Recurrent musculoskeletal pain in paediatric cerebral palsy

Relations to mental health, health-related quality of life and participation

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Table of contents

Acknowledgements ........................................................................................................... 4
Abstract .......................................................................................................................... 6
List of papers ............................................................................................................... 8
List of abbreviations ...................................................................................................... 9
1 Introduction ............................................................................................................... 10

2 Background ............................................................................................................... 11
  2.1 The biopsychosocial approach to health ................................................................. 11
  2.2 Cerebral Palsy ........................................................................................................ 12
    2.2.1 Definition and diagnosis .................................................................................. 12
    2.2.2 Classification .................................................................................................. 13
      2.2.2.1 Type ........................................................................................................ 15
      2.2.2.2 Functional effect of motor impairment ..................................................... 15
      2.2.2.3 Accompanying impairments .................................................................... 16
    2.2.3 Quality of Life and Health Related Quality of Life ..................................... 21
    2.2.4 Participation and the International Classification of Functioning, Disability and Health .......................................................... 24

3 Aims of the study ........................................................................................................ 27

4 Methods ...................................................................................................................... 28
  4.1 Study design and study population ....................................................................... 28
  4.2 Enrolment of participants .................................................................................... 28
  4.3 Measures ................................................................................................................ 29
    4.3.1 Outcomes ....................................................................................................... 30
    4.3.2 Explanatory variables ..................................................................................... 35
  4.4 Statistics .................................................................................................................. 36
  4.5 Ethics ...................................................................................................................... 37

5 Summary of results, papers I-IV ............................................................................. 38

6 Discussion .................................................................................................................... 41
  6.1 Discussion of major findings .................................................................................. 41
  6.2 Methodological issues ............................................................................................ 49
    6.2.1 Study design and stability of findings ............................................................. 49
    6.2.2 Representativeness of the study population ................................................... 49
    6.2.3 Measures – validity and overlap ..................................................................... 51
  6.3 Implications ............................................................................................................. 53
    6.3.1 Clinical implications ....................................................................................... 53
    6.3.2 Research implications ...................................................................................... 53
    6.3.4 Concluding remark ......................................................................................... 54

References ...................................................................................................................... 55

Erratum

Papers I – IV

3
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My deep frustration as a clinical consultant started the process. Oslo University Hospital (OUS) was early in offering intrathecal baclofen therapy (CITB) to children, and the child habilitation unit was involved in the selection of patients together with the neurosurgeons. A protocol aimed to assess the impact of CITB on the first 50 patients with cerebral palsy (CP) had been set up, and I was given the opportunity to present the results. Trying to do this revealed more questions than answers both on how to select the right patients and how to assess the impact of treatment - in other terms- what frames of reference should guide our understanding and evidence gathering about patient well-being, and what instruments should we use to assess these outcomes? The struggle with these questions brought me to neurologist Professor Ola H. Skjeldal and physiotherapist PhD Reidun B. Jahnsen who were able to translate a clinical based multi-dimensional approach into research questions. Through this process, pain relieve remained as an important outcome measure for CITB. At that time, Reidun Jahnsen had already published her innovative work on pain in adults with CP, and together we proceeded to gather evidence on pain in another group of children with CP; those who completed 3-Dimensional gait analyses at OUS. This time, the struggles on the same questions directed me to child psychiatrist Professor Trond H. Diseth as head of the OUS department with ongoing scientific work on pain in children. A most fruitful collaboration developed.

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Thank you to our almost grown-up children Jon, Espen and Else who of course are the constantly reminders of the real qualities of life. In addition, I really appreciate their cheering for their mother being a student. Also, thank you to my father, whose innovative reports on his own chronic health condition still disclose new relevant outcome measures and new aspects of Health Related Quality of Life (HRQL). His steady approach is: “My dear daughter, you ought to understand this, even though you are a physician.”
Abstract

Background

Cerebral palsy (CP) is a disorder of movement and posture resulting from disturbances in the immature brain. Accompanying impairments including secondary musculoskeletal problems and mental health problems are common, and impairment is life-long. Thus, from a health care perspective, CP is an excellent model disease for asking what frames of reference should guide our understanding and evidence gathering about patient well-being, and what instruments should we use to assess these outcomes.

Objectives

The overall aim of the study was to explore how recurrent musculoskeletal pain relates to mental health problems, Health Related Quality of Life (HRQL) and participation in children with CP.

Methods

In study A, children with CP 8-18 years old were recruited from the South-West of Norway (n=75) and from the gait laboratory at Oslo University Hospital (n=78). All levels of motor impairment were represented. Clinical assessment, interview (child and parents together), and completion of questionnaires (child and parents separately) were performed. The interviewer asked for any kind of recurrent pain. If present, pain characteristics were explored and followed by professional judgement whether recurrent pain probably was of musculoskeletal origin and related to CP (RMP). Characteristics of RMP were regarded as localisation to muscles and/or joints, occurrence during or after exercise and dull or aching quality. Mental health problems, HRQL and participation were assessed by questionnaires (Strengths and Difficulties Questionnaire, Pediatric Quality of Life Inventory and Assessment of Life Habits respectively, in addition to General Health Questionnaire for parental mental health). In study B, children with CP 8-18 years (n=38) that started continuous intrathecal baclofen therapy (CITB) at Oslo University Hospital were assessed the day before implantation of a pump for baclofen delivery and after 6 and 18 months of treatment. Assessment consisted of clinical workup and parental interview. In cases of pain (33 children), this was assessed to be RMP before the child was accepted for CITB. Outcomes and explanatory variables throughout the study are discussed in relation to the ICF (International Classification of Function) that is WHO’s framework for measuring health and disability.
Results
In study A, 95 children (62%) experienced RMP. Age above 14 years was the only significant predictor (OR 2.7). Children reported pain severity to be moderate. Parents reported pain to be more severe and with higher impact on sleep than their children did. Children and parents reported similar impact of pain on general activity and walking.

Eighty-three pairs of children and mothers reported mental health problems and HRQL. Mothers in addition reported their own mental health. Self-reported mental health and HRQL were both better than proxy-reported. RMP was associated with more mental health problems and reduced HRQL in self-reports, but not in proxy-reports. Mothers reported that more own mental problems were associated with more child mental problems and reduced child HRQL. Correlation (ICC) between mental health problems and psychosocial HRQL was ≥0.90 for both child and maternal report.

One hundred and five parents reported child participation. RMP and more mental health problems were both associated with reduced participation. More parental mental health problems were associated with reduced parental satisfaction with the child’s accomplishment of daily activities.

In study B, 35 children continued CITB for 18 months. Reduced pain and improved sleep occurred within 6 months of treatment. Social participation improved within 6 months and continued to improve until 18 months.

Conclusions
RMP is the main pain problem in paediatric CP. Systematic assessment of HRQL is suggested as a tool to broaden the scope of the consultation in (re)habilitation towards both pain and psychosocial issues. The child’s own perspectives on pain, mental health and HRQL should be recorded when possible in addition to that of the parents. The ICF concept of participation needs to be further clarified and operationalised; still the ICF reference frame is useful in both clinical work and research because of its comprehensiveness including the bio-psycho-social model and its non-categorical approach to health. Studies of children’s narratives on pain experiences and studies on self-reported mental health in CP are warranted.
List of papers


II. Ramstad K, Jahnsen R, Skjeldal OH, Diseth TH: “Mental health, health related quality of life and recurrent musculoskeletal pain in children with cerebral palsy 8-18 years old.” Disability & Rehabilitation 2012 Feb 22 (Epub ahead of print)


**List of abbreviations**

AED = Antiepileptic drugs  
BPI = Brief Pain Inventory  
CBCL = Child Behavior Checklist  
CFCS = Communication Function Classification System  
CHQ = Child Health Questionnaire  
CI = Confidence Interval  
CITB = Continuous Intrathecal Baclofen Therapy  
CP = Cerebral Palsy  
FDA = Food and Drug Administration  
FLACC = Face Legs Activity Cry Consolability Scale  
GHQ = General Health Questionnaire  
GMFCS = Gross Motor Function Classification System  
HRQL = Health related Quality of Life  
ICC = Intraclass Correlation  
ICD-10 = International Statistical Classification of Diseases and Related Health Problems, 10th Revision  
ICF = International Classification of Functioning, Disability and Health  
ICF-CY = International Classification of Functioning, Disability and Health – Children and Youth Version  
IQR = Interquartile Range  
LIFE-H = Assessment of Life Habits  
MACS = Manual Ability Classification System  
MRI = Magnetic Resonance Imaging  
NRS = Numeric Rating Scale  
OR = Odds Ratio  
PedsQL = Pediatric Quality of Life Inventory  
PRO = Patient Related Outcome  
QoL = Quality of Life  
RMP = Recurrent Musculoskeletal Pain  
SCPE = Surveillance of Cerebral Palsy in Europe  
SD = Standard Deviation  
SDQ = Strengths and Difficulties Questionnaire  
TDS = Total Difficulties Score  
WHO = World Health Organisation
1. Introduction

Cerebral palsy (CP) describes “a group of permanent disorders of the development of movement and posture, causing activity limitations that are attributed to non-progressive disturbances in the developing foetal or infant brain. The motor disorders of CP are often accompanied by disturbances of sensation, cognition, communication, perception, and behaviour, in addition to epilepsy and secondary musculoskeletal problems”(1). This definition of CP was launched in 2006 by an international expert group. The definition is obviously not in accordance with the traditional biomedical model where disease is conceptualised in a single cause, single effect model. As CP has no cure and life expectancy approaches normality in our society (2), the overall perspective is that a person with CP will have to cope with a lifelong impairment. CP is also relatively common with an estimated prevalence of about 2.1 per 1000 live births in developed countries (3-8). From a health care perspective, this makes CP an excellent model disease for asking what frames of reference should guide our understanding and evidence gathering about patient well-being, and what instruments should we use to assess these outcomes.
2. Background

2.1 The biopsychosocial approach to health

In his classical work from 1977, George Engel challenged the biomedical model of disease because “it leaves no room within its framework for the social, psychological, and behavioural dimensions of illness.” A biopsychosocial model was proposed that provides “a blueprint for research, a framework for teaching, and a design for action in the real world of health care” (9). He argued that medicine historically has strong humanistic roots, and that biomedicine has categorically excluded the subjective reports of the patients (10). Further, Engel advocated vigorously that subjective data need not violate the conventional requirement for scientific respectability. Referring to system theory, he presented the biopsychosocial model as a scientific model constructed to take into account the missing dimensions of the biomechanical model (9-11). Ancient Rufus of Ephesus was credited the first document solely about the values of the information patients can provide:

“It is important to ask questions of patients because with the help of these questions one will know more exactly some of the things that concern disease, and one will treat the disease better.”

Rufus of Ephesus, 1000 A.D.

