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Exploring Integrative Medicine for Back and Neck Pain

On the integration of manual and complementary
therapies in Swedish primary care



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*To my beloved Sofia, Emil and Jonatan
whose love and support made this thesis possible*

The strongest principle of growth lies in the human choice

George Eliot (1819-1880)

Integrate

Combine or be combined to form a whole. Bring or come into equal participation in an institution or body.

Compact Oxford English Dictionary (2010)

Medicine

The science and art dealing with the maintenance of health and the prevention, alleviation or cure of disease.

Merriam-Webster's Medical Dictionary (2010)

Life is short, the art long, opportunity fleeting, experience treacherous and judgement difficult. The physician must be ready, not only to do his duty himself, but also to secure the co-operation of the patient, of the attendants and of externals.

Hippocrates (ca. 460 BC – ca. 370 BC)
Aphorisms, I, 1 (ca. 400 BC)

ABSTRACT

Background and aims: The integration of complementary therapies (CTs) with an emerging evidence base into conventional care services is common, despite limited evidence as to the clinical effectiveness of comprehensive models delivering such care, i.e. integrative medicine (IM). Low back and neck pain (LBP/NP) are two of the most common reasons for people to use CTs. The objectives of this thesis were to develop, implement and explore the relevance of IM as a potential health service option in Swedish primary care.

Methods: Acknowledging IM as a complex health care intervention, both qualitative and quantitative research approaches were used in this thesis. During the development of the IM model, an action research approach with focus groups and key informant meetings with multiple conventional and CT stakeholders was utilised. The development progressed through iterative cycles of data collection, analysis, refinement of strategies and actions following research group consensus, followed by further data collection (immersion/crystallisation). Perceived facilitators, barriers and strategies were identified and findings were categorised within a public health science framework of IM model structures, processes and outcomes. The feasibility and comparative effectiveness of IM vs. conventional primary care was investigated in a pragmatic pilot randomised clinical trial (RCT) of 80 patients with LBP/NP. Parametric and non-parametric statistics were used to explore outcome changes between groups after four months: SF-36 (main); self-rated disability, stress and well-being (0-10 scales), days in pain and the use of health care resources including analgesics, conventional care and CTs. Perspectives on receiving care were explored through focus group discussions with patients from the RCT and analysed by content analysis. A health economic evaluation was conducted alongside the RCT to explore the likelihood of the IM model being a cost-effective health service option.

Results: The developed IM model adhered to standard clinical practice procedures and involved active partnership between a gatekeeping general practitioner collaborating with a team of certified/licensed CT providers (Swedish massage therapy, manipulative therapy/naprapathy, shiatsu, acupuncture and qigong) in a consensus case conference model of care. The implementation of the IM model was feasible and most patients were women with chronic (≥ 3 months) LBP/NP. The conventional care mainly consisted of pain management advice (stay active) and analgesics, occasionally complemented by short-term sick leave or a physiotherapy referral. In addition to this, the IM model integrated seven sessions of two different CTs over 10 weeks on average. It was found that the pilot RCT was underpowered to detect statistically significant differences between groups, and that a full-scale RCT would require a minimum of 120 patients. However, the trend in the clinical quantitative results with an increase in the SF-36 domain "Vitality" and a decrease in the use of analgesics favoured IM. In addition, the qualitative findings indicated that the interviewed patients valued the IM combination of conventional biomedical diagnostic procedures with empowering CT self-help strategies. There was a conservative likelihood (67%) of the IM model being cost-effective at a threshold of EUR 50,000 per quality-adjusted life year gained.

Conclusion: Identification of IM facilitators, barriers and strategies by the different stakeholders contributed to feasible implementation within Swedish primary care. Triangulation of the various results suggests that IM is at least as effective as conventional care, with potential clinical benefits including empowerment and reduced need for analgesics. To verify the relevance of IM in Swedish primary care, future research should prioritise larger trials considering large variability, chronic pain duration, small to moderate effects, indirect costs and longer-term follow-up while adopting a mixed methods approach considering both general and disease-specific outcomes.

Keywords: *Integrative medicine, Primary care, Complementary therapy, Manual therapy, Pragmatic, Randomised clinical trial, Cost-effectiveness, Quality-adjusted life year, SF-36*

LIST OF PAPERS

The thesis is based on the following papers, which will be referred to in the text by their Roman numerals.

- I. Sundberg T, Halpin J, Warenmark A, Falkenberg T.
Towards a model for integrative medicine in Swedish primary care.
BMC Health Services Research 2007, 7:107.
- II. Sundberg T, Petzold M, Wandell P, Rydén A, Falkenberg T.
Exploring integrative medicine for back and neck pain – a pragmatic randomized clinical pilot trial.
BMC Complementary and Alternative medicine 2009, 9:33.
- III. Andersson S, Sundberg T, Johansson E, Falkenberg T.
Patients' experiences and perceptions of integrative care for back and neck pain.
Submitted.
- IV. Sundberg T, Hagberg L, Wandell P, Falkenberg T.
Integrative medicine for back and neck pain – exploring cost-effectiveness alongside a randomized clinical pilot trial.
Manuscript

ABBREVIATIONS

CAM	Complementary and alternative medicine
CEA	Cost-effectiveness analysis
CT	Complementary therapy
CUA	Cost-utility analyses
EBM	Evidence-based medicine
ICER	Incremental cost effectiveness ratio
IM	Integrative medicine
LBP	Low-back pain
NMB	Net monetary benefit
NP	Neck pain
QALY	Quality-adjusted life year
RCT	Randomised clinical trial
SBU	Swedish Council on Technology Assessment in Health Care
SF-36	Short-form 36, a questionnaire targeting health related quality of life
TCM	Traditional Chinese medicine
TM	Traditional medicine
WHO	World Health Organisation

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1 PREFACE

I have been active in the fields of manual medicine and physical training since the early 1990s. Originally trained in the Swedish systems of therapeutic massage and physiotherapy and subsequently in European osteopathy my studies and work has brought me to different countries all with their unique medical systems and healing traditions. Regardless of where I have been visiting, training or practicing, at large university hospitals, private clinics or sports centres, the uncritical enthusiasts as well as the uninformed sceptics confidently proclaiming "*this is how it is...*" have always fascinated me. This has taken me on a parallel journey in medical science. During these travels I have been fortunate to meet and work with numerous talented people and groups. My first "real research" work was in 1998 as a clinician in a Swiss randomised clinical trial (RCT) on physical training and active management of patients with chronic low-back pain (LBP) at the Spine Unit, Schülthess Klinik in Zürich. A few years later I had the pleasure of joining the multidisciplinary Research Group for Studies of Integrative Health Care at Karolinska Institutet in Stockholm. It was here that the idea towards exploring IM in Swedish primary care had previously started as a dialogue out of an academic course about complementary and alternative medicine (CAM). This dialogue had continued with varying intensity under a couple of years within a loose network of clinicians, researchers and students affiliated with the CAM course. I had the privilege to join this network in 2003 and was later trusted to become its research coordinator. In conjunction with this I was also generously awarded PhD funding by Insamlingsstiftelsen för Forskning om Manuella Terapier. By the end of 2004 we had collaboratively managed to build the dialogue into an active clinical research project with external funding and a team of conventional and complementary therapy (CT) clinicians and researchers committed to scientifically explore integrative medicine (IM) as a potential health service option in the Swedish primary care setting. More recently I have had the great honour of being invited as a Swedish representative and temporary advisor to the World Health Organization (WHO) on the topic of "Integration of TM/CAM into national health systems" at the Traditional Medicine (TM) unit at WHO in Geneva, and being invited to present Swedish massage/manual therapy at the first WHO Symposium on Manual Methods of Health care organised by the World Federation of Chiropractic at the WHO Congress on TM in Beijing. These and many other research related activities have been invaluable professional and personal experiences. They have also presented a colourful palette of diverse stakeholders' perspectives on "medicine", medical management and scientific investigation. After bachelor, master and now doctoral studies in medical science I am still fascinated and amazed. The current gap between conventional and CAM/IM needs further attention from a multiple stakeholder perspective in order to create a shared and acceptable scientific evidence base. It is therefore my hope that the research presented in this thesis may be of interest to readers of various backgrounds, not only researchers, but also clinicians, persons with back/neck pain, the public, health care policy and decision makers as well as current and future students in multiple fields of practice.

Let the journey continue.

Tobias Sundberg

Stockholm, January 2010

2 BACKGROUND

2.1 Concepts and frameworks

This thesis set out to explore IM, an emerging area in clinical health care delivery, medical education and research that generally targets an evidence-based approach to the integration of conventional medicine and complementary therapies (CTs) [1]. IM expands on multiple concepts and frameworks in medicine. Approaches to integration may therefore not only relate to the merging of different clinical perspectives and professional specialties, but may also involve different political, theoretical and philosophical aspects. To facilitate the understanding of some of the foundations for IM, and hence this thesis, some basic concepts and frameworks are introduced.

"Medicine" in this thesis is defined as the overarching representation of different therapies, each consisting of different methods combining certain techniques, dealing with the maintenance of health and the prevention, alleviation or cure of disease. Care is defined as the clinical application and delivery of these therapies, methods and techniques to patients.

2.1.1 *Conventional medicine*

Conventional medicine can be referred to as the type of medicine practised by state licensed/registered medical doctors and allied health professionals such as physiotherapists, nurses and psychologists [1-3]. Common characteristics of conventional medical professions in Sweden, which may also be applicable in other countries, include, but are not necessarily limited to: formalised medical training at publicly funded non-profit universities; professional and academic clinical health care degrees at bachelor, master or doctoral level; transparent licensing/regulation procedures at state level organised within the National board of health and welfare (Socialstyrelsen); and clinical practice settings that include non-profit university hospitals and community-based care centres as well as private practices often supported by public funding. There are many synonyms for conventional medicine, e.g. biomedicine, allopathic medicine, western medicine, mainstream medicine, orthodox medicine, regular medicine or in the Scandinavian and Swedish context, "skolmedicin".

2.1.2 *Complementary, alternative and traditional medicine*

Health care practices not generally considered to form part of conventional medical education or practice, and/or not fully integrated into the dominant health care system in a country, and/or not part of a country's own medical tradition, may be referred to as *complementary medicine* [1, 4-6]. Although this may be a very broad definition, a key concept is that there is no conflict in using complementary therapies (CTs) together with conventional care [1]. Notably, many CTs such as massage and manipulative therapies share basic concepts with, and have frameworks similar to those of, conventional medicine, for example, diagnostic and therapeutic rationales based on anatomy, physiology and pathology [7]. However, with few exceptions, such as chiropractors, naprapaths and osteopaths, CT providers generally do not share the same level of education, practice standards and credentialing procedures as conventional health care providers [7, 8]. Hence, CT education and practice are typically characterised by clinical rather than academic or research training at private and fee-paying educational institutions; do not generally have transparent national licensing/regulation procedures at state level organised within a national board of health and welfare. Similarly, most

CT providers are likely to work in private and for-profit contexts since CTs are generally not covered by health insurance [9, 10].

The practice of *alternative medicine* involves using a therapy in place of, rather than as a complement to, conventional care [1]. Alternative medical practices may also include the application of health care procedures with contradictory clinical concepts or philosophical frameworks compared to conventional care. For example, homeopathy is often said to conflict with basic biomedical and scientific concepts to such a degree that leading biomedical journals have published editorials with political statements against its practice, e.g. proclaiming “the end of homeopathy” [11]. Needless to say, the more alternative a therapy is considered to be in relation to conventional medicine, the more difficult it will be for it to gain acceptance in biomedical settings, academia and even in the conventional research community.

Many approaches to medicine, be they considered conventional, complementary or alternative, have their origin in ancient cultural contexts. The concept of *traditional medicine* (TM) hence often refers to health and healing practices that have been used, taught and practised by people where knowledge has been passed on from generation to generation without the influence of conventional or “western” medicine [4, 5]. Some typical examples of what may be considered traditional medical practices in different regions of the world include traditional Chinese medicine (TCM), the ayurvedic tradition in India and the practice of Sami medicine in the northern regions of Scandinavia [12, 13]. However, when a TM health care practice or a selected part thereof is brought into another context or framework, for example when acupuncture originating in TCM is practised as a conventional pain management therapy in a European country, it may be considered a CT rather than a TM practice. This reductionist derivative of a TM practice often involves replacing some or all of the concepts within the original framework with alternatives accepted in the new context. In the case of acupuncture this may be exemplified by “western acupuncturists” adhering to biomedical concepts and clinical reasoning in diagnosis and therapy rather than relying on the original philosophical principles underlying the practice of TCM [14, 15].

2.1.3 Manual medicine

The concept of manual medicine, i.e. manual (“using or working by hand”) [16] and medicine (“the science and art dealing with the maintenance of health and the prevention, alleviation or cure of disease”) [17], is typically characterised by the skilled application of various massage and manipulative therapy techniques [1, 6]. The concept is interesting from several perspectives. One aspect is that different TM traditions, which may involve a multitude of diverse healing practices, seemingly regardless of their developing context or culture, almost always involve manual treatment methods. This may e.g. include the practice of Chinese massage and tuina in TCM [18], ayurvedic massage in India [19] or massage and bone setting, i.e. manipulation of myofascial structures, bones and joints, in European, Latin American and African countries [20-25].

