Multidisciplinary management of Complex Regional Pain Syndrome Type 1 in Children admitted to Red Cross War Memorial Hospital:

A case series describing long-term effects on Pain, Function and Quality of Life

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Declaration

I, …Mariesa Nock……., hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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Abstract

Background

Complex regional pain syndrome (CRPS) is characterised by neuropathic-type pain in a regional distribution with associated signs and symptoms including: swelling, change in temperature, change in skin colour and motor dysfunction. Although CRPS is not a common condition, the disease burden is high and can lead to long-term impairment and disability. Current guidelines for the management of paediatric CRPS are mostly extrapolated from adult data. Literature regarding treatment and long-term prognosis of paediatric CRPS is sparse and often lacks well-defined and reproducible outcome measures.

Aim

This study aims to assess the efficacy of treatment of CRPS Type 1 in children admitted to Red Cross War Memorial Children's Hospital (RCWMCH) in eliminating pain and improving function.

Methods

A retrospective folder review and follow-up telephonic survey of all children admitted to RCWMCH over a 5 year period was performed. Long-term follow-up was defined as a minimum of 6 months after discharge from hospital. Follow-up questionnaires included the Faces Pain Scale, and the Paediatric Quality of Life Inventory Version 4 generic core scales (PedsQL 4.0).

Results

Nine children with confirmed CRPS Type1 were included in the study, all of whom participated in long-term follow-up. Children received in-hospital treatment from a multidisciplinary team, including intensive physiotherapy and psychological therapy. Pharmacological treatment consisted of an intravenous ketamine infusion and varying combinations of gabapentin, clonidine and amytriptilline. One child received epidural local anaesthetic infusion. On average, pain scores improved by 67.8% by the time of discharge. At an average long-term follow-up interval of 10.3 months (ranging between 6 to 21 months), the pain score had worsened by 10.5% compared to discharge. Two children (22.2%) experienced complete recovery while the remainder experienced partial recovery. Three children (33.3%) suffered a relapse, of which one recovered completely. At long-term follow-up, children for whom PedsQL 4.0 data was available from admission all demonstrated clinically meaningful improvements in all four functional

domains (physical, social, emotional and school). Children scored on average similar to healthy peers in terms of social, emotional and school function, but worse in terms of overall quality of life. The area most affected was that of physical function, in which children with CRPS scored worse than other children with chronic health conditions.

Conclusion

Children with CRPS experience significant improvement in pain and function with an in-patient, multidisciplinary, non-invasive treatment approach. Most children return to a level of school functioning comparable to healthy peers. However, the rate of complete recovery is low, relapse is common, and most children have significant persistent impairment of physical function. We recommend a long-term support program for children with CRPS and their families, and standardisation of follow-up intervals and outcome measures to enable comparison between future studies.

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Abbreviations

CRPS	Complex Regional Pain Syndrome
RCWMCH	Red Cross War Memorial Children's Hospital
PedsQL 4.0	Paediatric Quality of Life generic core scales version 4
IASP	International Association for the Study of Pain
CNS	Central Nervous System
fMRI	functional magnetic resonance imaging
NMDA	N-Methyl-D-Aspartate
TCA	Tricyclic antidepressant
SNRI	Serotonin Noradrenaline Reuptake Inhibitors
IV	Intravenous
DMSO	Dimethylsulphoxide
NSAIDs	Non-steroidal anti-inflammatory drugs

PT	Physiotherapy
GMI	Graded Motor Imagery
PRF	Pain Related Fear
LASB	Local Anaesthetic Sympathetic Block
VAS	Visual Analogue Scale
PPDI	Paediatric Pain Disability Index
SF-36	Medical outcome short form 36
CRPS1	Complex Regional Pain Syndrome Type 1
CRPS2	Complex Regional Pain Syndrome Type 2
FPS-R	Faces Pain Scale Revised
HRQOL	Health Related Quality of Life
GAD	Generalised Anxiety Disorder
ADHD	Attention Deficiency and Hyperactivity Disorder

SD	Standard Deviation
SEM	Standard Error of the Mean
MRI	Magnetic Resonance Imaging
MCID	Minimal Clinically Important Difference

Note on language and formatting of this document:

The article 'Multidisciplinary management of Complex Regional Pain Syndrome Type 1 in Children admitted to Red Cross War Memorial Hospital: A case series describing long-term effects on Pain, Function and Quality of Life" is presented in this dissertation in the format required for publication by "Pediatric Anesthesia". South African English was used for the literature review, but American English was used in the article section since this is an American journal. Vancouver style referencing is used, according to the author guidelines. Furthermore, Arial font size 10 was used, with double spacing, as specified by the journal.

CHAPTER 1 INTRODUCTION AND LITERATURE REVIEW

1 Objective

The objective is to perform a critical review of the current literature on complex regional pain syndrome (CRPS). Particular emphasis will be placed on literature regarding CRPS in children including the current understanding of its pathophysiology, treatment recommendations and long-term outcomes after treatment.

2 Literature search strategy

A search was conducted on Pubmed of publications from 1995-2015 using the following keywords: complex regional pain syndrome; children; paediatric; incidence; treatment; epidemiology; and pathophysiology. Research in adult and paediatric populations was reviewed with an emphasis on paediatric literature. Only articles in English or with a readily available English translation were included.

Focus was placed on systematic reviews, randomised controlled trials, prospective studies, cohort studies and case series. In areas where little information regarding paediatric CRPS was available, the search was extended to include adult CRPS. In adult studies, the focus was on systematic review articles.

3 Introduction

CRPS is characterised by neuropathic-type pain with significant autonomic features occurring in a regional distribution, usually involving one of the extremities, but it can also extend to the trunk (1,2).Neuropathic pain is defined by the international association of the study of pain (IASP) as ``pain caused by a lesion or disease of the somatosensory nervous system`` (http://www.iasp-pain.org/Taxonomy#Neuropathicpain). This differs from nociceptive pain that is defined by the

IASP as ``pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors`` (http://www.iasp-pain.org/Taxonomy#Nociceptivepain).

The pain is disproportionate to the initiating event and is complicated by other symptoms and signs in the affected area, including: sensory (allodynia, hyperalgesia); vasomotor (temperature and/or skin colour asymmetry); sudomotor (oedema and/or sweating asymmetry); motor (weakness, decreased range of motion, tremor) and trophic changes (changes in hair/nail growth)(3). It is most commonly preceded by a mild to moderate injury, but in about 10% of cases can occur spontaneously (4).

3.1 Diagnostic criteria

There is no gold standard diagnostic test available therefore, CRPS is a diagnosis of exclusion, based on clinical criteria, and relying on physician awareness of the disorder (5). The International Association for the Study of Pain (IASP) has validated the Budapest Criteria for the diagnoses of CRPS (6,7)(Appendix A) . Although these criteria have only been validated for the adult population, they are currently recommended for, and used in, the paediatric population (8). Distinction is made in the literature between CRPS Type I (no demonstrable nerve injury) and Type II (nerve injury demonstrated, but symptoms extend beyond dermatome), however, signs and symptoms are similar and there is no evidence of differences in the pathophysiology or treatment outcomes of the two groups (1).

3.2 Epidemiology

CRPS occurs in both adults and children, although the exact incidence in both groups is unclear (9). Incidence in adults is between 5.7-26 patients per 100 000 person years (10,11). In children, incidence is less well defined. Some of the large paediatric pain centres treat between 1-9 cases per year (12). Incidence could be higher, as milder forms of the disease may never present to paediatric pain centres. Although the incidence is fairly low, the impact of the disease can be devastating, leading to severe impairment and disability, both short- and long-term (13).

Increasing public and health-care worker awareness of CRPS is important in lowering the disease burden, since early diagnosis and initiation of treatment is associated with improved functional outcomes (14).

3.3 Pathophysiology

Current theories and evidence regarding the pathophysiology of CRPS suggest multifactorial mechanisms, which include: abnormalities of inflammation and immune response; central and peripheral nervous system sensitization; changes in somatosensory representation in the brain; autonomic disturbances; underlying genetic factors; local tissue hypoxia and psychophysiologic interactions (1,2).

Studies investigating the pathophysiological mechanisms have mostly been performed in adults, and whether the same mechanisms apply in children is uncertain (8). There are some differences between the clinical presentation of CRPS in children and adults, which would suggest the possibility of a differing pathophysiology. In a review by Stanton-Hicks *et al*., it was concluded that the current evidence suggests that the pathophysiology in adults and children is most likely identical, although the grading of the evidence upon which this conclusion was based is unclear (15).

Specific paediatric studies have investigated the hypothesis of cortical reorganisation in the Central Nervous System (CNS) by using functional Magnetic Resonance Imaging (fMRI). The outcomes demonstrate central reorganisation in the intrinsic brain networks of children with CRPS during the disease state compared to healthy controls, involving the sensory and motor cortices as well as in the hippocampus and hypothalamus. There is additional evidence of reversal of these changes following 3-4 week treatment interventions (16–18). This provides a fascinating avenue for assessing therapeutic effects, as well as a means of investigating underlying brain changes in non-responders, thereby enhancing our understanding of the disease process (8).

3.4 Validation of need for this research

There is a need for more comprehensive studies in the paediatric population, but the low incidence leads to problems of randomisation, blinding and adequate sample size (13). Currently, most knowledge is based on retrospective studies and case series, which are often of poor methodological quality and lack validated outcome measures, hampering comparison of outcomes (19). No studies regarding paediatric CRPS in Africa could be found in the literature search. Pain and functional outcome after injury is influenced by socio-economic, cultural and environmental factors (9,20,21). It is therefore important to assess whether CRPS in South Africa, has similar clinical features and treatment outcomes to that reported in studies from other countries. Using exact reporting of treatment and reproducible and validated outcome measures will enable comparison with other studies

4 Treatment

The current recommended treatment approach for both adult and paediatric CRPS consists of multidisciplinary management, including, but not limited to, the domains of pharmacological therapy, physiotherapy, occupational therapy, psychological and family therapy and invasive procedures in certain circumstances (5,22–25).

4.1 Pharmacological management

Current recommendations of pharmacological management in paediatric CRPS are predominantly based on data from adult CRPS or on paediatric non-CRPS neuropathic pain (12,24). Possible pharmacological treatment regimens include: simple analgesia, anticonvulsants, antidepressants, corticosteroids, bisphosphonate, calcitonin, free-radical scavengers and N-Methyl D-Aspartate (NMDA) antagonists (i.e. Ketamine, Memantine) (3,26,27). Multiple treatments are often used in conjunction, and dosing schedules vary or are not clearly reported in the literature, making it difficult to establish the effectiveness of a single treatment (27).

It is unclear whether anticonvulsants are indicated in the management of CRPS. The meta-analysis of treatment for CRPS in adults, published in 2014 by Wertli *et al*., reports gabapentin as having similar efficacy to placebo (26). Birklein *et al*. in a narrative review in 2015 similarly concluded that gabapentin may have only marginal effectiveness, which is unlikely to have clinical importance (28). In contrast, a more recent systematic review by Finnerup *et al*., (2015) recommends anticonvulsants, specifically pregabalin and gabapentin, as part of the first line treatment for neuropathic pain. However, it must be noted, that this review included studies of CRPS type 2, but not of CRPS type 1 (29). Despite this uncertainty in adult literature, anticonvulsant use is reported in various paediatric CRPS studies and case series (15,30). In the focused review by Katholi *et al*., it was concluded that anticonvulsants may be indicated in paediatric CRPS based on case reports of its benefit in paediatric CRPS (24). Gabapentanoids block the α2δsubunit on calcium channels in the dorsal horn of the spinal cord (31). Although reported as having minimal side-effects and being well tolerated, the long-term safety of these medications and effect on the central nervous system in children remains a concern (8).

The use of a tricyclic antidepressant (TCA), most commonly amitriptyline, is reported in various paediatric CRPS studies (15,17,23,30,32,33). This practice should be questioned, since Cossins *et al*., in a systematic review in 2013, concluded that there is no evidence for the use of antidepressants in adult CRPS (34). In contrast, the more recent 2015 systematic review of adult neuropathic pain recommends antidepressants, specifically TCA and serotonin-noradrenaline reuptake inhibitors (SNRI) as part of the first line treatment (29). As stated above, it has to be noted that this review only included studies of CRPS type 2 and not type 1. The SNRIs have not been widely used in the paediatric CRPS population, possibly due to less experience of its use relative to the TCAs. Similar concerns as with the anticonvulsants exist with regards to the long-term safety of the use of antidepressants in children (8), and considering the lack of evidence, one has to question the advisability of its use in the paediatric population.

