Recommendations and additional considerations.

Treatment	Evidence level	Considerations	Recommendations
Drug treatment and invasive treatment			
Pain medication - paracetamol - NSAID's - tamadol - opioids - ketamine	III-IV	Use of paracetamol has a low threshold of administration and a minor side-effects profile. NSAIDs are often associated with side-effects (i.e. gastrointestinal, renal, circulatory, central nervous system, and cardiac function). Many side effects have been described for weak and strong-acting opioids. Systematic reviews for neuropathic pain have found tramadol to be effective [14]. Long-term effects of opioids or problems associated with tolerance and addiction for CRPS-I are unkown [15]. Use of ketamine should be limited to the clinical setting.	• A sub-anaesthetic dose of ketamine can be considered for patients with CRPS-I who are experiencing pain symptoms. The project group is of the opinion that pain medication should be administered in accordance with the WHO pain ladder up to and including step 2. Strong opioids should not be administered to this patient group. • The project group also recommends that further research should be carried out into the specific effect of pain medication on CRPS-I.
Co-analgesics - gabapentine - carbamazepin - pregabaline - amitryptiline - nortryptiline	II-IV	Pain associated with CRPS-I may be neuropathic in nature. The use of antidepressants, anticonvulsants to treat neuropathic pain in CRPS-I should be considered. Possible side effect profiles of these medications (for instance dizziness, sleepiness and fatigue) should be taken into consideration.	• Administration of gabapentin can be considered for patients with CRPS-I. This should be discontinued if no clear reduction in pain symptoms, allodynia or hyperaesthesia occurs within an eight-week trial period. • A trial course of carbamazepine, pregabalin or other anti-epileptic drugs can be considered for patients with CRPS-I suffering significant attacks of neuropathic pain. • A trial course of amitriptyline or nortriptyline can be considered for patients with CRPS-I who are suffering from continuous

			neuropathic pain.
Capsaicin	IV		• Capsaicin has no place in the treatment of CRPS-I.
Free radical Scavengers - DMSO - N-acetylcystein	II-IV	In light of a possible inflammatory pathofysiological mechanism of CRPS-I, treatment with free radical scavengers has been proposed, with positive results reported in different studies. This treatment method is predominantly used in The Netherlands.	• A three-month course of 50% DMSO (dimethylsulphoxide) cream five times a day (for local application on skin) is recommended for patients who have had CRPS-I for less than a year. • A one-month trial course of DMSO applied locally can be considered for patients who have had CRPS-I for more than a year. If the results are favourable, the treatment can be continued for three months. • A three-month course of 600 mg of N-acetylcystein 3 times a day can be considered for patients with CRPS-I who have a primary cold skin temperature.
Muscle relaxants - baclofen (oral) - diazepam - clonazepam - botulin toxin - baclofen (IT)	III	Descriptive studies show that anticholinergics do not lead to (lasting) effects [29,30]. Physicians using diazepam or clonazepam must be alert to the possible addiction risk. The main side-effects of the screening process and continuous administration of intrathecal baclofen are post-puncture headache, diminished consciousness and urine retention [33].	• The members of the project group recommend that CRPS-I patients suffering from dystonia, myoclonias or muscle spasms should be started on 1) oral baclofen according to the standard dose increase pattern, 2) diazepam or clonazepam, which should be slowly titrated in the light of the effect and side-effects. • The project group considers that botulin toxin has no place in the treatment of CRPS-I-patients with dystonia. • Intrathecal baclofen has no place in the treatment of patients with CRPS-I. Intrathecal baclofen can only be considered for patients with CRPS-I if dystonia is a major problem and conventional therapy has proven ineffective. This treatment must be administered in the context of a trial.
Corticosteroids	III	Some studies of limited quality indicate that	• Routine administration of corticosteroids has no place in the

		corticosteroids have a beneficial effect.	treatment of CRPS-I patients.
Calcium regulating medication - calcitonin - bis-phosphonates	I	Experience with calcitonin and bisphosphonates for CRPS-I patients in The Netherlands is limited. Intravenous bisphosphonates cause few side effects, but dosage, frequency and duration of use are unclear. Treatment with 40 mg of alendronate/day for eight weeks may be considered, especially for patients with elevated bone metabolism.	• The project group is of the opinion that in view of the conflicting results of research, it is impossible to give any clear advice about the use of calcitonin in patients with CRPS-I. • As there is little experience with the use of bisphosphonates in patients with CRPS-I, it is currently advised that these drugs should only be considered in the context of a trial.
Calcium channel blockers	III		• A calcium channel blocker can be prescribed for patients with a cold CRPS-I. The effect must be assessed a week after administration. The drug must be discontinued if it has no effect.
Sympathetic block - Intravenous - Percutaneous	I-II	The task force is of the opinion that percutaneous sympathetic blockade may be helpful in improving the circulation in patients with cold CRPS-I.	• Intravenous sympathetic blockade has no place in the treatment of patients with CRPS-I. • Treatment with percutaneous sympathetic blockade using local anaesthetics may be considered for patients with cold CRPS-I who do not respond adequately to vasodilating medication. • If a trial blockade has proved successful, definitive sympathetic blockade using radiofrequent lesions, phenol or alcohol can be considered in the context of a study.
Surgical sympathectomy	III	Surgical sympathectomy is proposed to be indicated for 'sympathetic-dependent pain' [64], but there is discussion on this issue [63]. Compensatory hyperhidrosis and neuropathic complications are common with this intervention [60]	• Extreme caution is necessary when considering surgical sympathectomy for pain control in CRPS-I. The procedure should be conducted in the context of a trial in order to ascertain the efficacy and potential risks.

