmark 2009).

The decision to include children at GMFCS levels I and II was made to ensure valid data from the 3-dimensional instrumented gait analysis and to reflect clinical practice. It is important to keep in mind that our study sample was not representative of the population of children with CP. However, to promote a representative sample of young children with spastic CP at GMFCS levels I and II, our inclusion and exclusion criteria were kept open. The study sample was comprised of relatively young and well-functioning children with only a few having ankle ROM affected above threshold values. This can be caused by the fact that reduced ROM usually first arises later in life (Nordmark 2009). There remains a need to investigate the ROM categories for samples of older children, children on higher levels of the GMFCS and the categories for the remaining joints and movements of the lower extremities (i.e. hip rotation and knee

extension). Furthermore, the relatively small study sample did not allow analyses of subgroups of children with certain characteristics, such CP subtype, weight or age. The current results using these thresholds for ROM suggest it would be important to investigate if certain subgroups behave differently and thus, may benefit from current thresholds.

A design limitation of this cross-sectional study is that data collection was only performed during one testing session and therefore no conclusions about causality can be inferred. Furthermore, the strength of our results is limited by the small sample size. In addition, measurement error of 10-15° of goniometric measurements of ROM have been reported (Nordmark 2009). A study using the Generalizability Theory has shown a measurement error in DF of 6.5° in within-day measurements and 8.9° in between-day measurements, when performed by three physiotherapists (McDowell et al. 2000). Due to an inclusion period of 25 months and changes in staff, a total of six physiotherapists were involved in data collection in the current study. All physiotherapists underwent thorough training in the research protocol. However, we did not investigate the consistency of their measurements and thus, this may have increased the variability of the measurements and, thus, must be seen as a limitation of the study.

In conclusion, our study found that DF is associated with ankle-specific measures of gross motor function (Gait Variable Score of the ankle and peak dorsiflexion) and that the mean scores of the ankle-specific measures are different in the three groups based on the categories. In contrast to our hypothesis, we did not find an important relationship between DF and the three related categories to overall measures of gross motor capacity and the use of gross motor skills in everyday life.

The implications of our findings suggest that the current threshold values of DF used in the CPUP are of limited clinical value for assessing overall gross motor function, but may be used to identify isolated deviation of ankle function during gait. As a consequence, other measures that are more related to gait

function should be considered in the identification of children at risk of functional decline and who may benefit from interventions.

Contribution of authors

All the authors participated in the concept and design of the study. HMR and AHL were involved in drafting the manuscript. JS, NWP, MT and SO revised the first draft and commented and revised the subsequent draft. All authors have read and approved the final manuscript.

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Conflict of interest statement

All the authors of this manuscript declare that they have no conflict of interest related to the current study.

Abbreviations

CP: Cerebral palsy; CPUP: Cerebral Palsy follow-Up Program; DF: Passive range of motion in dorsiflexion; GMFCS: Gross Motor Function Classification System; ROM: Passive range of motion.

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Table 1. Patient characteristics

Gender, age, height and weight and body mass index			
Girls / boys, n			21/39
Age (years, months), mean (SD)			6y 10m (1y 3m)
Height (meters), mean (SD)			1.23 (0.1)
Weight (kgs), mean (SD)			24.01 (6.8)
Cerebral palsy subtype and function			
CP spastic subtype, Unilateral / bilateral			43/17
GMFCS levels I/II			42/18
Passive range of motion			
Dorsiflexion with knee 90°(degrees), mean (SD)			20.62 (10.5)
Dorsiflexion with knee 0°(degrees), mean (SD)			13.67 (10.1)
Ankle ROM categories	**Red**	**Yellow**	**Green**
Dorsiflexion (knee 90°), range	≤10°	>10° - <20°	≥20°
Number of participants	14	6	40
Dorsiflexion (knee 0°), range	≤0°	>0° - <10°	≥10°
Number of participants	6	5	49
Gait summary measures and peak dorsiflexion			
GDI score, mean (SD)			76.41 (12.6)
GVS ankle, median (IQR)			7.89 (6.6)
Peak dorsiflexion (degrees), mean (SD)			12.86 (6.5)
Gross motor capacity and performance			
1-min walk test (meters), mean (SD)*			64.20 (10.9)
GMFM, mean (SD)			82.40 (8.4)
Pedsql movement and balance, mean (SD)			74.65 (19.4)
PODCI transfer and basic mobility, median (IQR)			93.18 (15.2)

* Data are only available for 57 participants.