The use of corticosteroids is based on the hypothesis of abnormal immune activation in CRPS (1). Corticosteroids reduce posttraumatic inflammation, oedema and swelling and may be useful as treatment of the acute stages of the disease(28). Direct clinical-trial evidence for its use in the early stages of CRPS exists and its use is recommended in adults with CRPS (26–28).

Once again, its use has not been specifically examined in paediatric CPRS and Katholi *et al*., expressed concern that appropriate clinical indicators may not have been adequately elucidated for its use in children (24).

Three phase bone scans in people with CRPS often show patchy osteoporosis and osteopenia of the affected limb, presumably from osteoclast activation (1). The rationale for the use of bisphosphonate and calcitonin as treatment is based on its osteoclast inhibition properties (35). In their meta-analysis Wertli *et al*., found bisphosphonates and calcitonin to be the most effective in terms of pain reduction compared to other treatment modalities. Bisphosphonate is recommended where symptom duration has been less than 12 months and calcitonin for symptoms present for longer than 12 months (26,28). The use of bisphosphonate has shown promising results in a case report of an 11 year old girl with CRPS (36). The use of calcitonin (mostly in the intranasal form) as treatment in paediatric CRPS is reported (12,19), but the efficacy and safety of treatment in the paediatric population has not been formally investigated (24).

The use of NMDA antagonists as treatment is based on the theory of underlying central sensitisation in CRPS and the effect of NMDA as a neurotransmitter. Pain relief is believed to be achieved via modulation of spinal cord NMDA receptors (34,37). The systematic review by Cossins *et al*., the meta-analysis by Wertli *et al*., and the recent Cochrane review by O'Connell *et al*., all concluded that there is low to moderate quality evidence for the use of low-dose intravenous (IV) ketamine in adult CRPS (26,34,38). A recent study of longitudinal intravenous subanaesthetic ketamine infusion in children with pain syndromes has reported it as both safe and effective treatment, with the greatest effect seen in CRPS (39). Despite its potential as a drug of abuse and its side effects at higher doses, reviews on the topic do suggest ketamine as a treatment option in paediatric CRPS (24,27).

The use of free-radical scavengers is based on the underlying theory of local tissue hypoxia leading to cellular damage via oxygen free radicals (1,40). Topical dimethylsulphoxide (DMSO) cream (50%) has shown better efficacy than placebo in improving CRPS symptoms (22,38). Comparable results were achieved with 50% DMSO cream and oral N-acetylcysteine, another free radical scavenger, in improving CRPS symptoms (22,41). Vitamin C in high doses (500mg per day for 50 days) has prophylactic use in decreasing the incidence in CRPS after dorsal radius

fracture in adults (22,34). Tan *et al*., reports using free-radical scavengers as part of the standard treatment protocol in paediatric CRPS (4,40). Although no specific evidence for the use of free-radical scavengers in paediatric CRPS could be found, in a focused review by Katholi *et al*., it was concluded that Vitamin C may be indicated in paediatric CRPS (24).

Simple analgesia, including acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs), have often been neglected by patients and practitioners in the treatment of CRPS, possibly because of the belief that these drugs are too simple for such a complicated condition (27). There is however Level 4 evidence[1] for the use of NSAIDS in CRPS and Level 3 evidence[2] for their use in other neuropathic pain conditions (27). Due to good safety profiles and efficacy, its use is recommended as part of the multimodal treatment approach to pain management in CRPS (3,22,26).

Evidence of the pathophysiological contribution of underlying vasoconstriction to CRPS has led to vasodilators being trialled as treatment (1,2,28,37). Tadalafil is the vasodilator that has been specifically studied in CRPS and the meta-analysis by Wertli *et al*., concluded that vasodilators showed better long-term pain reduction in CRPS than placebo (26). Contradicting this, the Cochrane review by O'Connell *et al*., judged that there was only very poor quality evidence that Tadalafil may have a short-term benefit in pain reduction but that this was unlikely to be clinically significant (38). The evidence for the use of vasodilators in adults does not currently hold sufficient medical advantages to warrant clinical trials in children (40).

[1] Level 4 evidence includes anecdote, case reports and clinical experience

[2] Level 3 evidence includes retrospective studies, open-label trials and pilot studies

4.2 Non-Pharmacological management

4.2.1 Physiotherapy

Physiotherapy (PT) is recommended in the literature as an essential component for the treatment of CRPS, in both adults and children (12,24,25,28). Functional restoration should be the focus of treatment and all other treatment modalities should be aimed at facilitating participation in rehabilitation (27). In adults, there has been low quality evidence that PT, combined with medical management, is more effective than occupational therapy and social work combined with medical management (38). However, the effectiveness of PT as stand-alone therapy has been difficult to establish, due to the fact that multiple treatment modalities are often employed concurrently (19,38,42).

Within PT, there is a wide variety of possible treatment modalities (19). Of these, graded motor imagery (GMI) has received the most support in recent literature (42,43). This treatment is based on the observation of cortical abnormalities in CRPS, and is aimed at activation of cortical networks that represent the affected limb without actual limb movement. Various techniques are employed, such as: hand laterality discrimination; imagined movements and the use of mirror box therapy (44). Mirror box therapy involves observing the movement of the reflected image of the unaffected limb in a mirror (45). Level II evidence exists that GMI is effective in reducing pain in adults with CRPS-1 and that the effect persists six months after treatment (42,43).

A recent systematic review on the use of PT for children with CRPS points out that the evidence to support PT in adults is of greater volume and higher methodological quality (19). However, the authors still conclude that the current evidence in paediatric CRPS suggests that PT (when prescribed with other interventions) may lead to short-term improvement in signs and symptoms as well as improve function.

4.2.2 Psychological Therapy

Various studies have refuted the once popular belief that people with underlying psychological problems or personality types may have a tendency to develop CRPS (46–50). That being said, it is well established that suffering from a chronic pain condition has profound psychological impact and this should be addressed as part of the multidisciplinary treatment approach (1,25). For example, pain related fear (PRF) manifests itself in chronic pain conditions as a behavioural adaptation that leads to avoidance of use of the affected body area(51,52).

A recent study by Simons *et al.,* using functional MRI, demonstrated blunted activation in brain regions associated with emotional processing in children suffering from CRPS(53). Bruehl *et al*., suggest a psychological treatment approach that includes education about the pathophysiology of CRPS, the negative effects of disuse and possible psychological/behavioural interactions (49).

Children affected by CRPS are at an increased risk of developing depression and anxiety when compared to the general population (25). When compared to children with chronic back pain or headache, children with CRPS report greater functional disability and somatic symptoms, however overall psychological functioning appears to be similar between the groups, including similar scores on measurements of depression and anxiety (54). The importance of including psychological treatment as part of the multidisciplinary approach has been mentioned in various paediatric studies (30,32,46,55–57). Psychological therapies focus on teaching pain coping strategies and addressing pain-related beliefs and behaviours, relaxation therapy, assertiveness training and problem solving (24,42). In children with CRPS, family education becomes an integral part of the psychological treatment. In some instances admitting the child to hospital may be helpful in terms of disrupting underlying abnormal family dynamics (25). However, good results can also be achieved with an outpatient treatment approach including psychological and family treatment as part of the multidisciplinary team (58).

4.2.3 Other forms of treatment

A multidisciplinary approach is the current treatment recommendation in paediatric CRPS (25). Other forms of treatment mentioned in the literature with regards to treating paediatric CRPS include, but are not limited to, occupational therapy, recreational therapy, child life therapy, aromatherapy and acupuncture (12,30,32,57,58). In their review, Perez *et al*., concluded that occupational therapy may be beneficial in children with CRPS as part of the multidisciplinary approach (22,55). Recreational therapy may include activities like aquatic-, art-, music- and play therapy. By providing children with an opportunity to engage in preferred leisure activities, children may be more inclined to use the affected limb (24). While the focused review by Katholi *et al*., suggests that acupuncture may be a safe and beneficial option in children, the risk would be further reduced if needleless techniques like electro-acupuncture were used (24).

The exact role of adjunctive forms of treatments is difficult to establish since no studies investigating the efficacy of these modalities as stand-alone therapy could be found.

4.3 Invasive treatments

Various invasive treatments have been attempted as part of management in both adult and paediatric CRPS, including but not limited to IV regional blocks, sympathetic nervous system blocks, sympathectomies, neuraxial blocks and spinal cord stimulation (38). In adult CRPS, two 2013 Cochrane reviews concluded that the available data do not suggest that local anaesthetic sympathetic block (LASB) is effective for reducing pain (38,41). In addition, one of the reviews by O'Connel *et al*., evaluated the evidence for a range of other interventions in CRPS and graded the quality of evidence too low for any conclusions to be drawn regarding these interventions (38,41).

Recently, two narrative reviews of the paediatric literature with regards to invasive treatments for CRPS have been published (23,56). In terms of frequency of use in children, single sympathetic blocks are currently most commonly used, followed by local anaesthetic infusion via epidural

catheters and continuous sympathetic blocks. Spinal cord stimulation, regional anaesthesia and pain-directed surgery are also used, but less frequently (56). Both reviews conclude that the evidence for invasive procedures in paediatric CRPS is weak (56,59).

Good outcomes are often reported in studies employing invasive techniques, but the lack of control groups and validated outcome measures, limit the value of these results (56,59). Only one placebo controlled cross-over trial was found in children, testing the efficacy of lumbar sympathetic block with lidocaine, compared to IV lidocaine, and reported positive results with the lumbar block (60). However, treatment was part of a multidisciplinary treatment group and numbers were small, so the significance of the results is uncertain.

Some paediatric studies are steering away from any medical or invasive therapy and follow a purely rehabilitative approach, discontinuing all medication and performing no invasive procedures. Many of these patients have had previous invasive procedures. These studies report satisfactory outcomes, although, as seen later in this review, the lack of a clear definition of satisfactory outcome limits the interpretability of results (12,55).

In contrast, Rodriguez-Lopez *et al*. published a case series of 10 children in whom novel drugs (the 8% capsaican patch) and invasive techniques (epidural bupivacaine infusion for two weeks, followed by spinal cord stimulation if still symptomatic) were used in patients who failed to respond to a non-invasive treatment approach. They reported a good response in terms of pain and function with these interventions (23). Similar to other studies on invasive treatments, interpretation of results is hampered by the fact that there is no randomisation, no control group and small patient numbers with a selection bias.

Overall, current consensus in both adult and paediatric literature is that, since the evidence for invasive procedures is weak, these should be reserved for patients who fail to respond to non-

invasive approaches, with the aim of treatment being to enable more effective participation in rehabilitation (28,37,38,41,56,59).

5 Outcomes

Long-term outcome from a chronic pain condition is of interest both to the health-care worker and to the patient as a means of judging treatment success. Outcome is defined in terms of pain and function, both of which affect quality of life.

5.1 Pain

Improvement in pain scores is one of the main goals of treatment. Most paediatric studies report high percentages of complete recovery but do not always specify whether pain resolution was specifically measured. Brooke *et al*., report complete pain resolution in 78% of patients in their study) (57). Zernikow *et al*., used an 11-point numerical rating scale to measure pain. Their study reports an improvement in maximal pain score and average pain score from admission to follow-up from 9.2 to 5 (45% improvement) and from 7.8 to 3.9 (50% improvement), respectively (12).Tan *et al*., conducted a longitudinal study on children with CRPS and reported that 52% of patients were still complaining of pain at a median follow-up of 12 years. Using a Visual Analogue Score (VAS), they report a mean pain score of 6.0 at admission, and of 4.5 at follow-up (constituting a 25% improvement) (4). Sherry *et al*., used a VAS of 0-100 for reporting pain, and report that 43 out of 49 (88%) of patients were pain-free at a median follow-up of 5 years 3 months. Those with residual pain had a median score of 58 (55). Various studies don't report the specific measurement tool used to assess pain or pain outcome, but may refer to patients as being symptom free or having fully recovered (30,40,61,62). This could potentially lead to bias since patients might not report pain if not specifically asked about it. The time interval from admission to follow-up also varies between studies, and between different patients within studies, hampering comparison of outcomes.

