Non-progressive congenital ataxia

advancing diagnosis to enhance chances for targeted therapy

ARTEMIS – The ARTEMIS Cohort

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History of protocol updates

Version	Date	Reason for update
1.0	04/10/2024	

List of abbreviations

ADHD	attention-deficit–hyperactivity disorder
ASD	Autism spectrum disorder
BFMF	Bimanual Fine Motor Function
CP	Cerebral palsy
DVP	Data Validation Plan
eCRF	electronic Case Report Form
EEG	Electroencephalography
FICD	Family Impact of Childhood Disability
GHQ	General Health Questionnaire
GMFCS	Gross Motor function Classification System
ICD	International Classification of Disease
IQ	Intelligent quotient
MACS	Manual Ability Classification System
MRI	Magnetic Resonance Imaging
MRICS	Magnetic Resonance Imaging Classification System
NNiCS	Neonatal neuroimaging Classification System
NPCA	Non-progressive congenital ataxia
QoL	Quality of life
SARA	Scale for the Assessment and Rating of Ataxia
SCPE	Surveillance of Cerebral Palsy in Europe

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1. SUMMARY OF THE RESEARCH

COORDINATING/ PRINCIPAL INVESTIGATOR	Dr Kate HIMMELMANN University of Gothenburg, Gothenburg, Sweden kate.himmelmann@vgregion.se
TITLE	ARTEMIS. Non-progressive congenital ataxia advancing diagnosis to enhance chances for targeted therapy
JUSTIFICATION/ CONTEXT	Non-progressive congenital ataxia (NPCA), also classified within the cerebral palsy (CP) concept as ataxic CP, is a very rare early-onset condition characterised by an abnormal pattern of movement with a loss of orderly muscular coordination, so that movements are performed with abnormal force, rhythm and accuracy. The pathogenic mechanisms are poorly known. 1/ The disability profile is more pronounced with respect to cognitive than gross motor function, underlining that NPCA is different from other subtypes of CP. 2/ Neuroimaging findings do not indicate acquired injuries of the brain in most cases, and suggest a possible high contribution of genetic aetiologies, up to now poorly investigated. In this context, we need to investigate additional evidence to understand the origins of NPCA/ataxic CP, predict its natural history and measure its impact, by combining data on clinical features, systematic analysis of brain images and advanced genomic testing. More specifically, we need to (i) enhance the application of clinical criteria by refining training instruments to allow a more reliable identification of patients (ii) develop a detailed neuroimaging classification with better identification of patterns suggestive for acquired or genetic background (iii) improve our understanding of the underlying pathophysiology and identify indicators for a genetic background (iv) provide a comprehensive description of the functional profile, in particular cognition (v) assess children's quality of life and parental burden
OBJECTIVES	The objectives are : – To establish the detailed impairment profile: cognitive profile, neuropsychiatric disorders/signs, speech and communications abilities, vision and hearing, gross and fine motor function, epilepsy – To chart developmental trajectories in motor and language areas

	– To perform a systematic analysis of MRI brain images (detailed analysis of brain maldevelopments beyond cortical maldevelopments and of images hitherto classified in a "miscellaneous" group), and to assess cerebellar and cerebral volumetry. MRI volumetry will be compared to that of typically developing age- and sex-matched children – To record the standardised genetic results from individuals with a firm definite genetic diagnosis – To perform a comprehensive advanced re-analysis of exome datasets from genetically undiagnosed cases (i.e. children still remaining without a definite diagnosis after comprehensive data re-analysis) – To document the quality of life of the children (proxy report) and their parents' burden (psychological health, perceived burden and social support, impact on work) – To document care use and patient journey in children with NPCA/ataxic CP.
OUTCOME MEASURES	– Characterisation of ataxic features (muscle tone/tremor/balance/signs of spasticity or dystonia), and Scale for the Assessment and Rating of Ataxia (SARA) – Impairment profile: IQ or developmental quotient; diagnosis of attention-deficit–hyperactivity disorder (ADHD), diagnosis of autism spectrum disorder (ASD) and/or ASD traits, according to Diagnostic and Statistical Manual of Mental Disorders (DSM-V); Speech and communications abilities assessed with Viking Speech Scale and Communication Function Classification System; Vision (bilateral vision loss and blindness, visual field defects, strabismus, nystagmus, refractive errors, optic atrophy) and hearing (severity and type of hearing loss on both ears, hearing aids); Gross and fine motor function, using Gross Motor function Classification System and Bimanual Fine Motor Function or Manual Ability Classification System; Epilepsy: type (focal, generalized, multiple types), EEG, seizures age at onset, frequency, antiseizure medication – Brain MRIs: Detailed description, coding using Neonatal neuroimaging classification system and MRI classification system for children with CP, according to the timing (neonatal or post neonatal period), cerebellar and cerebral volumetry

	– Identification of genomic variations (single nucleotide variants, small insertions and deletions, structural variants, repeat expansions) that likely explain or contribute to the clinical features – Proxy-reported quality of life using Kidscreen-27 – Psychological health of parents using the General Health Questionnaire (GHQ-12), perceived burden of parents using the Family impact of Childhood Disability (FICD+4) – Families contacts to the healthcare system and overall treatment and care
OUTLINE OF THE RESEARCH	Observational European multicenter historical cohort study, implemented in six reference centres (university hospitals, regional hospitals, out-patient neurology/rehabilitation clinics, and CP registries) in Belgium, Denmark, Germany, Greece, Norway, and Sweden. No follow-up is planned.
INCLUSION CRITERIA	– male or female children – confirmed diagnosis of NPCA/Ataxic CP (SCPE definition) – aged ≥ 5 years and ≤ 8 years at time of data collection – written informed consent of at least one parent or legal representative in accordance to country regulations, and verbal assent of the child when possible
EXCLUSION CRITERIA	Children with all other diagnoses of movement disorders or other CP subtypes
RESEARCH PROCEDURES	Identify children with NPCA/ataxic CP within the SCPE network prospectively, where parents will be addressed by the centres with respect to additional aspects (agreement to collect additional health care data, to assess development with standardized measures, to send MRI, agreement for genetic analysis – in existing blood samples or new samples)
STUDY SIZE	50
DURATION OF THE RESEARCH	Duration of the inclusion period: 24 months Participation duration of each participant: a few days according to organisation of care Total duration of the research: 36 months
STATISTICAL ANALYSIS OF THE DATA	The aim is to better understand patterns within the data using univariate visualization and summary statistics of each field in the raw datasets, and to relate brain images findings and the genetic diagnosis generated to functional parameters (motor, cognition, language) (bivariate analyses). No formal hypothesis testing will be carried out.

EXPECTED BENEFITS	We propose an observational study of children with NPCA/ataxic CP, identified using a harmonized approach, collecting comprehensive data to relate function, brain images and genetic work-up results that will first contribute to identify biomarkers to enable more targeted genetic diagnoses, and to improve knowledge of the underlying pathophysiology. A better understanding of the condition will contribute to earlier appropriate management. A genetic origin also carries counselling implications. This study will also provide original insights on the impact of the condition, that will help to target interventions aimed at improving function and quality of life.

2. SCIENTIFIC JUSTIFICATION AND GENERAL DESCRIPTION

2.1. CURRENT STATE OF KNOWLEDGE

Non-progressive congenital ataxia (NPCA)/ ataxic cerebral palsy (CP) is an early-onset condition characterised by an abnormal pattern of movement, with a loss of orderly muscular coordination, so that movements are performed with abnormal force, rhythm and accuracy (Surveillance of Cerebral Palsy in Europe, SCPE definition, http://scpe.edu.eacd.org/scpe/cerebral-palsy.php). It is the least common subtype of cerebral palsy (CP), accounting for 4% of CP cases in Europe (Horber *et al*, 2023), 5.3% in Australia (Smithers-Sheedy *et al*, 2016), and 2% in the Canadian CP registry (Levy *et al*, 2020). The prevalence is 0.8 per 10,000 livebirths, stable over the past 30 years (Horber *et al*, 2023).

Pathogenic mechanisms are poorly known. The phenotype with a disability profile more pronounced with respect to cognitive than gross motor dysfunction, the neuroimaging findings not indicating acquired injuries of the brain in a large proportion of cases, a low percentage of children born preterm (recent analysis of a SCPE series of 679 children with ataxic CP born 1980-2010, Horber *et al*, 2023) have questioned the inclusion of an ataxic subtype in the CP concept.