(Sigerist, 1951, pp.326-327)

The biopsychosocial model is incorporated in the World Health Organisation’s (WHO’s) International Classification of Functioning, Disability and Health, known more commonly as ICF (12). The ICF is WHO’s framework for measuring health and disability at both individual and population levels and it shifts the focus from cause to impact of disease. A key concept is participation, defined as a person’s involvement in life situations. In contrast, the WHO’s International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) (13), gives users an etiological framework for the classification of diseases. The ICF and the ICD-10 are complementary both in this respect and because the ICF offers a dimensional approach to health contrary to the ICD-10 which approach to disease is the categorical. While the ICF is used on the initiative of researchers and clinicians working in the fields of (re)habilitation and developmental medicine, the ICD-10 is the common metric used in Norwegian hospitals by prescription from the Norwegian health authorities. The ICF and its relations to the ICD-10 are further discussed in paragraph 2.2.4.
Returning to the definition of CP from 2006 (1); bringing in activity limitation extends the approach to health from the biopsychosocial into the newer ICF concept. According to the authors of the definition, the ICF recognises the importance of Quality of Life (QoL), including the persons’ views of their own participation (14). The concept of QoL makes explicit the relevance of whose perspective is considered – the person with CP himself or a proxy (e.g. parent, teacher or health care provider) – which represents a clarification of important aspects of the biopsychosocial health approach.

2.2 Cerebral palsy
2.2.1 Definition and diagnosis
A diagnosis identifies explicitly which cases are to be recorded under that term, and by implication, which are to be excluded. A diagnosis might also serve as the basis for planning treatment and for counting cases in a population. A pioneer in orthopaedic surgery, Sir William John Little (1810-1894), was the first to describe CP (15). In 1957, devoted clinicians started the “Little Club” in England which moved the concepts and descriptions of CP forward (16). In 1964, a new annotated definition was suggested, which may be recognised as the marker of the modern era of CP. According to this definition, CP is a disorder of movement and posture due to a defect or lesion of the immature brain (17); i.e. the concept of CP is shifted from an orthopaedic condition to a prototype of a developmental disability. The definition from 1964 remained more or less unchanged for several decades (18), which is remarkable in light of the concurrent progress achieved in both imaging techniques that shed new light on the underlying brain injury and studies on the neurobiology of and pathology associated with brain development that further explored aetiological mechanisms. At last, in 2004, an international consensus group was settled to explore relevant new information. A proposed new definition of CP from the group was published in 2005 (19), followed by the final version cited in the introduction (1).

A main intention with the refined definition and classification was to give more prominence to the non-motor neuro-developmental disabilities that commonly accompany CP and to the progression of musculoskeletal difficulties that often occurs with advancing age (1). Still, abnormal motor behaviour (reflecting abnormal motor control) is the core feature, and the definition also clarifies that disorders of movement and posture that are not associated with activity limitations are not considered part of the CP group. CP is linked to the ICD-10 (13)
through the coding as a condition with a separate number within the chapter on diseases of the nervous system (Chapter VI, G 80) and to the ICF (12) through the emphasis of activity limitation.

A diagnosis of CP is based on history and a thorough physical examination. In accordance with the definition, the most common presenting feature is delay in obtaining motor milestones. The history should therefore comprise attainment of developmental milestones and in addition gestation and perinatal events (20;21). No single physical sign is diagnostic of CP, whereas clusters of indicators or evolving abnormal motor patterns may be indicative. The major physical signs that together may lead to a diagnosis of CP are abnormal muscle tone, persistence of primitive reflexes, and abnormal postural reactions (22). Once abnormal motor behaviour is recognised, it should be verified that it is neither progressive nor resolving before a diagnosis of CP is made. A minimum age at which a child can reliably be considered to have CP is not established (23) and the diagnosis can often be made during the first 12-18 months, except for the mildest forms. Although neuroimaging, and especially magnetic resonance imaging (MRI), is helpful in establishing aetiology and prognosis, no single imaging pattern or groups of patterns fully encompass the diagnostic findings associated with CP (24). For the 9% to 16% of children with CP who have normal brain imaging, further testing for metabolic and/or genetic conditions has been recommended. Still, in a recent study of a large cohort of children with CP and normal MRIs, comprehensive metabolic testing failed to clarify the aetiology of CP further, even in children with atypical features (25). In the end, CP is a diagnosis of exclusion, and measures not to overlook a metabolic or neurodegenerative disease should be considered on an individual base. Another consequence of CP being diagnosis of exclusion, is that European CP registers does not accept children definitely until the age of 5 years (26).

2.2.2. Classification

Classification within a diagnosis categorises cases with similar characteristics together and distinguishes cases with diverse features apart. The design of a classification system will vary depending on the concept being classified and the intended purpose for which classification is being made (1). The challenges in classifying CP are expressed very to the point in a paper on the natural history from 1988: “Classification of cerebral palsy is difficult and important. It
is, of course, evident that ordinary medical criteria are almost impossible to apply. There is
no single cause; there is no characteristic course; and in a very real sense there is no
morbidity and mortality. Above all, the accurate description of the motor patterns may not
give any insight into other important elements, such as intellectual and emotional difficulties’’
(27).

Throughout the 1960s and 1970s, the main perspective on the classification of CP was the
clinician’s, while in the 1980s rapidly changing neonatal care gave rise to a desire to monitor
the prevalence and subtypes of CP as a public health marker of perinatal and neonatal health
care. Developed countries followed Sweden (28), where surveillance of CP started as early as
1954 (7;29-34). In 1998, 14 population based registers in eight European countries established
the network Surveillance of CP in Europe (SCPE), founded by the European Commission.
The aim was to develop a common database of children with CP to monitor trends, gather
information necessary for service planning, and provide framework for collaborative research
(35). The SCPE network has proposed a simplified classification of CP type and offers both
an algorithm for diagnosis, a classification tree and a reference and training manual in order to
implement a uniform way of classifying CP subtypes within the participating centres (35). In
Norway, a national register was established in 2006 (Cerebral Parese Registeret i Norge,
CPRN) as a part of the SCPE collaborative network. The register and its national
collaborators promote the SCPE classifications to health care providers and health authorities.

The consensus group that launched the 2006 definition of CP discusses the challenges of
classification and refers to the SCPE classifications in its report. From the paediatric
perspective, it is concluded that a classification of CP should include CP type, the functional
effect of the motor impairment across trunk and limbs, accompanying impairments and the
child’s Quality of Life (QoL) and participation (1). Each of these elements is discussed within
separate paragraphs in the following.
2.2.2.1 CP type

According to the SCPE, CP type should be classified by means of topography of the disturbance of movement and posture (unilateral or bilateral distribution) and which motor disorder is the dominating (spasticity, dyskinesia or ataxia) in terms of having the greatest influence on the activity limitation (35). The consensus group support that cases continue to be classified by the dominant type of tone or motor abnormality (1). In contrast, in the ICD-10, the classification of CP type is based partly on which type of motor disorder is present, and partly which limbs are affected. The ICD-10 also allows for a diagnosis of both “mixed type” and “unspecified” CP contrary to the SCPE classification.

2.2.2 Functional effect of the motor impairment

The consensus group states that the functional involvement of the upper and lower extremities should be separately classified using objective functional scales (1). For the key function of ambulation, the Gross Motor Function Classification System (GMFCS) has been widely accepted and the validity and reliability is systematically tested (36-39). The GMFCS was developed in response to the need for a standardised system for classifying the severity of movement disability among children with CP (36). The underlying construct is self-initiated functional abilities in sitting and walking and the need for assistive devices, such as walkers or wheelchairs. The Manual Ability Classification System (MACS) provides a method analogous to the GMFCS for classifying the ability of children with CP to handle objects (40). As bulbar and oromotor difficulties can produce important activity limitations on the field of communication, the Communication Function Classification System (CFCS) is developed within the same concept as a method to record communication ability (41). Table 1 gives estimates of the distribution of CP types and ambulatory function from European studies covering similar birth cohorts as the present study.
Table 1. Distribution of CP type and ambulatory function in three European population based studies (5;42-44)

<table>
<thead>
<tr>
<th>Area</th>
<th>Norway</th>
<th>West Sweden</th>
<th>SPARCLE*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants</td>
<td>374</td>
<td>167</td>
<td>818</td>
</tr>
<tr>
<td>CP type (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unilateral spastic</td>
<td>33</td>
<td>30</td>
<td>34</td>
</tr>
<tr>
<td>Bilateral spastic</td>
<td>49</td>
<td>45</td>
<td>52</td>
</tr>
<tr>
<td>Dyskinetic</td>
<td>6</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>Ataxic</td>
<td>5</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>Unclassified</td>
<td>7</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>Gross motor function (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GMFCS I**</td>
<td>55</td>
<td>59</td>
<td>31</td>
</tr>
<tr>
<td>GMFCS II</td>
<td></td>
<td></td>
<td>20</td>
</tr>
<tr>
<td>GMFCS III</td>
<td>17</td>
<td>14</td>
<td>17</td>
</tr>
<tr>
<td>GMFCS IV-V</td>
<td>28</td>
<td>27</td>
<td>32</td>
</tr>
</tbody>
</table>

*SPARCLE = The Study of Participation of Children with CP living in Europe  
** Gross Motor Classification System

2.2.2.3 Accompanying impairments

Accompanying impairments may be caused by the same disturbances as those that caused CP, and/or represent indirect consequences of the motor impairment and/or be caused by independent factors (hence the term ‘accompanied by’ as opposed to ‘associated with’) (1). In general, the proportion of children with accompanying impairments increase with increasing GMFCS levels (45). The consensus group states that accompanying impairments should be classified as present or absent, and if present, the extent to which they interfere with the individuals’ ability to function or participate in desired activities should be described. In concurrence with the SCPE recommendations, the consensus group recommends that the presence or absence of epilepsy should be recorded, and IQ, hearing and vision should be assessed (1). The American Academy of Neurology has recommended screening of children with CP for intellectual impairment, visual and hearing impairments, as well as speech and language disorders (20).
**Disturbances of sensation**

"Disturbances of sensation" reflects that vision, hearing, and other sensory modalities may be affected. In a population-based study comprising all CP types, severe visual impairment (defined as functional blindness or an acuity after correction of refraction errors of no more than 0.3 (20/60) in the better eye) was present in 19% (45). About 7-9% of children with spastic CP have severe visual function disorders, defined as retroschiasmatic and visual recognition disorders. These disorders frequently referred to as cortical or cerebral visual impairment (CVI), comprise reduced visual acuity, visual field deficits, and difficulties in visual recognition. Oculomotor disorders and strabismus is also common and adds to the visual impairment. About 50% of children with CP have milder visual defects (46;47). In general, the likelihood of severe visual impairment increases with increasing motor impairment (44;45;48;49).

In population-based studies, severe hearing impairment is reported in 2% of children with CP when defined as need for hearing aid or no hearing (45) and in 13% when defined as a 70dB or greater hearing loss (bilateral) in an audiometric testing (49). A literature review revealed considerable variation in the definitions and proportions of hearing loss (range 4–13%) and severe hearing loss (range 2–12%) reported by CP registries in developed countries. In a recent Australian population-based study, 7% of individuals with CP had bilateral hearing loss of a moderate to profound degree, whereas the subgroup with a severe–profound degree of hearing loss constituted 3% to 4% of the CP population. The degree of hearing loss was described as moderate/moderately severe if the hearing loss was 41 to 70dB, severe if the hearing loss was 71 to 90dB, and profound if the hearing loss was assessed as >90dB (50). Both dyskinetic type of CP and GMFCS IV-V increases the likelihood of severe hearing impairment (49;50).