5.2 Functional outcome

In treating chronic pain conditions, it is recommended to steer away from a focus on pain resolution and focus instead on functional outcome as a measure of recovery. There are various challenges in establishing what the long-term outcome of paediatric CRPS is, including variation between studies in treatment regimes, length of time to follow-up and measures of functional outcome used. Follow-up intervals also vary widely, for example Murray *et al*., had a mean follow-up of 6 months and Sherry *et al*., a mean follow-up of 5.3 years (55,61).

Measurement of functional outcome also differs between studies. Both Kachko *et al.,* and Sherry *et al.,* used an evaluation at follow-up, which included pain scores, physical assessment of limb function and questions regarding school attendance and ability to take part in age-appropriate activities to assess functional status. The studies reported a 78.5% and 88% complete recovery rate respectively (55,62). Zernikow *et al*., used the Paediatric Pain Disability Index (PPDI) and a Five-point scale of impairment in sport to assess outcome and reported a 50% average improvement in PPDI at follow-up and a 60% improvement of impairment in sporting performance (56).

In the longitudinal study, Tan *et al*., used the Medical Outcome Study Short Form-36 (SF-36) to assess functional status. They report that CRPS patients scored lower than the general healthy population in two out of the eight domains assessed at long-term follow-up. From the findings the authors argue that childhood-onset CRPS does not have better outcomes than adult-onset CRPS (4), differing from other studies quoting a more favourable outcomes in children.

6 Conclusion

CRPS in children is a diagnostic and therapeutic challenge, with profound impact on the quality of life of those who are affected by it. There is currently no gold standard diagnostic test or standardised treatment regime, and both the exact incidence and long-term prognosis are

presently unclear. Diagnosis and treatment is often based on guidelines for adult CRPS and non-CRPS neuropathic pain.

Therapeutic options consist of various pharmacological agents as well as non-pharmacological treatment modalities like physiotherapy and psychological therapy. The success rate of treatment is uncertain in the literature due to poor standardisation of treatment modalities, therapeutic goals and outcome measurement tools.

There is a need for high quality studies in children with CRPS, including randomised controlled trials, but the low incidence leads to problems of sample size and there are ethical concerns with having control groups. Currently, case series studies add valuable knowledge regarding incidence and treatment outcomes of paediatric CRPS. New or unconventional treatment regimens should be reported to build data on possible therapeutic options. In performing this case series, we aim to contribute to the growing body of data regarding possible treatment options and outcomes in paediatric CRPS. Additionally, we aim to determine whether CRPS in the setting of a developing country, has similar clinical features and prognosis to that reported elsewhere.

7 References

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CHAPTER 2 PUBLICATION-READY MANUSCRIPT FOR SUBMISSION TO PEDIATRIC ANAESTHESIA

For author guidelines of this journal, see Appendix B

1 Introduction

Complex regional pain syndrome (CRPS) is characterized by neuropathic-type pain, in a regional distribution, usually involving one of the limbs, but not limited to a specific dermatome. It may follow an injury, but can occur without any prior injury in about 10% of cases, and is characterised by continued pain that is disproportionate to the inciting event (1). Distinction is made between CRPS Type 1 (CRPS I) and Type 2 (CRPS II), which refers to the absence or presence of demonstrated nerve injury, respectively (1). It is a diagnosis of exclusion and depends on reported symptoms and observed signs from four categories, including: sensory (i.e. allodynia, hyperalgesia), vasomotor (temperature or skin colour asymmetry), sudomotor (oedema or sweating) and motor/trophic changes (weakness, decreased ROM, hair, skin or nail changes) (1). The current recommended diagnostic criteria is the Budapest criteria of the International Association of the Study of Pain (IASP) (2). Although only validated for adults, it has been adopted for use in the paediatric population (3).

The incidence of CRPS in children is unclear, but the largest pain centers in the USA and Europe reportedly treat 1-9 paediatric patients with CRPS per annum (4). The most effective treatment regime for paediatric CRPS is uncertain, and is mostly extrapolated from adult data or guidelines for non-CRPS neuropathic pain (5). Treatment usually consists of a multidisciplinary approach, with physiotherapy as the cornerstone, but can involve various forms of pharmacological treatments and invasive interventions (6,1). A higher quality of research is needed, but the low incidence of the disease poses a challenge, thus current paediatric data consists mainly of retrospective descriptive studies and case series (1). Long-term outcome data often does not report the time from treatment to follow-up or specify the outcome measures used (3). Furthermore, no case series in Africa could be identified in the literature search.

With this case series we aim to add to the growing body of data regarding paediatric CRPS. Pain and disease presentation can be socially and culturally influenced (7). Therefore, it is important to investigate whether children with CRPS in South Africa display a similar clinical course as children treated in other pain centers internationally. To facilitate comparisons we have used reproducible outcome measures and a minimum defined outcome period of 6 months or longer.

2 Methods

2.1 Recruitment

For the purpose of the study, we collected and reviewed all the folders of children who were admitted to Red Cross War Memorial Children's Hospital (RCWMCH), Cape Town, South Africa, with a diagnosis of CRPS Type I over a period of 5 years (1 June 2010 - 31 May 2015). Approval for the study was obtained from the Hospital's ethics committee as well as the University of Cape Town Faculty of Health Sciences Human Research Ethics Committee (Appendix C). All patients and their parents or caregivers were contacted for telephonic consent before the folders were analyzed retrospectively (Appendix D and E). Information regarding symptoms and signs were obtained from the folder and subjected to the Budapest criteria to confirm a diagnosis of CRPS I (8).

2.2 Retrospective folder review

Socio-demographic history and clinical course until referral to RCWMCH was extracted from the folders. No specific standard of classifying severity of the initial injury that led to CRPS could be found in the literature. Therefore, we used the following criteria to define injury severity: none (no known injury), mild (bruise, sprain, or repetitive strain injury), moderate (fall from height or hairline/stress fracture on x-ray) and severe (fracture or surgery). The clinical course, treatment received, invasive procedures performed, total number of days spent in hospital and readmission rates were recorded for inpatient treatment.

Patients were admitted to the orthopedic ward, under the joint management of orthopedics and the RCWMCH pain management team. The pain management team consisted of an anesthetist-directed, nurse-driven, multidisciplinary team, including physiotherapy, recreational therapy, aromatherapy and child life therapy by a therapist trained in child psychology. A psychiatric consultation was included if deemed necessary by the pain management team or requested by the patient or their family. Patients received daily intensive physiotherapy of between 2-4 hours. Modes of treatment included mobilization, graded motor imagery (including left-right discrimination, imaginary play, and in a few cases mirror box therapy) and graded exercise therapy(9).

2.3 Long-term follow-up

Long-term follow-up consisted of a telephonic interview and completion of questionnaires (Appendix F). Long-term was defined as a minimum of six months since admission to RCWMH. The Faces Pain Scale-Revised (FPS-R) was used to measure pain at follow-up (10)(Appendix G). This is a self-report measure, with possible values ranging from 0-10, using six animated faces representing varying expressions of pain and validated for use in children aged 4 and older (10).

The Pediatric Quality of Life Inventory Version 4 (PedsQL 4.0) Generic Core Scales was used to assess Health Related Quality of Life (HRQOL). The scale includes Physical functioning (8 items), Emotional functioning (5 items), Social functioning (5 items) and School functioning (5 items). The participant was asked how much of a problem each item has been during the past month (Appendix H and I). A 5-point response scale was utilized (0=never a problem; 1=almost never a problem; 2=sometimes a problem; 3=often a problem; 4=almost always a problem). Items were reverse scored and linearly transformed to a 0–100 scale (0=100, 1=75, 2=50, 3=25, and 4=0), so that higher scores indicate better HRQOL. The mean was computed as the sum of the items divided by the number of items answered (11). The scores from the study population as well as the change in scores over time, were compared to the normative data for healthy children and children with a chronic health condition, as defined by Varni *et al,* (11).

The telephonic interview included questions regarding full or partial recovery, time to symptom resolution, experience of a relapse and need for readmission, as well as any current treatment or medications taken related to CRPS pain (Appendix J). Time to Symptom resolution was defined as the time from admission to RCWMCH until being completely free of symptoms relating to CRPS. Partial recovery is described by Low *et al*., as persistent symptoms of CRPS, but a significant improvement in pain and ability to resume age-appropriate activities. A relapse is defined as recurrence of debilitating CRPS-related symptoms after being completely or near-completely (having been able to resume age-appropriate activities) symptom-free for a period of at least three months. (12)

3 Results

3.1 Sociodemographic and medical history

Ten children with a confirmed diagnosis of CRPS I were admitted to RCWMH pain centre over the study period. Nine patients were included since one patient could not be reached for telephonic consent. The socio-demographics and history of injury of the study population are summarized in Table 1.

Table 1: Sociodemographic characteristics of participants and nature of injury

Age	Gender	Injury	Site	Medical history	Psychiatric history	Referral Base
13	male	mild	lower limb	none	none	Private
9	male	mild	lower limb	none	none	Private
14	male	moderate	lower limb	Pyloric stenosis (repaired), GERD, Hashimoto's thyroiditis	none	Private
10	female	mild	lower limb	none	GAD, ADD	Private
9	female	moderate	lower limb	Asthma	none	Private
14	female	none	upper limb	Insulin resistance, Iron deficiency	none	Private
12	female	moderate	upper limb	Stargardt's disease	none	Private
12	female	mild	upper limb	Asthma, Allergic Rhinitis	none	Private
11	female	mild	lower limb	Constipation, recurrent abdominal pain, umbilical hernia surgery,	none	Private

All children were referred from the private medical sector. Stressors such as financial strain in the family was mentioned in two cases; a recent death of a close family member in one case and bullying at school in another.

Three children had no previous medical history, while two had asthma and one had iron deficiency and insulin resistance. One child had abdominal surgery for pyloric stenosis as well as a diagnosis of “sensory defensiveness” as a small baby, and as an older child, developed Hashimoto’s thyroiditis as well as gastro-esophageal reflux disease. One child was diagnosed with Stargardt’s disease (macular degeneration) shortly after being diagnosed with CRPS and another had a history of extensive investigations for unexplained abdominal pain, as well as umbilical hernia surgery a month prior to the onset of their CRPS symptoms. Only one child had a specific psychiatric diagnosis prior to the onset of CRPS symptoms.

The diagnosis was of generalized anxiety disorder (GAD) and attention deficiency and hyperactivity disorder (ADHD), for which the child was on treatment with Escitalopram and Methylphenidate respectively.

The time from initial injury to first seeking medical attention ranged from 1-30 days with a mean of 9.2 days (SD ± 9.1). The time from initial injury to referral to RCWMCH ranged from 2.5-27 months with a mean of 7.5 months (SD ± 7.8). Positive findings on investigations were reported in two children. One showed a bone bruise and the other signs of possible peroneus brevis tendonitis on MRI. The average number of health care consultations that patients attended before referral to RCWMCH was 7 (range 5-10). The average number of medications taken at the time of admission was 2.4 (range 1-3). The investigations conducted, consultations sought and treatment received prior to referral to RCWMCH are summarized in Table 2.

Table 2: Previous treatments, investigations and consultations prior to referral

Treatment/Investigation/Consultation	n=9
Pharmacological treatments	
Acetaminophen	9
Nonsteroidal anti-inflammatory drugs	9
Tramadol hydrochloride	6
Pregabalin	6
Amitriptyline	5
Oral steroids	2
Antidepressant	2
Non-pharmacological treatments	
Cast or splint of extremity	7
Outpatient physical therapy	9
Interventions	
Intra-articular steroid	1
Brachial plexus block	1
Femoral nerve block	1
Investigations	
X-ray	9
Magnetic Resonance Imaging(MRI)	8
Blood Pathology	7
Ultrasound	3
Nerve Conduction	1
Consultants	
Physiotherapist	9
Orthopedic Specialist	9
General Practitioner	9
Alternative Health	8
Physician/Rheumatologist	4
Emergency Room Doctor	3

Note that with regards to interventions, the numbers are non-overlapping, i.e. three different children each had one type of intervention.