Children with NPCA/ataxic CP often display a high occurrence of impairments. The frequency of intellectual disability is higher than might be expected from the overall prevalence in CP (almost 40% presented with severe intellectual impairment (IQ<50) in the SCPE series of Ataxic CP, see Fig. 1), and the severity of the cognitive impairment could not be predicted by the severity of ataxia or the imaging findings. A large proportion of children also display signs of neuropsychiatric disorders, language impairment in addition to increased occurrence of epilepsy, ocular signs or behaviour problems.

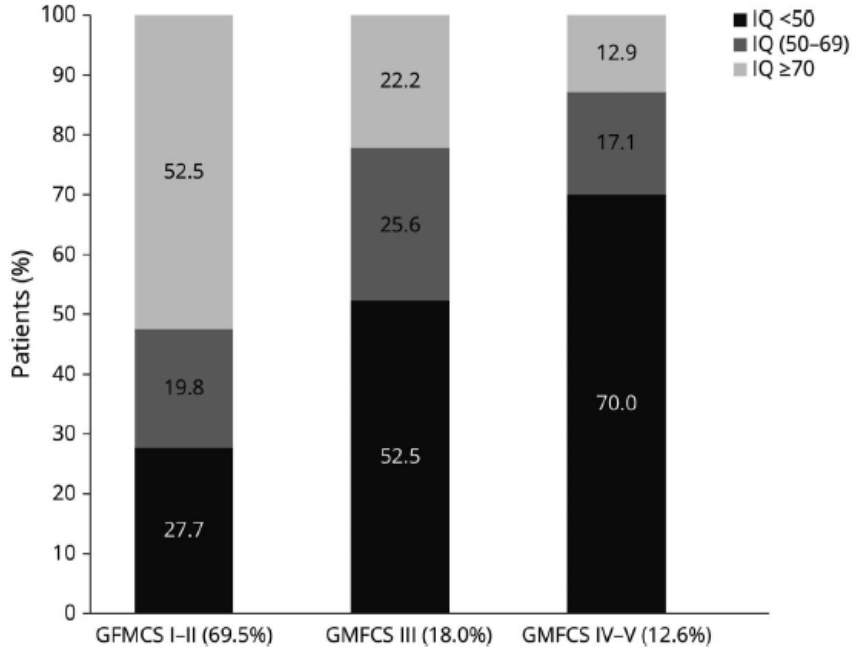


Fig1. Intellectual Impairment by Severity of Motor Impairment in Ataxic cerebral palsy in the SCPE Database (Birth Years 1980–2010).

GMFCS: Gross Motor Function Classification System

SCPE: Surveillance of Cerebral Palsy in Europe

Source: Horber *et al*, 2023

Neuro-anatomic correlates on brain MRI are more heterogeneous than in other CP subtypes and rarely identify acquired lesions. The finding of normal result in more than 50% of cases has been highlighted in small convenience samples (Esscher *et al*, 1996; Steilin *et al*, 1998), or in systematic collection of neuroimaging findings in CP (Levy *et al*, 2020; Smithers-Sheedy *et al*, 2016). In the European series, the MRIs analysis revealed normal images in 29.0%, miscellaneous findings in 23.5%, and malformations other than disorders of cortical formation in 20% (Horber *et al*, 2023).

These results indicate a possible high contribution of genetic aetiology (Raslan *et al*, 2024; Fahey MC *et al*, 2017; Schnekenberg PR *et al*, 2015, Delague V *et al*, 2002), up to now poorly investigated. The causes remain uncertain despite genetic work-up. Current diagnosis approaches, such as exome or panel sequencing, leave a major fraction of children without a firm diagnosis. And interpretation is limited by the relatively small number of patients in studies, the large genetic heterogeneity, and the paucity of validation studies that have been carried out to definitively link variants and genes with ataxic CP. In total, there is a need for studies bringing together data on function, brain imaging and genetic testing to investigate additional evidence for a genetic origin in NPCA/ataxic CP.

Quality of life (QoL) is an important concern for all children with CP, particularly for those with such complex and severe symptomatology, and has so far not been documented in the subgroup of ataxic CP. The importance of specific cognitive impairments in NPCA/ataxic CP highlights the need to focus not only on general intellectual functioning, but also on a broader set of functions (visual and executive perception functions), whose influence on QoL has been recently shown (Blasco *et al*, 2023), together with neuropsychological variables (Autism spectrum disorder (ASD) traits), to identify, as determinants on QoL, targets for intervention. The impairments also often put a heavy load on families, that also needs to be documented.

2.2. EXPECTED RESULTS

We propose an observational study of children with NPCA/ataxic CP, identified using a standardized approach, collecting comprehensive data to relate function, brain images and genetic work-up results that will first contribute to identify biomarkers to enable more targeted genetic diagnoses, and to improve knowledge of the underlying pathophysiology. A better understanding of the condition will contribute to earlier appropriate management. A genetic origin also carries counselling implications. This study will also provide original insights on the impact of the condition, that will help to target interventions aimed at improving function and quality of life.

2.3. RISKS AND BENEFICTS ASSESSMENT

The individual benefit of this research for the patient is the re-analysis of data by experts, which enables to refine the diagnosis at no financial cost. The collective benefits are to refine the diagnostic strategy to allow a more reliable identification of patients and earlier appropriate management, to identify biomarkers to allow more targeted genetic diagnostics, to relate function, brain images and genetic work-up results to improve knowledge of the underlying pathophysiology, and to obtain new data on the impact of the condition.

The risks related to the research protocol are low, and are limited to the blood test for those patients concerned by this examination, or to the psychological consequences of an incidental finding.

3. OBJECTIVES

The objectives are :

- To establish the detailed impairment profile of children with NPCA/ataxic CP: cognitive profile, neuropsychiatric disorders/signs (autism, attention deficit/hyperactive disorder), speech and communications abilities, vision and hearing, gross and fine motor function, epilepsy
- To chart developmental trajectories (based on the record of age at key developmental milestones in motor and language areas) and trace them back to infancy
- To perform a systematic analysis of MRI brain images (available in common practice, film or digital), to carry out a detailed analysis of brain maldevelopments beyond cortical maldevelopments and of images hitherto classified in the “miscellaneous” group (see MRCI CS, Himmelmann K, Horber V *et al*, 2016), and to assess cerebellar and cerebral volumetry (Evans, 2006). MRI volumetry will be compared to images of typically developing age- and sex-matched children, using the NIH Pediatric Data Repository of anonymised MRI brain images.
- To record the standardised genetic results from individuals with a firm definite genetic diagnosis
- To perform a comprehensive advanced re-analysis of exome datasets from genetically undiagnosed cases using the diagnostic-grade open source bioinformatics pipeline megSAP (https://github.com/imgag/megSAP). New-sequencing technology will apply in unsolved cases, i.e. children still remaining without a definite diagnosis after comprehensive data re-analysis, using extended combined RNA-seq/genome sequencing (GS) approaches `beyond the exome` and trio GS. If necessary, additional long-read (LR-)GS and complementary RNA-seq of available tissues will be performed.
- To document the quality of life of the children (proxy report) and the family burden (psychological health of parents, perceived burden and social support, impact on work).
- To document care use and patient journey

in children with NPCA/ataxic CP.

4. OUTCOME MEASURES

All examinations are carried out as part of routine care, except for some of the genetic analysis that are flagged as appropriate.