Impaired stereognosia may increase activity limitation in the task of handling objects, and impaired stereognostic sense was present on the affected side in as much as 44% of children with unilateral CP in a Swedish population-based study (51).

Standardised instruments are available to measure vision and hearing, and categories describing specific levels of dysfunction (e.g. visual impairment, profound hearing loss) have come to be generally accepted (1).
Disturbances of cognition
Population-based studies have reported intellectual disability (IQ<70) in 31 to 65% of children with CP (5;28;29;52-54) and according to SCPE data, the estimated prevalence of severe intellectual disability (IQ ≤ 50) in children 5 years old with CP is 30% (26). Standardised instruments are available to measure IQ, and categories describing specific levels of dysfunction (e.g. mild mental retardation) are generally accepted (1).

Disturbances of communication
Communication problems may arise from motor, intellectual and/or sensory processing deficits (55). Population-based studies indicate that about 20% of children with CP are unable to produce intelligible speech while up to 50% have some form of communication disorder (4;56-59). Dysarthria is the most common form of communication disorder (59). Generally, language assessment in children with severe CP is challenging, and frequently there is uncertainty as to whether test failures are due to physical disability or limited intellectual and verbal comprehension abilities (60). Whatever the cause of limitation/participation restriction, communication performance may be assessed with the Communication Function Classification System (CFCS) (41).

Disturbances of perception
Though described as common in CP, I am not aware of reports where complete cohorts of children with CP have been screened for specific perceptual impairments. In the literature, the potential contribution of a perceptual impairment is often not clarified, which is also reflected in the above paragraphs on disturbances of sensation and communication. Visual perceptual impairment and its association to spastic CP and premature birth are probably the most described (46;47). Recognition of perceptual impairment may require a neuropsychological assessment in addition to a medical and educational work-up.

Disturbances of mental health
In general, children with disabilities, and especially those with chronic neurological disorders, are at higher risk of experiencing mental health problems compared to their non-disabled peers. Externalising problems with behavioural disorders and ADHD (Attention Deficit Hyperactivity Disorder) seem to have the strongest association to neurological disorders, but also emotional problems are more common than in the general population (61). Further, there is a certain association between intellectual disability and mental health problems (61) as
demonstrated in a Norwegian epidemiological survey where the prevalence of psychiatric diagnoses according to the ICD-10 in children with mental retardation (IQ<70) was estimated to 37% and hyperkinesia was the most common disorder (62). Parental stress is found to be a predictor of child emotional and behavioural difficulties both in the general population (63) and in CP (64;65), giving a reminder that social environmental factors have the potential to contribute to the aetiology of mental health problems.

In CP, the population prevalence of significant emotional and behavioural problems in children 8-12 years old has been estimated to 26 %, with severe pain being a major predictor (66). Other studies have shown that levels of behavioural problems are elevated in preschool children (67) and in school age (68) but tend to diminish during adolescence (65). A Swedish study concludes that mental health problems are common in children with CP, and even more common when epilepsy is present (69). However, these studies all rely on proxy-reports. An epidemiological survey of children with hemiplegia found that psychiatric disorders as judged by individual diagnostic assessment affected 61% of subjects. In this study, intelligence quotient (IQ) was the strongest consistent predictor of psychiatric problems (70).

The diagnosis of a psychiatric disorder usually relies on the integration of results from observations, semistructured interviews and completion of questionnaires (self- and proxy-reports from different sources such as parents and teachers).

**Epilepsy**

Virtually every seizure type and many epileptic syndromes may be observed in persons with CP (1). The estimated overall prevalence of epilepsy in children with CP is 25-45% compared to 0.3-0.6 % in the general population (71;72). In a population-based study of Swedish children born 1987 to 1994, all children with tetraplegic CP and about one-third of the children with other CP types developed epilepsy. Children with tetraplegic CP tended to have an earlier onset of epilepsy than children with other CP types and partial seizures were the most common seizure type. Further, children with cognitive impairment had a higher frequency of epilepsy than those without cognitive impairment (73). The consensus group tells epilepsy to be recorded as the presence or absence of two or more afebrile, non-neonatal seizures, thereby following the recommendations from SCPE (1).
Secondary musculoskeletal problems

People with CP may develop a variety of musculoskeletal problems, such as muscle/tendon contractures, bony torsion, hip displacement and scoliosis (1). Pain is a symptom often accompanying musculoskeletal problems (1) and is discussed separately in the below paragraph.

Pain

From a health care perspective, recognition of pain is important because untreated or under-treated nociceptive pain in childhood may predispose to persisting pain in adulthood through conditioning (74) or through generation of neuropathic pain, as stimulation of nociceptors may result in changes in the nervous system leading to chronic pain states (75). The International Association for the Study of Pain (IASP) defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” (76).

Pain is common in children with CP (74;77) and the prevalence increases with age (74). Children with pain have reported that pain interfered with self-care, sleep (78) and with QoL (79) and parents have reported that children with pain participated less than other children with CP (80). However, in these studies the origin of pain or the pain’s relation to CP was not evaluated.

Clinical assessment of pain includes assessment of intensity, frequency, quality, location and temporality. The term severity should be avoided if possible, holding elements of both intensity and frequency. Measurement tools adapted to child age are developed; most of them are in the paper-based questionnaire format, in which a standardised questionnaire is to be filled in. Diaries represent another option. Interview can replace written self-report if motor or visual impairment limits reading or writing. Pain intensity may be reported on a visual analogue scale (VAS) or a numeric rating scale (NRS). If the purpose is comparison across study populations, one has to be aware that children tend to rate significantly more pain when using a smiling face to denote “no pain” than if a neutral “no pain” face is used (81). Pain may also be regarded as an observable measure, and standardised methods for the observation of
pain behaviour is developed that makes it possible to obtain information from the non-verbal person (82).

2.2.3 Quality of Life and Health Related Quality of Life

Quality of life (QoL) is defined by the WHO as “individuals’ perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns”(83). It is a broad ranging concept incorporating in a complex way the persons’ physical health, psychological state, level of independence, social relationships, personal beliefs and their relationships to salient features of the environment. The concept of QoL may also be regarded as a continuum of issues from existentiality to single symptoms (e.g. pain). The “gap theory” pinpoints the gap between expectations and experience as the essence of QoL. According to this, QoL is described as an inverse relationship to the difference between an individual’s expectations and his perception of a given situation. That means “the smaller the gap, the better the quality of life”(84).

Quality of life (QoL) research started in sociology and has been adopted in medicine. In the early literature, there was a great overlap with terms such as handicap, function and activities of daily living. Present literature is clearer, and the subjective, self-reported element is now common to all definitions and instruments in use. Most instruments identify a number of crucial dimensions e.g. the perception of emotional, social, material and physical well-being, self-esteem and self-determination. QoL is individual, and QoL assessment thereby highlights the fact that an apparently similar medical condition or even similar levels of functioning can be perceived by individuals in many different ways (14).

It is a challenge for researchers and clinicians to capture this subjective aspect in CP, since the patient may be a small child or intellectually or visually impaired. The tradition is to rely on proxy-report when self-report is impossible to obtain. Although much has been written about the relationship between child and proxy ratings in QoL/HRQL research, the impact of child and parent characteristics on agreement between children and parents has not been consistently considered within studies (85). However, there are trends; parents of children in a non-clinical sample tend to report better child HRQL than children themselves, while parents of children with health conditions tend to underestimate child HRQL (85). Further, parental well-being is found to influence parents' perception of their
child's QoL (65;86) emphasising that in a family perspective, parent proxy-report adds valuable information.

The slogan taught in paediatrics for generations that “children are not small adults” is reflected in the relatively new sociology of childhood where status is given to the lives of children and adolescents “here and now” rather than valuing childhood simply as a transitional phase to adulthood. In accordance with this view, modern QoL instruments are generated de novo from what young people say, rather than being modified adult instruments or instruments with items that professionals think are relevant to children and young people (87). Over the years, a lot of instruments are developed (88) – to an extent that a “mania” for measurement of QoL has been addressed (89).

Paediatric quality of life work has developed primarily from concerns about the impact of aggressive treatment on children especially in the early days of cancer treatments, as well as for premature children undergoing high-tech treatment (90). As a consequence of this shift in focus from survival to life quality (both in paediatrics and in adult medicine), Health Related Quality of Life (HRQL) has emerged as an outcome measure of health care (85). HRQL is usually considered a subgroup of QoL consisting at the minimum of physical, psychological and social health dimensions as described by WHO (91). One definition of HRQL is “an individual’s perception of various aspects of their lives that they think is affected by a particular medical condition and its treatment ”(92). This HRQL concept is readily understood if an aspect of life is considered that is unique to this particular medical condition, but if the aspect considered is experienced by all children, the concept of HRQL is more difficult to grasp. In other words, if HRQL is about aspects of QoL which are particular to children with a specific condition, then it cannot apply to all children (92).

In paediatric CP, the Study of Participation of Children with Cerebral Palsy Living in Europe (SPARCLE-I study) (42) has provided substantial insight into the health and QoL of children 8-12 years old. In the SPARCLE-study, children self-reported QoL comparable to non-disabled peers, but pain was associated with reduced QoL in all domains (79) and self-reported severe child pain was the main factor explaining parents’ ratings of their child’s QoL better than the children themselves (93). In children with intellectual disability (IQ<70) parents reported better child QoL than professionals (teachers, therapists, residential carers).
on the psychological domain and reduced QoL on the social support domain. Further, high
level of stress in parenting was associated with parents reporting reduced child QoL compared
to professionals, while child pain was associated with professionals reporting reduced child
QoL compared to parents (94). Parents also reported that gross motor function level correlated
with health from the physical well-being perspective, but not with the psychological and
emotional aspects of health (95). Although mental health is thought to be close to
psychosocial well-being, I am not aware of studies on mental health and QoL in CP. More
important, self-reported mental health was not included in the SPARCLE-study and I have not
been able to find any studies on this topic in CP.

Proceeding to adolescents, a literature review from 2007 on QoL among adolescents with CP
summarised findings into important trends: 1) Individuals with CP have decreased QoL and
HRQL compared with a normative population in some, but not all areas of well-being,
2) Functional status measures such as the GMFCS are reliable indicators of variations in
physical function, but do not correlate consistently with psychosocial well-being and
3) Although adolescents with CP have different life issues than adults or children, limited
research on factors associated with QoL and HRQL has been performed in this age group
(96). The SPARCLE - II study (97) collecting data from the same children four years after
SPARCLE-I is expected to provide new insights into QoL and health status in adolescents
with CP.