Another aspect is that manual therapies including massage and manipulative therapy have been found to be among the most utilised non-pharmacological practitioner-based therapies [26, 27]. Which types of manual therapies are most commonly used in different countries is likely to depend on both contextual and cultural factors, including the presence of specific proponents. For example, in Sweden the practice and utilisation of Swedish massage is almost twice as popular as other manual therapies, with a lifetime prevalence of about 50%, and there are approximately up to five times as many

certified/licensed providers as there are manual therapy providers such as chiropractors or naprapaths (20% to 30% life time prevalence) [27, 28]. Swedish massage originated in the early 1800s when Pehr Henrik Ling (1776-1839) was one of the first in the world to organise a system of manual therapy and physical exercise in relation to current western concepts of anatomy and physiology, i.e. what was later to become known as the Swedish system of physiotherapy and massage [29, 30]. The therapeutic approach of Ling and his followers grew remarkably and became one of the greatest cultural and scientific exports of Sweden during the 1800s including the publication of several medical textbooks in England, France and USA detailing the practice and science of "medical gymnastics and therapeutic manipulation" [31-35]. Notably, many of Ling's students emigrated to practise in other regions of the world including mainland Europe and the US [29] where they may have influenced other therapeutic approaches including manual medicine. Conversely, it may be interesting to note that one of the most popular systems of manual therapy taught to physiotherapists and physicians internationally today, i.e. the Nordic system of orthopaedic manual therapy, with roots and concepts in the framework of Ling and physiotherapy, also contains clinical influences from osteopathy and chiropractic [36]. Today there are so many concepts and technique similarities within and between the three largest groups of manipulative therapy providers, i.e. the physiotherapy, osteopathic and chiropractic professions, that large-scale clinical research investigating clinical and cost-effectiveness even has utilised a combined approach involving these professions in the delivery of manipulative therapy services [37-39].

A third aspect is that manual medicine enjoys a rather high status compared to many CTs among conventional providers such as physiotherapists and physicians. This may in part relate to that physiotherapists have the option of becoming a specialist in manual therapy after additional postgraduate training [40]. Additionally this may be due to the sharing of basic biomedical and scientific concepts between manual therapy and conventional biomedicine including for example anatomy, physiology, pathology and biomechanics [41]. As such manual medicine may be viewed as a health care practise that fits the definitions of both conventional and complementary care. The osteopathic profession in the US can exemplify this, where by current definition its providers practise a conventional health care profession of equal status as that of allopathic medical doctors [7]. However, when American osteopaths practise osteopathic manual therapy, i.e. the very core of the osteopathic professional identity [42, 43], they are considered to be practising CT [1]. Apparently there are many aspects to the concepts and frameworks of manual medicine, and as such it might be currently best described as being positioned in between conventional and complementary medicine, sharing aspects of both.

2.1.4 Integrative medicine

Integrative medicine (IM) can be defined as an evidence based attempt to integrate conventional medical therapies with CTs [44]. Additionally, there are other proponents that suggest that the concept of IM should not simply involve assimilating CTs into conventional biomedicine focusing on disease and symptomatic treatment, but rather emphasise a framework for true integration focusing on health and healing that may include biomedical as well as CT oriented interventions targeting biological, psychological, social and – if relevant – spiritual aspects of health and illness [45]. In 2009 the US National Library of Medicine included IM as an separate medical subject heading (MeSH) in PubMed, one of the world's most prominent databases of medical research [46].

Researchers have reported large-scale public use and recognition of CTs in western societies in the last decade [26, 47, 48] and it has been estimated that today more than 100 million citizens in the EU are regular users of CTs [49]. Multiple stakeholders including patients, health care providers and allies have changed perspectives regarding CT and IM during this time. This can be exemplified by the increased integration of CTs into conventional care settings, health care organisations and insurance plans [7, 50-53], the increased number of medical training programmes that include courses on CTs and IM [54, 55], as well as academic centres and hospitals integrating selected CTs into their services and research [56, 57]. These trends indicate that there has been a narrowing of the gap between conventional and complementary care, i.e. two previously opposing domains. Possibly due to a combination of consumer pressure and political will on the one hand, and emerging evidence base of effectiveness and safety, and normative recommendations, e.g. by the World Health Assembly [58], on the other.

Sweden and Scandinavia have noted a similar CT trend [28, 59]. In 2000, the recently founded CT centre at Stockholm County Council [27, 60] commissioned a population survey into the public use and recognition of CTs in Stockholm county [27]. The results showed an increased popularity and utilisation of CTs and an increased public demand for collaboration between conventional and CT care providers [27]. The survey findings subsequently contributed to strategic financial support for informing and educating selected health care professionals employed by Stockholm County about CTs and IM. Another survey targeting CT provision within the county councils of Sweden [61] reported that two types of CTs, i.e. massage and acupuncture, were offered in all 16 county councils. Additionally, at least half of all county councils provided an additional range of CTs, provided in various ways by various conventional and CT practitioners [61, 62].

The great diversity of CTs, modes of health care delivery, and the degree of legitimacy and acceptance (or lack thereof) that CTs are afforded in various national policies, reveal that commonly accepted working definitions and terms are lacking, as well as official policies on how various CTs might be applied or integrated in the management of common medical conditions [58, 63-65]. Similarly, the clinical evidence base for comprehensive IM models integrating multiple professional, cultural and philosophical aspects of health and healing in conventional care settings is virtually lacking, especially results from relevant large pragmatic RCTs.

2.1.5 Evidence-based medicine

Examining the references provided by the Cochrane Collaboration, one of the most creditable scientific institutions in the world, on the topic of evidence-based medicine (EBM), it is possible to distinguish three stages defining the framework of EBM [66]. Arranging these stages chronologically by publication date, the first stage is based on the writings of Cochrane in 1972 and target “evidence-based health care”:

“Evidence-based health care is the conscientious use of current best evidence in making decisions about the care of individual patients or the delivery of health services. Current best evidence is up-to-date information from relevant, valid research about the effects of different forms of health care, the potential for harm from exposure to particular agents, the accuracy of diagnostic tests, and the predictive power of prognostic factors.” [67]

As can be seen from the above, Cochrane emphasises the description of current best evidence. The second stage published some 24 years later in 1996 focused on the concept of EBM:

“Evidence-based medicine is the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence-based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research.” [68]

This text builds on Cochrane’s initial writings but adds the notion of the provider’s individual clinical expertise in the decision-making process as well as stating that there is a specific type of research method that produces the best available clinical evidence, i.e. systematic research. The third stage published the following year, in 1997, brought another term into the EBM framework, i.e. “evidence-based clinical practice”:

“Evidence-based clinical practice is an approach to decision-making in which the clinician uses the best evidence available, in consultation with the patient, to decide upon the option which suits that patient best.” [69]

Importantly, this stage actively acknowledges and opens the decision-making process to include the patient. The current framework and concept of EBM employed by the Swedish Council on Technology Assessment in Health Care (SBU) [70] can be summarised in Figure 1 below.

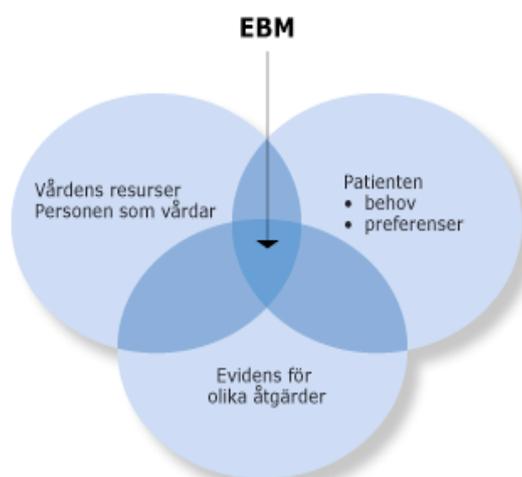


Figure 1. The framework and concept of evidence-based medicine (EBM) proposed by the Swedish Council on Technology Assessment in Health Care. Top left: The health care resources. The provider of care. Top right: The patient’s needs and preferences. Centre: Evidence for different interventions.

It is evident that SBU relates to an EBM framework that acknowledges the writings of Cochrane, Sackett and Gray. Additionally, SBU pays specific attention to health care resources and states that "the goal of EBM is for health care to employ the most beneficial methods" (*“Målet med EBM är att vården använder de metoder som gör störst nytta”*) [70].

Interestingly, in recent years there has been an increased concern that the established EBM framework of a hierarchical evidence-based pyramid, with quantitative systematic reviews and meta-analysis of double or triple blind, placebo-controlled randomised clinical trials at the top and qualitative investigations and clinical case studies at the

bottom, may not be the most appropriate approach for identifying, understanding and appreciating the evidence base for certain health care interventions, especially in terms of the clinical relevance and applicability of CTs [71, 72]. What has instead been discussed is whether a more circular evidence framework which acknowledges that different research questions require different methods. By combining diverse methodological approaches and synthesising their results, i.e. triangulating of various methods and results, a stronger basis, or an “evidence house”, can be provided to enable evidence based decision making in health care [71, 72].

2.1.6 Health systems

The Swedish health system, as those of many other countries, strongly emphasises EBM when making decisions relating to clinical health care delivery [3, 62, 70]. In the Swedish context, at least in theory, this means that registered health care providers are not allowed to practise any form of CT that does not have a solid evidence base proven through rigorous systematic reviews or meta-analysis. In other words, this in effect excludes the application of most TM therapies or CTs within their original conceptual frameworks. Here the Swedish health system differs from that of many other countries where health systems may support the provision of CTs by conventional health care providers, provided that they are safe and that the providers have received the appropriate training/credentials in CT practice [7]. Paradoxically however, in Sweden CT provision outside of the health system is virtually un-regulated. This basically implies that anyone except formal health care professionals can without any kind of medical or even CT training, open a clinic and offer CT treatments to the public. This issue has been debated [62] and there have been attempts to set up a minimum form of control through national register procedures of CT providers fulfilling certain criteria, for example with regard to minimum standards of education, clinical practice, insurance and ethical guidelines [73]. However, so far this process has been rejected, e.g. by the medical establishment itself, without any sustained legislative or regulatory impact in Sweden [73]. In contrast, legislation in Norway has recently been revised so that the current medico-legal framework in fact supports and facilitates increased dialogue, collaboration and integration between conventional and CT practices [73, 74].

Interestingly, from a global health policy perspective, Sweden can be recognised as having a tolerant health system, i.e. the lowest form of integration towards TM/CTs into national health systems [5]. That means a national health system based entirely on conventional medicine, although the practice of TM/CTs is legally tolerated in society. In contrast, many other countries, including western nations such as the UK, Germany, Norway, Canada and USA, are categorised as having inclusive health systems. This implies that TM/CTs are actively recognised and can be integrated into conventional care [5]. However, a fully integrative health care system that officially recognises and incorporates TM/CT practices into all aspects and areas of health care delivery has only been identified in four Asian countries, i.e. China, North and South Korea and Vietnam [5].

2.1.7 Health economics

Limited resources and increasing costs are everyday challenges when making health care decisions at personal, professional and societal levels. There is an obvious need for safe and effective medical interventions. However, there is also a strong need to identify cost-effective, sustainable solutions in health care. Health economics is a field where research questions may be asked to answer whether one type of intervention should be favoured over another, not only in terms of clinical effects, but also in terms of costs

and costs in relation to effects. This type of research has received increasing attention in the last decade and may now be considered a mandatory area complementing conventional approaches to clinical research such as the RCT [75].

There are various approaches to health economic evaluations of clinical interventions. Ideally an economic evaluation should be conducted alongside an RCT. There is also a preference for full rather than partial economic evaluation as the former is considered more valuable in answering research questions targeting resource allocation pertinent to policy- and decision-making in health care [75]. To be considered a full economic evaluation the analysis must include at least two different interventions and assess both the costs and the consequences, i.e. effects, of those interventions [75].

The most commonly used full economic evaluations include cost-effectiveness analysis (CEA) and cost-utility analysis (CUA) [75, 76]. Effects in CEA are commonly evaluated by disorder-specific outcomes such as pain, function and disability [75]. A cost-effectiveness ratio is then calculated by relating the incremental treatment effects to the incremental cost. In CUA effects are not expressed as disorder-specific outcomes but as quality-adjusted life years (QALYs) [76]. A QALY is an outcome based on patients' preferences that relates to both the quality and the quantity of life produced by different interventions by putting a weight on time in different states of health [77, 78], for example by rating (visual analogue scale), risk (standard gamble), or time preferences (time trade off). This produces a "common currency" used to assess the potential benefits gained from different treatments over time. One year in full health equals one QALY. Results from CUA studies are presented as cost per QALY gained. In reality it may be difficult to attain the full spectrum of costs and benefits relating to different disorders and interventions. CEA and CUA may then provide good starting points for identifying patterns of current best evidence before making decisions in the rapidly changing health care arena.

2.2 Complex health interventions

2.2.1 What is it?

Clinical health care interventions such as surgery, physiotherapy, manual therapy or the integration of conventional care and CTs are characterised by multi-component service strategies [71, 72, 79, 80]. Hence, by definition, these types of health interventions are also likely to have complex mechanisms of action compared to single-component interventions such as the delivery of single pharmacologically active drugs. Thus, it may be argued that complex health interventions might require different research approaches compared to single-component interventions with fewer plausible, often biologically based, mechanisms of action. Whole systems research is an investigative approach that acknowledges that complex health interventions with multiple components require multiple perspectives in order to be adequately understood [71, 72, 79, 80]. Such research perspectives may involve exploratory, explanatory and pragmatic studies.

2.2.2 Exploratory, explanatory and pragmatic

Research that investigate phenomenon, interventions or procedures of which little is known can be defined as exploratory studies [81]. Qualitative research approaches such as collecting data through focus group discussions and interviews are often part of clinical exploratory designs and the analytical process may be tailored to facilitate the generation of new hypotheses. As research progress follow-up studies may then be aimed at verifying and confirming findings and hypothesis gained from earlier studies.

Explanatory studies are scientific investigations generally designed as quantitative RCTs focusing on placebo-controlled comparisons of isolated compounds in an attempt to isolate specific biological effects such as changes in certain biomarker levels. Specific efficacy studies, for example, are highly focused on explaining “how” (cause and effect) a specific treatment might work [82, 83]. Explanatory trials strive to achieve the highest possible internal validity and are therefore often highly standardised operating procedures in controlled laboratory settings.