Table 1: Detailed outcome measures

Background information	Relevant family history: Any early onset condition with neurological symptoms in the family, any maldevelopments/ anomalies or intellectual disability in the family, any miscarriages or stillbirths in the mother's history Pregnancy: parents 'age at conception, assisted procreation, hypertensive disorders, preeclampsia, foetal growth restriction, diabetes mellitus, gestational diabetes, maternal TORCH infection, maternal autoimmune conditions, tobacco consumption, pre conceptional BMI, parity, twin -or higher- pregnancy, chorioamnionitis, drugs intake during pregnancy Delivery and complications: mother's age at birth, delivery mode, place of birth, placental abruption, intra partum haemorrhage, other complications Parents' education level and employment status
Peri- and neonatal information	birth date, sex, birthweight, gestational age, Apgar 5 min, arterial umbilical cord PH, meconium-stained amniotic fluid, meconium aspiration, other complications, intra-uterine growth restriction (IUGR), admission to Neonatal Intensive Care Unit (NICU), neonatal seizure (<72h), neonatal neuroimaging results (using NNiCS, http://scpe.edu.eacd.org/scpe/reference-and-training-manual/rtm/neonatal-imaging/classification.php, see § brain images)
Characterization of specific ataxic features	Age at diagnosis Age at assessment Clinical examination: balance/ pointing/ intention tremor/ muscle tone/ reflexes/ additional features/ comments Scale for the Assessment and Rating of Ataxia (SARA; Schmitz-Hübsch *et al*, 2006; Weyer *et al*, 2007) with eight categories - *Gait, Stance, Sitting, Speech disturbance, Finger chase, Nose-finger test, Fast alternating hand movement, Heel-shin slide*, total score ranging from 0 (no ataxia) to 40 (most severe ataxia) Known diagnoses at inclusion in the study
Impairment profile	Age at assessment of all measures (target age: 5 to 8 years) **Cognition:** age at assessment, Intellectual or developmental quotient measured by a test according to current practice (Wechsler, Griffith scales, …) or estimated from clinical observation **Neuropsychiatric disorders:** age at assessment, diagnosis of attention-deficit–hyperactivity disorder (ADHD), diagnosis of

	autism spectrum disorder (ASD) and/or ASD traits, according to DSM-V by a paediatric neurologist or child psychiatrist **Speech and communications abilities**, *assessed at minimum age of 4 years:* Viking Speech Scale (VSS; Virella *et al*, 2016) Communication Function Classification System (CFCS; Hidecker *et al*, 2011); Augmentative and alternative communication **Vision** (bilateral vision loss and blindness, visual field defects, strabismus, nystagmus, refractive errors, optic atrophy) **and hearing** (severity and type of hearing loss on both ears, hearing aids) **Gross** *(assessed at age of independent walking)* **and fine motor function**, *assessed between the 4th and 6th birthdays*: Age at assessment, Gross Motor function Classification System (GMFCS, Palisano *et al*, 1997, https://cparf.org/what-is-cerebral-palsy/severity-of-cerebral-palsy/gross-motor-function-classification-system-gmfcs/), Bimanual Fine Motor Function (BFMF; Elvrum *et al*, 2016) or Manual Ability Classification System (MACS; Eliasson *et al*, 2006; Plasschaert *et al*, 2009, http://www.macs.nu/files/MACS_English_2010.pdf) **Epilepsy:** age at assessment, date of onset, type of epilepsy (focal, generalized, multiple types), EEG (most recent EEG, epileptic discharges: focal, multifocal, generalized, continuous spike-and-wave during sleep (CSWS), normal), seizures frequency (last year, classified as free, seldom, monthly, weekly, daily, cluster, unclear), antiseizure medication (monotherapy, polytherapy – specify, none)
Syndromes and genetic diagnoses	Clinical detailed description in clear text and ICD10/ICD11, and Orphacode code. Disease-causal genomic variation using ISCN (chromosomal aberrations) or HGVS nomenclature / genomic position (molecular findings)
Developmental milestones	Motor - Age (in months) at: (Shortlist) stable head control/grasps with both hands/moves in prone position/sits without support/standing alone/walking alone/squat and rise to feet see Appendix 10 for additions Language - Age (in months) at: (Short list) vocalises /responds/double syllables/mama, papa/points named body parts/identifies pictures/speaks in sentences see Appendix 10 for additions
MRI Brain images (carried out in neonatal & infant periods) (digital)	Age at imaging For children with NPCA/Ataxic CP – Detailed description on images (in DCM tags) – Coding using Neonatal neuroimaging classification system (NNICS; See SCPE Reference &Training Manual,

	http://scpe.edu.eacd.org/scpe/reference-and-training-manual/rtm/neonatal-imaging/classification.php) in neonatal period (in 5 main categories - Maldevelopments, *Predominant white matter injury, Predominant grey matter injury, Miscellaneous, Normal* - and sublevels categories) – and MRI classification system (MRICS; http://scpe.edu.eacd.org/scpe.php; Himmelmann, Horber *et al*, 2017) for images performed in post neonatal period (in 5 main categories - *Maldevelopments, Predominant white matter injury, Predominant grey matter injury, Miscellaneous, Normal* - and sublevels categories) For children with NPCA/ataxic CP **with normal images** (Group E in NNiCS and MRICS) – cerebellar and cerebral volumetry: volumes of brain stem, cerebellum, thalamus, basal ganglia and total brain will be measured and analyzed semi-quantitatively in patients and controls (typically developing age (±6 months)- and sex-matched children) using ITK-SNAP(ITKsnap.org) according to Ekert *et al*. 2016
Data and metadata for genetic analysis	Retrospective genetic data (e.g. exome and/or genome data) where available, with consent, and relevant metadata (e.g. assay type, sequencing platform, sex, Human Phenotype Ontology terms) Prospective next generation sequencing data of the genome
Proxy-reported quality of life of the children	Using the generic, cross-culturally validated instrument KIDSCREEN-27 (Ravens-Sieberer *et al*, 2007), 27 items, 5 domains (physical well-being 5 items; psychological well-being 7 items; autonomy and parent relations 7 items; social support and peers 4 items; school environment 4 items), higher values indicating better quality of life; parent version,10-15 minutes to be filled in; population norm mean 50, sd 10
Psychological health of parents, perceived burden and social support	**Psychological health of parents,** using the General Health Questionnaire (GHQ, Williams and Golberg, 1988; Goldberg *et al*, 1997), 12-item form, total score 0-36 (the higher the score is, the more likely parents are experiencing psychological distress), **Family Impact of Childhood Disability** (FICD, 20 items, 6 dimensions: time, expenditures, social and family relationships, attitudes and stress), responses on four-point Lickert scale, two subscales (negative and positive) scores from 10 to 40, higher scores indicating a higher impact on family; Trute *et al*, 2007; Trute *et al*, 2010)

	+ 4 additional questions (FICD +4) on impact on work, health and relationships within the family (Guyard *et al*, 2012) For both questionnaires, preferably self-report, otherwise interview, both parents
Families contacts to the healthcare system and overall treatment and care	child's first visit at a specialist (pediatric neurologist) after birth; regular appointments at specialist's center; interdisciplinary evaluation; therapies/ frequency; social counseling; disability certificate; support/ medical aids; insurance; special institution for disabled

Questionnaires for parents.

- Kidscreen-27 is open access and available in all the languages needed for the project.
- GHQ 12 is available into the following languages (among others): German, Greek, Hungarian, Dutch for Belgium (Flemish), Norwegian and Swedish. The Danish version available is GHQ 30 so that we should be able to retrieve the GHQ 12 questions from this longer version.
- FICD is open access. The questionnaire is available in English and in French. Translations and back translations according to the international standards will be performed for the remaining countries.
- The 4 additional questions (FICD +4) will also be translated according to international standards and used as independent items.
- The questions exploring families contacts to the healthcare system and overall treatment and care are not issued from validated questionnaires and are extensively presented in annex

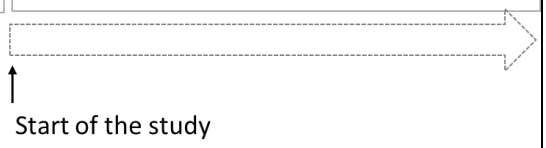
5. STUDY DESIGN

This is a European multicenter historical cohort study, combining data on history, phenomenology, brain imaging and genetic testing, and capturing the impact of the condition for the child and their family. The cohort will be implemented in six reference centres (university hospitals, regional hospitals, out-patient neurology/rehabilitation clinics, and CP registries) in Belgium, Denmark, Germany, Greece, Norway, and Sweden.

The study will consist of a screening period and a data collection period. No follow-up is planned as part of this project.

Table 2. Study schema

History	Screening	Data collection period
Retrospective data collection Family history Pregnancy and delivery Neonatal period Developmental milestones Neonatal & Post natal MRI brain images and results Genetic work-up results Previous diability profile assessments	Eligibility Consent	Child Clinical examination Questionnaires' completion Additional sample for genetic analysis (if neccessary) Parents Questionnaires' completion or interview



Details of schedule of assessments and procedures are provided in section 7

6. ELIGIBILITY CRITERIA

A patient will be eligible for the study only if complying with all of the inclusion/non-inclusion criteria.