A good measure of QoL/HRQL is regarded to at least offer both self-report and proxy
versions to allow for parent completion, be brief, age-appropriate and have documented
reliability and validity (90). For HRQL assessment, measurement tools may be generic or
disease-specific. Disease-specific measures are designed to assess symptoms and functions
associated with a particular disease and treatment effects (98). A compromise between a
generic and a disease-specific measure is the development of measures holding a generic core
set of items with disease-specific add-ons or modules. Current advise is not to measure
QoL/HRQL for its own sake, but to choose the appropriate measurement tool in order to
answer a specific question (88,92). Self-report and proxy-report provides different
information and both should be obtained when possible also because it is the parent’s
perception of their child’s HRQL that is the principal determinator of utilisation of paediatric
health care services (99).
2.2.4 Participation and the International Classification of Functioning, Disability and Health (ICF)

The ICF was officially endorsed by all WHO Member States in May 2001 and describes health through the lens of functioning. It assesses interactions among body functions (including psychological function) and body structures (referring to anatomy), activities (tasks and demands of life), and participation (engagement in life situations). The WHO website tells: ”Health and health-related domains are classified from body, individual and societal perspectives by means of two lists: a list of body functions and structure, and a list of domains of activity and participation. Since an individual’s functioning and disability occurs in a context, the ICF also includes a list of environmental factors” (12). Figure 1 illustrates the conceptual components of the ICF and their relations. Health condition (disorder or disease) refers to the ICD-10 taxonomy:

Figure 1. ICF

![Diagram of ICF](image)

The diagram identifies the three levels of human functioning classified by ICF: functioning at the level of body or body part, the whole person, and the whole person in a social context. Corresponding to this, disability involves dysfunctioning at one or more of these levels: impairments, activity limitations and participation restrictions. Further, impairments are defined as problems in body function or structure, such as organs, limbs and their
components. Activity limitations are defined as difficulties an individual may have in executing activities, and participation restrictions are problems an individual may experience in life situations. At last, the environmental factors make up the physical, social and attitudinal environment in which people live and conduct their lives (12).

The list of domains in ICF becomes a classification when qualifiers are used. Qualifiers record the presence and severity of a problem in functioning at the body, person and societal levels. For the classifications of body function and structure, the primary qualifier indicates the presence of impairment and, on a five point scale, the degree of the impairment of function or structure (no impairment, mild, moderate, severe and complete). In the case of the Activity and Participation list of domains, two qualifiers are provided that make the ICF helpful in describing what a person with a health condition can do in a standard environment (their level of capacity), as well as what they actually do in their usual environment (their level of performance). The Performance qualifier measures the difficulty the respondent experiences in doing things, assuming that they want to do them. In contrast, the Capacity qualifier focuses on limitations that are inherent or intrinsic features of the person themselves. These limitations should be direct manifestations of the respondent's health state, without the assistance. The level of capacity should be judged relative to that normally expected of the person, or the person's capacity before they acquired their health condition (12).

The International Classification of Functioning, Disability and Health for Children and Youth (ICF–CY) (12) was launched in 2007 as the rapid growth and changes that occur in the first two decades of life were not sufficiently captured in the ICF. The ICF-CY allows coding of learning and child-specific environmental factors. In addition, it permits developmental aspects of functioning to be coded, such as learning through actions and playing and acquiring language. The ICF-CY adds the term and the concept of ‘developmental delay’ to the universal severity scale included in the ICF. This enables the documentation of lags in the emergence of structures, functions, capacity, performance of activities and participation in children and youth, and recognises that severity of the observed delay(s) may change over time. A recent study describes the clinical application of ICF-CY in the neurorehabilitation of a 12 year old child with dyskinetic CP (100). The ICF-CY is also regarded to provide an excellent framework in comparing the content of HRQL measures for children and youth with CP (101). Both the ICF and the ICF-CY are translated into Norwegian.
In paediatric CP, a recent study considering treatment outcomes supports that participation is regarded a domain of importance both by parents, medical professionals and the youths themselves (102). Adolescents in another study identified issues related to active leisure, mobility, school and socialisation as important areas for improvement of participation (103). In the SPARCLE - I study (42), parents reported that children CP 8-12 years old with CP participated less frequently in many, but not all areas of everyday life, compared with children in the general population (104) and that children with pain had even lower participation (80). Mental health problems were not included in the assessment of participation, and as earlier mentioned, the origin of pain was not evaluated.

Participation may be assessed by observation, questionnaires or semistructured interviews. Aspects such as difficulties with the accomplishment of daily activities and social roles (105), satisfaction (105), independence, enjoyment, diversity (106) and frequency (104) or intensity (107) may be incorporated. Assessment tools are said to vary widely in their operationalisation of participation, measure participation only to a limited extent, and refer to both objective and subjective aspects in the assessment (108,109). Further, a consensus on how to describe participation restriction in CP does not exist (110), as core sets of ICF categories to be included in the assessment have not been developed (in contrast to a range of other chronic conditions) (111). Still, the description of activity limitation/participation restriction relevant to the motor impairment is approaching consensus. According to the developers, the basic ideas concerning capacity and performance included in the original GMFCS concepts were sharpened considerably with the publication of the ICF, and it has become clearer that the major focus of the GMFCS is on motor function under ordinary circumstances, rather than on capacity as observed under optimal conditions and assessed with formal tools (112). The equivalent classification systems for manual function (MACS (40)) and communication (CFCS (41)) were developed using lessons learned from the development of the GMFCS (112). In contrast, I am not aware of any consensus on how to describe activity limitation/participation restriction relevant to pain and mental health problems in CP.
3. **Aims of the study**

The overall aim of the study was to explore how recurrent musculoskeletal pain related to CP (RMP) relates to mental health problems, HRQL and participation.

The specific aims were:

1. To explore the prevalence, predictors, severity and impact of RMP (Paper I).

2. To extend previous knowledge on mental health problems with children’s own report and relate RMP to mental health and HRQL (Paper II).

3. To relate RMP and mental health problems to participation (Paper III).

4. To describe the course of participation after introduction of treatment for RMP (Paper IV).
4 Methods

4.1 Study design and study populations

Two studies on RMP are included; Study A that has a cross-sectional design and Study B that has a prospective, longitudinal design. The main criterion of inclusion was a diagnosis of CP.

Study A (paper I-III) includes two groups of participants:


2) A hospital-based group covering patients 8-18 years old who completed 3-dimensional gait analyses at Oslo University Hospital. Inclusion period was Feb.1. 2009 to Jan. 31. 2010.

In Study B (paper IV), participants are children and adolescents < 18 years who started continuous intrathecal baclofen therapy (CITB) at Oslo University Hospital, Rikshospitalet. Inclusion period was Sept.16. 2002 to Sept. 15. 2005. Observation time was 18 months.

4.2 Enrolment of participants

Study A, population-based group:

Letters of invitation to potential participants were sent to all habilitation units within the specialist health care system, to all general practitioners and to the public system for special education in all municipalities. The region comprises both urban (e.g. Oslo), suburban and rural areas and covers about half of the Norwegian population (4.8 mill. in 2008). The Norwegian Cerebral Palsy Association in addition advocated the study to their members. The present study is part of a larger study of transition from childhood to adulthood, and the actual birth cohorts were chosen because they attended the last two years in primary school at the time of inclusion.

Study A, hospital based group:

Letters of invitation were sent from the hospital together with the appointment for 3-dimensional-gait analysis. Eighty-nine per cent of potential eligible patients participated. One patient did not want to participate and the remaining was lost because of logistic coincidences in the gait laboratory. The flowchart (figure 2) outlines the study populations in paper I-III.
Study B:
All children with CP who started CITB during the inclusion period were enrolled.
38 patients participated. One patient discontinued CITB after 3 months because the family suspected intolerable side-effects (agitation). In two patients the infusion pump had to be removed because of infection and the families did not want another pump. The remaining 35 (92 %) continued treatment throughout the observation period.

4.3 Measures
Psychometrics is the field of study concerned with the theory, technique and functioning of psychological measurements. The field is primarily concerned with the construction and validation of measurement instruments such as questionnaires, interviews and tests. Key concepts are reliability and validity. A reliable measure is one that measures a construct
Content validity refers to whether a measure appears to measure what it claims to do. Content validity is usually evaluated by the judgement of several experts (both real life experts and professionals) within the field of interest. Construct validity refers to a measure’s consistent relations to the concepts (i.e. constructs) that are being measured. Construct validation is therefore a continuous process involving the theory behind the concepts and various psychometric testing. Internal consistency is a measure that refers to the correlations between different items on the same test (or the same subscale on a larger test). It measures whether several items that propose to measure the same general construct produce similar scores. Internal consistency may be measured with Cronbach's alpha, a statistic calculated from the pairwise correlations between items. Further, a construct such as HRQL/QoL and participation cannot be measured directly; it is captured by calculating from a group of questions the value of an underlying latent variable. An alternative way of thinking about internal consistency, is that it is the extent to which the items of a test measure the same latent variable. In cases of translations, cross-cultural studies are usually conducted to ensure that the properties of an instrument do not change for different cultures and settings. In the following, outcomes and explanatory variables are listed and comments on their psychometric properties are given where appropriate.

4.3.1 Outcomes

- **Recurrent musculoskeletal pain** is the main outcome in paper I. The assessment was performed stepwise. During an initial interview, children and parents together were asked for any kind of recurrent pain and if present, pain characteristics were explored. After clinical assessment performed by the same paediatrician and/or therapist that performed the interview, the professionals judged whether recurrent pain probably was of musculoskeletal origin and related to CP. More details are given in paper I (113).

- **Pain intensity and frequency** (paper I, II and IV) was assessed in three ways: In paper I, the children recorded maximum pain intensity within the last month on the Faces Pain Scale-Revised (FPS-R). The FPS-R is a 0-10 scale with a neutral no pain face that has demonstrated a linear relationship with visual analogue pain scales in the age range 4-16 years (114). In paper I and II, children and parents both responded to the two questions
on pain from the Child Health Questionnaire (CHQ) (115); “How much bodily pain or discomfort” and “How often is there bodily pain or discomfort” during the last month. CHQ is a generic instrument for assessment of health status or HRQL in children that has been translated, cross-culturally adapted, and evaluated according to international guidelines for use in a number of countries including Norway (116), and also is validated for CP (117) and used in the SPARCLE study (English version)(118). The two responses on pain are reversely scored, and the mean is linearly transformed into a 0-100 scale where 100 is no pain. In paper IV, the average daily number of episodes of pain when not sleeping and the all over intensity of pain the last four weeks as observed by parents were recorded by a therapist during the assessment of the patient. Number of pain episodes was spelled out from 0= “none” to 4= “pain almost all the time” and pain intensity was spelled out from 0= “no pain” to 4 = “pain of very high intensity”.

- **Impact of pain** (paper I and IV) was reported by children and parents in paper I and by parents in paper IV. In paper I, impact of pain was assessed with selected items from the Brief Pain Inventory (BPI), Norwegian version (119). BPI measure the level of pain interference with function using 0 (no interference) to 10 (complete interference) numerical rating scales. Three items were chosen (general activity, walking and sleep) and the time span changed from pain experienced during the last 24 hours to pain experienced the last four weeks. In paper IV, how often (on average) the child woke up during night the last four weeks was recorded by the interviewer on a 5 point scale spelled out with 0= “never or almost never” to 4= “almost all the time”.

