UMEÅ UNIVERSITY

Interventional Pain Management Focused on Zygapophysial Joint Pain

–

a Health-Economic Evaluation

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To my father:
ᚱᛁᛋᛏᚨᚱ ᚾᛉ ᛒᛁᚾᚨ ᛋᛒᚾᚱᛁᚠᚱ ᚾᚢᚱᚢ ᛒᚾᚾᛁᚴᚠᚱ ᛉᚨ ᚾᛁᚨᚢᛒᚨ

To Kjerstin:
Carried by your love, I dare everything. Without your support, nothing would have been achieved.

Department of Epidemiology and Global Health

Umeå 2023

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Abstract

The pain-system is a central mechanism in our life. Chronic pain is one of the major causes of impaired health-related quality of life according to the World Health Organization's "Global Burden of Disease"-studies. Zygapophysial joint pain has been shown to account for the pain in 30% - 50% of patients with chronic pain. There are several well-established, evidence-based methods to treat zygapophysial joint pain in the cervical and lumbar regions.

This thesis originates from this and starts by exploring whether the treatment of zygapophysial joint pain can improve health-related quality of life. This thesis describes methods for the diagnosis and treatment of zygapophysial joint pain in the thoracic region that can be applied to the treatment of all pain-foci localized to the zygapophysial joints. I show that the health-related quality of life was significantly improved after treatment, and that the clinical methods used for treating thoracic pain were similar to the methods that have been established previously for cervical and lumbar pain.

In order to better understand the patients' experiences we performed qualitative interviews with patients who underwent diagnostic tests and treatments. The overall theme revealed by these interviews was that of empowerment, in which the patients were empowered by the process of diagnostic tests and treatments.

The next question was whether the method was cost-effective or not. In the first cost-effectiveness analysis, the patients served as their own controls and we evaluated the results against the limits set by the Swedish national board of health and welfare. The results showed that it was cost-effective in the moderate to low range.

Finally, we compared the treatment to the "gold standard" for pain management in Sweden; i.e.pain rehabilitation. We mimicked a randomized controlled trial by using propensity score weighting to compare 254 patients agains 15,357 patients registered in the Swedish National Register of Pain Rehabilitation. The results showed that interventional pain management was cost-effective in the moderate (12 months after treatment) to low (≥24 months after) range whereas pain rehabilitation was in the very high range (after 12 months) and became cost-effective in the high range after 24 months of treatment. Currently, interventional pain management accounts for just 2% of all specialized pain management procedures in Sweden. If this could be increased to 25%, it may be possible to save 106 million SEK annually, while simultaneously gain 14 quality adjusted life years of health. If an interventional pain assessment is performed early in the process, treatable patients could be directed toward interventional treatment and away from interdisciplinary pain management programs, with the potential for further reductions in costs.

Enkel sammanfattning på svenska

Nästan var 5:e människa i världen (15-20%) har haft ont mer än 3 månader. Utesluter man dem som har smärtor pga cancer, reumatiska sjukdomar, nyligen opererats eller fått frakturer så kvarstår ca hälften. Ländryggsvärk, tätt följd av huvudvärk, är den viktigaste orsaken till funktionsnedsättning i världen enligt de studier WHO genomfört mellan 1990 och 2017. Ca 30-50% av dessa har facettleds-relaterad smärta. Sedan slutet av 1980-talet har mycket arbete skett för att säkerställa hur man på ett evidensbaserat sätt ska kunna diagnostisera och behandla en facettleds-relaterad smärta. Diagnostik och behandling av facettleds-relaterad smärta från halsrygg och ländrygg är väl etablerad så länge man följer de internationella guidelines som finns framtagna, dvs där diagnostik sker med hjälp av exakta nervblockader vid minst två tillfällen och att minst 80% smärtlindring uppnås varje gång, och behandlingen sker så att nerven nås av behandlingen.

Denna avhandling utgår härifrån.

Det första steget var att ta fram en metodik för diagnostik och behandling i bröstryggen eftersom detta inte tidigare var bra beskrivet. Behandling i halsrygg och ländrygg användes som referenser att jämföra mot. Men eftersom smärta är en av de viktigaste orsakerna till försämrad livskvalitet ville vi även ta ett steg till, och se om det gick att använda livskvalitets-skattning som utfalls-mått. Så istället för att följa upp hur ont patienter hade 3,6 och 12 månader efter behandling frågade vi efter hur de skattade sin livskvalitet. Vi kunde då se att behandlingsresultaten i bröstryggen var likvärdiga med dem vi såg i ländrygg och halsrygg, och vi kunde se att hos dem som fick en förbättring av behandlingen så beskrev de en i det närmaste normalisering av livskvaliteten, och att förbättringen ofta kvarstod ett år efter behandling.

Att livskvaliteten förbättrades så kraftigt efter behandling väckte en ny fråga: Vad var det som gjorde detta? Vi genomförde därför en kvalitativ intervju studie där vi frågade efter hur patienterna upplevde utredningen. Det var flera delar som blev tydliga, men det övergripande temat som beskrevs var ökad egenkontroll (Empowerment). Patienterna beskrev att de genom utredningen upplevde att de stärktes i sin egenkontroll. Empowerment är en faktor som lyfts fram både när man pratat om försämrad livskvalitet och om stärkt livskvalitet, och nämns ofta som ett viktigt mål när det gäller smärtbehandling.

Nästa frågeställning var ifall det var kostnadseffektivt att genomföra denna typ av utredningar. Facettleds-relaterade besvär utgör enbart 30-50% av orsakerna till smärtor, men det är först när vi genomför diagnostiska blockader det går identifiera vilka dessa är, så många patienter måste utredas för att en mindre mängd ska kunna få behandling. Vi genomförde därför en studie där vi

inkluderade kostnaderna för alla patienter som utreddes (873 st), och alla blockader och besök dessa genomgick. Vi hämtade uppgifter från socialstyrelsen över medicinering och sjukvårdskonsumtion och lade in förändringarna i kostnadsberäkningarna. Sedan satte vi detta i relation till den genomsnittliga förbättring av livskvaliteten vi såg hos de 331 patienter som behandlades. Det mått man då får fram, kostnad per kvalitets-justerat levnadsår (QALY), använder Socialstyrelsen för bedömning av i princip all sjukvård i Sverige. Vi beräknade kostnaden till 220 tkr/QALY, och det räknas med Socialstyrelsens terminologi som en ”moderat” kostnad.

Följdfrågan blir naturligtvis hur denna typ av utredning/behandling står sig jämfört med gängse behandling, dvs smärtrehabilitering. Att genomföra en randomiserad studie där patienter slumpmässigt fördelas till smärtrehabilitering respektive interventionell behandling är inte praktiskt genomförbar. Istället har vi efterliknat samma procedur genom att vikta resultaten med hjälp av s.k. propensity score. På det sättet får man jämförbara patientgrupper där de 254 patienter som genomgått behandling för facettleds-smärta jämförs mot 15 357 patienter som genomgått smärtrehabilitering under samma period. Kostnader räknades på samma sätt som i den föregående studien, men den här gången tog vi även in data över sjukskrivning från Försäkringskassan. Interventionell smärtbehandling resulterade i en förbättring av 0.186 kvalitetsjusterade levnadsår (QALY) per individ efter 1 år medan smärtrehabilitering resulterade i 0.164 QALY per person efter 1 år. Kostnaden per QALY var för interventionell behandling 119 tkr (”Moderat” kostnad) och för smärtrehabilitering 1 187 tkr (”Mycket hög” kostnad). Förlängs uppföljningsperioden till 2 år så sjönk kvoten för interventionell smärtbehandling till 49 tkr/QALY (”Låg”) och smärtrehabilitering till 553 tkr/QALY (”Hög”).

Idag utgör interventionell smärtbehandling 2% av den specialiserade smärtvården. Om andelen skulle öka till 25% skulle man årligen spara motsvarande 106 millioner kr samtidigt som hälsovinsten skulle bli ca 14 QALY/år. Om en interventionell utredning genomförs tidigt så finns det även förutsättningar för att behandlingsbara patienter kan tas bort från dem som behöver smärtrehabilitering, vilket kan ge ytterligare besparingseffekter.

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Abbreviations

ATC	Anatomical Therapeutic Chemical codes

DDD	Defined daily doses
EQ-5D	EuroQOL five-dimension questionnaire with 3 levels, EQ-5D 3L
EQ-VAS	EuroQOL visual analog scale
HAD	Hospital Anxiety and Depression scale
HRQoL	Health-related quality of life
ICD-10	International Classification of Diseases, version 10
IPM	Interventional pain management
MBB	Medial branch block (nerve block of the median branch from the dorsal root)
MRI	Magnetic resonance imaging
NBHW	National Board of Health and Welfare (Socialstyrelsen)
NRPR	National Register of Pain Rehabilitation (Nationella Registret Över Smärtrehabilitering)
NSAID	Non-steroidal anti-inflammatory drugs
REH	Pain rehabilitation program
RFC	Radiofrequency coagulation. Equivalent to radiofrequency neurotomy and radiofrequency denervation
SD	Standard deviation
Z-joint	Zygapophysial joint
ZJP	Zygapophysial joint pain
ZNB	Zygapophysial joint nerve block (usually equivalent to MBB)

Explanations of key terms

Cost-effectiveness	A form of economic analysis that compares the relative costs and the health outcomes (effects)
Empowerment	The degree of autonomy and self-determination a person possess.
Nociception	Pain perception from damaged tissue (i.e., the sensation of pain)
Propensity score	The probability of receiving intervention-1 in relation to intervention-2
Quality adjusted life years	A generic measure of health, including both quantity and quality. One QALY is equal to 1 year of life in perfect health or 2 years of life with 50% health.
Zygapophysial joint	The joints between the vertebrae, that steer the movements when bending the spine.

Original papers

This thesis is based on the following papers.

Study I. Hambraeus, J. Hambraeus, K. Persson, J. Radiofrequency Denervation Improves Health-Related Quality of Life in Patients with Thoracic Zygapophysial Joint Pain. Pain Med. 2017;19:914–919. Available from: https://academic.oup.com/painmedicine/article/19/5/914/3869829

Study II. Hambraeus J, Hambraeus KS, Sahlen K-G. Patient perspectives on interventional pain management: thematic analysis of a qualitative interview study. BMC Health Services Research [Internet]. 2020 [cited 2020 Jul 2];20(1). Available from: https://bmchealthservres.biomedcentral.com/articles/10.1186/s12913-020-05452-7

Study III. Hambraeus J, Pulkki-Brännström A-M, Lindholm L. Cost-effectiveness of Radiofrequency Denervation for Zygapophysial Joint Pain. Pain Physician. 24 (2021) E1205–E1218. Available from: https://www.painphysicianjournal.com/linkout?issn=&vol=24&page=E1205

Study IV. Hambraeus J, Norström F, Lindholm L. Cost-Effectiveness of Radiofrequency Neurotomy to Treat Zygapophysial Joint Pain Compared with Pain Rehabilitation Programs. Interventional Pain Medicine. 1(2022)100147. Available from: https://doi.org/10.1016/j.inpm.2022.100147

Preface

I learned from my father that there are always new things to discover, and nothing can be too large or too small to be important. I'm told that Martin Luther said "If there is something in the Scripture you don't understand, just lift your hat and walk on!", but my relationship to the unknown - as my father taught me - is closer to what Sven Reichmann once said: "If there is something that you can't understand and that looks impossible, a paradox – then it is probably important and needs more studying". Human progress has been based on collaboration (as was predicted in the text on the Tower of Babylon in the Book of Genesis), with no one being able to grasp everything but when collaborating there are no limits ("*...and now nothing will be restrained from them.*"). This thesis is another example of what can be achieved when building a web of collaboration and following this yarn-string, trying to understand the pattern and how different things are connected. Just like the spider-webs will full-fill their purpose, even if some strings break, the same can be said about this thesis. I am not trying to grasp all aspects of pain. However, to try to understand the effects measured, I felt that I also needed to understand the processes involved. Where I found gaps in prior studies, I have tried to fill those gaps – if not with solid bridges at least with a walkable footbridge. I hope you are willing and able to follow the track described in this thesis; it is similar to the attempts made to solve the Rubik's cube - you must look at the problem from different angles and switch your viewpoint frequently. Similarly, the

complexity of pain has forced me to use several different methods to glimpse the bigger picture.

1 Introduction

1.1 Pain

The pain perception system is a basic biological system, seen in all animals from the simplest of organisms all the way to humans [1]. When we try to understand pain and how pain perception is handled in the nervous system, as well as the effects of pain, we must dive down to the basic philosophic theories. Sometimes, the discussion implies that we regard nature from totally different, incompatible viewpoints. Since humanity is but one viewpoint, a clearer picture was drawn by Mårtensson, who described how our understanding extends from branches of the same tree, rooted in both rationalism and empiricism [2]. When the branches diverge toward deductive thinking, a positivistic approach is applied and we can explain and prove how everything works; i.e. a typical natural science approach. In my thesis, the first study is an example of this. However, when the branches diverge toward inductive thinking, we instead start to interpret what we see in order to understand it, as is typical in human sciences. If the branches are allowed to stretch toward the light with neither inductive nor deductive diversion, they follow a phenomenological course, in which we describe our experiences without explanation or understanding. This thesis has been like a squirrel, jumping from branch to branch, sitting still and eating on a cone here and there. Sometimes resting on the positivistic branches, and other times on the more inductive branches and sometimes climbing up the phenomenological trunk.

The concept of pain and its relation to tissue damage is one of the first things we learn as a child. My granddaughter, who at the time was 3 years old, put it best when she saw the plaster on my wife's broken ankle and exclaimed: "Grandma, pain, leg!". This was described in the definition of pain by the International Association for the Study of Pain (IASP) 1979 [3]:

> *"Pain*
>
> *An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.*
>
> *Note: The inability to communicate verbally does not negate the possibility that an individual is experiencing pain and is in need of appropriate pain-relieving treatment. Pain is always subjective. Each individual learns the application of the word through experiences related to injury in early life*."

The Irish philosopher Dr. George Berkeley (1685-1753) posed the philosophical question: "If a tree falls in a forest and no one is around to hear it, does it make a sound?" [4]. A similar question has been raised about pain: can pain exist without the ability to express it? The obvious answer, is that pain does of course exist, independent of the individual's ability to express what is felt, rendering the previous definition outdated. After several years of discussion, the IASP proposed a new definition in 2020 [5]:

> *"An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage.*

- *Pain is always a personal experience that is influenced to varying degrees by biological, psychological, and social factors.*

- *Pain and nociception are different phenomena. Pain cannot be inferred solely from activity in sensory neurons.*
- *Through their life experiences, individuals learn the concept of pain.*
- *A person's report of an experience as pain should be respected.*
- *Although pain usually serves an adaptive role, it may have adverse effects on function and social and psychological well-being.*
- *Verbal description is only one of several behaviors to express pain; inability to communicate does not negate the possibility that a human or a nonhuman animal experiences pain."*

Interventional pain management (IPM) is performed through cooperation between the care-giver and the patient, whereby the care-giver performs several tests in the form of nerve blocks and the patient is the only expert capable of perceiving the pain by evaluating the effects and describing whether the pain focus is located in the tested structure or not. Hence, the new definition is consistent with how pain has been viewed by interventionists.

1.2 Pain perception

The perception of acute pain starts with pain receptors in the tissue, propagated through Aδ-fibres (fast, myelinated axons) and C-fibres (slow, unmyelinated fibers) passing the dorsal root to the spinal cord where they connect to the ascending nerves that propagate in the ventral contra-lateral so called spino-thalamic tract [6]. Everyone who has hit their thumb with a hammer or have stubbed their little toe while walking barefoot has gained firsthand experience of this phenomenon: First you immediately feel an

electric flash (Aδ-fiber) after the insult and then, several seconds later (C-fiber), you feel the burning, pulsating numbing pain from the thumb or toe.

In the thalamus, the ascending nerves connect with fibers reaching the post-central gyrus in the cortex and temporal region. The latter, the limbic system, is important for ascertaining whether the pain should be considered dangerous or not. This process is involved in the reason why people can sit calmly when giving a blood sample, but get scared when walking barefoot in the grass and suddenly feel a sharp pain. (“Is it a snake-bite?”).

There are several mechanisms that modulate the pain signals at different levels. Opioid receptors in the dorsal horn inhibit pain signals from reaching the brain whereas NMDA-receptors facilitate the propagation of the pain signal to the brain. Similar mechanisms, involving both facilitating and inhibiting receptors, exist at several physiological levels, at the pain receptors, the spinal cord, the thalamus and at higher levels in the brain. These mechanisms serve to evaluate the pain and answer the question – “Is this dangerous or not?”

1.3 Chronic pain

Pain is considered chronic if it persists for ≥3 months. The transition from acute pain to chronic pain is unclear. Acute pain related to physical trauma or infection, for example, can transform into chronic pain or it might increase the vulnerability for evolving into chronic pain after trauma or negative physical factors [7–10].

When the pain persists and transforms into chronic pain, some of the mechanisms involved in acute pain are still valid but other, less well-defined mechanisms, are also drawn in. The attempts to predict which patients will develop chronic pain were unsuccessful although some risk-factors were described [11–13]. Although numerous studies have provided evidence of altered pathways and central nervous system reactions, including different autonomic nervous reactions [14], the scientific community is still lacking knowledge of the interplay between the different nervous system actions and reactions in chronic pain.

1.4 The complexity of chronic pain

Chronic pain is maintained by several mechanisms and by complex interactions between endogenous modulatory pathways, cortical processing, and peripheral and central sensitization that integrated with numerous psychological and behavioral factors and co-morbidities [15,16], with a high degree of individual variation.

The importance of the pain generators in chronic pain has been delineated although their exact roles remain obscure [17,18]. The relationship between pain generators and sensitization is indicated by the epidemiological findings that sensitization is more common after neck trauma and by observation that sensitization is reduced after treatments of pain generators in the neck [18]. However, even less is known about how the autonomic nervous system interacts with pain perception, although several studies have described some interactions [14,19].

1.5 Social effects

The social effects of chronic pain have been well described in several qualitative and quantitative studies [20–22]. This includes the relationships with family members and other people, and the ability to adopt to altered performance owing to pain-related impairments and how the effects on the ability to work. However, the negative social effects of pain, especially after a longer duration, have been hard to address therapeutically [20,23].

1.6 Treatment strategies

The health community uses several different strategies for managing patients with chronic pain. As previously stated, there are four major factors to consider: CNS reactions, social factors, psychological distress and pain generators [24]. The pharmacological industry has long focused on the CNS reactions, providing different medical therapies that aim to change and reduce the CNS reactions [25]. Social factors are often discussed but seldom approached, although they might be reviewed together with psychological distress in interpersonal and multimodal rehabilitation programs based on cognitive behavioral therapies and coping strategies [26–29]. The pain generators are targeted by orthopedic surgery and in IPM, in which diagnostic procedures with nerve blocks are performed under direct vision with X-ray or ultrasound localization of pain generators not otherwise seen on X-ray or magnetic resonance imaging (MRI) [30].

The first challenge in my work was therefor to see if it was

possible to achieve general effects on the health related quality of life (HRQoL) by treating pain generators.