Inclusion criteria:

- male or female children,
- confirmed diagnosis of NPCA /ataxic CP defined as an only-onset permanent disorder of movement and posture accompanied by the loss of orderly muscular coordination, so that movements are performed with abnormal force, rhythm and accuracy (SCPE definition, http://scpe.edu.eacd.org/scpe/reference-and-training-manual/rtm/cp-subtypes/ataxic.php)
- aged ≥ 5 years and ≤ 8 years at the time of data collection
- written informed consent of at least one parent or legal representative in accordance to country regulations, and verbal assent of the child if he/she is capable of assessing.

Non-inclusion criterion:

- Children with all other diagnoses of movement or other CP subtypes

Recruitment procedures:

- Consecutive screening and enrolment
- Patients enrolled during routine hospitalisations or care management
- List of centres: see 1st page
- Expected study duration enrolment: approximatively 24 months.

Feasibility:

- prior knowledge of the patients' condition is common
- the data collected are included in the expected follow-up for these children
- no brain imaging in addition to that performed routinely is necessary
- the inclusions will be made by the doctors who care the children on the long run

- a secondary assessment of the sequencing data sets and the possibility of in-depth genetic testing at no cost for the families may be an incentive
- the potential for recruitment is estimated as 3 to 5 children per birth year and per centre.

7. FLOWCHART OF ASSESSMENTS

Duration of the inclusion period: 24 months
Participation duration of each participant: a few days according to organisation of care
Total duration of the research: 36 months (including regulatory processes and analyses of data).

Table 3. Summary table of the data collection

	Children with NPCA/ataxic CP		Parents of children with NPCA/ataxic CP	
Screening period	Assent to the study	R	Informed consent	R
	Check of inclusion/non-inclusion criteria	R		
Prospective data collection	In-depth clinical examination	C		
	Impairment profile	C		
	Genetic analysis results Metadata	C	Genetic analysis results Metadata (if available)	C
	Biological sample for genetic analysis[1]	R	Biological sample for genetic analysis[2]	R
			Quality of life of the child (parent as proxy)	R
			Psychological health of parents, perceived burden	R
Retrospective data collection (medical records)	Background information	C		
	Peri and neonatal information	C		
	Developmental milestones	C		
	Brain MRI (results and images)	C		

R examinations carried out specifically for the research
C examinations carried out as part of routine care

[1] for those lacking a firm molecular diagnosis

[2] optional for affected/unaffected family members of index cases lacking a firm molecular diagnosis

To ensure the welfare of the child, in-depth clinical examination, as well as, where necessary, the taking of blood samples for further genetic analysis, will take place, as far as possible, during consultations scheduled for routine examinations. Children will be accompanied by their parent/legal guardian and examined by their regular doctor. The procedures may be interrupted at any time if the child is no longer comfortable. The reanalysis of brain images or genetic data results already collected will not affect the child's

well-being. Families will be clearly informed that these analyses may help to clarify the diagnosis, but that they may not be useful to them.

8. COLLECTION OF DATA, BIOLOGICAL SAMPLES AND SEQUENCING

Where genetic data (e.g. exome and/or genome data) has already been generated for the subject, these will be used retrospectively for the Artemis study, with consent, and as per local ethics approval.

For expanded genetic analyses, blood samples (EDTA blood, PAX-gene blood) will be taken by a trained healthcare professional following clinical procedures at approved study sites. Whenever possible, samples will be taken together with routine sample collections for diagnosis and disease management. However, there may be some instances when a draw of blood is specifically performed for this study.

Parental genetic data or data from similarly affected siblings have the potential to inform the clinical interpretation of identified variation in a combined analysis (e.g. de novo status or bi-parental inheritance of DNA-variant(s)). If already generated, these data should be made available as well for the reanalysis. For the expanded analysis, samples from family members can be taken (preferably within routine sample collections) and new datasets can be generated. However, availability of data or samples from additional family members is not obligatory and necessary follow-up genetic studies such as carrier testing of segregation analyses can be subsequently conducted in a routine clinical setting at the recruiting center.

The biological samples collected **for genomics and blood transcriptomics** include:

- 2.7 mL for children or adults EDTA-bloods for genomics
- 1-2.5 mL for children or 2.5 mL for adults PAX-gene blood for transcriptomics

Processing of samples according to **ARTEMIS SOP for biospecimens**. Selected symptomatic patients and selected family members will receive sequencing of their whole genome (>35x average coverage) and blood transcriptome conducted by the ARTEMIS study team.

Samples and/or datasets will be labelled with a pseudonymized unique identifier and sent to Artemis project laboratory for further analyses. Sample characteristics (including sampling date, volume, and sample collection conditions) will be stored in the central, password protected (meta)data management platform. The pseudonymized unique identifier will allow the linkage of clinical data with datasets derived from the biological samples. The link between pseudonym and identity of the participant will only be known to the enrolling study site (local pseudonymization) and will be kept secure.

For the purposes of this study, the data and left-over samples will be stored for 10 years after this project has been completed. The left-over samples will be stored for reuse in future research. Due to the rarity of individuals with NPCA, left-over samples from patients with such conditions hold significant value. They will serve as invaluable resources in future research projects on these disorders. At the core of sustainability lies the concept of a

learning healthcare system. It is imperative to gather and archive informative real-world data, such as clinically well-annotated omics results, to facilitate future research endeavors, in particular those that aim to continuously improve our knowledge of patient care. Therefore, the aim at the end of the project is that all data collected, generated and left-over samples will be stored pseudonymised in a permanent archive, or for the duration permitted by national regulation, and ethical approval will be sought for reuse in future research endeavors. The left-over samples will be stored at ARTEMIS project laboratory or returned to the study site for storage upon bilateral agreement.

All data collected and generated shall be stored, as necessary, by the respective ARTEMIS Partners, or ARTEMIS consortium members.

9. ETHICAL CONSIDERATIONS

Prior to child's participation in the study (i.e. before collecting any data specifically required for the study or conducting any assessments not performed routinely in the patient's care), the investigator will fully inform both parents (or the patient's legally acceptable representative) of all pertinent aspects of the study, including the purpose of the study, the nature of the constraints, the reasonably foreseeable risks or inconveniences, and the reasonably expected benefits. The investigator will also inform both parents (or the patient's legally acceptable representative) of their rights in relation to a research study, and stress that their participation is voluntary and that they may refuse to participate or withdraw from the study at any time without prejudice. All necessary information, oral and written notice drawn up in accordance with regulatory instructions, in clear and understandable language adapted to age and intellectual level, will be also delivered to the child by their medical doctor.

A Parent/Patient Information Sheet (PIS) and the informed consent form will be provided to both parents (or the patient's legally acceptable representative) and the child if he/she is capable of understanding. All questions about the study should be answered to the satisfaction of both parents (or the patient's legally acceptable representative) and of the child if he/she is capable of understanding. The investigator will provide both parents (or the patient's legally acceptable representative) ample time (48 hours maximum) and opportunity to inquire about details of the study and to decide whether or not to participate in the study.

Written informed consent will be obtained from at least one parent of the patient (or the patient's legally acceptable representative), depending on the country legal and ethical requirements. If the child is capable of understanding the information, his or her opinion will always be sought (verbal assent if he/she is capable of assessing) and recorded. This will be documented in the medical notes.

10. DATA MANAGEMENT

Data management activities will be under the responsibility of the Methodological Support Unit for Research at the Toulouse University Hospital and at Madrid Hospital 12 de Octubre.

All study relevant data will be collected, entered and stored in a standardized electronic CRF (eCRF) designed by the data manager. The implementation of the eCRF will be entrusted to the Methodological Support Unit for Research of Toulouse University Hospital. Once the eCRF is validated, the study staff, authorized by the investigator coordinator, ensures primary data collection based on the hospital source documents. It is the investigator's responsibility to ensure the accuracy of the data entered in the eCRF and to sign the pages accordingly. The electronic data are validated by the data manager and in case of any inconsistency that are automatically detected by the system, a query is generated and sent to the participating centre that performed the recruitment of the participant.

The detection of inconsistencies is set up from a Data Validation Plan (DVP) that defined checks to be programmed. Plausibility checks will be carried out in part based on already existing knowledge. Additional data validation can be done via listings. Responses to queries will be done directly in the database by the investigators and/or dedicated staff authorized by the investigator. Tracking of changes by the user will be performed.