3.2 Treatment at Red Cross War Memorial Children's Hospital

The average pain score on admission on the FPS-R was 8.7 (range 7-10, SD ± 0.97). The average number of investigations performed during admission at RCWMH was 0.5 (range 0-5, SD ±1.6), and no positive findings were reported. Eight children were admitted to hospital for an average number of 8.25 days (range 3-11, SD± 2.9). One patient was treated on an outpatient-only basis.

Only one child underwent an invasive intervention in the form of an epidural catheter with a local anaesthetic infusion. The catheter was inserted under general anaesthesia with the aim being to facilitate participation in physiotherapy, since the child could not tolerate touch or movement of the affected limb. The outcome of the intervention was poor. The child became severely distressed due to the decreased limb sensation and required sedation and removal of the epidural catheter. All the other children received non-invasive treatment only. See pharmacological therapy in Table 3.

Table 3: Pharmacological Treatment in hospital

Pharmacological Treatment	Dose	Number of Children
Gabapentin	15-35mg/kg/day	9
Amitriptyline	10mg nocte	4
Ketamine Intravenous Infusion	0.25-0.5mg/kg/hour for an average of 4.2 days	9
Clonidine	5-14 mcg/kg/day	9
Duloxetine	0.5-1mg/kg/day	2
Tilidine (Opiate) Oral Drops	1mg/kg/dose prn	1

Psychiatry was involved in the management of four of the patients. A fifth patient's family, in whom it was felt would benefit, declined these services. Specific psychiatric diagnoses included: Adjustment disorder (two children), GAD and ADHD in one patient (known with these diagnoses prior to development of CRPS), and a query of possible Somatoform disorder and preoccupation with pain (one child), whose family did not attend outpatient follow-up with psychiatry after discharge.

The average pain score on the Faces Pain Scale at discharge was 2.8 (range 0-8, SD ± 2.36). The average number of medications taken at the time of discharge was 2.5 (range 2-3, SD ± 0.52). These consisted of Gabapentin (nine patients), Clonidine (eight patients) and Amitriptyline (two patients), Duloxetine (one patient) or Fluoxetine (one patient) as well as Ibuprofen (nine patients) and Acetaminophen (nine patients) as needed.

3.3 Long term follow-up

The time from admission until follow-up ranged from 6 to 21 months, with an average time to follow-up of 10.3 months after admission. The average pain score at time of follow-up was 3.13 (range 0 -8) (Figure 1).

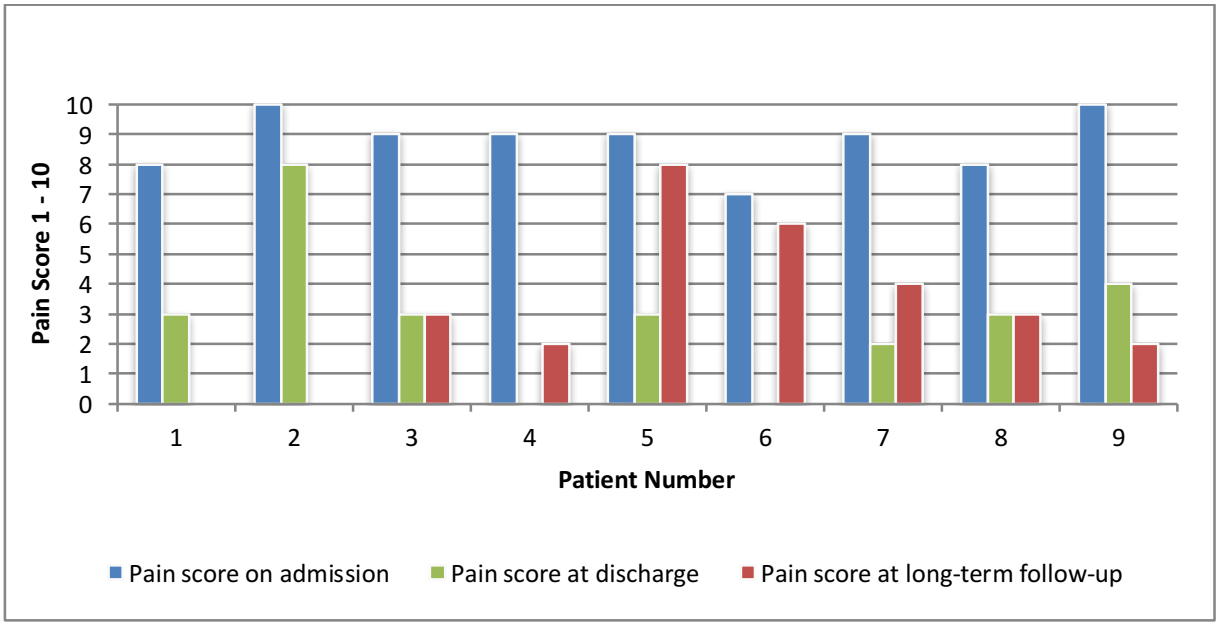


Figure 1. Pain score on admission vs. discharge vs. long-term follow-up

(Note: Columns that are absent represent a pain score of 0)

Of the nine children contacted for long-term follow-up, two (22.2%) were completely free of CRPS pain. The seven other children (78.8%) had residual symptoms of CRPS at the time of follow-up. Five children were still taking some form of medication for CRPS-related symptoms. The average number of medications taken was 1.12 (range 0-2).

Commonly used medications were Gabapentin and Clonidine. Others included Pregabalin, Amitriptyline, Fluoxetine and Sertraline.

Three children (33%) experienced a relapse of symptoms after having been free or nearly free of symptoms (able to resume age-appropriate activities) for longer than three months. In two cases, the relapse was linked to having decreased medication and resuming recreational activities. In both of these cases, the CRPS flare-up was in the same limb as the original case and the pain was rated of similar intensity. Both these children were still experiencing CRPS pain at the time of follow-up and one had required re-admission due to the relapse. In the other child, the relapse occurred eight months after having been pain free, triggered by a new injury and in a different limb than the original CRPS. The relapse was less severe than the first time and the child made a complete recovery within six months without requiring admission. One child experienced a recurrence of symptoms after having been free of pain for just over one week. This was linked to an episode of emotional distress. This did not qualify as a relapse according to our criteria, since the child was not pain-free for a period of three months or longer. This flare-up of pain required the child to be readmitted. Two children (22.2%) required readmission to hospital during the time of our follow-up.

Functional scores at long-term follow-up according to the PedsQL 4.0 are summarized in Figure 2. Mean scores for the study population in the various functional domains are compared to the scores for a healthy study population and for children with other chronic health conditions as derived from the work from Varni et al,(11).

Varni et al, defined a minimal clinically important difference (MCID) as being the smallest difference in a score in the various domains of physical function that would be perceived by patients as being beneficial and that would mandate a change in the patient's management. The MCID for PedsQL 4.0 scale scores was defined through calculating the Standard Error of Measurement (SEM), in which a change in score of one SEM represents a MCID. The value of the SEM for the respective functional domains are as follows: total score 4.36, physical function 6.66, emotional function 8.94, social function 8.36 and school function 9.12(11)

At long-term follow-up children from our study scored similar to healthy children (less than one SEM difference) in all three psychosocial domains (emotional, social and school functioning). In the domain of physical function, our study population's quality of life score was significantly (more than one SEM) lower than both healthy children as well as children with other chronic conditions (average score of 63.54 vs 87.27 and 79.47 respectively, the SEM being 6.66). The total score for children from our study population was also significantly (more than one SEM) lower than their healthy peers, but not lower than children with other chronic health conditions. ,

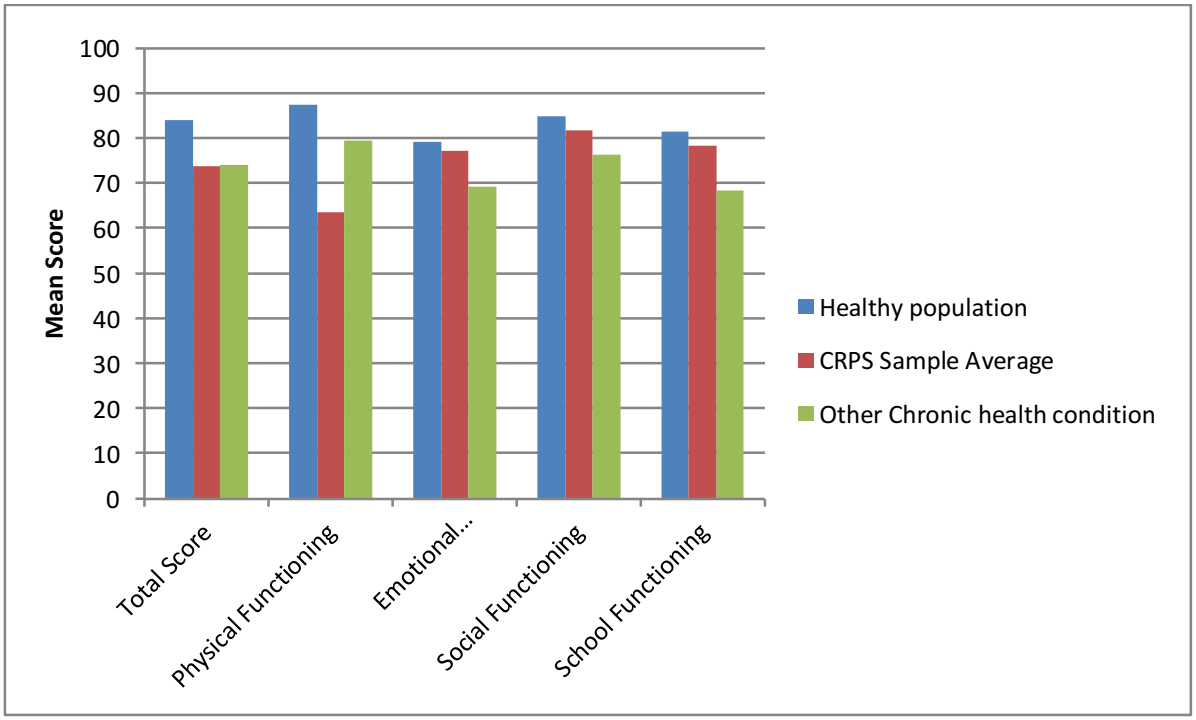
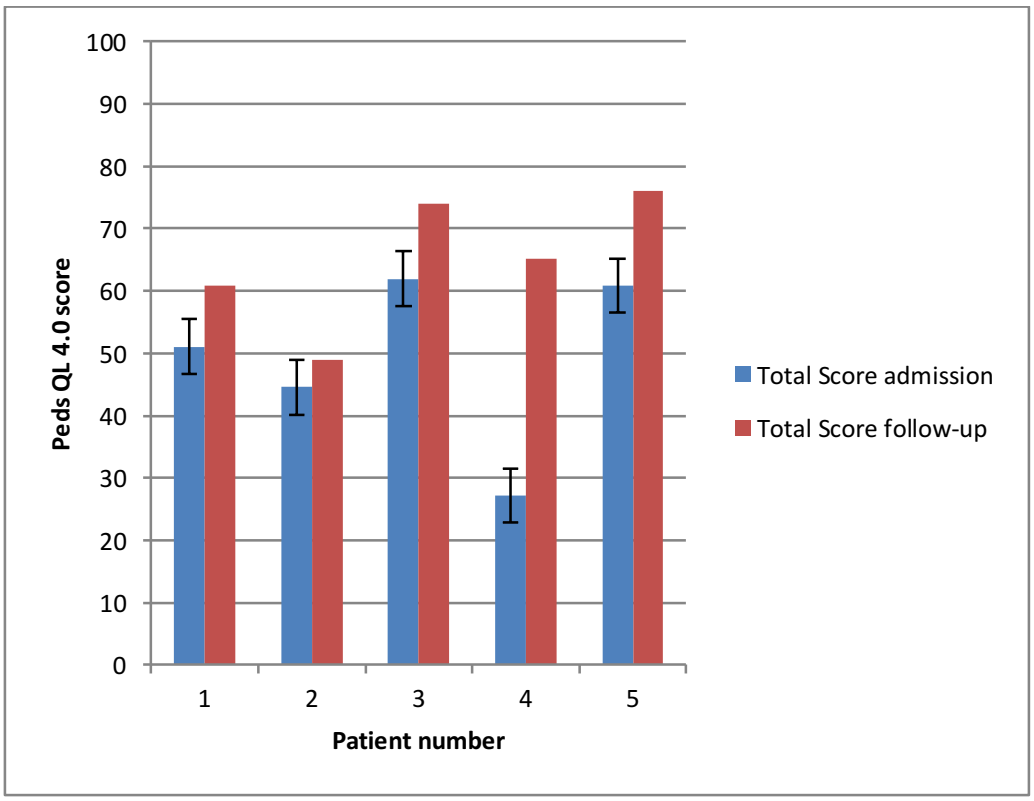


Figure 2: PedsQL 4.0 Scores: Comparison of CRPS sample to healthy and chronic health condition population groups at long-term follow-up

Five children had the PedsQL 4.0 tool administered during admission at RCWMCH. For these children a comparison was made between functional scores at admission and at long-term follow-up to determine change in HRQOL. As seen in Figure 3 all 5 children's overall functional score had improved by equal to or more than the MCID at the time of follow-up, in other words every child had a clinically meaningful improvement in quality of life (Figure 3).