1.7 Radiofrequency coagulation

Radiofrequency coagulation (RFC) is a technique developed in the mid-20th century. When a force meets resistance, the energy is transformed into heat. When the force is applied in the form of an electrical current, this phenomenon is achieved by the electrical resistance of the material. Alternating currents will create resistance in the form of an inductive impedance when passing through biological tissues. This impedance is increased at higher frequencies of the alternating current. This principle was used to develop the medical application of radiofrequency generators by using a generator to form an alternating current with a very high frequency, (100,000 – 500,000 Hertz i.e. in the realm of radio frequencies), the resistance (impedance) will be very high. When this current is applied through an insulated needle or catheter inserted in the body, heat is formed in the tissue close to the un-insulated tip of the needle or catheter. This technique has been used for deep brain surgery, liver surgery and, in the last 30 years, for catheter ablation to cure tachycardia by targeting accessory atrioventricular pathways in the heart [31].

The treatment of ZJP has been referred to as radiofrequency treatment, radiofrequency denervation, neurotomy, and “burning” in publications spanning over the 40 years. However, All these terms are inaccurate and leads in the wrong direction.

Radiofrequency treatment implies that radiofrequency is the treatment, but it in in fact the heat formed by the alternating current that yields the effect [32]. Likewise, denervation is inaccurate because this method exerts a temporary effect on the target nerve. In fact, the nerves regain their normal function when they heal, which may take 10-12 months. Finally, burning, may imply that a high temperature is used, but in fact the treatment is limited to a temperature of about 80 °C. Owing to this inconsistent terminology, Waring et al 2022 proposed the term coagulation instead [33]. In this thesis, I have adopted the term RFC.

1.8 Zygapophysial joints

The z-joints at all levels (cervical, thoracic, and lumbar) are important generators of spinal pain [34–39]. There are several established methods for the diagnosis of zygapophysial joint pain (ZJP) and RFC of z-joints in the cervical and lumbar regions [30,34,40–43]. However, significant inter-individual and inter-level variation has been found in the innervation of thoracic z-joints [41,44]. This makes it more difficult to apply diagnostic blocks or to perform RFC of thoracic z-joints than cervical or lumbar z-joints [45]. The anatomic study used in the guidelines to support an “only lateral” injection when performing medial branch blocks (MBB) in the thoracic region was published 1995, and in the following decade, several anatomic studies and clinical outcome studies were published [46–52]. However, a paradox was identified, that good outcomes were achieved when RFC was performed medially, even though the anatomical studies suggested that the needles would not be able to reach the medial branches, and no

studies yielded good outcomes when they used the study by Chua for treatment planning [44,53,54]. One possible reason for this could be found in the anatomic studies presented by Ishizuka 2012 and Youssef 2016, who explained that the thoracic z-joints are innervated by several nerves, both the medial branches located laterally at the tip of the transverse processes and descending branches located medially [55,56].

My second challenge was to describe a method for performing diagnostic tests and RFC in the thoracic region, then validating the method against the established methods used in the lumbar and cervical regions.

1.9 Patient experiences

Many qualitative studies have focused on the patient's experience of living with chronic pain. It has shown that healthcare providers might blame the patients for being responsible for their pain [57] while simultaneously disempowering the patient [58]; this has resulted in the stigmatization of patients with chronic pain [59]. Patients often describe how they strive for self-management [60,61], but they feel distrusted and disrespected when interacting with healthcare providers [62] and believe their needs are ignored [63]. Healthcare providers have confirmed this view of patients with chronic pain [64], which is based on a feeling of insufficiency among some healthcare providers [65]. The challenge faced by healthcare providers during encounters with patients with chronic pain is described by the incompatible requirements of empowering

patients [66] while keeping a professional perspective to avoid disempowering themselves [67,68].

A striking feature of using IPM to treat patients with chronic pain was the apparent psychological changes observed. I attempted to describe this observation and presented a rudimentary theory on the mechanism behind the changes I observed when I was working part-time in primary care [69]. However, a visible paradox remained unexplained: IPM that focuses on finding the pain generators results in psychological changes that are not seen after previous encounters with psychologists and rehabilitation wards.

Therefore, another challenge in my work was to better understand this process by exploring IPM from the patient's perspective.

Although a large portion of the healthcare-budget is used for chronic pain, few studies have evaluated the health economics of these treatments. The UK National Institute for Health and Care Excellence (NICE) based their guidelines "Low back pain and sciatica in over 16s" on a health economic assessment and, although they encouraging self-care and pain rehabilitation programs (REH), they also state that IPM focused on ZJP should be considered if conservative treatment has failed [70].

Accordingly, another challenge was to investigate whether IPM was cost-effective with the threshold defined by the Swedish National Board of Health and Welfare (NBHW).

1.10 Evaluation models

In the world of science, different types of studies have different impacts. Randomized controlled trials are considered the “gold standard”, especially if they are performed in a double-blind manner, where the patients and the researchers are unaware whether they receive the test or control (or sham) treatment. When we think about medical care and the enormous progress achieved during the last decades in the understanding and care of many diseases, we may get the impression that everything is based on solid scientific studies. This impression is also emphasized by the medical community, which refers to “evidence” and randomized controlled trials. However, when we lift the cover and start to explore which of the things we do for our patients are truly based on solid scientific facts, we get a feeling similar to that of trying to walk over a rope-bridge in the Andes: there are more holes than solid matter! This problem was raised by one of the founders of IPM, sir Nikolai Bogduk. When he studied the different interventional methods used for the diagnosis and treatment of chronic pain, he found that many of the methods were not well studied in terms of their effect, effectiveness, and adverse effects. He realized that if all of these methods are evaluated in randomized controlled studies, an enormous amount of time and money would be needed [71].

Observational studies, in which the researcher observe the effect of a treatment on a person or group of people, are considered to give less robust evidence than randomized controlled trials,

despite being closer to the approach used in real life. The main problem of interpreting observational studies is that treatment exposure might be associated with covariates that are also associated with the potential response. If these covariates are imbalanced between the treated group and the control group, the results might be biased. This was noticed by statisticians in the 1980s and several different approaches for matching controls, in order to balance the exposed and not exposed groups, have been proposed.

In 1983, Rosenbaum et al presented theories behind the propensity score and how the propensity score could be used as a balancing score in observational studies [72]. In statistical terms, the propensity score is the conditional probability of assignment to a particular treatment given the observed covariates. For this purpose, the researcher collects all data on the covariates in exposed and unexposed (control) group and performs a multiple regression to determine how likely it is that a single individual would be in the exposed group or in the control group based on the covariates. The propensity score has been used to match controls (i.e. matching one exposed individual to 1, 2 or more controls that are “similar” in terms of covariates) and for weighting. Lunceford and Davidian thoroughly described this method in 2004 and 2017 [73,74]. By using propensity score weighting, observational studies can mimic randomized controlled studies to generate evidence of high scientific value [75].

Using propensity score weighting, it would be possible to compare

IPM to patients treated with REH. To date, I have not been able to find any studies comparing the effects of IPM and REH on HRQoL, forming another challenge för this work. Furthermore, would resources be better used for REH in patients selected for REH than for IPM in patients selected for RFC?

Therefore, I felt it necessary to evaluate both the effects of IPM and REH on HRQoL and to compare their cost-effectiveness.

1.11 Aim

The purpose of this thesis, and the studies involved, was to increase our knowledge about IPM and its role in the health-care system. How is it performed? What kind of feelings are raised by the patients who receive IPM? What does it feel like? What patients are offered IPM and what are its outcomes? Is it cost-effective? Could IPM help the health-care system better adapt to the needs of the patients with chronic pain?

My first aim was to investigate whether the treatment of pain generators using the IPM methods described could improve HRQoL.

My second aim was to establish a method for diagnosis and treatment of thoracic ZJP.

My third aim was to explore the patients' perceptions of IPM in order to better understand how it affects them.

My fourth aim was to evaluate the cost-effectiveness of IPM

focusing on ZJP, relative to the thresholds set by the Swedish NBHW for the “gold standard” REH.

2 Methods

2.1 Study setting and design

2.1.1 Study design

Study I was an observational study that mainly focused on validating the medical treatment and to investigate whether the treatment of pain could affect HRQoL. Study II was a qualitative study designed to explore the psychological effects of IPM. Study III was a cost-effectiveness study in which the patients served as their own controls. Study IV was a cost-effectiveness study in which IPM was compared with REH (Table 1).

2.1.2 Study setting and population

In Sweden, patients with chronic pain can either be referred to one of many specialized pain rehabilitation clinics or to one of the few clinics that provide IPM. The assessments performed at pain rehabilitation clinics are designed to evaluate whether the patient would benefit from REH, while the assessments performed at IPM clinics mainly are focused on ZJP and whether it could be diagnosed and potentially treated.

All patients who underwent assessment of chronic pain in Sweden between 2010 to 2016 were eligible for the studies. All 23 counties in Sweden had access to specialized pain rehabilitation centers, either in one of their own hospitals or referral. A total of 36,712 patients were assessed at pain rehabilitation clinics, of which 18,471 (50.3%) were selected for REH. Data from all of the centers were registered in the National Register of Pain

Rehabilitation (NRPR) after providing informed consent [76]. During the study period (2010-2016) the number of pain rehabilitation centers included in the register increased from 20 in 2010 to 40 in 2016. The settings were diverse, although the clinics are supposed to follow similar guidelines for assessing and treating pain [76].

The studies on IPM was performed at one of the few IPM clinics in Sweden (Smärtkliniken Eques Indolor), located in a rural part of Stockholm county. Patients are referred to the clinic from all counties in Sweden (60% from primary care). The referred patients were accepted for assessment regardless of their previous treatments. The assessments for RFC involve diagnostic blocks to localize the pain foci, mainly ZJP, that can be treated by RFC. Once ZJP is diagnosed, RFC of the nerves that supply the identified z-joints is performed.

The medical facility is housed in a private residential building and occupied most of the ground floor. The patients had access to the garden outside the building and to a waiting room with freely available coffee. The staff included one physician, one nurse, and one dog trained in animal-assisted therapy for the relief of stress and anxiety. The healthcare provided by the clinic was reimbursed mainly through procured contracts with national health insurance schemes. General practitioners referred patients from all parts of Sweden when conservative therapy with physiotherapy, medications, and coping strategies had failed to give sufficient relief. All clinical procedures were performed according to the

Spine Intervention Society guidelines [41]. IPM was focused mainly on ZJP, and to search for pain generators by performing MBB of the cervical, thoracic, and lumbar spinal nerves.

According to official statistics from the Swedish NBHW, there were 21,083 encounters with specialized pain physicians in 2017, and 1712 of those encounters involved nerve blocks for the diagnosis and/or treatment of pain [77]. The IPM clinic involved in these studies provided 7% (1411 visits) of the specialist encounters for chronic pain and 93% (1587) of the nerve blocks registered in Sweden in 2017.

2.1.3 Patient recruitment

The patients assessed for IPM between 2010 and 2016 were asked to participate in the research studies (studies I, III and IV). Patients were eligible if they had not been previously assessed or treated at the IPM clinic.

For study II, a purposive sample of patients who had been treated or were undergoing treatment at the clinic was created. The selection process was designed to provide a heterogeneous group of patients. Patients were selected by the clinic nurse in February and March, 2017, focusing on disparities in age, living conditions, gender, pain localization, and pain duration and for patients with good ability to communicate their feelings and experiences.

Study IV also included patients registered in the NRPR as a comparator group. Patients were eligible if they had been selected for and treated with REH (Table 1).

Table 1 Description of the studies

	Study I	Study II	Study III	Study IV
Research questions	How could a practical approach for the diagnosis and treatment of thoracic ZJP be described? What are the effects on HRQoL?	How do patients describe their feelings and perception during an IPM program, and how are they affected?	Is RFD focused on ZJP cost-effective for from a societal perspective?	How does RFC after the diagnosis of ZJP compare to inter-disciplinary REH in terms of: - characteristics of the patients assessed - effects on HRQoL - cost-effectiveness?
Setting	IPM: one specialist clinic recruiting from all regions in Sweden.	IPM: one specialist clinic recruiting from all regions in Sweden.	IPM: one specialist clinic recruiting from all regions in Sweden.	REH: national register from specialist clinics in Sweden. IPM: one specialist clinic recruiting from all regions in Sweden.
Design	Observational study	Qualitative study	Before and after treatment	Comparison of two treatments, with propensity score weighting.
Subjects	115 men, 200 women	8 men, 11 women	113 men, 218 women	REH: 3824 men, 11,533 women IPM: 96 men, 158 women
Inclusion	Patients with chronic pain assessed between 2010-2016	Purposive sampling of patients receiving IPM focused on diagnosis of ZJP and treatment with RFC	Patients with chronic pain assessed between 2010-2016	REH: patients treated with pain rehabilitation program and registered in the NRPR between 2010-2016 IPM: Patients diagnosed with ZJP and treated with RFC between 2010-2016

	Study I	Study II	Study III	Study IV
Exclusion	Patients not diagnosed with ZJP. Patients missing EQ-5D data.	n.a.	Patients not diagnosed with ZJP. Patients missing EQ-5D data.	Patients treated more than once. Patients who underwent both RFC and REH. Patients missing EQ-5D data.
Inter-vention	RFC after diagnosis of ZJP.	IPM before and after diagnosis.	RFC after diagnosis of ZJP.	REH: pain rehabilitation program including psychological methods. IPM: RFC after diagnosis of ZJP.
Outcome measure	EQ5D	Themes	cost/QALY gain	cost/QALY gain
Costs included	No	No	Yes, societal perspective	Yes, societal perspective

EQ-5D EuroQol 5-Dimension scale, IPM interventional pain management, NRPR National Register of Pain Rehabilitation, QALY quality-adjusted life year, REH rehabilitation program, RFC radiofrequency coagulation, ZJP zygapophysial joint pain

2.1.4 Informed consent

Patients registered in the NRPR gave informed consent for inclusion in future research studies that utilized data recording during the first assessment.

Patients assessed at the IPM clinic gave informed consent for inclusion in the specific studies at their first assessment. For the qualitative study (study II), patients provided informed consent before inclusion, at the start of the interview, and after completing the interview.

2.2 Clinical methods

In study I, a clinical method for the diagnosis and treatment of

chronic pain localized in the thoracic region was validated against the established methods for the diagnosis and treatment of pain localized in the lumbar and cervical regions. The outcome was HRQoL measured using the EQ-5D 3L. The clinical treatment methods used in study I were also used in the other studies.

2.2.1 Diagnosis of ZJP

All patients were first assessed by a physician, who assessed their pain using a semi-structured interview (Appendix 1). The z-joints in the cervical and lumbar region are innervated by medial branches from the dorsal nerve root [41]. By anesthetizing these nerves it is possible to test whether they are the source of the pain. In order to reduce the risk of false-positive responses two tests are performed on separate occasions, and both tests should reduce pain by at least 80% while under the effect of the local anesthetics [34,41].

The innervation of the z-joints in the thoracic region is more complex. Studies have shown marked inter-individual and intra-individual variation of the medial branches in the thoracic region, and that the medial branches are usually located at the lateral border of the transverse processes, mainly in the soft tissue and without consistent connection to a bony structure [44]. However, the medial branches are not the only nerves that innervate the joints in the thoracic region; descending branches also have innervate the joints in this region [55,56].

Z-joint nerve blocks (ZNB) were achieved by injecting bupivacaine (5mg/mL) close to the nerve(s) innervating the z-joints, as described in the Spine Intervention Society’s guidelines. [41]. This

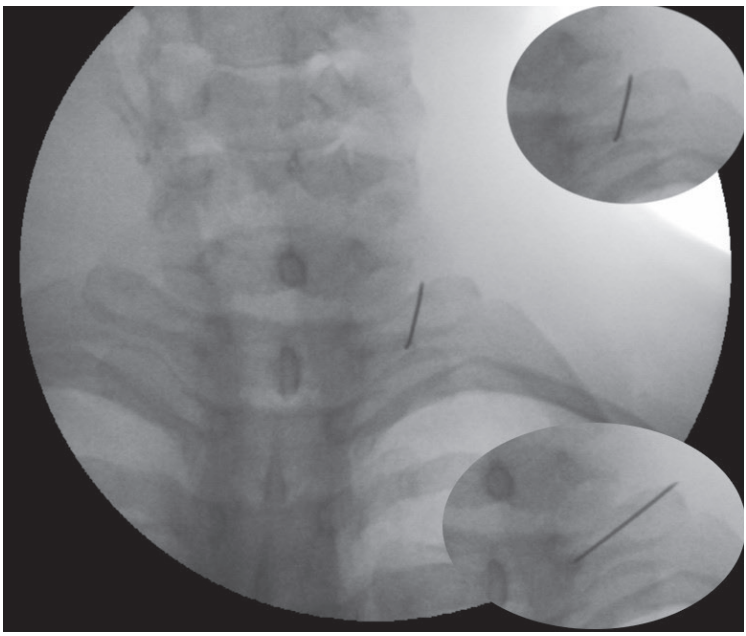
applies to the cervical and lumbar region, but the guidelines state that this method is “experimental” for the thoracic region.

We developed a technique based that is best described as targeting an area rather than a nerve [78]. By determining the area corresponding to the nerve that we intend to anesthetize and coagulate, and the orientation of the nerve, we could apply a similar technique for all spinal levels. We placed the needle at the border of the area, performed a coagulation, redirected the needle and placed it parallel to the first lesion. This was repeated until the total area was covered. In the cervical and lumbar regions where the variation is small, the target areas are small and few lesions are needed. By comparison, larger target areas with more lesions are needed for the thoracic region.

A more detailed description of the method used in the thoracic region follows.

For the diagnostic nerve blocks, the needle was inserted until it touched the bone at the medial part of the transverse process, and the tip of the needle was redirected in a cranial direction until it was aligned ventrally to the transverse process. Then, 0.6 mL of bupivacaine was injected. The needle was withdrawn, redirected laterally, and advanced until it touched the transverse process at the lateral cranial border. Then, the needle was moved until it was positioned along the ventral line of the process, and another 0.3 mL of bupivacaine was injected (Figure 1)

Figure 1 Diagnostic medial branch blocks in thoracic region study I



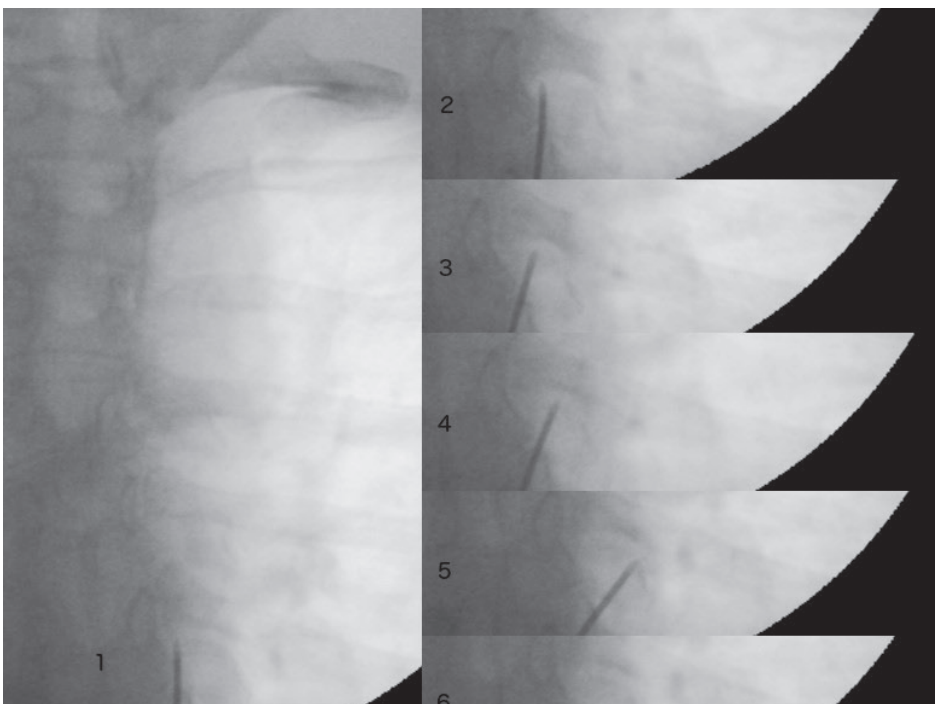
The patients recorded their pain level hourly for the next 7 hours. If pain relief of 80% or more was achieved with two or more ZNBs at the same level, the patient was diagnosed with ZJP and was considered for RFC.