Software used for data entry, and data validation is CLINSIGHT© (Ennov EDC, ISO 9001:2015 certified for all its operational processes) and for both data validation and coding activity is SAS®. Data are managed in strict compliance with confidentiality rules, access is controlled by SSL certificate and all exchanges are encrypted. Bandwidth and high application availability are contractually guaranteed. The data locking procedure is done once all data are in, validated and all queries are handled. The format of the locked exported data files is defined in accordance with the study statistician. All the data is backed up each day then archived monthly on a secure place (data centres located at two mirror sites, Poitiers and Roubaix, France), offering optimum security conditions. The data server is protected by a firewall and anti-virus software, which are regularly updated.

The MRI brain images of study subjects, performed in the clinical context during the neonatal or infant period, will be sent in pseudonymized form (without identifying information, i.e. no name or birth data), indicating only the age at time of imaging, sex, and an identification number to relate description of condition to the analyses of images. They will be sent in DCM format after parental consent and centralized in Tübingen, included in the UKT GE Centricity PACS (the University of Tübingen's image storage system) into a secure, data protection compliant UKT-cloud infrastructure. This enables high-performance computing resources to be used. An upload link to UKT cloud secured by password access will be provided for each separate collaborating center. Only the study team in Tübingen will have access to uploaded data over a HTTP-secured link for download. Links are only valid for 6 months and have to be extended personally and manually from the Tübingen study members if necessary (for a maximum of 6 months). The preferred upload form is as a zip/tar/7z Data. Data are to be checked by a standard Virus Scanner.

For genetic analyses,
Pseudonymized raw sequencing datasets (FASTQ files) will be transferred via an ftp server together with a core set of metadata necessary for quality control and data interpretation. Files and samples will be stored in-house at the Institute of Medical Genetics and Applied Genomics, University of Tübingen, according to clinical DAkkS-accredited diagnostic standards.
Pseudonymized biosamples for additional genetic studies will be processed according to established standards. For all samples collected within the ARTEMIS study, short-term storage is provided locally in accordance with the required storage conditions until further processing or shipment to the ARTEMIS project laboratory can take place. The samples and data are pseudonymised and linked to a unique code. Details on shipping are given in the ARTEMIS SOP for biospecimens. GS will be performed according to diagnostic standards at the Institute of Medical Genetics and Applied Genomics, University Hospital Tübingen, Germany. Clinical short-read GS has been accredited at the IMGAG by the DAkkS according to DIN EN ISO 15189:2014. Prospectively generated sequences and meta data will be managed according to FAIR principles (e.g. transfer to the German or European Genome Archive) relying on processes that have been established at Tübingen and successfully applied.

11. CONFIDENTIALITY OF DATA

All personal data will be handled in accordance with medical confidentiality and the European Union General Data Protection Regulation (EU GDPR) in conformity with the local laws.

Clinical data and data generated from samples will be transferred and shared, according to EU GDPR data minimization principles, in a pseudonymized form, by the consortium for analysis. These are located within the EU and/or in countries where the EU has recognised an adequate level of data protection.

A pseudonymised unique identifier will be generated for every participant within this study. These pseudonyms will also be used to link biological samples to data. Only the local healthcare team will be able to identify pseudonymized patients followed by their centre via a patient's identification key list, stored in a secure area which is not directly linked to the web-based database. This identifying data does not leave the study site.

The Clinical Data Partners and the ARTEMIS laboratories will be responsible for storing and processing the clinical data, and thus, they will be under the jurisdiction of all relevant European laws, directives, or guidelines. At the local study sites, access to the data is limited to the local study team and is password protected. Third parties will not have access to the data.

All servers involved are managed on a physical network protected by a firewall and a reverse-proxy. Encrypted communication and secure identification of the network web server are enabled by https. Only the sender (study center) and the receiver (ARTEMIS consortium) will have access to readable data. The servers are protected by a professional safety concept. During the data sharing, data are only available in an unidentifiable, pseudonymised form.

As soon as it is possible according to the research or statistical purpose, the personal data will be anonymized for publication.

12. STATISTICAL ASPECTS

12.1. STUDY SIZE

We aim to recruit 50 children.
There was no formal sample size calculation. The planned recruitment for the ARTEMIS cohort was proposed on the basis of the expected number of patients treated in the participating centers over a two-year period and the possibility of carrying out extensive genetic analyses. The extent to which the available data can be considered as representative of the entire population of patients with the condition will be assessed against 'external controls,' i.e. children with ataxic CP born in previous years and included in the SCPE database.

12.2. STATISTICAL ANALYSIS

The study will provide data on the aetiology and pathophysiology of NPCA/ataxic CP, along with insights into the phenotypic diversity, and impact of the condition using patient-reported outcomes. The aim is to better understand patterns within the data using univariate visualization and summary statistics of each field in the raw datasets, and to relate brain images findings and the genetic diagnosis generated to functional parameters (motor, cognition, language) (bivariate analyses). No formal hypothesis testing will be carried out.

13. RULES GOVERNING PUBLICATION

The analysis of the data provided by the investigating centres will carried out by the USMR of the Toulouse University Hospital. A written report will be provided.

Any written or oral communication of the results of the research must receive the prior agreement of the coordinating investigator and the ARTEMIS project coordinator, according to the rules agreed in the agreement.

Any written or oral communication of the results of the research must acknowledged the funders: “This project was supported by the *YOUR NATIONAL AGENCE NAME (project identifier)* and has received funding from the European Union’s Horizon 2020 research and innovation programme under the EJP RD COFUND-EJP N° 825575”

Participants will be informed, at their request, of the overall results of the research.

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15. ANNEXES

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Communication Function Classification System (CFCS)	Hidecker MJC, Paneth N, Rosenbaum PL, Kent RD, Lillie J, Eulenberg JB, Chester K, Johnson B. Michalsen L, Evatt M, Taylor K. Developing and validating the Communication Function Classification System (CFCS) for individuals with	34

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Appendix 1

SARA

Scale for the assessment and rating of ataxia (SARA)

1) Gait	2) Stance
Proband is asked (1) to walk at a safe distance parallel to a wall including a half-turn (turn around to face the opposite direction of gait) and (2) to walk in tandem (heels to toes) without support.	Proband is asked to stand (1) in natural position, (2) with feet together in parallel (big toes touching each other) and (3) in tandem (both feet on one line, no space between heel and toe). Proband does not wear shoes, eyes are open. For each condition, three trials are allowed. Best trial is rated.
0 Normal, no difficulties in walking, turning and walking tandem (up to one misstep allowed) **1 Slight difficulties, only visible when walking 10 consecutive steps in tandem** **2 Clearly abnormal, tandem walking >10 steps not possible** **3 Considerable staggering, difficulties in half-turn, but without support** **4 Marked staggering, intermittent support of the wall required** **5 Severe staggering, permanent support of one stick or light support by one arm required** **6 Walking > 10 m only with strong support (two special sticks or stroller or accompanying person)** **7 Walking < 10 m only with strong support (two special sticks or stroller or accompanying person)** **8 Unable to walk, even supported**	**0 Normal, able to stand in tandem for > 10 s** **1 Able to stand with feet together without sway, but not in tandem for > 10s** **2 Able to stand with feet together for > 10 s, but only with sway** **3 Able to stand for > 10 s without support in natural position, but not with feet together** **4 Able to stand for >10 s in natural position only with intermittent support** **5 Able to stand >10 s in natural position only with constant support of one arm** **6 Unable to stand for >10 s even with constant support of one arm**
Score	**Score**
3) Sitting	**4) Speech disturbance**
Proband is asked to sit on an examination bed without support of feet, eyes open and arms outstretched to the front.	Speech is assessed during normal conversation.
0 Normal, no difficulties sitting >10 sec **1 Slight difficulties, intermittent sway** **2 Constant sway, but able to sit > 10 s without support** **3 Able to sit for > 10 s only with intermittent support** **4 Unable to sit for >10 s without continuous support**	**0 Normal** **1 Suggestion of speech disturbance** **2 Impaired speech, but easy to understand** **3 Occasional words difficult to understand** **4 Many words difficult to understand** **5 Only single words understandable** **6 Speech unintelligible / anarthria**
Score	**Score**

5) Finger chase

Rated separately for each side
Proband sits comfortably. If necessary, support of feet and trunk is allowed. Examiner sits in front of proband and performs 5 consecutive sudden and fast pointing movements in unpredictable directions in a frontal plane, at about 50 % of proband´s reach. Movements have an amplitude of 30 cm and a frequency of 1 movement every 2 s. Proband is asked to follow the movements with his index finger, as fast and precisely as possible. Average performance of last 3 movements is rated.

