Statistical Analysis Plan (SAP) for

The effectiveness of interdisciplinary interventions on family-centered services and gross motor function in children with cerebral palsy – a secondary analysis from a randomized controlled trial

Collaborators:

Christina Esmann Fonvig[1], Helle Mätzke Rasmussen[1,], Niels Wisbech Pedersen[1], Søren Overgaard[1], Anders Holsgaard-Larsen[1]

[1]The Orthopaedic Research Unit, Department of Orthopaedic Surgery and Traumatology, Odense University Hospital and Department of Clinical Research, University of Southern Denmark, Odense, Denmark

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Introduction

This study is a secondary analysis (on tertiary outcome measures) of a randomised controlled trial; 'The use of instrumented gait analysis for individually tailored interdisciplinary interventions in children with cerebral palsy', trial registration: ClinicalTrials.gov NCT02160457. Registered June 2, 2014.

Data collection for this study started August 2014 and was finalized in July 2017, from a prospective, single blind, randomised, parallel group study including children aged 5 to 8 years with spastic cerebral palsy (CP), classified at Gross Motor Function Classification System (GMFCS) levels I or II.

Patient characteristics and GMFM-66 were performed at baseline and at 52 weeks post start of intervention. MPOC-20 was 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 the 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. Examinations at 52-weeks follow-up were finalized July 2017.

The interventions under investigation are: 1) individually tailored interdisciplinary intervention based on measures performed as part of the Cerebral Palsy follow-up Program (CPUP), other clinical examinations, standardized measurements of walking and recommendations from the gait analysis, 2) 'care as usual', defined by individually tailored interdisciplinary intervention based on measures performed as part of the CPUP and other clinical examinations, without recommendations from the gait analysis.

Deviations from trial protocol

Selected items of the Gross Motor Function Measure (GMFM-66) were examined at baseline and at 52-weeks follow-up to support the interpretation of the biomechanical data for the three-dimensional IGA.

GMFM-66 was not listed as an outcome measure in the study protocol (1) or in the clinical trial registration (NCT02160457). However, in the current secondary analysis, the GMFM-66 will be used as a measure of overall gross motor capacity of the child.

Study synopsis

Children with cerebral palsy (CP) often exhibit an altered gait pattern. Orthopedic surgery, spasticity management, physical therapy and orthotics are used to improve gait. Such interventions are typically planned based on clinical examinations and standardized measurements to assess walking, which in Denmark at present is the standard clinical practice ('care as usual'). However, a 3-dimensional instrumented gait analysis (IGA) will provide objective and valid measures of gait to identify features in gait and possible underlying neuro-musculoskeletal impairments (2). Using the IGA report and the interdisciplinary intervention recommendations ('the use of IGA') as part of planning an interdisciplinary intervention, the physiotherapist, orthopedic surgeons and neuro-pediatricians are provided with information on the impairments affecting gait, allowing tailored individualized treatment plans for the children and their families.

Family-centered services (FCS), where the parents are actively involved throughout setting and implementing treatment goals for individual tailored interventions for their child, is an acknowledged approach to secure the child's development and needs within the context of the child's family (3-5). The Measure of Processes of Care (MPOC-20) (3) covers families' perception of issues such as *enabling and partnership*, *providing general information*, *providing specific information about the child*, *respectful and supportive service* and *coordinated and comprehensive care* and is widely used in pediatric rehabilitation to evaluate FCS (6). However, it is uncertain if the use of IGA in the planning of individually tailored interdisciplinary intervention results in a higher perceived experience of FCS in proximity to receiving the IGA report (at 26 weeks) or a year after the gait analysis (at 52-weeks follow-up).

In children with CP, the level of gross motor function correlates with the child's extent of participation in society, school, and at home (7) as well as parent-reported quality of life (8), suggesting that impairment has a close relationship with not only social activity, but also social functionality. Although the vast majority (50-80%) of children with CP are capable of walking independently, gait performance is almost always affected as a result of musculoskeletal deformity, abnormal muscle tone, inadequate balance and impaired motor control (2). The high physical strain of walking for children with CP results in fatigue and reduced walking distance (9) as well as activity limitations (10). Overall, children with CP who display good function as determined by the GMFM-66, show a tendency toward better

functional movement, allowing them to more effectively participate in daily activities (7).

The Gross Motor Function Measure (GMFM-66), a standardized clinical tool consisting of 66 items, created to detect gross motor function change in children with CP, is considered a valid outcome measure, sensitive enough to document clinically meaningful improvement, including responsiveness (11, 12) and is the gold standard measure of functional ability in the area of CP (13). The GMFM-66 score reflects the overall level of gross motor capacity (14). Using the Gross Motor Ability Estimator Scoring Software (15), a GMFM-66 score can be obtained using a minimum of 13 items. Due to the included children's high gross motor function (GMFCS level I-II) combined with the need to limit the amount of testing time for the children, a selection of minimum 13 relevant items of the GMFM-66 were chosen for this study.