- **Localisation of pain** (paper I) was obtained from the body outline (anterior and posterior view) of the Brief Pain Inventory (BPI) (119).

- **Gross motor function capacity** (paper IV) was assessed with the Gross Motor Function Measure (GMFM-66), Norwegian version. The GMFM is a criterion-referenced observational measure that originally was developed and validated to assess children with CP (120). Items are scored on a four point ordinal scale (0=does not initiate the activity, 3=completes the activity). By the age of five years, children without motor delays in general are able to accomplish all items. The current version has demonstrated good psychometric properties (intrarater reliability *ICC* =0.99, construct validity ascertained by Rasch analyses, and good sensitivity to change)
A Norwegian version is developed in which inter-rater reliability was found satisfactory (Pearson correlation 0.75-1.00) (123).

- **Spasticity** of the knee flexors (paper IV) measured as degree of resistance to passive knee extension was rated on a Modified Ashworth Scale (124) which has demonstrated adequate levels of inter-rater reliability in adults (weighed kappa =0.87 for overall agreement in lower limbs) (125;126). The test was performed at a moderate speed (180°/s) by two experienced therapists.

- **Child mental health** (paper II) was assessed with The Strength and Difficulties Questionnaire (SDQ) (127), Norwegian versions for self-report and proxy-report. The SDQ is a behavioural screening questionnaire consisting of 25 items. Each item has 3 response alternatives; “not true”, “somewhat true” or “certainly true.” The 25 items are divided between 5 scales: Emotional Symptoms, Conduct Problems, Hyperactivity, Peer Problems and Prosocial Behaviour. Responses to negatively worded items are scored 0-1-2 and positively worded items are scored 2-1-0. The scores for all items on the first four scales are summed to a Total Difficulties Score (TDS), higher scores indicating more problems. The SDQ shows satisfactory reliability (mean Crohnbach $\alpha$ =0.87 for internal consistency and mean=0.62 for test-retest correlation) and validity (low “contamination” between internalising and externalising scales, high predictability of independently diagnosed psychiatric disorder) (127;128). Studies on some psychometric properties of the Norwegian versions have been performed (129-131) and normative data based on a large representative Norwegian sample are obtained (132). In addition, a validation of the English version is undertaken in CP with good results except in the most impaired children for whom the validity of SDQ is questioned (66). In the present study, self- and maternal-reported TDS are given.

- **HRQL** (paper II) was assessed with the generic Pediatric Quality of Life (PedsQL) 4.0 (133) that includes subscales of physical, emotional, social and school function. The Psychosocial Summary Scale is the sum of the latter three subscales. All scales are comprised of parallel child self-report and
parent proxy-report formats. The instructions ask how much of a problem each item has been during the past month (0=never a problem; 1=almost never a problem; 2=sometimes a problem; 3=often a problem; 4=almost always a problem). The wording is negative (e.g. I hurt or ache, It’s hard for me to run, I feel afraid or scared). Items are reversely scored and linearly transformed into a 0-100 scale, so that higher scores indicate better HRQL. Reliability and validity of the original version are tested in the general population and in patient populations included CP with good results (internal consistency showing Crohnbach $\alpha >0.80$ for all child and parental scales, PedsQL distinguishing between healthy children and paediatric patients) (99;134) and the psychometric properties of the Norwegian translation are evaluated in the general population and found satisfactory (internal consistency showing Crohnbach $\alpha =0.77$-$0.88$, factor analyses showing results comparable with the original version except for the Physical Health Scale) (135). In the present study, self- and maternal-reported Total Scores and Psychosocial Summary Scores are given.

- **Participation** is the only outcome in paper III and the primary outcome in paper IV. Parents are the responders in both papers. In paper III, participation was assessed using the Assessment of Life Habits (LIFE-H) short versions; General Version 3.1 (136) for children $\geq 14$ years old and Child 5-13 Version 1.0 (105) for younger children – both in Norwegian translations. Both versions comprise 64 items distributed on 10 and 11 categories, respectively. The LIFE-H has been proven to be a reliable instrument in older adults (intrarater $ICC>0.75$ for 7 categories, inter-rater $ICC \geq 0.89$ for total score and daily activities subscore and $ICC=0.64$ for social roles subscore (136)). The child version is tested for reliability and validity in children with various impairments, including CP, showing moderate to excellent results (intrarater correlation $ICC \geq 0.78$ for 10 categories, content validity assessed as good by an expert group, content compared with 2 other measures used in child rehabilitation finding that the content of LIFE-H allows for a complete description of participation (105)). Participants are instructed that responses should reflect the young person’s usual way of carrying out life habits (i.e. performance). Both versions use an item score ranging from 0 to 9, developed by the combination of the two concepts of the scale (degree of difficulty and types of required assistance), where 0 indicates total impairment
(meaning that the activity or social role is not accomplished or achieved) and 9 indicates optimal participation (meaning the activity or social role is performed without difficulty and without assistance). In order to allow for the variable number of items in each category, and the number of ‘non-applicable’ items for the respondent, a transformation of scores (on a 0–10 scale) is used to give similar weighting to each category of life habits. After transformation, 0 means total impairment and 10 means the activity or social role is performed without difficulty and without assistance. The measure also comprises a second scale that evaluates the individual’s level of satisfaction with the accomplishment of life habits. This score varies from 1 (very unsatisfied) to 5 (very satisfied). We adjusted the range to -10 to +10 where 0=“more or less satisfied.” We calculated both accomplishment scores and satisfaction scores for each category, a global score for all items, and subscores for daily activities and social roles respectively.

In paper IV, participation was assessed by interview according to the Norwegian version of the Pediatric Evaluation of Disability Inventory (PEDI) (137). The PEDI was designed to measure both capacity and performance simultaneously and comprehensively in the domains of self-care, mobility, and social functioning in children with disabilities aged 6 months to 7.5 years. PEDI offers a Functioning Skills Scale and a Caregiver Assistance Scale. Together 197 items corresponding to the domains of the activity and participation classification of the ICF measures if the activities can be performed or not in most situations (138). Scoring is 1 (performed) or 0 (not performed). Age- standardised normative scores with mean (SD) of 50 (10) are provided. PEDI also assesses the number of assistive devices (ICF environmental factors). Several studies have examined the psychometric properties of the PEDI and provided evidence for the PEDI as a reliable, valid and sensitive-to-change assessment for both normally developing and disabled children (139-141) and the Norwegian version is also evaluated with good results (intra- and inter-rater ICC 0.95-0.99, cross-cultural validity of American normative data for a general Norwegian population satisfactory) (142-144). Interviews were performed by trained professionals, which is pointed out as important (143). In paper IV, the scaled scores (0 to 100, reflecting increasing level of functioning in each domain) of the Functional Skills Scale and the Caregiver Assistance Scale are reported.
4.3.2 Explanatory variables

- **CP diagnosis and classification of CP type** followed the recommendations from the consensus group published in 2006 (1) (paper I-IV).

- **Functional effect of the motor impairment** was recorded as gross motor performance according to the GMFCS (36) (paper I-IV). The GMFCS describes the ambulation of children with CP in one of five ordinal levels and includes descriptions for each level across four age groups: less than 2 years, 2 to 4 years, 4 to 6 years, 6 to 12 years, and 12-18 years (38). Children in Level I perform all the activities of their age-matched peers, albeit with some difficulty with speed, balance, and coordination; children in Level V have difficulty controlling their head and trunk posture in most positions and achieving any voluntary control of movement. After the age of 6 years, children at GMFCS level I-II walk without assistive devices, children at level III walk with assistive device, and children at level IV obtain mobility in a wheelchair.

- **Socioeconomic factors** (paper I-III): Questions were selected from Parental Account of Children’s Symptoms, Norwegian version (PACSNO)(145). We recorded whether the child lived together with two parents, whether the place of living was urban or rural, the length of mother’s education, and family economy.

- **Parental mental health** (paper II and III) was assessed with the General Health Questionnaire (GHQ-30), Norwegian version. The General Health Questionnaire (GHQ) (146) is designed to detect psychiatric disorders in community settings and nonpsychiatric clinical settings. The GHQ-30 includes 30 items covering symptoms considered to reflect distress and psychopathology in five dimensions corresponding to anxiety, feelings of incompetence, depression, difficulty in coping, and social dysfunction over the past 2 weeks (147). Both positive and negative questions are included. Possible responses to each item are “not at all, somewhat/same as usual, rather more than usual and much more than usual” respectively. Responses may be recorded as 0-1-2-3 giving a possible score of 0–90 or 0-0-1-1 giving a possible score of 0-30. A high score indicates more psychosocial distress. Reliability of the factor structure in the English version have proved excellent (148) and the Norwegian
translation has been used in several studies (149-152). In the current study, the 0-1-2-3 scoring was performed.

4.4 Statistics
Continuous data were described using median with 25\textsuperscript{th}-75\textsuperscript{th} centiles and in addition mean with standard deviation (\textit{SD}) when appropriate for comparison with other studies. Categorical data were described using proportions. Differences between independent groups for continuous data were quantified with the Independent-Samples T-test in cases of observations approximating the normal distribution and with Mann Whitney Wilcoxon test in cases of severe skewness of observations or few observations. For categorical data, Chi squared ($X^2$) test or Fisher’s exact test for small samples was applied. Differences between observed means and means reported in the general population were analysed with one-sample T-tests (paper II). Differences in mean between related samples were analysed with Related Samples Wilcoxon Signed Rank Test (paper I) or Paired-Samples T-test (paper II and IV). Differences in variances were analysed with one-way analyses of variance and post hoc tests for multiple comparisons was performed (Tukey) (paper I and III). Consistency between scores were analysed with intraclass correlation coefficients (\textit{ICC}) assuming random effects (paper I and II). Correlations were analysed with Spearman’s rank correlation because of skewness of observations (paper III). Regression models were fitted in order to analyse potential associations between explanatory variables and selected outcomes. Logistic regression was applied for binary outcomes (paper I) and linear regression was applied for linear outcomes (paper II and III). Residual diagnostics was performed to explore the fit between models and observed data. Bootstrapping was performed to derive estimates for the confidence intervals for the odds ratios (\textit{OR}) in the logistic regression model (paper I) and for the regression coefficients (\textit{B}) (paper III). In paper III, model validation was performed by a bootstrapping program performing 1000 bootstrapped repeats of backward stepwise linear regression on candidate variables. For each successive variable included from the bootstrapping, a resampling validation program was used to perform 250 replicated partitioning of the data into test subsamples. Then the coefficient of determination, $R^2$, from the test sample was used to assess best fit. Collinear diagnostics was also applied to avoid biased estimates and overfitting because of collinearity. Potential interaction terms were considered in the regression analyses, but none was included. Missing values were taken into account by casewise deletion. We had a 5 \% statistical significance level and performed two-tailed testing. Analyses were
performed in PASW Statistics, release 18.03 (IBM Corporation, Armonk, New York, USA) (paper I-III), SPSS 16.0 version (SPSS Inc, Chicago, IL, USA) (paper IV) and STATA/SE, version 12.0 (StataCorp LP, College Station, TX, USA) (regression model paper III).