Error bars on the admission column reflect SEM. Improvement by more than 1SEM is regarded as a MCID (see text)

Figure 3: PedsQL 4.0 score comparison between admission and long-term follow-up across functional domains for 5 patients

4 Discussion

The patients in our group demonstrated comparable socio-demographic characteristics as those reported in other paediatric studies (4,12–14). Similar to other studies, we noted the problems of delayed diagnosis, multiple consultations and investigations prior to referral and the use of invasive procedures prior to referral with poor treatment outcome(4,12,13). At the time of the study, all patients had been referred from the private medical sector. Possible reasons for this may have been established referral routes and awareness of the availability of treatment at RCWMCH.

Children demonstrated a good response to an inpatient, multidisciplinary treatment approach in terms of pain, function and quality of life. This corresponds well to positive results reported in other studies with a similar multimodal treatment approach (4,12,15,14,16), and recommendation of recent reviews on the subject (1,17). Hospital admission may not always be feasible and the improvement of the one child, managed as an outpatient, correlates with studies that show good results of outpatient management (18).

Our study showed an overall improvement in pain at discharge and follow-up as compared to admission. However, only two of the children (22%) had complete resolution of pain, markedly lower than reported elsewhere, for example a study by. Brooke *et al.,* reported complete pain resolution in 78% of 32 patients (14). These results may be influenced by the fact that 13 out of 32 children in the study were lost to follow-up. They reported that at the time of discharge, 34% of children were free of pain. It is unclear how many of these children took part in the final follow-up. Another possibility is that their longer follow-up period (21 months, compared to 10.3 months) allowed more time for full recovery. Our results are more comparable to those of Zernikow *et al.,* and Tan *et al*.(19,4) Zernikow *et al.,* reported an improvement in mean pain score from 7.8 at admission, to 3.9 at follow-up (4). One possible reason for the comparable results is that their follow-up interval of 6.7 months more closely resembles ours of 10.3 months. Tan *et al.,* reported that 52% of patients with childhood-onset CRPS still complained of pain after a median follow-up of 12 years (19). Possible reasons for the correlation with our results are that they had a fairly high survey response rate of 75% compared to 100 % in our study and 60% in the study by Brooke *et al*.,(19,14)

Another possible reason for similarity is that they used a specific pain measurement tool, the VAS, where we used the Faces Pain Scale that also makes use of visual representation of pain symptoms(19). Some studies do not specifically comment on pain outcome, rather a report on resolution of symptoms or recovery(12,16). Since specific follow-up measures were often not reported, it raises the question whether patients were truly free of pain in these studies, or refrained from reporting it.

The five children who had admission and follow-up data available for the PedsQL 4.0 questionnaire demonstrated functional improvement over time following treatment. Total functional score for all five children improved more than the standard error of the mean (SEM), which is the Minimal Clinically Important Difference (MCID) as specified by Varni *et al.*(11). With regards to the whole sample group, children with CRPS demonstrated a lower overall HRQOL than their healthy peers at follow-up and scored similar to children with other chronic health conditions. The area worst affected was the physical domain, with functional scores approximately one Standard Deviation (SD) lower than other children with chronic health conditions and close to two SD lower than their healthy peers (11). This correlates with the findings of Logan *et al*., that children with CRPS report greater functional disability and somatic symptoms compared to children with other pain conditions, although demonstrating similar psychological functioning (20). Of interest, is that despite the significant physical challenges, children with CRPS demonstrated excellent school functioning at long-term follow-up, comparable to healthy peers and better than children with other chronic health conditions. This could be a demonstration of the theme in literature that children with CRPS are often "high achievers" with strong personal drive and a tendency to be compliant (21,20).

Only two out of nine (22%) children had achieved complete recovery according to our definition (pain-free and having assumed age-appropriate activities), which is lower than the recovery rate reported in other studies. Low *et al.,* reported complete resolution in 92% of 13 children and Kachko *et al.,* in 78.5% of 14 children (12,16).The differences in reported recovery rates may be a consequence of unclear definitions of recovery in the literature and invalidated tools being used to assess outcome. Zernikow *et al.,* reported a 50% improvement in function at long-term follow-up, using the validated Paediatric Pain Disability Index, a result which more closely resembles the approach employed in this study (4).

Three children in our study (33%) experienced a relapse, comparing well to relapse rates reported in other studies (22% to 37%) (12,22,14,16)

We believe key elements in the success of treatment are the emphasis on intensive physiotherapy, with all other forms of treatment, including medication, psychological treatment and invasive interventions focused on enabling participation in physiotherapy. This corresponds well to other studies, which report a good outcome with conservative treatment emphasising physiotherapy (4,12,14,16). Physiotherapy should be aimed at mobilising and graded exposure, including graded motor imagery as a tool for treatment (23).

Informal conversation with caregivers highlighted that they found the support of the pain management team during admission and after discharge from hospital very beneficial. This was not formally assessed by us in our cohort, but is in agreement with other paediatric studies reporting support to be a crucial component of treatment (12,14,16). Important focus points contributing to the team's ability to provide support include teaching of pain management together with coping skills, behavioural and cognitive interventions delivered by all members of the pain management team. These include assistance in verbalisation of feelings, self-awareness and assertiveness. Family education and support also plays an integral role in treatment success (1,12).

Ketamine infusion at sub-anaesthetic dosages was used with good success in our series, reducing pain scores and enabling participation in physiotherapy, with minimal side effects reported. This is in agreement with recent paediatric literature, which reported an improvement in CRPS pain with sub-anaesthetic intravenous ketamine infusion (24). In our experience a longer duration of infusion was more beneficial than a shorter one, with our current aim being a minimum of three days, but ideally five days if tolerated.

The one child in our study that underwent an invasive procedure in the form of an epidural local anaesthetic infusion had a poor response. In line with current recommendations, our current treatment approach is to use invasive treatment options once non-invasive treatment has failed, and then only with the aim of supporting participation in physiotherapy (17,25).

Limitations of our study include the small number of patients, the retrospective nature of a case series, and the fact that there is no control group. The diagnosis was retrospectively confirmed by applying the Budapest Criteria to symptoms and signs recorded in the file. It is possible that some symptoms and signs were not asked about and therefore were not recorded. The PedsQL 4.0 tool was not consistently administered during admission, which hampered assessment of change in functional status over time. The normative data used for interpretation of functional outcome was obtained from a population different to our own. Normative data of the local population may be different, which could affect interpretation of results. At follow-up, patients were asked if they had ever been free from CRPS pain, but symptoms and signs were not objectively assessed using the Budapest Criteria. This could lead to patients reporting pain other than true CRPS symptoms and could affect the outcome data.

5 Conclusion

CRPS I in children can be effectively treated with a non-invasive multidisciplinary treatment approach, with an emphasis on physiotherapy, psychological support and family education. Often an inpatient treatment approach is required but good results are achievable in suitable outpatient candidates. In our study, intravenous ketamine at sub-anaesthetic doses was used with good effect to decrease pain and enable participation in physiotherapy. Overall, children demonstrated significant improvement in pain and good recovery of emotional, social and school functioning, despite having a lower physical functional status than other children with chronic health conditions. There is a need for clear definitions of treatment success and expectations, which should be discussed and agreed upon between the clinician, patient and the patient's family. Specifically, repeatable outcome measures of pain and function should be used to enable assessment of treatment progress and comparison between future studies.

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APPENDICES

Appendix A: Budapest Criteria

For a diagnosis of CRPS A-D must apply.

A) The patient has continuing pain which is disproportionate to any inciting event
B) The patient has at least one sign in two or more of the categories
C) The patient reports at least one symptom in three or more categories
D) No other diagnosis can better explain the signs and symptoms

Category	Explanation	Sign (you can see or feel a problem)	Symptom (the patient reports a problem)
1. Sensory	*Allodynia(* to light touch and/or temperature sensation and/or deep somatic pressure and/or joint movement) and/or *Hyperalgesia (*to pinprick)		*Hyperesthesia does also qualify as a symptom*
2. Vasomotor	Temperature asymmetry and/or skin colour changes and/or skin colour asymmetry	*If you notice temperature asymmetry: must be >1degree Celsius*	
3. Sudomotor/ oedema	Oedema and/or sweating changes and/or skin colour asymmetry		
4. Motor/Trophic	Decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia, and/or trophic changes hair/nail/skin)		

Reference: Harden RN, Bruehl S, Stanton-Hicks M, Wilson PR. Proposed new diagnostic criteria for complex regional pain syndrome. Pain Med. 2007;8(4):326–31.

Appendix B: Author guidelines for submission to Pediatric Anesthesia

SCOPE

***Pediatric Anesthesia*'s mission is to advance the science and clinical practice of paediatric anaesthesia, pain management and peri-operative medicine through dissemination of research, education and quality improvement.**

Priority is given to high-quality original research that advances knowledge, safety, organisation or methodology applicable to other settings and countries. We would particularly like to encourage the reporting of randomised controlled trials.

We will support our authors by posting the accepted version of articles by NIH grant-holders to PubMed Central upon acceptance by the journal. Authors must ensure that manuscripts are clearly indicated as NIH-funded using the guidelines below.

We accept articles with audio and video files (Podcasts). The published article links to the corresponding Podcast hosted on YouTube or iTunes. See our special feature page and submission policy below for more details**.**

POLICIES

Ethics

The journal's ethical policies are outlined in the separate document, Ethics Policy of Pediatric Anesthesia. These guidelines must be followed in full.

Consent for publication

Published article: If individuals might be identified from a publication (e.g. from images or description) authors must obtain explicit informed consent from the individual, or parent or guardian for children. Please do not confuse this with consent for the procedure. Consent, or IRB approved waiver of consent is required for studies involving human subjects.

A patient consent form is available in English: Patient Consent Form and in Chinese: Patient Consent Form - Chinese.

Audio/Video content: Authors are required to obtain the prior written consent of any other persons that are visible in the Video, or parental consent for any minor visible in the video, to use their image in the video clip.

In addition the author must complete an online broadcast release form available here

Plagiarism self-check policy

In line with most journals, *Pediatric Anesthesia* routinely screens all submissions for evidence of redundant material and plagiarism. We expect authors to have read and understood our originality requirements, specified in the journal's ethics policy.

The editorial team will contact the corresponding author if we discover significant overlap with published material.

Disclosures/conflicts of interest

Authors are required to disclose competing interests. A competing interest exists when a primary interest (such as patients' welfare or the validity of research) might be influenced by a secondary interest (such as financial gain or personal rivalry).The corresponding author, on behalf of all co-authors, should ensure the DISCLOSURE section (Submission step 5) is completed athttp://mc.manuscriptcentral.com/pan. A statement is required in the main document, at the end of the main text before the references.

For papers where there are no competing interests, include the statement 'Conflicts of interest: No conflicts of interest declared.'

Funding

All sources of funding **must** be disclosed in the Funding section of the paper. List governmental, industrial, charitable, philanthropic and/or personal sources of funding used for the studies described in the manuscript. Attribution of these funding sources is preferred. If in doubt – disclose. For further details, please refer to the Ethics Policy.