2.2.2 RFC of z-joint nerves

After anesthetizing the skin and the nerve branches, RFC of z-joint nerves was performed by positioning the needle medially, similar to that during ZNB. The needle (18 G, 10 mm active tip) was heated to 80 ºC for 60seconds. Then the needle was withdrawn, redirected, and positioned slightly laterally to the previous position.

If the temperature at the new position was greater than 60 ºC, the needle was repositioned laterally. If the temperature was less than 45 ºC, the needle was repositioned in a medially until the temperature was above 45 ºC. Then, a new lesion was made. The procedure was repeated until the lateral-cranial tip of the transverse process was reached. Then, the next nerve was treated in a similar manner. It was necessary to create 3 - 15 lesions to cover the intended area for each nerve (Figure 2)

Figure 2 RFC in the thoracic region study I



RFC of the medial branches in the cervical and lumbar region was performed according to established guidelines by placing the needles parallel to the nerves [41]. Multiple parallel lesions were created on each nerve in this region. However, because the target area was smaller, only 3—5 lesions were made on each nerve.

Because nerves were treated from C2 to L5, it was necessary to define the cervical, thoracic, and lumbar regions. Branches C2—C7 were usually treated with the patient placed in a lateral position, while branches at C8 and lower were treated with the patient placed in the prone position. The thoracic region was defined as the medial branches C8 and lower. Because the medial branch Th11 was chosen as the second dividing line, the medial branches Th11 and lower were defined as lumbar branches.

2.2.3 Pain rehabilitation program

The REH registered in the NRPR started with a team-based assessments conducted over 1 day. The team members conducted their examinations individually. At a joint meeting, they discussed the findings and recommendations for each patient. Patient who were considered to benefit from REH were invited to participate.

REH was a group-based program, but it differed among the clinical units in terms of group size, number of days per week it was conducted on, and the total duration in weeks [79]. We used data

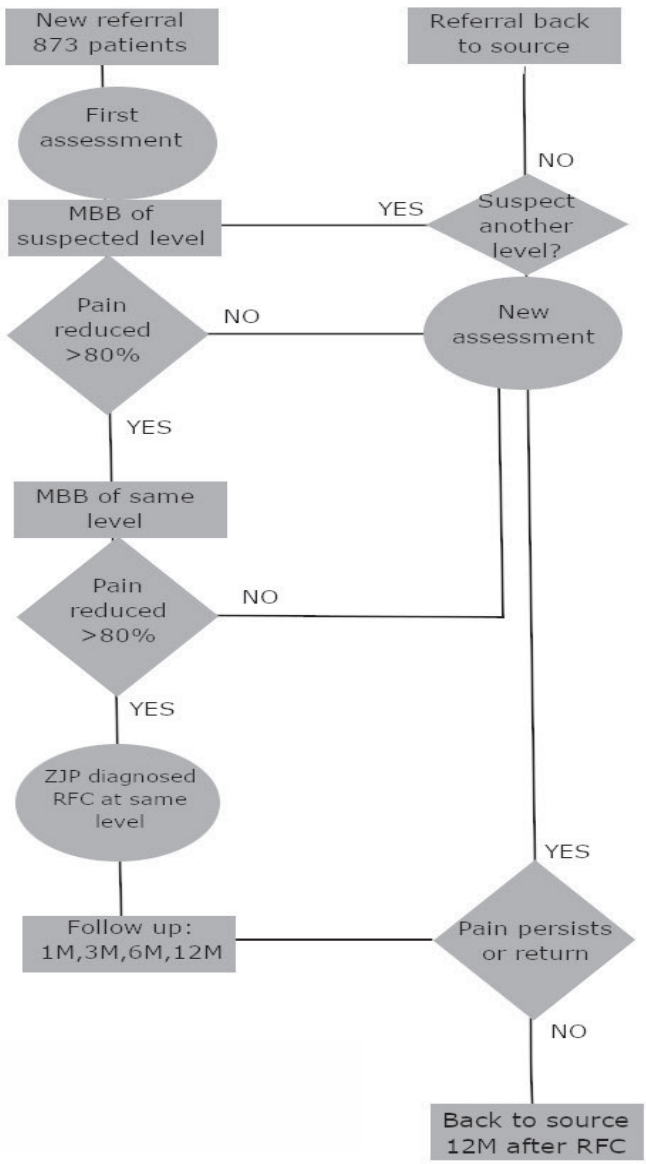
from Skåne region as the base case, where the groups consists of 8-10 individuals. The program started with patients attending two meetings during which they received information about the program, goal-setting practices, and other relevant information. Ten weeks later (on average), the patients underwent a 5-week outpatient program with sessions on 4 days per week. This goal-oriented, interdisciplinary pain program was based on cognitive behavioral therapy principles. Discharge meetings were held with each patient in week 5, to which the patients could invite additional guests. A 2-day follow-up was scheduled 9 weeks after discharge. At 1 year after discharge, questionnaires covering self-reported outcomes were posted to all patients [29].

2.3 Data

2.3.1 Data collection process

All data were collected prospectively. The patients at the IPM clinic completed questionnaires at the first visit, at the time of RFC, and at 3, 6, and 12 months after RFC. A short telephone interview was performed 1 month after RFC to ask how long the patients experienced pain after treatment.

Figure 3 Flow chart of data collection in study III



MBB Medial branch blocks, RFC Radiofrequency coagulation, ZJP Zygapophysial joint pain, M Month

Figure 4 Time-line of assessment, treatment, and follow-up

A - Assessment, M - Medial branch blocks to diagnose zygapophysial joint pain, Q - Questionnaire, R - Radiofrequency coagulation (RFC), 0 - 3 months before RFC, 3 – Time at RFC, 6 - 3 months after RFC, 9 - 6 months after RFC, 15 - 1 year after RFC

The patients from the clinics included in the NRPR completed questionnaires before the assessment, after the follow-up and at 1 year after discharge.

Linked data on medications, sick leave, and healthcare consumption were obtained from national registers (Swedish NBHW and the National Social Insurance System).

The patients selected for the qualitative study were informed of the study and invited to participate by the clinic nurse. The nurse provided information about the aim and design of the study orally together with a written sheet, which the patients were asked to read, after which the patients provided informed consent. The

study patients were informed that a research assistant would call them to schedule a recorded telephone interview. The research assistant, who was not involved in the patients' care, contacted each patient, asked again for consent and scheduled a telephone appointment. The research assistant also instructed the patients to be seated comfortably in a relaxed location where they would be able to talk undisturbed during the telephone interview.

At the scheduled time, the research assistant called the patients on a telephone line that was recorded. After reconfirming consent, the interview was performed.

2.3.2 Data collection instruments

All participating patients completed questionnaires recording information on patient demographics, psychological distress, and HRQoL.

Psychological distress was measured using the Swedish version of the Hospital Anxiety and Depression (HAD) Scale [80–85].

HRQoL was measured using the validated EQ-5D 3L index [86], which consists of five questions covering: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each question had three possible responses: no problems, moderate problems, and extreme problems [86,87]. These five questions and three answer options form 243 possible health conditions, which can be converted into a single value using the UK values-score formula [88,89]. There is no generally accepted, smallest clinically

important change in the EQ-5D index [90]. However, reductions of 0.08 to 0.12 were considered clinically relevant when describing how different chronic diseases affect the index [90,91] and an increase of 0.35 was deemed clinically significant when differentiating patients who had undergone surgery [92]. Using data from the Swedish NRPR, an improvement of 0.1 was considered clinically relevant [80]. The mean EQ-5D indexes for women and men in a Swedish population were 0.797 and 0.841, respectively [93].

2.4 Qualitative study

2.4.1 Researchers involved in the qualitative study

The research group in the qualitative study consisted of three people. I am specialist in anesthesiology, intensive care, family medicine, and pain management. I have treated patients with chronic pain in primary care for 25 years and have provided IPM in the last 23 years. KH is a nurse with 20 years' experience as nurse in stroke rehabilitation and she has been working full-time in IPM for 9 years. K-G S is an experienced qualitative researcher. He had been working as a nurse for many years, but had no experience of working with IPM or chronic pain.

2.4.2 Qualitative interviews

A pilot study was performed with seven patients and KH as the interviewer. However, it was apparent that the patients could not distinguish the research interviews from their ordinary healthcare

evaluation interviews.

Based on the pilot study, the questions were reformulated to focus more on the patients experiences of IPM, and an experienced interviewer without previous connection to neither the patient nor the clinic was recruited to perform the interviews. She had no conflicts of interest, she was not involved in the care of the patients at the IPM clinic, and she had never met the patients before the interviews.

The questions were intended to help the patients describe various aspects of their experience of IPM, including what they felt during the encounter at our clinic and their reflections during and after the encounter and procedures (Appendix 2). The interviewer also asked several follow-up questions to help the patients describe what they had felt and thought, without leading them, and to help them reflect on their experiences and feelings during the IPM program. After the interview ended, the research assistant disconnected the call and stopped the recording. The research assistant then called the patients 5 minutes later to allow them to comment on the interview or to withdraw from the study. The patients were also asked if they would like to add anything or if they had any further questions, and they were offered contact with the IPM clinic in case the interview had raised any feelings that they needed help with. The comments were written down by the research assistant. All interviews took place between May and August 2016. Each interview was 13–45 minutes long. All interviews were performed in Swedish, transcribed into Swedish

text, and analyzed.

2.4.3 Thematic analysis

Thematic analysis was performed as described by Braun and Clarke [94,95]. This is an analytical approach well-suited to exploring the views of patients. The research group read and familiarized themselves with the transcribed text, and codes were generated for the latent and manifest content. Themes were identified among the codes, and these were changed until consensus was reached. The transcriptions were coded after each interview on a line-by-line basis. We felt that saturation was reached before all the interviews were analyzed because no new codes were identified when coding the last interview. Nevertheless, the analysis continued until all of the interviews were coded [96]. The last interviews to be coded served more as confirmation rather than adding further data. The thematic analysis was based on our common knowledge and experience, and the themes ranged from self-explanatory (e.g., “hope of recovery” or “ambivalence about the future”) to more concrete (e.g., “acceptance of pain to become pain-free”) to detect manifest and latent content. The themes were discussed and categorized. Open Code 4.03 software, which was developed for qualitative research analysis, was used for the thematic analysis [97].

2.4.4 Triangulation in the qualitative study

Triangulation was performed continuously using several

approaches, namely, comparing the interviews, and comparing how the different researchers interpreted the text. The different pre-understandings the researchers had gained from encounters with patients in IPM or other healthcare settings provided a background to the analysis. The results were discussed by the research group until consensus was reached for all themes. The themes were also checked to see if there were differences by gender or age, or whether the patients were in a situation where they reported improvements in HRQoL compared with their first visit.

2.4.5 Validity check of the qualitative study

After the analysis, the patients were contacted by K-GS, who presented them with the results and asked them to elaborate on the results, add information, or clarify their responses.

2.5 Health economic evaluation

2.5.1 Intervention costs

2.5.1.1 Pain rehabilitation program

For REH, the costs associated with the assessment and treatment of pain were calculated by multiplying the number of treatment days by the unit cost per day. The unit cost per day had been negotiated with the purchasing neighboring regions to generate a “price-list” for each combination of diagnosis and possible treatment. In this study, we used 2016 as the price year and the price list from Skåne region. There is some variability in the REH between the different rehabilitation units in Sweden in terms of the size of the groups, duration (days per week and total), and number

of hours per day [79]. There is also variability in terms of the type of medical professions involved, although most units include physiotherapists, psychologists and physicians [79]. When calculating the costs, the only factors affecting the price is whether it is conducted by a team or a single provider, and whether a physician is included in the team. We assume that the assessment was performed by a team including a physician, while we have assumed that REH was conducted in daycare visits, and that physicians were not always present. The variability of duration of REH in terms of number of days was included in a sensitivity analysis [79].

The unit cost for a “team with a physician” (10,632 Swedish krona [SEK]) was used for the assessment of patients eligible for REH. The unit cost for “daycare without a physician” (4,637 SEK per day) was used to calculate the cost of the REH sessions. The assessment period was 1 day and the period of REH was 24 days.

2.5.1.2 Radiofrequency coagulation

For RFC, the mean number of visits to the clinic and the mean number of procedures performed were determined for all patients assessed (*n* = 873). On average, 3.2 visits and 4.3 procedures were needed to diagnose or rule out ZJP in the assessed patients, with a unit cost of 12,635 SEK for each assessed patient, and 8.3 visits and 33,324 SEK for each patient diagnosed with ZJP. The costs per procedure were obtained from the reimbursement price list for Swedish public procurement 2010–2016 (Appendix 3). Among the assessed patients who were not diagnosed with ZJP,

some were tested several times with MBB, and some received nerve root blocks or sympathetic blocks while trying to determine their pain focus. Only those diagnosed with ZJP and treated with RFC were included in the “benefit” calculations, whereas all patients were included in the “cost” calculation. This was performed to capture the complete pathway cost for RFC.

2.5.2 Medications

Data on prescribed and dispensed drugs were collected from the NBHW database for all patients included in the study. In Sweden, people are limited to purchasing prescribed drugs for a 3-month period, and the purchase is registered in a central register administered by the Swedish NBHW. Thus, each patient prescribed chronic medications must purchase their drugs at least four times/year, but more frequent purchases may be required when purchasing smaller amounts. All purchases are registered as the total amount of drugs (defined daily doses, DDD; i.e. the assumed average maintenance dose per day for a drug used for its main indication in adults) and the total cost of the drugs. Data were obtained for the 3-month period before RFC/REH and for the 3-month period from 1 year after treatment. Drugs associated with the treatment of chronic pain were identified using the Anatomic Therapeutic Chemical Classification codes listed in Appendix 4 [98].

2.5.3 Healthcare consumption

The patients’ use of all types of specialized healthcare was

obtained from the Swedish NBHW registers for the same period as for prescribed medications, and the data were analyzed similarly. Data were analyzed for the same periods as medication use. Only healthcare associated with chronic pain (i.e., with relevant diagnoses according to the International Classification of Diseases 10th Revision codes) was included in the cost calculations because diseases not associated with chronic pain (e.g., cardiovascular diseases, respiratory diseases, contagious diseases, or cancer) are not affected by pain management (Appendix 5).

To calculate the unit cost per visit, we used data from the Swedish Association of Local Authorities and Regions [99]. For specialist outpatient visits, the average cost was calculated as 3,792 SEK per outpatient visit and 11,423 SEK/day for inpatient visits (Table 2). Daycare visits, defined as inpatient care of <24 h, were handled similarly to the outpatient visits, with an estimated average cost of 3,792 SEK.

Table 2 Cost of outpatient visits and inpatient care-days in 2016

	Outpatients		Inpatients	
According to the Swedish Association of Local Authorities and Regions	**Specialized care**		**Specialized care**	
	Cost per visit (SEK)	**Visits (n)**	**Cost per day (SEK)**	**Care days (n)**
Physician, somatic care	3428	8 333 000	13 113	5 924 147
Advanced day-care	5866	1 079 000	-	-
Physician, psychiatric care	4750	831 000	5 126	1 590 007
Average cost	3 792 SEK/visit		11 423 SEK/care day	

2.5.4 Patients' time and travel costs

The patients' time spent at the clinics and their travel costs were estimated for all visits. The time and travel costs associated with the assessment (REH) and for the diagnostic procedures (RFC) were classified as diagnostic costs, whereas the time and travel costs during REH and those associated with RFC were classified as treatment costs (Table 3). The assessment at the REH clinics took 1 day (i.e., 6 hours) and the total treatment time was 24 days (6 hours/day). Each visit for assessment and treatment at the RFC clinic was assumed to be 1 hour. We used the Swedish average wage in 2016 as the unit cost for time (217 SEK/hour including 32.46% payroll tax) [100]. For travel time, we included 4 hours of

travel time and 300 km travel for each 60-minute visit in study III, and 2 hours (100 km/62 miles) in study IV, with a cost of 1.8 SEK per km per visit.

Table 3 Factors considered in the cost analysis in study III

	Costs	**Reduced costs**
Assessment	Healthcare costs for assessment (pain analysis) and diagnostic procedures performed on all patients assessed, until a zygapophysial joint pain has been diagnosed. Time to attend during assessment and visits when diagnostic procedures where performed Time and travel expenses to reach the unit for all visits	
Treatment	Healthcare costs for radiofrequency denervation Time to attend Time and travel expenses to reach unit	
Medication	Medication after treatment	Medication before treatment
Health service consumption	Outpatient visits after treatment Inpatient ward-days after treatment Inpatient daycare days after treatment	Outpatient visits before treatment Inpatient ward-days before treatment Inpatient daycare days before treatment
Sick leave	Cost for sick leave during 1 month after radiofrequency denervation Patients on sick leave after treatment	Patients on sick leave before treatment

2.5.5 Productivity loss and sick leave

Pain affects a patient's ability to work [101,102]. Changes to sickness compensation insurance made by the Swedish parliament over the last few decades have resulted in a disparity between sickness compensation and a patient's ability to work [103]. In study III, we used self-reported ability to work, which was recorded at the time of assessment and at each follow-up visit as 0%, 25%, 50%, 75%, and 100%, of their capacity [104]. To place a value on these changes, we used the average hourly wage of 217 SEK [105]. Full-time work was estimated as 1880 hours/year or 40 hours/week. After RFC, many patients are temporarily unable to work for a few weeks. Therefore, we included a sick-leave period of 4 weeks after RFC as a treatment cost for all patients aged <67 years whose prior ability to work was ≥25% of their capacity (Table 3).

In study IV we obtained linked data on the number of sick-leave days from the Swedish Social Insurance System. Data were collected for the same periods as for medications and health consumption to calculate the changes in sick leave after treatment. Data were also collected for 1 month before and 1 month after RFC because many patients are temporarily unable to work for a few weeks after RFC. If there were more days of sick leave during the first month after RFC than before RFC, it was classified as a treatment cost. We converted the number of days of sick leave to productivity by applying the average wage (217 SEK/hour including 32.46% payroll tax, 8 hours/day).

2.5.6 Patients served as their own controls

All patients were assessed and baseline data were collected at the first visit. During the following encounters, diagnostic nerve blocks were performed to determine the dominant pain focus. The number of tests that were needed and the time taken to complete them depended on the patient's communication skills, the physician's perceptions and ability to understand the patient's history, and non-causative administrative factors such as scheduling the subsequent visit. This introduced some randomness into how long it took from the first visit until ZJP was diagnosed and the patient was offered RFC. The patients were again assessed before the RFC, which yielded a second measurement and allowed us to determine the changes in HRQoL measures between the first visit and treatment, and whether the changes were related to this interval.

