Statistical Analysis Plan (SAP) for

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

The *CPinMotion* study

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Abstract

Children with cerebral palsy (CP) often have an altered gait pattern. Orthopaedic surgery, spasticity management, physical therapy and orthotics are used to improve gait. Such interventions 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 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.

Data collection in a prospective, single blind, randomised, parallel group study including children aged 5 to 8 years with spastic CP, classified at Gross Motor Function Classification System levels I or II, have been finalized in July 2017. The statistical analysis will be conducted from July 25th 2017. 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 between-group change from baseline in gait measured by the Gait Deviation Index. *Secondary* outcome measures are: walking performance (1-minute 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 is at 52 weeks after start of intervention. A follow up were also performed at 26 weeks; however, exclusively for the patient-reported outcomes.

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' (without IGA) 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.

List of abbreviations and definition of terms

1-min walk	1 minute Walk Test
CP	Cerebral palsy
FMS	Functional Mobility Scale
GDI	Gait Deviation index
GMFCS	Gross Motor Function Classification System
IGA	Instrumented Gait Analysis
PEDI	Pediatric Evaluation of Disability Inventory
PedsQL	Pediatric Quality of Life Inventory Cerebral Palsy ModuleTM
PODCI	Pediatric Outcome Data Collection Instrument
SAP	Statistical Analysis Plan

Study objectives and Outcomes

A study protocol elaborating the methods used in this study has been published[1] and the study is registered at Clinicaltrials.gov; NCT02160457.

Patient characteristics, IGA and 1-minute walk were performed at baseline and at 52 weeks post start of intervention (primary endpoint). The patient-reported outcome measures were obtained at baseline, 26 weeks, and 52 weeks post start of intervention. The time point 'start of intervention' was defined as the week where the gait analysis report and recommendations of interventions were released to the family and healthcare professionals responsible for the interdisciplinary interventions. The data collection in the control group was on a group level adjusted according to the planned time points in the experimental group.

The primary endpoint: 52 weeks-post follow-up examinations were finalized July 2017.

Descriptive outcomes

At inclusion the following descriptive outcomes were collected:

- Gender.
- Birthday (Age will be calculated based on the child birthday and the date of inclusion).
- Weight, Height and leg length.
- Cerebral palsy subtype.
- Gross Motor Function Classification System (GMFCS)[2].
- Functional Mobility Scale[3].

The descriptive outcomes will be presented in Table 1- Baseline characteristics.

Primary Objective and Outcome

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.

The primary hypothesis to be tested is that the use of IGA in the planning of individually tailored interdisciplinary intervention will be more effective in improving overall gait pathology (evaluated by Gait Deviation Index (primary outcome)) compared with 'care as usual' in children with CP at GMFCS levels I and II.

The primary objective of this study is to test the hypothesis that improvements in gait following individually tailored interventions when IGA used as part of the interdisciplinary follow-up are superior to those following 'care as usual'.

The primary outcome is change in gait measured with Gait Deviation index (GDI). The primary outcome is between-group change in Gait Deviation Index at 52-weeks post start of intervention. GDI 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[4]. For the primary outcome measure, the median of the five trials at self-selected walking speed for each leg is used to calculate the average of both legs to provide a single index for each child (overall Gait Deviation Index).

Secondary Objectives and Outcomes

The secondary hypotheses are that the use of IGA in the planning of individually tailored interdisciplinary intervention will be more effective compared with 'care as usual' in improving:

- Walking performance (1-minute walk test) measures as between-group difference in change from baseline to 52-weeks.
- Functional mobility (Pediatric Evaluation of Disability Inventory) measured as between-group difference in change from 1) baseline to 52-weeks and 2) baseline to 26-weeks
- Overall health, pain and participation in normal daily activities (Pediatric Outcomes Data Collection Instrument) measured as between-group difference in change from 1) baseline to 52-weeks and 2) baseline to 26-weeks
- Health-related quality of life (Paediatric Quality of Life Inventory Cerebral Palsy Module) measured as between-group difference in change from 1) baseline to 52-weeks and 2) baseline to 26-weeks.