Investigations of complex health interventions on the other hand are typically designed as clinical effectiveness trials looking at “if” a certain treatment works in relation to another as they are delivered in clinical settings. These trials are often conducted in less constrained settings, such as real-world primary care practices, and intervention procedures are often allowed to be modified according to patients’ ongoing needs and concerns during the course of the study. Such investigations are defined as having a pragmatic approach [82, 83]. Pragmatic clinical trials are thus less bound to standardisation of procedures, i.e. internal validity decreases in favour of reaching a higher external validity and achieving possibilities for clinical generalisation of findings. Similarly, the decision to use a pragmatic design is often accompanied by a shift from studying specific efficacy outcomes, for example isolated biological effects, to exploring and comparing the general clinical effectiveness in terms of e.g. pain, function, health related quality of life or utilisation of health care resources. It has been suggested that more studies that reflect the clinical situation and context in usual care settings are needed to appropriately estimate potential CT benefits and inform valid decision-making in health care in the future [71, 82, 83].

2.2.3 Specific vs. non-specific effects and placebo

During the process of care, specific pharmacological and physiological as well as non-specific or psychological mechanisms of action may take place which could affect the effectiveness of an intervention. The clinical effects of care through complex health interventions are hence likely to be the result of a different combination of mechanisms compared to those of singular interventions. The less explanatory the design of the intervention is, the more likely it is that a proportion of the results can be explained by non-specific rather than specific effects [71, 82, 84].

The concept of placebo (“to please”) is often included in the framework of non-specific effects. Placebos may be described as sham treatments, such as the “sugar pill”, without any known specific mechanism of action for the disease or symptom under investigation. However, the placebo may still have a clinical therapeutic effect, for example due to the patient’s relationship with the health care provider, which in turn might involve various degrees of attention and care that can influence the patient’s expectations, anxiety or awareness [85]. Outcome changes which are attributed to these types of non-specific effects are known as “placebo effects”. It has been discussed that CTs may involve management characteristics that are especially good at heighten placebo effects [85] hence possibilities for positive outcome changes despite (at least partly) lacking plausible mechanisms of action. However, as placebo response is a "free add-on to any well administered treatment", it has been argued that the promotion of therapies likely relying on non-specific placebo effects should be avoided [86]. Hence, the importance of relevant and rigorous research to detail mechanisms of action as well as clinical effectiveness.

2.3 Back and neck pain

2.3.1 Definitions, prevalence and costs

As previously stated, conventional, manual and complementary medicine may differ with regard to concepts and frameworks. Consequently, definitions of back and neck pain may also differ based on for example what type of health care provider is making the diagnosis and in what context and culture. For example, a certain type of manual therapist or CT provider, employing that therapy's unique explanatory models, diagnostic procedures and terminology, may define and explain back and neck pain differently than a general practitioner or orthopaedic surgeon in a conventional care context.

The term "back pain" in conventional care typically denotes the lower back, i.e. the lumbar region from the costal margins at the thoraco-lumbar junction down to the pelvis and the inferior gluteal folds [87]. Similarly, "neck pain" generally refers to pain in the cervical region between the occipital bone at the base of the head and the top of the shoulders and the upper thoracic spine. However, perceived low back and neck pain (LBP/NP) frequently covers more than just one segment or area of the spine as the pain might be both localised and referred. This often brings additional labels into defining and describing the pain patterns, for example referring to terms such as lumbago-ischias or sciatica when describing pain in the lower back that radiates down the leg.

The International Association for the Study of Pain (IASP) defines pain as: "*An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.*" [88]. For the working clinician or the person suffering from back or neck pain it is more commonly described as pain, muscle tension or stiffness localised to the low back or the neck [87, 89]. Interestingly, for about 90% of all patients seeking care for back pain there is no pathological-anatomical cause, i.e. they suffer from what has been termed non-specific LBP/NP [87, 89]. Hence, instead of classifying the pain according to the pathological structures at fault, non-specific LBP/NP is classified in relation to the duration of symptoms. Typical distinctions are made between acute and chronic back/neck pain. The acute pain phase has been defined as the first three to six weeks, whereas chronic pain refers to a duration of at least three months [90, 91]. Consequently, pain duration between the acute and chronic phases is defined as sub-acute.

LBP and NP are generally very common in high income countries and conventionally managed in primary care. The conditions cause disability and decreased quality of life and impose high costs on society [75, 90, 92, 93]. According to the Swedish Health Technology Assessment Board (SBU) the societal cost of back and neck pain reached SEK 29.4 billion in the mid 1990s [90]. The reported prevalence for LBP/NP varies highly reflecting a lack of consensus on how to define LBP/NP in terms of for example duration, frequency, intensity, location and disability etc among different studies. However, in adult populations the lifetime prevalence of LBP has been estimated being up to 60-85%, one month prevalence about 19-43%, and the point prevalence 15-30% [90, 94]. Recurrences of pain are not uncommon and research targeting LBP in primary care has concluded that many patients still have pain and related disability one year after consultation [95]. Similarly, it has been reasoned that LBP do not necessarily resolve itself over time if ignored [96]. Studies of NP prevalence also show a high variability with lifetime estimates ranging from 50-70%, prevalence measures less than one year are highly variable and it is difficult to draw any definite conclusions [90].

2.3.2 Conventional primary care and evidence-based guidelines

The management of LBP/NP in primary care is guided by evidence-based guidelines summarising what may be considered as the current best evidence. Current conventional primary care guidelines for the management of non-specific back and neck pain typically involve recommending that sufferers stay active and continue their day-to-day activities as far possible [90, 97]. Additionally, physicians may prescribe analgesics or complement management with referrals to allied health professions such as physiotherapists or occasionally recommend short-term sick leave. The guidelines differ slightly for acute vs. sub-acute and chronic duration of LBP/NP. Generally the guidelines for acute LBP/NP pain management focus more on methods for pain reduction, whereas guidelines for more chronic pain have an increased focus on functional restoration and multidisciplinary rehabilitation [72]. The integration of CTs in LBP/NP management guidelines is relatively sparse, although manipulation and mobilisation may be included in some countries [72, 90].

2.3.3 Manual and complementary care and emerging evidence base

Two of the most common reasons why patients seek help outside conventional care are LBP/NP [26, 27]. Apparently, from a health seeking behaviour there seems to be a public need for additional health service options in the management of LPB/NP. There are various reasons for patients turning to non-conventional therapies such as manual and complementary care. Research suggests that a wish to reduce negative side effects of conventional care and a lack of results from biomedical treatments may be important factors, as well as recommendations from colleagues and friends [98, 99]. Nevertheless, other research suggests that the majority of people turning to non-conventional therapies do so not because they are dissatisfied with conventional care but because they find CTs to be more congruent with their personal values, beliefs and philosophical orientation toward health and life [100, 101].

The most commonly used provider-based CTs are manual therapies including massage and manipulative therapy [26, 27]. Other popular CTs include acupuncture and activity-based CTs such as qigong. Emerging evidence indicating safety and effectiveness has been described for several of these therapies in the management of common primary care diagnoses such as LBP/NP, notably also in multimodal rehabilitation [6, 84, 90, 102-110]. Hence, an emerging evidence base for the integration of manual and CT management of LBP/NP is supported by recent research including data from systematic reviews/meta-analysis justifying their inclusion as therapies in the exploration of IM as a potential health service option.

3 AIM AND OBJECTIVES

The general aim of this thesis was to explore the relevance of IM as a health service option in Swedish primary care.

The specific objectives included:

- I. To develop a consensus-based IM model adapted to Swedish primary care adhering to multiple stakeholders' perspectives including researchers, conventional care and CT providers.
- II. To investigate the feasibility of implementing and testing the IM model's comparative effectiveness vs. conventional primary care in the management of patients with sub-acute to chronic non-specific LBP/NP in a pragmatic pilot RCT.
- III. To explore patients' experiences and perceptions of receiving conventional and complementary care and to identify care characteristics that can be used to describe IM management of sub-acute to chronic non-specific LBP/NP.
- IV. To evaluate the likelihood of IM being a cost-effective health service option compared to conventional management of patients with sub-acute to chronic non-specific LBP/NP.

4 METHODS

4.1 Design and setting (I-IV)

The general methodological strategy of the IM research project was to design the studies to gain a broad understanding of IM in the Swedish primary care setting. Accordingly, acknowledging IM as a complex health care intervention [71, 72, 79, 80], both qualitative and quantitative approaches were used.

In brief, the mix of study designs was combined in the following way: A qualitative health system research approach was initially used to develop the IM model (Paper I). The IM model was then implemented and tested compared to conventional primary care in the management of patients with sub-acute to chronic non-specific LBP/NP using a pragmatic RCT approach with quantitative outcome measures (Paper II). This was followed by a qualitative study conducting FGDs with patients from the RCT, exploring their experiences and perceptions of receiving conventional and complementary care (Paper III). Lastly a health economic evaluation was conducted alongside the pilot RCT to explore the likelihood of IM proving a cost-effective health care service option in Swedish primary care (Paper IV). Notably, this way of combining qualitative and quantitative research methodologies, often known as triangulation, has been suggested to generate broader evidence-based knowledge on the use of CTs and other interventions in clinical health care compared to research strategies using a single methodological approach [71, 81].

4.2 Participants, recruitment and interventions (I-III)

Different participant and recruitment strategies were employed during the IM project. Participants who took part in developing the IM model in the first study (Paper I) included a core group of about 15 professionals, including health care researchers, conventional and CT providers and primary care administrators/management. About 8-10 of these professionals were also part of the clinical IM team that was to deliver care in the subsequent RCT. Additional participants varied over time but included general practitioners, medical specialists in neurology, orthopaedics and physiotherapy as well as policy- and decision-makers at county council level. The identification and recruitment of most of these participants relied on snowballing procedures [81] initiated through the research group's academic and clinical contacts in the greater Stockholm area.

In the second study (Paper II) there were three main groups of participants. First, the IM team that had been recruited during the development of the IM model. Second, a network of 35 general practitioners who could refer patients to the pilot RCT were recruited following information meetings at four local primary care units in the same geographical area. Third, 80 patients with LBP/NP were recruited to the study to be randomised to receive either continued conventional care or the IM model of care. The main inclusion criteria were that patients were 18-65 years of age, diagnosed with non-specific LBP/NP of at least two weeks' duration, had consulted one of the participating general practitioners and been given a conventional care treatment plan. Known pathology or severe causes of LBP/NP including progressive neurological symptoms were reasons for exclusion.

To recruit informants to the third study (Paper III) all patients who had participated in the pilot RCT and completed the follow-up after four months were invited to FGDs to

share their experiences and perceptions of receiving conventional and complementary care for LBP/NP. Twenty-six of 63 patients volunteered to participate in the FGDs. Notably, there was no kind of financial or other type of compensation for participating in these discussions.

The two interventions in the IM project were pragmatic in nature and consisted of “usual primary care” and the IM model of care. In short, the usual primary care was the conventional care adhered to by the participating primary care units’ clinical practice procedures applying the county councils’ clinical practice guidelines, i.e. typically advice (stay active), drug prescription (analgesics), sick leave (limited) and/or physiotherapy (activity-based) [111]. The IM model of care (Paper I) involved consensus-based IM team conferences intended to integrate CTs into the conventional care treatment plan for a period of up to 12 weeks. The selected CTs with an emerging evidence base included Swedish massage therapy, manipulative therapy, shiatsu, acupuncture and qigong [104, 106, 112-119]. There were no specific constraints applied to the administered treatments for either intervention during the research project, as the goal was to pragmatically reflect usual and IM management as far as possible.

4.3 Qualitative procedures and analyses (I, III)

The development of the IM model (I) was a highly clinical process. A qualitative study design [81] with an action research approach [120, 121] was used to develop the IM model on site in the clinical setting of a Swedish primary care unit.

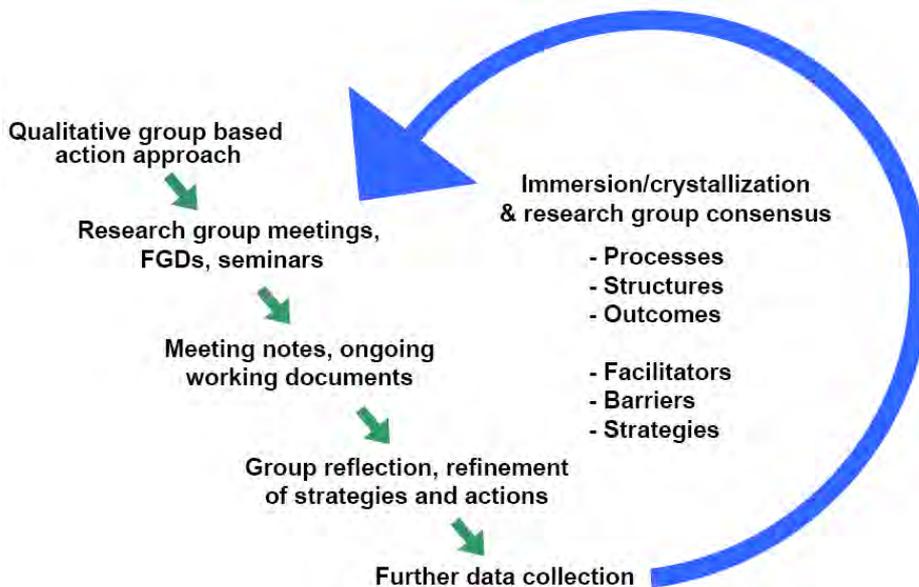


Figure 2. An outline of the qualitative procedures and analyses developing the IM model.

Through multiple cycles of clinical group meetings and discussions with various stakeholders the research group tried to gather increasingly focused information in order to exclude certain working possibilities and include others. As part of this process, different stakeholders’ perceptions and experiences relating to the integration of conventional care and CTs were discussed at patient-, provider- and Swedish health system-level. A public health science framework which specified processes, structures and outcomes of the IM model was used to guide the process [122, 123]. Perceived

facilitators, barriers and strategies for IM model development and implementation were discussed to aid clinical interpretation and applicability in the Swedish primary care setting. Data from group meetings included digital recordings and meeting notes which were used as ongoing working documents within the research group (I). The analytical process was based on the principles of immersion/crystallisation [124, 125] and research group consensus [63]. Immersion/crystallisation is a methodological strategy used in clinical primary care research entailing repetitive cycles of data collection, analysis, reflection and refinement of strategies and actions, followed by further data collection [124, 125]. A consensus approach, arrived at by means of participatory input from the research group was considered essential, as the IM model aimed for integration rather than parallel practice of conventional and CT care [63].