For research where no source of funding is declared, include the statement 'This research was carried out without funding.'

Peer review

All papers published in *Pediatric Anesthesia* are subject to peer review. Papers that are outside the scope of the journal, that do not comply with the guidelines below or are otherwise judged to be unsuitable by the editor will be rejected without review.

Appropriate papers are usually sent to at least two independent referees for evaluation. Authors are encouraged to suggest reviewers of international standing. Referees advise on the originality and scientific merit of the paper; the Editor-in-Chief, with advice from the Section Editor, decides on publication. The Editor-in-Chief's decision is final.

PRE-SUBMISSION ADVICE AND PREPARATION

Before submitting your manuscript, ensure that you refer to the requirements below, which explain the file types, structure and supporting information required for a successful submission.

SUBMISSIONS THAT DO NOT CONFORM TO OUR REQUIREMENTS WILL BE UNSUBMITTED. THE EDITOR MAY REJECT YOUR SUBMISSION IF THESE GUIDELINES ARE NOT MET.

Writing should be clear and simple, avoiding excessive use of the passive, and written in good clear 'international' English.

Particularly if English is not your first language, before submitting your manuscript you may wish to have it edited for language. This is not a mandatory step, but may help to ensure that the academic content of your paper is fully understood by journal editors and reviewers. Language editing does not guarantee that your manuscript will be accepted for publication. If you would like information about one such service please seehttp://authorservices.wiley.com/bauthor/english_language.asp. The Editor may recommend an English Language Editing Service to an author as a condition of acceptance. There are other specialist language editing companies that offer similar services and you can also use any of these. Authors are liable for all costs associated with such services.

Manuscripts and tables

In order to be processed by our production team, all files should be editable and saved as .doc or .rtf. Please note: PDF (.pdf) is not a .doc or .rtf file format and is therefore **not** an appropriate file type. Manuscripts should be double line spaced with 2.5cm margins. Use 10pt Helvetica or Arial font. Headings: main (section) headings [A] in bold sentence case; sub-headings [B] in italic sentence case; sub-sub-headings [C] in italic sentence case with the text continued on the same line.

Figures

Colour space Our printers use the CMYK colour space which refers to the four inks used in printing. RGB is a colour space based on the visible light spectrum and cannot be used for print publication. RGB uses red, green, and blue light added together to produce a broad array of colours mostly used on the web - computer monitors are made up of these three colours. The CMYK requirements exist, regardless of whether the image is black and white or greyscale or colour (the K in CMYK stands for Key or black ink).

Naming convention Figures should be prepared in an appropriate graphic package and named according to DOS conventions, e.g. 'figure1.tif'. Space in the print version is limited. Please consider if any of your figures (or tables) could appear online only as Supplementary Data. Additional figures and tables can be made available on the web version of the journal.

Requirements

Photographs - 300 dpi TIFF files at desired print size. A single column image would need to be 300dpi and 120mm wide. A full page image would need to be 300dpi and 230mm wide.

Line work - EPS is preferred as this is vector based software and allows smaller file sizes. The figure size requirements still apply - 120mm wide for a single column; 230mm wide for a whole page image.

Most graphic software can output to EPS via a 'print to' PS or PDF printer. If this is not possible, then we can accept high resolution tiff files - 600dpi at single column/ whole page widths. Lower resolutions will cause the text / line element to break up.

Lines should not be thinner than 0.25 pt and in-fill patterns and screens should have a density of at least 10%. Use 10pt Helvetica font for labels.

Combination images (figures with both linework or text and photographic elements) - EPS is preferred. The requirements are the same as for line work above.

Audio/ Video recordings

The recording must be continuous and of sufficient quality for us to publish online i.e. no shaking, blurring or interference.

The file must be saved in .mov format for video and MPEG, MP3 or MP4 format for audio.

The recording should last no longer than 10 minutes.

The file must be less than 2GB in size.

The resolution should be 1280 x 720 (16 x 9 HD) or 640 x 480 (4:3 SD), if possible.

Supporting Data

We do not publish appendices. Supporting material that is too lengthy for inclusion in the full text of the manuscript, but would nevertheless benefit the reader, can be hosted as online-only content, linked to the online manuscript. The material should not be essential to understanding the conclusions of the paper, but should contain data that is additional or complementary and directly relevant to the article content. Such information might include the study protocols, more detailed methods, extended data sets/data analysis, or additional figures (including colour).

All material to be considered as supporting data must be uploaded separately as such with the manuscript files during submission. It cannot be altered or replaced after the paper has been accepted for publication. Please indicate clearly the material intended as Supplementary Data upon submission. Also ensure that the Supplementary Data is referred to in the main manuscript. Please label these supplementary figures/tables as S1, S2, S3, etc. Full details on how to submit supporting data, can be found at http://authorservices.wiley.com/bauthor/suppinfo.asp

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All submissions to *Pediatric Anesthesia* should conform to the uniform requirements for manuscripts submitted to biomedical journals, drawn up by the International Committee of Medical Journal Editors (ICMJE)
see http://www.icmje.org/.

General requirements

All submissions should include the following:

Main document

1. TITLE PAGE

2. Title and running head (short title);

3. Article category;

4. First name, middle initial (if any) and family name of all authors – no degree/titles/ positions of responsibility. All those listed as authors must fulfill the ICMJE criteria – see above;

5. Affiliations should be written after the authors list as follows and linked to authors with corresponding superscript number. Only include: Department, division or unit name in English, (if any), affiliation name, city(without state), country;

6. Corresponding author details should be written after the affiliations list as follows: title (Mr/Mrs/Ms/Dr/Prof), first name(s) written with initials only, and followed by the last name – e.g. Dr. J. E. Smith; add Department, division or unit name in English, (if any), affiliation name, street address, city, postal code, country. Email address;

7. For research reports only, add 1-2 sentences answering the following questions in bullet points:
   a. What is already known
   b. What this article adds

8. A structured abstract for research reports with a clearly stated background, aim, method, results and conclusion;

9. A summary for educational reviews, systematic reviews special interest articles and case reports

10. Six MeSH-compliant keywords (http://www.nlm.nih.gov/mesh) that do not replicate the title

11. Disclosures: Indicate at the end of the text before references: 1. Any necessary ethical approval(s); 2. The source of funding for the study with grant numbers; and 3. Any conflict of interest. You are required to make a statement, even if the answer is 'none'.

12. A reference list in Vancouver style (number/author) endnotes in the order made in the text. Example: confirmed by other studies.[23] / [23] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009; 339: b2535. For books, names and initials of all authors, the full title, place of publication, publisher, year of publication and page number should be given.

13. Tables – if any, in tabulate text at the end of the main document, following the references. DO NOT submit tables as separate files. Tables submitted as pictures cannot be used.

14. Figure captions – if any, in a list following the references/ tables. (Figures must be uploaded additionally as individual graphic files. Please do not embed figures.) Figures embedded in word cannot be used by the publisher. Figures should be submitted as single separate image files: either resolution independent EPS files, or high resolution (600dpi at print size) TIFF files.

Supporting information/additional files if appropriate

1. Figures – prepared and labelled as advised in 'PRE-SUBMISSION ADVICE AND PREPARATION' above.

2. Audio/ Video - prepared as advised in 'PRE-SUBMISSION ADVICE AND PREPARATION' above. Please use the file designation 'audio/video data'.

3. Supplementary data - prepared and labelled as advised in 'PRE-SUBMISSION ADVICE AND PREPARATION' above. Please use the file designation 'supporting data'.

4. Study protocol – the appropriate study protocol (see 'Guidelines on specific papers' below)

5. Consent for publication– A completed / signed parental/patient consent form should be uploaded onto S1M as file designation 'Publication consent'. Download the links given in 'POLICIES', above.

6. Online video broadcast release – a completed form should be uploaded onto S1M as file designation 'online broadcast release'. Download the links given in 'POLICIES', above.

7. Permission – if reproducing others work (see 'PRE-SUBMISSION ADVICE' above).

Accepted article types

Research reports – Research reports should follow the "Minimal standards for reporting in Pediatric Anesthesia".

Clinical Implications, please add 1-2 sentences answering the following questions:

a. What is already known about the topic

b. What new information this study adds

A structured abstract of no more than 300 words should include the following: Background; Aims; Methods; Results; Conclusions.

Maximum words – 3500; maximum figures and tables – 6; maximum references – 25. Word counts include all text from the introduction to the end of the text after the disclosures.

Educational Reviews - Educational reviews should have the following structure: Introduction, Main Article, Summary, Reflective questions, References. Present 3-4 reflective questions that the reader should ponder upon when they have

assimilated the knowledge within the article.
Summary of no more than 300 words.
Maximum words – 5000-6000; maximum references – 20. Word counts include all text and references.

Systematic reviews – Systematic reviews are encouraged and should include a clear aim and search strategy. If the review is a meta-analysis it should be submitted and structured as a research report with an abstract, background methods, results discussion, and a clearly articulated aim, search strategy etc.
Summary of no more than 300 words giving information on methods of selecting the publications cited.
Maximum words – 4000; maximum figures and tables – 6; maximum references – no limit. Word counts include all text from the introduction to the end of the text after the disclosures.

Special interest articles – Novel papers that are neither research reports nor reviews on specific topics will be considered if they have a great and broad interest to the specialty.
Summary of no more than 300 words.
Maximum words – 4000; maximum figures and tables – 6; maximum references – no limit. Word counts include all text from the introduction to the end of the text after the disclosures.

Case reports – only exceptional reports that have important education or safety messages will be considered. Our current rejection rate is 90%. Conclude with 3 learning points for our readers. All case reports require parental/ patient consent for publication.
Summary of no more than 100 words.
Maximum words – 1000; maximum figures or tables – 1; maximum references – 5 Word counts include all text and references.

Editorials - Editorials are usually by invitation. They should be less than 1500 words and should refer to a paper in the issue within the first two sentences. They should have less than 6 references and no tables or figures. Usually they should have 3 or fewer authors.

Correspondence – Letters to the editor are encouraged, particularly if they comment, question or criticize research reports that have been published in the journal. Such letters MUST refer to the research reports in the first paragraph, and list that paper as reference 1.
Letters that describe cases are only considered if they have an important safety message and require parental/ patient consent for publication.
Maximum words – 800; maximum figures and tables – 1; maximum references – 5.
Word counts include all text and references.

Guidelines for specific papers

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Diagnostic studies must conform to the STARD statement http://www.stard-statement.org/. A flow diagram of subjects, the trial protocol, and the registration details of the trial must be included in the paper along with and a checklist provided as supplementary material.

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Appendix C: Ethics approval from UCT FHS Human Research Ethics Committee

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
Email: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

30 April 2015

HREC REF: 196/2015

Dr J van Nugteren
Anaesthesia
D23, NGSH

Dear Dr van Nugteren

PROJECT TITLE: MULTIDISCIPLINARY MANAGEMENT OF COMPLEX REGIONAL PAIN SYNDROME TYPE 1 IN CHILDREN ADMITTED TO RED CROSS WAR MEMORIAL HOSPITAL: A CASE SERIES DESCRIBING LONG-TERM EFFECTS ON PAIN, FUNCTION AND QUALITY OF LIFE (MMed candidate: Dr M Nock)

Thank you for your response to the Faculty of Health Sciences Human Research Ethics Committee dated 24 April 2015.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30th April 2016.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

We acknowledge that the student, Dr Mariesa Nock will also be involved in this study.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH

2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI),and Declaration of Helsinki guidelines.
The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

Appendix D: Letter of research approval from Red Cross War Memorial Children`s Hospital

Western Cape Government
Health

Dr R Mistry
Manager: Medical Services
Email: Roshni.Mistry@westerncape.gov.za
Tel: +27 21 658 5788 fax: +27 21 658 5166

Dr Mariesa Nock
Red Cross War Memorial Children's Hospital

Dear Dr Mariesa Nock

APPROVAL OF RESEARCH

PROJECT TITLE: MULTIDISCIPLINARY MANAGEMENT OF COMPLEX REGIONAL PAIN SYNDROME TYPE 1 IN CHILDREN ADMITTED TO RED CROSS WAR MEMORIAL CHILDREN'S HOSPITAL: A SERIES DESCRIBING LONG-TERM EFFECTS ON PAIN, FUNCTION AND QUALITY OF LIFE.