These outcomes are only supportive, which is why multiplicity not will not be considered to be a problem.

<u>Walking performance</u>

Walking performance were measured by using the 1-minute walk test and performed as described by McDowell et al. [5].

<u>Functional mobility</u>

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 [6].

Subscales to be analysed separately:

- Functional skills
- Caregiver assistance

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 [7].

Subscales to be analysed separately:

- Daily Activities
- School Activities
- Movement and Balance
- Pain and Hurt
- Fatigue
- Eating Activities
- Speech and Communication

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.

Global scale:

- Global Functioning Scale (Consisting of the means from the subscales: upper Extremity and Physical Function, transfer and Basic Mobility, sports and Physical Functioning and pain/Comfort Scale

Subscales to be analysed separately:

- Upper Extremity and Physical Function
- Transfer and Basic Mobility
- Sports and Physical Functioning
- Pain/Comfort Scale
- Happiness Scale

The primary and secondary outcomes will be presented in Table 2 – Mean change within groups and difference in change between groups at 26 and 52 weeks follow-up.

Explorative Outcomes

The recommended and applied interventions and participant-perceived responses to the intervention will be explored. Information about the recommended interventions was collected at the release of the instrumented gait analysis report. The applied interventions and the participants perceived responses to the interventions were collected with a short questionnaire to the participants at 52 weeks follow-up. The data will be used to explore adherence to the recommended interventions, to compare the interventions used in the two study groups and to

analysis differences in the perceived responses to the interventions.

Descriptive statistics and differences between the groups will be presented in Table 3 - Interventions and participant-perceived responses to the interventions.

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. These outcomes will only be explanatory and/or hypothesis generating and will not be described in further details in the current Statistical Analysis Plan.

Summary of outcomes to be collected
All outcomes collected at baseline, 26 weeks and at primary endpoint (52 weeks) are listed below.

Instrument	**Baseline**	**26 weeks**	**52 weeks**
Gait Analysis	x		x
1-min Walk	x		x
PEDI	x	x	x
PedsQL	x	x	x
PODCI	x	x	x
Recommended interventions	x		
Applied interventions			x
Participants perceived responses			x

1-min walk: 1 minute Walk Test; PEDI: Pediatric Evaluation of Disability Inventory; PedsQL: Pediatric Quality of Life Inventory Cerebral Palsy Module™; PODCI: Pediatric Outcome Data Collection Instrument and GVS: Gait Variable Score.

Adverse events
Any adverse events that occurred in the experimental or control groups were registered. Parents of the participants, local teams and the gait laboratory staff could report adverse events.

Study design

Sample size
The sample size for this study was calculated to create power for the primary hypothesis. The sample size calculation was based upon the GDI (primary outcome), collected 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 [8] . A minimum of 29 subjects in each group (n=58) were 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 dropout rate of 5%.

Randomisation
After baseline assessment, children were randomised to either the 'Experimental' or the 'Control' group. The randomisation was stratified according to the physiotherapist to whom the child is appointed. For children who were followed by a physiotherapist, who is responsible for two or more children, the first child randomised determined how the following children were allocated. Randomisation was computer-generated by a researcher with no other involvement in the study. Participants were allocated by a sequence of numbers: 0 – referring to 'Experimental', and 1 – referring 'Control'. The allocation sequence 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 child's parents and the local team about the allocation.

Blinding
Participants and the local team were not blinded due to the nature of the study design. Data collectors were blinded and the data analysts will be blinded.