Patients' experiences and perceptions of receiving conventional and complementary care were investigated by conducting FGDs [126, 127] on site at one of the participating primary care units (Paper III). All patients having completed the RCT were invited to participate in the FGDs after completion of the four months follow-up. Informants were interviewed in separate groups depending on group allocation in the pilot RCT (Paper II), i.e. five FGDs with a total of 11 informants from the conventional arm, and six FGDs with a total of 15 informants from the integrative arm. After an initial welcome procedure and a general introduction the moderator opened the FGDs by presenting the discussion topic and asking a broad open question, e.g. "Please tell us about your experiences and perceptions of the care that you have received for your LBP/NP". This was followed by open discussions exploring the informants' perspectives. Probes such as "where-what-why-how" in relation to the informants' discussion topics were used as required for more in-depth exploration. All focus groups were scheduled to last one hour, conducted in Swedish, digitally audio-recorded and transcribed verbatim. Subsequently the transcripts were spot-checked for accuracy and, once finalised, the identities of all informants were removed. Latent content analysis was the principle method used to analyse the FGD data [128]. The transcripts were read through multiple times to gain an overall perspective and initial thoughts. The transcripts were then imported into Open Code [129], a software designed for qualitative analysis, where meaning units can be digitally marked and condensed into codes. An aggregated dataset of meaning units and codes from all FGDs were subsequently used to compare and structure codes into sub-categories. The sub-categories were merged into categories after which one overarching theme emerged. The analytical process from coding to categorisation was performed inductively in several stages, moving back and forth between latent and manifest content analysis [128], with simultaneous access to the original meaning units and the codes. The final sub-categories, categories and theme were achieved by research group consensus.

4.4 Quantitative outcomes and statistics (II, IV)

The reliable and valid SF-36 questionnaire targeting eight health-related quality-of-life domains (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health) [130-132] was the main outcome measure used to investigate the feasibility and comparative effectiveness of the IM model vs. conventional primary care management for patients with sub-acute to chronic non-specific LBP/NP (Paper II). A set of clinically derived but not scientifically validated project-specific "IM-tailored outcomes" based on input from the research group was used as secondary outcomes. These targeted self-reported disability, stress, well-being (0-10 numerical rating scales), days in pain and the use of prescription and non-prescription analgesics, conventional care and CTs (outside the IM model).

Postal questionnaires administered outside the participating primary care units were used to collect the data and outcome changes between baseline and follow-up after four months were used to explore and compare the results between the IM and conventional care groups (Paper II). The Mann-Whitney test was used to perform statistical analyses of differences between the groups for ordinal data (SF-36 and numerical rating scales) and the two-sample t-test was used to analyse number of days in pain. Dichotomous variables were analysed by univariate and multivariate logistic regression models. All patients were kept in their assigned groups. Patients lost to follow-up, i.e. observations with missing data, were excluded from the primary analyses. To comply with a more comprehensive intention-to-treat strategy, a secondary analysis was performed where the last observed measures were imputed for missing data. A significance level of 5% was used and 95% confidence intervals were reported. All p-value calculations were two-tailed.

The economic evaluation (Paper IV) was conducted as a cost-utility analysis (CUA) [75, 76] alongside the RCT (Paper II). Costs were primarily estimated from a health care service perspective, and included the costs of planning and delivering integrative care and the costs of using selected health care resources, i.e. conventional care, CTs (outside the IM model), prescription and non-prescription analgesics. Health economic data was derived both via questionnaires administered at baseline and at follow-up after four months in the pilot RCT (SF-36 and use of health care resources) as well as from national county council salary data [133] and drug recommendations for pain management [134] paired with cost data acquired from the Swedish pharmaceuticals company Apoteket AB [135] where standard dosages and packages were assumed [136].

The SF-36 instrument [130-132] was used to measure and ascribe values to patient health states. SF-6D utility scores were then derived from the SF-36 data [137] to facilitate calculations of gained QALYs between baseline and follow-up (please see section 2.1.7 for a brief explanation of QALYs). When mean differences in costs and effects (QALYS gained) between groups were estimated, the incremental cost-effectiveness ratio (ICER) could be calculated. However, to account for the uncertainty and variability of the pilot trial data, the net monetary benefit method (NMB) [138, 139] was used in the analysis. The NMB expresses the likelihood that an intervention is cost-effective in relation to another intervention based on replacing the health effects with the maximum amount decision-makers are willing to pay for one gained QALY, i.e. euro (EUR) 50,000 in the current evaluation (base case) [140]. By expressing all costs and consequences as monetary values, the accuracy of estimating that an intervention is cost-effective in relation to a competing intervention may increase, i.e. the probability of cost-effectiveness, or the likelihood that NMB for IM is to be preferred compared to the NMB of conventional care, given a certain level of willingness to pay for a QALY.

Additionally, as the pilot RCT was underpowered to detect statistically significant differences between groups, the economic evaluation in Paper IV focused on identifying the direction of cost-effectiveness by presenting outcomes in probabilistic terms, i.e. the likelihood (as a %) that integrative care would be cost-effective, rather than presenting traditional hypothesis-testing of statistically significant differences between groups [141]. Using non-parametric bootstrapping a scatter plot of 5,000 bootstrapped ICERs was used by repeatedly drawing a random sample with replacement from the randomised clinical trial producing estimates of the average NMB, the associated 95% confidence intervals and the likelihood of the proposed integrative model to be cost-effective compared to conventional care for the selected economic threshold value of a QALY gained. The level of significance was set at 5%. The costs and effects were

projected over a one-year period without any discounting and the economic evaluation followed an “intention-to-treat” strategy. All patients were kept in their assigned groups. If data was missing, a basic conservative approach with constant and non-random single imputation procedures was utilised, i.e. mean substitution at baseline and last observation carried forward at follow-up [142]. To explore the impact of imputation of missing data on the probability of cost-effectiveness, a secondary “complete case” analysis was made including only the cases with complete cost-effectiveness data.

4.5 Ethics (I-IV)

The IM research project was approved by the regional ethics committee at Karolinska Institutet (Dnr: 668-03, 650-04 and 121-32). In accordance with the Helsinki declaration, all participation was completely voluntary. Patients received oral and written information about the research project from an external research unit at Karolinska Institutet independent of the patient-physician relationship, and patients had to grant written informed consent before inclusion. Patients were free to withdraw from the study at any time without having to state a reason, thereby ensuring no interference with the patient-physician relationship nor negative consequences for the patients’ health care.

5 RESULTS

5.1 The integrative medicine model (I)

The aim of the first study was to investigate a consensus-based IM model adapted to Swedish primary care adhering to multiple stakeholders' perspectives including researchers, conventional care and CT providers.

The answer was an IM model outcome that was characterised by a team-based integrative care process, intended to deliver a patient-centred mix of conventional and complementary medical solutions facilitated through consensus case conferences, managing patients with non-specific LBP/NP of at least at least two weeks' duration (Figure 3).

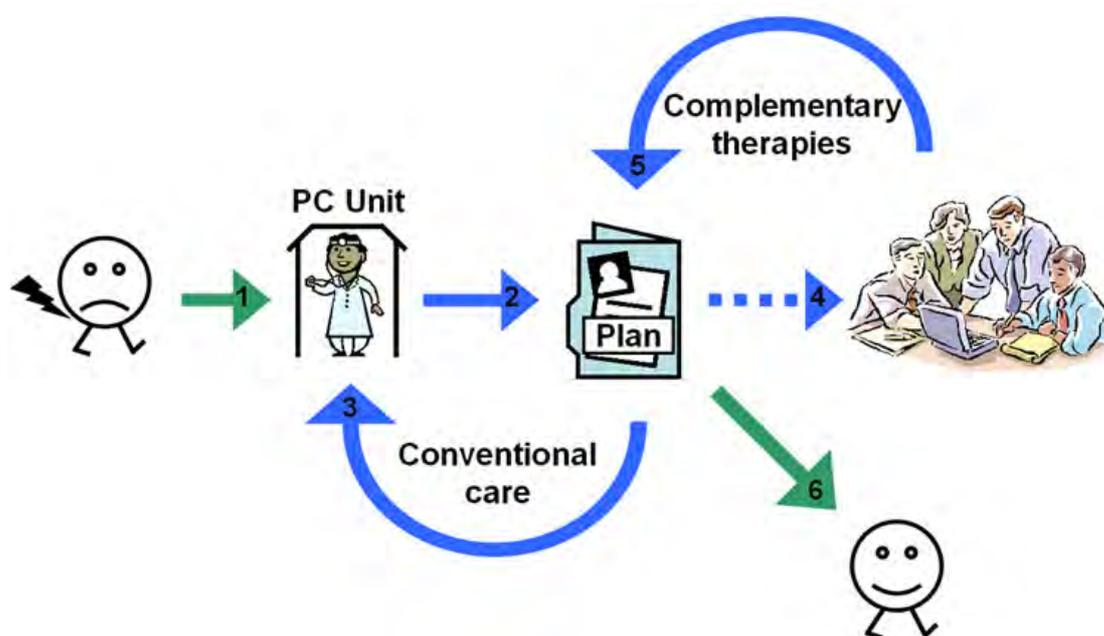


Figure 3. The integrative medicine (IM) care process. The IM model adapted to Swedish primary care illustrated as a clinical case management flowchart: 1) The patient with sub-acute to chronic non-specific LBP/NP consults the gatekeeping general practitioner at the primary care unit; 2) The general practitioner develops a conventional care treatment plan in dialogue with the patient; 3) The patient goes through the conventional care process, i.e. “treatment as usual”; 4) Should CTs be considered appropriate, these are integrated into the treatment plan by way of a consensus case conference with the IM provider team; 5) The patient receives CTs as an integrated part of the treatment plan, i.e. the integrative care process is initiated; 6) When the treatment plan is completed the case management is finished. Please note that integrative care was only delivered for up to 12 weeks. PC Unit, primary care unit.

Adhering to the Stockholm county council's clinical practice guidelines [111] the general practitioner of the IM team was assigned a gatekeeping role with overall medical responsibility for patients. The general practitioner's clinical role was to administer conventional care treatment plans and to discuss the appropriateness of integrating selected CTs in dialogue with the patients and the IM team. Cases where CTs were to be integrated into the treatment plans (please note that during the IM research project this was decided by randomisation) were discussed every two to three weeks in consensus case conferences with the whole IM provider team. During the conferences the general practitioner introduced a new case to the other team members by means of a presentation of the initial medical consultation with the patient and the set up of the conventional care treatment plan. The other team members then gave their

input and through the consensus case discussions that followed the IM team collaboratively identified treatment strategies tailored to the individual patient's ongoing needs and concerns. The patients participated in the health care process through personal interaction with the general practitioner and the CT providers during consultations. The IM management had a limitation of 12 weeks and 10 CT treatment sessions during the research project. Figure 3 describes the IM care process in the individual case management of patients with LBP/NP.

The IM model was developed through a number of key processes, i.e. research group activities, including regular meetings and educational seminars; snowballing for providers; deciding a target group and diagnostic criteria for patients; assessment of conventional and CT documentation procedures; the development of a project-specific documentation system with detailed IM patient records; testing and modifying logistical procedures including external and internal referrals and report mechanisms in relation to the inclusion and discharge of patients; and the identification of clinical outcome measures. An important structure of the IM model was the set up of the IM team, which crystallised as a general practitioner with knowledge of CTs and eight experienced CT providers with basic training in biomedicine. The represented CTs were Swedish massage therapy, manipulative therapy, shiatsu, acupuncture and qigong, i.e. both individual CTs and group-based self-help services were considered important in representing complementary aspects of care in the IM model. The integrative care was physically delivered using the structure of a conventional primary care unit and a decentralised network of external CT practices. This was supported by a referral network structure of general practitioners from four neighbouring primary care units. External funding was another structure that enabled CT patient fees to be set at a comfortable level in relation to conventional primary care fees.

Facilitators, barriers and strategies

Combining conventional and CT clinical reasoning with a non-hierarchical, open, continuous and parallel interchange of ideas through the consensus case conferences was positively experienced by the IM provider team, for example in increased team-building and cross-fertilisation of ideas, leading to a perceived increase in diagnostic and therapeutic team capacities to verify and improve the ongoing clinical management of the patient. Examples of additional facilitators, as well as barriers and strategies to developing and implementing IM in Swedish primary care are presented in Table 1.

Table 1. Stakeholder perspectives. Summary of conventional care (CC), complementary therapy (CT) and research (RES) stakeholder perspectives on facilitators, barriers and strategies for developing and implementing a model of integrative medicine (IM) in Swedish primary care.

	Facilitators	Barriers	Strategies
CC	<ul style="list-style-type: none"> - Documented public desire for increased collaboration - Limitations of conventional care in certain areas/cases - Personal interest in providing more holistic primary care - Improve knowledge, evidence base and recognition of IM 	<ul style="list-style-type: none"> - Lack of knowledge and expertise - Primary care resources - No formal IM recognition in Sweden - Scientific evidence base - Large variation of CT terminologies and documentation routines - The Swedish Health Services Act 	<ul style="list-style-type: none"> - General practitioner gatekeeper with CT interest, knowledge and experience of leading the clinical section - General practitioner meetings with management/administration about resource allocation and logistics - Priority of reimbursing CT providers - Part-time provider commitment - Ethical clearance
CT	<ul style="list-style-type: none"> - Increase respect for patients' treatment choices - CT access to interdisciplinary cooperation - Represent different medical models within Swedish primary care - Extend the evidence-based medicine concept - Improve national awareness and recognition of existing international IM practices - Improve focus on care, health promotion and prevention 	<ul style="list-style-type: none"> - Value added tax (25%) on CTs and no public insurance policy for CTs - No official recognition of CT professions - Interdisciplinary dialogue rare - Unfamiliarity with primary care documentation routines - The Swedish Health Services Act 	<ul style="list-style-type: none"> - CT providers with experience of sharing cases with conventional providers - An IM model broad enough to encompass all selected CTs/medical models - Consensus case conferences to facilitate and document interdisciplinary dialogue - Part time CT provider commitment - Include quality of life, stress and well-being outcomes
RES	<ul style="list-style-type: none"> - Explore stakeholder perspectives on IM in Swedish primary care - Explore patient experiences of integration of complementary therapies in primary care - Explore general clinical effectiveness of the IM model vs. treatment as usual - Improve the evidence base for integration of CTs into primary care 	<ul style="list-style-type: none"> - Limited evidence base for IM - Lack of published randomised clinical trials of IM in primary care - Difficulties in obtaining research funding - Unknown recruitment speed and recruitment pattern of patients - No pre-defined or given set of outcomes - No established referral network 	<ul style="list-style-type: none"> - Initial core group development meetings to facilitate research project - Include both qualitative and quantitative methods of evaluation - Information and educational seminars to improve understanding between stakeholders and facilitate shared documentation routines - Continuous grant writing to secure funding - Referral network of primary care units

5.2 A pragmatic pilot randomised clinical trial (II)

In the second study the aim was to investigate the feasibility of implementing and testing the IM model's comparative effectiveness vs. conventional primary care in the management of patients with sub-acute to chronic non-specific LBP/NP in a pragmatic pilot RCT. Of specific interest were patient and care characteristics, recruitment and retention rates, clinical differences and effect sizes between groups, and calculation of the adequate sample size for a full-scale trial supported by selected outcome measures and collected data.