A potential association between the parents' perception of the family-centeredness of the services they and their children received during the study period (by means of the MPOC 52-weeks follow-up score) and the child's gross motor improvement (change in GMFM-66 score), could indicate that improvement in gross motor function of a child with CP is related to the parents' involvement in the process of care. Thus, an association could serve as an indicator for the health personnel in terms of detecting those families who would benefit from enhanced information, service and care, to improve the child's gross motor function.

List of abbreviations and definition of terms

BMI SDS	Body Mass Index Standard Deviation Score
CP	Cerebral Palsy
FCS	Family-centered services
GDI	Gait Deviation Index
GMFCS	Gross Motor Function Classification System
GMFM-66	Gross Motor Function Measure - 66
MPOC-20	Measure of Processes of Care – 20
IGA	Instrumented Gait Analysis
IQR	Interquartile range
SAP	Statistical Analysis Plan
SD	Standard Deviation

Study aim, hypothesis and outcome measures

Aim

The aim of this secondary analysis (on tertiary outcome measures) of a randomized controlled study is to investigate whether individually tailored interdisciplinary intervention, based on the use of IGA, has a superior effect on perceived experience of FCS compared to 'care as usual' without the use of IGA. The study will furthermore investigate whether the availability of the IGA has a superior effect on gross motor function improvement as well as investigate potential associations between perceived experience of FCS and gross motor function improvement.

Primary hypothesis and outcome

The primary hypothesis to be tested is that the use of IGA in the planning of individually tailored interdisciplinary intervention will result in a higher parentally perceived experience of FCS evaluated by the MPOC-20, compared to 'care as usual' in relatively young children with CP at GMFCS level I-II.

The primary analysis is between-group change difference in all five MPOC-20 domains at 52-weeks. The five MPOC-20 domains comprise *enabling and partnership*, *providing general information*, *providing specific information about the child*, *respectful and supportive service* and *coordinated and comprehensive care*.

Data for the primary analysis, between-group change difference in MPOC-$20_{0\text{-}52}$, will be presented in table 2.

Secondary hypotheses and outcome

a) The above listed hypothesis will be analysed at 26-weeks follow-up.

Outcome measure, between-group change difference in MPOC-20 domains at 26-weeks post start of intervention, will be presented in table 2.

b) The planning of individually tailored interdisciplinary intervention will result in better gross motor function, evaluated by GMFM-66, compared to 'care as usual' in relatively young children with CP at GMFCS level I-II.

Outcome measure, between-group change score in GMFM-66 at 52-weeks post start of intervention, will be presented in table 2.

c) The experience of FCS is associated with gross motor function improvement in a unidirectional or bidirectional relation.

Outcome will be presented as multiple regression analysis in table 3.

Statistical analyses

Data

Descriptive outcome

At inclusion the following descriptive outcomes were collected:

- Sex (female or male)
- Age (in years)
- Weight and height
  (used to calculate Body Mass Index Standard Deviation Score (BMI SDS)) (16)
- Cerebral palsy spastic subtype (uni- or bilateral)
- Gross Motor Function Classification System (GMFCS level I or II)
- Randomization group: Intervention (the use of IGA) or control ('care as usual').

The descriptive outcomes will be presented in Table 1.

Outcome measures

- MPOC-20: Parent reported data obtained from a questionnaire with the five domains *enabling and partnership*, *providing general information*, *providing specific information about the child*, *respectful and supportive service*, *coordinated and comprehensive care*. Data comprise the timepoints at baseline, 26 weeks and 52 weeks post start of intervention and the differences between these timepoints: ΔMPOC-20$_{0\text{-}26}$ and ΔMPOC-20$_{0\text{-}52}$.
- GMFM-66: Standardized clinical tool created to detect gross motor function change in children with CP. Data comprise the timepoints at baseline and 52 weeks post start of intervention and the difference between these timepoints: ΔGMFM$_{0\text{-}52}$.

Data analyses

Analyses will be performed according to intention-to-treat, with last value carried forward for missing observations.

Descriptive statistics will be summarized as appropriate. Distribution of data will be investigated using normal probability plots and Shapiro–Wilk test, and will be presented with mean and standard deviation (SD) for parametric data and median and interquartile range (IQR) for non-parametric data. Data outliers will be identified with the use of scatterplots.

Between-group change differences will be estimated with a linear model (table 2, model A) in which relevant baseline scores are entered as covariates (table 2, model B). Model specifications will depend on evaluation of distributional properties of collected data and appropriate adaptation of point estimate and variation indicators.