- **0 No dysmetria**
- **1 Dysmetria, under/ overshooting target <5 cm**
- **2 Dysmetria, under/ overshooting target < 15 cm**
- **3 Dysmetria, under/ overshooting target > 15 cm**
- **4 Unable to perform 5 pointing movements**

Score	Right	Left
mean of both sides (R+L)/2		

6) Nose-finger test

Rated separately for each side
Proband sits comfortably. If necessary, support of feet and trunk is allowed. Proband is asked to point repeatedly with his index finger from his nose to examiner's finger which is in front of the proband at about 90 % of proband's reach. Movements are performed at moderate speed. Average performance of movements is rated according to the amplitude of the kinetic tremor.

- **0 No tremor**
- **1 Tremor with an amplitude < 2 cm**
- **2 Tremor with an amplitude < 5 cm**
- **3 Tremor with an amplitude > 5 cm**
- **4 Unable to perform 5 pointing movements**

Score	Right	Left
mean of both sides (R+L)/2		

7) Fast alternating hand movements

Rated separately for each side
Proband sits comfortably. If necessary, support of feet and trunk is allowed. Proband is asked to perform 10 cycles of repetitive alternation of pro- and supinations of the hand on his/her thigh as fast and as precise as possible. Movement is demonstrated by examiner at a speed of approx. 10 cycles within 7 s. Exact times for movement execution have to be taken.

- **0 Normal, no irregularities (performs <10s)**
- **1 Slightly irregular (performs <10s)**
- **2 Clearly irregular, single movements difficult to distinguish or relevant interruptions, but performs <10s**
- **3 Very irregular, single movements difficult to distinguish or relevant interruptions, performs >10s**
- **4 Unable to complete 10 cycles**

Score	Right	Left
mean of both sides (R+L)/2		

8) Heel-shin slide

Rated separately for each side
Proband lies on examination bed, without sight of his legs. Proband is asked to lift one leg, point with the heel to the opposite knee, slide down along the shin to the ankle, and lay the leg back on the examination bed. The task is performed 3 times. Slide-down movements should be performed within 1 s. If proband slides down without contact to shin in all three trials, rate 4.

- **0 Normal**
- **1 Slightly abnormal, contact to shin maintained**
- **2 Clearly abnormal, goes off shin up to 3 times during 3 cycles**
- **3 Severely abnormal, goes off shin 4 or more times during 3 cycles**
- **4 Unable to perform the task**

Score	Right	Left
mean of both sides (R+L) / 2		

Appendix 2

Gross Motor Function Classification (GMFCS) between the 4th and 6th birthdays:
For more details, please see https://cparf.org/what-is-cerebral-palsy/severity-of-cerebral-palsy/gross-motor-function-classification-system-gmfcs/

Level I: Children walk indoors and outdoors, and climb stairs. Emerging ability to run and jump.

Level II: Children walk without the need for any assistive mobility device indoors and for short distances on level surfaces outdoors. Children climb stairs holding onto a railing but are unable to run or jump.

Level III: Children sit on a regular chair but may require pelvic or trunk support to maximize hand function. Children walk with an assistive mobility device on level surfaces and may climb stairs with assistance from an adult. Children frequently are transported when travelling for long distances or outdoors on uneven terrain.

Level IV: Children may at best walk short distances with a walker and adult supervision but have difficulty turning and maintaining balance on uneven surfaces. Children are transported in the community. Children may achieve self-mobility using a power wheelchair.

Level V: Physical impairments restrict voluntary control of movement and the ability to maintain antigravity head and trunk postures. All areas of motor function are limited.

Appendix 3

Bimanual Fine Motor Function

Information for users

The Bimanual Fine Motor Function (BFMF) classifies fine motor function in children with cerebral palsy. BFMF describes five levels of fine motor function and covers the entire spectrum of limitations in fine motor function that may be found among children with various cerebral palsy sub-types. Level I includes children with minor limitations and levels IV-V describe children with severe functional limitations.

BFMF can be used for children aged 3–18 years, but ability to perform in-hand-manipulation must be considered in relation to the child's age. Naturally there is a difference in how a three-year old should be able to manipulate objects, compared with a teenager. For the youngest children the ability to rotate an object in the fingers cannot be expected, but the child may transform an object from the fingers to the palm. If ability to perform in-hand manipulation cannot be established for the youngest children, the BFMF level should be determined according to ability to grasp.

The five levels in BFMF form an ordinal scale, which means that the levels are 'ordered' but differences between levels are not necessarily equal, and each level includes children with relatively varied function. It is therefore unlikely that BFMF is sensitive to changes after an intervention.

The new BFMF version 2.0 offers explanatory figures and precise descriptions of the fine motor function levels to facilitate the use of the classification system.

Without restriction

In-hand-manipulation: with speed and precision
Grasps all kind of objects with speed and precision

Restriction in advanced fine motor skills

In-hand manipulation: reduced speed and precision
Grasps objects from table; reduced speed and precision

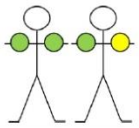
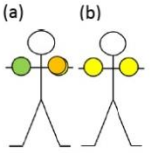
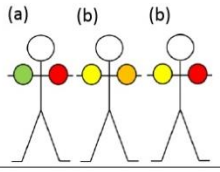
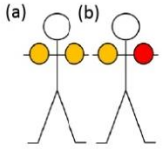
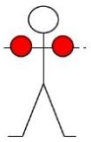
Can grasp and hold, no in-hand manipulation

No in-hand manipulation, may manipulate against table or body
Grasps selected objects from the table and other objects from an adapted position, reduced speed and precision

May hold

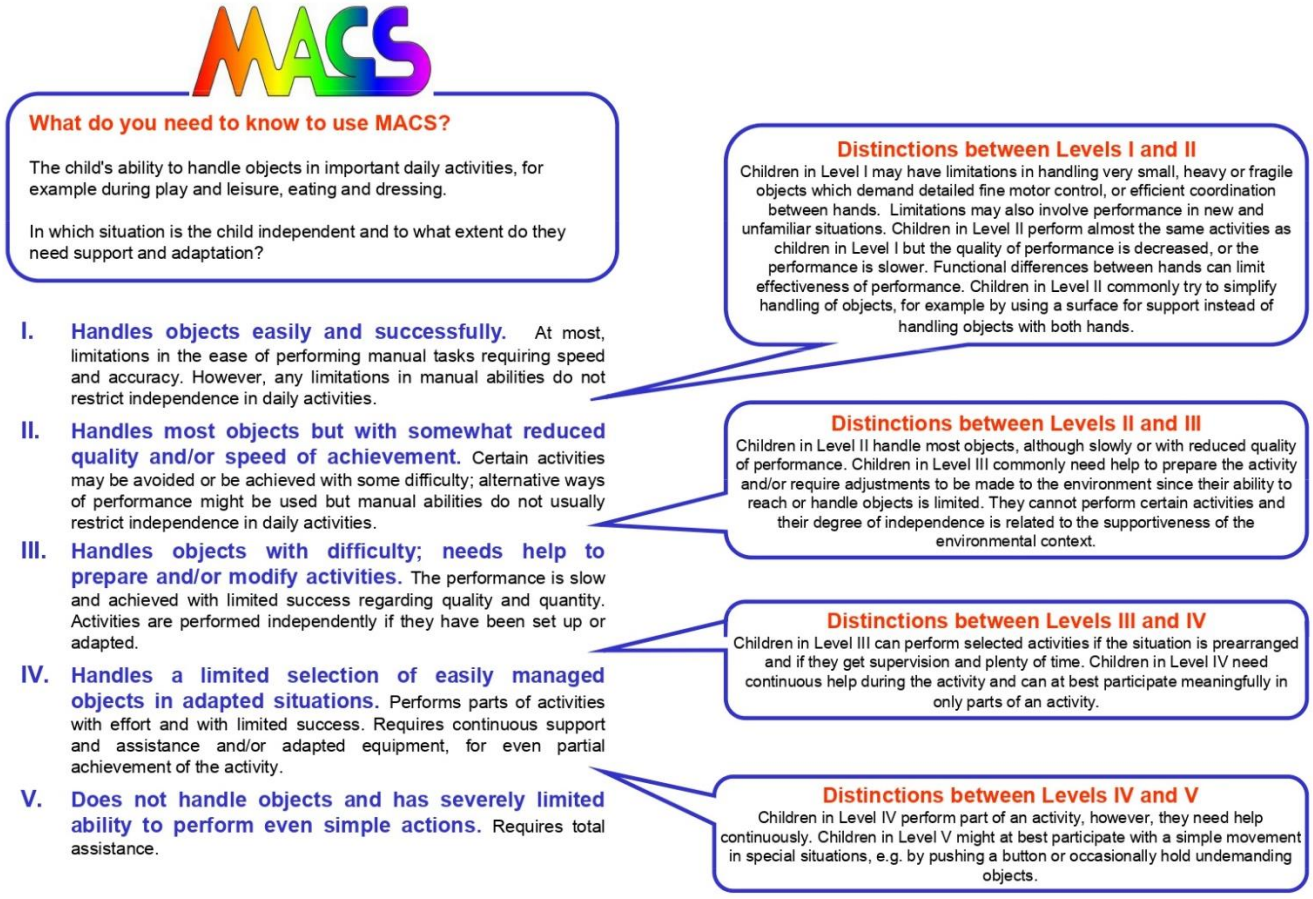
No manipulation of objects
Cannot grasp objects from the table may grasp a few objects from an adapted position May hold object placed in hand