Seventy-five percent (80/107) of patients seeking help for LBP/NP at the participating primary care units were eligible and feasible for inclusion in the pilot RCT. Baseline characteristics are presented in Table 2.

Table 2. Baseline characteristics of study participants by randomised groups.

	Conventional care (n 36)	Integrative care (n 44)
Age, mean (SD)	41.1 (10.4)	40.3 (9.4)
Female	72%	73%
EU nationality	89%	81%
Location of worst pain		
Low back	53%	52%
Neck	33%	36%
Low back and neck	14%	11%
Duration of pain		
Two weeks to three months	17%	12%
Three months or longer	83%	88%
SF-36 Health related quality of life*		
Physical functioning	69.4 (17.3)	70.1 (24.4)
Role physical	21.5 (33.4)	29.0 (35.3)
Bodily pain	32.0 (14.5)	34.0 (19.1)
General health	55.1 (18.6)	56.4 (24.0)
Vitality	36.4 (16.6)	32.3 (23.3)
Social functioning	61.5 (24.2)	56.3 (30.0)
Role emotional	54.2 (39.9)	58.3 (43.2)
Mental health	63.1 (19.3)	61.1 (21.2)
Days with pain over the last two weeks (0-14)	12.1 (2.8)	11.8 (3.8)
Disability due to back/neck pain (0-10)**	5.4 (2.6)	5.4 (3.0)
Stress (0-10)**	5.2 (2.7)	5.6 (2.7)
Well-being (0-10)**	4.8 (1.9)	5.1 (2.3)
Used health care resources over the last 2 weeks		
Prescription analgesics	54%	45%
Non-prescription analgesics	57%	63%
Conventional care	61%	65%
Complementary care	26%	20%

*Figures stated as mean (standard deviation) values and as proportions (%). *SF-36 quality of life domains, min-max score from 0 (worst) to 100 (best). **The anchors for the numerical ratings scales were 0 (zero) to 10 (maximum) levels of disability, stress and well-being respectively. There were no statistically significant differences between the randomised groups.*

Eighty-two percent (36/44) of IM and 75% (27/36) of conventional care patients completed follow-up after four months. In general the outcome effect size analyses showed large response variability with both types of care being equally as effective with no statistically significant differences between groups. A secondary intention-to-treat analysis where the last observed measures were imputed for missing data did not change the results and there was a lack of statistically significant differences between the groups.

Vitality was the only domain of the main outcome measure (SF-36) that was supported by both a clinically relevant difference between groups [143, 144] and a small to moderate distribution-based effect size [145], i.e. -7.27 points (Cohen's *d* -0.34), which was in favour of IM (Table 3). Secondary outcomes in terms of self-rated disability and stress returned small clinical differences (0.66 and 1.18 points) and small effect sizes (Cohen's *d* 0.23 and 0.43) between groups supporting IM.

Sample size calculations for SF-36 (vitality) with 80% power, 5% significance, a 10 points clinical difference in change over time between groups [143, 144] and the standard deviations derived from the pilot trial data, demonstrated the need for a minimum of 60 patients per arm to adequately power a future large-scale trial. If the need for a distribution-based effect size was ignored, SF-36 role emotion might be an alternative option for sample size calculations, returning a need for at least 339 patients per arm. Notably, the other six SF-36 domains did not show any relevant clinical or distribution-based effect size differences between groups (Table 3).

Table 3. Change in SF-36, numerical rating scales and days in pain from baseline to follow-up after four months (Paper II).

Outcome measure	Conventional care		Integrative care		Conventional vs. Integrative care		
	Mean (SD)	N	Mean (SD)	N	Diff.	<i>d</i>	P
Physical functioning*	10.99 (16.77)	27	9.08 (13.15)	35	1.91	0.09	0.920
Role physical*	28.70 (46.88)	27	29.17 (39.42)	36	-0.46	-0.01	0.875
Bodily pain*	19.11 (22.48)	27	21.17 (23.43)	36	-2.06	-0.12	0.813
General health*	7.46 (21.01)	26	6.08 (10.78)	36	1.39	0.06	0.502
Vitality*	12.16 (16.63)	27	19.43 (21.82)	35	-7.27	-0.34	0.237
Social functioning*	13.43 (21.91)	27	14.58 (21.02)	36	-1.16	-0.04	0.703
Role emotional*	16.05 (44.69)	27	8.33 (48.06)	36	7.72	0.18	0.872
Mental health*	5.56 (18.94)	27	7.29 (15.98)	35	-1.73	-0.09	0.326
Disability (a)	-1.23 (3.46)	26	-1.89 (2.94)	36	0.66	0.23	0.458
Stress (b)	0.23 (2.75)	26	-0.94 (2.15)	36	1.18	0.43	0.090
Well-being (c)	1.46 (2.06)	26	1.53 (2.13)	36	-0.07	-0.03	0.873
Days with pain (d)	-3.12 (4.66)	26	-3.83 (5.48)	35	0.71	0.19	0.595

*SF-36 health domains, min-max score from 0 (worst) to 100 (best). Numerical rating scales targeting: (a) disability in activities of daily living due to back/neck pain; (b) perceived stress; (c) well-being. The anchors for the numerical ratings scales were 0 (nothing) to 10 (maximum) levels of disability, stress and well-being respectively. (d) Days with pain over the last two weeks (0-14). SD, standard deviation. Diff, clinical difference between groups in outcome changes over time (suggested magnitude for SF-36; 2 small, 5 clinically relevant, 10 moderate, 20 large [40, 41]). *d*, effect size by Cohen's *d* (0.20 small, 0.50 moderate and 0.80 large) [42]. Statistical analyses by Mann-Whitney (numerical rating scales and SF-36) and independent two sample *t*-tests (days with pain). Vitality was the only SF-36 domain that yielded both a clinically relevant and distribution-based effect size difference between groups (figures in bold).

Analysis of the use of health care resources showed a clinical, although not statistically significant, trend between groups that IM contributed to less use of prescription and non-prescription analgesics (-11.7 and -9.7 percent units respectively) compared to conventional care (Table 4).

Table 4. Change in self-reported use of analgesics and health care from baseline to follow-up after four months.

Health care resource	Conventional care			Integrative care			Conventional vs. integrative care	
	From % (n)	To % (n)	Percent units	From % (n)	To % (n)	Percent units	Diff.	P, OR (95% CI)
Prescription analgesics	54.3% (19/35)	40.0% (10/25)	-14.3	45.5% (20/44)	19.4% (7/36)	-26.0	-11.7	0.325, 0.34 (0.0 to 3.0)
Non-prescription analgesics	57.1% (20/35)	42.3% (11/26)	-14.8	63.4% (26/41)	38.9% (14/36)	-24.5	-9.7	0.703, 0.67 (0.1 to 5.2)
CC	61.1% (22/36)	15.4% (4/26)	-45.7	65.1% (28/43)	22.2% (8/36)	-42.9	2.8	0.720, 1.38 (0.2 to 8.0)
CT	25.7% (9/35)	33.3% (8/24)	7.6	19.5% (8/41)	19.4% (7/36)	-0.1	7.5	0.762, 0.75 (0.1 to 4.8)

All measures were for the self-reported use over the last two weeks. CC, Conventional care. CT, Complementary care (outside of the IM model). Diff, difference in change over time between groups. OR, Odd's ratio. CI, confidence interval. Analyses by logistic regression.

The characteristics of care showed that conventional management mainly included advice (85%) complemented by a prescription of analgesics (50%). Less-used general practitioner strategies were sick leave (33%) and written physiotherapy referrals (26%). The number of CT treatment sessions for each category and type of CT that were integrated into these conventional care strategies are presented in Table 5.

Table 5. Categories and types of CTs and the number of CT treatment sessions provided in the IM model during the treatment period*

Category	Western, body based		Eastern, energy based		Self help, activity based
	Swedish massage therapy	Manipulative therapy (a)	Shiatsu	Acupuncture (b)	Qigong
Sessions/CT	1.5 (2.7)	1.8 (2.6)	2.8 (3.4)	0.3 (1.6)	1.0 (1.8)
Sessions/category	1.6 (2.6)		1.5 (2.9)		1.0 (1.8)
Total sessions	7.3 (3.2)				

Table figures refer to mean (standard deviation) estimates. *The average length of the treatment period was 10.2 (1.4) weeks. (a) Manipulative therapy was provided by a naprapath. (b) A practitioner of traditional Chinese medicine provided acupuncture.

The IM management typically integrated two different types of CTs (Table 6). Swedish massage was the most common type of therapy to be combined with other types of CTs. Shiatsu and qigong were the two most common CTs to be combined together. Manipulative therapy was the most common CT to be integrated as a single add-on treatment to conventional care. There were no reports of crucial adverse events with either conventional or integrative care.

Table 6. Combinations of complementary therapies provided in the IM model.

Categories	Types	Different CTs (n)	Patients % (n)
Western	Swedish massage	1	6.8 (3)
	Manipulative therapy*	1	22.7 (10)
Eastern	Shiatsu	1	15.9 (7)
	Acupuncture**	1	4.5 (2)
Western + Eastern	Manipulative therapy* + Shiatsu	2	11.4 (5)
	Swedish massage + Shiatsu	2	9.1 (4)
	Swedish massage + Acupuncture**	2	2.3 (1)
Eastern + Self help	Shiatsu + Qigong	2	13.6 (6)
Western + Self help	Swedish massage + Qigong	2	6.8 (3)
	Manipulative therapy* + Qigong	2	2.3 (1)
Western + Western	Swedish massage + Manipulative therapy*	2	2.3 (1)
Western + Eastern + Self help	Manipulative therapy* + Shiatsu + Qigong	3	2.3 (1)
Total			100.0 % (44)
<p><i>Western, body based therapies: Swedish massage and manipulative therapy*. Eastern, energy based therapies: Shiatsu and acupuncture**. Self help, activity based therapy: Qigong. *Manipulative therapy was provided by a naprapath. **A practitioner of traditional Chinese medicine provided acupuncture.</i></p>			

5.3 Patients' experiences and perceptions (III)

The research aim of the third study was to explore experiences and perceptions of receiving conventional and complementary care among patients from the pilot RCT. Specifically, were there any emerging characteristics of care that could be used to describe integrative vs. conventional management of sub-acute to chronic non-specific LBP/NP? The final theme describing IM management, the categories and the sub-categories that emerged from the analysis of focus groups with patients from the pilot RCT are presented in Table 7.

Table 7. Sub-categories, categories and theme describing conventional and integrative care characteristics derived from FGDs with a subgroup of LBP/NP patients from the pilot RCT.

Theme	Integrative care combines valuable conventional medical diagnosis with empowering self-help strategies		
Categories	Management characteristics	Care strengths	Care weaknesses
Sub-categories	Specialist and reductionist management (CC)	Valuable diagnostic support (CC)	Lack of accessibility, time and guidance (CC)
	Health insurance paradox (CC)	Increased treatment response and reduced need for analgesics (IC)	Financial and collaborative challenges (IC)
	Whole-person management (IC)	Individual support, empowerment and self-help strategies (IC)	

CC=conventional care characteristics; IC=integrative care characteristics.

Management characteristics, strengths and weaknesses of care were the three categories that emerged in the data. The sub-categories showed that diagnostic support from general practitioners and conventional medical specialists were experienced as representing an important strength of conventional care. Patients felt safe knowing specific pathology had been ruled out as a cause of their LBP/NP. However, other support and safety concerns such as sick leave procedures and public health insurance were to some extent perceived as a paradox within the Swedish health system. For example, Försäkringskassan (the Swedish Social Insurance Department) was occasionally found to invalidate sick leave that had been granted patients by general practitioners, thereby forcing the patients back to work despite persistent LBP/NP. The conventional management was also perceived by some as being reductionist and lacking guidance, and patients had commonly experienced difficulties accessing the general practitioner or the primary care unit, for example, by phone. A male participant expressed it like this:

“...then I had sciatica problems and that’s why I went for help from the beginning and then I ended up at Xxx Health Care Centre. And the help they gave me there, apart from a pat on the shoulder, was a box of painkillers.” (Man, FG1:1.)

Weaknesses of integrative care included increased costs of CT treatments and experiences of collaborative challenges. The latter were frequently expressed in terms of patients lacking communication and dialogue about CTs with their conventional health care providers. However, emerging strengths of IM management included experiences where IM had positively influenced treatment outcomes, for example by identifying “new” dysfunction patterns and subsequently new treatment solutions contributing to less pain.

“I can see a huge benefit in what I’ve just been through, you know, if I had contacted allopathic medicine, they would just have focused on my back. What this naprapath (manipulative therapist) discovered was in fact that a knee injury I’d been suffering was linked to my back, so he helped me establish that a lot of the back pain was in my knee and I don’t think a doctor would have discovered that. (Woman, FG4:4.)