2.5.7 Cost-effectiveness calculations

Quality-adjusted life years (QALYs) were calculated from the propensity score-weighted mean for the EQ-5D index versus time. We assumed that the EQ-5D index changed evenly between the measurement times, from the start of treatment (i.e., 5 weeks before the first follow-up for REH and at the time of RFC). Data were obtained for 2 years after starting treatment.

Cost-effectiveness was calculated by dividing the total net costs (i.e. cost – "savings") with the gain in QALYs (cost/QALY gain) in both groups. The results were compared between the two group

and against the limits set by the Swedish NBHW. All calculations were made in SEK at the 2016 price level.

The Swedish NBHW classify cost-effectiveness ratios (cost/QALY gain) into four ranges: low (<100,000 SEK), moderate (100,000–500,000 SEK), high (500,000–1,000,000 SEK) and very high (>1,000,000 SEK), which we used in this study [106,107].

An increase in the EQ-5D index of 0.1 was considered to be clinically relevant [80].

2.6 Statistical analysis

Descriptive statistics were used to present the characteristics of the study groups, and stratified results were derived for each covariate for the outcome variables. Analyses were carried out for the EQ-5D index, EQ-VAS, HAD, medications, healthcare consumption, and sick leave. Age, gender, and pain duration were compared using the Tukey-Kramer test. Wilcoxon's test was used for pairwise comparisons. A *P* value of <0.05 was considered to indicate statistical significance. For each patient, their EQ-5D index score at the time of their first RFC was compared with their EQ-5D index score at the follow-up visit. The treatment was considered successful if the EQ-5D index score improved by more than 0.1 [80]. This was used as a marker for successful treatment. Because some patients, regardless of their improvement, continued to undergo more diagnostic tests and RFC at another level during the follow-up time, repeated RFC was considered a

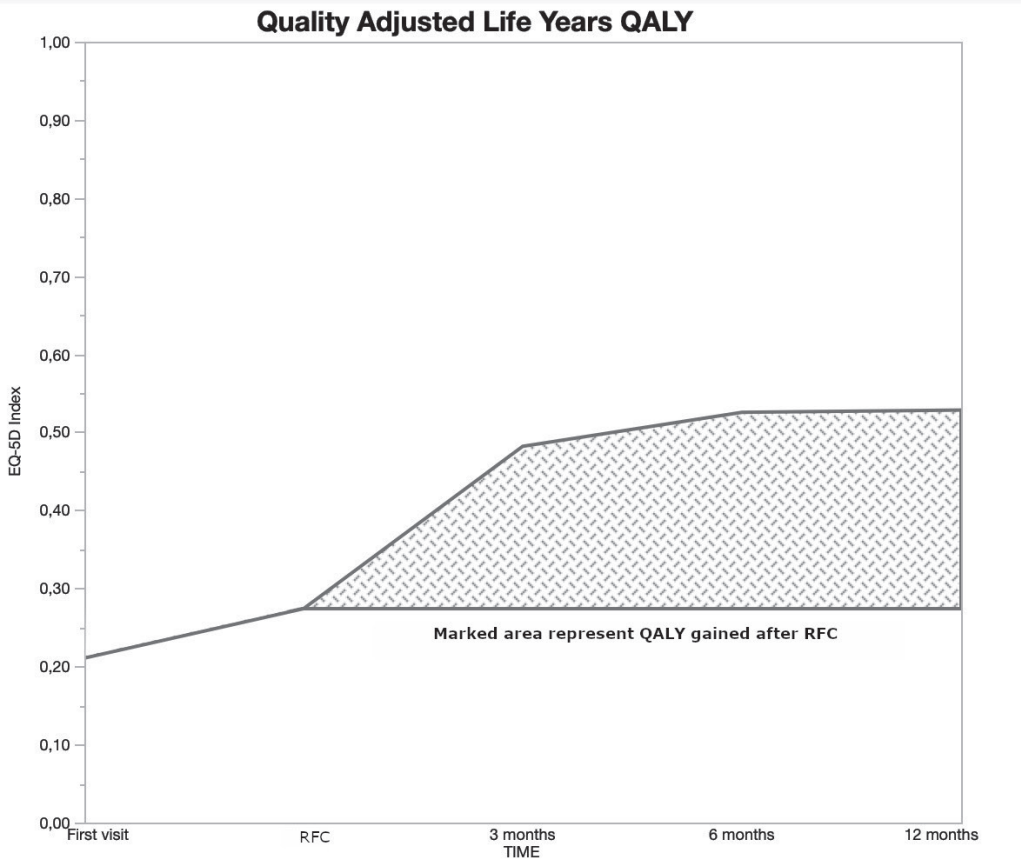
marker for treatment failure. Successful treatment was evaluated in a survival plot for up to 12 months after the first RFC. Survival plots were compared using the log- rank test. Missing data were handled by backward extrapolation of data from a later period.

Paired *t* tests were used to compare the outcomes at 1 and 2 years after treatment versus those at the time of treatment. Student's *t* test was used to compare outcomes between the two groups (mean EQ-5D index score and the proportion of patients with clinical relevant improvement in the EQ-5D index score).

The costs of assessment and treatment were calculated by multiplying the number of procedures by the unit cost for each procedure. For medications and healthcare use, the baseline cost was calculated for the 3 months preceding RFC, and the outcome period was defined as the 3 months from 1 year after RFC. If the outcome period costs were lower than the baseline costs, the reduction was considered a consequence of the treatment. The patients' time and travel costs were calculated by multiplying the number of encounters by the time needed for the encounters (including travel) and the travel costs for each encounter. Productivity gains were calculated individually for each patient and were summed to determine the total productivity gain for all patients combined.

Changes in the EQ-5D index were transferred into quality-adjusted life years (QALY) by calculating the area under curve for the mean EQ-5D index versus time (Figure 5). We assumed that the EQ-5D index changed evenly between measurements.

Figure 5 Changes in HRQoL after treatment in study III



EQ-5D EuroQOL 5-dimension scale, HRQoL health-related quality of life, QALY quality-adjusted life years, RFC Radiofrequency coagulation

Propensity score weighting was used in study IV [73,74]. A thorough description and explanation of the use of propensity scores is available in Norström et al [75].

We used logistic regression with potential confounders (gender, age, pain duration, and previous health measured by the EQ-5D index) as covariates to estimate the propensity scores. The propensity score corresponds to the probability of receiving RFC

for ZJP instead of being treated with a team-based REH. Thus, a comparison between an exposed and unexposed individual with the same propensity measure is similar to analyzing exposure in a randomized controlled trial. Using this propensity score approach in observational studies represents a quasi-experimental approach.

We used propensity score weighting using an inverse probability weight estimator (*W*), as suggested by Lunceford and Davidian [73],

$$W = \frac{Z}{ps} + \frac{(1 - Z)}{(1 - ps)}$$

where $Z = 1$ for RFC, $Z = 0$ for REH, and ps = propensity score.

The standardized difference (*d*) was calculated, both with and without weighting, to assess the balance of covariates between the REH and RFC groups for each potential confounder (Table 4) [75,108,109]. A standardized difference of >10% represents a meaningful imbalance in the given covariate between groups [108].

$$d = \frac{100 * (xRFC - xREH)}{\sqrt{\frac{(vRFC^2 + vREH^2)}{2}}}$$

Here, *xRFC* = mean value for RFC, *xREH* = mean value for REH, sqr = square root, *vRFC* = variance for RFC, and *vREH* = variance for REH. Furthermore, for dichotomous values,

$$d = \frac{100 * (pRFC - pREH)}{\sqrt{\frac{(pRFC \cdot (1 - pRFC) + pREH \cdot (1 - pREH))}{2}}}$$

where *pRFC* = proportion for RFC and *pREH* = proportion for REH.

All cost calculations were made in SEK in 2016 values. The euro (EUR):SEK exchange rate was 1:9.62 and the USD: SEK exchange rate was 1:8.51 in 2016. All analyses were conducted using JMP software versions 13.0.0 – 16.1.9 (SAS Inc., Cary, NC, USA).

Table 4 Absolute values and standardized difference of baseline demographics and clinical characteristics in study IV

Variable	Radiofrequency coagulation group	Pain rehabilitation program	Unweighted standardized differences	Weighted standardized differences
Age, mean, years	52.2	43.4	4.42	0.07
Gender (women), %	62.2	75.1	28.1a	7.46
Pain duration, mean, months	116	99	0.13	<0.01
HAD-anxiety, mean	7.0	9.6	10.0a	0.12
HAD-depression, mean	7.9	8.9	4.17	0.10
EQ-VAS, mean	42	42	0.07	0.01
EQ-5D index, mean	0.201	0.276	60.74[a]	0.25
DDD pain medications, mean	187	115	0.11	<0.01
DDD other drugs, mean	276	138	0.03	<0.01
Outpatient visits pain, mean	0.48	0.65	10.3[a]	0.03
Outpatient visits other problems, mean	0.45	0.65	11.8[a]	0.21
Inpatient days pain, mean	0.102	0.208	4.97	1.20
Inpatient days other problems, mean	0.204	0.123	3.87	0.05
Cost of sick leave, mean SEK	32,949	27,410	<0.01	<0.01

DDD defined daily dose, SEK Swedish krona, EQ-5D EuroQOL five-dimension scale for health, EQ-VAS EuroQOL visual analog scale for health, HAD Hospital Anxiety Depression scale

[a]Variables with standardized differences of >10%

2.7 Sensitivity analysis

Sensitivity analyses were performed for all variables that were deemed likely to affect the outcome (cost/QALY gained).

In study III, we diagnosed ZJP in 37.9% of the patients assessed. According to prior studies, the prevalence of ZJP in patients with chronic pain varied from ~30% (lumbar region) to ~50% (cervical region) [8,35,38]. Therefore, we performed sensitivity analyses in which we assumed that 30% and 50% of the patients received RFC. In study IV, we diagnosed 46.0% of the patients assessed. In the sensitivity analyses we assumed that 30% and 50% of the patients underwent RFC. Likewise, 50.3% of those assessed were considered suitable for REH. Therefore, we developed scenarios in which only 30% of those assessed would receive REH and if everyone (100%) underwent REH.

We also examined the effects of an increase/decrease in treatment costs and healthcare use of ±10% in study III, and ±25% in study IV. In study III, we also performed a sensitivity analyses of the time and travel costs by considering the recruitment of local patients (2 hours/visit and 50 km travel), and including an accompanying person and a full day's visit (16 hour/visit and 300 km travel). In study IV we tested by increasing the travel costs by 25% and 100%.

In study III we also calculated a scenario in which sick leave was valued for all patients, regardless of their age, and reduced the duration of sick leave from 4 weeks to 2 weeks to reflect the fact that the mean duration of pain after RFC was 2 weeks in these patients and that many patients resumed full time work immediately after RFC. In study IV, we tested the impact of excluding the effects of healthcare consumption. We also tested

possible differences in the effects on HRQoL by changing the mean improvement in the EQ-5D index after treatment by ±10%.

Since the improvement in pain after RFC often lasts for >1 year [110–113], we re-calculated the results in study III assuming the effect on HRQoL would last for 2 or 4 years. When analyzing the data in study IV, we found that the 1-year follow-up after treatment was actually performed later than planned, which allowed us to analyze the effects at 2 years after treatment, although in a smaller group. Because the aim of REH is to help the patient cope with the problems and manage their pain, these effects are considered to last for several years. Similarly, the effects of RFC in adequately diagnosed patients was shown to last longer than 1 year [110,112,113]. Therefore, we performed a sensitivity analysis in which we calculated the cost/QALY gained if the effects lasted for up to 6 years.

We also performed a sensitivity analysis that focused on the costs only, assuming that the improved HRQoL would have been similar between the REH and RFC groups.

Finally, because REH differs between clinical units in Sweden, we performed a sensitivity analysis in which varied the duration of the rehabilitation period. In a prior report, on average, the programs consisted of treatments for 5 hours/day (calculated from Table 1 in Rivano Fisher et al) [79]. The duration of the rehabilitation was reported to range from 7 to 46 days with a mean of 22 days (SD= 13; calculated from Table 1 in Rivano Fisher) [79]. Therefore, we performed a sensitivity analysis by varying the duration of

rehabilitation by ±1 SD.

2.8 Ethical consideration

Ethical approval was obtained from the regional ethics board in Umeå, Sweden (Dnr 2012-446-31M, Dnr 2017-542-32M, Dnr 2020-04586). The patients enrolled at the IPM clinic were assured that confidentiality would be maintained and that it would not be possible to identify them individually. They were given written information about the study and provided written informed consent to participate in terms of inclusion in the studies, for the use of their medical records, and for data collection and analysis. The patients registered in the NRPR had been informed that their data could be used in register-based research, that their confidentiality would be maintained and that it would not be possible to identify them individually. They were given written information concerning this procedure and provided written informed consent to participate in future studies using data from the NRPR.

In study II, informed consent was obtained when scheduling the interview, at the start of the interview, and after the interview. The patients could leave the study at any time, and one patient withdrew from the study after providing written consent at the time of scheduling the interview.

The studies were registered on Clinicaltrials.gov (Protocol ID SE-Dnr-2012-446-31M-3, SE-Dnr-2012-446-31M-1, IPM-PRP2020, ClinicalTrials ID NCT01838603, NCT01836666, NCT04657159). The COREQ Equator checklist was used for qualitative study

[114], and STROBE check list for health economic evaluations.

This research did not receive any specific grants from funding agencies in the public, commercial, or not-for-profit sectors.

3 Results

Table 5 Characteristics of patients in studies I, III, and IV

		RFC group			REH group
		Study I	Study III	Study IV	Study IV
All patients	n	315	331	254	15,357
Women,	n (%)	200 (63%)	218 (66%)	158 (62%)	11,533 (75%)
Men,	n (%)	115 (37%)	113 (34%)	96 (38%)	3,824 (25%)
Age, years	mean (SD) range	51 (15.1) 17-89	51 (15.6) 17-89	51 (15.6) 17-89	43 (11.9) 14-92
Pain duration, months	mean (SD) range	125 (130) 2-744	122 (124) 2-744	120 (120) 2-744	99 (108) 0-1152
Cervical	n (%)	55 (17%)	55 (17%)	43 (17%)	n.d.
Thoracic	n (%)	82 (26%)	76 (23%)	52 (20%)	n.d.
Lumbar	n (%)	178 (57%)	200 (60%)	159 (63%)	n.d.
HAD anxiety	mean (SD)	n.d.	6.9 (4.3)	7.0 (4.4)	9.6 (5.5)
HAD depression	mean (SD)	n.d.	7.9 (4.5)	7.9 (4.6)	8.9 (5.2)
EQ-5D index	mean (SD)	0.284 (0.321)	0.212 (0.279)	0.221 (0.285)	0.276 (0.314)
EQ-VAS	mean (SD)	n.d.	42 (18.2)	42 (19)	42 (19)

HAD Hospital Anxiety and Depression scale, EQ-5D EuroQOL 5-dimension scale, n.d. not determined, REH pain rehabilitation program, RFC radiofrequency coagulation, SD standard deviation

3.1 Study I: Observational study

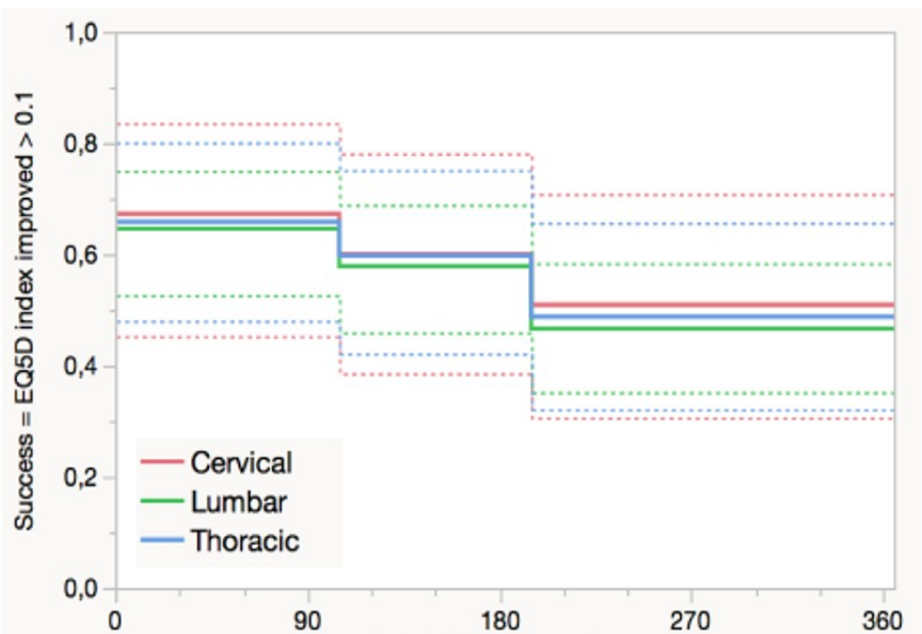
The observational study was designed to describe the clinical methods for the diagnosis and treatment of ZJP in the thoracic region, and to evaluate whether the clinical methods are effective in terms of improving HRQoL.

The improvement in HRQoL was similar in all three groups, and

there was no significant difference in the proportion of patients with successful outcomes among the groups.

The survival plot for up to 1 year after the first RFC showed no significant difference between the groups (Figure 6). Failure was defined as repeated RFC or a lack of improvement in the EQ-5D index. The percentage of patients with successful outcomes after 1 year was 49% in the thoracic group, 51% in the cervical group, and 47% in the lumbar group. The results support the hypothesis that RFC to treat thoracic ZJP is as effective as the standard methods used to treat cervical and lumbar ZJP.