BFMF version 2.0

Level I One hand: manipulates without restrictions. The other hand: manipulates without restrictions or limitations in more advanced fine motor skills	
Level II (a) One hand: manipulates without restrictions. The other hand: only ability to grasp or hold (b) Both hands: limitations in more advanced fine motor skills	
Level III (a) One hand: manipulates without restrictions. The other hand no functional ability (b) One hand: limitations in more advanced fine motor skills. The other hand: only ability to grasp or worse	
Level IV (a) Both hands: only ability to grasp (b) One hand: only ability to grasp. The other hand: only ability to hold or worse	
Level V Both hands: only ability to hold or worse	

Appendix 4

Manual Ability Classification System



Appendix 5

Viking Speech Scale, 2010

Descriptions of children's speech

I. Speech is not affected by motor disorder.

Children in Level I will be following the usual pattern of speech development. They may have some speech immaturities, similar to other children of their age/developmental level.

Children in Level II have speech that is affected by their motor disorder. Their speech is usually understandable but is not following the usual pattern of development and does not sound like children of their age/developmental level.

II. Speech is imprecise but usually understandable to unfamiliar listeners.

Loudness of speech is adequate for one to one conversation. Voice may be breathy or harsh sounding but does not impair intelligibility. Articulation is imprecise; most consonants are produced, but deterioration is noticeable in longer utterances. Although difficulties are noticeable, speech is usually understandable to unfamiliar listeners ***out of context***.

Children in Level II have speech that is affected by their motor disorder. Their speech may sound weak, slushy, slurred or loudness may be inappropriate but is usually understandable without contextual cues.

Children in Level III will usually have speech that is severely affected by their motor disorder at multiple levels (e.g. breath control, vocal cord movement/voice, articulation). The severe difficulties that children experience in controlling each level act together to make the children's speech very difficult to understand without contextual cues.

III. Speech is unclear and not usually understandable to unfamiliar listeners out of context.

Difficulties controlling breathing for speech - can produce one word per utterance and/or speech is sometimes too loud or too quiet to be understood. Voice may be harsh sounding; pitch may change suddenly. Speech may be markedly hyper nasal. A very small range of consonants are produced. The severity of the difficulties makes the speech difficult to understand out of context.

Children in Level III use speech as a method of communication. Their speech may be understandable to unfamiliar adults when they speak in single words or occasional words may be understood within longer phrases.

Children in Level IV may produce vocalisations but cannot produce any words or word approximations that unfamiliar listeners can understand out of context.

IV. No understandable speech.

Appendix 6

Communication Function Classification System (CFCS)

Communication Function Classification System (CFCS) for Individuals with Cerebral Palsy

I. Effective Sender and Receiver with unfamiliar and familiar partners. The person independently **alternates between sender and receiver** roles with most people in most environments. The communication occurs easily and at a **comfortable pace** with both **unfamiliar and familiar conversational partners**. Communication misunderstandings are quickly repaired and do not interfere with the overall effectiveness of the person's communication.

II. Effective but slower paced Sender and/or Receiver with unfamiliar and/or familiar partners. The person independently **alternates between sender and receiver** roles with most people in most environments, but the **conversational pace is slow** and may make the communication interaction more difficult. The person may need extra time to understand messages, compose messages, and/or repair misunderstandings. Communication misunderstanding are often repaired and do not interfere with the eventual effectiveness of the person's communication with both **unfamiliar and familiar partners**.

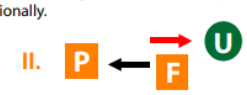
III. Effective Sender and Receiver with familiar partners. The person **alternates between sender and receiver roles with familiar** (but not unfamiliar) conversational partners in most environments. Communication is **not consistently effective** with most **unfamiliar partners**, but is **usually effective** with **familiar partners.**

IV. Inconsistent Sender and/or Receiver with familiar partners. The person does **not** consistently alternate **sender and receiver** roles. This type of inconsistency might be seen in different types of communicators including: a) an occasionally effective sender and receiver; b) an effective sender but limited receiver; c) a limited sender but effective receiver. Communication is **sometimes effective** with **familiar partners**.

V. Seldom Effective Sender and Receiver even with familiar partners. The person is limited as both a **sender and a receiver**. The person's communication is difficult for most people to understand. The person appears to have limited understanding of messages from most people. Communication is **seldom effective** even with **familiar partners**.

Key
P Person with CP
U Unfamiliar Partner
F Familiar Partner
Effective
Less effective

The difference between Levels I and II is the **pace** of the conversation. **In Level I**, the person communicates at a **comfortable** pace with little or no delay in order to understand, compose a message, or repair a misunderstanding. **In Level II**, the person **needs extra time** at least occasionally.



The differences between Levels II and III concern **pace and the type of conversational partners**. **In Level II**, the person is an effective sender and receiver with all conversational partners, but pace is an issue. **In Level III**, the person is consistently effective with familiar conversational partners, but not with most unfamiliar partners.

The difference between Levels III and IV is **how consistently the person alternates between sender and receiver roles with familiar partners**. **In Level III**, the person is generally able to communicate with familiar partners as a sender *and* as a receiver. **In Level IV**, the person does not communicate with familiar partners consistently. This difficulty may be in sending and/or receiving.

The difference between Levels IV and V is the **degree of difficulty that the person has when communicating with familiar partners**. **In Level IV**, the person has some success as an effective sender and/or an effective receiver with familiar partners. **In Level V**, the person is rarely able to communicate effectively, even with familiar partners.

3

Appendix 7

Kidscreen -27 parental version

Dear Parents,
How is your child? How does she/he feel? This is what we would like to know from you.

Please answer the following questions to the best of your knowledge, ensuring that the answers you give reflect the perspective of your child. Please try to remember your child's experiences over the last week...