4.5 Ethics

Study A: The study protocol was approved by the National Committee for Research Ethics. Written informed consent to the research and publication of the results was obtained from parents and from participants adjusted to age and ability to give informed consent. Separate written information was provided for adolescents 12-16 years old. Adolescents ≥16 years old gave their written consent, and adolescents 12-16 years old were encouraged to give their written consent if they wanted to do so. If intellectual disability was present, parents judged whether written informed consent from the adolescent was possible to obtain. In the population-based group, potential participations got no more than one postal reminder if they did not respond to the first letter.

Study B: As no changes in hospital routines were made, consent from the local ethical committee was not applied for. The study was set up as quality assurance of a given medical treatment, and written consent from participants was therefore not obtained. At the time of publication, the duration of the observation time was long compared to other studies, thus publication of the results was regarded to be of potential general utility for families considering CITB. It was secured that identification of the participants is not possible.

The Commissioner for the Protection of Privacy in Research at Oslo University Hospital approved data storage in both studies.
5 Summary of results

Table 2 gives an overview sorted by paper of the health problems studied and their domains of potential impact:

<table>
<thead>
<tr>
<th></th>
<th>Health problem</th>
<th>Domain of potential impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paper I</td>
<td>Recurrent musculoskeletal pain</td>
<td>General activity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Walking</td>
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<td></td>
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<td>Sleep</td>
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<tr>
<td>Paper II</td>
<td>Recurrent musculoskeletal pain</td>
<td>HRQL</td>
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<tr>
<td></td>
<td>Mental health problems</td>
<td></td>
</tr>
<tr>
<td>Paper III</td>
<td>Recurrent musculoskeletal pain</td>
<td>Participation</td>
</tr>
<tr>
<td></td>
<td>Mental health problems</td>
<td></td>
</tr>
<tr>
<td>Paper IV</td>
<td>Recurrent musculoskeletal pain</td>
<td>Sleep</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gross Motor Function Capacity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Participation</td>
</tr>
</tbody>
</table>
Paper I: “Characteristics of recurrent musculoskeletal pain in children with cerebral palsy 8-18 years old.”

One hundred and fifty three participants, aged 8-18 years, were assessed with clinical examination, interview and questionnaires. The assessment of pain was performed stepwise. First, children and parents together were asked for any kind of recurrent pain. If recurrent pain occurred, the child indicated its maximum intensity within last month on the FPS-R before children and parents responded separately to the two questions on pain in the CHQ and to questions on localisation and impact of pain. CP type distribution was unilateral spastic 38 %, bilateral spastic 55 %, dyskinetic 6 % and ataxic 1 %. GMFCS levels were I 35%, II 37%, III 13%, IV 5% and V 10%. Ninety-five (62 %) children across all GMFCS levels experienced recurrent musculoskeletal pain related to CP (RMP) as judged by the professionals running the study. Age above 14 years was the only significant predictor with (OR 2.7). Children reported pain intensity to be moderate. Parents reported pain to be more severe and with higher impact on sleep than their children did. Children and parents reported similar impact of pain on general activity and walking. Multiple pain sites were usual and lower limbs (included hips) was the site of maximum pain in 70% of the children. The most common pain intensifier was walking or running and immobilisation. The most common pain relievers were rest and massage or change in position. Over-the-counter drugs alone or in combination with other measures had been used during the last month by 35% of the children. Three children did not take any measures to relieve pain.

Paper II: “Mental health, health related quality of life and recurrent musculoskeletal pain in children with cerebral palsy 8-18 years old.”

Eighty-three participants, median age 15.7 years, were assessed with clinical examination, interview and questionnaires. Gross motor function was GMFCS level I 42%, level II 42%, level III 12% and level IV-V 5%. Children self-reported mental health on the SDQ, HRQL on the PedsQL, and pain on the CHQ. Mothers proxy-reported on the same questionnaires and in addition reported their own mental health on the GHQ. Compared to Norwegian typically developing children, children reported similar TDS and lower PedsQL total scores while mothers reported higher TDS and even lower PedsQL total scores. ICC between SDQ total difficulties score and PedsQL psychosocial summary score was ≥ 0.90 for both child and maternal report. RMP was associated with more mental health problems and reduced HRQL in
self-reports, but not in proxy-reports. Mothers reported that higher own GHQ scores were associated with more child mental problems and reduced child HRQL.

**Paper III: “Parent-reported participation in children with cerebral palsy 8-18 years old: The contribution of recurrent musculoskeletal pain and mental health problems.”**

One hundred and five participants, median age 14 years, were assessed with clinical examination, interview and parental questionnaires. CP type distribution was unilateral spastic 37 %, bilateral spastic 56 % and dyskinetic 7 %. GMFCS levels were I 33 %, II 40 %, III 15% and IV-V 11 %. All parents reported child participation on LIFE-H, 95 parents reported child mental health on the SDQ, 88 reported socio-economic status, and 88 recorded own mental health on the GHQ. Parents reported that child RMP was associated with reduced accomplishment and reduced satisfaction with the accomplishment of both daily activities and social roles. Higher SDQ scores were associated with reduced accomplishment of daily activities and social roles and with reduced satisfaction with the accomplishment of social roles. Parents also reported that higher GHQ scores were associated with reduced satisfaction with the accomplishment of daily activities. The operationalisation of participation concept in general is discussed in the paper.

**Paper IV: “Continuous intrathecal baclofen therapy in children with cerebral palsy; the timing of effects may have implications for therapy.”**

Thirty-five children who started CITB were followed for 18 months. GMFCS levels were III (two children), IV (13 children), and V (20 children) respectively. In cases of pain (33 children), this was assessed to be RMP before the child was accepted for CITB. Pain, number of awakenings during night, spasticity, gross motor capacity and participation were recorded the day before implantation of a pump for intrathecal drug infusion and after 6 and 18 months of treatment respectively. Reduced pain intensity, reduced pain frequency and improved sleep occurred within 6 months of treatment. Social participation improved within 6 months and continued to improve until 18 months. Gross motor function also improved, but with a latency.
6 Discussion

The present study claims that recurrent musculoskeletal pain is the main pain problem in children with CP, it gives self-reported mental health, and it includes both recurrent musculoskeletal pain and mental health in the assessment of participation. Further, a report on the course of pain and participation after the introduction of CITB is given. At the time of publication, such reports were scarce or absent. Strengths and limitations of the study are discussed in the following paragraphs. A discussion of how major outcomes relate to the ICD-10 and the ICF respectively, and how all variables relate to the ICF is included.

6.1 Discussion of major findings

Referring to the introduction - what frames of reference should guide our understanding of patient well-being? For a physician, the obvious answer – and the professional obligation - is knowledge and understanding of the medical condition; in paediatrics the developmental and familial perspectives included. In the present study, aetiology of CP and influence on the ICF level of body structure are not considered. Focus is on the accompanying features recurrent musculoskeletal pain and mental health problems, their potential relationship and potential impact on selected outcomes. The a priori assumption that pain as an unpleasant sensory and emotional experience (76) and mental health problems (153) are relevant to well-being is made. Both are subjective, and both may be regarded as patient reported outcomes (PRO) defined by the U.S. Food and Drug Administration (FDA) as “any report coming directly from patients about a health condition and its treatment” (154).

Pain

Inherent limitations considered; a main contribution of the current study is the finding that pain was musculoskeletal and related to CP across all GMFCS levels. A journal commentary on paper I (155) call attention to several papers on pain in paediatric CP from 1965 until today and states that most pain related to CP can be treated effectively with well-tuned multidisciplinary care; thus suggesting that pain is recognised in research, but still under-treated in medical practice. As discussed in the Introduction section, most reports on pain in paediatric CP do not review the origin of pain. Claiming that pain is related to CP and of musculoskeletal origin adds weight to the obligation of health care measures to relieve pain and forwards a direction of such measures.
The assessment of pain was piloted in the gait laboratory for a year before study start. The aim was to record all kinds of recurrent pain, but we soon experienced that few children reported headaches or stomach pain. This made us refine the questions and present a body outline for the recording of pain localisation two times - first the interviewer recorded pain localisations during the interview, then children and parents recorded localisations while completing questionnaires in private. In general, more localisations were recorded by the children and parents themselves, but still headache and stomach pain were recorded very seldom. This is not in accordance with a Swedish study of children in the general population, studying recurrent pain in the head, stomach or back (156). In this study, two thirds of the children reported at least monthly pain, one third reported weekly pain and 4 of 10 experienced pains from multiple locations. One might speculate that the experience of recurrent pain related to a specific health condition influence on reports of other kinds of pain, but I have not been able to find relevant literature on this topic.

Paper IV contributes with an example of medical treatment of RMP in multidisciplinary care and discusses how to tune the care after pain relief. Later reports on CITB do not address musculoskeletal pain in particular, but a recent retrospective study of 25 non-walking adults with CP also concludes that CITB relieved pain (157). A prospective study of children with severe spastic CP compared children receiving CITB to children waiting for CITB (158). Changes on the ICF level of body function (reduced spasticity and increased joint range of movement) after initiation of CITB treatment occurred together with an improvement of QoL in terms of comfort and ease of care. Changes in participation as expressed by PEDI total summary scores could not be demonstrated. In a randomised controlled study of non-walking children with bilateral spastic CP, children that received CITB obtained pain relief and mental health improvement as assessed by the CHQ, but PEDI total summary scores did not differ in the two groups (159). A follow-up study confirmed that pain relief and improved mental health persisted after 12 months, and also that PEDI total summary scores did not change (160). As only PEDI total summary scores are given in these studies, a comparison with the changes on the PEDI domain of social function in the present study is not applicable. Thus, the finding of pain relief in the present study is supported by later studies, while the finding of improved participation still has to be confirmed.

Recommended primary treatment goals for CITB are reduction in pain, reduced caregiver burden, improvements in sleep, sitting, QoL and activities of daily living (161); i.e. primarily
PROs. CITB is expensive, the carrying-out relies on considerable efforts from both families and health care providers and the treatment has a certain frequency of potential serious complications. Still, CITB is recommended in the treatment of severe spasticity in children with CP at GMFCS levels IV-V; despite lack of evidence that CITB could affect disability, function or QoL (162). However, caregivers’ satisfaction with CITB is reported to be high (157;160;163). A reason why CITB has remained a treatment option in this selected patient group might be that doctors do listen to patients and their caregivers.

In the ICD-10 (13), pain is not assigned to CP. Neither can pain be recognised in Chapter XIII “Diseases of the musculoskeletal system and connective tissue” (M00-M99). In the ICF (12), pain is coded on the list of body functions & structure (Chapter b2 Sensory Functions and Pain), but no specifications in the direction of tissue involved or localisation can be made in accordance with the ICF shifting the focus from cause to impact of disease. This indicates that the ICF, but not the ICD-10 gives a frame of reference for understanding pain in CP.