Figure 6 Survival plot of clinically relevant improvements after RFC in study I



EQ-5D EuroQOL 5-dimension, RFC radiofrequency coagulation

Table 6 Characteristics of the patients in study II

Age (years)	Pain duration (years)	Living condition	Pain localization	Cause	Previous treatments received	Procedures received on the ward	EQ-5D index change from first visit	Clinically significant change in EQ-5D index (difference > 0.1)
30–40	12	City, So	T, L	N	Phys, Med, Fusion	MBB, RFC, ia, LBB	+0.707	+
>60	5	Rur, No	H, C	N	Phys, Med, REH	MBB, RFC, IL	+0.094	0
40–50	4	City, So	C, L	N	Phys, Med, REH	MBB, RFC	-0.069	0
50–60	40	Rur, So	L, O	N	Phys, Med, REH	MBB, RFC, ia	-0.104	-
20–30	2	City, So	L	T	Phys, Med	MBB, ia, RFC, TR		
50–60	20	City, No	C, T, L	T	Phys, Med, REH, CII, MBB, RFC	MBB, RFC, ia, LBB, Symp	+0.173	+
50–60	30	Rur, So	L	N	Phys, Med, Fusion, DCS, MBB	MBB, RFC	+0.568	+
50–60	17	Rur, No	H, C, L	R	Phys, Med, TP	MBB, IL, RFC, ia	+0.258	+
40–50	17	Rur, No	L	N	Phys, Med	MBB, IL, RFC TR, Symp, ia	0.000	0
50–60	15	City, So	H, C	R	Phys, Med, REH, Fusion, TP	MBB, RFC	+0.167	+
50–60	3	City, No	L	N	Phys, Med	MBB, RFC	+0.263	+
40–50	6	City, So	C, T	N	Phys, Med, Fusion, TP	MBB, RFC	+0.601	+
40–50	2	City, So	L	R	Phys, Med, REH	MBB, ia, RFC, Symp	-0.327	-
50–60	3	Rur, So	T	N	Phys, Med, REH	MBB, RFC	+0.033	0
40–50	4	City, No	L	T	Phys, Med, REH	MBB, RFC, ia	+0.264	+

Age (years)	Pain duration (years)	Living condition	Pain localization	Cause	Previous treatments received	Procedures received on the ward	EQ-5D index change from first visit	Clinically significant change in EQ-5D index (difference > 0.1)
50–60	18	Rur, No	C, T	R	Phys, Med, MBB, pulsed-RF	MBB, RFC	+0.263	+
50–60	3	City, No	H, C, L	N	Phys, Med, MBB, pulsed-RF	MBB, RFC	+0.071	0
50–60	4	City, So	L	N	Phys, Med, REH	MBB, RFC	+0.601	+
50–60	25	City, No	C, T, L	T	Phys, Med, Fusion	MBB, RFC, IL, ia, TR,	+0.105	+

City – living in a larger city, Rur – living in a small city/countryside, No – Northern Sweden, So – Southern Sweden

H – headache, C – cervical pain, L – lumbar pain, T – thoracic pain, O – other pain localizations

N – no trauma, R – road traffic accident, T – other trauma

CII – continuous intrathecal opioid infusion, DCS – dorsal column stimulation, Fusion – surgery with vertebral fusion, ia – intraarticular injections, IL – interlaminar nerve root block, LBB – lateral branch blocks to diagnose sacroiliac joint pain, MBB – medial branch blocks to diagnose zygapophysial joint pain, Med – medication (usually paracetamol, NB – peripheral nerve block, NSAIDs, opioids, gabapentin, and pregabalin and/or amitriptyline), Phys – physiotherapy, pulsed-RF – nerve stimulation with pulsed radiofrequency current, REH – pain rehabilitation program, RFC – conventional radiofrequency denervation, Symp – nerve block of sympathetic nervous system, TP – trigger point injections, TR – transforaminal nerve root block.

3.2 Study II: Qualitative study to explore the treatments from the patient's perspective.

One patient initially agreed to participate but withdrew at the time of the interview. The characteristics of the 19 patients who participated in the interviews are shown in Table 6.
The themes recognized in the interviews covered several topics: individually focused themes (intrinsic factors) that were related to and expressed by the patients themselves; healthcare-focused themes (the importance of care-givers) related to the services provided; and outcome-focused themes related to the outcomes and goals expressed by the patients.

3.2.1 Individually focused themes: Intrinsic factors

The intrinsic themes expressed by the patients were "hope of recovery", "ambivalence about the future", and "accept pain to become pain-free".

The first two themes were present when the patients expressed their relationship to pain and when they described their thoughts about possible treatments. The patients expressed similar themes when they described how they perceived the treatments and what the outcome of these treatments could be.

The patients' ambivalence about the future was also related to the treatment process, which involved painful procedures followed by periods without pain, and the later return of pain. It could also be

related to the patients' prior treatments that had not improved their pain.

The theme "accept pain to become pain-free" was related to the service that was provided and was intrinsic to the patients, and it was apparent in all of the interviews. However, regardless of how painful the patients described the procedures to be, they all described the pain as being worthwhile. They also elaborated this by describing how they felt safe and calm during the encounters and that they had gained knowledge from the information and the explanations given by the healthcare team.

3.2.2 Healthcare-focused themes: The importance of caregivers

Themes categorized in the group regarding the importance of caregivers were "availability for questions", "previous caregivers' ignorance and prejudice", and "feeling safe".

The first two themes were only expressed by women, who expressed frustration regarding the difficulty of getting in contact with the clinic they had previously been in contact with, as well as their frustration, especially among women, about the "previous caregivers' ignorance and prejudice". The patients said that physicians had negated their pain because their X-ray images and MRI appeared normal, and their pain was therefore attributed to psychological distress.

The theme "feeling safe" described our patients' experience of a stress-free environment where they could relax and felt they were

listened to. The holistic approach was emphasized when they described the process of tests, assessments, and new tests, which started with the diagnostic procedures, and how this continued with them getting better, but that their pain returned and new diagnostic procedures were performed until the diagnosis was confirmed and the treatment was given. They described the importance of the scheduled follow-ups and that they knew that they could return to the clinic if the pain returned.

3.2.3 Outcome-focused themes

The theme “gain knowledge and understanding” was partly related to the services received and partly related to the outcomes. The patients felt that they were informed and that different aspects of their problems were explained allowing them to understand their pain. This was also connected to their general feelings of safety and their improved health.

The reason why patients sought help after their previous care was that they still longed for a reduction in their pain level and improved quality of life. However, these goals were not in focus when they described their experiences, they just mentioned them. The patients mostly focused on what they felt was the result of going through the program.

Although the patients did not mention the goals often, and never elaborated upon the goals, they were eager to describe how their life had changed as a result of the treatments. This theme, “improve health – a new life”, was not described as being a result of the reduction in pain, but rather the feeling of safety, the

availability for further questions, and the knowledge they have gained.

The theme “help others” was clearly expressed by the patients as a result of their own improved health, and they said that other patients with pain should be provided with an opportunity to receive similar treatment.

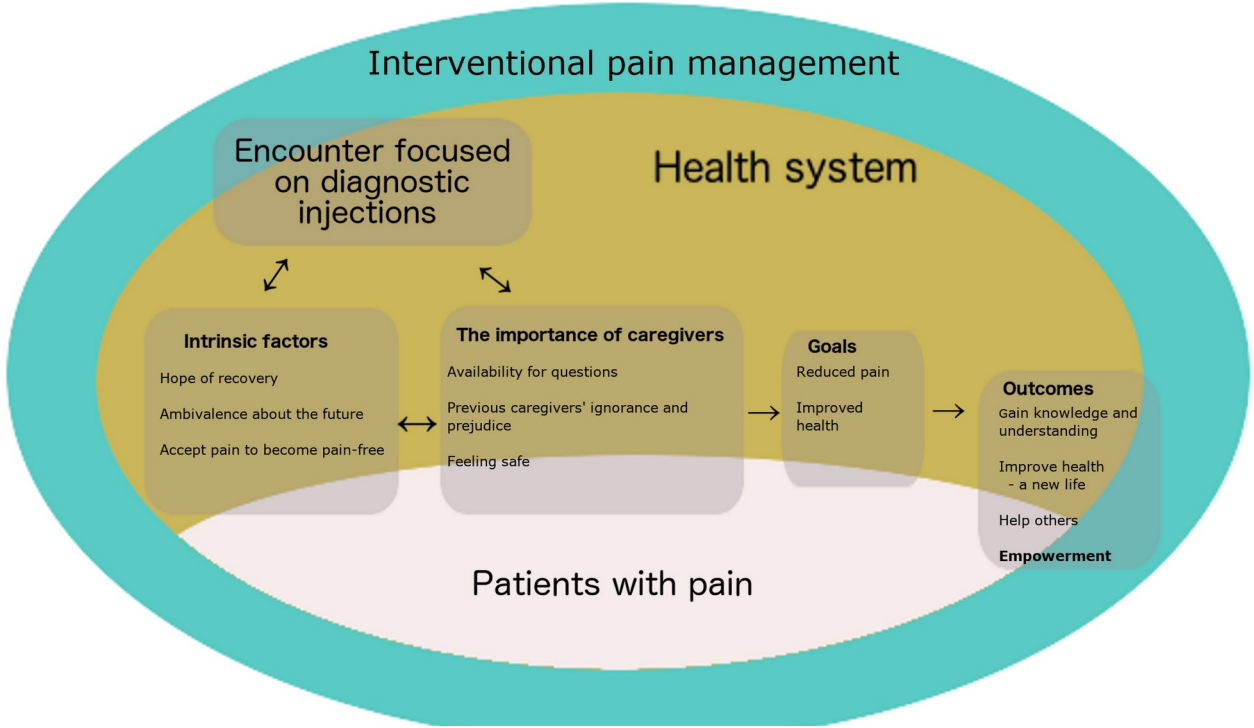
The themes dit not differ when the patients were categorized according to their living conditions, for how long they had been suffering from pain, or whether their HRQoL had improved or not at the time of the interviews.

3.2.4 Empowerment

In summary, the interviews show that the patients’ perceptions shifted among three key themes. The first was the patients themselves as objects; this theme included the treatment they received, how they felt, and their fears. The second theme included the caregivers, tests and retests, the encounters and interactions with the professionals, and the availability of help. The third theme covered the outcomes, which included the results of the tests and treatments, and how the outcomes inspired the patients to say that other people with pain should be offered the same opportunity. The patients partly said this to emphasize how much they value the care, partly to demonstrate frustration with waiting for so long to get help, and partly to express a genuine feeling for other peoples with pain. Linking these themes, the patients expressed something best described as “gained empowerment” during IPM. They described their feeling of being

heard and seen, of gaining knowledge that helped them understand their problem better, of being able to ask questions and receive answers, and of feeling safe and listened to.

Figure 7: Themes identified in study II and their relations



3.2.5 Confirmation of results

After the analysis, eight of the patients were contacted by the last author (K-GS); the others could not be reached. These eight patients confirmed the results and stressed that "*…it is very emotional, that we all seem to have the same experiences*" or "*I have nothing to add; it is amazing how well you have understood me*".

3.3 Study 3: Cost-effectiveness of IPM

3.3.1 Characteristics of the assessed patients

During the study period (2010–2016), 873 patients were assessed at the IPM clinic. After a total of 2759 visits and 3788 procedures, 331 patients (37.9%) were diagnosed with ZJP and underwent RFC (Table 4). The mean interval between the first visit and RFC was 86 days but ranged from 2 days to 2.5 years. There were more women than men: 63% of assessed patients and 66% of treated patients were women ($P = 0.279$). The mean duration of pain before assessment was 110 months. Most patients were working (67% of assessed and 71% of treated patients).

3.3.2 HRQoL and psychological distress at the initial assessment

The mean EQ-5D index score at the initial assessment was very low (0.252 among assessed patients and 0.212 among treated patients) (Table 4). The mean EQ-5D index did not differ significantly between the first visit and the time of RFC. In patients diagnosed with ZJP, there were no significant differences in the

EQ-5D index, EQ-VAS, HAD-anxiety, or HAD-depression scores among various age groups (Table 6). The EQ-5D index was significantly lower among patients who were unable to work, but there were no significant differences in EQ-VAS, HAD-anxiety, or HAD-depression scores according to the patient's ability to work (Table 6).

3.3.3 Changes in HRQoL at 12 months after RFC

The mean duration of pain after RFC was 13.1 days, and did not differ significantly between genders or by the patient's ability to work (Table). The mean EQ-5D index increased significantly (from 0.212 to 0.530, $P < 0.0001$) between the initial assessment and 12 months after RFC. This was consistent in all age-groups and in both genders.

Table 7 HRQOL and HAD at the time of assessment in patients divided by age or sick-leave in study III

	Patients diagnosed with ZJP			
Age group	**EQ-5D Index mean (SD)**	**EQ-VAS mean (SD)**	**HAD-anxiety mean (SD)**	**HAD-depression mean (SD)**
≤17 n=1	0.088 n=1	30 n=1	14 n=1	12 n=1
18-29 n=28	0.239 (0.290) n=28	41 (15.4) n=27	8.2 (5.5) n=20	8.0 (4.7) n=20
30-44 n=88	0.209 (0.303) n=88	44 (20.5) n=81	7.3 (4.4) n=73	7.8 (5.0) n=73
45-66 n=154	0.222 (0.283) n=154	42 (17.9) n=143	6.5 (4.1) n=131	8.1 (4.4) n=131
≥67- n=60	0.179 (0.233) n=60	38 (16.3) n=47	7 (4.3) n=51	7.6 (3.8) n=51
All n=331	0.212 (0.279) n=331	42 (18.2) n=299	6.9 (4.3) n=276	7.9 (4.5) n=276
Work ability %	**EQ-5D index mean (SD)**	**EQ-VAS mean (SD)**	**HAD anxiety mean (SD)**	**HAD depression mean (SD)**
0	0.137 (0.238)[ab]	39 (17.8)	7.3 (4.6)	8.5 (4.4)
25	0.267 (0.293)	39 (17.8)	7.1 (3.9)	7.4 (4.2)
50	0.187 (0.252)	39 (19.8)	6.1 (4.1)	7.6 (5.1)
75	0.373 (0.294)[b]	50 (14.8)	4.4 (3.2)	6.1 (3.7)
100	0.340 (0.314)[a]	48 (18.3)	6.9 (3.9)	7.3 (4.4)
Region with ZJP	**EQ-5D index mean (SD)**	**EQ-VAS mean (SD)**	**HAD anxiety mean (SD)**	**HAD depression mean (SD)**
Cervical	0.256 (0.285)	48 (19.6)	6.6 (4.0)	7.2 (4.6)
Thoracic	0.218 (0.290)	42 (19.1)	7.8 (4.4)	7.9 (4.4
Lumbar	0.205 (0.276)	40 (16.6)	6.6 (4.3)	8.0 (4.5)

[a] p<0.0001, [b] p=0.0010

SD, standard deviation; EQ-5D, EuroQol five-dimensional questionnaire; EQ-VAS, EuroQol visual analog scale; HAD, Hospital Anxiety and Depression scale; ZJP Zygapophysial Joint Pain

Table 8 Effects of treatment according to sick-leave in study III

	Before				Duration of pain after treatment	1 year after			
Work ability	**EQ-5D Index** mean (SD) n	**EQ-VAS** mean (SD) n	**HAD-A** mean (SD) n	**HAD-D** mean (SD) n	**Days** mean (SD) n	**EQ-5D Index** mean (SD) n	**EQ-VAS** mean (SD) n	**HAD-A** mean (SD) n	**HAD-D** mean (SD) n
0%	0.137 (0.238) n=179	39 (18) n=156	7.3 (4.6) n=154	8.5 (4.4) n=154	11.9 (11.9) n=179	0.407 (0.377) [a] n=77	51 (24) [b] n=77	7.2 (6.0) [n.s.] n=22	7.3 (5.1) [n.s.] n=22
25 %	0.268 (0.293) n=18	39 (15) n=18	7.1 (3.9) n=13	7.4 (4.2) n=13	12.8 (11.5) n=18	0.654 (0.219) [e] n=6	60 (13) [f] n=6	-	-
50 %	0.187 (0.252) n=34	39 (20) n=30	6.1 (4.1) n=28	7.6 (5.1) n=28	15.2 (9.1) n=34	0.627 (0.234) [a] n=16	60 (20) [c] n=16	4.8 (3.3) [n.s.] n=5	2.8 (2.0) [d] n=5
75 %	0.373 (0.294) n=22	50 (15) n=21	4.4 (3.2) n=16	6.1 (3.7) n=16	15.9 (14.4) n=22	0.666 (0.310) [g] n=12	75 (14) [a] n=12	5 (4.2) [n.s.] n=2	5 (5.7) [n.s.] n=2
100 %	0.340 (0.314) n=77	48 (18) n=73	6.9 (3.9) n=64	7.3 (4.4) n=64	14.3 (11.2) n=77	0.683 (0.240) [a] n=35	68 (20) [a] n=34	6.6 (4.9) [n.s.] n=14	6.1 (5.0) [n.s.] n=14
Cervical	0.256 (0.285) n=54	48 (20) n=50	6.6 (4.0) n=43	7.2 (4.6) n=43	14.0 (11.4) n=34	0.545 (0.303) [a] n=24	63 (19) [a] n=24	8.2 (5.2) [n.s.] n=6	7.2 (4.2) [n.s.] n=6
Thoracic	0.218 (0.290) n=70	42 (19) n=68	7.8 (4.4) n=60	7.9 (4.4) n=60	13.4 (12.4) n=50	0.503 (0.346) [a] n=36	57 (24) [a] n=36	5.9 (5.2) [n.s.] n=14	4.6 (4.9) [n.s.] n=14
Lumbar	0.205 (0.276) n=184	41 (17) n=162	6.6 (4.3) n=160	8.0 (4.5) n=160	11.7 (11.1) n=125	0.530 (0.364) [a] n=83	58 (24) [a] n=83	7.0 (5.5)[n.s.] n=21	7.1 (5.2) [n.s.] n=21
Men	0.218 (0.302) n=114	44 (19.0) n=103	6.9 (4.5) n=97	8.7 (4.6) n=97	11.2 (12.0) n=114	0.524 (0.324) [a] n=51	62 (22.1) [a] n=50	5.8 (6.1) [n.s.] n=12	6.9 (4.8) [n.s.] n=12
Women	0.209 (0.268) n=217	41 (17.7) n=196	7.0 (4.3) n=179	7.5 (4.4) n=179	14.2 (11.4) n=217	0.533 (0.356) [a] n=96	57 (23.5) [a] n=96	6.9 (4.9) [n.s.] n=31	6.0 (5.0) [n.s.] n=31
All	0.212 (0.279) n=331	42 (18.2) n=299	6.9 (4.3) n=276	7.9 (4.5) n=276	13.1 (11.7) n=331	0.530 (0.344) [a] n=147	59 (23.1) [a] n=146	6.6 (5.2) [n.s.] n=43	6.3 (4.9) [n.s.] n=43

[a] P<0.0001, [b] P=0.0001, [c] P=0.0015, [d] P=0.0024, [e] P=0.0053, [f] P=0.0081, [g] P=0.0137, [n.s.] P>0.05, EQ-5D - EuroQol five-dimensional questionnaire, EQ-VAS - EuroQol visual analog scale, HAD - Hospital Anxiety and Depression scale, SD - standard deviation, HAD-A – HAD-anxiety, HAD-D - HAD-depression

3.3.4 Healthcare costs

The total costs associated with assessing and establishing a diagnosis of ZJP was 14.9 million SEK, or 45,060 SEK per patient, based on 3788 procedures and 2759 visits (Table 9).

The total treatment cost was calculated as 2.3 million SEK, or 6,908 SEK per patient (Table 9).

The annual pain-related medication cost at 1 year after treatment had decreased by 1.1 million SEK in patients treated with RFC based on an annual reduction of 68,628 defined daily doses (DDD; Table 9).

The cost of pain-related healthcare use decreased by 8.2 million SEK for outpatient care and by 0.08 million SEK for inpatient care (Table 9).

3.3.5 Ability to work

The total cost of 4 weeks' sick leave after RFC was 3.9 million SEK. The ability to work increased after RFC, and the increase was valued at 1.1 million SEK (Table 9). Among 271 patients of working age (<67 years old), there were five fewer who were unable to work and three more who reported a capacity of 100% after RFC. Overall, 31 patients reported an increase in their ability to work and 19 reported a reduction in their ability to work after RFC, resulting in an average of 2.75 patients with an increased

full-time ability to work.