1. Physical Activities and Health

1. **In general, how would your child rate her/his health?**
   - ○ excellent
   - ○ very good
   - ○ good
   - ○ fair
   - ○ poor

Thinking about the last week ...	not at all	slightly	moderately	very	extremely
2. Has your child felt fit and well?	○	○	○	○	○
3. Has your child been physically active (e.g. running, climbing, biking)?	○	○	○	○	○
4. Has your child been able to run well?	○	○	○	○	○

Thinking about the last week ...	never	seldom	quite often	very often	always
5. Has your child felt full of energy?	○	○	○	○	○

2. General Mood and Your Child's Feelings

Thinking about the last week...	not at all	slightly	moderately	very	extremely
1. Has your child felt that life was enjoyable?	○	○	○	○	○

Thinking about the last week...	never	seldom	quite often	very often	always
2. Has your child been in a good mood?	○	○	○	○	○
3. Has your child had fun?	○	○	○	○	○

Thinking about the last week...	never	seldom	quite often	very often	always
4. Has your child felt sad?	○	○	○	○	○
5. Has your child felt so bad that he/she didn't want to do anything?	○	○	○	○	○
6. Has your child felt lonely?	○	○	○	○	○
7. Has your child been happy with the way he/she is?	○	○	○	○	○

3. Family and Your Child's Free Time

Thinking about the last week...

	never	seldom	quite often	very often	always
1. Has your child had enough time for him/herself?	○	○	○	○	○
2. Has your child been able to do the things that he/she wants to do in his/her free time?	○	○	○	○	○
3. Has your child felt that his/her parent(s) had enough time for him/her?	○	○	○	○	○
4. Has your child felt that his/her parent(s) treated him/her fairly?	○	○	○	○	○
5. Has your child been able to talk to his/her parent(s) when he/she wanted to?	○	○	○	○	○
6. Has your child had enough money to do the same things as his/her friends?	○	○	○	○	○
7. Has your child felt that he/she had enough money for his/her expenses?	○	○	○	○	○

4. Friends

Thinking about the last week...

	never	seldom	quite often	very often	always
1. Has your child spent time with his/her friends?	○	○	○	○	○
2. Has your child had fun with his/her friends?	○	○	○	○	○
3. Have your child and his/her friends helped each other?	○	○	○	○	○
4. Has your child been able to rely on his/her friends?	○	○	○	○	○

5. School and Learning

Thinking about the last week...

	not at all	slightly	moderately	very	extremely
1. Has your child been happy at school?	○	○	○	○	○
2. Has your child got on well at school?	○	○	○	○	○

Thinking about the last week...

	never	seldom	quite often	very often	always
3. Has your child been able to pay attention?	○	○	○	○	○
4. Has your child got along well with his/her teachers?	○	○	○	○	○

Appendix 8

GHQ12

Introduction: "In the next few questions we would like to know if you have experienced any medical complaints, and how your health has been in general, over the past few weeks".

1. Over the past few weeks, have you been able to concentrate on whatever you're doing? (0 = better than usual, 1 = same as usual, 2 = less than usual, 3 = much less than usual),
2. Over the past few weeks, have you felt that you are playing a useful part in things? (0 = more so than usual, 1 = same as usual, 2 = less so than usual, 3 = much less than usual),
3. Over the past few weeks, have you felt capable of making decisions about things? (0 = more so than usual, 1 = same as usual, 2 = less so than usual, 3 = much less than usual),
4. Over the past few weeks, have you been able to enjoy your normal day-to-day activities? (0 = more so than usual, 1 = same as usual, 2 = less so than usual, 3 = much less than usual),
5. Over the past few weeks, have you been able to face up to your problems? (0 = more so than usual, 1 = same as usual, 2 = less so than usual, 3 = much less than usual),
6. Over the past few weeks, all things considered, have you been feeling reasonably happy? (0 = more so than usual, 1 = same as usual, 2 = less so than usual, 3 = much less than usual),
7. Over the past few weeks, have you lost much sleep because of worry? (0 = not at all, 1 = no more than usual, 2 = rather more than usual, 3 = much more than usual),
8. Over the past few weeks, have you felt constantly under strain? (0 = not at all, 1 = no more than usual, 2 = rather more than usual, 3 = much more than usual),
9. Over the past few weeks have you felt you could not overcome your difficulties? (0 = not at all, 1 = no more than usual, 2 = rather more than usual, 3 = much more than usual),
10. Over the past few weeks, have you been feeling unhappy and depressed? (0 = not at all, 1 = no more than usual, 2 = rather more than usual, 3 = much more than usual),
11. Over the past few weeks, have you been losing confidence in yourself? (0 = not at all, 1 = no more than usual, 2 = rather more than usual, 3 = much more than usual),
12. Over the past few weeks, have you been thinking of yourself as a worthless person? (0 = not at all, 1 = no more than usual, 2 = rather more than usual, 3 = much more than usual).

Appendix 9

Family Impact of Childhood Disability. FICD +4

‘‘In your view, what consequences have resulted from having a child with a disability in your family?’’

1. There have been extraordinary time demands created in looking after the needs of the child with disability.(N)

2. There has been unwelcome disruption to ‘‘normal’’ family routines.(N)

3. The experience has made us more spiritual.(P)

4. It has led to additional financial costs.(N)

5. Family members do more for each other than they do for themselves.(P)

6. Having a child with disability has led to an improved relationship with spouse.(P)

7. It has led to limitations in social contacts outside the home.(N)

8. The experience has made us come to terms with what should be valued in life.(P)

9. Chronic stress in the family has been a consequence.(N)

10. This experience has helped me appreciate how every child has a unique personality and special talents.(P)

11. We have had to postpone or cancel major holidays.(N)

12. Family members have become more tolerant of differences in other people and generally more accepting of physical or mental differences between people.(P)

13. It has led to a reduction in time parents could spend with their friends.(N)

14. The child’s disability has led to positive personal growth, or more strength as a person in mother and/or father.(P)

15. Because of the situation, parents have hesitated to phone friends and acquaintances.(N) 16. The experience has made family members more aware of other people’s needs and struggles which are based on a disability.(P)

17. The situation has led to tension with spouse.(N)

18. The experience has taught me that there are many special pleasures from a child with disabilities.(P)

19. Because of the circumstances of the child’s disability, there has been a postponement of major purchases.(N)

20. Raising a disabled child has made life more meaningful for family members.(P)

A. The child's disability has resulted in a change in the professional situation of one or both of the parents (i.e. reduction in working time or job loss).(+)

B. Having a disabled child has led to at least one of the parents having to revise and reduce their professional ambitions.(+)

C. It has resulted in a decrease in time that the family members can spend with each other, not counting the time spent with the disabled child.(+)

D. The physical health of the family members has been affected by the situation.(+)

(N) Item included in negative family impact scale;

(P) Item included in positive family impact scale;

(+) Additional item

Appendix 10

Developmental milestones (90th percentile)

In grey are items for a short version

Motor	**Age**
In ventral suspension head in line with body	1 month
Stable head control	3 months
Grasps with both hands (palmar grasp)	5-6 months
Sits without support	7.5 months
Moves in prone position (rolling, creeping etc.)	10 months
Standing with assistance	10 months
Crawls on hands and knees	11 months
Standing alone	14-15 months
Walking alone	15-16 months
runs; squats to pick up, rises to feet alone	2 years
Stands on one leg for some seconds	3 years
Walks stairs without holding on, alternating	4 years
Stands on one leg for at least 5 sec. or hops on one leg at least 5 times	5 years

*When two ages are given, references (*3. and 5.) differ

Language	**Age** *Boys slower than girls - indicated is average*
Guttural noises	1 month
Vocalizes spontaneously	3 months
Vocalizes in response	5.5 months
Chains of syllables (wawawa)	9 months
Imitates language ‚conversational cadences', double syllables (mamam)	12 months
'mama' and 'papa' + 1 additional word	18 months
Points named body parts	20 months
2-word sentences; Identifies 2 pictures	2 years
4- word sentences;	3 years
Tells experiences	3 years

Appendix 11

Questions about the family's contacts to the healthcare system and overall treatment and care

1. When was your child's first visit at a specialist (pediatric neurologist) after birth?
2. Did your responsible pediatrician send you there? If not, who sent you there?
3. Do you have regular appointments at your specialist's center? If yes, how many times a year?
4. Is your child evaluated interdisciplinary which means by different professions as physician, physiotherapist, speech therapist, occupational therapist? If yes, which professions are available?
5. Did the pediatric neurologist recommend special therapies? If yes, does your child get regular therapies? If yes, which ones and how often (e. g. 1x/week)?
6. Do you have contact persons regarding questions concerning the therapies?
7. Do you receive social counseling? Do you have a contact person regarding socio-legal questions?
8. Does your child have a disability certificate? If yes, when did you apply for it? (time after diagnosis)
9. Do you get support for the care of your child by e. g. nursing service, care products (paid by the insurance) or care money?
10. Does your child get medical aids?
11. Does you child get special medications?
12. Has your insurance ever refused to pay for therapies or medical aids or medications recommended by the specialist/ pediatric neurologist/ interdisciplinary team?
13. Does your child attend an institution for disabled children (integrative kindergarten/ special kindergarten or school/ inclusive school/ regular school with inclusion assistant)?