IM was also perceived as conceptualising a whole-person approach, facilitating individual support and self-help strategies that seemed to empower patients to take increased responsibility for their health.

*“So that’s (self-help/exercises at home) still on the cards?” (Moderator)
“Yes, definitely, and the clear difference you see makes you want to continue.” (Woman 4.)
-“That it might be connected in a different way than you thought and that you might not even have had those thoughts before.” (Woman 2.)
“And I think about it almost all the time I’m walking, the fact that I have to use both feet, even though it’s several months since I stopped that (relating to a self-help strategy learned during integrative care).” (Woman 4.)
(Women, FG1:2, 4.)*

5.4 Cost-effectiveness (IV)

The aim of the health economic study was to evaluate the likelihood of IM being a cost-effective health service option compared to conventional management of patients with sub-acute to chronic non-specific LBP/NP in Swedish primary care.

Cost-effectiveness analysis

The likelihood that the IM model was a cost-effective health service option compared to conventional care in the base case scenario was estimated at 67% at a willingness to pay threshold of euro (EUR) 50,000 per QALY (Table 8). The IM model gained 0.018 QALYs compared to the conventional care and the cost per QALY gained was estimated at EUR 23,538.9 per QALY (Table 8). The NMB of the IM model was calculated at EUR 470.0 (EUR -1,563.9 to EUR 2,508.8) (Table 8).

Table 8. Costs, gained QALYs, costs/QALY and the likelihood of cost-effectiveness for the proposed IM model compared to conventional care.

		Base case scenario*	Alternative case scenario*
	Intervention cost	483.0	309.9
	Reduced cost	-59.3	-59.3
	Gained QALYs	0.018	0.018
	Cost per QALY	23,538.9	13,922.2
P NMB (1) > NMB (0)	WTP=50,000 (Base case)	0.67	0.73
	WTP=100,000 (High)	0.74	0.77
	WTP=10,000 (Low)	0.18	0.39

All costs in euro (EUR). QALY, Quality adjusted life year. P, likelihood of cost-effectiveness. (1) Integrative care; (0) Conventional care. NMB, Net monetary benefit. WTP, Willingness-to-pay for one QALY. *Market prices were applied in the base case scenario; employment/production prices were applied in the alternative case scenario.

The costs of CT services as well as the total cost of integrative care provision could be reduced in an alternative case scenario where employment/production prices replaced market prices. In total this led to a cost reduction of EUR 173.1 (from EUR 483.0 to EUR 309.9) for providing integrative care. Accordingly, the alternative case scenario contributed to an increase in the NMB from EUR 470.0 (EUR -1,563.9 to EUR 2,508.8) to EUR 643.1 (EUR -1,390.8 to EUR 2,681.9) (Table 8). Similarly, the likelihood of cost-effectiveness increased from 67% to 73% at the EUR 50,000 per QALY threshold. Applying a higher economic threshold increased the likelihood of cost-effectiveness to 74% applying market prices and up to 77% applying production prices. Notably, the IM model was not likely to be cost-effective at a threshold of EUR 10,000 per QALY regardless the scenario (Table 8).

6 DISCUSSION

6.1 Methodological considerations

IM aims to contribute to a health care approach that is something greater than the mere sum of its parts [146]. In a similar way a synthesis of evidence is increasingly enforced by health technology assessment (HTA) boards to make informed decisions about evidence based health care [147, 148]. This research project has embraced the concept of synthesis by applying a mixed methods approach to evaluation where by the integration of different study designs, data collection methods and evaluation strategies have contributed to a comprehensive framework to explore IM for LBP/NP in Swedish primary care. Figure 3 presents an overview of the methodological strategy used in this research project.

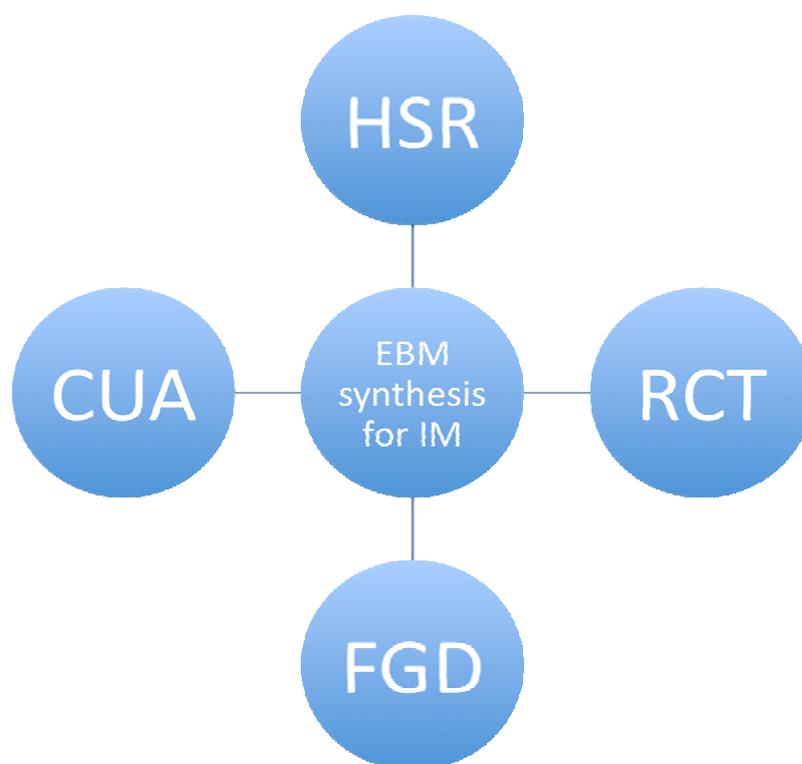


Figure 3. Towards an evidence based medicine (EBM) synthesis exploring integrative medicine (IM) for back and neck pain in Swedish primary care. Ranging from health services to patient perspectives the IM research project explored the following domains: HSR, Health services research – developing the IM model; RCT, Randomised clinical trial – pragmatically implementing and testing the comparative effectiveness of the IM model; FGD, Focus group discussion of patients’ experiences and perceptions; CUA, Cost-utility analysis – cost-effectiveness of IM as a health service option.

Several reasons and advantages of using a mixed methods approach have been proposed. For example, the use of mixed methods by definition contributes to overcoming the weaknesses of using any one method in isolation in order to understand a complex phenomenon [81]. This is commonly known as complementarity of designs and methods, i.e. how different approaches may be fit together to supplement each others lack. In the current project there were four main studies with different principle designs reasoned to provide complementing perspectives: A health services research approach based on a qualitative iterative group-based process was used to develop the IM model (Paper I). This was followed by a pilot RCT with quantitative outcome measures to implement and test the comparative effectiveness of the developed IM model vs. conventional primary care (Paper II). Third, a qualitative inquiry involving FGDs with patients from the RCT was conducted to explore experiences and perception about conventional and complementary care in order to generate possible care characteristics of IM (Paper III). Last, a CUA was done to investigate the likelihood of IM being a cost-effective health service option in Swedish primary care (Paper IV).

Incrementality, which can be defined as the step-wise-progression by which different approaches to design and methods are combined or intertwined, is another factor that may have impact on the quality of different phases in the development of a research project [81]. Acknowledging this and the fact that development is rarely linear and unidirectional the IM project had constant feed back loops within the research group during the clinical development, implementation and testing of the IM model in the clinical setting.

The overall emergent design of the IM project required the IM research group to become intensively involved, i.e. immersed, in the research process during the course of the study before the IM model crystallised [124, 125]. This process has been described as researchers “becoming the research instrument” [81]. Here, reflexivity has been described as a key process involving self-reflection drawing upon previous personal and professional knowledge, clinical experiences and perceptions to contribute to the validity (the degree which an instrument or different processes measures what they are intended to measure) of interpretations and results [81, 124, 125]. During the IM project reflexivity was an important and necessary element drawn upon in the consensus discussions driving the development of the IM model forward. This process naturally included member checks, i.e. the process where the research group coordinator (TS) or the IM team members summarised previous meetings or activities to the research group before new strategies or actions progressed. Another central component of this process was investigator triangulation, i.e. the use of multiple perspectives during the consensus case conferences and the analytical iterative development of the IM model [81]. These qualitative measures enhanced the credibility and confirmability of the qualitative research process contributing to the overall study quality, i.e. the trustworthiness of the study [81, 128].

An alternative approach that was briefly considered for developing a relevant IM model was to conduct a Delphi survey [81]. Based on several rounds of questionnaires put to a group of experts this would also have been a group-based consensus approach. However, there was a lack of experienced IM model stakeholders in the Swedish primary care setting and, perhaps even more importantly, the face-to-face meetings of the IM team on site at the primary care unit where the IM model was to be implemented emerged as such an important element in increasing mutual reflexivity and “ownership” of the IM model, that the Delphi design was discarded.

Instrument/outcome development (I)

Another strength of the qualitative approach of the IM research project was the flexibility of the design and methods used to account for different perspectives, not only in terms of practical or clinical issues, such as the set up of the structural components of the IM model, but also concerning issues such as instrument development for the subsequent quantitative RCT evaluation. As a result a number of new “IM-tailored” outcome variables were proposed to complement other relevant outcomes such as the reliable and valid Swedish version of the SF-36 [130-132]. The IM-tailored outcomes were considered especially relevant from a clinical CT provider perspective as they were perceived to represent common enquiry areas in CT practice often contributing to clinical reasoning and decision-making in the care of patients. Hence, despite the IM-tailored outcomes’ lack of proper scientific validity or reliability testing, after internal testing among peers and students, the face validity of these outcomes was considered sufficient to explore those outcomes in the upcoming RCT (Paper II).

Generalisability and external validity of the IM model (I)

Population-based surveys of CT utilisation have shown users to be predominantly well educated and from middle/high income groups [27, 28]. However, the geographical area purposively selected for IM implementation was largely characterised by higher rates of unemployment, lower incomes, more sick leave and more welfare support compared to the average levels in Stockholm at the time of the project [149]. Accordingly, the generalisability of the findings in relation to external validity, i.e. the relevance of the proposed IM model to other suburban primary care settings in general or other low income contexts specifically, is believed to be high. Additionally, for solidarity and health equity reasons this approach was an important aspect of the IM research project.

However, there are a number of health services issues that may challenge the reproducibility of the IM model in future trials. This includes the dependence on a gatekeeping general practitioner who is knowledgeable about CTs, something that cannot be taken for granted due to the lack of CT/IM information in medical education in Sweden today. Notably, there is however a number of general practitioners from other countries practicing within the Swedish health system knowledgeable about CTs, e.g. from Germany. The IM model is also dependent on CT providers with adequate knowledge and training in biomedicine. Such CT professionals may be hard to verify since there is currently no national registry or even authorisation acknowledging the degree of training among the various CT professionals in Sweden. Nonetheless, well-established CTs in Sweden, such as those represented in our trial, have commonly professional umbrella organisations that provide education, practice and ethical guidelines facilitating the identification of properly trained CT providers, which could facilitate the reproducibility.

Additionally, the “black box” characteristics of the IM trial, where different intervention components may be identified but their contribution to the general effectiveness of the care in terms of specific efficacy can not be quantified [71], may challenge the possibility to reproduce consistent levels of intervention effectiveness in future studies. The interactive dialogues and decision making processes of the IM team may also be difficult to standardize, which might indeed contribute to large variability between different IM teams. Nonetheless, the recruitment process of patients through the primary care units, not via advertising in media, is an important aspect that may contribute to improve the generalisability of implementing the IM model in future clinical studies, i.e. addressing “regular” patients seeking conventional primary care.

Implementation and recruitment (II)

The implementation of a pilot trial is a highly relevant initial clinical research step for investigating the appropriateness of selected outcomes, logistical procedures and feasibility of implementation at provider and patient level, in order not to waste unnecessary resources before a large-scale trial is conducted. The Consort guidelines for pragmatic trials were followed as far as possible in the pragmatic pilot RCT to increase validity measures [150]. One challenge faced by the project was that it took an unexpectedly long time to recruit the 80 patients deemed necessary for the pilot RCT (about one and a half years) despite a network of about 35 general practitioners. Interestingly, about 80% of the physicians from the same primary care unit as the general practitioner of the IM team, but only about 10% of general practitioners of the other primary care units, referred patients to the IM trial (Paper II). This possibly reflects the need for continuous dialogue and reinforcement of IM concepts with referring general practitioners so that the relatively unknown IM model would over time be considered a relevant treatment option.

Response rate and missing data (II)

The response rate in the pilot trial was relatively low after four months, range 75-80% (Paper II). One reason for the rather low response rate might have been that the participating patients' motivation to comply with the study procedures were low compared with participants in other comparable trials whom may have been recruited through media campaigns or being specially invited from a pool of volunteers actively seeking to be part of a clinical trial. The patients in this pilot study were "regular" primary care patients seeking care at their primary care units typically not knowing that IM was offered as a treatment option at the unit.

Another reason for the low response rate might have been that all administration of the questionnaires took place outside of the primary care unit, and importantly not linked in any way to the patient-provider relationship, to make sure that patients felt comfortable answering in an unbiased way. None of the health care providers had access to the patients' questionnaires. Nonetheless, future research may want to take some measures to assure a higher response rate. Perhaps through the judicious use of data collection procedures "closer" to the patients, e.g. by means of telephone interviews.

When the response rate is low the level of missing data will be high. There is no universally accepted rule or consensus on how to deal with missing data. Hence there are many strategies on how to deal with this issue. One approach recommended by organisations that often deal with large scale RCTs, such as the Cochrane collaboration, recommends to approach missing data with a technique called intention to treat (ITT) [151]. This implicates that all patients are kept in their assigned groups and that various ways of imputing, i.e. replacing missing data with "invented" numbers, are performed. Although some strong advantages such as a retaining a complete data set allowing for higher accuracy in outcome estimations and statistical calculations, there may also be challenges to the ITT approach. For example, a high drop out rate implicates a high rate of invented number being imputed into the data set, which paradoxically in turn may also return a level of uncertainty into the interpretation of findings. Advanced statistical procedures such as different "multiple imputation" techniques have been suggested to handle missing data by adjusting for multiple variables and covariates that relate to the missing data in certain ways. Other methods are simpler, but might be still be justified and useful depending on what type of data that is missing. Such approaches include imputation of mean values or last observed measures [142].