Table 9 Calculation of costs in study III

		IPM	
		Costs	Reduced costs
Costs for assessment and diagnostic procedures n=873 patients Healthcare costs Time Travel costs ***Total costs:***	 3,788 procedures (Appendix 3 for cost/procedure) 2,759 visits * 4 h/visit 2,759 visits * 300 km/visit	 11,030,100 2,394,812 1,489,860 **14,914,772**	
Treatment costs n=331 patients Healthcare costs Time Travel costs ***Total costs:***	 5,500 SEK/patient 4 h/patient 300 km/patient	 *1,820,500* 287,308 178,740 ***2,286,548***	
Cost of pain-related medication	Reduction of 68,628 DDD/year (128,276 to 59,648)		-1,101,072
Health consumption Outpatient care Inpatient care	Reduction of 2,156 visits (2,660 to 504) Reduction of 8 care-days (72 to 64) Increase of 4 daycare days (0 to 4)		-8,175,552 -91,384 +15,168
Sick leave n=151 patients After RFC Changed ability to work after 1 year	 4 weeks at 34,400 SEK/patient Increase of 2.75 full time work, 407,906 SEK/year	 *3,914,680*	 -1,121,890
Subtotal		21,091,160	-10,474,730
Total costs **costs/pt**		**10,641,270** **32,149**	
Total QALY-gained after 1 year	331 pt		48.08
Cost/QALY-gained		**221,324**	

DDD defined daily doses, IPM interventional pain management, RFC radiofrequency coagulation, QALY quality adjusted life-years

3.3.6 QALY and cost per QALY gained

At 1 year after treatment, the total QALY gained was 48.08, or 0.145 QALYs per patient. The total cost was 10.6 million SEK, or 32,149 SEK/patient. Thus, the cost/QALY gained was 221,324 SEK(Table 11), which is below the threshold value for acceptable cost-effectiveness in Sweden (500,000SEK /QALY gained) [106,107].

3.3.7 Sensitivity analysis

In all sensitivity analysis scenarios, the cost-effectiveness ratio remained within the moderate range for cost-effectiveness according to the Swedish NBHW threshold (100,000–500,000 SEK) [106,107].

The three factors that had the greatest effect on the cost/QALY gained were (1) how many of the assessed patients were diagnosed with ZJP and treated, (2) the duration of the increase in HRQoL, and (3) the number of patients that required sick leave after treatment and how long sick leave lasted. In this study, 18% of the patients were >66 years, for whom sick leave and the ability to work do not apply. Table 10 shows the results of the sensitivity analyses with different values for the number of diagnosed patients, the number of retired patients, and the duration of sick leave after RFC. All scenarios yielded a cost/QALY gained below 500,000 SEK.

Changes in treatment cost by +10% and −10% yielded cost/QALY

gained of 248,052 and 194,597 SEK, respectively. Changes in healthcare consumption by +10% and −10% yielded cost/QALY gained of 248,052 and 194,597 SEK, respectively. Increasing the time per visit and travel costs to 16 h and 300 km increased the cost/QALY gained to 388,678 SEK, whereas reducing the time and travel costs to 4 h and 50 km changed the cost/QALY gained to 169,366 SEK.

Table 10 Sensitivity analysis. Cost/QALY gained (SEK) in study III

		Duration of effect 1 year			Duration of effect 2 year			Duration of effect 4 year		
		Amount of patients diagnosed with ZJP								
Age of patients	Sick leave after RFC	30%	37.9%	50%	30%	37.9%	50%	30%	37.9%	50%
All patients under 67 years old	No sick leave	216434	134738	60032	101326	63079	28105	49099	30566	13619
	2 weeks	228845	147150	72444	107136	68889	33915	51915	33382	16434
	4 weeks	241257	159561	84855	112947	74700	39726	54731	36198	19250
18% retired patients	No sick leave	221600	139904	65198	103744	65497	30523	50271	31738	14791
	2 weeks	262310	180614	105908	122803	84556	49582	59507	40974	24026
	4 weeks	303020	221324	146618	141862	103615	68641	69742	50209	33261

RFC radiofrequency coagulation, ZJP zygapophysial joint pain

3.4 Study 4: Cost-effectiveness of IPM compared to REH

3.4.1 Characteristics of the assessed patients

The sociodemographic and clinical variables of eligible patients in the REH and RFC groups were compared with all patients assessed for REH and RFC to confirm whether the eligible patients were representative of the overall populations (Table 4

and 11).

Pain localization was registered for those assessed för REH by asking the question: “Mark all parts of your body where you feel pain”, whereas those assessed for IPM were asked: “Where do you feel pain that bothers you?”. The differing wording of these questions resulted in higher frequencies of pain in all regions for patients assessed for REH (In average 6.1 pain locations in REH group vs 2.5 locations in RFC group), and there were significantly higher frequency of pain in all regions (except the thoracic region) in the REH group than in the RFC group. However, because of the different wordings of these questions, comparing them directly may yield false results. Direct comparisons were not made, and this variable was not included in the analyses reported below.

After applying propensity score weighting, the standardized differences showed no significant imbalances between the two groups (Tables 4 and 11).

Table 11 Characteristics of patients in study IV

	REH group			RFC group		
	Assessed	Patients selected for rehabilitation		Assessed	Patients treated with radiofrequency coagulation	
	2010–2016	2010–2016	Included in study	2010–2016	2010–2016	Included in study
n	36,712	18,471	15,357	873	402	254
Selected for treatment (%)		50.3%			46.0%	
Age, years, mean (SD) [range]	44.3 (12.3) [13–95]	43.3 (11.0) [14–92]	43.4 (11.0) [14–92]	52.2 (15.7) [16–94]	51.0 (15.6) [17–89]	52.2 (15.9) [17–89]
Women, *n* (%)	26,312 (71.7%)	13,855 (75.0%)	11,533 (75.1%)	553 (63.3%)	260 (64.8%)	158 (62.2%)
Men, *n* (%)	10,400 (28.3)	4,616 (25.0%)	3,824 (24.9%)	320 (36.7%)	142 (35.2%)	96 (37.8%)
Pain duration, months, mean (SD) [range]	103 (110) [0–1346]	100 (108) [0–1152]	99 (108) [0–1152]	110 (113) [1–768]	120 (120) [2–744]	116 (118) [2–744]
HAD-anxiety, mean (SD)	9.7 (6.0)	9.6 (5.5)	9.6 (5.6)	7.2 (4.5)	6.9 (4.3)	7.0 (4.4)
HAD-depression, mean (SD)	9.1 (5.7)	9.0 (5.2)	8.9 (5.2)	7.7 (4.4)	7.9 (4.5)	7.9 (4.6)
EQ-5D index, mean (SD)	0.254 (0.317)	0.267 (0.312)	0.276 (0.314)	0.262 (0.318)	0.216 (0.281)	0.221 (0.285)
EQ-VAS, mean (SD)	41 (20)	42 (19)	42 (19)	44 (20)	42 (18)	42(19)

EQ-5D EuroQOL five-dimension scale of health, *EQ-VAS* EuroQOL visual analog scale of health, *HAD* Hospital Anxiety Depression scale, REH pain rehabilitation program, RFC radiofrequency coagulation, *SD* standard deviation,

3.4.2 HRQoL and psychological distress at the initial assessment

The mean EQ-5D index score was 0.221 in the RFC group and 0.276 in the REH group, the EQ-VAS score was 42 in both groups, the HAD-anxiety score was 7.0 in the RFC group and 9.6 in the REH group, and the HAD-depression score was 7.9 in the RFC group and 8.9 in the REH group. There were no statistically significant differences in these variables between the two groups after applying propensity score weighting (Tables 4 and 11).

3.4.3 Changes in HRQoL at 1 year after treatment

In the REH group, the mean EQ-5D index (from 0.275 to 0.468, $P < 0.0001$), EQ-VAS (from 42 to 54, $P < 0.0001$), HAD-anxiety score (from 9.6 to 7.7, $P < 0.0001$), and HAD-depression score (from 8.9 to 6.9, $P < 0.0001$) improved significantly from the initial assessment to 1 year after treatment.

In the RFC group, the mean EQ-5D index (from 0.288 to 0.537, $P < 0.0001$), EQ-VAS (from 45 to 58, $P < 0.0001$), HAD-anxiety score (from 7.9 to 6.1, $P = 0.0207$), and HAD-depression score (from 8.3 to 7.0, $P = 0.0057$) also improved significantly from the initial assessment to 1 year after treatment.

At 1 year after treatment, there were statistically significant differences between the REH and RFC groups in terms of the EQ-5D index (0.468 vs 0.537, respectively, $P < 0.0001$) and the percentage of patients with a clinically relevant improvement (39% vs 59%, respectively, $P < 0.0001$).

The mean QALY gained calculated from the propensity score-weighted EQ-5D index values was 0.164 and 0.186 in the REH and RFC groups, respectively, at 1 year, and 0.352 and 0.448, respectively, at 2 years after treatment.

There were no major complications in the RFC group. Complications are not handled or registered in the NRPR.

3.4.4 Intervention costs

As described in Section 2.1, 50.3% of the patients assessed at the pain rehabilitation clinics were deemed likely to benefit from a REH and were thus selected for treatment. Therefore, we assumed that 30,525 patients were assessed, and 15,357 patients were included in the study. The cost per assessed patient was 10,632 SEK and the total cost of assessment was 42,263 SEK/treated patient (Table 14). Assuming a treatment cost of 4,637 SEK/day for 24 days yielded a treatment cost of 111,288 SEK/treated patient in the REH group.

For RFC, 831 patients were assessed and tested at 2,759 visits and 3,788 procedures, with a total cost of 11,030,100 SEK. Of these, 402 patients (46%) were diagnosed with ZJP and treated. Therefore, the costs for the 254 patients included in the study were estimated based on 254/402 of the total measured costs, corresponding to 27,589 SEK per patient and an average of 6.9 visits per treated patient. RFC was performed during one visit at a cost of 5,500 SEK per patient.

Table 12 Calculation of costs in study IV

		REH group			RFC group		
			Total costs	Cost/patient		Total costs	Cost/patient
Costs associated with assessments and diagnostic procedures	Patients assessed, *n* Patients treated, *n* Patients in study, *n* Estimated visits, *n* Visits per patient, *n* cost/visit Total cost Time/visit, *h* Travel time/visit, *h* Travel costs Patient time cost Total time cost Travel costs	36,712 18,471 15,357 30,523 2.0 10,632 6 2 180 217 	 649,036,296 105,975,076 10,988,199	 42,263 6,901 716	873 402 254 1,743 6.9 1 2 180 217 	 7,007,652 1,140,943 315,468	 27,589 4,492 1,242
Treatment costs	Patients treated, *n* Visits, *n* Time/visit, *h* Cost/visit Healthcare cost Total time cost Travel costs	15,357 24 6 4,637 	 1,709,049,816 639,834,048 66,342,240	 111,288 41,664 4,320	254 1 1 5,500 	 1,397,000 165,354 45,720	 5500 651 180
Cost of pain-related medication	DDD/year before (after) Cost before (after) DDD after/before: *Antiemetics* *Constipation* *NSAID* *Muscle relaxants* *Opioids* *Antiepileptics* *Anxiolytics* *Hypnotics/sedative* *Antidepressants*	460 (448) 2,664 (2,876) 117% 100% 69% 76% 85% 121% 112% 113% 110%			704 (676) 8,372(8,552) 68% 120% 57% 126% 95% 84% 74% 113% 108%		
Healthcare consumption	Outpatient visits Before, mean *n* After, mean *n* Cost/visit, total Inpatient care days Before, mean *n* After, mean *n* Cost/day, total	 7.6 7.2 3,792 3.2 3.2 11,423	 −23,293,498 0	 −1,516 0	 11.7 3.6 3,792 0.3 2.7 11,423	 −7,801,661 6,963,461	 −30,715 27,415
Sick-leave	Average days/year Before After Days after RFC Total cost Before After Sick leave after RFC	 154 103 511,083,918 343,099,692	 −167,984,226	 −10,939	 128 60 2.07 7,037,172 3,301,776	 −3,735,396 113,913	 −14,706 448
Total costs			**2,989,948,017**	**194,696**		**5,612,454**	**22,096**
QALY-gain	At 1 year At 2 years		2,518.55 5,405.66	0.164 0.352		47.24 113.792	0.186 0.448
Cost/QALY-gained	At 1 year At 2 years	**1,187,171 SEK/QALY gained** (~139,503 USD, ~123,407 EUR) **553,114 SEK/QALY gained** (~64,996 USD, ~57,496 EUR)			**118,797 SEK/QALY gained** (~13,960 USD, ~12,349 EUR) **49,322 SEK/QALY gained** (~5,796 USD, ~5,127 EUR)		

DDD defined daily doses, NSAID non-steroid anti-inflammatory drugs, QALY quality-adjusted life years, RFC radiofrequency coagulation, SEK Swedish krona, *USD* US dollars, EUR Euro

3.4.5 Medications

There were some apparent differences in terms of whether the usage of drugs increased vs decreased in the two groups. In particular, the use of antiemetics, antiepileptics and anxiolytics, increased in the patients in the REH group but decreased in the RFC group. The use of muscle relaxants decreased in the REH group, whereas muscle relaxants and constipation drugs increased in the RFC group. Both groups showed a slight increase in the use of hypnotics and antidepressants and decreased intake of opioids. The total intake of pain-related drugs decreased slightly in both groups (Table 12).

In the REH group, the total average annual medication consumption was 1,016 DDD before treatment and 1,044 DDD at 1 year after treatment. The average annual pain-related medication consumption decreased from 460 DDD to 448 DDD at 1 year after treatment, whereas the average annual cost of pain-related medications increased from 2,664 SEK to 2,876 SEK. Therefore, the total additional cost per patient was 212 SEK.

In the RFC group, the total average annual medication consumption increased from 1,302 DDD before treatment and 1,384 DDD at 1 year after treatment. The annual pain-related medication decreased from 704 DDD to 676 DDD, but this resulted in an additional cost of 180 SEK/patient. Because there was a reduction in pain-related medications (i.e., reduced DDD), the increased cost was considered not to be a consequence of the treatment but was instead considered to be related to external

causes, thus the changes were not included in the cost calculations (Table 14).

3.4.6 Healthcare consumption

There were changes in healthcare consumption in both groups when comparing propensity score-weighted visits during the 3-month periods before the assessment and 1 year after treatment. The annual average number of pain-related visits decreased from 7.6 to 7.2 in the REH group and from 11.7 to 3.6 in the RFC group. The number of inpatient pain-related-care days remained at 3.2 in the REH group and increased from 0.3 to 2.7 in the RFC group.

In economic terms, these changes in healthcare consumption resulted in a reduced cost for outpatient care by 1,516 SEK/patient in the REH group and 30,715 SEK/patient in the RFC group. The cost of inpatient care increased by 27,415 SEK/patient in the RFC group. The numbers of visits and ward days were small and it is uncertain whether the changes were an effect of the treatment. Nevertheless, we decided to include these changes in the cost calculation (Table 12).

3.4.7 Patient time and travel costs

The costs incurred by patients in the REH group were calculated to be 6,901 SEK for the assessments and 716 SEK for travel costs, including time incurred, per patient. The corresponding costs in the RFC group were 4,492 SEK and 1,242 SEK. For the treatment sessions, the costs incurred by patients were calculated

to be 41,664 SEK for treatment and 4,320 SEK for travel in the REH group, and 651 SEK for treatment and 180 for travel in the RFC group (Table 14).

3.4.8 Productivity and sick leave

The annual average number of sick leave days decreased from 154 days to 103 days in the REH group and from 128 days to 60 days in the RFC group. Patients in both groups reduced their sick leave after treatment, albeit with a greater reduction in the RFC group. During the period after RFC, 90 patients reduced their sick leave from the month before treatment, 125 patients had no change in sick leave, and 39 patients required an increase in sick leave during the month after RFC. The reduced sick leave was not considered to be caused by the treatment and was therefore not included in the calculations. However, the increased sick leave was considered to be caused by post-RFC pain and was included in the analysis. These values reduced the cost by 10,939 SEK in the REH group and by 14,706 SEK in the RFC group. The cost increased by 448 SEK/treated patient for those with increased sick leave during the post-RFC period (Table 12).

3.4.9 Cost-effectiveness

The total net cost was 194,696 SEK/patient in the REH group and 22,096 SEK/patient in the RFC group. The total QALY gained was 0.164 and 0.186 per patient in the REH and RFC groups, respectively, resulting in a cost/QALY gain of 1,187,171 SEK (~139,503 USD, ~123,407 EUR) for REH and 118,797 SEK

(~13,960 USD, ~12,349 EUR) for RFC. After 2 years, the cost/QALY gain declined to 553,114 SEK (~64,996 USD, ~57,496 EUR) and 49,322 SEK (~5,796 USD, ~5,127 EUR), respectively (Table 12).

3.4.10 Sensitivity analysis

In all sensitivity analysis scenarios, the cost-effectiveness ratio for RFC remained within the moderate to low range for cost-effectiveness according to the Swedish NBHW. For REH, a calculated effect duration of >2 years was needed to reach the moderate range for cost-effectiveness (Table 13) [106,107].

Table 13 Results of the sensitivity analysis in study IV

Values per patient		REH group		RFC group	
Assessed patients	*n*	30,523		670	
Treated patients	*n*	15,357		254	
Cost for healthcare	Assessment	42,263		27,589	
	Treatment	111,288		5,500	
Patient time cost	Assessment	6,901		4,492	
	Treatment	41,664		651	
Travel costs	Assessment	716		1,242	
	Treatment	4320		180	
Rate treated/assessed	Cost/QALY gain	50.3%	1,187,171	46.0%	118,797
		30%	1,220,948	30%	139,207
		100%	1,162,390	50%	101,593
Duration of REH					
Days	9	24	39		
cost/QALY gain	587,814	1,187,171	1,786,534		
Cost of healthcare		+25%	-25%	+25%	-25%
	Cost/QALY gain	1,421,246	953,102	163,271	74,321
Travel costs		+25%	+100%	+25%	+100%
	Cost/QALY gain	1,194,850	1,217,878	120,707	126,441
Health consumption		Excluded	1,196,418	Excluded	136,538
Similar effect both	QALY	0.164	0.186	0.164	0.186
	Cost/QALY	1,187,174	1,046,755	134,732	118,797
Changed effect		1 year	2 years	1 year	2 years
	−10%	1,319,082	614,572	131,996	54,802
	+10%	1,079,249	502,832	107,996	44,838
Duration of effect	Per patient	QALY gain	cost/QALY gain	QALY/gain	cost/QALY gain
	1 year	0.164	1,187,171	0.186	118,797
	2 years	0.352	553,114	0.448	49,322
	3 years	0.534	364,600	0.634	34,852
	4 years	0.716	271,922	0.892	24,771
	5 years	0.898	216,811	1.406	15,716
	6 years	1.080	180,275	1.662	13,295
Color coding of range	Very high	High	Moderate	Low	
cost/QALY gained	>1,000,000	>500,000 <1,000,000	>100,000 <500,000	<100,000	

All costs are given in Swedish krona (SEK). Base-line figures in red

A sensitivity analysis was performed to check the effects of the assessment costs. In the REH group, 50% of the assessed patients were expected to benefit from rehabilitation and were treated. When we decreased this proportion to 30%, the cost/QALY gained increased by 3%. If all patients assessed were treated, the cost/QALY gained decreased by 2%, resulting in a cost/QALY gained of 959,540 SEK at 1 year and 446,424 at 2 years.