Statistical analysis
The primary outcome (Gait Deviation Index) will be analysed according to intent-to-treat (ITT) principles. Furthermore a per-protocol (PP) analysis is planned as appropriate: In the EXP group, we define the per-protocol population as those participants where all four steps of the intervention where performed (Data collection, Impairment Focused Interpretation, Recommended interventions and dissemination of knowledge). In the CON group, we define the per protocol population as those participants that did not complete the four steps of the intervention. This means if any of the participants in the CON group are referred to a clinical gait analysis as part of routine practice (cross-over of interventions) and the four steps are performed before the 52 weeks follow up, they will be defined as 'per-protocol'. Since no participants in the control group completed the four steps of the intervention, the "per-protocol" will not be performed.

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 [9,10]. Model specifications will depend on evaluation of distributional properties of collected data and appropriate adaptation of point estimate and variation indicators.

If differences between the groups in the participant perceived responses to the intervention are documented, proportional odds models will compare the difference between the two groups.

The trial is designed as a superiority trial, i.e. we expect that the group allocated to EXP-group in comparison with the CON-group will improve Gait Deviation Index more at 52 weeks follow up.

Interpretation of results

To minimize bias, we have a priori decided how to interpret the possible follow-up data scenarios:

a) If Gait Deviation Index is improved more in the EXP group compared with the CON group, then EXP is the preferred treatment;
b) If Gait Deviation Index is improved more in the CON group compared with the EXP group, then CON is the preferred treatment; or
c) If Gait Deviation Index does not differ between the two treatment groups, the treatment associated with better outcomes in secondary outcomes including walking performance and functional mobility, overall health, pain and participation in normal daily activities and Health-related quality of life, and adverse events will be favoured.

Summary of protocol deviations

- Applied intervention

  We planned to use records from the Cerebral Palsy Follow-Up Program on the applied interventions. In order to ensure data from same the time period on all participants (around the 52 weeks follow-up), we chose to collect information about the applied interventions with a short questionnaire to the parents.

- Primary outcome – walking speed

  The primary outcome were planned to be GDI at matched walking speed, since walking speed *per se* might affect GDI. If there were more than 15% differences between the self-selected walking speed at baseline and 52 weeks follow-up, we planned to instruct the children to walk at the same walking speed at the instrumented gait analysis at the 52 weeks follow-up as at the baseline assessment. Ten participants had a self-selected walking speed that varied more than 15% between the two sessions. Six participants walked too fast and four participants walked to slow at the 52 weeks follow up. Since it proved impossible to instruct the children to walk at a certain walking speed, the primary outcome were changed to self-selected walking speed. Differences in the walking speed will be explored and if relevant supplementary analysis with will be conducted.

- Secondary analysis on the children randomised first

  A secondary analysis to explore differences with regard to whether a child was randomly assigned to the intervention or followed another child in the randomisation were planned. Since only two participants (one from each treatment group) were randomised with another participant. Therefore the analysis on the participants randomised (n=58) first will not be conducted.

- Per-protocol (PP) analyses on 52 weeks post orthopaedic surgery follow-up
  To acknowledge that outcome of surgery might be influenced by a long planning phase and rehabilitation a second post intervention examination were planned to be performed at 52 weeks post operation and included in a per protocol analysis. Since only one patient had a minor orthopaedic surgery approximately 6 month before the 52-weeks assessment, the per-protocol analysis will not be conducted.

- Per-protocol (PP) analysis of participants that cross-over of interventions
  The per-protocol (PP) analysis will not be conducted since no crossover of interventions was observed (i.e. no participants in the control group completed the four steps of the intervention).

Implementation of the analysis plan

The implementation of the analysis plan will be as follows:

1. Data collection (finalized in July 2017).
2. Blinding of the collected data
   A research assistant will code each treatment arm into 'treatment A' and 'treatment B' and thus leaving all others blinded from treatment during the analyses.
3. Data analysis
   Primary and secondary analyses will be made blinded from treatment group..
4. Results will be presented to the co-authors of the RCT-report any uncertainties will be clarified and blinded interpretation of the primary endpoints will be conducted prior to un-blinding of data.