We have the pleasure of informing you that approval is hereby granted to conduct the above-mentioned study at Red Cross War Memorial Children's Hospital.

Yours sincerely,

DR ROSHNI MISTRY
MANAGER: MEDICAL SERVICES
DATE: 29 JUNE 2015

Appendix E: Telephonic Interview Script: Parent Consent

Good day, is this Mr/Mrs/Ms (Name)?

My name is Mariesa Nock; I am a medical doctor at Groote Schuur Hospital and I am specialising in Anaesthesia through the University of Cape Town. I am conducting a research study at Red Cross War Memorial Hospital involving children who were admitted and treated for the diagnosis of Complex Regional Pain Syndrome over the last few years. The purpose of the study is to look at the treatment the hospital currently provides and determine what the long-term outcomes are of the children who suffer from this condition.

The study has two parts:

Firstly, with your consent, I will access your child's folder and collect information from it. This information will include things like age, nature of initial injury, investigations and treatment received prior to admission to hospital and also what treatment was received during admission to Red Cross War Memorial Hospital.

Secondly, I would like to evaluate how your child is doing at the moment. To do this I would like to evaluate their pain severity, and how their pain interferes with their daily activities using two questionnaires. The one is called the Faces Pain Scale-revised which will ask your child to point at a picture of the face which best represents their pain at present. The second questionnaire is the Paediatric Quality of Life Inventory, which both you and your child will need to complete. This questionnaire asks how much of a problem your child's pain has been to them in different areas of ordinary life. It will take approximately 10 minutes to complete. Both these questionnaires were probably used by the pain management team with you and your child when you were at RCWMCH.

The risks to your child are that talking about the subject might be distressing to him/her or that thinking about it and talking about it might cause a flare up of pain. If this occurs I will refer you to the necessary health care provider.

Everything we discuss will be kept strictly confidential, for all recording purposes we will be using only your child's folder number and their name will not be included in any of the information. His/her folder will also be kept in a safe location so that no one else but me will have access to it. If the findings of the study are published in a medical journal, the identity of your child will remain anonymous.

There is no specific benefit to you or your child by taking part in the study. We hope that the study will increase our understanding of CRPS and the outcomes we achieve with our treatment so that we can continue to improve the care we give to other children who suffer from CRPS.

If during the completion of the questionnaire I realise that your child still has a lot of pain that is significantly interfering with their life, I will recommend that you see your local healthcare provider and if you give permission I will provide a referral letter to them. The medical costs of this will be for your own account.

If you do not want to take part you don't have to. If at any point you want to stop taking part or you don't want to answer a question, you can inform me and we shall stop the interview. Whether you choose to participate or not will not affect your child's management at RCWMH in any way now or in the future. You will not receive any payment for participating in the study.

Do you have any questions?

Would you be willing to participate in this study?

If they say no: thank you for your time, have a good day. Bye.

If they say yes – continue: I would also like to make sure (Your child's name) is happy to take part in the study; can you please ask them to come to the phone? Or indicate a convenient time to speak to your child if you would like to speak with them first?

If (your child) is also happy to take part, I would like to set up an appointment date when I can phone you again to complete the questionnaires. I will be sending you a copy of the questionnaires, so you can have a copy in front of you while I ask the questions over the phone. How do you prefer me to send the questionnaires to you?

(Record email or postal address…..)

When would be a convenient time for me to phone you again for completion of the questionnaires?

(Record date and time…..)

Please record the following contact details in case you need to get hold of me for any reason…

(Provide parent with my name and contact telephone number..)

Please also take down the number for the University of Cape Town's Ethics Committee if you have any questions with regards to your child's rights and welfare in taking part in research.

(UCT FHS Research Ethic Committee Tel 021 4066338)

Appendix F: Telephone script for Child Assent

Good day is this (Child's name)?

My name is Mariesa Nock; I am doctor from Red Cross Hospital in Cape Town.

Do you remember the time when you came to Red Cross with your mom and dad because of the pain in your (leg/arm)? (Make sure the child remembers the time and admission that I am referring to).

Do you remember the name the doctors gave the pain in your (leg/arm)? The name they gave it is CRPS, which is a short name for Complex Regional Pain Syndrome.

This type of pain is very rare, that means not many children will ever have the type of pain you had. It also means that when doctors see children with this kind of pain they do not always know what it is or how to make it better.

There have been just a few other children who came to Red Cross hospital because of the same type of pain that you had. I am phoning you and all these other children to ask for help with research.

Research is something we do to find out about the way things work. We use research studies to better understand an illness and find better ways of helping and treating children who are sick.

I want to find out whether your visit to Red Cross helped you get better. This will help doctors in the future to know what to do when other children with pain because of CRPS come to us for help.

To find this out I will be doing two things:

Firstly, I will look at your hospital file and read the notes that the doctors made while you were here. I will make my own notes from this, like how old you are, how you got hurt, what medicine and treatments (like visits to the Physiotherapist) you tried before coming to Red Cross. I will also write down what the doctors, nurses and physiotherapists did to help you get better while you were at Red Cross.

Secondly, I want to find out how you are doing now. For this I will ask you a few questions over the phone about whether you still have pain and if you do still have pain, how much of a problem the pain is in your daily life. It will take about 10 minutes to complete the questions.

Sometimes people worry that something bad might happen to them if they are asked to take part in research. One possible “bad thing” that can happen is that you might find it hard to talk about the pain and perhaps that talking about it and thinking about it, may make the pain get worse again. If this does happen, I will make sure you get the help you need.

You may worry that other people may find out who you are and about your visit to Red Cross by saying yes to helping me with the research. I will make sure that no one else but I look at your hospital file and when I write down notes I will not use your name anywhere so no one will know who I am talking about.

If you do not want to take part you don’t have to. Even if you say yes now, you can still change your mind later and tell me that you want to stop and I won’t be upset or angry. Whether you choose to take part or not will not change how people treat you if you ever have to come to Red Cross Hospital again. You and your parents will not get any money for helping me with the research. Your parents or the person responsible for taking care of you will also have to agree that you can take part in the study before we can go ahead.

Do you have any questions you would like to ask me?

I will give your mom/dad my telephone number, so if you think of any questions later, please call and I will be happy to explain.

Would you be willing to let me look at your hospital file and for me to phone you again at a different time to ask you some questions?

If yes: continue to making telephonic appointment with parent/legal guardian for completion of questionnaires

Appendix G: Script for Telephonic follow-up interview

Hi there, is this Mr/Mrs X?

This is Mariesa Nock, the doctor from Red Cross Hospital that phoned you a while ago regarding the research study I am doing about children who were treated at Red Cross Hospital for Complex Regional Pain Syndrome. Do you remember?

If no: Explain again (revert to precious telephonic script)

If yes: Continue…

Are you and (child's name) still happy for me to ask you both a few questions? Do you have any questions you would first like to ask me?

If still happy and once all questions answered, proceed…

Is now a good time for you both or would you like to reschedule?

Reschedule or continue…

Did you receive the questionnaires that I sent you?

If no: Get details to resend and make new appointment for follow-up

If yes: Continue...

Do you have the questionnaires in front of you so you can look at them while I ask you the questions? (*Give them time to get hold of the questionnaires.*)

First I would like to start with the questionnaire with all the pictures of faces on it. Can you please have it ready for (child's name) to look at and then put (him/her) on the phone? After that I will be doing the questionnaire called "PedQL Child Report", please have that ready for him/her as well.

Administer Modified Brief Pain Inventory

Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains and toothaches). Have you had pain other than these everyday kinds of pain today?

Yes _____continue on to Faces Pain Scale, if No _____Omit Faces Pain Scale

Administer Faces Pain Scale

Look at the faces on the paper in front of you. The face on the far left side marked as number 1 shows no pain. The faces show more and more pain, up to the one on the far right, marked as number 6, which shows very much pain. Please point to the face that shows how much you hurt (right now). Can you (or your mom/dad) tell me the number of the face that you are pointing to?

Administer PedsQL 4.0 Child

Read through the introduction and questions of PedsQL child version and record answers

Thank you very much for helping me by answering these questions. Please can you put your mom/dad back on the phone for me?

Hi Mr/Mrs X, thank you for assisting (child's name) with completing the questions.

Do you have the Questionnaire named PedsQL Parent proxy-report in front of you?

Administer PedsQL 4.0 parent proxy-report

Follow the lay-out of the questionnaire and record the answers

Thank you very much for your help in answering those questions. I have just three more questions and then we are done.

Is (child's name) taking any medication for pain at the moment?

Record names of pain medicine, frequency and dosage

Is (child's name) taking any other types of medicine at the moment?

Record names of medicine and dosage

Has (child's name) been admitted to hospital again for the symptoms of CRPS since he/she was discharged from Red Cross Hospital?

Appendix H: Faces Pain Scale-Revised

Note that the faces on the questionnaire are upside-down because the instrument is designed to be printed and then folded along that dotted line so the child points to a face and the clinician records a number. I will just be sending a paper copy of the faces to the child and will be reading the instructions verbally. Example of upright faces also provided below. The faces will be given a number (1 to 6) to make it easier to communicate which face the child has chosen.

Faces Pain Scale – Revised (FPS-R)

In the following instructions, say "hurt" or "pain", whichever seems right for a particular child.

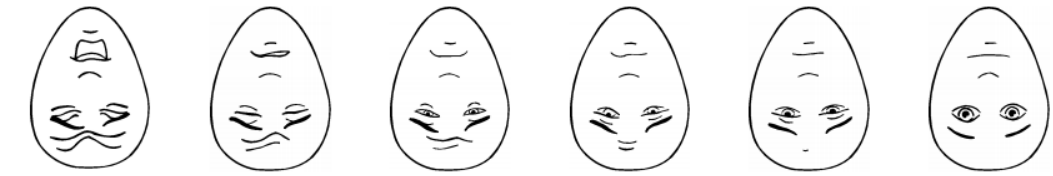
"These faces show how much something can hurt. This face *[point to face on far left]* **shows no pain. The faces show more and more pain** *[point to each from left to right]* **up to this one** *[point to face on far right]* **- it shows very much pain. Point to the face that shows how much you hurt** [right now]."

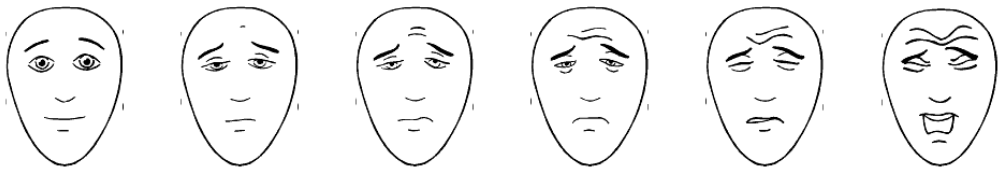
*Score the chosen face **0**, **2**, **4**, **6**, **8**, or **10**, counting left to right, so "0" = "no pain" and "10" = "very much pain". Do not use words like "happy" or "sad". This scale is intended to measure how children feel inside, not how their face looks.*

Sources. Hicks CL, von Baeyer CL, Spafford P, van Korlaar I, Goodenough B. The Faces Pain Scale – Revised: Toward a common metric in pediatric pain measurement. Pain 2001;93:173-183. Bieri D, Reeve R, Champion GD, Addicoat L, Ziegler J. The Faces Pain Scale for the self-assessment of the severity of pain experienced by children: Development, initial validation and preliminary investigation for ratio scale properties. Pain 1990;41:139-150.