In the RFC group, 46% of the assessed patients were diagnosed with ZJP and treated. Decreasing this value to 30% increased the cost/QALY gain by 17% to 139,207 SEK. When the proportion was increased to 50% of those assessed, the cost/QALY gained decreased by 14%.

Changing the costs of healthcare given by −25% and +25% resulted in a change in cost/QALY gained of 20% in the REH group, corresponding to values of 953,102 and 1,421,246 SEK at 1 year. In the RFC group, this changed the cost/QALY gained by 37%, corresponding to values of 74,321 and 163,271 SEK at 1 year.

According to the study by Rivano-Fisher et al., who showed that the duration of REH varied significantly between units [79], we calculated the costs after changing the mean duration (in terms of rehabilitation days) by ±1 SD. As such, when REH was only 9 days (-1 SD) and assuming similar outcomes in terms of HRQoL,

medication and sick-leave, the cost/QALY gained after 1 year would be 587,814 SEK (i.e. in the high range). However, if the program was 39 days (+1 SD) the cost/QALY gained after 1 year would be 1,786,534 SEK (i.e. in the very high range).

Increasing the travel costs by 25% or 100% resulted in a maximum change of 3% in the REH group and 6% in the RFC group, with no major changes in the outcomes.

We also performed sensitivity analyses by excluding healthcare consumption. This resulted in a cost/QALY gain of 1,196,418 SEK in the REH group and 136,538 SEK in the RFC group, indicating no major changes in the outcomes.

When we considered changes in the effectiveness of REH and RFC in terms of the improvement in HRQoL a 10% reduction of the EQ-5D index resulted in a cost/QALY gained of 1,319,082 SEK at 1 year and 614,572 SEK at 2 years in the REH group. Increasing the effect by 10% resulted in a cost/QALY gained of 1,079,249 SEK and 502,832 SEK, respectively. In the RFC group, reducing the effect by 10% resulted in a cost/QALY gained at 1 and 2 years of 131,996 SEK and 54,802 SEK, respectively, and increasing the effect by 10% yielded results of 107,996 SEK and 44,838 SEK, respectively.

We also performed a sensitivity analysis, in which the effects of treatment were maintained for >2 years. In this analysis, REH was cost-effective in the moderate range, and RFC was cost-effective in the low range (Table 13).

Finally, we estimated the consequences of expanding IPM from the current 2% to 25% of patients with chronic pain. During the years 2010-2016 there were 18,471 patients that received REH and 402 (2.2%) that received RFC. If this was expanded to 25% of the patients receiving IPM, it could potentially save the Swedish healthcare system 106 million SEK annually and the patients HRQoL could improve by 14 QALY.

4 Discussion

4.1 Main findings

There are two main findings of this research, concerning the cost-effectiveness and psychological effects of IPM.

The main health economic finding is that IPM focused on ZJP is more effective, and more cost-effective, than REH, which is the “gold standard” for pain management in Sweden. The difference is so large that expanding IPM from the current 2% of patients to 25% would save 106 million SEK annually in Sweden, while at the same time gain 14 QALY.

The main psychological finding is that the participating patients described gaining empowerment as the most important benefit of IPM. Why this is important is discussed further in section 4.4.

How robust are the cost-effectiveness values? The results are based on several factors, and the two main determinants were the effects of the different treatments on HRQoL and the cost of the treatments. IPM showed favorable values for both factors compared with REH. In section 4.2 I will discuss this more.

The effects of IPM were described in study 1, 3, and 4. All three studies show similar improvements in the EQ-5D index, although there was some overlap in the patients enrolled in the three studies. No prior studies have reported changes in the EQ-5D index after RFC, but several have shown a significant improvement in the Oswestry Disability Index after RFC of painful

z-joints [110,115,116], supporting the current findings. So far, there have been very few cost-effectiveness studies of IPM, other than those I have published. Those publications confirm our findings that IPM is cost-effective, although they mostly involved a health-care perspective [70,128,129].

There are very few published studies describing the cost-effectiveness of multidisciplinary REH for chronic pain. Gauthier et al did not find any cost-effectiveness studies on multidisciplinary pain management [117], and recently (2022) Chowdhury et al found that among nearly 2800 publications on multidisciplinary interventions for chronic pain, only seven publications examined cost-effectiveness [118]. Four of those publications did not report the cost-effectiveness of multidisciplinary treatment, two reported “favorable cost-effectiveness” compared with non-multidisciplinary interventions, and one reported greater effect but at greater cost [118–125]. LoMartire et al found no significant improvement in the sick-leave benefit of interdisciplinary rehabilitation [126], and the Swedish Agency for Health Technology Assessment recently expressed doubt that the effects seen after REH might be caused by natural processes rather than the treatment itself [127].

The purpose of this research was to increase our knowledge of IPM. In this thesis I have approached the problems from several different angles, using different scientific methods and, as I stated in the introduction, I have acted like a squirrel jumping from branch to branch in the “tree of science”, leaning on different scientific

theories. Therefore, some of the methods I have used deserve in-depth review, which I will do in the following sections.

The first study established a method for the diagnosis and treatment of ZJP in the thoracic region and validated this method against the methods used for ZJP in the cervical and lumbar regions. The study revealed that the treatment could significantly improve the HRQoL, and that the improvement was similar regardless of whether the pain was located in cervical, thoracic or lumbar regions.

In the second study, we tried to clarify some of the mechanisms for why patients described an improvement in HRQoL. The thematic analysis revealed that the IPM helped the patients gain empowerment, a topic seen among all the interviewed patients, even though some of them reported more pain and reduced HRQoL at the time of the interview.

The third study evaluated the cost-effectiveness of IPM focusing on RFC of ZJP. This study revealed that the cost-effectiveness ratio of IPM was within moderate to low range according to the thresholds set by the Swedish NBHW.

The fourth study, compared the cost-effectiveness of IPM with that of REH, to the “gold standard” for pain management in Sweden. We found that, although the cost-effectiveness of REH was within the very high to moderate range, IPM was in the moderate to low range. If IPM could be expanded to a larger number of patients, it may contribute to large annual savings of health-care resources.

4.2 Methodological aspects

4.2.1 HRQoL and EQ-5D index

The NRPR in Sweden was initiated in 1998 and was slowly expanded to cover nearly all of the units in Sweden offering REH. The register publishes annual reports with statistics on the patients and outcomes of the programs. The EQ-5D index is one of the outcomes reported in the publications [80,130–136], and as shown in Table 14 the values in study IV are similar to the data published in the reports between 2010 to 2020.

Table 14 EQ-5D index per year presented in the annual NRPR reports in Sweden in study IV

	EQ-5D Index	
	Before	After
2010	0.29	0.38
2011	0.28	0.40
2012	0.29	0.40
2013	0.29	0.40
2014	0.3	0.5
2015	0.2	0.4
2016	0.2	0.4
2017	0.283	0.438
2018	0.299	0.475
2019	0.31	0.5
2020	0.3	0.49
Study IV	0.275	0.468

EQ-5D EuroQOL five-dimension questionnaire, NRPR National Register of Pain Rehabilitation

In many studies on pain management and effects of treatment, the main outcome was pain [42,43,110]. Early in the study design process, I decided not to focus on the pain as the outcome and instead focused on HRQoL. Among the different instruments developed to assess HRQoL, I decided to use EQ-5D because it is widely used in different patient groups [137–140], and because of its usability in patients with cognitive problems (e.g. patients with stroke or patients suffering from severe pain). The five dimensions of EQ-5D must be translated into a single cardinal value on a scale where 1.0 equals best possible health and 0.0 equals death

in order to be useful as an outcome measure and to be utilized for the subsequent calculation of QALYs. This scale can be applied using either a time-trade-off method, compared with a rating scale, or using a standard gamble in population or patient studies. When I started the first study in 2010 the largest time-trade-off derived index values was the UK-index tariff which was established using a general UK population [89,141]. At that time, there was a Swedish tariff that was based on a rating scale comparison. However, the statisticians belonging to the EuroQOL group that had developed the EQ-5D recommended that, if there was no time-trade-off value for the population of interest, the UK values should be used instead [141]. The UK index tariff allowed weighting beneath death, yielding values ranging from -0.6 to +1.0, which was widely debated. In particular, it was debated how HRQoL could be worse than death. Burström et al. postulated that no condition could result in states worse than death, and hence the Swedish index tariff had a minimum value of 0 [87,93,142]. However, in the context of chronic pain, a common situation is that patients believe their condition is so bad that they consider suicide [143,144]. Therefore, a value set spanning with a lower limit below zero is appropriate to evaluate the actual perceived HRQoL. In this situation, a problem could arise if the treatment achieves a clinical relevant change (i.e. a change in the EQ-5D index of ≥0.1) while remaining below 0 (i.e. “death”). However, as shown in the first study, among patients with a clinically relevant improvement, the outcome EQ-5D index was close to that seen in the general population in Sweden [78]. Therefore, the main value of using the EQ5D index to reflect the true feeling of HRQoL outweighs the

disadvantages of using a value that can be hard to understand because of its virtual, abstract nature.

Using EQ-5D as the outcome measure was questioned by a group of pain researchers because they could not find any latent variable that could be related to all the five dimensions [145]. However, because EQ-5D is a formative constructed instrument, there is no latent variable and therefore one cannot find one, however deep the researcher digs [146]. One strength of the EQ-5D index is that it comprises five domains, each with three levels, and yields 243 unique values for HRQoL.

4.2.2 Variability in rehabilitation programs among units

The NRPR consists of data for patients that were assessed and patients that were treated by REH. Although the national guidelines have emphasized the importance of interdisciplinary REH, there is much variability between different units [79]. The differences affect the costs because a longer duration of REH results in higher treatment costs as well as higher costs associated with the patient's time and travel. However, it is not possible to determine whether the HRQoL is altered based on the registered data because the duration of the program is not recorded. However, when we performed a sensitivity analysis in which we considered the duration of REH to be 9 days (mean –1 SD) and 35 days (mean +1 SD), the cost/QALY gained for REH remained in the range of very high to moderate and did not affect the conclusions made in study IV.

4.2.3 Propensity score weighting

The Holy Grail in clinical research is that of double blind randomized controlled trials, in which the patients are randomized to the optional treatments and neither the patients nor the investigator know which treatment the patient receives. However, this design is usually only possible for pharmacological treatments because it is difficult to perform clinical treatments in a blinded manner, especially when the research involves two very different treatments. Non-blinded randomized controlled trials are considered the second-best option, but the costs and time needed to perform such studies for every procedure and treatment would be enormous [71]. Therefore, we must rely on observational studies when evaluating different treatment methods. In order to reduce bias some mode of matching or weighting patients based on covariates are needed. In 1983, Rosenbaum described how a multivariable analysis could be used to calculate the propensity score by determining the conditional probability of assignment to a particular treatment based on a vector of observed covariates [72]. In the decades since that publication, multiple studies have used propensity scores to reduce bias in observational studies [108,109]. Propensity score matching, in which cases and controls are matched based on the propensity score, is one of the most commonly used matching methods [147]. However, there are problems when using propensity scores for matching, because an imbalance in two covariates might even the propensity scores and cause false matching [148]. Therefore, Lunceford proposed a better method that involved propensity score weighting [73,74].

Using propensity score weighting, we could mimic a randomized controlled trial that included all controls regardless of the difference in numbers of patients in the case and control groups [74,149]. The cost/QALY gained for IPM differed slightly between studies III and IV, although both studies yielded results in the moderate range. In my opinion, study IV, in which the results were based on propensity score-weighted data, provides the most reliable substantiated data for the cost/QALY gained of IPM focused on ZJP.

4.2.4 Sickness compensation versus ability to work

It is obvious that pain affects a patient's ability to work [101,102,104]. The cost of sick-leave depends on several factors, and imposes an economic burden on the affected patients, their employers and society as a whole. According to Persson et al., the production loss accounts for about 90% of the total cost of sick-leave, and rehabilitation and health-care interventions account for the remainder of the costs [150]. The changes in sickness compensation insurance made by the Swedish parliament over the last few decades have resulted in some disparity between the level of sickness compensation and the patient's ability to work [103]. When we discussed the design of the studies, one topics was how should we measure sick leave? In study III, we decided to use self-reported ability to work because of the perceived discrepancies between the sickness benefits and the patients ability to work [151], whereas in study IV, we decided to use the official register data on sickness benefits. The discrepancy between the sickness benefits and the perceived ability to work

seams to have balanced the problem of missing data when using self-reported ability to work, yielding comparable results in both studies. My conclusion is that both methods can be justified.

4.2.5 Selection of the method for qualitative analysis

We discussed several different methods for analyzing the data. Because the main aim of the qualitative analysis was not to formulate a theory but rather to uncover the patients' perceptions, the grounded theory was never an option [152]. Instead, we discussed whether qualitative content analysis or thematic analysis could be used to reveal and describe the breadth of experiences by the patients [153,154]. After some consideration we decided to perform thematic analysis [94,95]. We view thematic analysis as a method for identifying, organizing, and reporting themes found in our interviews [94]. Boyatzis also stressed that thematic analysis is very suitable when we want to use both the qualitative and quantitative language [155]. He describes thematic analysis as a means to bridge "*...methods and results in forms accessible to others from different fields…*" in order to overcome the "*major challenge in the social sciences*" that he identifies as "*epistemological chauvinism*" [155]. Therefore thematic analysis also complies with the goal for my research, to bridge the gap between interventional pain management and pain rehabilitation in order to improve how pain is managed by forming a more logical structure where diagnostic procedures precede rehabilitation efforts.

Josefien van Olmen described a method of analyzing health systems in order to identify weaknesses that could be strengthened [156]. The method involved categorization of different aspects and localization of the categories in their context and visualizing how they relate to each other. We applied a similar method in order to relate the different themes to each other and show the context in which they exist. Some of the themes, such as “accept pain to become pain-free” have resembled the goals often associated with acceptance commitment therapy (ACT). However, although this could have been found among the goals when studying ACT, it was among the intrinsic factors described in the context of the encounters and diagnostic injections in the study and is apparent in the data.

4.3 Subjectivity of pain perception.

Research is often performed in an air of objectivity, implying that the results are independent of both the researcher and the Study patients. Therefore, if someone else repeats the study using a similar but different cohort, the same results would be achieved. In this respect this thesis is no different from other research. However, as stated in the IASP definition of pain: “*Pain is always a personal experience that is influenced to varying degrees by biological, psychological, and social factors.” [3]* Thus, the subjectivity of pain perception poses a special challenge. It is well known that pain perception is affected by social and psychological conditions, and its effects are unpredictable [157]. Often, difficult social situations

may reduce the persons ability to cope with pain and may result in greater pain perception [158]. Alternatively, difficult social situations may make a person neglect their pain in a struggle for survival or when focusing on a special goal [159,160].

When I started to follow patients more systematically, it became clear that pain perception and the description of pain were poor outcomes. It was useful when evaluating the short-time effects of a diagnostic nerve block but for longer periods after RFC, my impression was that when the pain level declined, the patients reduced their intake of analgesics and other drugs, and they became more active, working longer days and more frequently until their pain level returned to the level before treatment. Despite this increase in pain to the level before treatment, the patients described an improvement in HRQoL. The mutual interaction between pain perception and psychological distress also became clear because the patients described a reduction in their psychological distress after treatment. Thus, the treatment of pain foci, paradoxically, resulted in significant improvement in HRQoL and psychological distress without an apparent reduction of pain.

4.4 Empowerment

The necessity of patient empowerment in healthcare has been described and discussed in several studies [161–163], although disempowering patients with chronic pain is commonly described by patients in the context of bad encounters with healthcare providers [58,59,62,63,164]. The question of empowerment or disempowerment is therefore central when analyzing whether or

not to promote pain management [165,166]. IPM is reliant on the subjectivity of pain perception, which means that only the patient can measure the current level of pain. Therefore, all diagnostic tests must be performed through cooperation between the provider and the patient, which makes the participation of the patients obsolete. Therefore, despite the technically advanced methods and the focus on pain, painful structures, and nerve-blocks, the effect is mainly psychological, and the effects on the perceived empowerment as well as HRQoL tend to be greater than those achieved by pain management programs focusing on psychological factors. Qualitative studies like this, despite focusing on the patient's perception of a certain treatment, are unable to delineate the effects of previous health-care contacts on the patient's perceptions. However, the similar feelings expressed by the patients in this study, regardless of their previous treatments, strengthens my belief that the empowerment described by the patients is mainly achieved by the IPM.

4.5 Gender disparities

There is consensus in the medical community that there are gender differences in terms of the prevalence of chronic pain and their responses to treatment. The magnitude of these differences and whether the differences are based on biological sex or social gender are uncertain [167]. In large epidemiological studies such as the survey of chronic pain in Europe, there was a slight gender disparity because 56% of the patients with chronic pain were female, but 52% of the total population were female [168]. In the NRPR 72% of those assessed were women and 75% of those

selected for rehabilitation between 2010 and 2016 (Table 13). By contrast, only 44% of those scheduled for lumbar disc herniation surgery were women, and their medical condition was worse than that of men which implies that it is significantly more difficult for women to be accepted for surgery [169]. Among those assessed for IPM between 2010 and 2016, 63% were women and 64% of those diagnosed with ZJP were women (Table 13). According to DePalma et al., female sex, together with higher BMI and age, is a risk factor for ZJP which could partly explain the gender disparities among patients diagnosed with ZJP. However, the reason for the greater gender disparity among the patients assessed and accepted for pain rehabilitation is unclear. Because patients with chronic pain often describe that their pain had been neglected and they had been told that, since nothing is visible on X-ray or MRI, their pain must have a psychological cause (as expressed by the women in study II), and there is a well-known gender bias in how patient problems are assessed, one can suspect that this gender bias contributes to the gender difference in pain rehabilitation [170]. When we stratified the analysis by gender, there were no differences in the results between men and women after RFC of the medial branch nerves.

4.6 Ethical considerations

This thesis started with typical clinical research, in which a method for the diagnosis and treatment of an illness (ZJP) was described and evaluated, followed by qualitative research exploring the

feelings and experiences of patients undergoing IPM, and finally public health research. Thus, the ethical considerations differ among these different components of the research. But the major ethical challenges relate to the effects on the patients, namely the risks of harming the patient and the risk for the patients benefits by using more health-care resources compared to others (i.e. bystander risks). There is also a risk of bias because of the patient's dependency on the researcher that is stronger in situations where there is a strong patient-physician relationship between the patient and the researcher [171].

As stated previously, patients with chronic pain often have a very low HRQoL, and they often describe bad experiences of previous encounters with health-care providers, making them a vulnerable group [62]. This poses special considerations when performing research in this setting, especially when the patients are patients receiving health-care from the researcher, resulting in a clear power difference [172,173]. In the qualitative study, this was first managed by recruiting an independent interviewer to help collect unbiased information from the patients during the interviews, and second by recruiting patients from different stages in the management program, including some who were in early stages of treatment and had not yet experienced a treatment-related improvement, whereas others had already been treated and were only in contact with the clinic for follow-up assessments and were thus less dependent on the clinic. When designing the quantitative research, we sought to consider the patients' vulnerability and dependency and designed the studies in order to reduce the risks

of bias as well as the risks that the patient's participation in the research or lack thereof could affect the treatments they received [174]. The patients were informed about the research before their first visit, and informed consent was obtained at the same time. Data collection was performed as part of their ordinary health-care, with similar follow-up visits at 1, 3, 6, and 12 months after RFC, regardless of whether the patient participated in the study or had declined to participate. In addition, the analysis was performed separately from clinical care and utilized de-identified records to maintain confidentiality and reduce bystander risk [175,176]. The method of data collection was similar for IPM and REH because the NRPR involves a similar method of data collection [177]. Triangulation, both against previously published research and other patients and patient groups, was also performed in order to ascertain minimal bias [178–180], and the results of the sensitivity analyses yielded results in ranges rather than absolute values, thus enhancing the transparency of the research [181]. With these measures, I believe we have minimized the risks for the patients [173,182] as well as the bystander risks [176] of not receiving similar quality of care. I also believe that we reduced the risk for bias [183] associated with the power difference between the patients and the researchers (physician and nurse) [184].