Other intravenous treatment: - ketanserine - bretylium - reserpine - droperidol - atropine	I	Bretylium is not registered in the Netherlands. Reserpine, droperidol and atropine have insufficient effect.	• Intravenous administration of 10-20 mg of ketanserine can be considered for the treatment of CRPS-I patients. • Routine administration of reserpine, droperidol and atropine is not recommended for CRPS-I patients.
Spinal cord stimulation (SCS)	III	Evidence for use of SCS in non-chronic CRPS-I is lacking. SCS studies were performed in carefully selected refractory CRPS-I patients. SCS is more cost-effectiveness than standard therapy for chronic CRPS-I [102]. Life-threatening complications are rare, but complications occur frequently [70].	• Pain control with spinal cord stimulation is a sound option for carefully selected CRPS-I patients who have not responded to other treatments. Spinal cord stimulation should ideally only be administered to other CRPS-I patients in the context of a trial.
Amputation	III	Amputation of the affected limb cannot be considered for symptom relief in CRPS-I. It should only be considered in cases of potentially life-threatening, untreatable or recurrent infections.	• Amputation for CRPS-I patients can only be considered in order to improve the quality of life in the case of severe, recurrent infections and severe functional disorders. This intervention should be performed at a specialised centre.
Paramedical, rehabilitation medicine and psychological treatment			
Physiotherapy and TENS	II-IV	In the view of the task force, physiotherapy can positively influence the patient's ability to exert control as a part of a pain-focused treatment protocol. There are no contraindications for physiotherapy.	• It is recommended that physiotherapy aimed at restoration of function be started as soon after the onset of CRPS-I as possible. • TENS (transcutaneous electrical nerve stimulation) can be tried out without risk in CRPS-I patients as an additional treatment. It is only sensible to continue with the treatment if it is found to be effective.
Occupational therapy	III	Promoting functional limb use within pain limits and promoting independence are aims of occupational	• The project group recommends that patients with upper-limb CRPS-I be referred for occupational therapy.

		therapy [103]. Desensitisation programmes are used to normalise sensitivity [6,104,105]. Splints are used to provide functional support, protection and minimising clinical symptoms [6,103,106]. There are no known contraindications for occupational therapy.	
Psychological treatment	IV	There is no evidence for a specific psychological profile or predisposition for CRPS-I patients. Reasons for further psychological investigation relate to assessment of possible psychological factors maintaining and/or aggravating the syndrome.	• The project group advises that CRPS-I patients should consult a psychologist if the practitioner observes a discrepancy between clinical symptoms and the patient's (pain-related) behaviour, if stagnation in (somatic) treatment occurs, if the burden of suffering caused by the symptoms is great, or if the patient requests this.
Multidisciplinary treatment	IV	Treatment of CRPS-I may require the involvement of various disciplines due to its multidimensional character. Regular consultation between practitioners is desirable to provide uniform information to the patient.	• Where a number of practitioners are treating a CRPS-I patient at the same time, it is advisable that one of them acts as case manager.
Treatment of children with CRPS-I			
Drug and invasive treatment	III	Too little data is available to allow a balanced conclusion with regard to the effects of the different interventions on children with CRPS-I. Particular attention should be given to medication dosage and to support for the child during the disease process. Close cooperation with a paediatrician appears justified. Psychologists are often involved in the treatment of children with CRPS-I [85,86,89-92]. When treating children it is advisable to include the	• The project group is of the opinion that further research is needed to determine the effects of drug treatment and invasive treatment on children with CRPS-I. Caution is advised when applying the treatments described in these guidelines to children. Particular attention must be paid to measurement of the dose and giving (medical) support to the child.
Physical therapy	III		• The project group recommends that children with CRPS-I should be given physiotherapy.
Occupational therapy	III		• The project group advises that occupational therapy should be a

		parents or family.	component of multidisciplinary treatment for children with CRPS-I.
Psychological therapy	II		• Psychological diagnosis and treatment of children with CRPS-I should ideally be carried out by a child psychologist.
Primary and secondary prevention of CRPS-I			
Primary prevention - Vitamin C - Guanethidine - Calcitonin	II-III	Vitamin C is available at low cost. Guanethidine is not available in The Netherlands. Perioperative administration of calcitonin has insufficient effect on primary prevention of CRPS-I	• Consideration should be given to prescribing 500 mg of vitamin C to be taken orally for 50 days in order to reduce the risk of CRPS-I in adults who have had a wrist fracture. • Perioperative administration of intravenous guanethidine is not advised for primary prevention of CRPS-I. • Perioperative administration of subcutaneous calcitonin is not advised for primary prevention of CRPS-I.
Secondary prevention	III-IV	It appears sensible to wait until the signs and symptoms of CRPS-I have abated before performing surgery on CRPS-I patients [98-101,107]. Surgery should not be postponed in case the surgery is intended to reduce factors maintaining the CRPS-I [98]. Surgery on cold, oedematous limbs is not advisable [98].	• Timing of surgery: It is recommended that surgery of the (previously) affected limb be postponed until the signs and symptoms of CRPS-I have almost disappeared. This does not apply to operations intended to eliminate an underlying factor that may be responsible for the CRPS-I. • It is recommended that the duration of the operation and use of tourniquet be minimised. • Adequate pre-, per- and postoperative pain control is recommended. • Perioperative blockades of the ganglion stellatum or IV regional blockades using clonidine 1 µg/kg (not guanethidine) can be considered in the case of upper-limb surgery on patients who previously suffered from CRPS-I. • The use of regional anaesthesia with a sympathicolytic effect

	(epidural/spinal analgesia, plexus brachialis blockade), either alone or in combination with general anaesthesia, can be considered in the case of surgery on patients who previously suffered from CRPS-I. • The perioperative use of calcitonin can be considered.