Abbreviations: CP: Cerebral palsy; GDI: Gait Deviation Index; GMFCS: Gross Motor Function Classification System; GMFM: Gross Motor Function Measure; GVS: Gait Variable Score; IQR: Inter-quartile range; Pedsql: The Pediatric Quality of Life Inventory Cerebral Palsy Module; PODCI: Pediatric Outcomes Data Collection Instrument; SD: Standard deviation.

Table 2. Correlation coefficients, coefficient of determination, mean / median scores of the outcome measures in the groups formed by their ankle ROM and results of the ANOVA / Kruskal-Wallis test.

	Correlation			Ankle ROM						Diff
				Red		Yellow		Green		
				n = 14		n = 6		n = 40		
Dorsiflexion (knee 90°)	r	95% CI	p-value	Mean	SD	Mean	SD	Mean	SD	p-value
GDI score	0.12	[-0.14 - 0.36]	0.367	75.01	(10.3)	77.60	(21.1)	76.72	(12.0)	0.89
Peak dorsiflexion	0.49	[0.26 - 0.67]	<0.001	8.21	(5.8)	14.74	(7.0)	14.21	(6.0)	0.007*
1-min walk test*[1]	0.11	[-0.15 - 0.35]	0.406	76.29	(18.3)	78.08	(15.2)	80.29	(12.9)	0.67
GMFM	0.09	[-0.17 - 0.34]	0.491	82.84	8.3	82.43	(11.2)	82.25	(8.2)	0.98
Pedsql	-0.01	[-0.26 - 0.24]	0.956	78.13	22.26	72.50	(18.6)	73.75	(18.8)	0.74
				Median	IQR	Median	IQR	Median	IQR	p-value
GVS ankle	-0.37	[-0.57 - -0.13]	<0.05	13.74	(10.7)	7.18	(3.7)	7.58	(4.5)	0.030*
PODCI	0.01	[-0.24 - 0.26]	>0.05	95.45	(17.4)	92.42	(31.1)	92.0	(13.6)	0.683
				Red		Yellow		Green		
				n = 6		n = 5		n = 49		
Dorsiflexion (knee 0°)	r	95% CI		Mean	SD	Mean	SD	Mean	SD	p-value
GDI score	0.05	[-0.21 - 0.30]	0.735	77.75	(7.6)	70.73	(17.6)	76.82	(12.6)	0.571
Peak dorsiflexion	0.55	[0.35 - 0.71]	<0.001	4.90	(4.3)	6.61	(5.6)	14.48	(5.7)	<0.001*
1-min walk test*[1]	0.17	[-0.09 - 0.41]	0.207	72.71	(28.4)	79.90	(13.6)	79.82	(12.1)	0.529
GMFM	0.09	[-0.17 - 0.34]	0.495	82.84	8.3	82.43	(11.2)	82.25	(8.2)	0.975
Pedsql	0.06	[-0.20 - 0.31]	0.677	70.00	16.12	83.75	(20.3)	74.29	(19.7)	0.489
				Median	IQR	Median	IQR	Median	IQR	p-value
GVS ankle	-0.37	[-0.57 - -0.13]	<0.05	16.79	(5.2)	15.65	(13.4)	7.62	(4.2)	0.020*
PODCI	0.04	[-0.22 - 0.29]	>0.05	85.35	(29.5)	92.94	(17.4)	93.94	(13.6)	0.791

*[1] Data available for 57 participants (data are missing for three participants in the green category).

Abbreviations: Diff: Difference between the groups formed by the three categories; GDI: Gait Deviation Index; GMFM: Gross Motor Function Measure; GVS: Gait Variable Score; IQR: Inter-quartile range; Pedsql: The Pediatric Quality of Life Inventory Cerebral Palsy Module; PODCI: Pediatric Outcomes Data Collection Instrument; SD: Standard deviation.