Associations will be evaluated using multiple linear regression. To evaluate whether the child's change in gross motor function is associated to the parent's perceived experience of FCS, MPOC-20 52-weeks follow-up domain scores will be used as the dependent variable and ΔGMFM-$66_{0\text{-}52}$ score as the independent variable, adjusted for baseline GMFM-66 score (table 3, model A). Further, potential confounding variables as sex, age, BMI SDS, CP spastic subtype and GMFCS level will be adjusted for as covariates (table 3, model B).

To evaluate whether the parents perceived experience of FCS is associated with the child's change in gross motor function, ΔGMFM-$66_{0\text{-}52}$ score will be used as the dependent variable and MPOC-20 52-weeks follow-up domain scores as the independent variable, adjusted for baseline MPOC-20 domain scores (table 3, model A). Further, potential confounding variables as sex, age, BMI SDS, CP type and GMFCS level will be adjusted for as covariates (table 3, model B).

Results will be presented with an alpha of 0.05 and a 95% confidence interval, statistical significance level set at $p<0.05$.

Statistical analysis will be conducted from April 2018 and performed using Stata/IC version 14.2 or later.

Data interpretation

To investigate whether individually tailored interdisciplinary intervention based on IGA has a superior effect on perceived experience of FCS compared to 'care as usual', between-group change score for each of the five MPOC-20 domains will be reported in the primary analysis. To minimize bias, interpretation of variation of outcome will be defined *a priori*:

a) If more domains exhibit significantly positive outcomes in one group compared to the other, this group will be considered as superior.

b) If both groups have the same number of significantly positive domains, neither group will be considered superior.

c) If neither group has a significant positive domain, neither group will be considered superior.

Tables and figures

Table 1: Demographics and baseline data of included children

	Intervention (n=)	**Control (n=)**
Sex (girls/boys)		
CP spastic subtype (uni-/bilateral)		
GMFCS level (I-II)		
Age (years)		
Height (m)		
Weight (kg)		
Body Mass Index SDS		
Measure of Processes of Care – 20 domains		
enabling and partnership		
providing general information		
providing specific information about the child		
respectful and supportive service		
coordinated and comprehensive care		
Gross Motor Function Measure - 66		

Reported as mean and standard deviation (SD) or median and interquartile range (IQR).

Table 2: Between-group change difference at 26-weeks and 52-weeks follow up

	Between-group change difference											
	Model A						**Model B**					
	Baseline to 26 weeks			Baseline to 52 weeks			Baseline to 26 weeks			Baseline to 52 weeks		
	β (95% CI)	R^2	p	β (95% CI)	R^2	p	β (95% CI)	R^2	p	β (95% CI)	R^2	p
Δ MPOC-20 domains												
Δ *enabling and partnership*												
Δ *providing general information*												
Δ *providing specific information about the child*												
Δ *respectful and supportive service*												
Δ *coordinated and comprehensive care*												
Δ GMFM-66												

Dependent variable: ΔGMFM-66 or ΔMPOC-20 domains.
Independent variable: Randomization group.
Model A: Unadjusted model.
Model B: Model A adjusted for relevant baseline score.
Abbreviations: GMFM – Gross Motor Function Measure. MPOC – Measure of Processes of Care.

Table 3: Associations between MPOC-20 and GMFM-66

Dependent variable: MPOC-20 52-weeks follow-up domain scores	**Independent variable:** $\Delta GMFM_{0\text{-}52}$ score	**Model A**			**Model B**		
		β* (95% *CI	**R^2**	***p***	***β* (95% *CI***	**R^2**	***P***
enabling and partnership							
providing general information							
providing specific information about the child							
respectful and supportive service							
coordinated and comprehensive care							

Dependent variable: MPOC domains at 52-weeks follow-up.
Independent variable: $\Delta GMFM_{0\text{-}52}$ score.
Model A: Adjusted for baseline GMFM.
Model B: Model A adjusted for sex, age, BMI SDS, CP type and GMFCS level.
Abbreviations: GMFM – Gross Motor Function Measure. MPOC – Measure of Processes of Care.

Dependent variable: $\Delta GMFM_{0\text{-}52}$ score	**Independent variable:** MPOC-20 52-weeks follow-up domain scores	**Model A**			**Model B**		
		β (95% CI	**R^2**	***p***	**β (95% CI**	**R^2**	***p***
	enabling and partnership						
	providing general information						
	providing specific information about the child						
	respectful and supportive service						
	coordinated and comprehensive care						

Dependent variable: $\Delta GMFM_{0\text{-}52}$ score
Independent variable: MPOC domains at 52-weeks follow-up
Model A: Adjusted for baseline MPOC-20 domain scores
Model B: Model A adjusted for sex, age, BMI SDS, CP type and GMFCS level.
Abbreviations: GMFM – Gross Motor Function Measure. MPOC – Measure of Processes of Care.

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