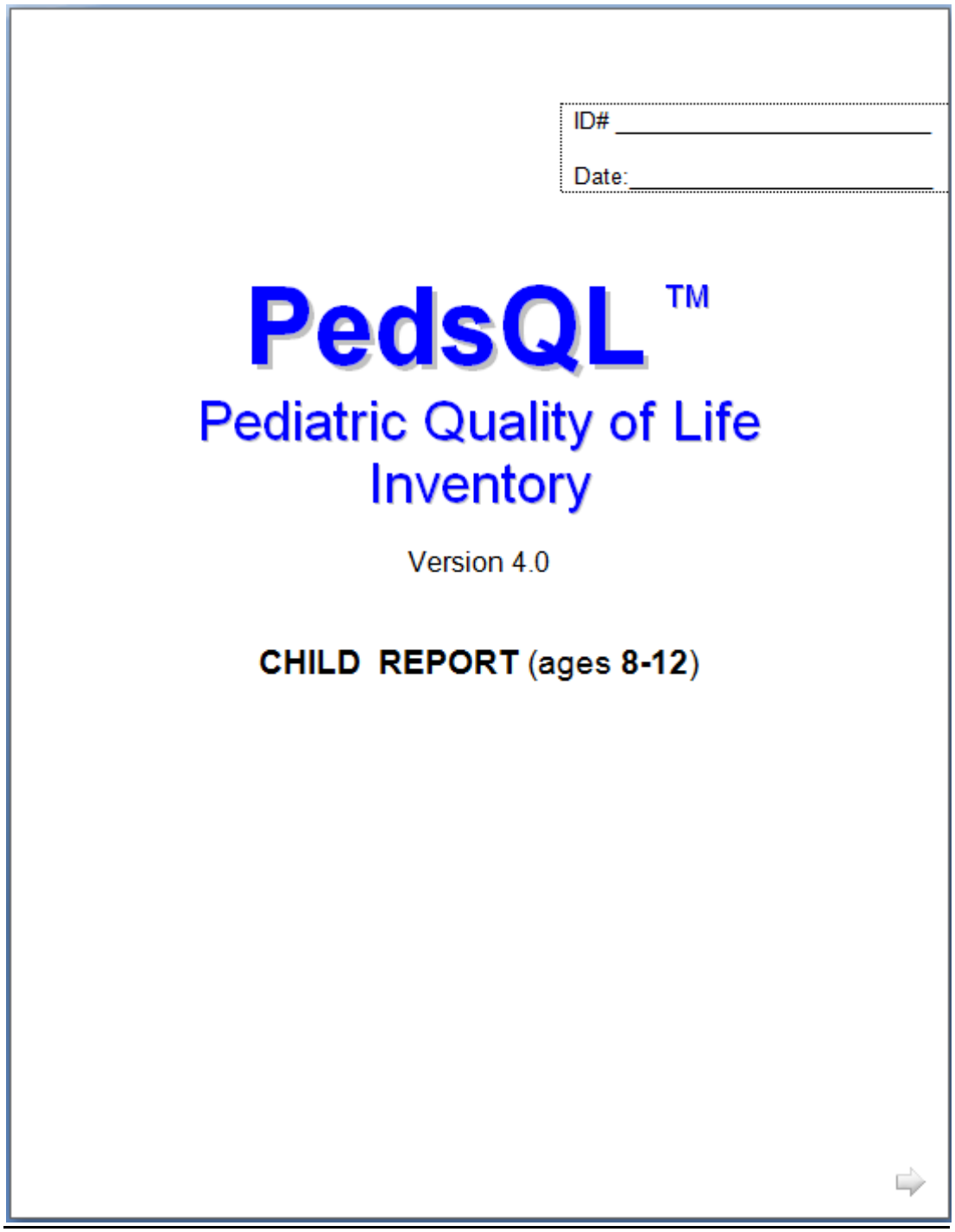
(fold along dotted line)

10 **8** **6** **4** **2** **0**





Appendix I: PedQL 4 Child Report



ID# _____

Date:_____

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0

CHILD REPORT (ages **8-12**)

DIRECTIONS

On the following page is a list of things that might be a problem for you.

Please tell us **how much of a problem** each one has been for you during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

*In the past **ONE month**, how much of a **problem** has this been for you …*

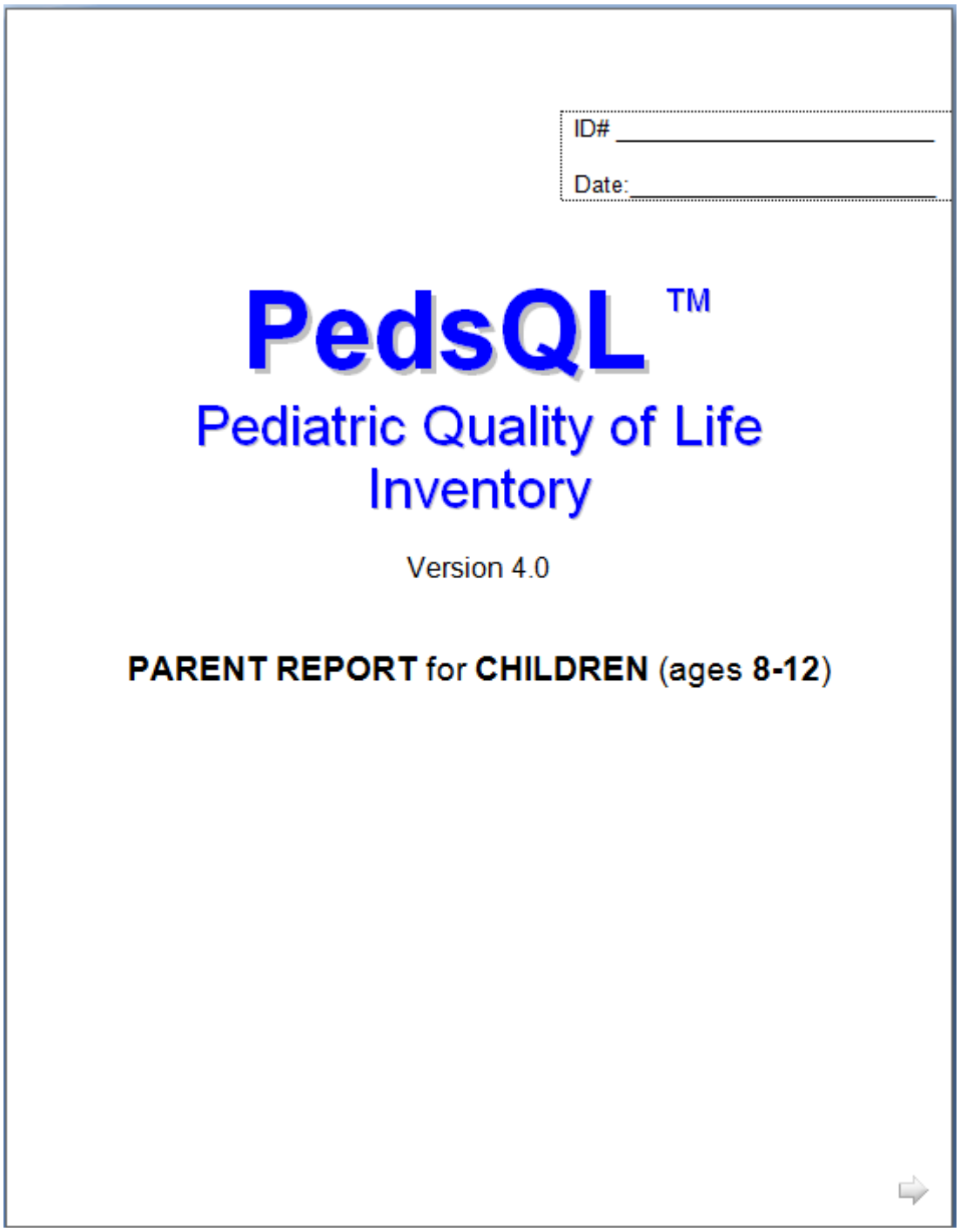
ABOUT MY HEALTH AND ACTIVITIES *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard for me to walk more than one block	0	1	2	3	4
2. It is hard for me to run	0	1	2	3	4
3. It is hard for me to do sports activity or exercise	0	1	2	3	4
4. It is hard for me to lift something heavy	0	1	2	3	4
5. It is hard for me to take a bath or shower by myself	0	1	2	3	4
6. It is hard for me to do chores around the house	0	1	2	3	4
7. I hurt or ache	0	1	2	3	4

8. I have low energy	0	1	2	3	4

ABOUT MY FEELINGS ***(problems with…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. I feel afraid or scared	0	1	2	3	4
2. I feel sad or blue	0	1	2	3	4
3. I feel angry	0	1	2	3	4
4. I have trouble sleeping	0	1	2	3	4
5. I worry about what will happen to me	0	1	2	3	4

HOW I GET ALONG WITH OTHERS ***(problems with…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. I have trouble getting along with other kids	0	1	2	3	4
2. Other kids do not want to be my friend	0	1	2	3	4
3. Other kids tease me	0	1	2	3	4
4. I cannot do things that other kids my age	0	1	2	3	4

Appendix J: PedsQL 4 Parent Report



ID# _____

Date:_____

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0

PARENT REPORT for **CHILDREN** (ages **8-12**)

DIRECTIONS

On the following page is a list of things that might be a problem for **your child**.

Please tell us **how much of a problem** each one has been for **your child** during the **past ONE month** by circling

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help

*In the past **ONE month**, how much of a **problem** has your child had with …*

PHYSICAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Walking more than one block	0	1	2	3	4
2. Running	0	1	2	3	4
3. Participating in sports activity or exercise	0	1	2	3	4
4. Lifting something heavy	0	1	2	3	4
5. Taking a bath or shower by him or herself	0	1	2	3	4
6. Doing chores around the house	0	1	2	3	4
7. Having hurts or aches	0	1	2	3	4
8. Low energy level	0	1	2	3	4

EMOTIONAL FUNCTIONING	Never	Almost Never	Some-times	Often	Almost Always

(problems with…)					
1. Feeling afraid or scared	0	1	2	3	4
2. Feeling sad or blue	0	1	2	3	4
3. Feeling angry	0	1	2	3	4
4. Trouble sleeping	0	1	2	3	4
5. Worrying about what will happen to him or her	0	1	2	3	4

SOCIAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Getting along with other children	0	1	2	3	4
2. Other kids not wanting to be his or her friend	0	1	2	3	4
3. Getting teased by other children	0	1	2	3	4

4. Not able to do things that other children his or her age can do	0	1	2	3	4
5. Keeping up when playing with other children	0	1	2	3	4

SCHOOL FUNCTIONING ***(problems with…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Paying attention in class	0	1	2	3	4
2. Forgetting things	0	1	2	3	4
3. Keeping up with schoolwork	0	1	2	3	4
4. Missing school because of not feeling well	0	1	2	3	4
5. Missing school to go to the doctor or hospital	0	1	2	3	4

Appendix K: CRPS long-term outcome questionnaire

Your name: _____

Today's date: _____

Please tick next to the most appropriate answer and expand in your own words where necessary

1. Were you free of your CRPS pain at the time that you were discharged from Red Cross Hospital? **Yes_____ (Continue to Question 4) No_____ (Continue to Question 2)**
2. If **no**, have you ever been completely free from your CRPS pain since leaving Red Cross Hospital? **Yes_____(Continue to Q3)No_____ (Continue to Q 8)**
3. If **yes**, how long after leaving Red Cross Hospital did it take before you became free of pain?

   _____
4. Did the symptoms of your CRPS ever return after you became pain free?

   Yes, it returned_____ When did this happen?_____(Continue to Q5)

   No, the symptoms never returned_____ (if no, Continue to Q8)
5. What do you think triggered the return of your CRPS symptoms**? An injury_____ Stopping medication_____ Other_____**
6. In which part of your body did the symptoms return? **Same limb as initial CRPS_____Different limb as initial CRPS_____Specify limb_____**

7. How would you rate the symptoms of the relapse compared to your first episode of CRPS? **Not as bad as the first time _____ Similar to the first time_____ More severe than the first time_____**
8. Were you ever re-admitted to hospital for your CRPS symptoms? **Yes_____No_____**
9. Are you currently still taking any medication for CRPS-related pain? **Yes_____No___**
10. **If yes, please give names of medication_____**
11. Are you currently still undergoing any physiotherapy treatment for your CRPS symptoms? **Yes_____ No_____**
12. Are you currently receiving any other form of treatment for help with your CRPS symptoms? **Yes_____ No_____**
13. **If yes, please specify_____**
14. **Anything else you'd like to tell me**

_____

Please return the completed questionnaire to: mariesa.schutte@gmail.com

Please phone if you have any queries: Tel 0764020864

Dr Mariesa Nock,

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