Reversely, another main strategy in data analysis can be to do a “per protocol” analysis. This means that only patients with complete data are part of the main analysis. By adhering to this standard there is no invented figures only “real data” in the dataset. On the other hand it is still important to find out possible reasons for the missing data. Was it due to adverse effects of administered treatments? Or perhaps due to disappointment with treatment allocation? In the pilot RCT (Paper II) we choose the per protocol strategy for the main analysis considering the pilot phase of the RCT and the relatively high drop out rate. All patients were kept in their assigned groups (one patient assigned to conventional care received integrative care due to logistical reasons). Interestingly, a secondary analysis was performed adhering to the ITT principle and data were imputed by the last observed measure [142]. The results were not affected by this, indicating that our data were robust to sensitivity testing.

There were no reports of drop outs due to adverse effects of any treatments. On the other hand, it can not be excluded that some patients might have dropped out due to not being satisfied with the allocated intervention. However, among those patients staying in the trial there was no statistically significant change in CTs use outside of the study between baseline and follow up. This may indicate that for the majority of patients the allocation per se was not a strong enough reason to change health care seeking behaviour towards using more CTs. Perhaps a relatively low purchase power or other socio-economically factors in the area of implementation of the project, coupled with rather high costs for CTs outside of the study, also contributed to keeping the use of external CTs low.

Patients experiences and perceptions (III)

The aim of the FGD study was to explore patients’ experiences and perceptions of conventional and complementary care in order to identify emerging care characteristics that could be used to describe integrative vs. conventional management of sub-acute to chronic non-specific LBP/NP.

Interestingly, the majority of patients stated they could not participate in the FGDs due to lack of time. There were also frequent cancellations and persons who did not attend despite having confirmed their appointments. This was despite FGDs being offered both in late afternoons and early evenings in the neighbouring area. Although just speculative, perhaps other reasons not disclosed to the researchers could also be an issue. One potential reason might have been distrust in sharing health care experiences with unknown people, especially if the health care process might have been personally transforming as indicated through some of the consensus case conferences for some of the patients (data from consensus case conferences is currently being analysed). This may have favoured interviews as an alternative data gathering method. Logistically though it would not have been possible to conduct that many interviews during that time. There were also potential methodological advantages with FGDs, such as group dynamics and interactions facilitating broad aspects of conventional and complementary care to be exposed and discussed. Hence, albeit with few informants, the so called mini-FGDs [126] with 2-4 participants were experienced to bring increased intimacy and openness to the discussions facilitating the sharing of experiences and perceptions among informants.

Nonetheless, it cannot be excluded that those who volunteered to participate might have been biased in relation to their perceptions and experiences of different types of care (selection bias), which in turn might have influenced the findings. The combination of potential bias with the relatively small number of informants raise an important question

about transferability, i.e. could the results from the FGDs be transferred to other settings or groups of patients [81]? Likely not, at least not to the whole target group of patients with LBP/NP. However, transferability was not the aim of the study. Rather the objective was to inductively generate emerging characteristics of conventional and complementary care, from the views of patients with sub-acute to chronic non-specific LBP/NP that could be used to describe IM management characteristics.

Further, although the focus was to discuss recent experiences and perceptions from encounters with conventional and complementary care, it was not uncommon that some informants, regardless of treatment allocation in the pilot RCT, also mentioned or spontaneously related to past treatment experiences during the discussions. This type of "confounding" might be a hinder towards referring the results directly to the pilot RCT. However, in a larger context, acknowledging that the FGDs to some degree might have addressed other providers than those from the research project, this may in fact increase the information load towards identifying and understanding potential care characteristics of conventional, complementary and IM. Hence, the strategy during data analysis and categorisation was to use an aggregated data set where all meaning units and codes were pooled.

The prolonged engagement and persistent observation [81] of three of the four authors in the research IM project over several years, from planning, to data collection, to analysis and interpretation, was seen as important quality measures during the research process. Additionally, the mix of different clinical, research and theoretical backgrounds (conventional, manual and complementary medicine, public health, nursing, pharmacology and social anthropology) among the researchers became evident with triangulation of perspectives during data analysis, which ultimately helped challenge different perspectives throughout the analytical phase and increase the study's credibility and trustworthiness. Interestingly, the FGDs were found to have reached saturation despite the relatively few informants and group sessions, a fact that might contribute to the overall credibility and trustworthiness of the FGD results.

Cost-effectiveness (IV)

In the health economic evaluation (Paper IV) the external validity of findings relate to many of the same factors as for those relevant for the evaluation of the pilot RCT (Paper II). Additionally, the study was conducted as a full economic evaluation analysing both costs and consequences in terms of a CUA alongside the pilot RCT, i.e. a preferred method for increased interpretation of findings [75, 76]. The use of a non-parametric algorithm for converting SF-36 data into SF-6D for QALY calculations is another step that is recommended to compensate for typical attributes of cost data, such as they may be skewed and subject to large variability. Here we followed a Bayesian approach proven to be more tolerant and provide better estimates than corresponding parametric algorithms [137]. Additional measures used to increase the validity of the CEA included using NMB [152] rather than estimates of mean values; the use of non-parametric bootstrapping to increase sample size to increase accuracy of estimates and the identification of direction of cost-effectiveness rather than statistically significant differences [141] considering the pilot trial status of the RCT and non-statistical findings in paper II. ITT was the primary analysis in the health economic analysis due to the use of aggregated variables for calculating costs. However, a secondary complete case analysis was also conducted showing an overall direction of cost-effectiveness that was similar to the ITT analysis, suggesting (as in Paper II) the findings to be robust to sensitivity testing.

Interestingly, no patients were reported to have dropped out of the study despite the slight extra cost of receiving CTs in the IM model. This may have important clinical implications with regard to implementation and sustainability of IM in public health care settings where CTs are not normally reimbursed. Future studies will have to investigate at what levels the economical thresholds lies, i.e. exactly how much patients are willing to contribute financially to IM health services, in different clinical settings.

Limitations of this study included a short-term follow-up and limited data that did not allow for the possibility of exploring and estimating indirect costs such as sick leave and work absence relating to back/neck pain, both of which are major factors relating to the overall cost of back/neck pain [90].

Likewise, the validation of cost-effectiveness of any intervention relates to the duration of clinical effects. The projection of effects from four months to one year in our base case scenario may be supported by results of other clinical trials investigating the effects of CTs over longer term follow-ups, e.g. massage [153] or acupuncture [154]. Although these studies were not clinical trials of comprehensive IM models, the types of CTs and the duration and numbers of CT treatment sessions were similar to those in our pilot trial (Paper II) [155]. Utilising more detailed data collection procedures such as diaries, perhaps combined with access to electronic database records, monitoring sick leave and use of public health care resources could further improve the accuracy and the interpretation of findings in future larger-scale trials of IM in primary care.

Duration of intervention and outcomes to measure the effect (I-IV)

The pragmatic approach with development of the clinical treatment plans in two to three weeks time periods allowed for highly personalized care services. Interestingly, EBM guidelines [156] implicate that the process of care might be as important as the outcomes of care. However, more information is needed about the actual care process development, both in terms of the patients' and the providers' perspectives over time. Notably, the consensus case conferences were digitally recorded during the IM project and are currently being analyzed outside the scope of this thesis work towards gaining such insights.

Interestingly, it was found that the average patient in the trial received seven CT treatment session over ten weeks on average, i.e. less than the stipulated 10 sessions over 12 weeks in the IM project (Paper II). So was this long enough considering the lack of differences between the two groups of care? For example, is it reasonable to expect that seven CT sessions over 10 weeks are enough to help patients that maybe have suffered from LBP/NP over many months or even years? Perhaps the clinical outcome trend that was identified after the pilot RCT (Paper II) could have progressed further if there had been a longer intervention period? Considering the natural progression of non-specific spine related pain, which seems to be cyclic in nature varying over time [157], a future research focus might be to identify when to intervene, and how to tailor the treatments during different cycles of pain intensity. For example, should the most intensive management take place during an “active pain period” when the patients have disabling pain or when the LBP/NP is in a less aggravated phase? What clinical decision making rules should decide what kind of intervention/s is implemented and when? Should there be long or short treatment series? Should re-visits or “booster sessions” be provided on a “need basis” to reflect real health seeking behaviour? How should the outcomes of management and care processes be monitored and evaluated? Such questions largely remain to be explored.

The current results with generally small clinical differences and effect sizes between groups (Paper II) may challenge a narrow use of outcomes measured in isolation to understand the relevance of IM in primary care. The findings may further attest to the need of identifying additional more relevant evaluation strategies, as suggested by recent outcomes research targeting IM and complex health interventions [158]. The trend of decreased use of analgesics for IM in this pilot trial may support that the use of health care resources might be one such important target area. More disease specific instruments with valid psychometric properties such as the Oswestry Low Back Pain Disability Questionnaire, the Quebec Back Pain Disability Scale, and the Roland-Morris Low Back Pain Disability Questionnaire [159] might potentially be another relevant area not specifically targeted in this pilot project. Additionally, aspects of prevention, life-style changes and health promotion [160] and more patient tailored outcomes such as the MYMOP [161] as well as a focus on processes of personal transformation and empowerment [162] may also be important to consider.

However, acknowledging the potential shortcomings of different instruments per se the current evaluation strategy of iterative cycles integrating and triangulating quantitative and qualitative methods might still be one of the best approaches towards exploring complex interventions such as IM in clinical care settings [72].

6.2 Main results

Developing the IM model (I)

The developed IM model was characterised by the adoption of a team-based approach to deliver a patient-centred integration of conventional care and CTs, facilitated through consensus case conferences for patients with sub-acute to chronic non-specific LBP/NP. Acknowledging the diversity in ways of delivering CTs with conventional care, different stages of collaboration have been proposed [63]. Accordingly, the developed IM model may be described as an “integrative health care” service option where health care providers collaborate on equal non-hierarchical terms in the clinical delivery of care to patients. The importance of consensus adhered to in the IM project has been suggested as being more significant the further a health care practice model moves towards integrative care [63]. Interestingly, it was rare for the IM team providers to have experienced interactive medical dialogues elsewhere. A lack of communication and dialogue have also been described as barriers to IM implementation [163, 164]. The fact that all providers of the IM team, despite different clinical and philosophical backgrounds and medical models, shared a basic knowledge of biomedicine and CTs, may indeed have contributed to the atmosphere of respectful sharing of views on the patient cases that emerged [165].

The group-based consensus approach of the developed IM model was seen as having several potential advantages over parallel or referral models of IM [63, 166, 167]. Hypothetically, such advantages might include providing an IM model with increased team-building and cross-fertilisation of ideas, which could lead to increased diagnostic and therapeutic capacities, increased safety cross-checking, decreased risk of negative treatment interactions, increased sharing of resources, reduced length of treatment cycles, reduced number of revisits in primary care, and improvement of health care cost-effectiveness by reducing health care costs, including cost of drugs. However, although the IM team experienced a positive trend in terms of the collaborative group management of patients, most comparative advantages of IM over conventional care are yet to be statistically confirmed in future larger-scale trials.

In accordance with the Swedish medico-legal framework (“the Professional Activity in the Health Services Act”; 1998:531) [3] only licensed medical doctors have access to the full range of medical services, lab-testing, referrals, sick leave certificates etc. for their patients. Hence, the choice of a general practitioner with knowledge about CTs as the gatekeeper for the IM model was made in order to comply with this framework and to develop the initial version of the IM model in “safe mode”. Similarly, general practitioners have previously been proposed as gatekeepers in research on IM [166]. Nonetheless, the option of additional CT gatekeepers might be justifiable considering adequate “dual competence” of CTs and biomedicine facilitating communication and referral mechanisms for conventional care.

The recruitment of specialised, trained CT providers to deliver care in a conventional setting may increase the representation of different health care traditions and philosophies in primary care, which could be of importance for patients including CTs in their health seeking [100, 101]. Additionally, the representation of different CT professions, rather than CT techniques, may also provide complementing aspects to biomedical clinical reasoning regarding how the selected therapies in the IM model could complement each other during health care delivery. For example, in an (over-)simplified biomedical framework: massage and stretching target muscle function; mobilisation and manipulative therapy target joint function; acupuncture and acupressure/shiatsu target pain modulation and qigong targets activity-based self-help and home treatment. A complementing aspect may indeed be that the selected CTs could also have parallel explanations of interaction, originating in their original philosophical, cultural and medical frameworks, e.g. traditional Chinese medicine and the five-element theory [6]. The integrated use of these frameworks may possibly improve patient-provider dialogue by providing options for additional clinical or even philosophical perspectives on care, thereby acknowledging different individual perspectives and sometimes even belief systems [100]. This IM concept could not only increase patients’ compliance with conventional care treatments but also improve medical management, identification of side effects and negative (or even positive) interactions of administered treatments. However, most of these hypotheses are yet to be tested.

Alternative provider options for delivering integrative care might be to involve conventional providers with “dual training” in biomedicine and specific CTs. Although it may be appealing to have “multiple professional perspectives” in one provider, during the development of the IM model it was generally difficult to find such providers with adequate professional training. The general practitioner and the research coordinator of the IM team were two exceptions. Hence, although specialist trained conventional health care providers might indeed be suitable to provide e.g. manipulative therapy or other services as part of an IM team, some of these providers may be difficult to attain due to the limited number of trained specialists. Rather, the integration of specialist trained manipulative therapists and CT providers may significantly increase the recruitment base for IM teams, e.g. in the case of manipulative therapy by approximately 2,000 additional chiropractic, naprapathic and osteopathic providers nationally (estimate from 2009). The feasibility and generalisability of developing IM teams to implement IM in Swedish primary care might then increase substantially when it comes to aspects of manual therapy services as part of IM.