Acknowledgements

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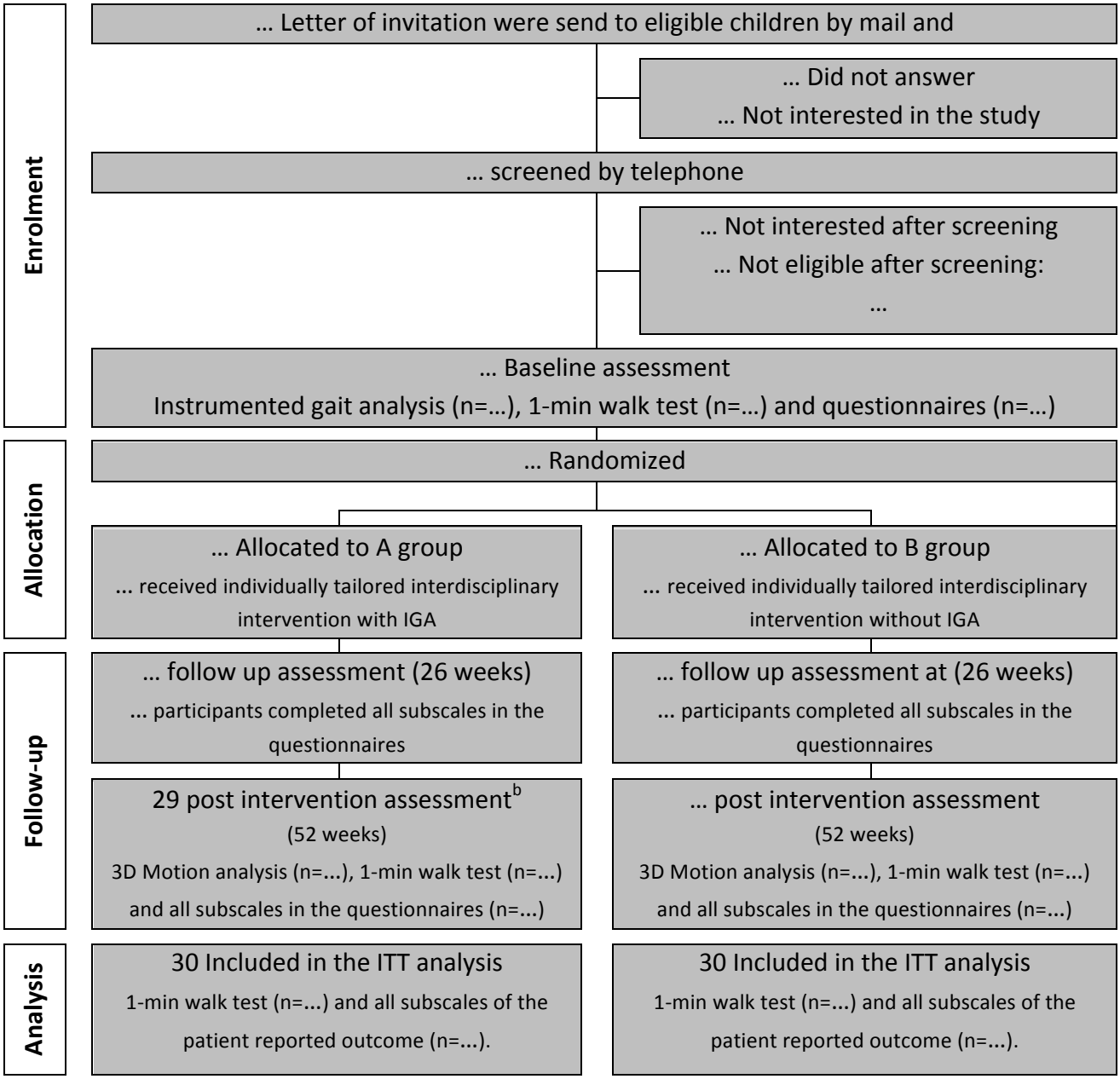
Figures