*Mental health problems*

Mental health problems is another known consequence of the underlying brain lesion in CP that tend to go under-recognised and therefore under-treated (62;164;165). The finding in the present study (paper II) of mothers reporting more child mental health problems than parents of typically developing youth contributes with a reminder of this health care challenge. From a research point of view, the finding is reassuring because it corresponds to previous findings, thereby indicating representativeness of the study population. The self-report on mental health represents the novel contribution of the study together with the report that RMP and mental health problems are associated according to the children. Corresponding to the latter, parents in the SPARCLE –study reported that pain was associated with more mental health problems (66). In contrast, in the present study, a potential association between RMP and maternal reported SDQ total difficulties scores did not obtain statistical significance. This may represent a type II error in the present study (less powered) or reflect real differences because of dissimilarities in study populations (current study population not representative for the total CP population), differences in the definition of pain (RMP versus pain in general) or different proxy-reporters (mothers versus parents).

Although the literature on self-reported mental health in children with chronic health conditions seems very scarce, reports on children with chronic health-conditions not involving
the central nervous system indicates that parents tend to overestimate mental health problems and in particular internalising problems (166;167). The SDQ website (153) gives normative data from eight countries, but self-reported data only from United Kingdom and Australia. In both countries, self-reported SDQ total difficulties scores are higher than parent-reported (UK: 10.3 SD 5.2 versus 8.4 SD 5.8 and Australia: 9.0 SD 5.6 versus 8.2 SD 6.1). Given the overlap between mental health and psychosocial HRQL/QoL issues, a reasonable hypothesis is that a similar pattern as in HRQL/QoL reports is about to emerge; that means children with health conditions report less problems than parents do while children without health conditions report more problems.

Mental health problems are covered in Chapter V “Mental and behavioural disorders” (F00-F99) in the ICD-10 and are, like pain, coded on the list of body functions & structure in the ICF (Chapter b1 “Mental Functions”). Where the approach of the ICD-10 is the categorical depending on reliable diagnostics of mental health disorder, the ICF offers a dimensional approach being able to encompass all levels and combinations of mental health problems. Thus, in the understanding of mental health problems in CP, the ICD-10 and the ICF are complementary, as stated on a general base in the background section.

**HRQL**

Proceeding to potential impact of disease, the framing is extended from impact on function in paper I to impact on HRQL in paper II; the HRQL construct thought to be closer to well-being than function. The distribution of HRQL scores in the present study contributes to the body of knowledge from similar studies. Mothers’ report being influenced by own mental health and underestimating child HRQL is in accordance with other studies (65;85;86;168), thereby indicating representativeness of the study population. A more original contribution is the observation that children with RMP reported that pain was less severe, but influenced more on HRQL than mothers believed. The children in the current study join Swedish children from the general population in stating that recurrent pain highly influence HRQL as assessed with PedsQL 4.0 generic score scale (156). The last contribution is national with a comparison of the HRQL of children with CP able to self-report and the general Norwegian population.

The HRQL concept can be retrieved neither in the ICD-10 nor in the ICF. It is argued that the ICF recognises a person’s own view of his health, but concerns have also been raised claiming
that the ICF overlooks the subjective experience of the individual and because the notion of client-centeredness is not built into the framework (14). According to the ICF manual, the concept of *personal factors* include “gender, age, coping styles, social background, education, profession, past and current experience, overall behavior pattern, character and other factors that influence how disability is experienced by the individual” (12). Thus, a reasonable statement is that the HRQL concept overlaps with the concept of personal contextual factors in the ICF, indicating that the ICF incorporates some aspects of well-being related to health. It has also been argued that the ICF recognizes the QoL concept, including the persons’ view of his own participation (1). Again with reference to the ICF personal contextual factors, it may as well be argued that the ICF incorporates elements of well-being that applies to all children.

*Participation*

In paper III and IV the framing of impact of disease is that of participation—a key concept or the key concept of the ICF. Study A contributes with a description of scores among children with CP on the full LIFE-H tool and an assessment of participation taking both pain and mental health problems into account. The results indicate that RMP and mental health problems are both associated with reduced participation and that parents’ satisfaction with child participation is influenced by their own well-being (paper III). Study B gives an indication that effective pain treatment may be associated with increased participation in a selected patient group (paper IV). On pain, the findings add to those of the SPARCLE-study (80) and contributes to an increasing body of knowledge of a sequence “CP → pain → reduced participation.” In contrast, I have not been able to identify other reports on relations between child mental health and participation.

A weakness of the study is that only proxy-reported LIFE-H scores are available. The LIFE-H holds elements of both objectivity (which tasks are performed and what assistance is needed) and subjectivity (perceived difficulty with performing a task and satisfaction). The LIFE-H domains follow the ICF closely and the questions correspond to the ICF performance qualifier that measures the difficulty the respondent is experiencing in doing things. Separate formats for self- and parent-report are not developed, and in general I am not aware of studies that compare self-reported and parent-reported participation. Given that parents of children with health conditions tend to underestimate child HRQL/QoL (85) and the similarities between
some HRQL/QoL and participation items, one might hypothesise that parents of children with CP may be prone to underestimating child participation as well.

A question of general interest is to which extent parental satisfaction is relevant in the assessment of child participation. The notion of participation as an objective outcome (87) does certainly not support neither the relevance of satisfaction (whether parent- or self-reported) nor incorporating the aspect of perceived difficulty in performing a task. Incorporating aspects such as intensity (107), child independence and child enjoyment (106) are in accordance with the definition of participation requiring “involvement in life situations,” but still challenges participation as an objective outcome. If participation is regarded an observable rather than an objective outcome, the latter challenges are overcome to a certain extent. On the other hand, both the “objective” and the “observable” view promote the inclusion of aspects such as frequency and diversity of participation. Thus, regarding participation as an observable, but not objective outcome might be a more fruitful approach along the road to both clarifying the interface between activity and participation and operationalising the participation concept.

One may also be allowed to question how participation is useful in understanding patient well-being. As discussed in the Introduction section, measures that claim to capture participation differ in their approach to the subjective element (108;109). The ICF itself is clearer than the LIFE-H instructions in telling that the Performance qualifier measures the difficulty the respondent is experiencing in doing things, assuming that they want to do them. In accordance with this, the CP consensus group promotes that “accompanying impairments should be classified as present or absent, and if present, the extent to which they interfere with the individuals’ ability to function or participate in desired activities should be described” (1). Thus, in participation, the gap between actual and desired performance may be a key factor, like the gap between experiences and expectations is said to be a key factor in the HRQL/QoL concept (84). At present, HRQL and QoL both seem to be closer to well-being than participation and the relations between HRQL/QoL and the ICF still need to be clarified. One recommendation is that of including an individual’s satisfaction with various aspects of life and overall quality of life as codes in the personal factors component of both the ICF and ICF-CY, when codes for that component are developed (169).
Family factors

The findings that parental mental health was associated with parental view on child mental health, child HRQL and satisfaction with child participation were not unexpected. Several studies have reported that child well-being, parental well-being and family function are related. Examples are studies from other health conditions than CP reporting that in general, poorer physical child health is associated with more problematic family situation (170-172), a study from Northern Russia including adolescents with diabetes, asthma and epilepsy finding that longer disease duration contributed to family dysfunction (173), and a recent Canadian study of school-aged children with CP reporting that parents are likely to experience high stress, increased time constraints and financial and psychological burden (174). In general, the literature on the associations between child and parental well-being seems to have obtained sufficient robustness to claim that parental stress, parental mental health or a similar construct should be included in most studies on child well-being as assessed by parents.

A shift from the family perspective to the ICF reference frame promotes a linking of family related variables to the ICF as contextual factors. The ICF contextual factors allow for the discussion of and evidence-gathering about how impact of disease may be modified by facilitators or barriers. Personal contextual factors are so far not further operationalised, while a list of environmental factors are provided. In the present study, the factors “Living together with both parents”, “Mother’s education” and “Parental mental health” have relevance for both “Support and relationships by immediate family members” and “Attitudes by immediate family members” on the ICF list of contextual factors, indicating that the ICF reference frame has the potential to take care of the family perspective and facilitate the inclusion of parental mental health (or similar constructs). This is also in accordance with the bio-psycho-social health approach being incorporated in the ICF.

Framing of the study

Given that participation may be too demanding to assess in an unambiguous fashion, the ICF still offers a reference frame useful to obtain a comprehensive understanding of a child’s status. The current study contributes with an example from paediatric neurodisability of how outcomes described by professionals (spasticity and joint range of movement), comprehensive PROs (HRQL and participation) and a variety of explanatory variables all may be framed by the ICF together with the health condition in question. In table 3, variables are sorted according to a tentative placement within ICF domains. The relations of GMFCS,
PedsQL, LIFE-H and PEDI to the ICF are discussed in the text. Elements of socioeconomic state are contextual factors that may be both environmental and personal as socioeconomic state may impact personal views. The same argument might be presented for family characteristics and probably also for parental mental health and parental satisfaction with participation. For the placement of variables such as spasticity, age and sex, the ICF is self-instructing.

<table>
<thead>
<tr>
<th>Impairments</th>
<th>Limitations and restrictions</th>
<th>Contextual factors (barriers or facilitators)</th>
</tr>
</thead>
<tbody>
<tr>
<td>x RMP</td>
<td>Gross motor capacity</td>
<td>Age and sex (I-III)</td>
</tr>
<tr>
<td>x Pain localisation</td>
<td>Pain impact</td>
<td>Social background (I-III)</td>
</tr>
<tr>
<td>x Pain localisation</td>
<td>Body map (I)</td>
<td>x</td>
</tr>
<tr>
<td>x Pain</td>
<td>Self-care</td>
<td>Mother’s education Years (I-III)</td>
</tr>
<tr>
<td>x Global intellectual Function, indicator (III)</td>
<td>Social function</td>
<td>x</td>
</tr>
<tr>
<td>x Mental health SDQ (II, III)</td>
<td>Social function</td>
<td>Parental mental health GHQ (II, III)</td>
</tr>
<tr>
<td>x Joint range of movement (IV)</td>
<td>x</td>
<td>Parental satisfaction with Global participation LIFE-H (III)</td>
</tr>
<tr>
<td>x Spasticity</td>
<td>x</td>
<td>Parental satisfaction with Accomplishment of daily activities LIFE-H (III)</td>
</tr>
<tr>
<td>x x x x</td>
<td>x</td>
<td>Parental satisfaction with Accomplishment of social roles LIFE-H (III)</td>
</tr>
</tbody>
</table>

* Limitations and alternative placements are discussed in the “Discussion” section of the text.
6.2 Methodological issues

6.2.1 Study design and stability of findings.

Due to the cross-sectional design of study A, the stability of findings can be questioned. In general, a potential lack of stability may relate to the measures or to the states being measured. The reliability of the Norwegian versions of PedsQL and CHQ is tested and found satisfactory (116;135). The reliability of the Norwegian version of SDQ is not formally tested, but the SDQ is widely used both for research and clinical purposes (130;132;175;176) and the distribution of SDQ scores in typically developing youths are found to be very similar across the Nordic countries (129). The Norwegian version of LIFE-H has been translated according to international guidelines and cultural validity and reliability studies (content- and construct validity and test-retest reliability) have been performed, but not yet published (Reidun Jahnsen, personal communication). Concerning the states being measured, pain is a fluctuating phenomenon. The time span asked for by the instruments used correspond to a certain extent; the CHQ asks for “last 4 weeks”, the PedsQL asks for “last month” while the SDQ asks for “last six months.” We chose the shortest time-span for the impact and localisation of pain reported on the BPI and the maximum pain intensity reported by the children on the FPS-R to ensure that the time-span of last four weeks was covered by all instruments. During the interviews, some children gave the impression of uncertainty of a time span of four weeks or one month, but still seemed confident with the term recurrent pain. This may indicate that they recognised a state of recurrent pain as something stable enough to help them answer the other questions on pain. Another major limitation of cross-sectional observational studies is the limited possibility to conclude on causality because all information is collected at the same time (177).