4.7 The role of pain management in the health system

An expansion of IPM can only be achieved through the budget processes in about 20 regions in Sweden. These processes are, to varying degrees, influenced by the model for priority setting developed by the Swedish NBHW. There are four criteria that are considered when setting priorities for health care: the severity of the condition, the effectiveness of the treatment, the cost-effectiveness of the treatment and the evidence base for the treatment. The overall judgement is based on a combination of these four criteria.

The severity of the condition is apparent. Pain and psychological distress are the two most important factors affecting HRQoL [185]. Pain is one of the most common problems that make patients seek help in primary care [186]. When primary care physicians assesses the patient's ability to work, pain is one of the major symptoms reported [187]. Still, the management of chronic pain is considered to be frustrating because there are no objective findings to confirm the patient's suffering, and the sick leave certificates that are written by the physician are often questioned [62,187,188]. The combination of impaired HRQoL and a reduced ability to work impose a burden and stressor on the healthcare system and demonstrate the significant severity of the condition.

When treating chronic pain, the healthcare systems have taken different approaches. Orthopedic surgery focuses on MRI and X-ray images, and if they find radiological features that are believed

to cause pain, surgery is performed in an attempt to normalize the anatomy with the hope that the procedure reduces the patient's pain. Pain modulation methods involve different methods to modulate the pain signals in the nervous system, such as dorsal column stimulation, in which the signals in the nervous system are modulated in order to reduce the pain perception. Alternatively, spinal infusions of opioids, for example, may achieve similar results. By comparison, pain rehabilitation focuses on the psychological effects of the pain to help the patient cope with their pain and to reduce their impairments caused by their pain. Finally, IPM focuses on the pain felt by the patient. In cooperation with the patient, structures are tested to see if there is a pain focus in the tested structure that reduces pain under the effect of local anesthesia. If a pain focus is identified, a long-acting nerve block is achieved by coagulating the nerve.

Because the HRQoL is the most important aspect, followed by the ability to work, among patients with chronic pain, the effectiveness of treatment must be assessed in terms of these outcomes. In this thesis, I studied IPM and compared it with REH. Although both methods are effective in terms of improving HRQoL, IPM had greater effects than REH in terms of the magnitude of change in the mean EQ-5D index and in the number of patients with a clinically relevant reduction or no change in the EQ-5D index.

The cost effectiveness of a treatment is dependent on the actual cost of the treatment, the effect of the treatment in terms of HRQoL, and the duration of the improvement. Concerning cost

effectiveness I have shown that IPM was cost-effective in the moderate range when calculated for a duration of 1 year only, whereas REH was cost-effective in the very high range. When the duration was assumed to last for >2 years, the cost-effectiveness of IPM was in the low range, whereas REH reached the moderate range; this difference persisted when the duration was extended to 6 years.

The Swedish Council on Technology Assessment in Health Care recently published a report on multimodal and interdisciplinary treatments of chronic pain in which they performed a cost-effectiveness study that was based on theoretical calculations due to the lack of consistent data. They concluded that "..multimodal and interdisciplinary treatments might be cost-effective if the effects on HRQoL and sick-leave lasts for at least two years after treatment…" [127,189], which supports our findings. The report has been criticized primarily in relation to the outcome measures used in the report, rather than the cost-effectiveness analysis itself [190,191]. Furthermore, a study by Rivano Fisher et al showed that the intention of a national, uniformly designed REH has not been achieved [79,192]. Instead, there is much variability in both the duration and the content of the programs. Unfortunately, because the NRPR lacks detailed data on the programs, we were unable to investigate the extent to which the different programs affect the outcomes. Instead, I performed a sensitivity analysis in which the duration of the program was varied by ±1 SD of the mean duration based on the study by Rivano-Fisher et al. [79]. The analysis showed that the overall results remained: even if the

REH was only 9 days long and achieved similar patient outcomes, it would only be in the range of “moderately cost-effective”.

The national system for knowledge-driven management within Swedish healthcare recently published a report on long-lasting pain among adults [193,194]. The report divided patients with chronic pain into three subgroups: people with pain and transient disability who had <10 healthcare visits per year, patients with pain and significant disability who had <10 healthcare visits per year, and patients with significant disability and who had more than 10 (often 20-25) healthcare visits per year. The authors concluded that a systematic and coherent course of care will increase the short-term healthcare costs, while reducing the long-term society costs [194]. The authors wrote that “An improved handling and a raised ambition to offer more patients an early assessment and structured treatment in the primary care is expected to in the short term increase the need for healthcare resources.” (page 5, my translation). As a specialist in both family medicine and anesthesiology, I have good experience of this. When I started work as a primary care physician in a rural setting 25 years ago, pain problems became obvious to me, and I started to assess them in a more systematic manner [69]. Consequently, I identified several patients with suspected treatable pain foci that needed interventional pain assessment in order to obtain further treatment.

The evidence base for IPM and treatment has been widely debated over the last few decades. Despite the concerns that RFC of the nerves to the Z-joints might give adverse effects, no major

side-effects have been seen in the numerous studies published. A recent study, focused specifically on the lumbar paraspinal musculature, could not reveal any signs of iatrogenic muscle denervation in the area where the RFC was performed [195]. To perform a treatment without a diagnosis is obviously hazardous, and the likelihood that it will help is very low. RFC of the nerves to the Z-joints will only be effective against the pain if the treated nerves are responsible for mediating the pain. When a primary care physician has identified a patient with suspected ZJP, IPM is the only method available to confirm whether or not the suspicion is correct because there are no diagnostic radiologic modalities that can provide usable information in this setting [196–198]. Furthermore, this thesis has shown that IPM focused on ZJP is cost-effective in the moderate to low range. According to a report on the consequences of knowledge-driven management of pain, the cost-effectiveness might actually be better, because the assessment and treatment exclude many patients that would otherwise use resources that could be directed to those without an identifiable pain focus. Pain rehabilitation is based on the theory that pain is a disease in itself and that chronic pain is maintained by sensitization and psychological mechanisms. Therefore, a precise diagnosis is not required before REH. In 2006, The Swedish Council on Technology Assessment in Health Care assessed several different treatments against un-diagnosed pain and concluded that, when including treatments without a diagnosis, there was weak evidence for RFC of ZJP (grade 3) [192]. The importance of selecting patients for treatment with diagnostic procedures has been a topic in several reviews and

studies [42,196,199]. The UK National Institute for Health and Care excellence concluded in their guidelines for low back pain and sciatica that RFC against ZJP should be considered when conservative treatment (i.e. physiotherapy) did not help [70]. The conclusion is that there is strong evidence supporting RFC if ZJP is diagnosed in an appropriate manner.

To summarize we know that chronic pain is a very severe condition and a major cause of significant impairment in HRQoL. Chronic pain is a challenge for the health-care system in terms of the number of affected patients and how to manage them, and this was apparent in several qualitative studies of patients and health professionals. IPM focusing on ZJP helps to empower patients and is cost-effective according to national thresholds and in comparison with REH. Therefore, expanding IPM to more patients has the potential to both improve the health care given and save healthcare resources. This expansion should ideally be directed toward primary-care by encouraging primary care physicians to refer the patient for interventional pain assessment early in the process in order to direct treatable patients toward IPM rather than interdisciplinary pain management programs.

4.8 The thesis in a global perspective

4.8.1 The global burden of disease

Chronic pain is one of the major causes of impaired health and/or early death. In the Global Burden of Disease study 2015 chronic pain was ranked 4th [200]. The Relieving Pain in America 2011

report identified chronic pain as a public health challenge because approximately 100 million Americans are affected, it contributes greatly to national rates of morbidity, mortality and disability and the prevalence is rising [201].

The annual costs associated with pain are estimated to exceed $560-$635 billion of which $261 – 300 billion is due to incremental health care costs. In 2008, it was reported that the Medicare program covered one quarter of the US medical expenditures for pain; i.e., $65.3 billion (14% of all Medicare costs) 2008 [201]. Similarly, a 2006 Swedish Council on Technology Assessment in Health Care report on methods for treatment of chronic pain estimated the annual Swedish costs to be 87.5 billion SEK in 2003, of which 7.5 billion SEK was calculated to be direct healthcare costs, equivalent to 12.8% of the total health budget in 2010 [27,192]. The prevalence of chronic pain is high in all countries, including developing and post-industrialized countries. Although the management of acute pain is often considered a marker for the quality of pain care [202,203], the management of chronic pain is often neglected by healthcare providers [62,204].

From a global perspective, there is a constant lack of resources in the healthcare system, which makes it important to focus on how to use the available resources most efficiently and to achieve the best outcomes in terms of HRQoL. The establishment of REH is a process that may permit stepwise expansion, by starting with a physician and physiotherapist, and then recruiting psychological expertise permitting multidisciplinary assessments, discussions,

and conclusions for patients. This makes it attractive to start building a unit for the management of chronic pain. It is also appealing to expand this into group-based programs. However, it is much more difficult to establish a clinic offering IPM. For this, it is necessary to start with the education and training of physicians and nurses, preparing a treatment ward with X-ray and emergency facilities. Increasing the initial costs and work-load, thus hiding the future benefit. Therefore, the type of research presented in this thesis is important in assisting with planning new chronic pain management units, which will hopefully consist of a rehabilitation unit and an interventional unit within the same clinic. In this way, the benefits of both treatments can be achieved while providing the best patient outcomes for the least cost.

4.9 Strengths and weaknesses

A strength of this thesis is that the studies address many aspects of IPM, and use effectiveness data instead of efficacy data. However, the lack of efficacy data generated by RCTs is a potential weakness. My analysis started with the technical aspects of performing the procedures, continued with the effects of IPM on HRQoL, followed by the psychological effects perceived by the patients (participants), and finally concluded with an evaluation of the cost-effectiveness of IPM relative to REH as the “gold standard” for pain management in Sweden. A weakness is that only one IPM clinic was included in the cost-effectiveness studies, although the clinic included is one of the very few that provide this

treatment in Sweden. Ideally, future studies should be expanded to include several clinics in different countries to better evaluate the effects of the treatments.

Another limitation is that we only studied the problem from the patient's perspective. Many studies have demonstrated that chronic pain and the management of patients with chronic pain are distressing to the care-givers because of their feeling of insufficiency [65,188]. Neglecting care-givers' feelings might contribute to greater healthcare costs owing to potentially irrational actions that are taken by the caregivers.

4.10 Further research

Expanding the cost effectiveness studies beyond Sweden and including both IPM clinics and pain rehabilitation clinics is an obvious opportunity for further research. Concerning the qualitative research, it would be interesting to consider the caregivers perspectives to find out what they feel when referring patients for IPM and REH. A third topic would focus on the healthcare systems studying how a pain management unit could be established in countries with rudimentary pain management systems, such as in Africa, and how an education program combined with dedicated health care focusing on chronic pain could improve HRQoL.

4.11 Conclusions

In conclusion, IPM focusing on ZJP can restore HRQoL in a large

proportion of patients suffering from chronic pain. The patients reported that they gained empowerment following IPM. IPM was also cost-effective relative to national thresholds and compared with REH. Expanding IPM from the current 2% to 25% of patients with chronic pain could potentially improve the HRQoL by 14 QALY and save the Swedish healthcare system 106 million SEK annually. If interventional pain assessment is performed early in the process, treatable patients could be directed toward IPM, instead of interdisciplinary pain management programs, achieving further synergistic cost-effectiveness.

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Appendices

Appendix 1 Templates for the semistructured interview in study I

Topic	Description
Problem	What are the main pain problems? Where is it located? Radiation?
Sympathetic	Subjective autonomic nervous system problems: Sensory: hyperesthesia and/or allodynia Vasomotor: temperature asymmetry, skin color changes, color asymmetry Sudomotor/edema: edema, sweating, sweating asymmetry Motor/trophic: Decreased range of motion, weakness, tremor, dystonia, trophic changes (hair, skin, nail) Problems to pass urine, incontinence, obstipation Eye-problems (focusing, pupillary adjustments)
Start	How did the pain start? Trauma? What trauma and how? How was it transferred into chronic pain?
Other problems	Other diseases? Previous problems before the chronic pain?
Previous treatments	Pain rehabilitation programs? Surgery? Interventional pain managements? Dorsal column stimulation?
Pain level	Visual analogue scale (When the least pain, when worst pain and in average last week)
Pain description	How does it feel? Itching? Pricking? Burning? Ask the patient to describe with own words.
Worsening	What activities makes the pain worse? Getting cold? Changes during the day?
Better	Are there activities that can make the pain better?
Sleep	How long time before falling asleep? How many times do you wake up during the night? Overall perception of sleep. Do you still feel tired when waking up or are you relieved?
Medication	What medications do you take. Doses.
Work	What are you working as? On sick-leave? What percent are you working if any?
Social	Family description (children, living alone or with a partner) Psychological distress. Anxiety? Depression? Suicide?
Goal	Why are you here? What do you hope to achieve by attending? What do you hope we can help you with?

The interview is performed with minimal feed back, in order to receive information as free as possible from the influence of the interviewer. The aim is to collect information about feelings and believes that the patient has, regardless whether the interviewer understands it or see it as relevant. The consideration and evaluation of the information is postponed until after the physical examination.

Appendix 2 Interview guide used in study II

We would like to know about your experiences with interventional pain management. Therefore I would like you to tell me what you have felt and experienced during the management and what thoughts you have had. I will help you with extra questions during the interview.

What did you think when you were in the waiting room before the first visit?

Do you remember what you were thinking during the first encounter with the doctor, when he posed the questions?

How did you experience the first test injections? Have you had similar experiences before?

What did you feel immediately after the injections when you got up from the table?

Was your pain affected by the injections? Was it reduced?

Do you remember what you thought when you left for home after the first encounter?

When the pain returned, what did you think? How did you feel?

An investigation means that you start with pain, get an injection and the pain is reduced, then the pain returns again and this is repeated several times. What was your experience of this?

Has your understanding of your problems changed in any way? If so, how?

Has the investigation led to a radiofrequency denervation? What was your experience of this? Do you remember what you thought before the first time that was done? How did you feel afterwards? Were you very affected by the treatment? Did you get better because of the treatment? If so, how long did this improvement last?

Do you think you have changed as a person by the investigation? Has your relation to your pain changed? If so, how?

Many of the test injections and treatments are painful. And sometimes the pain is reduced after the injections, but sometimes not. And sometimes the improvements only last for a short while. If you had a friend who was going to be examined, how would you describe your experiences?

Appendix 3 Procured reimbursements for diagnostic and therapeutic procedures in study III and IV

Procedure	Reimbursement (SEK)
Pain analysis assessment at first visit	3100
Assessment without other procedures	900
Interlaminar root-blocks	2400
Transforaminal root-blocks	3100
Medial branch blocks	3100
Intraarticular joint injections	1800
SI-joint injections	3400
Lateral branch blocks	3900
Radiofrequency denervation of medial branch	5500
Radiofrequency denervation of lateral branch (SI-joint)	6000
Sympathetic nervous system blockade	3100
Other nerve blocks	1800

Appendix 4 ATC codes for drugs used to manage chronic pain in study III and IV

ATC-codes (part of)	Description
A04A	Antiemetics and antinauseants
A06A	Drugs for constipation
M01A	Antiinflammatory and antirheumatic products, non-steroids
M02AA	Antiinflammatory preparations, non-steroids for topical use
M02AB	Capsaicin and similar agents
M03A	Muscle relaxants, peripherally acting agents
M03B	Muscle relaxants, centrally acting agents
N02A	Opioids
N02B	Other analgesics and antipyretics
N02C	Antimigraine preparations
N03A	Antiepileptics
N05A	Antipsychotics
N05B	Anxiolytics
N05C	Hypnotics and sedatives
N06A	Antidepressants
N07BC	Drugs used in opioid dependence

Appendix 5 ICD-10 codes related to chronic pain in study III and IV

ICD-Code chapter	Description	Relevance for chronic pain
A00 – B99	Infections	No
C00 – D48	Malignancies	No
D50 – D89	Diseases in blood and immunological system	No
E00 – E90	Endocrine diseases	No
F00 – F03	Dementia	No
F04 – F09	Organic psychosis	No
F10 – F19	Psychological symptoms from drugs	Yes
F20 – F21	Schizophrenic	No
F22 – F29	Psychotic symptoms	Yes
F30 – F39	Depressive and maniac problems	Yes
F40 – F48	Neurotic and stress-related syndromes	Yes
F50 – F59	Behavioral problems and insomnia	Yes
F60 – F69	Personality disorders	No
F70 – F79	Mental retardations	No
F80 – F89	Psychological retardations	No
F90 – F98	Behavioral and emotional problems	No
F99	Unspecific psychological problem	Yes
G00 – G09	Inflammatory diseases in CNS	No
G10 – G14	Atrophic diseases	No
G20 – G26	Diseases in basal gangliae	No
G30 – G32	Degenerative diseases	No
G35 – G37	Demyelinated diseases	No
G40 – G41	Epileptic diseases	No
G43 – G44	Migraine and headache	Yes
G45 – G46	Vascular diseases in the CNS-reactions	No
G47 – G47	Insomnia	Yes
G50 – G59	Mononeuropaties	Yes
G60 – G64	Polyneuropaties	Yes
G70 – G73	neuromuscular transmission diseases	Yes
G80 – G83	Cerebral paresis and hemiparesis	Yes
G90 – G99	Other neurological diseases	Yes
H00 – H59	Eye diseases	No
H60 – H95	Ear diseases	No
I00 – I99	Vascular diseases	No
J00 – J99	Respiratory diseases	No
K00 – K93	Gastrointestinal diseases	No
L00 – L99	Dermatological diseases	No

ICD-Code chapter	Description	Relevance for chronic pain
M00 – M99	Musculoskeletal diseases	Yes
N00 – N99	Urinary tract diseases	No
O00 – O99	Obstetric diseases	No
P00 – P96	Neonatal diseases	No
Q00 - Q99	Congenital problems	No
R00 – R09 R10 – R19 R20 – R23 R25 – R29 R30 – R39 R40 – R46 R47 – R49 R50 – R69 R70 – R89 R90 – R94 R95 – R99	Symptoms from vascular & respiratorysystem Symptoms from gastrointestinal system Symptoms from skin Symptoms from nerve- and musculoskeletal system Symptoms from urinary tract Psychological & behavioral symptoms Symptoms from speech General symptoms Aberrant findings in blood, urine and other bodyfluids Aberrant radiological findings Unknown or not defined causes of death	No No No Yes No Yes No Yes No Yes Yes
S00 – T98	Injuries and intoxications	No
V01 – Y98	External causes of injury and disease	No
Z00 – Z99	Other causes for health-care contact	No

Original articles