The current IM model, in addition to various other approaches adopted to integrate CTs in patient care, has received critique for not addressing the phenomenon of integrative health care in broader social and historical contexts [168]. Such aspects were not deemed a priority considering the pilot phase characteristics of the current IM model.

However, future studies may indeed analyse the IM model from more theoretical perspectives, including transition theory. Critique from another perspective might argue that the IM model lacks some essential CT perspectives, e.g. dietary and nutritional aspects. Arguably, these may be important, however most Swedish population-based surveys have not been able to show that these types of CTs are represented among the most prevalent provider-based CTs in Sweden [27, 28]. Hence, from a societal perspective, it could be argued that the selected CTs in this IM model do indeed have a more frequent representation in Sweden. Something which is also supported by the availability of major professional CT organisations.

The characteristics of the conventional care provided within the IM model generally complied with the clinical primary care guidelines [111], i.e. the general practitioners' management strategies mainly consisted of advice and prescription of analgesics. To this the IM model integrated seven CT sessions over ten weeks, typically from two different CT types. The average number of CT treatments was roughly equally distributed between the western/body-based and eastern/energy-based CTs. This well distributed mix of CTs may reflect the actual need of the patients referred to the IM team. However, it cannot be excluded that the interactive team process among providers of the IM group may also have contributed to the manner in which the various CTs were selected. For example, were the team members concerned that each CT should be equally well represented? Who should see the patient first and why? The decision-making process itself within the IM team remains to be analysed in future studies.

Implementing and evaluating the model (II)

The current research project is unique in that it has investigated a comprehensive IM model compared to conventional care, i.e. treatment as usual, in the management of regular primary care patients with LBP/NP by means of a mixed methods research approach. Most internationally reported research has been investigating different CTs in isolation.

Interestingly, although the individual CTs in the IM model can be argued to have an emerging evidence base in general [6, 104, 169-172] clinical trials evaluating comprehensive IM models are scarce in the scientific literature in general, and particularly within the field of LBP/NP management in primary care. It may be questioned why there are so few published RCTs on comprehensive IM models, especially since LBP/NP are two of the most common reasons for people using CTs [26] and that primary care has been proposed as a main target field relevant for CT integration [53]. Some recent insights to this lack of research include lack of resources, organizational culture and logistical challenges for IM clinics [173].

However, a relevant and recent example of an RCT attempting to implement and test a more comprehensive IM model included a "choice model" for patients with acute LBP [174]. Here the patient's individual choice, rather than a consensus approach of an IM team, provided the basis for delivery of CTs (massage, chiropractic or acupuncture) in addition to conventional care. Patients were randomised to the choice model combined with conventional care or conventional care alone. Follow-up of symptoms, functional status and satisfaction with care was performed after five weeks. Costs of medical care were assessed after 12 weeks. Results showed no clinically significant improvements in symptoms or functional status between groups although the choice group was more satisfied with the care. The CT care resulted in added costs, which were expressed in US dollars rather than costs per QALY [174]. It was reasoned that future research should focus on patients with longer pain duration. Incidentally, our study complements

this trial by investigating patients with sub-acute to chronic LBP/NP. The current clinical findings (Paper II-IV) indicate that patients with chronic LBP/NP might be a more suitable study population for IM interventions than acute pain patients, although the current study was underpowered to be able to statistically verify clinical trends in data (Paper II, IV).

Similarly, there are other RCTs reported of more isolated “CT models”, commonly acupuncture and/or manipulative therapy, that may support the integration of CTs in primary care for patients with spinal pain conditions such as LBP/NP [171, 175]. The results from our pilot trial (Paper II) also showed that manipulative therapy was provided both as a single add on to conventional care as well as combined with other CTs. Taken together these studies may support the integration of manipulative therapy as a valid part of a comprehensive IM model.

Initially, during the development of the IM research project, the IM team met different stakeholders to share experiences and perceptions about conventional care, CTs and IM in the Swedish context. It became clear that very few providers were able to share experiences from the delivery of comprehensive IM models in Sweden. One exception to this were the providers at Vidarkliniken, an anthroposophical hospital south of Stockholm [176]. They represented a type of IM where conventional and holistic anthroposophic modalities are integrated in hospital care services. It has been estimated that anthroposophic medicine is practised today in 65 countries worldwide and that more than 30,000 physicians prescribe anthroposophic medicinal products. With specific relevance to our study recent research indicate that IM approaches such as anthroposophic medicine may be valuable, both from a quality of life and total health costs perspective, in the long-term management of patients suffering from chronic illnesses including musculoskeletal conditions [177-179]. Aspects of these trials, such as larger cohort studies with high external validity and longer follow-ups may play an important role in exploring our IM model further in clinical practice.

Outcome measures and clinical differences (II-IV)

The outcome measures that displayed the largest clinical differences in the pilot RCT (Paper II), albeit within small ranges, were SF-36 vitality and the decreased use of prescription and non-prescription analgesics, both were in favour of IM. Clearly, less use of prescription analgesics, if confirmed, would be an important clinical finding that could reduce reported negative side effects linked to prolonged use of such drugs [180, 181]. Perhaps the IM model, due to the individualisation of back/neck pain management through integration of CTs, facilitated additional and more individual ways of supporting and empowering patients compared to existing possibilities within conventional care services today, as indicated by the patient’s interviewed in Paper III. However, the added CT treatments might have lead to more intensive management, which in turn by itself may help to explain the trend towards more positive results for IM identified for some of the variables. However and importantly, this increased “attention” effect was intentionally part of the IM model, and allowed for in pragmatic and exploratory approaches towards investigating differences between models of care. Whether or not this was a cost-effective approach, considering the extra cost imposed, was subsequently tested as reported in Paper IV.

Patients' experiences and perceptions (III)

The theme in the FGD study describes IM care characteristics based on data gathered from patients' experiences and perceptions about conventional and complementary care.

It was found that the biomedical health services were highly appreciated for providing advanced diagnostic procedures in the process of excluding pathology as the reason for the patients' LBP/NP. Similarly, pain and potential pathology were strong reasons for patients to seek primary care. Interestingly though, the majority of patients with spinal pain will not receive an anatomical pathological diagnosis explaining the cause of their pain [87]. Hence, most end up with having "non-specific" LBP/NP. It is easy to imagine a degree of frustration here on behalf of the patients since the pain per se can be very "specific", severe and disabling. Additionally, this may also be a challenge for many conventional providers that are used to engage in care processes relying on the verification of causative pathology. This may in part provide an insight to why LBP/NP are the top two reasons for patients to consult with CT providers [26]. This may be an intriguing fact and a strong incentive for investigating the integration of selected CTs with an emerging evidence base into conventional care management of patients with LBP/NP.

The FGD findings further indicated that conventional and complementary care characteristics may indeed be quite different in some aspects. For example, patients seemed to feel empowered and supported by CT treatments much more than from conventional care. This empowerment may relate to different aspects of processes and goals [182]. Perhaps CT or IM strategies, through clinical, philosophical and theoretical frameworks that complements conventional care, can support patients transformation from being "stuck" with LBP/NP towards finding new care processes and goals including self management solutions [183]. Indeed this may be an important aspect with any type of care, but perhaps even more so for those patients suffering from long standing pain, such as LBP/NP.

Cost effectiveness (IV)

The health economic evaluation indicated that IM may be a cost-effective health service option in Swedish primary care (Paper IV). At the very least it seems as cost-effective as conventional care. However, with some potential advantages such as reduced use of analgesics (Paper II) and care characteristics that include increased empowerment of patients (Paper III). Taken together this pilot evidence may indicate an interesting trend worth exploring further in larger scale studies. However, a major limitation with the current pilot trial that need to be adjusted is the monitoring and data collection of indirect costs such as cost relating to work absence due to LBP/NP, i.e. significant societal costs associated with the investigated diagnoses.

There are few if any large scale pragmatic RCTs that have investigated the cost-effectiveness of comprehensive IM models. However, there are several such RCTs on more isolated CTs. For example, a large-scale acupuncture RCT in primary care which included 401 headache patients adopted a similar mixed methods evaluation strategy as utilised in our study, including a health economic evaluation [184]. Interestingly, the general results were also similar to ours, favouring a strategy of integrating rather than avoiding acupuncture in the management of patients with headache. Although it may be difficult to compare costs and QALYs between different studies due to e.g. different contexts and methods, it was interesting to note that the QALYs gained were also similar to findings in our trial, i.e. 0.021 in the acupuncture RCT vs. 0.018 in our pilot RCT (Paper IV). However, the base case estimate of cost per QALY gained was lower in the acupuncture trial, possibly in part due to that we added the cost of the planning phase of the IM services in our estimates. Similarly, there are other examples of studies that have adopted more isolated approaches to comparing different CTs and conventional care in the management of back/neck pain. The delivery of such CTs, e.g.

acupuncture or osteopathy [154, 185], has generally reported more favourable compared to our findings in terms of cost per QALY. From a cost-effectiveness perspective this may challenge the use of a team-based rather time consuming consensus approach to plan the IM care. However, there is a need for larger-scale follow-up trials of the IM model before any definite conclusions can be drawn.

Global health policy perspective

Most CTs are derived from ancient TM therapies and systems. From a global health policy perspective it is interesting to note that the WHO has issued normative recommendations for the appropriate use of TM/CAM/IM in national health systems [58, 186]. Reasons declared by WHO for their first global strategy ever for TM [5] include that many people suffer from various chronic illnesses, for which there may be no conventional treatment readily available in many nations, and the recognition that TM/CAM/IM may have many positive features such as improving quality of life which may aid activities in daily living.

The increases in CT use globally [5] challenge national health policies across the globe to simultaneously prioritize patient safety and treatment efficacy yet offer choices that promote patient ownership of health [62]. In response to these challenges, many countries have established or are in the process of establishing a national CAM policy. Indeed, the Executive Board in WHO's resolution on TM has urged member states *"...to draft and implement national policies and regulations on traditional and complementary and alternative medicine in support of the proper use of traditional medicine, and its integration into national health care systems, depending on the circumstances in their countries."*

Norway may serve as an example of a member state which has recently changed its legal framework to promote dialogue and a narrowing between the CT and conventional medicine sectors to partly stimulate IM research and development [73, 74]. Coincidentally, Norway has also established a national research and information centre for CAM (The National Research Centre in Complementary and Alternative Medicine) [187], a strategy that is encouraged by the WHO towards providing *"evidence-based information on the quality, safety, efficacy and cost-effectiveness of traditional therapies so as to provide guidance to Member States on the definition of products and procedures to be included in national directives and proposals on traditional-medicine policy as used in national health systems"*.

Health conditions such as LBP/NP impose huge costs in many societies, and may be extra troublesome in countries lacking access to advanced technological medical care including pharmaceuticals. As suggested by the WHO the TM/CAM/IM sectors may add important additional resources and relevant practices in the context of primary health care services, particularly in scarce low-income settings, provided that they are proven safe, effective and appropriately used. Here experience and supportive evidence from IM healthcare services research and development may contribute to health sector reform for countries in general and for low- and middle income countries in particular, by bridging the gap between ancient TM systems and therapies and modern medicine. It is likely that the health economic analysis (Paper IV) would be more favourable towards IM service provision in such countries given the fact that CT professional labour costs are generally much lower compared to the costs of the infrequent general practitioners.

7 CONCLUSIONS

In general it can be concluded that the identification of IM facilitators, barriers and strategies by the different stakeholders contributed to feasible IM services implementation within Swedish primary care. Triangulation of the various results suggests that IM is at least as effective as conventional care, with potential clinical benefits including empowerment and reduced need for analgesics. The concept of IM in the management of patients with sub-acute to chronic LBP/NP appears promising in enabling the combination of excellent conventional medical diagnosis with empowering self-help strategies. Based on a synthesis of the results derived from the different study designs, data collection methods and evaluation strategies recommendations for future clinical trials of IM could be made.

More specifically this thesis concludes that:

- ✓ IM is an emerging area of relevance for providers of conventional and complementary care in Sweden.
- ✓ The developed IM model adhered to standard clinical practice procedures and involved active partnership between a gatekeeping general practitioner collaborating with a team of certified/licensed CT providers (Swedish massage therapy, manipulative therapy/naprapathy, shiatsu, acupuncture and qigong) in a consensus case conference model of care.
- ✓ It was feasible to conduct a pragmatic RCT comparing the IM model with conventional primary care in the management of patients with LBP/NP of mostly chronic duration.
- ✓ Recruiting regular primary care patients to the RCT in routine practice was also feasible but a somewhat lengthy process, in part due to fewer external referral rates compared to in house referral rates from the network of participating general practitioners.
- ✓ Exploring clinically relevant differences and the use of SF-36 as the basis for a main outcome measure showed that the sample sizes needed per arm would range from 60 (vitality) to 339 (role emotion) to adequately power a full-scale trial.
- ✓ Patients' experiences and perceptions of conventional care and CTs for sub-acute to chronic non-specific LBP/NP showed that support from conventional medical providers to diagnose and exclude pathology was an important strong aspect characterising conventional care.
- ✓ Conventional management was negatively perceived by some as a more reductionistic treatment service with reported weaknesses including lack of accessibility, time and guidance. In contrast, integrative care was reported by some as being able to conceptualise the patient as a whole person, facilitating increased treatment response and support, empowerment and self-help strategies.
- ✓ The health economic evaluation indicated a conservative 67% estimated likelihood of the IM model to be cost-effective in managing patients with sub-acute to chronic non-specific LBP/NP compared to conventional care at an economic threshold of 50 000 EUR/QALY.

Implications for research

- ✓ The current research project was explorative in nature and based on pilot trial data, therefore the results should be interpreted with some caution.
- ✓ The findings attest to the need to further investigate IM as a complex healthcare intervention and to continue to explore relevant combinations of outcomes to help understand the relevance of IM in primary care, e.g. by including patient and provider perspectives, detailed use of drugs and health care resources and health economic evaluations.
- ✓ To verify the relevance of IM in Swedish primary care, future research should prioritise larger trials considering large variability, chronic pain duration, small to moderate effect sizes, indirect costs and longer-term follow-ups while adopting a mixed methods approach considering both general and disease-specific outcomes.

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