Figure 1 Flow diagram



Abbreviations: Intention to treat (ITT)

Tables

Table 1 - Baseline characteristics

	Experimental (n=30)	**Control** (n= 30)
Gender and classification of diagnosis and function		
Girls / boys		
CP spastic subtype, Unilateral / bilateral		
GMFCS level I/II		
FMS 5 meters; level 5/6		
FMS 50 meters; level 2/5/6		
FMS 500 meters; level 1/2/5/6		
Age, height and weight and body mass index		
Age (Years, month)		
Height (meter)		
Weight (kg)		
Body Mass Index		
Outcome measures		
Gait Deviation Index		
Gait speed (meter / sec)		
1-min walk test (meter / min)		
Pediatric Evaluation of Disability Inventory		
Functional skills		
Caregiver assistance		
The Pediatric Quality of Life Inventory		
Daily Activities		
School Activities		
Movement and Balance		
Pain and Hurt		
Fatigue		
Eating Activities		
Speech and Communication		
The Pediatric Outcomes Data Collection Instrument		
Global Functioning Scale		
Upper Extremity and Physical Function		
Transfer and Basic Mobility		
Sports and Physical Functioning		
Pain/Comfort Scale		
Happiness Scale		

Cerebral palsy (CP), Gross Motor Function Classification System (GMFCS), Functional Mobility Scale (FMS),
Values are presented as mean ± SD if not otherwise stated

Table 2 – Mean change within groups and difference in change between groups at 26 and 52 weeks follow up.

	Change within-group				**Between-group difference**	
	Baseline to 26 weeks		Baseline to 52 weeks		Baseline to 26 weeks	Baseline to 52 weeks
	EXP (n=?)	CON (n=?)	EXP (n=?)	CON (n=?)		
Gait Deviation Index, self-selected speed	-	-			-	
Gait Deviation Index, matched speed						
1-minute walk test	-	-			-	
PEDI, Mobility scale						
Functional skills						
Caregiver assistance						
PedsQL, Cerebral Palsy Module						
Daily Activities						
School Activities						
Movement and Balance						
Pain and Hurt						
Fatigue						
Eating Activities						
Speech and Communication						
PODCI						
Global Functioning Scale						
Upper Extremity and Physical Function						
Transfer and Basic Mobility						
Sports and Physical Functioning						
Pain/Comfort Scale						
Happiness Scale						

Pediatric Evaluation of Disability Inventory (PEDI), The Pediatric Quality of Life Inventory (PedsQL), The Pediatric Outcomes Data Collection Instrument (PODCI),
Values are presented as mean and 95% confidence intervals

Table 3 – Interventions and participant-perceived responses to the interventions

The applied interventions (reported by the participants), recommended interventions based on instrumented gait analysis, compliance and the distribution of different answer categories for the anchor questions.

Applied interventions (n=x /x)	**Experimental**	**Control**	**Chi²** *p*-value
Physical Therapy			
Orthotics			
Spasticity management			
Orthopaedic surgery			
Recommended interventions (n=30)			
Physical Therapy			
Orthotics			
Spasticity management			
Orthopaedic surgery			
	+ Rec & + app / +Rec		
Compliance[1] (n=x)			
Physical Therapy	/		
Orthotics	/		
Spasticity management	/		
Orthopaedic surgery	/		

	Experimental	**Control**	**Chi²** *p*-value
Anchor: Interventions (n=x/x)			
Excellent			
Very good			
Good			
Fair			
Poor			
Anchor Walking (n=x /x)			
Much better			
A little better			
About the same			
A little worse			
Much worse			
Anchor: Overall health (n=x /x)			
Much better			
A little better			
About the same			
A little worse			
Much worse			

[1] Compliance of recommended interventions (number of participants where the intervention where recommended AND applied / participants where the intervention where recommended).