The longitudinal design of study B is the stronger regarded the stability of findings. Spasticity defined as “velocity dependent increase in stretch reflexes” should be a precise sign (178) reflecting a stable state, but the MAS also reflects muscle tone that may fluctuate in a child. The stability of MAS should therefore be questioned.

6.2.2 Representativeness of the study population

In study A, a major weakness is that participants are not selected randomly from a population-based register. Unfortunately, recruitment from the Cerebral Palsy Register in Norway was not an option, as this register only covers birth cohorts from 1996 and younger. Looking at the representativeness of the population-based group, an estimated prevalence of 2.1 per 1000 live births 1996 -1998 in Norway (5) indicate 131 potential participants born in the area and a
capture rate of 57% with no correction for migration. An estimated CP point-prevalence of 2.4 per 1000 inhabitants born 1992-1993 in Sweden (179) indicate 164 potential participants living in the geographic area, giving a capture rate of 47%. Most participants (76%) were recruited from the habilitation units. There is one habilitation unit in each county having the responsibility for the county’s inhabitants. The number of invitation letters sent from each unit was compared to the estimated number of potential participants from the corresponding county. The results varied from 41 -110%. Inadequate patient registers in the habilitation units are therefore considered a main reason for the somewhat disappointing enrolment in the study, but give no concerns in the direction of selection bias beyond the general concern that children with the most minor impairments may not be registered. We regard the distribution of CP types and GMFCS levels as comparable to that found in population studies (5;42-44), indicating that the group may be non-biased with respect to these aspects. Still, a volunteer bias (177) may be present, as we do not know whether the volunteers that participated in the study differ from those who did not. Proceeding to the hospital-based group, obviously, non-walkers are not represented. We also expected a bias in the direction of children with minor motor impairment not being referred. Somewhat reassuring, the gross motor impairment was classified as GMFCS I in 32%.

In study B, the study population is regarded representative for children found eligible for CITB at the time present as the selection of patients followed recommendations in a consensus document from 2009 (161). Further, the majority of patients being non-walkers (94%) are in accordance with both previous (180;181) and more recent studies (157;182). Rikshospitalet was the first Norwegian hospital to offer CITB treatment to children, and started to do so in 1998. The number of patients treated was increasing from 1998 and reached a plateau in 2003, indicating that a steady state between referrals and treatment was obtained. Rikshospitalet is still the only hospital in the South-East part of Norway offering CITB. Professional communication between actual hospitals is good and patients living in South-East Norway are not expected to be referred to other hospitals. Neither are hospitals in regions not offering CITB expected to refer to other hospitals than Rikshospitalet. As all medical pump implants are registered at the time of implantation, we know that no patients were lost to follow-up.

Both gait analyses and CITB were performed within the public health care system; thus major selection biases on socioeconomic factors in the two hospital-based groups are not expected.
6.2.3 Measures – validity and overlap

**Pain**

The PedsQL include one question on pain on the domain of physical functioning. Only pain frequency is assessed, which was regarded insufficient in the present study. Still, one should be aware that pain influence on PedsQL total score. Study B relies on parents’ observations of pain behaviour that are not standardised. A validated observational instrument such as the Face Legs Activity Cry Consolability Scale (FLACC) (82) or a questionnaire with known psychometric properties might represent more reliable options.

**Mental health and HRQL**

The validity of the SDQ is questioned in children with severe motor and intellectual impairment (66), while the validity as a screening instrument for mental health problems in children without intellectual or physical disabilities seems well established (128;130-132). Thus, in the present study, the assessment of mental health in children that were able to self-report is probably more valid than the assessment of children not able to self-report.

The items in the PedsQL focus on functioning and what the child can do, which obviously may be affected by the motor impairment in CP. This is relevant both for the physical domain and for some questions on the psychosocial domains, exemplified by the item “it is hard for me to keep up with my peers” on the domain of social function. Further, even if the PedsQL demonstrates some general challenges of the HRQL construct as pointed out in the Background section, PedsQL might still be regarded a relevant measure in CP because motor function is an important part of the CP health condition. A CP module of PedsQL is developed with more items reflecting the motor impairment on all domains in addition to four items on Pain and Hurt on the physical domain (134). In longitudinal studies or in studies not intended to compare scores with typically developing youth or across health conditions, the CP module is probably the better choice because of greater sensitivity than the generic core set alone (134). In general, despite the conceptual challenges discussed in the Background section, HRQL might be regarded a more relevant outcome measure than QoL in (re)habilitation medicine; simply because health issues and impact of health conditions are the primary focus of health care services.
Similarities between the items of SDQ and the PedsQL psychosocial domains are reflected in observations of correlation (167;183), but to my knowledge, results of content analyses comparing the two constructs has not been published. Still, PedsQL is reported to be strongly related to behaviour assessed with Child Behavior Checklist (CBCL) (184).

**Participation**

As discussed previously, the LIFE-H holds elements of both objectivity and subjectivity and separate formats for self- and proxy-report are not developed. Thus, the process of validation seems not yet to be completed even if the content validity is regarded as satisfactory (105). On the other hand, the instruction is clear in asking for how the person *usually* accomplishes a life habit. The domains follow the ICF closely and the questions correspond to the ICF performance qualifier that measures the difficulty the respondent is experiencing in doing things in daily life. The PEDI is clearer on who is the reporter than LIFE-H in asking for the *observations of a primary caregiver*. It is also clear in using the interview format, where LIFE-H may be administered as a questionnaire or given as an interview. The Functional Skills Scale of the PEDI asks about what a child *can* do in his/hers daily environment, by some authors labelled capability (138). Still, the scoring instruction tells to give a score of one only if the child *usually* performs a task, indicating that PEDI captures performance as necessary for being a measure of participation. In accordance with this, the conceptual basis of both PEDI and LIFE-H is found to match the ICF concepts of activity, participation and environmental factors (adaptations and devices) to a large extent (138). Also the PedsQL is reported both to cover the ICF substantially (185) and to be strongly related to function assessed with PEDI in 2-3 years olds (184). In general, the reasons given for the suggestion to incorporate QoL and participation in the classification of CP (1) might as well be applied for other complex, chronic paediatric health conditions. Examples are rheumatoid arthritis, cancer survivorship, post organ transplants and severe congenital heart defects.

**Motor function**

In study B changes in motor function was assessed both with PEDI and GMFM. The two measures comprise different approaches, and are complementary rather than overlapping. Reliability tests of the Norwegian version of GMFM are not published internationally, but the GMFM is widely used and is still regarded useful by the Norwegian National Cerebral Palsy Follow-up program (186). The issue of changes in motor function due to natural child
development is generic and is incorporated in the validation process of all measures that intend to assess paediatric function.

**Spasticity**

The MAS assesses resistance to rapid, passive movements. Even if the inter-rater reliability in measuring muscle tone is regarded acceptable (125;126), the validity of MAS in the assessment of spasticity has been profoundly questioned (187;188). The importance of spasticity for functional outcome in children with CP is also doubtful (189), indicating that the MAS outcome does not contribute substantially to the validity of study B.

### 6.3 Implications

#### 6.3.1 Clinical implications

The findings in the current study support that a bio-psycho-social approach is relevant in the health care for children and adolescents with CP. Monitoring of pain, mental health and family wellbeing should be part of the clinical follow-up across the whole range of motor impairment. The child’s own perspectives should be recorded when possible in addition to that of the parents, as children and parents tend to have different views on impact of pain, on mental health and on HRQL. Systematic assessment of HRQL may serve as a tool to broaden the scope of the consultation in (re)habilitation towards both pain and psychosocial issues. Close cooperation between (re)habilitation and child psychiatry can assist in making proper psychiatric diagnoses, tailor individual measures to relieve mental health problems and take care of the family perspective. The ICF classifications might be helpful in describing the child’s condition precisely in a shared language, but participation as a comprehensive PRO at present seems to be less useful for clinical purposes because of its limited operationalisation.

#### 6.3.2 Research implications

The main limitations of the present study (small numbers, cross-sectional design of study A) invite to conclude that more powered or better designed studies are needed on the specific topics addressed. I find it more fruitful to draw attention to the ongoing discussion on how to develop the evidence base in paediatric neurodisability in general. An editorial in a leading journal on the field states that “the criterion of a randomised controlled study may not be able to address the big questions in
neurodisability (190). Further, the need for multicenter studies and long-term-follow-up is widely agreed upon (191;192). Bearing this in mind while returning to the topics of the current study, the course of pain and mental health problems from childhood through the transition into adult life need to be explored across all GMFCS levels, as do the impact of interventions aimed to prevent or relieve pain and/or mental health problems. Studies on children’s narratives on pain experiences have the potential to give new insights into the pain problem. On self-reported mental health, more powered studies are warranted; both on mental health in general and in more detail on the different elements of mental health.

As previously discussed, the concept of participation needs to be further clarified and operationalised both in general and in relation to children with CP. In addition, much is yet to be explored about how the ICF-CY relates to other measurement tools useful in paediatric neurodisability research. In CP, the impact of mental health problems on participation deserves further study, in addition to research on resilience factors or which factors promote activity and participation. An example of the latter is a Canadian study reporting that in school-aged children, high motivation in mastering challenging tasks was associated with fewer activity limitations and behavioural problems and reduced family burden (193). A path of potential interest would be to include resilience factors in studies of the impact of interventions such as intensive motor training and orthopaedic surgery that tend to decrease participation and probably also QoL/HRQL in the short run even if the aim of the interventions in the long run are said to be increased QoL/HRQL and participation. In general, a bio-psycho-social approach will be needed in most studies to catch the comprehensiveness of the CP disorder.

6.3.3 Concluding remark
The WHO defines health as “a state of complete physical, mental and social well being and not merely the absence of disease or infirmity”(194). In CP, a basic element in the understanding of the medical condition is that a state of absence is unattainable with today’s knowledge. The ICF is mandatory in paying respect to the impact of disease and offers a comprehensiveness that in my opinion makes it the reference frame of highest relevance in both clinical practice and research concerning chronic conditions. The ICF also offers the common language that is necessary to incorporate the patient’s own views of what concerns disease. Ancient Rufus prepared the field.
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Erratum:
In Paper I, the first word in the main document should be “Pain”, not “Musculoskeletal pain”.